STEREOSELECTIVE OLEFINATIONS EMPLOYING TRIALKYLPHOSPHORANYLIDES
STEREOSELECTIVE OLEFINATIONS EMPLOYING TRIALKYLPHOSPHORANYLIDES: NEW METHODS AND SYNTHETIC APPLICATIONS

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy

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(Chemistry)

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ABSTRACT:

The Wittig reaction has constantly evolved during the last half-century and is one of the most strategic, reliable, widely-applicable carbon-carbon olefin bond forming processes available in organic synthesis. The reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity and may be conducted in many cases with predictable stereocontrol. Triphenylphosphoranylidines are ubiquitously employed and despite the myriad benefits these reagents bestow there are known disadvantages to their use—most prominently related to issues surrounding stereoselectivity and phosphine oxide removal which is notoriously problematic.

Trialkylphosphoranylidines, by contrast, undergo olefination in the presence of carbonyls with high \((E)\)-stereoselectivity and the corresponding short chain trialkylphosphine oxides are water soluble. Previous work in our group has shown that semi-stabilised ylids of this type readily undergo olefination with a broad range of aldehydes under mild aqueous conditions. This aqueous Wittig reaction was then extended to the synthesis of substituted styrenes using aqueous formalin. In the search for ever milder conditions for the Wittig reaction we were also able to develop an organocatalytic Wittig reaction which was amenable to a bioorthogonal process. Thus, we were able to perform the first Wittig reaction \textit{in vivo} by feeding the two reactants to \textit{Castylegia sepium}.

Alkenals (colloquially enals) are strategic intermediates in organic synthesis; their importance is growing each year due to the expanding breadth of iminium and vinylogous enamine organocatalysis. Unfortunately their preparation remains problematic requiring labour and reagent intensive multi-step sequences. A new pincolacetal-phosphonium salt (DualPhos) for the stereoselective two-carbon homologation of aldehydes has been developed which allows for the one-pot homologation of aldehydes to enals under aqueous and/or anhydrous conditions; its application to the total synthesis and stereochemical reassignment of phomolides G & H is discussed.
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Abbreviations

[a] specific rotation [expressed without units; the actual units, deg mL g\text{-1} dm\text{-1}, are understood

Ac acetyl

AIBN azobis(isobutyronitrile)—radical initiator

Ar aryl

atm atmosphere

aq aqueous

Bn benzyl

Boc t-butyloxycarbonyl (CO\text{tBu})

BPO benzoyl peroxide—radical initiator

br broad

Bu butyl

Bz benzoyl

n-Bu n-butyl

s-Bu s-butyl

calcd. calculated

CAN ceric ammonium nitrate

CCDC cambridge crystallographic data centre

cod cyclooctadiene

CSA camphorsulphonic acid

δ chemical shift in ppm

d doublet

DABCO 1,4-Diazabicyclo[2.2.2]octane

DBP dibenzophosphole

DCM dichloromethane (solvent)

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de diastereomeric excess

DIBAL diisobutylaluminum hydride

DIPEA diisopropylethylamine

DMAP 4-dimethylaminopyridine

DMF dimethylformamide (solvent)

DMSO dimethyl sulfoxide (solvent)
dr diastereomeric ratio

E entgegen (opposite, trans)

ee enantiomeric excess
equiv. molar equivalent

EI electron impact ionization

Et ethyl

EtOH ethanol (solvent)

ESI electrospray ionization

FG functional group

ΔG Gibb’s free energy

h hour

HMDS hexamethyldisilazide

HRMS high resolution mass spectrometry

hv light

Hz hertz

IPA isopropyl alcohol

IR infra red

J coupling constant (NMR)

KOTBu potassium t-butoxide

λ wavelength

L litre
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
<td>TBDMS</td>
<td>t-butyldimethylsilyl (alcohol protecting group)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
<td>TBS</td>
<td>t-Butyldimethylsilyl (also TBDMS)</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
<td>THF</td>
<td>tetrahydrofuran (solvent)</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
<td>THP</td>
<td>tetrahydropyran (alcohol protecting group)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
<td>TIPS</td>
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<td>Ts</td>
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DECLARATION OF ACADEMIC ACHIEVEMENT:


Chapter 1

The Wittig Reaction: Historical perspective and modern mechanistic insights

1.1 The Classical Wittig Reaction

1.1.1 Introduction

The Wittig reaction, discovered in 1953, is the reaction of an alkylidene phosphorane (a phosphorus ylid) with an aldehyde, or ketone, to afford an alkene and the corresponding phosphine oxide (Scheme 1-1). Since its discovery, a number of other olefination reactions have been reported including: the Horner-Wittig, the Horner-Wadsworth-Emmons, the Peterson, the Johnson, and the Julia reactions. In each case, a functionalised carbanion or equivalent reacts with a carbonyl compound to yield the corresponding alkenyl product.\(^2\,^3\,^4\)

\[
\begin{align*}
\text{Scheme 1-1. The classical Wittig reaction} \\
R_1^3P - R^2_2 + O^3 \rightarrow R_3^2R_4^3 + R^2_2R^3_3P
\end{align*}
\]

Olefination reactions are among the most widely used reactions in synthesis today due to the high degree of control in terms of regio-, chemo-, and stereo-control.\(^5\) They are regarded as strategic C-C bond forming reactions due to their reliability, and are frequently encountered in complex organic syntheses, as well as having applications in numerous industrial and pharmaceutical syntheses.

The classical Wittig reaction using a phosphonium salt-derived phosphorus ylid provides a method for the relatively straightforward and general synthesis of alkenes with reasonable \((E):(Z)\) stereosecontrol. The generality and effectiveness of the Wittig has led to its use in natural product syntheses and large scale industrial syntheses. An example of the former is illustrated by Nicolau in his total synthesis of Brevetoxin B\(^6\) while the latter is exemplified by the synthesis of vitamin A.\(^7\) In both syntheses the Wittig reaction is pivotal; joining the two fragments together with high stereoselectivity.
1.1.1.1 Classification of phosphonium ylids

The stereoselectivity of any particular Wittig reaction is the aggregate of a number of factors—the stabilisation of an ylid, the substituents bound to phosphorus, the solvent, etc. Historically the largest predictor of stereochemical outcome in the Wittig reaction was the degree to which ylids were stabilised as, until recently, triphenylphosphoranylides predominated. Phosphonium ylids are thus broadly categorised according to the nature of the substituents attached to the α-carbon. If $R^2$ (Scheme 1-1) provides little stabilisation such as alkyl then the ylid is unstabilised whereas if $R^2$ provides a moderate degree of stabilisation ($R^2 = \text{Ph, vinyl, CN}$) then the
yrid is classified as *semi-stabilised*. Logically then groups which confer a high degree of stabilisation \((R^2 = \text{carbonyl, ester, sulfone, etc.})\) are classified as *stabilised* ylids. To illustrate the differences in ylid reactivity and stereoselectivity observed—and to highlight the chemoselectivity and ubiquity of the reaction—selected total syntheses which use the Wittig reaction will be explored.

Double bonds are ubiquitous in biologically active secondary metabolites and serve as versatile starting materials for a large number of chemical transformations. Stereoselective access to alkenes is paramount; either isomeric form not only conveys biological activity to the molecules themselves but also, in most cases, alters the stereochemical outcome of subsequent transformations. Methods for selective access to \((Z)\)-alkenes are fewer than those for \((E)\)-alkenes because it is the less thermodynamically favoured isomer. The Wittig reaction has allowed regioselective and importantly highly stereoselective access to both \((E)\)- and \((Z)\)-alkenes and has found widespread use in the synthesis of natural products as a result. In particular, fatty acids, prostaglandins, pheromones, carotenoids and other early terpene syntheses relied heavily on recent (at the time) advances in olefination chemistry and use of the Wittig reaction continues unabated.

Unsaturated fatty acids constitute a large class of primary metabolites and are biochemical precursors to many secondary metabolites including prostaglandins. They are also important chemical intermediates toward the synthesis of other natural products. Recognizable by their long carbon chains \((C_{12} \text{ to } C_{28})\) and principally *cis*-alkenes, the Wittig reaction employing *non*-stabilised ylids has been advantageously applied. Prostaglandins are cyclopentane derivatives of arachadonic acid, a \(C_{20}\)-tetraenoic acid with myriad biological effects. Access to primary prostaglandins, both natural and unnatural analogues, is possible using the bicycloheptene route which applies non-stabilised phosphoranes generated using the “salt-free” method to furnish the \(\Delta^5\)-alkene—one particular example is shown in Scheme 1-4.

![Scheme 1-4. Synthesis of a number of prostaglandins](image)

More complex natural products also highlight the utility of the Wittig reaction of *non-stabilised* ylids well. In an impressive example, Smith and co-workers on route to
(+)-discodermolide coupled two complex fragments 1-16 & 1-17 at a late-stage in a highly (Z)-selective manner (Scheme 1-5). Interestingly, while molten triphenylphosphine led to displacement of the iodide the corresponding phosphonium salt was recovered in only 37% yield. Quaternisation of the phosphine was therefore performed under ultra-high pressure. Subsequent deprotonation at low temperature with NaHMDS was followed by addition of the aldehyde which underwent the Wittig reaction with high (Z)-selectivity (>49:1, Z/E) and in good yield.

Another useful (Z)-selective Wittig reaction employs halomethyl phosphonium salts which once deprotonated react with aldehydes and ketones to give (Z)-vinyl halides useful for subsequent transition metal catalysed cross-coupling reactions.\textsuperscript{14}

Stabilised ylids offer the ability to synthesize (E)-olefins with a high degree of stereocontrol and an even greater degree of functional group tolerance. Overman and co-workers\textsuperscript{15} were able to complete the first synthesis of pumiliotoxin B employing a late-stage Wittig reaction to couple the two complex fragments together stereospecifically (Scheme 1-6) The Wittig with stabilised ylid 1-20 and aldehyde 1-19 was carried out in refluxing dichloromethane and gave the (E)-alkene in good yield with none of the (Z)-olefin observed. Importantly, no ylid epimerization was observed either.
Scheme 1-6. Late-stage Wittig reaction of a stabilized ylid during the total synthesis of pumiliotoxin B

Chen and co-workers\textsuperscript{16} reported the preparation of a key intermediate towards human rhinovirus protease inhibitor AG7088 (Scheme 1-7). In a two-step process, alcohol 1-22 is oxidised to the aldehyde under Parikh-Doering oxidation conditions and immediately reacted with triethylphosphoranylide 1-23 at low temperature to give only the (E)-alkene. The increased reactivity of trialkylphosphoranylides compared with the analogous triphenylphosphoranylide derivative allows the reaction to be performed at lower temperature and provides better stereoselectivity.

Scheme 1-7. Wittig reaction employing a stabilized trialkylphosphoranylide

\textit{Semi}-stabilized ylids haven’t been used to nearly the same effect as the other ylid classes due to the prevalence of selectivity issues during olefination. Despite the challenges, these ylids are commonly employed in the preparation of carotenoids, fatty acids and terpenes.\textsuperscript{12} One such example, the preparation of leukotriene A 1-29\textsuperscript{17} was performed using three olefinations (two of which are shown, Scheme 1-8). Reaction of the (E)-α,β-unsaturated epoxyaldehyde 1-27 (itself the product of a Wittig reaction involving a stabilised ylid) with the allylic triphenylphosphoranylide 1-28—generated using BuLi from the corresponding phosphonium salt—furnished the expected tetraene as a mixture of isomers (2:1, \(E/Z\)).
Though the Wittig reaction has advantageously been employed in the synthesis of a variety of biological or natural targets, its use was for a long time semi-empirical. Many mechanistic studies over decades provided insight into the reaction pathway but for most applications a mechanistic understanding was if not irrelevant at least unnecessary.

1.1.2 Historical Mechanistic Insight

A number of features make the Wittig reaction the most commonly employed olefination reaction: its regiospecificity, mild reaction conditions and foreseeable stereochemical outcomes. The reason for a given stereochemical outcome has been the subject of intense debate; the operable mechanism of the Wittig reaction has been a source of controversy since its inception. It is unfortunate that incongruous and contradictory evidence (relating to the operation of several factors which have a bearing on the mechanism and, importantly, the stereoselectivity of the reaction) obscured the operable mechanism of the Wittig reaction. Conflation of two distinct mechanisms operable under separate reaction conditions has also prevented consensus until recently. The following section will explore the eight distinct mechanistic proposals from a historical perspective. For a discussion of the modern Wittig mechanism, see section 1.1.3

1.1.2.1 Betaine Mechanisms

Although a carbonyl olefination reaction using a phosphorus ylid had been reported by Staudinger and Meyer in 1919, Wittig was the first to recognize and develop its practical importance. Within a few years of a systematic investigation by Wittig and Schöllkopf, which appeared shortly after the first brief report of the Wittig reaction, numerous groups were exploring the synthetic utility of Wittig’s discovery. While the initial reactions done by Wittig and co-workers were on methyltriphenylphosphonium bromide, Wittig and Schollkopf’s more thorough investigation was the first to report the (E):(Z) selectivity of so called moderated ylids (allylidenediphenylenophosphorane, and benzyldenediphenylenophosphorane). During this time, isolated reports employing non-stabilized ylids began to appear which showed extremely high (Z)-selectivity stoking interest in the mechanism of the reaction.
Though 1,2-oxaphosphetane intermediates were favoured early on, the zwitterionic phosphorus betaine had gained broad acceptance by the 1970’s. The betaine mechanism involves nucleophilic addition of the phosphorane to the carbonyl to give a betaine followed by ring closure to an oxaphosphetane intermediate which undergoes irreversible decomposition to give alkene and phosphine oxide (Scheme 1-9).

The most significant evidence for betaines as intermediates in the Wittig reaction came from several ylides, generated by deprotonation with phenyllithium, which produced a precipitate upon reaction with carbonyls at low temperature. Isolation and structural elucidation of the precipitate showed it to be a betaine-LiBr complex. Upon warming, these precipitates would decompose to afford alkene and the corresponding phosphine oxide; if treated with anhydrous HBr however, they gave β-hydroxyphosphonium salts.

As a corollary, independent generation of betaines by deprotonation of β-hydroxyphosphonium salts or, conversely, by nucleophilic opening of epoxides with phosphines—both of which were of defined stereochemistry—were shown to decompose to alkene and phosphine oxide.

The characteristics of the phosphorus ylid (phosphorane) have an enormous effect on the stereochemical outcome of a Wittig reaction. Consequently, the stereochemical outcomes of Wittig reactions were described by the nature of the ylid using betaine intermediates and were described as follows. Kinetic studies on stabilised phosphoranes seemed to show that formation of the betaine, in the absence of solvation effects, is slow and reversible. The thermodynamically stable form was thought to predominate due to interconversion; a conformation which would be determined largely by the electrostatic
attraction of the $P$ and $O$ atoms, and favour the sterically decongested *threo*-betaine (*trans*-oxaphosphetane).

In the reaction of methylcarbomethoxymethylenetriphenylphosphorane with acetaldehyde, House and Rasmusson\textsuperscript{34} proposed that rapid and reversible formation of two stereoisomeric betaines, one of which decomposes faster than the other, would lead to an increased amount of a given olefin. The transition state for decomposition of the *threo*-betaine would be stabilized by $\pi$-orbital overlap of the carbomethoxy group with the incipient double bond while steric interactions between the carbomethoxy group and the eclipsed methyl group would disfavour a similar effect in the *erythro*-betaine.

Conversely, the universally high (Z)-selectivity observed in lithium salt-free Wittig reactions of aldehydes with alkyldiencophosphoranes is a result of rapid addition of the phosphoranylide to the carbonyl. Betaine formation was still thought to be reversible but its decomposition much slower as no mechanism existed to expedite the process. Schlosser and Christmann appeared to demonstrate unequivocally the reversibility of betaine formation\textsuperscript{35} in crossover experiments of *erythro*-forms of betaine 1-39 with $p$-chlorobenzaldehyde. Unfortunately reversal of triphenylphosphoranyliades isn’t general.

![Figure 1-1. Crossover experiments of *erythro*-betaine 1-39 with $p$-chlorobenzaldehyde](image)

Bestmann and Kratzer\textsuperscript{36} meanwhile, upon reaction of tricyclohexylalkyldene-phosphorane with carbonyl compounds, found a higher incidence of the *trans*-olefin compared to reactions using triphenylalkyldene-phosphorane. Bestmann proposed that betaine decomposition would be retarded by the increased electron density on phosphorus as a result of the cyclohexyl-ligands.\textsuperscript{36} As such, complete equilibration between stereoisomeric betaines was possible. It was during these early days that the mechanism for the Wittig reaction involving betaine intermediates gained broad acceptance.
Bergelson's Betaine Mechanism

Bergelson proposed a variation of the ‘classic’ betaine mechanism, specifically for non-stabilised ylids, whose essential feature was nucleophilic attack of the carbonyl oxygen at phosphorus to give a ‘C-P-O-C’ betaine which was followed by ring-closure to the oxaphosphetane and decomposition to the alkene (Scheme 1-10).

\[
\begin{align*}
\text{Ph}_3\text{P} + \text{R}^1\text{CHO} & \rightarrow \text{Ph}_3\text{P} \text{C} = \text{O} \text{R}^1 \\
& \rightarrow \text{Ph}_3\text{P-O} \text{R}^2 \text{R}^1 \\
& \rightarrow \text{R}^1 \text{C} = \text{O} \text{R}^2 + \text{Ph}_3\text{P(O)}
\end{align*}
\]

Scheme 1-10. Bergelson’s alternative betaine mechanism

The substituents around the phosphorus atom during the reaction are an area of importance for non-stabilised phosphoranes. Schneider postulated, like Bergelson previously, that in the case of non-stabilised phosphoranes, nucleophilic attack by O\(^-\) on P\(^+\) occurs before the carbon-carbon bond is formed while accounting for the trigonal bipyramidal geometry at phosphorus in the transition state.\(^30\) In this description the most electronegative element is in the apical position, while the ylid carbon is in the equatorial position (Figure A). This structural description represents a situation in which there is very little steric crowding for R\(_1\). Free-rotation about the O-C bond leads to the lowest energy conformer, where R\(_1\) is the farthest possible position away from the substituents in the vertical plane of the carbenium ion. Oxaphosphetane formation requires the plane of the carbenium ion to be perpendicular to the orbitals of the ylid carbanion. This leads to rotation about the O-C bond in one of two ways (Figure 1-2), and leads to the formation of the *erythro* betaine and subsequently the *cis*-oxaphosphetane, avoiding a negative steric interaction between R\(_1\) and a phenyl substituent (Figure 1-3).
Schweizer Betaine Mechanism

Schweizer and coworkers, on observing that certain stabilised and semi-stabilised ylids react with carbonyl compounds in alcoholic solvents to afford, in addition to the typical alkene/phosphine oxide products, vinylphosphine oxides, proposed a particular betaine mechanism (Scheme 1-11). Nucleophilic attack of the ylid onto the carbonyl affords a betaine 1-46 which, in this particular medium, becomes protonated and subsequently undergoes an E1cB elimination of the β-hydroxyl to give vinylphosphonium salt 1-48. Nucleophilic attack by an alkoxide/hydroxide on the cationic phosphorus atom would then give an intermediate which could expel an alkene, creating phosphine oxide (typical Wittig products) or phenyl, producing benzene and vinyl phosphine oxide 1-49.
**Bestmann’s Betaine Mechanism**

Bestmann proposed a mechanism which included direct OPA formation from ylid and aldehyde. During or after the conversion of OPA 1-32a into the C-apical OPA 1-32b cleavage of the C-P bond occurs to give a P-O-C-C betaine 1-50a (Scheme 1-12). The electronic nature of the substituents $R^2$ and $R^3$ of 1-50a determines the lifetime of the zwitterionic species and therefore the stereochemistry of the olefinic products. If $R^3$ is phenyl and $R^2$ and electron donating group rapid elimination of phosphine oxide occurs. Whereas if $R^2$ is an electron withdrawing group and/or $R^3$ are alkyl groups the betaine is sufficiently long lasting to isomerise to the thermodynamically more stable diastereomer 1-50b prior to elimination.

**Scheme 1-12.** Bestmann’s mechanism for the Wittig reaction

Though these models and figures explained the stereochemical outcomes quite well they were only post-experimental justifications for observations and, as the burden of evidence amassed, they have been proven to be incorrect (*vide infra*).

**1.1.2.2 Radical Mechanisms**

Radical-based Wittig mechanisms were proposed to explain a few particular unexpected results; they were never broadly accepted nor thought to be general. They are discussed here merely for completeness.
Olah's single electron transfer mechanism

Wittig reactions of non-stabilised ylids with deactivated carbonyls (bicycle[3.3.1]nonan-9-one, benzophenone) in refluxing solvents furnished the product of ketone reduction and the starting phosphonium salt in addition to the expected Wittig products. Additionally, when these reactions were performed in toluene, benzylated tolenes were observed seemingly indicating the operation of a radical mechanism. Olah and co-workers proposed a single electron transfer mechanism, wherein the ylid and carbonyl form a tight radical ion pair which is in equilibrium with the P-O diradical below (Scheme 1-13). The diradical intermediate would lead to betaine which would decompose to alkene and phosphine oxide.

\[
\begin{align*}
\text{1-1} & \rightarrow \text{1-2} \\
\text{1-51} & \leftrightarrow \text{1-52} \\
\text{1-53} & \rightarrow \text{1-54}
\end{align*}
\]

Scheme 1-13. Olah’s single electron transfer mechanism

McEwan's spin-paired diradical mechanism

McEwan and co-workers proposed two similar yet distinct diradical mechanisms. The first involved C-C bond formation leading to a spin-paired diradical intermediate whose geometry arose from orthogonal approach of the ylid and carbonyl. The resultant erythro-diradical eventually closed to cis-OPA which could then dissociate into the observed (Z)-alkene and phosphine oxide. Five years later a second mechanism was published which involves an analogous process but creates an intermediate with two carbon radicals instead of the P,O radicals previously proposed (Scheme 1-14). The presence of a stabilising group on the ylid was proposed to extend the radical lifetime, thereby permitting bond rotation prior to ring closure to the trans-OPA. The latter mechanistic hypothesis was thought to supersede the former only in those instances where no lithium cation nor sodium iodide were present and to explain the enhancement of (E)-selectivity observed for semi-stabilised and stabilised ylids.

\[
\begin{align*}
\text{1-1} & \rightarrow \text{1-2} \\
\text{1-51} & \leftrightarrow \text{1-52} \\
\text{1-53} & \rightarrow \text{1-54}
\end{align*}
\]

Scheme 1-14. McEwan’s spin-paired diradical mechanism
Radical based mechanisms introduce more contradictions to the Wittig reaction mechanism than they solve and have been, in general, thoroughly and rigorously disproven. In a series of experiments designed to probe the potential of radical species in the Wittig reaction, Vedejs and Marth found that no such mechanism was operable; every experiment in which radical-side reactions would be expected the only isolable products were of a normal Wittig reaction. Further, reaction of cyclopropylidenephosphoranes with cyclopropanal furnishes the Wittig product with high (Z)-stereoselectivity. If an electron transfer mechanism was operable, side-reactions stemming from cyclopropylcarbinyl radicals (which ring open with a unimolecular rate constant of k~$10^{10}$ s$^{-1}$) would be expected. The absence of these products conclusively eliminates the possibility of a radical mechanism in all but exceptional cases.

### 1.1.2.3 Cycloaddition mechanisms

Vedejs and Snoble were the first to propose the direct asynchronous [2+2] cycloaddition of ylids with aldehydes, in the absence of inorganic salts, to give oxaphosphetanes which upon warming decompose via stereospecific cyclo-reversion (Scheme 1-15) based upon their initial observation that oxaphosphetanes are the sole observable intermediate by LT-NMR. The cycloaddition mechanism eliminated ionic intermediates (betaines); instead it favoured the least hindered orthogonal approach of the carbonyl and ylid π-bonds prior to $\pi_2$ + $\pi_a$ cycloaddition leading to the cis-oxaphosphetane (Scheme 1-16, see B, C). The cycloaddition mechanism is also supported by a Hammett study of ArCHO and Ph$_3$P=CHR.

![Scheme 1-15. Cycloaddition mechanism of the Wittig reaction](image-url)
In contrast, Schlosser and Schaub proposed the *cis*-selectivity observed in the Wittig reaction of unstabilised ylids was the result of a conformational bias in the late-stage transition state of the [2+2] cycloaddition (Scheme 1-17). The measured relative rate of oxaphosphetane formation indicated that *cis*-OPA was generated at an ordinary rate, whereas, formation of the *trans*-OPA was hindered by comparison. Schlosser suggested this was a result of steric crowding in the transition state, postulated to be planar with a trigonal bipyramidal geometry at phosphorus (noticeably product-like). The ylid α-substituent forces the neighbouring phenyl ring to twist 50° out of the plane expected for a trigonal bipyramidal arrangement about phosphorus. The axial P-phenyl is oriented perpendicular to the forming oxaphosphetane, while the equatorial P-phenyl orients itself in such a way that the ortho-hydrogen interacts with the substituents on the carbonyl carbon (1,3-interaction) leading to a negative agostic interaction in the *trans*-oxaphosphetane.

**Scheme 1-16.** Early cycloaddition mechanisms for the Wittig reaction

**Scheme 1-17.** Schlosser’s proposed late stage transition state for *cis*-selectivity in the Wittig reaction of unstabilised ylids
The late-stage transition state above implies greater thermodynamic stability of the cis-OPA yet there exists no evidence trans-OPA isomerizes to cis-OPA under any conditions leading to the contradiction that trans-OPA must be more thermodynamically stable. The fact trans-OPA is more stable is intuitive (significantly decreased 1,2-interactions). This implies that the cis-selectivity observed must be the product of an early stage transition state, eroding confidence in the model. It is also difficult to rationalize the high (E)-stereoselectivity of stabilised ylids within the parameters of this model.

Exhaustive work by Vedejs and co-workers over a decade definitively established the cycloaddition mechanism of the Wittig reaction for non-stabilised, semi-stabilised and stabilised ylids (see 1.1.3 for an in depth discussion of ylids and the modern mechanism). Non-stabilised ylids react via an early puckered transition state (Figure 1-4-A) which attenuates 1,2- and 1,3-interactions between the approaching aldehyde and the ylid whose phosphorus is still sp³ hybridised. For stabilised ylids, a late transition state is likely as the trans-OPA is thermodynamically the most stable. Vedejs proposed that these ylids would prefer a four-centre transition state (Figure 1-4-B) which noticeably resembles the oxaphosphetane.

Though reasonably well understood the description of the modern Wittig mechanism is neither one single mechanism nor complete. There are still questions as to the exact effect of lithium halide salts, the mechanism of OPA decomposition and cycloreversion and explanations are required for the myriad anomalous effects observed throughout the literature.

1.1.3 Modern Mechanism

The modern mechanistic interpretation of the Wittig reaction has been constructed and elaborated slowly using the accumulated wealth of—at times contradictory—experimental information. Understanding the operational mechanism of the Wittig reaction and the resultant stereochemistry of the alkene requires nuanced study; subtle
changes to reaction conditions can have an enormous impact of the stereoselectivity of the furnished alkene.

The preponderance of evidence available suggests that the first step of the Wittig reaction proceeds—in the absence of Li-salts—irreversibly via a [2+2] cycloaddition (O-apical, see 1.1.3.2) to give oxaphosphetane as developed by Vedejs and co-workers. The stereochemistry of the oxaphosphetane, and therefore the product alkene, is set by the orientation of the substituents during the transition state of the cycloaddition. Non-stabilised ylids react via an early puckered TS which is highly cis-selective while stabilised ylids react via a late puckered TS opposite in sense to that of non-stabilised ylids to give trans-OPA selectively. The oxaphosphetane then undergoes facile pseudo-rotation to place the ring oxygen in an equatorial position followed by stereospecific decomposition by syn-cycloreversion to afford alkene and the corresponding phosphine oxide.

The persistence of betaines and the implication of thermodynamic control in modern descriptions of the Wittig reaction is surely due to conflation of distinct mechanisms. It is therefore important to articulate that there exists a clear distinction between the mechanisms that operate in the presence and absence of Li-salts. Early experiments concerning the involvement of betaines and reversible formation of intermediates, though rigorously conducted, were fundamentally flawed as they were deliberately designed to produce betaines, and clearly betaines give oxaphosphetanes. Subsequent work has unequivocally demonstrated that acid quenching of spectroscopically pure oxaphosphetane solutions gives β-hydroxyphosphonium salts; oxaphosphetanes also react with LiBr to give betaine–LiBr complexes. That these compounds will subsequently react to produce oxaphosphetanes and ultimately alkene/phosphine oxide mixtures does not necessarily mean they are a reactive intermediate. Further, no uncomplexed betaines have ever been observed spectroscopically. The fact that betaine lies at a relatively higher energy than oxaphosphetane and there exists an alternative mechanism for oxaphosphetane formation that is consistent with all available experimental observations indicates that betaine is not part of the lithium salt-free Wittig mechanism.

No clear mechanism has yet been established for Wittig reactions in the presence of lithium salts. Lithium salts are only one of four distinct interrelated pathways for the stereochemical modification of Wittig reaction intermediates. Each will be covered in further detail (as indicated) but are summarized here.
1. Lithium-halide salts not only promote increased trans-OPA formation they also promote stereochemical drift via betaine lithium halide adducts and reversal of cis-OPA to ylid and aldehyde (see 1.1.3.4).

2. Lithium halides may also promote the partial epimerisation of oxaphosphetanes through the reversible formation of β-hydroxy ylids.

3. The non-salt catalysed reversal of cis-OPA into ylid and aldehyde allowing some measure of equilibration is restricted to oxaphosphetanes derived from P-trialkyl ylids with aromatic or tertiary aliphatic aldehydes and ethylidenetriarylphosphoranylides with aromatic aldehydes. The reaction is only spontaneous near or above the decomposition temperature of the oxaphosphetanes.

4. The Schlosser modification employs a kinetically controlled epimerisation sequence—involving β-oxido ylids—to establish stereochemistry of the oxaphosphetane and therefore resultant alkene.

1.1.3.1 Effect of the Ylid

The substitution of the α-carbon of a phosphorus ylid has an intrinsic effect on the stereochemical outcome of a Wittig reaction. Though the substituents on phosphorus arguably exhibit a greater degree of control over the expected stereoselectivity of the Wittig reaction (see 1.1.3.2), historically the Wittig reaction has been separated into three classes of ylids based on the degree to which the carbanion is stabilized/delocalized conferring less sensitivity to moisture. In the case of triphenylphosphine-derived ylids it is certainly the case that the resultant stereoselectivity is, in general, directly related to the substitution.

![Figure 1-5. Depiction of ylid classes and expected stereoselectivity](image)

It seems relevant at this juncture to discuss the electronic nature of phosphorus ylids (and the related phosphine oxides, phosphonates). The ability of phosphorus to
stabilise an adjacent carbanion has historically been attributed to dπ-pπ interactions,\textsuperscript{61,62} which conveniently describe the shortening of the formal PC single bond observed in crystal structures of ylids\textsuperscript{63} and formalize P=C bond length data\textsuperscript{64} which suggests a bond order of two. Though convenient, the involvement of outer ‘low-lying’ d orbitals in bonding has been dismissed as an “artefact of the electronic structure model”.\textsuperscript{65} As predictive models have become more refined, electrostatic interactions,\textsuperscript{66} high polarisability,\textsuperscript{67} and negative hyperconjugation\textsuperscript{68} have gained broad acceptance. The evidence for ylids suggests that while the ylid carbon retains a substantial amount of carbanionic character a small amount of the charge density located in the p orbital of the α-carbon is back-bonded by overlap into the σ* LUMO of the phosphine (Figure 1-6a).\textsuperscript{69} The physical manifestation of this interaction has been characterized more thoroughly using \textsuperscript{1}Bu\textsubscript{2}Cl═CPh\textsubscript{2}.\textsuperscript{70} The P-Cl bond has a σ* which is lower in energy than that of either P-C bond and is therefore expected to be the dissimilar ligand (Figure 1-6a). As the dihedral angle approaches 90° the P-Cl bond lengthens as expected for backbonding. Further, free rotation about the P=C bond in solution has been shown by \textsuperscript{13}C-NMR\textsuperscript{71} while other physical measurements suggest the ylid bond is highly polar.\textsuperscript{72}

![Figure 1-6. Structure of an ylid](image-url)

**Non-stabilised ylids**

Triphenylphosphoranylides comprise the bulk of literature reports concerning non-stabilised ylids and it is generally accepted that in the absence of lithium salts these ylids will furnish high (Z)-selectivity (Table 1-1). Typical non-stabilised ylids of the type Ph\textsubscript{3}P=CHR are >90% selective for the (Z)-alkene with selectivity increasing as the temperature decreases (Table 1-1, entries 1-5) and is highest with tertiary aldehydes (Table 1-1, entries 8-10).\textsuperscript{25,41,73} The reaction of n-butylidenetriphenylphosphorane (generated from NaNH\textsubscript{2}) with hexanal proceeds with exceptional (Z)-selectivity (E:Z, 98:2) while the same reaction performed using LiHMDS shows eroded selectivity (E:Z, 5.8:1) (Table 1-1, entries 11 & 12). Crucially, stereospecific conversion of the OPA
(cis:trans, 5.8:1) to alkene (E:Z, 5.8:1) was observed which is consistent with reports that Li⁺ influences stereoselectivity during OPA formation but does not generally affect the the stereochemical ratio of OPAs once formed. Thus for aliphatic aldehydes, results are essentially independent of solvent and oxaphosphetane dissociation to aldehyde and ylid (reversal) is not a factor, implying kinetic control. It is now generally agreed that non-stabilised ylids do not revert to starting materials under normal Wittig conditions.²¹,³²,⁷⁴ Typical oxaphosphetanes are stable below –35 °C and decompose at –25 °C or above though the rate of decomposition is subject to steric hindrance—methylide adducts decompose faster than ethylide adducts.²⁵,⁴⁸

Table 1-1. Wittig reactions of non-stabilised ylids

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Y</th>
<th>Z</th>
<th>X</th>
<th>Base</th>
<th>Temp</th>
<th>OPA cis/trans ratio</th>
<th>Alkene Z/E ratio</th>
<th>ref.</th>
</tr>
</thead>
</table>
Stereochemical drift is the non-correspondence of an observed diastereomeric ratio of OPA and the \((E)/(Z)\) ratio of the resultant product. In every case there is an accumulation of the \((E)\)-isomer relative to the \(cis/trans\) OPA ratio which cannot be described by the increased stability of the alkene as OPA decomposition is irreversible. Stereochemical drift in the absence of lithium salts is quite rare and limited to a select few systems. One such example, the reaction of ethylidenetriphenylphosphorane with aromatic aldehydes, has long been known to undergo stereochemical drift (Table 1-1, entry 6). \(^{48,59}\) Interestingly, stereochemical drift only occurs above the temperature at which the OPA decomposes. \(^{48}\) The propensity of the \(cis\)-OPA of ethylides and benzaldehyde to undergo reversal was further probed by studying the condensation of ethyldiphenylethylidenephosphorane and phenyldibenzophosphylethylidenephosphorane with benzaldehyde; neither showed any proclivity for interconversion nor decomposition below \(-20\, ^\circ\text{C}\). \(^{78}\) The only other examples of this type of stereochemical drift occur in the reaction of alkylidenephoranylides with aromatic or tertiary aldehydes. \(^{52,57,59}\)

Stereochemical drift is much more commonly associated with the presence of lithium salts (Li\(^+\)). It should be noted that two distinct processes are operable under these conditions and that only one is stereochemical drift; the presence of lithium salts affects both the initial stereoselectivity of OPA formation with alkylidenetriphenylphosphoranes resulting in a higher proportion of \(trans\)-OPA (see section 1.1.3.4) and exerts an influence on the subsequent diastereomeric OPAs—specifically on those derived from aromatic aldehydes—leading to enrichment of the \((E)\)-isomer. The role of Li\(^+\) in the process of stereochemical drift may be related to the formation of betaine–lithium halide complexes, which have been isolated from reactions of non-stabilized ylids. Positive crossover experiments indicate that the conversion of \(cis\)-OPA into \(trans\)-OPA in the reactions of alkylidenetriphenylphosphoranes with benzaldehyde in the presence of Li\(^+\) involve OPA reversal to ylid and aldehyde.

As is apparent from the discussion above, the Wittig reaction of non-stabilised ylids, under most conditions, operates under kinetic control. \(^{79}\) Independent stereospecific generation of betaines and thus OPAs (synthesised from chiral epoxides) have been reported to undergo stereospecific decomposition to alkene (Scheme 1-18). A \(trans\)-epoxide is opened with lithium diphenylphosphide and subsequently quaternarised with methyl iodide to give \(cis\)-OPA which exhibits no interconversion. It can therefore be
concluded that cycloreversion of OPA is stereospecific and irreversible in the absence of lithium salts.

Scheme 1-18. Independent stereoselective generation of cis-OPA via nucleophilic epoxide opening

Non-stabilised ylids react via an early, puckered transition state leading to cis-OPA in which the carbonyl oxygen occupies a pseudo-axial position in accordance with Westheimer’s rules for trigonal bipyramidal geometries of phosphorus (Figure 1-7). An early transition state is necessarily flexible as the P-O and C-C bonds are long and rehybridisation isn’t particularly advanced allowing for significant puckering. This near-tetrahedral arrangement about phosphorus destabilises a planar transition state—which would be trans-selective (Figure 1-7) due to increased 1,2-interactions—as one of the P-Ph must necessarily project toward the approaching carbonyl. Puckering minimises 1,2-steric interactions by placing the carbonyl substituent (R\textsuperscript{1}) in a pseudo-equatorial position and the ylidic substituent (R\textsuperscript{2}) into a pseudo-axial position. Also minimised are potential 1,3-interactions between the substituent on phosphorus and the pendant carbonyl group.

The corresponding trans-selective transition states are harder to discern. The puckered trans-selective transition state would presumably be similar to the cis-selective TS aside from the orientation of the ylidic substituent which would be pseudo-equatorial leading to significant 1,2-interactions. The corresponding planar transition state minimizes this negative interaction, however, bond rehybridisation hasn’t yet occurred—the transition state is still early—leading to significant impediment of the carbonyl as one of the phenyl rings on phosphorus necessarily projects towards the approaching carbonyl.

Figure 1-7. Proposed transition states of non-stabilised ylids: A. cis-selective transition state B. the trans-selective transition state.

Cycloaddition of non-stabilised ylids and aldehydes is generally irreversible (vide infra) and cycloreversion to alkene stereospecific. The OPAs formed necessarily place oxygen in the axial position prior to rapid pseudorotation which leads to the less stable C-
apical OPA and cycloreversion (see 1.1.3.2). The barrier to decomposition is dependent on the diastereomer of the OPA under consideration; cycloreversion of cis-OPA has been found to be faster than trans-OPA\textsuperscript{52,59} in direct contrast to theoretical work done by Harvey and co-workers which indicates that the barrier to cycloreversion is higher for cis-OPA than for trans-OPA.\textsuperscript{56} It has been postulated that the barrier to cycloreversion may be similar to the barrier for reversal in cases were stereochemical drift is operable.

The ligands on phosphorus exert a power influence over the stereochemical outcome of reactions of non-stabilised ylids. Replacement of a single phenyl ring by an alkyl group leads to significantly less (Z)-selectivity, presumably due to less puckering in the transition state since 1,3-interactions should be attenuated.

\textit{Semi-stabilised ylids}

Wittig reactions employing semi-stabilised ylids are notorious for poor stereoselectivity, typically only slightly (E) or (Z) selective (Table 1-2). What is immediately evident is the lack of consistency in stereochemical outcomes. Under identical conditions and with the same reactants the reported (Z)-selectivity among lithium halide free reactions can vary from 25\% to 75\% making rational mechanistic interpretation complicated.\textsuperscript{81} It is difficult to obtain detailed mechanistic information for semi-stabilised ylids for two reasons: their OPAs are, except for a single example,\textsuperscript{53} not observable by variable temperature \textsuperscript{31}P-NMR nor do crossover experiments furnish meaningful results as reactions of semi-stabilised ylids are so fast that the reaction is complete prior to addition of the crossover aldehyde. Semi-stabilised ylids were therefore primarily investigated using β-hydroxyphosphonium salts and nucleophilic cleavage of epoxides\textsuperscript{82} as detailed above. All evidence demonstrates semi-stabilised ylids are under kinetic control, that is there is no reversal of OPA formation.
Table 1-2. Select examples of reactions of semi-stabilised ylids (adapted from ref. 4)

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Y</th>
<th>Z</th>
<th>X</th>
<th>Base</th>
<th>Temp</th>
<th>Alkene Z/E ratio</th>
<th>ref.</th>
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<td>Ph</td>
<td>Ph</td>
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<td>H</td>
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<td>BuLi</td>
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<td>68:32</td>
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<td>Ph</td>
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<td>Ph</td>
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<td>25:75</td>
<td>4</td>
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<td>35:65</td>
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<td>Ph</td>
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<td>(CH₃)₂CH</td>
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<td>Br</td>
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<td>72:28</td>
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</tr>
<tr>
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<td>Ph</td>
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<td>c-C₆H₁₁</td>
<td>H</td>
<td>Br</td>
<td>BuLi</td>
<td>-78 °C</td>
<td>53:47</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>Ph</td>
<td>Ph</td>
<td>CH=CH₂</td>
<td>c-C₆H₁₁</td>
<td>H</td>
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<td>22:78</td>
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<td>H</td>
<td>Br</td>
<td>KHMDS</td>
<td>-78 °C</td>
<td>50:50</td>
<td>4</td>
</tr>
</tbody>
</table>

Reactions of semi-stabilised ylids proceed to OPA irreversibly through a transition state which occurs later along the reaction coordinate and features a C-C bond which is more advanced than P-O bonding. The decreased steric demands of a more trigonal bipyramidal phosphorus centre and the sp²-hybridised ylidic substituent results in a more sterically decongested transition state. The highly puckered transition state of non-stabilised ylids minimised both 1,2- and 1,3- interactions and relieved the burden of approaching too close to one of the spectator ligands on phosphorus. The tighter arrangement about phosphorus in a trigonal bipyramid attenuates 1,3-interactions, meaning that a parallel or planar approach of the ylid and aldehyde is energetically competitive. Theoretical work at the B3LYP/6-31G* level of theory indicates the puckered cis-OPA TS to be marginally favoured over the planar TS. The obvious increase in 1,2-interactions necessitates any planar TS to be trans-selective. Competitive
anti-sense transition states neatly explain the erosion of stereoselectivity observed for semi-stabilised ylids.

Computational work by Aggarwal, Harvey and co-workers\textsuperscript{56} indicates the barrier for OPA decomposition is lower than formation, making OPA formation the rate determining step in accordance with spectroscopic observations. The initially formed OPA—with oxygen in an axial position—undergoes facile pseudorotation to place the ylidic carbon in an apical position in the phosphorus-centred trigonal bipyramid which then undergoes stereospecific and irreversible cycloreversion to alkene and phosphine oxide.

![Figure 1-8. The possible transition states of semi-stabilised ylids: A. the puckered transition state towards cis-OPA B. the planar transition state towards trans-OPA](image)

Replacement of a single phenyl ring by an alkyl group on phosphorus leads to a reduction in 1,3-interactions; an alkyl group effectively reduces steric congestion around phosphorus—the sum of steric interactions. As a consequence 1,2-interactions predominate and the trans-selective transition state becomes kinetically favoured leading to reasonable to high \((E)\)-selectivity. Stereoselectivity in semi-stabilised ylids is broadly governed by 1,3-interactions, or the lack thereof, no matter the specific ylid/aldehyde combination.

\textit{Stabilised ylids}

\textit{Stabilised} ylids—which have an electron-withdrawing group adjoining the ylidic carbon—exhibit a high degree of \((E)\)-selectivity. In contrast to non-stabilised and semi stabilised ylids, stabilised ylids display pronounced solvent and substituent effects which erode stereoselectivity (see 1.1.3.3 for an elaborated discussion of solvent effects). Ethereal solvents furnish the \((E)\)-enoate while the highest percentage of \((Z)\)-enoate is consistently observed in reactions performed with methanol. The Wittig reaction of simple ester-stabilised ylids can be performed with high \((E)\)-selectivity in ether solvents but \textit{in situ} generation of the ylid can be problematic as stereoselectivity appears base dependent. Conversely, the substitution on phosphorus does not alter the stereoselectivity of the reaction nor does steric bulk of the aldehyde significantly influence stereoselectivity.
Thermodynamic control has long been employed to describe the high (E)-selectivity displayed by stabilised ylids. Preferential reversal of the less stable cis-OPA—which was thought to have a higher barrier to cycloreversion—would lead to mostly trans-OPA and therefore mostly (E)-alkene. Despite the appeal of thermodynamic equilibria, kinetic control was proven operable with stabilised ylids via \( \beta \)-hydroxyphosphines obtained from nucleophilic opening of epoxide which were then quaternarised and to give the \textit{erythro}-\( \beta \)-hydroxyphosphonium salt.\(^{53}\)

Stabilised ylids of the type \( \text{Ph}_3\text{P}=\text{CHCO}_2\text{R} \) display an interesting \( \alpha \)-heteroatom substitution effect. Systemic comparisons suggest in complex aldehydes remote heteratoms may enhance or negate the effect. Aldehydes which possess \( \alpha \)-oxygenation exhibit a characteristic bias toward (Z)-selectivity in contrast to the natural (E)-selectivity generally observed for this ylid class.\(^{4,89}\) It seems likely that the exceptional solvent and substrate dependence of \( \alpha \)-unsubstituted ester-stabilised ylids directly reflects preferences in transition state.

Vedejs proposed that stabilised ylids react through a late transition state that is noticeably oxaphosphetane-like\(^{51,53}\) which implied the transition state was planar and therefore 1,2-interactions would predominate and afford high (E)-selectivity. Though quite reasonable there are a few noticeable inconsistencies with a planar transition state. In particular, a planar transition state cannot explain the high (E)-selectivity observed for \( \alpha \)-substituted ylids. Computational efforts by Aggarwal, Harvey and coworkers have thankfully elaborated on Vedejs’ mechanism and provided insight into these ubiquitous olefinations.

Stabilised ylids do indeed react via a late transition state to form an OPA—an endothermic process which is also rate-determining—that subsequently undergoes facile cycloreversion to alkene and phosphine oxide. The initial cycloaddition occurs through a transition state that is \textit{anti-sense} to that observed for non-stabilised ylids which helps to minimise dipole-dipole interactions (Figure 1-9, A). Bond formation is quite advanced and while any OPA must proceed through an \( O \)-apical intermediate new evidence suggests that the \( C \)-apical OPA may be more stable. Interestingly, OPA pseudorotation and cycloreversion may be a single step process\(^{90,91}\) which would likely make the \( C \)-apical OPA an artefact of calculations. The barrier to cycloreversion is thought to be far lower than the barrier for reversal and even lower than the barrier to cycloreversion in oxaphosphetanes derived from other ylids. Thus OPA formation is irreversible.
Both puckered cis-transition states are disfavoured, the first because of large 1,3-interactions and the second due to negative dipole interactions (Figure 1-9, C & D). The lowest energy cis-selective transition state was actually found to be planar but isn’t competitive due to the large 1,2-steric interactions and disfavourable reactant dipoles (Figure 1-9, B).

1.1.3.2 The role of substituents at phosphorus and the mechanism of decomposition of oxaphosphetanes

The nature of the phosphorus environment comprises much more than simply ylidic substitution. The nature of the ligands on phosphorus—typically triaryl—effect a considerable influence on the stereochemical outcome of the Wittig reaction. There is a qualitative trend towards increasing (E)-selectivity when one or more of the P-phenyl groups of Ph₃P=CHCH₃ is replaced by an alkyl group (Table 1-3, entry 1 vs. Entries 3 & 14) because of reduced 1,3-interactions. However, if the aldehyde is tertiary, increased 1,3-interactions lead to modest cis-selectivity (Table 1-3, entries 5, 7, 9, 15). Semi-stabilised ylids exhibit the same trend on switching to RPh₂P=CHX from PPh₃=CHX (Table 1-3, entries 19-22).
Table 1-3. Comparison of \( P \)-ligand compounds with a range of aldehydes (adapted from ref. 4)

<table>
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<th>Entry</th>
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<th>( R^2 )</th>
<th>( R^1 )</th>
<th>( X' )</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp(^\circ C )</th>
<th>Alkene Z/E ratio</th>
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</thead>
<tbody>
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<td>( \text{PhCH}_2\text{CH}_3 )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{Br} )</td>
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<td>THF</td>
<td>-78, 25</td>
<td>94:6 20</td>
</tr>
<tr>
<td>2</td>
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<td>( c-\text{C}<em>6\text{H}</em>{11} )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{Br} )</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78, 25</td>
<td>99:1 42</td>
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<td>( \text{I} )</td>
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<td>THF</td>
<td>-78, 20</td>
<td>30:70 20</td>
</tr>
<tr>
<td>4</td>
<td>( \text{PEtPh}_2 )</td>
<td>( \text{PhCH}_2(\text{CH}_3)\text{CH} )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
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<td>THF</td>
<td>-78, 20</td>
<td>27:73 20</td>
</tr>
<tr>
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<td>( \text{PhCH}_2(\text{CH}_3)\text{C} )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
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<td>THF</td>
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<td>85:15 20</td>
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<td>( \text{PhCH}_2\text{CH}_3 )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78, 20</td>
<td>18:82 20</td>
</tr>
<tr>
<td>7</td>
<td>( \text{iPrPPh}_2 )</td>
<td>( \text{PhCH}_2(\text{CH}_3)\text{CH} )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78, 20</td>
<td>50:50 20</td>
</tr>
<tr>
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<td>( \text{PhCH}_2\text{CH}_2 )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78, 20</td>
<td>25:75 20</td>
</tr>
<tr>
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<td>( \text{PhCH}_2(\text{CH}_3)\text{CH} )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78, 20</td>
<td>45:55 20</td>
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<tr>
<td>10</td>
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<td>( \text{PhCH}_2\text{CH}_3 )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78, 20</td>
<td>94:6 20</td>
</tr>
<tr>
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<td>( \text{PhCH}_2(\text{CH}_3)\text{CH} )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
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<td>THF</td>
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<td>99:1 20</td>
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<td>( \text{PhCH}_2(\text{CH}_3)\text{CH} )</td>
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<td>( \text{I} )</td>
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<td>90:10 20</td>
</tr>
<tr>
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<td>NaNH(_2)(^b)</td>
<td>THF</td>
<td>-78, 20</td>
<td>10:90 20</td>
</tr>
<tr>
<td>14</td>
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<td>( \text{PhCH}_2\text{CH}_3 )</td>
<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
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<td>36:64 20</td>
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<tr>
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<td>( \text{CH}_3 )</td>
<td>( \text{I} )</td>
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<td>THF</td>
<td>-78, 20</td>
<td>10:90(^d) 20</td>
</tr>
<tr>
<td>18</td>
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<td>( \text{n}-\text{C}<em>5\text{H}</em>{11} )</td>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>--</td>
<td>--</td>
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<td>-60, 20</td>
<td>10:90 22a</td>
</tr>
<tr>
<td>19</td>
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<td>( c-\text{C}<em>6\text{H}</em>{11} )</td>
<td>( \text{CH=CH}_2 )</td>
<td>( \text{Br} )</td>
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<td>THF</td>
<td>-78</td>
<td>22:78 42a</td>
</tr>
<tr>
<td>20</td>
<td>( \text{PMePh}_2 )</td>
<td>( c-\text{C}<em>6\text{H}</em>{11} )</td>
<td>( \text{CH=CH}_2 )</td>
<td>( \text{Cl} )</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78</td>
<td>&lt;5:95 40</td>
</tr>
<tr>
<td>21</td>
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<td>Ph</td>
<td>Ph</td>
<td>Cl</td>
<td>NaNH(_2)</td>
<td>THF</td>
<td>20</td>
<td>47:53 63</td>
</tr>
<tr>
<td>22</td>
<td>( \text{PMePh}_2 )</td>
<td>Ph</td>
<td>Ph</td>
<td>Cl</td>
<td>KHMDS(^e)</td>
<td>THF</td>
<td>-78</td>
<td>14:86 39b</td>
</tr>
</tbody>
</table>

---

a. The temperature for the ylid reaction is given first, followed by the decomposition temperature

b. The experimental conditions and yield are given in ref. However, DBP ylids generated using NaNH\(_2\)/THF tend to decompose

c. The ylid was distilled, therefore, no counterion or metal salts were present

d. Significant (>5%) stereochemical drift is likely

e. The solution was filtered to remove precipitated salts

Birum and Matthews were the first to isolate an OPA.\(^{92}\) According to the rules for the occupation of the apical positions\(^{93,94}\) for the formation of trigonal bipyramidal phosphorus centres and for the conversion and collapse of the OPA,\(^{80}\) during the formation of the oxaphosphetane, the oxygen atom must enter the apical position of the trigonal bipyramid formed. This was confirmed by X-ray analysis.\(^{95,96,97}\) Cleavage of the original ylid P-C bond necessary for olefin formation therefore requires a ligand rearrangement process, \textit{pseudorotation}, which brings this bond into the apical position. The interchange of apical and equatorial ligands in trigonal bipyramid geometries of OPAs has been described as a Berry \textit{pseudorotation}\(^{98}\) or turnstile rotation,\(^{99}\) though they
are equivalent. Indeed computational work by Aggarwal and Harvey supports a C-apical OPA intermediate.\textsuperscript{56b} Nevertheless there remains ambiguity as recent \textit{ab initio} calculations indicate a one-step process rather than a stepwise mechanism may be operable.\textsuperscript{106} Further, C-apical OPA species such as III may only be semi-stable.\textsuperscript{101}

![Figure 1-10. Pseudorotation of the initial $O$-apical OPA towards $C$-apical OPA necessary for syn-cycloreversion](image)

Examination of \textit{anti}-apicophilic trigonal bipyramidal phosphoranes\textsuperscript{102} is somewhat instructive on this topic though not necessarily definitive. Elegant work by Akiba and co-workers has shown that the $O$-apical OPA is thermodynamically more favourable than the C-apical OPA ($\Delta G_{393K} \geq 3.6$ kcal mol$^{-1}$) and as expected the apical P-C bond (1.914 \AA) was found to be much longer than the corresponding equatorial P-C compound (1.820 \AA).\textsuperscript{102c} The opposite trend was observed for the four-membered P-O bond. Heating a crystal of the C-apical derivative at its melting point (ca. 120 °C) gave only the $O$-apical pseudorotamer prior to—after prolonged heating—decomposition to olefin, demonstrating \textit{stereomutation} is faster than cycloreversion. The degree to which these systems model potential Wittig intermediates is arguable, certainly no C-apical OPA has ever been observed spectroscopically during the course of a Wittig reaction. That doesn’t necessarily preclude involvement of a C-apical intermediate though.

Elaborating on work by Muetterties\textsuperscript{103,104} concerning topological stereoisomerism, Lamertmsma and co-workers demonstrated \textit{stereomutation} of ligands in trigonal bipyramids may involve multiple consecutive Berry pseudorotations in a single step process.\textsuperscript{105} Further, one or more of these processes are operable in the stereomutation of OPAs which are similar to those produced using standard Wittig reactions.\textsuperscript{90} Above all, such processes may allow a mechanism for OPA cycloreversion which does not proceed through a discrete C-apical intermediate, that is, it may occur \textit{via} a single step asynchronous mechanism and a C-apical OPA lies along the reaction coordinate from $O$-apical OPA to olefin.

\subsection*{1.1.3.3 Effect of the Solvent}

The ubiquity of stabilised ylids is certainly due to their high degree of stereoselectivity and functional group compatibility. However substituent effects (\textit{vide}
 supra) and solvent counteract the inherent trend towards high ($E$)-selectivity (Table 1-4). Polarity of the solvent has much less influence on the stereoselectivity of the reaction than does the use of a protic solvent (e.g., methanol). Although lithium salts in solution have some effect on the stereoselectivity of the reaction, it is not as great as the use of a protic solvent. Lithium salts reduced ($E$)-selectivity in DMF but displayed no additional effect when used in methanol. Vedejs succinctly demonstrated the effect using representative unbranched (hydrocinnamaldehyde) and α-branched-α-alkoxy (2-formyltetrahydropyran) aldehydes in reaction with $\text{Ph}_3\text{P} = \text{CHCO}_2\text{Et}$ which was generated in situ by DBU or used subsequent to recrystallization (both are shown). Substantial solvent effects are evident for each aldehyde but clearly there isn’t the same broad inherent preference for ($E$)-selectivity with the α-alkoxy aldehyde. The presence of DBU•HBr had a deleterious effect on the stereochemical outcome of the reaction in polar solvent media. Recrystallized or pre-formed ylids should be used in non-polar solvents for the highest ($E$)-selectivity. In all cases use of alcoholic solvents resulted in major rate enhancements.  

Table 1-4. Solvent effects of stabilised ylids

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
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<td>MeOH</td>
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<td>38:62</td>
<td>41:59</td>
<td>10</td>
<td>75:25</td>
<td>73:27</td>
</tr>
<tr>
<td>CF$_3$CH$_2$OH</td>
<td>3</td>
<td>9:91</td>
<td>13:87</td>
<td>12</td>
<td>46:54</td>
<td>46:54</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>4</td>
<td>7:93</td>
<td>30:70</td>
<td>13</td>
<td>11:89</td>
<td>52:48</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>5</td>
<td>4:96</td>
<td>25:75</td>
<td>14</td>
<td>10:90</td>
<td>50:50</td>
</tr>
<tr>
<td>DMF</td>
<td>6</td>
<td>5:95</td>
<td>20:80</td>
<td>15</td>
<td>8:92</td>
<td>38:62</td>
</tr>
<tr>
<td>THF</td>
<td>7</td>
<td>8:92</td>
<td>9:91</td>
<td>16</td>
<td>8:92</td>
<td>22:78</td>
</tr>
<tr>
<td>CCl$_4$</td>
<td>8</td>
<td>4:96</td>
<td>6:94</td>
<td>17</td>
<td>8:92</td>
<td>21:79</td>
</tr>
<tr>
<td>C$_6$H$_6$</td>
<td>9</td>
<td>5:95</td>
<td>6:94</td>
<td>18</td>
<td>14:86</td>
<td>24:76</td>
</tr>
</tbody>
</table>

- a. ($E$:$Z$) ratios were determined by NMR using relative integration after chromatography over silica gel
- b. The ylid was recrystallised prior to use
- c. The ylid was generated in situ from the phosphonium bromide and diazabicycoundecene (DBU)
- d. Partial ester exchange occurs under the reaction conditions

Non-stabilised ylids do not display a notable solvent effect nor do semi-stabilised ylids. However, reasonably high ($E$)-selectivity may be achieved with non-stabilised ylids by addition of methanol to the mixture of OPAs at low temperature though this is presumably a solvent-promoted epimerisation via a β-hydroxy ylid or a Schlosser modification.

1.1.3.4 Cation Effects

Lithium cations ($\text{Li}^+$) in the form of lithium bases/lithium halides exert a pronounced influence on the Wittig reaction. However, little is known concerning the
origin of this effect. Non-stabilised salt-free ylids (excluding ethyldenetriphenylphosphoranes) react with aldehydes in a highly stereoselective manner to afford \((Z)\)-alkenes (>90%) regardless of solvent (Table 1-5, entries 1 & 7).\(^{21,25}\) Conversely, if deprotonation of the antecedent phosphonium salt is performed with a lithium base (i.e. \(\text{Li}^+\) is present in solution upon addition of the aldehyde) stereoselectivity is greatly eroded (Table 1-5, entries 2-6, 8-14).\(^{21,25,110,111}\) While oxaphosphetanes derived from aliphatic aldehydes form betaine-lithium halide adducts whenever \(\text{LiBr}\) is present\(^{32}\) there is no detectable equilibration.\(^{48}\) Similarly, epoxide deoxygenation via the betaine and oxaphosphetane in the presence of \(\text{LiI}\) occurs with <1% loss of stereochemistry.\(^{46,47}\) By comparison, aromatic aldehydes exhibit \((E):(Z)\) ratios in the presence of lithium halides which are difficult to rationalize without OPA reversal. Indeed, positive crossover experiments indicate that cis-OPA generated from triphenylphosphoranylides and aromatic aldehydes undergo reversal to ylid and aldehyde in the presence of \(\text{Li}^+\).

Table 1-5. Lithium salt effects on the Wittig reaction (adapted from ref. 4)

<table>
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<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(Y)</th>
<th>(Z)</th>
<th>(X)</th>
<th>Base</th>
<th>Temp ([\text{Li}^+]) (M)</th>
<th>Alkene ratio (Z:E)</th>
<th>ref.</th>
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</thead>
<tbody>
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<td>Ph</td>
<td>Ph</td>
<td>(n)-Pr</td>
<td>(n)-C(<em>6)H(</em>{11})</td>
<td>H</td>
<td>Br</td>
<td>NaNH(_2)</td>
<td>-78 °C</td>
<td>98:2</td>
<td>77</td>
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<tr>
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<td>Ph</td>
<td>(n)-Pr</td>
<td>(n)-C(<em>6)H(</em>{11})</td>
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<td>Br</td>
<td>LiHMDS</td>
<td>-78 °C</td>
<td>90:10</td>
<td>111c</td>
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<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>(n)-Pr</td>
<td>(n)-C(<em>6)H(</em>{11})</td>
<td>H</td>
<td>Br</td>
<td>LiHMDS</td>
<td>-78 °C</td>
<td>85:15</td>
<td>111c</td>
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<tr>
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<td>Ph</td>
<td>(n)-Pr</td>
<td>(n)-C(<em>6)H(</em>{11})</td>
<td>H</td>
<td>Br</td>
<td>LiHMDS</td>
<td>-78 °C</td>
<td>80:20</td>
<td>111c</td>
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<td>Ph</td>
<td>(n)-Pr</td>
<td>(n)-C(<em>6)H(</em>{11})</td>
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<td>78:22</td>
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<td>91:9</td>
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<tr>
<td>14</td>
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<td>Ph</td>
<td>H</td>
<td>Br</td>
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<td>84:16</td>
<td>111c</td>
</tr>
<tr>
<td>15</td>
<td>Ph</td>
<td>Ph</td>
<td>CH=CH(_2)</td>
<td>(c)-C(<em>6)H(</em>{11})</td>
<td>H</td>
<td>Br</td>
<td>KHMDS</td>
<td>-78 °C</td>
<td>22:78</td>
<td>4</td>
</tr>
<tr>
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<td>Ph</td>
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<td>(c)-C(<em>6)H(</em>{11})</td>
<td>H</td>
<td>I</td>
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<td>&lt;5:95</td>
<td>4</td>
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<tr>
<td>17</td>
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<td>Ph</td>
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<td>(c)-C(<em>6)H(</em>{11})</td>
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<td>Br</td>
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<td>53:47</td>
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<tr>
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<td>Ph</td>
<td>CH=CH(_2)</td>
<td>(c)-C(<em>6)H(</em>{11})</td>
<td>H</td>
<td>I</td>
<td>BuLi</td>
<td>-78 °C</td>
<td>33:67</td>
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<td>H</td>
<td>Cl</td>
<td>BuLi</td>
<td>20 °C</td>
<td>57:43</td>
<td>84</td>
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</table>
For semi-stabilised ylides, almost opposite effects are found. Thus, McEwen reported that benzylidene-phosphoranes reacted with aldehydes to give product mixtures that were enriched in the (Z)-alkene when Li⁺ was present, while the (E)-isomer predominated in the presence of sodium or potassium ions. Whether lithium ions bias the transition state towards puckering and cis-OPA or a different mechanism is operable is unknown. Without a clear understanding of the Li⁺ concentration it is difficult to postulate a proper mechanistic rationale.

The addition of protic solvents to Li⁺-containing Wittig intermediates at low temperature can promote partial equilibration of OPA intermediates. Negative crossover experiments prove that OPA reversal was not operable, rather an α-deprotonation mechanism is involved as indicated by deuterium labelling experiments. As previously discussed lithium halide will induce oxaphosphetane ring cleavage to the corresponding betaine lithium halide adduct. Subsequent α-deprotonation upon addition of the alcohol presumably furnishes β-hydroxy ylid rather than the β-oxido ylid; the conditions are only weakly basic. Thus epimerization upon reprotonation allows a mechanism for equilibration of cis-OPA to the more thermodynamic trans-OPA.

![Scheme 1-19](image)

Scheme 1-19. Equilibration of OPAs through β-hydroxy ylids in the presence of lithium halide and alcohol

### 1.1.3.5 Anomalous stereoselectivity and modifications to the Wittig reaction

**The Schlosser Modification**

While good stereoselectivity is achieved with non-stabilised ylids and aliphatic and α,β-unsaturated (including aromatic) aldehydes, the direct synthesis of (E)-alkenes is
problematic. However, the Schlosser modification allows access to (E)-alkenes in reasonable yields. Alkylidenetriphenylphosphorane must be generated in an ethereal solvent from PhLi or another suitable alkyl lithium containing a sufficient concentration of LiBr to assure betaine-lithium halide formation and crucially to prevent dissociation of the α-lithiated betaine ylid.\textsuperscript{112} The \textit{erythro}-betaine is then epimerized by addition of a second equivalent of a lithium base to generate the α-lithiated betaine which undergoes spontaneous pyramidal inversion to give the \textit{threo}-configuration. Protonation with ethereal hydrochloric acid at low temperature followed by addition of KOtBu and warming gives the (E)-alkene in reasonable yield and excellent stereoselectivity (except with tertiary aldehydes). Notably, it seems phenyllithium—which shows little propensity to aggregate\textsuperscript{113}—effects the most efficient and repeatable deprotonation to give α-lithiated betaine ylid.\textsuperscript{114}

![Scheme 1-20. Schlosser modification of the Wittig reaction](image)

\textit{Anionic Effects in the Wittig reaction}

The effect of anions present during the Wittig reaction is somewhat unclear. Hauser and co-workers noted that better yields and faster reactions were observed from phosphonium chlorides than from bromides.\textsuperscript{115} Meanwhile the presence of iodide ions leads to an enhancement of (Z)-alkene production,\textsuperscript{86} though this appears to only be the case in the presence of Na\textsuperscript{+}. Little to no effect was observed in the presence of KI while the presence of LiI has been noted to increase (E)-selectivity in reactions of benzylides\textsuperscript{116} this is presumably due to Li\textsuperscript{+} rather than an effect of I\textsuperscript{−}.

\textit{Ortho-Effects in the Wittig reaction}

Seemingly contradictory results are obtained with \textit{ortho}-substituted aryl groups—whether on phosphorus or the aldehyde—as they’ve been shown to modulate stereoselectivity. \textit{Ortho}-methoxy groups on phosphorus have been shown to increase (E)-stereoselectivity\textsuperscript{117} while increasing (Z)-selectivity in the case of \textit{ortho}-methoxymethyl-substituted aryl groups.\textsuperscript{118} Substitution on both the ylid and aldehyde components can shift the selectivity in either direction depending on the substitution pattern.\textsuperscript{119}
of the semi-stabilised ylid benzylidenetriphenylphosphorane with ortho-methoxy and halo substituted benzaldehydes gave predominantly (Z)-stilbenes. Yamataka and co-workers proposed that this selectivity was due to a chelating interaction in the initial σ-complex.\textsuperscript{120}

The reaction of benzylidenetriphenylphosphorane with aldehydes that possess ortho-substituents are more (Z)-selective because they react via an earlier transition state and that the halogen can bond to phosphorus thereby stabilising the cis-puckered OPA and destabilising the trans-OPA by an unfavourable 2,3-interaction.\textsuperscript{119} More (E)-alkene is observed when the salt possesses an ortho-halo substituent which is expected to slow the reaction.

1.2 Non-Classical Wittig Reactions

The Wittig reaction is classically thought of as the reaction of triphenylphosphoranylides with aldehydes and ketones under inert solvent conditions. The versatility and synthetic power of this combination of reagents is quite astonishing and is on display throughout natural product synthesis (\textit{vide supra}). The Wittig reaction offers a number of advantages compared to other olefination methods including but not limited to its high regio- & chemoselectivity, its known stereochemical outcomes and, generally, its high yields. Despite these advantages, there are well known drawbacks: the phosphorus ylids required for the Wittig reaction must be made from phosphonium salt precursors, in many cases using strong bases, necessitating the use of anhydrous conditions and cryogenic temperatures limiting industrial use. The phosphonium salts must be prepared using lachrymators and potent alkylating agents. In most cases protection of all sensitive functional groups and acidic protons is required due to the high basicity of the ylids produced and the generation and subsequent removal of triphenylphosphine oxide, a stoichiometric by-product, can be extremely challenging. While all of these problems are somewhat limiting, the biggest problem encountered through use of the Wittig reaction is stereoselectivity. Although its known stereochemical outcome in a variety of situations is an advantage, the inability to produce the desired geometric isomer or, worse a single geometric isomer, is a fundamental problem.

While good, predictable levels of stereocontrol are achievable in many cases, there are still unresolved stereochemical issues such as the direct synthesis of (E)-aliphatic olefins from non-stabilised ylides and the poor level of stereocontrol that is often encountered employing semi-stabilised ylides. Phosphonium salt precursors are typically prepared through quaternisation of triphenylphosphine with alkyl halides many of which are toxic lachrymators, especially allylic, benzylic and other activated halides. The required ylid is typically prepared from the phosphonium salt precursor requiring the
use of a strong base in an anhydrous organic solvent (such as THF, toluene or diethyl ether), often at cryogenic temperatures that may be a limiting factor in industrial applications. The use of petroleum-based solvents accounts for most of the carbon footprint left by the global chemical industry contributing to the generation of greenhouse gases, volatile organic compounds and ozone depleting substances.\textsuperscript{5} Solvent choice is considered critical in eventually developing a sustainable, carbon neutral economy. All of these issues come into play in the example of a Wittig reaction involving the asymmetric synthesis of sphingomimetics (Scheme 1-21).\textsuperscript{121} Protection of the C2-hydroxyl group was required in this work. The reaction was conducted in dry THF at -78 °C using the strong base NaHMDS to generate the required ylide. Only the (Z)-alkene could be readily obtained, and the product required chromatographic purification to remove the phosphine oxide. The reaction reliably delivers the (Z)-olefin with complete regiocontrol and without epimerisation of the α-stereogenic centre. Notwithstanding the problems and side issues described, the synthetic power of the reaction is obvious. While some of these problems have been overcome by using modified Wittig reactions, such as the Ando-\textsuperscript{122}, Still-Genari-\textsuperscript{123}, and Schlosser modifications\textsuperscript{109} more recently, numerous groups have explored alternative methods to help mitigate and/or eliminate these problems.

Scheme 1-21. Representative example of a Wittig reaction in the preparation of sphingolipids

Amongst the recent developments in the Wittig reaction are ball milling techniques,\textsuperscript{124} phosphine recycling,\textsuperscript{125} use of carbonyl surrogates (see section 1.2.1), phase transfer catalysis\textsuperscript{126} (including Boden’s conditions\textsuperscript{127}), and aqueous procedures (see section 1.2.3.1). These are in addition to the myriad one-pot protocols,\textsuperscript{128,129} sequential reactions,\textsuperscript{130} and new methods of ylid generation.\textsuperscript{131}
1.2.1 The Wittig reaction of non-classical carbonyls

The previous sections have emphasized the reaction of phosphorus ylids with aldehydes and to a lesser degree ketones. These are certainly the most generally employed Wittig reactions but olefination of carboxylate derivatives is also known. These non-classical carbonyls exhibit contrariety of reaction and can most easily be categorised as inter- or intramolecular processes. The main limitation of a Wittig reaction with a carboxylic acid derivative is the poor reactivity exhibited by non-activated esters and amides with phosphoranes. The reaction initially proceeds by attack of the ylidic carbanion at the carbonyl carbon furnishing an oxyanion intermediate which can eliminate phosphine oxide in a Wittig-type pathway to produce an alkene or eliminate an anion to afford an acylated phosphonium salt. In general, the expected product depends on the ketonicity of the carbonyl and variation in the experimental conditions is often quite significant.\textsuperscript{132}

\textit{Esters and Lactones}

Simple esters (and lactones) react with phosphoranes to furnish β-ketophosphoranes by displacement of alkoxide.\textsuperscript{19,132} The expected vinyl ether Wittig product is only obtained where strong electron withdrawing groups are present,\textsuperscript{133} though formate esters also reliably afford vinyl ethers in good yields (Scheme 1-22).\textsuperscript{134} The intermediate betaine—from initial attack of the ylid onto the carbonyl (\textit{vide supra})—may be complexed (typically with Li\textsuperscript{+})\textsuperscript{135} or uncomplexed leading to a dichotomy of reactivity. Complexation of the oxygen interrupts OPA formation and subsequent elimination of phosphine oxide thereby biasing the system towards alkoxide elimination. Unsurprisingly, intramolecular reactions of esters exhibit improved reactivity and both reactions have been applied to the synthesis of cyclic compounds. Intramolecular acylation of phosphoranes was first observed by Bergelson and co-workers\textsuperscript{136} while preparing fatty-acid derivatives and further extended by House and Babad.\textsuperscript{137} Enol ether formation, meanwhile, has been extensively applied to the preparation of numerous compounds, especially heterocycles.\textsuperscript{138}

![Scheme 1-22. Reaction of a stabilized phosphorane with a glycosidic formate ester](image-url)
Amides, imides and carbonates

Amides most frequently undergo Wittig reaction at the carbonyl group, though acylation is not unknown. Initial reports leveraged this reactivity to construct pyrroles through intramolecular Wittig reaction.\textsuperscript{139} Since then a wide number of heterocycles have been constructed using analogous strategies—often employing multicomponent reactions. In this way indoles may be constructed from the corresponding benzylides (Scheme 1-24).\textsuperscript{141a,b} When considering intermolecular reactions, if the amide is sufficiently electron deficient only the enamine predominates while conversely, tertiary amides and amides with sufficiently stabilised leaving groups (ex. imidazole) generally afford the acylated products. Interestingly, imides furnish N-acyl enamines as the sole observable products.

1.2.2 Carbonyl surrogates in the Wittig Reaction

Triphenylphosphoranylidnes have gained widespread utility in the Wittig reaction. Despite the myriad benefits these reagents bestow there are known disadvantages to their use—most prominently related to issues surrounding stereoselectivity. In general, the Wittig reaction of alkylidenetriphenylphosphoranes affords preferentially (Z)-alkenes whereas benzyldene- or allyldenetriphenylphosphoranes produce isomeric mixtures. Efforts to alter these stereochemical outcomes are numerous\textsuperscript{109,142} though habitually concern themselves, unsurprisingly, with modification of the ylid or reaction protocol. There exist limited examples of modification of the carbonyl to improve stereoselectivity.

Bestmann and co-workers were the first to explore the use of Schiff bases as carbonyl surrogates in the Wittig reaction.\textsuperscript{143} As early as 1963, they had reacted non-stabilised\textsuperscript{143b} and semi-stabilised ylids\textsuperscript{143a} with N-phenyl imines in the Wittig reaction
though the conditions were rather harsh (130-150 °C). *Semi*-stabilised ylids reacted in typical Wittig fashion to give the expected products—stilbene and 1,4-diphenylbutadiene—whereas *non*-stabilised ylids furnished allenes and an equimolar amount of triphenylphosphine. Rather, after initial carbon-carbon bond formation the betaine intermediate undergoes proton transfer to the ylid followed by decomposition to the allene releasing triphenylphosphine.\textsuperscript{143c}

\[
\begin{align*}
\text{Ph}_3\text{P} &\rightleftharpoons \text{Ph} \quad 1-74 \\
\text{Ph}_3\text{P} \rightleftharpoons \text{R}^1 &+ \text{N}^+ \quad 1-79
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_3\text{P} &\rightleftharpoons \text{Ph} \quad 1-75 \\
\text{Ph}_3\text{P} &\rightleftharpoons \text{R}^1 \quad 1-79
\end{align*}
\]

Scheme 1-25. Bestmann’s use of Schiff bases

Presumably as a result of the harsh reaction conditions, these were the only reported Wittig reactions involving Schiff bases until Tian and co-workers extended the reaction to *N*-sulphonyl imines.\textsuperscript{144} Initially, benzylidenetriphenylphosphorane was reacted with a range of *N*-sulphonyl derivatives of benzaldehyde at low temperature. Certain sulphonyl substituents were able to confer very high stereoselectivity to the resulting olefin (>99:1 *E* or *Z*) and so the method was extended to other semi-stabilised ylids and aldehydes (as the *N*-sulphonylimines) using structurally diverse sulphonamides. It is difficult rationally interpret the mechanism though, as no data is reported as to whether the starting imines are (*E*) or (*Z*). Little explains neither the high stereoselectivity observed nor the seeming randomness of the selectivity with a given sulphonamide.

\[
\begin{align*}
\text{Ph}_3\text{P} \rightleftharpoons \text{R}^1 &+ \text{SO}_2 \cdot \text{N}^+ \quad 1-83 \\
\text{Ph}_3\text{P} &\rightleftharpoons \text{R}^1 \quad 1-84c
\end{align*}
\]

Scheme 1-26. Reaction of triphenylphosphoranylides with *N*-sulphonyl imines

In subsequent publications, Tian and co-workers were able to extend this methodology to non-stabilised ylids and stabilised ylids. Reactions of non-stabilised ylids
with imines attempted by Bestmann furnished allene and triphenylphosphine as the major product due to the basicity of the Schiff base. The more electrophilic N-sulphonyl imine allows the reactions to be conducted at low temperature and the resulting weakly basic sulphonamide moiety, by contrast, allows access to the expected Wittig product in excellent yields and stereoselectivity—no proton shuttling was observed. Unsurprisingly, stabilised ylids required higher temperatures and longer reaction times but yields and stereoselectivity were good. Stabilised ylids did not allow for a high degree of tuneability though and so were generally selective for only the (E) or the (Z) product.

1.2.3 Aqueous Wittig Reactions

1.2.3.1 Phase transfer catalysis

Phase transfer catalysis (PTC) as applied to the Wittig reaction provides a mild and convenient alternative to the classical Wittig reaction. Concentrated aqueous alkali solutions are not only cheaper and easier to handle than n-butyllithium or sodium hydride, they’re much safer. For these reasons, Wittig reactions have been carried out under heterogeneous conditions with inorganic bases, including liquid-liquid, liquid-solid and solid-solid phases. Interestingly, these reactions proceed in the absence of any added catalyst as the phosphonium salts are themselves PTCs.

Liquid-Liquid Phase Transfer Wittig reactions

The liquid-liquid phase transfer Wittig reaction employing alkyltriphenylphosphonium salts and NaOH(aq) has been reported with a wide variety of aromatic and unsaturated aldehydes in numerous solvents. The yield of olefin is determined by a competition between the rate of formation of the olefin and the rate of decomposition of the starting salt which are themselves functions of the concentration of the base. Stereoselectivity under these conditions is generally poor. Interestingly, though maybe not surprising, the anion of the phosphonium salt also plays a noticeable role in these reactions.

Relatively few aliphatic aldehydes had been successfully used due to the prevailing aldolisation reaction which markedly restricted the generalisation of the phase transfer process. While Boden was the first to employ K$_2$CO$_3$—which is a poor catalyst for aldol condensations—in a phase-transfer Wittig reaction (vide supra), Bigot and co-workers extended its use to biphasic systems. The replacement of hydroxides by carbonates allowed for the reaction of aliphatic aldehydes in good yield while reactions of aromatic aldehydes also benefited as Cannizaro reactions were significantly reduced. In all cases moderate (~3:1) (Z)-selectivity is observed. The strict control of the
concentration of base was necessary for optimal results, a result previously observed for the phase transfer Horner-Wittig reaction employing KF.

There are situations where phase transfer catalysis is not only simpler but necessary. An apposite example is the reaction of cyclopropylidenetriphenylphosphorane with aldehydes toward alkylidencyclopropanes. Classical conditions proved uniformly unsuccessful leading to recovery of unreacted starting material or complete decomposition. Use of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in THF with NaH allowed for facile formation of the desired alkene with aromatic and unsaturated aldehydes and even allowed for the reaction of enolizable ketones—conspicuously absent from comment are enolizable aldehydes. The Wittig reaction of (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide with aromatic and aliphatic aldehydes under PTC conditions has also been reported for the two-carbon homologation of aldehydes. The reaction is high yielding and quite (Z)-selective.

Semi-stabilised ylids react in a similar manner to non-stabilised ylids under phase transfer conditions though they are usually higher yielding. The stereoselectivity of these ylids is analogous to more classical conditions showing poor selectivity while being generally (Z)-selective. Notably aqueous formalin has been used to synthesize styrenes in good yield while aqueous glyoxal allows access to substituted butadienes, though in poor yield.

Liquid-Solid Phase Transfer Wittig reactions

While not totally distinct from liquid-liquid PTC, Wittig reactions employing liquid-solid PTC are nonetheless a closely related but distinct class of reaction. These systems employ solid, sparingly soluble inorganic bases which are solubilised into the organic solvent containing the reactants by the transfer catalyst. A wide range of bases, solvents and catalysts have been attempted with varying degree of success. Alkylidenetriphenylphosphoranes have been generated by addition of either NaF or tetramethyl ammonium fluoride as catalysts. Moreover, semi-stabilised ylids have been prepared from the corresponding phosphonium halides using excess KF/18-crown-6 via the phosphonium fluorides.
Interestingly, the effect of the solvent polarity in the stereoselectivity of the Wittig reaction is different when using the conditions disclosed by Boden.\textsuperscript{127} For non-stabilised ylides, Boden observed a predominance of the (Z)-alkene in THF, whereas in dichloromethane solution a reversal of the product distribution was obtained. Semi-stabilised ylids exhibit decreasing stereoselectivity on increasing solvent polarity; an effect independent of whether the solvent is protic or otherwise.\textsuperscript{162} The stereoselectivity of reactions of benzylidenetriphenylphosphoranes with benzaldehydes under Boden’s conditions displayed significant temperature dependence.\textsuperscript{163} When performed at low temperature (-70 °C) mostly the (Z)-stilbenoids are obtained while the geometrical isomers was obtained if carried out at room temperature.

### 1.2.3.2 Aqueous Wittig reactions

Phase transfer catalysis has been well explored compared to truly aqueous Wittig reactions which have only risen in prominence over the last decade; the benefits of each are manifest. Water is a desirable solvent for organic reactions for environmental, economical, safety and chemical processing reasons.\textsuperscript{164,165} Despite early evidence—\textit{p}-nitrostyrene was prepared from the corresponding semi-stabilised ylid and formalin using Na\textsubscript{2}CO\textsubscript{3}(aq),\textsuperscript{166} work which was extended to encompass a range of functionalised styrenes\textsuperscript{167}—aqueous Wittig reactions remained largely unexplored for decades. Early attempts at aqueous Wittig reactions focused heavily on solubility of the phosphonium salts. Extensive efforts led to the development of carboxy- and hydroxylaryl semi-stabilised ylids\textsuperscript{168} which were labour intensive to produce and furnished products with poor stereoselectivity; many of these ylids display poor reactivity. Similarly, water soluble PEG-supported semi-stabilised phosphonium salts\textsuperscript{169} undergo the Wittig reaction with aromatic aldehydes in reasonable yield but with little stereoselectivity. Despite the drawbacks, each of these methods does allow for simple separation of the resultant phosphine oxide.

Water exhibits unique properties as a solvent due to the hydrophobic effect—its inherent ability to exclude non-polar molecules thereby forcing their association and reducing the Gibbs energy of solvation.\textsuperscript{170} Water not only increases the rate of reaction but can improve selectivity,\textsuperscript{171} even in cases where the reactants are sparingly soluble, leading Sharpless to describe these reactions as ‘on water’.\textsuperscript{172} The importance of interfacial processes—the unique properties of molecules at macroscopic phase boundaries—has been thoroughly investigated both theoretically and experimentally and may in fact comprise multiple effects including solvaphobicity,\textsuperscript{173} ground-state destabilisation,\textsuperscript{174} cohesive energy density,\textsuperscript{175} micellar catalysis,\textsuperscript{176} enhanced hydrogen bonding at the transition state (Lewis acid-like catalysis),\textsuperscript{177} and hydrophobic association of the reactants.\textsuperscript{178}
Bergdahl and co-workers were the first to recognize that stabilised ylids would benefit from the hydrophobic effect, performing the Wittig reaction of these poorly soluble ylids in water without additives.\textsuperscript{179} Although the reactants and products were poorly soluble in water the rate of reactions was incredibly quick compared to organic solvents. Aldehydes of all types were tolerated and importantly high (\(E\))-stereoselectivity was achieved. The high stereoselectivity observed for reactions of stabilised ylids in water is interesting considering alcoholic solvents (MeOH) promote increased (\(Z\))-alkene formation. In any case, Wittig reactions of stabilised ylids are generally higher yielding and faster in aqueous media. Likewise, Wu and co-workers reported similar reactions of stabilised ylids using LiCl to further enhance the rate of reaction.\textsuperscript{180a} They further extended the method to a one-pot process in which LiCl promoted both the phosphonium salt formation and the Wittig reaction after the addition of aldehyde and base.\textsuperscript{180}

\[ \text{CH}_3\text{CHO} + \text{R} \rightarrow \text{CH}_3\text{CH}=\text{R}\text{OTBS} \]

Scheme 1-28. Representative aqueous Wittig reaction employing a stabilised ylid\textsuperscript{179}

Trialkylyphosphonoacetates by contrast reportedly undergo significant decomposition in concentrated basic solution.\textsuperscript{181} Orsini and co-workers exploited micellar catalysis using sodium dodecyl sulphate (SDS)-water solutions for the preparation of stabilised trialkylphosphoranylides which were subsequently reacted with aldehydes at room temperature to furnish \(\alpha,\beta\)-unsaturated esters in one-pot.\textsuperscript{182} All aldehydes were tolerated and neither decomposition of the phosphonium salts nor ylids was observed. Yields of the alkene were higher in every case when using the SDS-water solution as compared to water alone. Stereoselectivity was unsurprisingly high and (\(E\))-selective. Importantly the reactions were run at room temperature.

The ability to perform Wittig reactions under mild aqueous conditions has allowed new avenues of exploration. Han and co-workers were able to perform a Wittig reaction on peptides allowing access to protein bioconjugates (Scheme 1-29-A).\textsuperscript{183} Employing previously developed strategies for incorporation of aldehydes into peptides,\textsuperscript{184} treating N-terminal Ser or Thr residues of a protein with sodium periodate (\(\text{NaIO}_4\)) generated an aldehyde. These aldehyde reporters were then subjected to Wittig olefination with preformed stabilised ylids. Penta- and hexapeptides—\(\text{H}_2\text{N-Ser-Val-Thr-Arg-Ala-OH}\) and \(\text{H}_2\text{N-Ser-Leu-Lys-Phe-Tyr-Gln-OH}\) respectively—were also successfully modified as well as chemokine interleukine-8 (IL-8)(8-79). Incredibly myoglobin was also successfully subjected to similar reaction conditions though in that case the PLP oxidation method\textsuperscript{185} was required to obtain the necessary aldehyde.
functionality. Rademann and co-workers performed the reverse chemical ligation to prepare inhibitors of caspase-3 using unprotected peptidyl phosphoranes in water (Scheme 1-29-B).

![Scheme 1-29. Aqueous Wittig reactions involving peptides](image.png)

Recently, Gröger and co-workers performed an enantioselective one-pot sequential Wittig-chemoenzymatic protocol towards chiral allylic alcohols. Whereas Bergdahl and co-workers reported the synthesis of α,β-unsaturated ketones in pure water, in this case an aqueous buffer/2-propanol mixture was used to allow chemoenzymatic ketone reduction in one-pot. The Wittig reaction performed using this solvent system afforded the expected alkenes in good yields and exceptional stereoselectivity. Chemoenzymatic reduction was carried out using alcohol dehydrogenase from Lactobacillus kefir (R-enantioselective) and Rhodococcus sp. (S-enantioselective) as biocatalysts and NAD(P)H cofactor in 44-82% yield and >99% ee. The process was further refined to a one-pot process albeit with lower yields.

The use of triphenyl-substituted semi-stabilised ylids reacting with aromatic aldehydes has also been reported in water, providing stilbenes with poor configurational selectivity requiring chromatographic separation and removal of triphenylphosphine oxide. Further advances involving the use of carboxyl- and sulphonyl-substituted Wittig reagents in water and methanol have been reported. These methods allow for easier phosphine oxide removal; however, the functionalised triarylphosphines employed require multi-step syntheses and stereocontrol in the Wittig reaction is quite low.

A major advance came from employing semi-stabilised ylids derived from trialkyl(benzyl)phosphonium salts containing small alkyl-groups in water (Figure 1-11). These ylids allowed for the stereoselective formation of (E)-olefins derived from aliphatic
or aromatic aldehydes in good yields with minimal purification as the corresponding phosphine oxides are completely water soluble.\(^{192}\)

\[
\text{Et}_3\text{P} + \text{Br-}\text{Ar} \rightarrow \text{Et}_3\text{P}=\text{O} + \text{Ar}-\text{CHO}
\]

**Figure 1-11.** Synthesis of stilbenes using the aqueous Wittig reaction

Principle methods for the preparation of stilbenes involve the Wittig reaction for (Z)-stilbenes and the Wittig-Horner olefination reaction for (E)-stilbenes. The Wittig reaction employing triphenyl(benzylidene)ylides remains the most common route to stilbenes, despite its notoriously low stereoselectivity. Though use of trialkylphosphine-derived ylides in Wittig olefination reactions had been shown to give higher (E)-olefin content these remained largely unexplored.\(^4\) Given the solubility of short-chain phosphine oxides in water, it was surprising that the reaction of benzyl and allylic salts derived from such phosphines had not been investigated in water. Ylid formation introduces a regiochemical issue (Figure 1-11) not encountered using triphenyl analogs; McNulty and Das showed that deprotonation occurs exclusively at the benzylic position (H\(_b\)) over the alkyl positions (H\(_a\)).\(^{192}\) Similar regioselectivity is known with both allylic and benzylic salts in organic media.\(^{193}\) This reaction provided for the synthesis of a wide range of stilbenes with very high (E)-stereoselectivity. Operationally, after addition of the aldehyde and base to the phosphonium salt and warming, the stilbene product precipitates from solution. Upon cooling, the (E)-stilbene is simply collected by suction filtration and washed with water. The stilbene is not contaminated with triethylphosphine oxide, inorganic salts or any remaining base, all of which fully partition in the aqueous phase, as shown by \(^{31}\)P-NMR.

These salts have also allowed for the protecting-group free syntheses of some high value heterocyclic stilbenes including 3-vinylindoles and 2-vinylpyrroles. Vinylindoles represent valuable synthetic precursors to indole alkaloids, carbazoles and carbolines which possess potent biological activity. Typically 3-vinylindoles and 2-vinylpyrroles prepared \textit{via} Wittig-type carbanion chemistry require protection of the nitrogen to prevent deactivation of the carbonyl under the strongly basic conditions.\(^{194}\) Recently though, \textit{semi}-stabilised trialkylphosphoranylides were generated and reacted \textit{in situ} under aqueous basic conditions employing microwave irradiation to give unprotected indolyl-stilbenes in good yield and excellent selectivity.\(^{195}\) The reactions displayed a pronounced microwave effect\(^{196}\) furnishing greater than six times the amount of product.
obtained using thermal heating in an equivalent time under otherwise identical conditions. In an analogous process, gramine reacts with tributylphosphine to furnish an indolylphosphorane which reacts with aromatic aldehydes to give $N$-unprotected indolyl-stilbenes though the reaction is performed under inert conditions in acetonitrile.$^{197}$

![Scheme 1-30. Synthesis of heterocyclic stilbenes by aqueous Wittig reaction](image)

In terms of green chemistry, the use of water as solvent is a considerable improvement. However, disadvantages of the processes described above include the need to handle benzylic halides, many of which are toxic, and trialkylphosphines, which are odorous, pyrophoric liquids. To circumvent this requirement McNulty and co-workers$^{195}$ were able to convert a range of benzylic and allylic alcohols directly to the corresponding phosphonium salts using Et$_3$P•HBr in an analogous process to that reported by chemists at BASF—employing Ph$_3$P•HBr rather—toward the synthesis of vitamin A.$^{198}$ This process was subsequently applied to the synthesis of immunosuppressant FTY720 in a one-pot phosphonium salt formation-aqueous Wittig protocol (Scheme 1-31) with LiOH$_{\text{aq}}$ under microwave irradiation to give 1-113. FTY720 was obtained from 1-113 after hydrogenolysis and acidic deprotection of the polar head group. The microwave aqueous Wittig reaction was used to good effect in the preparation of discrete donor-acceptor flanked $p$-phenylene vinylenes$^{199}$ which are a large class of dyes for light-harvesting.
The synthesis of functionalized 1,3-diienes and homologous polyenes is a central concern in synthetic organic chemistry. The 1,3-diene sub-unit is itself found in a wide range of bioactive materials including terpenoids, fatty acid-derived lipids, pheromones, and polyketides. Trialkylallyllphosphonium salts are reportedly readily available from the corresponding allylic alcohols (vide supra) and have been shown to undergo aqueous Wittig reactions with high stereoselectivity and good yield with a range of aldehydes. Interestingly, the chain length of the spectator ligands on phosphorus played a critical role in controlling the stereoselectivity of the alkene; stereoselectivity was observed to increase with decreasing chain length. McNulty and Das synthesized myriad 1,3-diienes and 1,3,5-trienes using these salts including the antileukemic sesquiterpene (+)-caparratriene 1-117 (Scheme 1-32).}

1.3 Conclusion

As a synthetic process the Wittig reaction is almost without equal. It has constantly evolved during the last half-century and has become one of the cornerstones of synthetic chemistry as one of the most strategic, reliable, widely-applicable carbon-carbon olefin bond forming processes available in organic synthesis. The reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity and may be conducted in most cases with predictable stereocontrol. Its use in the synthesis of
naturally occurring molecules and as a general method for the preparation of alkenes is unparalleled.

1.4 Notes and References

55 The Wittig reaction of all three classes of ylid (non-stabilised, semi-stabilised and stabilised) has been shown to proceed under kinetic control in all but a few exceptional cases (see references).
60 For a review of the chemical bonding in organophosphorus compounds, see: Gilheany, D. G. Chem. Rev. 1994, 94, 1339-1374.
108 107 106 105 104 103

101 99 98 97 96 95 94 93 92 91

90 89 88 87 86 84 83 81 80 79 78 77 76 74 73 72 71 70 69 68 67 66 65 64 63 62 61 60 59 58 57 56 55 54 53 52 51 50 49 48 47 46 45 44 43 42 41 40 39 38 37 36 35 34 33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

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81 It has been suggested that the large variance in stereochemical outcomes reported for semi-stabilised ylids is as a result of poor temperature control; semi-stabilised ylids being unusually sensitive to temperature.
116 Hauser, C. F.; Brooks, T. W.; Miles, M. L.; Raymond, M. A.; Butler, G. B.; Cooney, J. V.; Christmann, K. F.; McEwen, W. E.; Piskala, A.
117 Chem. Sci.


For modifications to semi-stabilised ylids by replacement of a phenyl group, see: with an aryl group: (a) Delmas, M.; Le Bigot, Y.; Gaset, A.


Cannizzaro, S. Liebigs Annalen 1853, 88, 129-130.


196 The microwave effect has generally been discredited. In this context it is merely used to describe the effect on the yield due to efficiency of heating along with micellar catalysis.


Chapter 2

A direct synthesis of functionalized styrenes and terminal 1,3-dienes via aqueous Wittig chemistry with formalin

2.1 Introduction

Styrene and functionalised styrenes are among the most versatile of olefins with an extensive range of applications in fine chemical synthesis and as precursors to functionalised polymers. Functionalised styrenes are routinely employed in developments in a variety of processes including the Mizoroki-Heck reaction, hydrogenation, epoxidation, metathesis, hydroboration, carbonylation, hydroamination, hydrophosphination, hydroarylation, and aziridination. In addition, applications in the area of functionalised polymers have called for efficient access to styrene and functionalised styrene monomers.

Unfunctionalised styrene is prepared industrially via a two step sequence from benzene involving a Friedel-Crafts alkylation (Badger process) with ethylene yielding ethylbenzene followed by either of two high temperature metal catalyzed dehydrogenation processes. Mild conditions are necessary for the synthesis of styrenes due to their propensity towards polymerization under a wide range of conditions. On a laboratory scale, functionalized styrenes have been prepared by elimination reactions, partial reduction of alkynes over Lindlar’s catalyst and via carbonyl olefination based methods. More recently several transition metal catalyzed methods have been developed based on the cross-coupling of aryl or vinyl organometallic reagents with vinyl or aryl halides respectively including Suzuki-Miyaura, Stille, Hiyama and other processes. The synthesis of styrenes containing aryl bromide and iodide functionalities would be complicated with crossover couplings using these methods and we were particularly interested in a transition-metal-free synthesis of aryl-ring halogenated styrenes from which useful polymer supported ligands/catalysts and reagents could be generated.

2.2 Results & Discussion

We recently described the successful aqueous Wittig reactions of semi-stabilised ylides derived from trialkylbenzyl and trialkylallyl phosphonium salts with a range of carbonyl-containing compounds yielding a range of stilbenes, alkenes and 1,3-dienes. As an extension of this work, we have now investigated the corresponding Wittig

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1 This work was published as Das, P; McLeod, D.; McNulty, J. Tetrahedron Lett. 2011, 52, 199-201.
reaction with aqueous formalin. Herein we report a new microwave-assisted synthesis of
triethylbenzyl and triethylallyl phosphonium salts from the corresponding benzyl and
allyl alcohol and their direct aqueous Wittig reactions with aqueous formalin in the
presence of potassium carbonate as a highly efficient route to functionalised styrenes and
terminal 1,3-dienes.

In our earlier report,\textsuperscript{18a} trialkylbenzyl phosphonium salts were prepared in
traditional fashion from the reaction of a trialkylphosphine and a corresponding
benzylc or allylic halide. The resulting olefin generally precipitated during the course
of the reaction and solid products could be isolated by simple filtration while
extraction could be used in the case of oils. A significant advantage of this process is
the high aqueous solubility of short-chain trialkylphosphine oxides that allows for
clean separation through simple phase-separation. Phosphine oxides are ubiquitous,
difficult to remove side products in traditional triarylephosphine mediated Wittig
chemistry.

In terms of green chemistry, the use of water as solvent is a considerable
improvement however disadvantages include the need to handle triethylphosphine
itself and benzylic or allylic halides. Triethylphosphine is an odoriferous lachrymator
and is a pyrophoric liquid requiring specialised handling. Benzylic and allylic halides
are also lachrymators and in some cases are considered toxic alkylating agents.
Further consideration of the green aspects\textsuperscript{19} of the above process in terms of safety,
atom economy, economy of steps and avoidance of auxiliary chemicals, prompted us
to develop the route shown in Scheme 2-1 as an alternate to the desired trialkyl
phosphonium salts. Prior to our work, we were not aware of any reports on the direct
conversion of benzylic alcohols to phosphonium salts. A synthesis of allylic
triphenylphosphonium salts from allylic alcohols and acidic Ph\textsubscript{3}P-HBr was reported
by chemists at BASF in the late 1950’s in the synthesis vitamin A and analogues.\textsuperscript{20} It
is not obvious that triethylphosphine hydrobromide (\(pK_a=8.69\))\textsuperscript{20d} would be acidic
enough to allow conversion of such a species to the corresponding phosphonium salt.
Triethylphosphine hydrobromide was prepared directly from the reaction of
triethylphosphine with 47% HBr. The salt proved to be a hygroscopic, colourless
crystalline solid, stable to aerial oxidation upon direct exposure to open laboratory

![Scheme 2-1. Microwave-assisted synthesis of styrenes](image-url)
conditions over several weeks. In addition, the salt is almost odorless and proved easy to handle.

**Table 2-1.** Synthesis of functionalized styrenes in water with aqueous formalin

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Styrene</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[1-2a]</td>
<td>[2-2a]</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>[1-2b]</td>
<td>[2-2b]</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>[1-2c]</td>
<td>[2-2c]</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>[1-2d]</td>
<td>[2-2d]</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>[1-2e]</td>
<td>[2-2e]</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>[1-2f]</td>
<td>[2-2f]</td>
<td>96</td>
</tr>
</tbody>
</table>

We first determined that heating a mixture of a benzylic alcohol with triethylphosphine hydrobromide without solvent in an oil bath at 100 °C allowed slow conversion to the phosphonium salt. This process required up to 8h to achieve full conversion. We next determined that the reaction was subject to a remarkable microwave-effect, the same reaction was completed with microwave irradiation at 100 °C in 10 minutes and within 15 minutes for ortho-substituted derivatives. The addition of water, potassium carbonate and 37% aqueous formaldehyde followed by microwave irradiation again at 100 °C induced rapid Wittig olefination which was completed within 5 minutes. This overall process could be conducted sequentially in a single microwave reaction vial and proved to be general for a range of both ortho- and para-electron rich and electron deficient benzylic alcohols, shown in Table 2-1. Notably, electron deficient styrenes undergo rapid polymerisation, for example both 2-chlorostyrene and 4-chlorostyrene are employed in rapid-cure resins and are also used in flame-resistant styrene composites. The preparation of desirable aryl bromo and iodo styrenes was likewise achieved in near quantitative yield under the mild conditions employed.

In all cases, the triethylphosphonium salts were prepared in the first part of the two-step sequence from the corresponding benzylic alcohol followed by addition of aqueous potassium carbonate and formalin solution (Scheme 2-1). The styrene precipitates as an oil and upon cooling can be directly separated from the aqueous phase or extracted with hexane. In all cases, a clear partition of the styrene product was observed. It proved
convenient to extract the styrene derivative into a small volume of hexane, the only organic solvent utilised at any stage of this process. The hexane extract contains no trace of triethylphosphine oxide which remains fully dissolved in the aqueous phase. Tripropylphosphine hydrobromide can also be used in an identical manner, allowing clean phase separation of the phosphine oxide. The chemistry works equally well with tributylphosphine hydrobromide, however in this case clean partitioning of tributylphosphine oxide does not occur, contaminating the styrene product.

\[ \text{As Above} \]

Scheme 2-2. Synthesis of terminal 1,3-dienes from allylic alcohols

Using the same two-stage method, cinnamyl alcohol 2-3a and the 2-methyl analogue 2-3b could be successfully converted to the terminal 1,3-diene through the intermediacy of the allylic phosphonium salts, Scheme 2-2. In addition, geraniol 2-5 could likewise be converted to triethylgeranylphosphonium bromide, which underwent ylide formation and olefination with aqueous formalin to give 2-4c under these mildly basic conditions. Thus the overall process appears to be general for both benzylic and allylic alcohols.

2.3. Conclusion

In conclusion, we advance a green approach to the synthesis of functionalised styrenes and terminal 1,3-dienes employing aqueous Wittig chemistry. We show that triethylbenzyl and allyl phosphonium salts can be prepared directly from the corresponding alcohol using triethylphosphine hydrobromide conventionally (100 °C, 8h) or under microwave irradiation (100 °C, 10 mins). Furthermore, addition of aqueous potassium carbonate and formalin followed by microwave irradiation (100 °C, 5 mins) is sufficient to allow the aqueous Wittig reaction. The product olefin generally oils out upon cooling the reaction mixture and could be directly removed, or more conveniently on a small scale, isolated by extraction into a small volume of hexane, the only organic solvent employed at any stage of this process. The overall procedure, conversion of a substituted benzylic alcohol to a functionalised styrene derivative, can be conducted in under 30
minutes, including product isolation. High yields of functionalized styrenes and terminal
1,3-dienes, uncontaminated with phosphine oxide, are rapidly accessible by this general
method.

2.4 Experimental Section

2.4.1 General Considerations

Reactions were carried out under nitrogen or argon atmosphere with dry solvents using
anhydrous conditions unless otherwise stated. Microwave reactions were carried out on a
Biotage Initiator 60 microwave reactor. All fine chemicals were obtained from Sigma-
Aldrich and used without further purification unless otherwise stated, except triethylphosphine, which was supplied by Cytec Industries. Yields refer to chromatographically and spectroscopically ($^1$H-NMR) homogeneous materials, unless otherwise stated. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV. HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. NMR spectra were recorded on Bruker AV-600 and AV-700 spectrometers and calibrated using residual undeuterated solvent as an internal reference (CHCl$_3$ @ δ 7.26 ppm $^1$H NMR, δ 77.16 ppm $^{13}$C NMR; Acetone-d$_6$ @ δ 2.05, $^1$H NMR, δ 29.84 ppm $^{13}$C NMR); $^{31}$P spectra were calibrated using an external reference of 85% H$_3$PO$_4$. Signal assignments were accomplished via analysis of HMBC, HMQC, COSY, NOESY experiments where necessary. The (E) to (Z) ratios were determined from the relative integration of the $^1$H spectra for the olefinic protons.

2.4.2 Preparative Procedures

General Preparative Procedure

\[
\begin{align*}
\text{X} \quad \text{II} \\
\text{R}^1 \quad \text{OH} \\
1. \quad \text{PET}_{3} \cdot \text{HBr} \\
\quad \text{neat, 100 }^\circ\text{C} \\
\text{H}^\text{II} \\
\text{R}^1 \quad \text{OH} \\
2. \quad \text{H}_2\text{CO}_{(aq)}, \text{K}_2\text{CO}_3, \text{H}_2\text{O}, 100 ^\circ\text{C}
\end{align*}
\]

To benzyl alcohol (1 mmol) was added triethylphosphine hydrobromide (1 mmol) and the
neat mixture heated in the microwave for 10 min at 100 °C. The septum was removed
and water was added to make a 2.5 M solution. K$_2$CO$_3$ powder (2 mmol) was added to the
vial followed by the addition of aqueous formalin solution (37% w/w, 5 mmol). The
vial was now crimp-capped and irradiated in the microwave for 5 min at 100 °C. The
resulting biphasic mixture was extracted with hexanes (3 x 5 mL) and the combined
organic extracts dried over Na$_2$SO$_4$ prior to concentration under reduced pressure\textsuperscript{23} to afford the corresponding styrene\textsuperscript{24}.

Styrene 2-2a\textsuperscript{25}

\[
\begin{align*}
\text{Ph} & \rightarrow \text{Ph} \\
\text{The title compound was prepared from benzyl alcohol according to the general procedure as a colorless oil in 98\% yield. }^1\text{H-NMR (600 MHz, CDCl}_3\text{)} & \delta: 5.19 (d, J = 10.8 \text{ Hz, 1H}), 5.71 (d, J = 10.8 \text{ Hz, 1H}), 6.69 (dd, J = 10.8 \text{ Hz, 17.6 Hz, 1H}), 7.2 (m, 5H).
\end{align*}
\]

4-Methoxystyrene 2-2b\textsuperscript{26}

\[
\begin{align*}
\text{MeO} & \rightarrow \text{Ph} \\
\text{The title compound was prepared from 4-methoxybenzyl alcohol according to the general procedure as a colorless oil in 96\% yield. }^1\text{H-NMR (600 MHz, CDCl}_3\text{)} & \delta: 3.81 (s, 3H), 5.12 (d, J = 11.0 \text{ Hz, 1H}), 5.61 (d, J = 18.0 \text{ Hz, 1H}), 6.65 (dd, J = 11.0 \text{ Hz, 18.0 Hz, 1H}), 6.86 (d, J = 9.0 \text{ Hz, 2H}), 7.36 (d, J = 9.0 \text{ Hz, 2H}).
\end{align*}
\]

4-Methylstyrene 2-2c\textsuperscript{25}

\[
\begin{align*}
\text{Me} & \rightarrow \text{Ph} \\
\text{The title compound was prepared from 4-methylbenzyl alcohol according to the general procedure as a colorless oil in 95\% yield. }^1\text{H-NMR (600 MHz, CDCl}_3\text{)} & \delta: 2.30 (s, 3H), 5.11 (d, J = 11.0 \text{ Hz, 1H}), 5.70 (d, J = 17.8 \text{ Hz, 1H}), 6.61 (dd, J = 10.8 \text{ Hz, 10.8 Hz, 1H}), 7.10 (d, J = 8.2 \text{ Hz, 2H}), 7.31 (d, J = 8.2 \text{ Hz, 2H}).
\end{align*}
\]

4-Chlorostyrene 2-2d\textsuperscript{27}

\[
\begin{align*}
\text{Cl} & \rightarrow \text{Ph} \\
\text{The title compound was prepared from 4-chlorobenzyl alcohol according to the general procedure as a colorless oil in 97\% yield. }^1\text{H-NMR (600 MHz, CDCl}_3\text{)} & \delta: 5.27 (d, J = 10.9 \text{ Hz, 1H}), 5.70 (d, J = 17.6 \text{ Hz, 1H}), 6.64 (dd, J = 10.9 \text{ Hz, 17.6 Hz, 1H}), 7.28 (m, 4H).
\end{align*}
\]

4-Nitrostyrene 2-2e\textsuperscript{26}

\[
\begin{align*}
\text{O}_2\text{N} & \rightarrow \text{Ph} \\
\text{The title compound was prepared from 4-nitrobenzyl alcohol according to the general procedure as a viscous yellow oil in 98\% yield. }^1\text{H-NMR (600 MHz, CDCl}_3\text{)} & \delta: 5.51 (d, J = 11.0 \text{ Hz, 1H}), 5.93 (d, J = 18.0 \text{ Hz, 1H}), 6.77 (dd, J = 11.0 \text{ Hz, 18.0 Hz, 1H}), 7.53 (d, J = 9.1 \text{ Hz, 2H}), 8.18 (d, J = 9.1 \text{ Hz, 2H}).
\end{align*}
\]
4-Bromostyrene 2-2f\(^28\)

The title compound was prepared from 4-bromobenzyl alcohol according to the general procedure as a colorless oil in 96% yield. \(^1\)H-NMR (600 MHz, CDCl\(_3\)): δ 5.31 (d, \(J = 11.0\) Hz, 1H), 5.78 (d, \(J = 18.0\) Hz, 1H), 6.68 (dd, \(J = 11.0\) Hz, 18.0 Hz, 1H), 7.30 (d, \(J = 8.0\) Hz, 2H), 7.50 (d, \(J = 8\) Hz, 2H).

2-Chlorostyrene 2-2g

The title compound was prepared from 2-chlorobenzyl alcohol according to the general procedure as a colorless oil in 97% yield. \(^1\)H-NMR (600 MHz, CDCl\(_3\)): δ 5.43 (d, \(J = 11.4\) Hz, 1H), 5.79 (d, \(J = 17.4\) Hz, 1H), 7.16 (dd, \(J = 11.4\) Hz, 17.4 Hz, 1H), 7.23 (m, 1H), 7.27 (m, 1H), 7.39 (d, \(J = 7.8\) Hz, 1H), 7.61 (d, \(J = 7.8\) Hz, 1H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)): δ 116.7, 126.7, 127.0, 129.0, 129.8, 133.3, 133.4, 135.9. HREI MS (M\(^+\)) calcd. for C\(_8\)H\(_7\)Cl: 138.0242, found 138.0236.

2-Methoxystyrene 2-2h\(^29\)

The title compound was prepared from 2-methoxybenzyl alcohol according to the general procedure as a colorless oil in 96% yield. \(^1\)H-NMR (600 MHz, CDCl\(_3\)): δ 3.88 (s, 3H), 5.28 (dd, \(J = 1.7\) Hz, 11.2 Hz, 1H), 5.79 (dd, \(J = 1.7\) Hz, 17.8 Hz, 1H), 6.87 (dd, \(J = 0.7\) Hz, 8.0 Hz, 1H), 6.95 (td, \(J = 1.0\) Hz, 8.0 Hz, 1H) 7.07 (dd, \(J = 10.9\) Hz, 17.6 Hz, 1H), 7.25 (td, \(J = 1.7\) Hz, 7.5 Hz, 1H), 7.50 (dd, \(J = 1.7\) Hz, 7.8 Hz, 1H).

2-Bromostyrene 2-2i\(^30\)

The title compound was prepared from 2-bromobenzyl alcohol according to the general procedure as a colorless oil in 92% yield. \(^1\)H-NMR (600 MHz, CDCl\(_3\)): δ 5.40 (d, \(J = 11.0\) Hz, 1H), 5.74 (d, \(J = 17.4\) Hz, 1H), 7.11 (dd, \(J = 10.9\) Hz, 17.2 Hz, 1H), 7.15 (t, \(J = 7.6\) Hz, 1H) 7.32 (t, \(J = 7.5\) Hz, 1H), 7.50 (d, \(J = 1.7\) Hz, 7.92 Hz, 2H).

2-Iodostyrene 2-2j\(^30\)

The title compound was prepared from 2-iodobenzyl alcohol according to the general procedure as a colorless oil in 96% yield. \(^1\)H-NMR (600 MHz, CDCl\(_3\)): δ 5.33 (d, \(J = 10.9\) Hz, 1H), 5.64 (d, \(J = 17.3\) Hz, 1H), 6.92 (dd, \(J = 10.9\) Hz, 17.3 Hz, 1H), 6.95 (t, \(J = 7.4\) Hz, 1H) 7.32 (d, \(J = 7.4\) Hz, 1H), 7.52 (d, \(J = 7.8\) Hz, 1H), 7.84 (dd, \(J = 7.9\) Hz, 1H).
4-Iodostyrene 2-2k\(^{26}\)

The title compound was prepared from 4-iodobenzyl alcohol according to the general procedure as a white solid in 97\% yield. \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.13 (d, \(J = 10.9\) Hz, 1H), 5.61 (d, \(J = 17.5\) Hz, 1H), 6.48 (dd, \(J = 10.9, 17.6\) Hz, 1H) 7.25 (d, \(J = 8.2\) Hz, 1H), 7.50 (d, \(J = 8.2\) Hz, 1H). HRCl MS (M\(^+\)) calcd. for C\(_8\)H\(_7\)I: 229.9592, found 229.9593.

\((1E)\)-1-Phenyl-1,3-butadiene 2-4a\(^{31}\)

\((1E)\)-2-Methyl-1-phenyl-1,3-butadiene 2-4b\(^{32}\)

\((E)\)-4,8-dimethylnona-1,3,7-triene 2-4c\(^{26}\)

2.5 Notes and References


Chapter 3

Development of a scaleable route towards Pterostilbene and related hydroxyl-stilbenes

3.1. Introduction

Stilbenes and their derivatives constitute important classes of both natural products and synthetic small molecules highly valued in areas as diverse as pharmaceuticals, imaging agents, in light emitting diodes and photovoltaic devices (as organic dyes) and also in an expanding array of other applications in the life sciences and materials chemistry. A selection of pharmacologically active stilbenes and derivatives is collected in Figure 3-1. These include the substituted (E)-stilbenes resveratrol 3-1, the anticancer agent DMU212 3-5 and pterostilbene 3-6, a compound that is associated with a wide range of cardiovascular activities including anti-inflammatory activity and the lowering of plasma lipoprotein and cholesterol levels. Pterostilbene formulations are currently under clinical evaluation for treatment of high blood pressure and in reducing oxidative stress. Several (Z)-stilbenes are endowed with potent anticancer activity including combretastatin A4 and the related stilstatins. Clinically approved stilbenes include florbetapir F18 3-2, a compound that binds to myelin and is used as a molecular imaging probes in positron emission tomography (PET) in the diagnosis of disorders such as multiple sclerosis, and the anti-asthmatic pharmaceutical singulair 3-4.

![Figure 3-1. A selection of pharmacologically active stilbenes and analogs](image)

While many synthetic methods are available to access stilbenes, including transition metal promoted CH/CH cross dehydrogenative cross-coupling reactions and Heck-type reactions, the principal direct methods employed generally involve Wittig
and related Horner-type reactions.\textsuperscript{9a-c} The Wittig reaction employing a triphenylbenzylidene phosphorane is still the most popular route to cis- and trans-stilbenes. Unfortunately, this classic Wittig olefination approach to stilbenes suffers from notoriously poor (\(E\)):\((Z)\) stereocontrol and introduces processing issues related to removal of triphenylphosphine oxide. These problems have largely been solved through the use of aqueous Wittig methods employing ylides derived from short chain trialkylphosphines. We have extensively investigated aqueous Wittig olefination reactions over the last few years showing that stabilized and semi-stabilized ylides can be efficiently generated and trapped under increasingly milder chemical conditions. We showed that high (\(E\))-olefin stereoselection can be achieved allowing access to a wide range of stilbenes and heterostilbenes,\textsuperscript{10a-c} including DMU212 3-5 and resveratrol 3-1.\textsuperscript{10a} A diverse range of functionalized alkenes and pharmacologically active compounds have been made using this aqueous Wittig methodology.\textsuperscript{10d-h} We also established the first organocatalytic aqueous Wittig olefination reactions using weakly and non-basic amines such as L-proline, tosylamide and diphenylamine in water\textsuperscript{10i} and more recently demonstrated this first bioorthogonal Wittig olefination process, generating a reporter stilbene in a living organism.\textsuperscript{10j} Concerning the synthesis of stilbenes specifically, in addition to high (\(E\))-olefin stereoselection,\textsuperscript{10a,c} the aqueous Wittig reaction with short-chain trialkylphosphine-derived ylides provides remarkably simplified post-reaction processing in comparison to classic Wittig protocols. Short chain trialkylphosphine oxides such as triethylphosphine oxide and tripropylphosphine oxide are water-soluble and processing is straightforward allowing clean separation and filtration of crystalline stilbene products in most cases.\textsuperscript{10a,c} Where the products are oils, the phosphine oxide side products can easily be removed through simple aqueous/organic solvent partition.\textsuperscript{10a-d}

In view of the current high interest in the development of a pterostilbene based therapeutic\textsuperscript{6} and the high cost of commercial (\(E\))-pterostilbene,\textsuperscript{11} we decided to investigate the possibility of a scalable aqueous Wittig approach to (\(E\))-pterostilbene from readily available precursors that would benefit from the chemical and processing advantages described above. Two possible Wittig-disconnections can be considered as shown in Scheme 3-1 as routes A and B. At the outset of this work, both routes appeared similarly attractive, neither approach appears to suffer from ortho-alkoxy directing effects, a situation that is known to lead to increased (\(Z\))-stereoselectivity in olefination reactions conducted in the presence of salts and under salt-free conditions.\textsuperscript{12a,b} In this paper we report the investigation of both the direct Wittig routes to pterostilbene, the discovery of a non-intuitive remote meta-substituent effect on the stereoselectivity of the reaction and the development of a scalable, highly optimized route to this valuable stilbene.
Scheme 3-1. The two possible Wittig disconnections A and B towards the synthesis of pterostilbene.

3.2. Results & Discussion

We initially focused on the synthesis of pterostilbene following the route A disconnection (Scheme 3-1). To this end 3,5-dihydroxybenzoic acid 3-11 was triply methylated in a one pot reaction with just two equivalents (4 normalized equivalents) of dimethylsulfate delivering the methyl ester 3-12 in 95% yield (Scheme 3-2). Reduction of the ester was economically achieved using sodium borohydride in a mixed solvent system consisting of THF-methanol in the presence of silica gel, giving the benzyl alcohol 3-13 in 92% yield. We have previously shown that benzylic alcohols can be directly converted to benzylphosphonium salts through direct treatment with trialkylphosphine hydrohalide salts under solvent-free conditions. In this case, the benzyl alcohol 3-13 readily converted to the phosphonium salt 3-15 on treatment with tripropylphosphine hydrochloride on a small scale (150 mg), however, the reaction required heating at 110 °C for an extended period when conducted on a multigram scale.

Scheme 3-2. Synthesis of pterostilbene 3-6 following Wittig disconnection A
Conversion of benzyl alcohol 3-13 to the benzyl chloride 3-14 followed by treatment with tripropylphosphine gave the desired phosphonium salt 3-15 in high yield from 3-14. This route was readily scalable allowing batches of phosphonium salt 3-15 to be made reliably on a 10g scale. Reaction of this salt was initially attempted on the unprotected 4-hydroxybenzaldehyde 3-16 but showed no product formation using a variety of aqueous bases. The phenol 3-16 was therefore protected as its THP acetal using 3,4-dihydro-2H-pyran and pyridinium p-toluenesulfonate as catalyst, and the Wittig reaction with phosphonium salt 3-15 was re-attempted. Gratifyingly, the protected aldehyde was shown by TLC to be completely consumed within 3 h (Table 3-1, Entry 1) leading cleanly to the protected pterostilbene. Unfortunately, the (E):(Z)-stereoselectivity of this reaction was determined to be unsatisfactory, particularly in comparison to other stilbenes synthesized employing trialkylbenzylphosphonium salts in aqueous media.\textsuperscript{10a,b,c,i}

The reaction of 3-15 with 3-16 and with other protected derivatives (3-17, 3-18 and 3-19) was investigated under a variety of conditions as summarized in Table 3-1 (Entries 1 to 10). In every case, the stoichiometric phosphine oxide by-product was completely water soluble allowing for ease of removal and analysis of the alkene stereoselectivity. Isolated yields were also satisfactory in most cases, however changing the phenol protecting group and nature of the base afforded little improvement in the stereoselectivity observed and we thus investigated the alternative synthesis following disconnection B (Scheme 3-1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Disconnection</th>
<th>Protecting Group\textsuperscript{a}</th>
<th>Base</th>
<th>Time (h)\textsuperscript{b}</th>
<th>Concentration (M)</th>
<th>(E):(Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>THP</td>
<td>LiOH</td>
<td>3</td>
<td>2</td>
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<td>2</td>
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<td>LiOH</td>
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<td>0.5</td>
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<tr>
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<td>THP</td>
<td>LiOH</td>
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<td>0.5</td>
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</tr>
<tr>
<td>4</td>
<td>A</td>
<td>THP</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>6</td>
<td>0.5</td>
<td>81:19</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>THP</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>6</td>
<td>0.5</td>
<td>87:13</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>THP</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>3</td>
<td>0.5</td>
<td>85:15</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>Ts</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>3</td>
<td>0.5</td>
<td>73:27</td>
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<td>Ts</td>
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<td>Ts</td>
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<td>LiOH</td>
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<tr>
<td>11</td>
<td>B</td>
<td>Ts</td>
<td>LiOH</td>
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<td>0.5</td>
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<tr>
<td>12</td>
<td>B</td>
<td>Ts</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>12</td>
<td>0.5</td>
<td>92:8</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Ts protecting group was slowly cleaved during the reaction.
\textsuperscript{b} The reaction is complete in 3 h, while running it for 6 h led some decomposition products.
\textsuperscript{c} A trace amount of product was obtained but the major product was cleavage of the benzoyl protecting group.

The required aldehyde 3-24 was prepared cleanly from the previously synthesised alcohol 3-13 using the Dess-Martin periodinane. With the aldehyde in hand, work began on the \textit{para}-hydroxy (or protected derivative) phosphonium salt 3-29 (Scheme 3-3). We
initially decided to attempt the olefination reaction using the protecting group free phosphonium salt 3-29. Reduction of 4-hydroxybenzaldehyde using NaBH$_4$ gave the benzyl alcohol 3-27 which was directly converted to the tripropylbenzyl phosphonium salt using tripropylphosphine hydrobromide, affording 3-29 in good yield as a crystalline solid. Once again, the Wittig reaction of aldehyde 3-24 using this unprotected salt 3-29 failed to produce pterostilbene 3-6, however during the course of experimentation on protected alternatives, we made an interesting discovery with use of the tosyl protected phosphonium salt 3-30 that allowed for a satisfactory conclusion to the pterostilbene synthesis. The tosyl-protected tripropylphosphonium salt 3-30 was prepared in three steps from commercial 4-hydroxybenzaldehyde 3-25. Protection of 3-25 as the tosyl derivative gave aldehyde 3-26 (95%) which was reduced to the alcohol 3-28 using a similar route described above for alcohol 3-27. The benzyl alcohol 3-28 was again directly converted to the benzylic phosphonium salt 3-30 through treatment with tripropylphosphine hydrochloride. Phenolic tosylates are known to slowly saponify under aqueous basic conditions$^{13}$ and so there was initially some concern about the aqueous Wittig reaction of salt 3-30 with 3-24. In the event, the Wittig reaction with aldehyde 3-24 and phosphonium salt 3-30 under our standard aqueous conditions at 100 °C was observed to be rapid (aldehyde disappearance <3h), but was not clean. The reaction gave both the tosyl derivative of pterostilbene as well as the final, fully deprotected pterostilbene 3-6. Simply extending the reaction time to 12h resulted in a clean, stepwise olefination/deprotection sequence and pterostilbene was isolated in high yield (91%) and, more importantly, with high stereoselectivity (>95:5, (E):Z)). Of several bases studied in this reaction, lithium hydroxide provided the highest overall yield and the highest stereoselectivity in favor of the (E)-isomer. As described above, as tripropylphosphine oxide is fully water soluble, the phosphine oxide was removed through partitioning with water/ethyl acetate and (E)-pterostilbene was isolated in 91% yield through filtration through a silica plug and recrystallisation.
It is interesting to consider the possible origin of the stereochemical differences observed in conducting the two regioisomeric Wittig approaches to pterostilbene. The Wittig reactions of semi-stabilised ylids derived from short-chain trialkylphosphonium salts has been shown to provide higher than expected \((E)\)-olefin stereoselection in aqueous, salt-containing media.\textsuperscript{10a,b,c} This result may be either kinetic in origin, that is connected to preference for the planar transition state leading to \((E)\)-olefination via a \textit{trans}-oxaphosphetane,\textsuperscript{12c} or thermodynamic through oxaphosphetane reversal and/or isomerization of intermediates prior to elimination. In this regard, it is known that the presence of weakly Lewis basic \textit{ortho}-substituents (halogens or methoxy groups) in benzylic phosphonium salts can result in increased \((Z)\)-olefin stereocontrol through enhanced kinetic control.\textsuperscript{12a,b,d} It is interesting to speculate involvement of a minor “meta”-alkoxy effect contributing to the increased formation of the \((Z)\)-stilbene in reactions with phosphonium salt \textit{3-15}, although steric factors do not appear favorable to stabilizing the initial oxaphosphetane. It appears that the dominant factors determining stereochemistry are the employment of short chain alkyl groups on the intermediate trialkylphosphorane resulting in kinetic preference for the \textit{trans}-oxaphosphetane as well as the potential for equilibration under these aqueous, lithium salt-containing conditions.

Lastly, we’ve recently been able to demonstrate\textsuperscript{14} that salt \textit{3-29} allows olefination of a range of aldehydes in reasonable to good yields and importantly high \((E)\)-stereoselectivity (Scheme 3-4). Deprotonation of salt \textit{3-29} is performed using BuLi in anhydrous THF to give the lithium phenolate ylid. Addition of the aldehyde is performed after cooling the reaction to \(-78 \, ^\circ\text{C}\); multiple trials indicated that stereoselectivity and yield are both highest upon addition of the aldehyde at low temperature. The reaction
even tolerates aliphatic enolisable aldehydes in addition to \( \alpha,\beta \)-unsaturated and aromatic aldehydes. Pterostilbene synthesized in this way was prepared in a 63% yield and readily solidified. In contrast to literature routes to these compounds—which typically employ transition metal catalysed cross coupling reactions or Wittig-type chemistry on the protected aldehydes—this reaction protocol is versatile, highly stereoselective and comparatively mild.

\[
\begin{align*}
3-29 & \quad \text{PPr}_{3}^+ \text{Cl}^- \\
& \quad \text{BuLi, THF, } 0^\circ \text{C} \\
& \quad \text{RCHO, } -78^\circ \text{C} \\
\rightarrow & \quad \text{3-31} \\
& \quad 50\%-80\% \\
& \quad (\geq 9:1 \text{ E/Z})
\end{align*}
\]

**Scheme 3-4.** Synthesis of phenolic styryl units

### 3.3. Conclusion

In conclusion, the two possible regioisomeric Wittig olefination routes toward the synthesis of the pharmacologically active\(^4\) stilbene pterostilbene 3-6 were investigated under aqueous Wittig conditions. A highly efficient, process-friendly route to pterostilbene was developed involving a high yielding (\(E\))-selective stilbene formation, and in-situ deprotection leading to 3-6. This process takes advantage of many of the green features of the aqueous Wittig reaction that have been disclosed in recent years that involve the intermediacy of stabilized or semi-stabilized ylides.\(^{10}\) The use of phosphonium salts derived of short-chain trialkylphosphines allows for high (\(E\))-stereoselection as well as simple post reaction processing allowing clean, chromatographically-free removal of these water soluble phosphine oxide side products in many cases. The successful use of water as solvent and weak bases ranging from lithium hydroxide, to potassium carbonate and even weakly basic amines such as L-proline, tosylamide etc makes this mild olefination chemistry attractive from a green-chemistry perspective. In addition, we wish to highlight the direct conversion of benzylic (or allylic)\(^{10c}\) alcohols directly (for example Scheme 3-3, 3-27 to 3-29) to the corresponding trialkylphosphonium salts through treatment with short-chain trialkylphosphine hydrohalide (HBr or HCl) salts. This process eliminates the requirement for the use of benzylic and allylic halides, which are generally cytotoxic alkylation agents/lachrymators, and removes the requirement for the direct use of pyrophoric trialkylphosphines. Triethyl- and tripropylphoshine hydrobromide salts are crystalline, air-stable materials and essentially odorless. Although hygroscopic, they can be handled easily in the open laboratory. This direct benzylic/allyl alcohol to phosphonium salt process has now been utilized successfully in a number of useful aqueous Wittig applications.\(^{10c,d,e,f,g}\) The synthesis of pterostilbene achieved using this chemistry is
readily scalable and economic with respect to the number of steps required and the limited purification required throughout the process.

3.4 Experimental Section

3.4.1 General Considerations

Reactions were carried out under nitrogen or argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et₂O), tetrahydrofuran (THF), Toluene (PhMe) and triethylamine and N,N-diisopropylethylamine were distilled from Na⁰ with benzophenone as an indicator. Dry dichloromethane (CH₂Cl₂) was distilled from calcium hydride while dry methanol (MeOH) was distilled from Mg⁰. All fine chemicals were obtained from Sigma-Aldrich and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H-NMR) homogeneous materials, unless otherwise stated. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV. HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. NMR spectra were recorded on Bruker AV-600 and AV-700 spectrometers and calibrated using residual undeuterated solvent as an internal reference(CHCl₃ @ δ 7.26 ppm ¹H NMR, δ 77.16 ppm ¹³C NMR; Acetone-d₆ @ δ 2.05, ¹H NMR, δ 29.84 ppm ¹³C NMR ); ³¹P spectra were calibrated using an external reference of 85% H₃PO₄. Signal assignments were accomplished via analysis of HMBC, HMQC, COSY, NOESY experiments where necessary. The (E) to (Z) ratios were determined from the relative integration of the ¹H spectra for the olefinic protons. All melting points are corrected.

3.4.2 Preparative Procedures

**Methyl 3,5-dimethoxybenzoate (3-12)**

![MeO]( MeO_3_5-dimethoxybenzoate) To 3,5-dihydroxybenzoic acid (15.4 g, 0.1 mol) dissolved in acetone (150 mL) was added potassium carbonate (42.8 g, 0.3 mol, 3.1 equiv.) followed by dimethyl sulphate (19 mL, 2 equiv.). The mixture was then heated to reflux for 4 h with vigorous stirring. Upon cooling to room temperature, water was added so as to completely dissolve all the potassium carbonate and the mixture extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over magnesium sulphate anhydrous and concentrated under reduced pressure to afford the title compound without the need for further purification. Yield 98%, Beige solid; Mp 43-44 °C {lit. ¹⁵ 42-44 °C}; TLC (EtOAc/Hexane, 1:4 v/v): Rf = 0.38; ¹H-NMR [CDCl₃, 600 MHz] δ: 7.16 (d, J = 2.3
Hz, 2H), 6.62 (t, J = 2.3 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 166.9, 160.7, 132.1, 107.2, 105.8, 55.6, 52.3.

### 3,5-dimethoxybenzyl alcohol (3-13)$^{16}$

To a mixture of methyl ester 3-12 (12.0 g, 61.2 mmol, 1 equiv.) and NaBH$_4$ (12.7 g, 336 mmol, 5.5 equiv.) in THF (260 mL) was added MeOH (74 mL) dropwise under reflux over 1 h. After heating under reflux for 40 min, the reaction was cooled down to room temperature, and the pH was adjusted to 7 by the dropwise addition of 1 M HCl. The reaction mixture was filtered through a Celite pad. The filtrate was extracted with EtOAc (4 x 30mL), and the combined organic extracts were washed with brine (100 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give alcohol 3-13 which was used for the subsequent reaction without purification. An analytical quantity may be further purified by recrystallization from cyclohexene. Yield 92%, White crystalline solid; Mp 47-48 °C {lit. $^{17}$ 47-48 °C}; TLC (EtOAc/Hexane, 1:4 v/v): R$_f$ = 0.08; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 6.52 (d, J = 2.2 Hz, 2H), 6.39 (t, J = 2.2 Hz, 1H), 4.64 (s, 2H), 3.80 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 161.2, 143.5, 104.7, 99.8, 65.6, 55.5.

### 3,5-dimethoxybenzyl chloride (3-14)

A round-bottomed flask equipped with magnetic stirring bar was charged with 3-13 (3.36 g, 20 mmol), pyridine (0.1 mL) and Et$_2$O (50 mL). The mixture was cooled in an ice bath while the addition of SOCl$_2$ (2.95 g, 1.25 equiv) was made dropwise over 30 min. The ice bath was removed and the mixture was allowed to stir at rt for 12 h. The mixture was poured into H$_2$O (100 mL) and extracted with Et$_2$O (3 x 20 mL). The extracts were combined and washed H$_2$O (2 x 40 mL) followed by brine (40 mL). After drying over anhydrous MgSO$_4$ the solution was rotary evaporated leaving compound 3-14 an off-white solid that required no further purification Yield 93%, White crystalline solid; Mp 42-43 °C {lit. $^3$ 46 °C}; TLC (EtOAc/Hexane, 1:4 v/v): R$_f$ = 0.9; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 6.59 (d, J = 2.3 Hz, 2H), 6.47 (t, J = 2.3 Hz, 1H), 4.55 (s, 2H), 3.82 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 169.0, 139.5, 106.4, 100.4, 55.3, 46.3.

### (3,5-dimethoxybenzyl)tripropylphosphonium bromide (3-15)

To the substituted benzyl alcohol 3-13 (10.0 g, 59.4 mmol, 1 equiv.) was added tripropylphosphine hydrobromide (14.3 g, 59.4 mmol, 1 equiv.) and acetonitrile (10 mL). The reaction was then heated to 110 °C for 8 h. The reaction was cooled and dried under reduced pressure to afford the title compound. Yield 95%, White powder; Mp 169-171
°C; 1H-NMR [CDCl₃, 600 MHz] δ: 6.63 (t, J = 2.3 Hz, 2H), 6.39 (q, J = 2.2 Hz, 1H), 4.15 (d, J = 15.2 Hz, 2H), 3.80 (s, 6H), 2.44-2.37 (m, 6H), 1.59-1.51 (m, 6H), 1.09 (td, J = 1.6, 7.2 Hz, 9H); 13C-NMR [CDCl₃, 150 MHz] δ: 161.6 (d, 4J(C-31P) = 2.5 Hz), 130.7 (d, 2J(C-31P) = 8.4 Hz), 108.2 (d, 3J(C-31P) = 4.8 Hz), 100.3 (d, 5J(C-31P) = 2.7 Hz), 55.8, 21.1 (d, 1J(C-31P) = 16.2 Hz); 31P-NMR [CDCl₃, 240 MHz] δ: 31.3. HRES MS (M) calcd. for C₁₈H₃₂O₂P: 311.2140, found 311.2133.

4-(tetrahydro-2H-pyran-2-yl)oxy)benzaldehyde (3-19)

To a suspension of 4-hydroxybenzaldehyde 3-25 (2.0 g, 16.3 mmol, 1 equiv.) in methylene chloride (60 mL) was added pyridinium p-toluenesulphonate (0.08 g, 0.32 mmol, 0.02 equiv.) followed by 3,4-dihydro-2H-pyran (3.74 g, 49 mmol, 3 equiv.). The reaction mixture was left to stir at room temperature for 1.5 h. Water was added to quench the reaction mixture which was subsequently poured into brine and extracted with ethyl acetate (3 x 20 mL). The extracts were then dried over sodium sulphate anhydrous. Concentration of the combined organic extracts under reduced pressure and column chromatographed over silica gel (EtOAc/Hexane, 1:6 v/v). Yield 89%, Colourless oil; TLC (EtOAc/Hexane, 1:9 v/v): Rf = 0.20; 1H-NMR [CDCl₃, 600 MHz] δ: 9.88 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 5.53 (t, J = 3.1 Hz, 1H), 3.84 (td, J = 3.1, 10.9 Hz, 1H), 3.62 (dt, J = 1.2, 3.9, 11.4 Hz, 1H), 2.04-1.96 (m, 1H), 1.90-1.86 (m, 2H), 1.74-1.66 (m, 2H), 1.61-1.58 (m, 1H); 13C-NMR [CDCl₃, 150 MHz] δ: 191.0, 162.3, 131.9, 130.6, 116.6, 96.2, 62.2, 30.2, 25.1, 18.5.

Pterostilbene (THP-protected) (3-23)

To a round-bottomed flask was added phosphonium salt 3-15 (3.35 g, 11 mmol, 1.1 equiv.), aldehyde 3-19 (2.06 g, 10 mmol, 1.0 equiv.) and lithium hydroxide (0.72 g, 30 mmol, 3 equiv.). Water (10 mL) was added to make a 1 M solution and the reaction heated to 100 °C for 3 h with vigorous stirring. The crude product was extracted with EtOAc (2 x 5 mL) and concentrated under reduced pressure prior to column chromatography (silica gel, 1:3 EtOAc/hexanes) to afford the protected pterostilbene. Yield 86%, Yellow oil; TLC (EtOAc/hexane, 1:3 v/v): Rf = 0.32; 1H-NMR [CDCl₃, 600 MHz] δ: 7.43 (d, J = 8.8 Hz, 2H), 7.06-7.00 (m, 3H), 6.91 (d, J = 16.3 Hz, 1H), 6.65-6.63 (m 2H), 6.38 (t, J = 2.3 Hz, 1H), 5.45 (t, J = 3.5 Hz, 1H), 3.83 (s, 6H), 3.94-3.88 (m, 1H), 3.65-3.60 (m, 1H), 2.04-1.98 (m, 1H), 1.90-1.85 (m, 2H), 1.72-1.64
(m, 2H), 1.63-1.58 (m, 1H); $^{13}\text{C-NMR } \text{[CDCl}_3, 150 \text{ MHz]} \delta: 161.1, 157.0, 139.8, 128.9, 128.2, 127.8, 127.0, 116.8, 104.5, 99.8, 96.5, 62.2, 55.5, 30.5, 25.3, 18.9.

4-hydroxybenzyl alcohol (3-27)

To a suspension of 4-hydroxybenzaldehyde 3-25 (1.5 g, 12.3 mmol, 1 equiv.) in methylene chloride (20 mL) was added silica (2.5 g), followed by sodium borohydride (0.475 g, 12.5 mmol, 1.02 equiv.). The reaction mixture was stirred for five minutes prior to the dropwise addition of methanol (3 mL) after which it was left to stir for a further thirty minutes. The entire reaction mixture was poured onto a short silica pad and was flushed with acetone. Concentration of the eluent under reduced pressure afforded the title compound without the need for further purification. Yield 81%, White crystalline solid; Mp 120-122 °C {lit. 18 124-125 °C}; TLC (EtOAc/Hexane, 2:3 v/v): $R_f = 0.13$; $^1\text{H-NMR } \text{[MeOD-d}_4, 600 \text{ MHz]} \delta: 7.19$ (d, $J = 8.4$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 4.50 (s, 2H); $^{13}\text{C-NMR } \text{[MeOD-d}_4, 150 \text{ MHz]} \delta: 153.6, 132.1, 128.9, 115.2, 64.1.$

(4-hydroxybenzyl)tripropylphosphonium bromide (3-29)

To the phenolic benzyl alcohol 3-27 (1.24 g, 10 mmol, 1 equiv.) was added tripropylphosphine hydrobromide (2.41 g, 10 mmol, 1 equiv.) and acetonitrile (1 mL). The reaction was then heated to 100 °C for 8 h. The title compound crystallized upon cooling and was subsequently filtered. Yield 91%, White crystalline solid; Mp 233-235 °C; $^1\text{H-NMR } \text{[MeOD-d}_4, 600 \text{ MHz]} \delta: 7.20-7.15$ (m, 2H), 6.87 (d, $J = 8.3$ Hz, 2H), 3.70-3.63 (m, 2H), 2.19-2.12 (m, 6H), 1.65-1.57 (m, 6H), 1.12 (td, $J = 1.5, 7.2$ Hz, 9H); $^{13}\text{C-NMR } \text{[MeOD-d}_4, 150 \text{ MHz]} \delta: 159.2, 132.2$ (d, $^3J_{13\text{C}-31\text{P}} = 4.4$ Hz), 119.6 (d, $^2J_{13\text{C}-31\text{P}} = 8.5$ Hz), 117.4, 26.4 (d, $^1J_{13\text{C}-31\text{P}} = 45.4$ Hz), 21.3 (d, $^1J_{13\text{C}-31\text{P}} = 46.9$ Hz), 16.3 (d, $^2J_{13\text{C}-31\text{P}} = 4.0$ Hz), 15.7 (d, $^3J_{13\text{C}-31\text{P}} = 16.5$ Hz); $^{31}\text{P-NMR } \text{[MeOD-d}_4, 240 \text{ MHz]} \delta: 32.1$; HRES MS (M)$^+$ calcd. for C$_{16}$H$_{28}$OP: 267.1878, found 267.1889.

4-(Formyl)phenyl 4-Methylbenzenesulfonate (3-26)

To a suspension of 4-hydroxybenzaldehyde 3-25 (3.0 g, 24.5 mmol, 1 equiv.) in methylene chloride (50 mL) was added triethylamine (4.1 mL, 1.2 equiv.) followed by tosyl chloride (4.68 g, 24.5 mmol, 1 equiv.). The reaction mixture was left to stir overnight. Water was added to quench the reaction mixture which was subsequently poured into brine and extracted with ethyl acetate (3 x 20 mL). The extracts were then dried over sodium sulphate anhydrous. Concentration of the combined organic extracts under reduced pressure afforded the title compound without the need for further purification. Yield 95%,
White solid; Mp 71-72 °C {lit. 19 72-73 °C}; TLC (EtOAc/Hexane, 1:9 v/v): R_f = 0.08; ^1H-NMR [CDCl_3, 600 MHz] δ: 9.97 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 2.46 (s, 3H); ^13C-NMR [CDCl_3, 150 MHz] δ: 190.8, 154.0, 146.0, 135.0, 132.2, 131.4, 130.1, 128.6, 123.2, 21.9.

4-(Hydroxymethyl)phenyl 4-Methylbenzenesulfonate (3-28)

To a suspension of aldehyde 3-26 (2.0 g, 7.2 mmol, 1 equiv.) in methylene chloride (25 mL) was added silica (4.4 g), followed by sodium borohydride (0.28 g, 7.5 mmol, 1.5 equiv.). The reaction mixture was stirred for five minutes prior to the dropwise addition of methanol (4 mL) after which it was left to stir for a further thirty minutes. The reaction was filtered by column chromatography over silica gel (20g, CH_2Cl_2). Concentration of the eluent under reduced pressure afforded the title compound without the need for further purification. Yield 90%, Yellow oil; TLC (EtOAc/Hexane, 2:3 v/v): R_f = 0.17; ^1H-NMR [CDCl_3, 600 MHz] δ: 7.70 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 4.66 (s, 2H), 2.45 (s, 3H); ^13C-NMR [CDCl_3, 150 MHz] δ: 149.0, 145.5, 139.9, 132.5, 129.9, 128.6, 128.2, 122.6, 64.5, 21.8.

O-p-toluenesulphonate (4-hydroxybenzyl)tripropylphosphonium bromide (3-30)

To the protected benzyl alcohol 3-28 (2.0 g, 7.2 mmol, 1 equiv.) was added tripropylphosphine hydrobromide (1.7 g, 7.2 mmol, 1 equiv.) and acetonitrile (0.5 mL). The reaction was then heated to 100 °C for 8 h. The title compound crystallized slowly over four days. Yield 93%, White amorphous solid; ^1H-NMR [CDCl_3, 600 MHz] δ: 7.66 (d, J = 8.0 Hz, 2H), 7.53 (dd, J = 2.4, 8.7 Hz, 2H), 7.32 (m, 2H), 6.95 (d, J = 8.3 Hz, 2H), 4.38 (d, J = 15.4 Hz, 2H), 2.45 (s, 3H), 2.38-2.31 (m, 6H), 1.56-1.48 (m, 6H), 1.03 (td, J = 1.6, 7.2 Hz, 9H); ^13C-NMR [CDCl_3, 150 MHz] δ: 149.5 (d, J_{13C-31P} = 3.9 Hz), 145.9, 131.9, 131.7 (d, J_{13C-31P} = 4.4 Hz), 130.0, 128.4, 128.1 (d, J_{13C-31P} = 8.8 Hz), 123.3 (d, J_{13C-31P} = 1.6 Hz), 26.2 (d, J_{13C-31P} = 45.2 Hz), 21.8, 20.9 (d, J_{13C-31P} = 46.5 Hz), 15.7 (d, J_{13C-31P} = 40.0 Hz), 15.6 (d, J_{13C-31P} = 16.0 Hz), ^31P-NMR [CDCl_3, 240 MHz] δ: 30.8; HRES MS (M) calecd. for C_{23}H_{34}O_{3}PS: 421.1966, found 421.1965.

3,5-dimethoxybenzaldehyde (3-24)

To a solution of benzyl alcohol 3-13 (1.5 g, 8.9 mmol, 1 equiv.) in methylene chloride (20 mL) was added Dess-Martin periodinane (3.8 g, 8.9 mmol, 1 equiv.) at which point the reaction turned a cream colour. After 1 h the reaction mixture was filtered through Celite, rinsing with diethyl ether. The combined organic layers were subsequently washed with
water, dried over sodium sulphate anhydrous and concentrated under reduced pressure to afford the title compound. Yield 91%, White solid; Mp 43-44 °C {lit. 21 44-45 °C}; TLC (EtOAc/Hexane, 1:4 v/v): R$_f$ = 0.40; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 9.91 (s, 1H), 7.01 (d, $J$ = 2.4 Hz, 2H), 6.71 (t, $J$ = 2.2 Hz, 1H), 3.85 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 192.1, 161.4, 138.6, 107.3(5) 107.2(9) 55.8.

**Pterostilbene (3-6)**

To a round-bottomed flask was added phosphonium salt 3-30 (1.65 g, 3.3 mmol, 1.1 equiv.), aldehyde 3-24 (0.500 g, 3 mmol, 1.0 equiv.) and lithium hydroxide (0.240 g, 9.9 mmol, 3 equiv.). Water (3 mL) was added to make a 1 M solution and the reaction heated to 90 °C for 12 h with vigorous stirring. Upon cooling to room temperature the mixture was acidified to a pH of 2 with 1 N HCl and stirred vigorously for 10 minutes. The crude product was extracted with EtOAc (2 x 5 mL) and concentrated under reduced pressure prior to filtration through silica. This crude product can then be either column chromatographed over silica gel or recrystallized from EtOH/H$_2$O. Yield 89%, Colourless solid; TLC (EtOAc/Hexane, 2:3 v/v): R$_f$ = 0.39; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.40 (d, $J$ = 8.5 Hz, 2H), 7.03 (d, $J$ = 16.3 Hz, 1H), 6.90 (d, $J$ = 16.3 Hz, 1H), 6.84 (d, $J$ = 8.7 Hz, 2H), 6.66 (d, $J$ = 2.3 Hz, 2H), 6.40 (t, $J$ = 2.0 Hz, 1H), 5.52 (bs, 1H), 3.84 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 161.1, 155.5, 139.8, 130.2, 128.8, 128.1, 126.8, 115.8, 104.5, 99.8, 55.5.

**Pterostilbene (3-6)**

To phosphonium salt 3-29 (300 mg, 1 mmol) in THF (1.2 mL) at 0 °C was added n-BuLi (1.6 M in hexanes, 1.6 mL). After 40 minutes at this temperature aldehyde 3-24 (170 mg, 1 mmol) in THF (0.8 mL) was added and the reaction left to warm to room temperature overnight. The mixture was acidified to a pH of 2 with 1 N HCl and stirred vigorously for 10 minutes. The crude product was extracted with EtOAc (3 x 5 mL) and concentrated under reduced pressure prior to filtration through silica. This crude product can then be either column chromatographed over silica gel or recrystallized from EtOH/H$_2$O. Yield 63%, Colourless solid; TLC (EtOAc/Hexane, 2:3 v/v): R$_f$ = 0.39; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.40 (d, $J$ = 8.5 Hz, 2H), 7.03 (d, $J$ = 16.3 Hz, 1H), 6.90 (d, $J$ = 16.3 Hz, 1H), 6.84 (d, $J$ = 8.7 Hz, 2H), 6.66 (d, $J$ = 2.3 Hz, 2H), 6.40 (t, $J$ = 2.0 Hz, 1H), 5.52 (bs, 1H), 3.84 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 161.1, 155.5, 139.8, 130.2, 128.8, 128.1, 126.8, 115.8, 104.5, 99.8, 55.5.
3.5 Notes and References


11. Commercial samples of pterostilbene have recently been quoted at $801 for 1g (TCI) and
$259 for 10mg (Sigma-Aldrich)


14 Lin, W.-J.; Nielsen, A. J.; McLeod, D. Unpublished results


Chapter 4

Development of an amine and sulphonamide promoted Wittig reaction

4.1 Introduction

The burgeoning field of organocatalysis—the acceleration of a chemical transformation through addition of a substoichiometric amount of an organic compound which does not contain a metal atom—has become a pillar of synthetic organic chemistry since the turn of the century and yet its roots stretch into the latter half of the 19th century. The first organocatalytic transformation, conversion of cyanogens to oxamide using aqueous acetaldehyde, was performed in 1860 by Justus von Liebig, while the first reported asymmetric variant dates to 1912. However, the ability of small molecules to catalyse asymmetric reactions remained largely ignored despite sporadic evidence of its utility until two seminal papers by List and MacMillan. The field has since expanded to rival transition metal catalysis (due to its versatility, operational simplicity, low cost and chemical efficiency), while the use of dual catalysis has allowed access to previously inaccessible reaction modes.

4.1.1 Background

The Wittig reaction has constantly evolved during the last half-century and occupies a vaulted position as one of the most strategic, reliable, widely-applicable carbon-carbon olefin bond forming process available in organic synthesis. The reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity and may be conducted in many cases with predictable stereocontrol. For example, the Wittig reaction employing ylides derived from triphenylbenzyl phosphonium salts is the most popular route to cis- and trans-stilbenes. The process is typically high yielding but suffers from poor to moderate stereocontrol requiring both removal of the phosphane oxide as well as separation of the stereoisomers.

In recent work, we showed that ylides derived from short chain trialkylphosphanes could be generated in water as solvent employing bases such as LiOH and that these conditions allowed for high (E)-olefination yielding a wide range of stilbenes and other alkenes. Separation of the water-soluble phosphine oxide was readily achieved through simple alkene filtration (if solid) or solvent partition in the case of liquid olefins.
Bestmann had earlier shown that replacement of the carbonyl component in the Wittig reaction with a Schiff-base provide \((E)\)-stilbenes in moderate yield,\(^{11}\) a variation that received little attention until recently (Scheme 1-25). Tian and co-workers\(^{12}\) have shown that replacement of the Schiff-base (\(N\)-phenyl imine) with a tunable \(N\)-sulfonyl imine (Scheme 1-26, various \(R\) groups) allows for tunable olefin stereoselection, providing a notable advance toward the synthesis of both \((E)\)- and \((Z)\)-stilbenes. In this work, the required semi-stabilised ylides were generated under standard kinetically controlled Wittig conditions using LDA in dry THF as solvent at -78 °C. The ylide undergoes olefination with the pre-formed sulfonyl imine, which is required in stoichiometric amounts, yielding stilbenes with high stereocontrol.

These stoichiometric imine/sulfonyl imine protocols\(^{11,12}\) were appealing for two reasons. Analysis of the steps involved revealed the possibility that distinct amine and/or sulfonylamide catalysed variations of these Wittig-olefination pathway might be realised directly from the reaction of a phosphonium salt and aldehyde. Iminium-ion catalysis\(^{13}\) has emerged as one of the keystones in organocatalytic and asymmetric organocatalytic processes that have revolutionized synthetic organic chemistry over the last decade.\(^{13a}\) To-date, there have been no reports of Wittig olefination reactions catalyzed by amines.\(^{13c,14}\) Secondly, the development of an organocatalytic Wittig process ammenable to aqueous conditions, by analogy with iminium ion and enamine mediated organocatalytic processes,\(^{13d}\) would allow for the increased stereochemical and processing advantages previously described.\(^{10}\)

### 4.2 Results and Discussion

#### 4.2.1 Development of suitable conditions for the organocatalytic Wittig

In previous work on aqueous Wittig reactions conducted in this laboratory, bases such as LiOH and \(K_2CO_3\) were shown to be capable of ylide formation under aqueous conditions,\(^{10d}\) although the olefination reactions required microwave irradiation at 75-100 °C for 30 mins. Sodium bicarbonate was shown to be ineffective under these conditions and was thus chosen as the required base to minimize background reactions. We postulated the net reaction (Figure 4-1) to be catalytic in the presence of an amine 4-1, possibly proceeding via an iminium intermediate 4-2. In a similar fashion, the reaction of a catalytic quantity of a sulfonamide may be expected to produce the \(N\)-sulfonyl imine intermediate allowing a similar catalytic olefination process. Herein we describe the first examples of weakly basic amine and sulfonylamide catalysed Wittig olefination reactions.
Figure 4-1. Proposed catalytic cycle

Table 4-1. Secondary amine catalysed synthesis of stilbene 4-4a via the aqueous organocatalytic Wittig reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Phosphonium Salt</th>
<th>Conversion (%)</th>
<th>Stilbene 4-9a (E): (Z)</th>
<th>Entry</th>
<th>Amine</th>
<th>Phosphonium Salt</th>
<th>Conversion (%)</th>
<th>Stilbene 4-9a (E): (Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>4-7</td>
<td>0</td>
<td>-</td>
<td>7</td>
<td>Ph$_2$NMe$_2$</td>
<td>4-8</td>
<td>&gt;99</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>4-7</td>
<td>35</td>
<td>84:16</td>
<td></td>
<td>8</td>
<td>Ph$_2$NMe$_2$</td>
<td>4-8</td>
<td>15</td>
<td>44:56</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>4-7</td>
<td>4</td>
<td>-</td>
<td>9</td>
<td>Ph$_2$NPh$_2$</td>
<td>4-8</td>
<td>99</td>
<td>50:50</td>
</tr>
<tr>
<td>4</td>
<td>4-7</td>
<td>&gt;99</td>
<td>84:16</td>
<td></td>
<td>10</td>
<td>TsNH$_2$</td>
<td>4-8</td>
<td>99</td>
<td>46:54</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>4-8</td>
<td>13</td>
<td>45:55</td>
<td>11</td>
<td>TsNH$_2$Bu</td>
<td>4-8</td>
<td>99</td>
<td>42:58</td>
</tr>
<tr>
<td>6</td>
<td>4-8</td>
<td>&gt;99</td>
<td>43:57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model and control reactions involving the synthesis of 4-chlorostilbene 4-9a were initially investigated with the triethyl- and triphenylbenzyl phosphonium salts 4-7 and 4-8, (Table 4-1). A protocol involving the reaction of the aldehyde (1.00 eq), phosphonium...
salt 4-7 or 4-8 (1.00 eq) at 2.0 M in water with a catalytic amount of amine (2 to 20 mol%) and NaHCO₃ (1.00 eq) at 50 ºC (100 ºC in the case of entries 3 and 4 only) was used. Under these conditions, no reaction occurs with salt 4-7 in the absence of any added amine at 50 ºC (entry 1). Addition of L-proline caused the reaction to proceed slowly (entry 2). This olefination reaction went to completion at 100 ºC over 3 days to give the stilbene in quantitative yield (entry 4). A control experiment showed that only 4% olefin conversion occurred over 3 days at 100 ºC (entry 3). Reaction with the triphenyl salt 4-8 proved to be much faster than 4-7. Control experiments indicated 13% background olefination (entry 5) under the standard condition (50 ºC, 6h) however addition of L-proline (entry 6) drove the reaction to completion under the same conditions. Other amines such as morpholine and ephedrine were also effective in catalysing the olefination. We deemed it necessary to focus on weakly basic amines in order to differentiate possible iminium catalysed process from further base-mediated background processes. To this effect, the reaction was effectively catalysed using N-methylaniline (pKa 4.56 (BH⁺)) under the standard conditions (entry 7), while the use of the tertiary amine N,N-dimethylaniline (pKa 5.20 (BH⁺)) resulted in only background olefination (entry 8). This reaction was efficiently catalysed with only 2 mol% of N-methylaniline. Entry 7 demonstrates the efficacy of a weakly basic secondary amine in catalysing the olefination, while entries 7 and 8, taken together, indicate the involvement of only the secondary amine in this alternative pathway. The most logical alternative reaction pathway is that proceeding through the iminium intermediate. The success of N-methylaniline in catalysing the olefination encouraged us to pursue even weaker bases. Diphenylamine (pKa 0.78 (BH⁺)) also proved highly effective in promoting the reaction (entry 9) at low catalyst loading, as did a catalytic amount of the very weakly basic p-toluenesulfonamide (entry 10). Under the standard consitions reported in Table 4-1, the use of 2 mol% tosylamide promoted the reaction to full conversion within 6h at 50 ºC. This reaction completes a circle and now ties the possible iminium ion mediated pathway to a catalytic variant of the stoichiometric N-sulfonyl imine-mediated pathway described by Tian. The (E)/(Z)-olefination stereochemistry observed is fully in accord with expected results with semi-stabilised ylides derived from triethyl and triphenylphosphane under thermodynamic aqueous conditions.¹⁰

4.2.2 Scope and selectivity of the organocatlytic Wittig reaction employing semi-stabilised ylids

The new amine and sulfonylamide catalysed olefination process was successfully extended toward the synthesis of a small panel of trans-stilbenes using the triethylphosphonium salt 4-7 in the presence of either a catalytic amount of morpholine, N-methylaniline or tosylamide. While salt 4-7 reacts slower than 4-8 as indicated above
(Table 4-2), the reaction provides high \((E)\)-olefin stereoselectivity, and full conversion is attained within 72h. Under the conditions shown in Table 4-2, in the absence of any added amine, <5% stilbene formation was observed (entry 1). Using 10 mol% of morpholine as catalyst, a range a range of both electron-poor and electron-rich aldehydes underwent olefination successfully (entries 2 to 8). The choice of morpholine as catalyst was not critical and indeed, the present reaction was also highly successful when catalyzed by either \(N\)-methylaniline (entries 9 and 10) or tosylamide (Table 4-2) and a range of \((E)\)-stilbenes were readily produced.

**Table 4-2. Scope & selectivity of amine catalysed Wittig reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Conv. (Isolated Yield)</th>
<th>((E):(Z))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>4-6a</td>
<td>&lt; 5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-6a</td>
<td>99 (92)(^b)</td>
<td>97 : 3(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 (93)(^c)</td>
<td>98 : 2(^c)</td>
</tr>
<tr>
<td>3</td>
<td>4-6b</td>
<td>99 (88)(^b)</td>
<td>91 : 9(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 (92)(^c)</td>
<td>99 : 1(^c)</td>
</tr>
<tr>
<td>4</td>
<td>4-6c</td>
<td>99 (93)(^b)</td>
<td>90 : 10(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 (86)(^c)</td>
<td>94 : 6(^c)</td>
</tr>
<tr>
<td>5</td>
<td>4-6d</td>
<td>99 (94)(^b)</td>
<td>95 : 5(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 (95)(^c)</td>
<td>97 : 3(^c)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Conv. (Isolated Yield)</th>
<th>((E):(Z))</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>MeO-</td>
<td>99 (91)(^b)</td>
<td>99 : 1(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 (93)(^c)</td>
<td>97 : 3(^c)</td>
</tr>
<tr>
<td>7</td>
<td>MeO-</td>
<td>99 (85)(^b)</td>
<td>99 : 1(^b)</td>
</tr>
<tr>
<td></td>
<td>MeO-</td>
<td>99 (84)(^b)</td>
<td>99 : 1(^c)</td>
</tr>
<tr>
<td>8</td>
<td>Me,N-</td>
<td>99 (87)(^b)</td>
<td>95 : 5(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 (88)(^c)</td>
<td>95 : 5(^c)</td>
</tr>
<tr>
<td>9</td>
<td>O2N-</td>
<td>&gt;99 (94)(^d)</td>
<td>95 : 5(^d)</td>
</tr>
<tr>
<td>10</td>
<td>O2N-</td>
<td>&gt;99 (85)(^d)</td>
<td>&gt;99 (E)(^d)</td>
</tr>
</tbody>
</table>

- a. No amine added
- b. Morpholine used as amine
- c. Tosyl amide used as amine
- d. \(N\)-methylaniline used as amine

Product isolation and purification are often tedious processes in standard Wittig olefination reactions. One of the biggest advantages encountered using
triethylphosphonium salts is the ease of purification in view of the high aqueous solubility of the phosphine oxide. In all of the cases reported (Tables 4-1, 4-2) product isolation is relatively straightforward. Upon completion of the reaction, the mixture is simply cooled and the solid stilbene isolated by suction-filtration and washing with water. The products are uncontaminated with phosphine oxide or amine/sulfonamide catalyst. High isolated yields of the trans-stilbenes was achieved in all cases and no Cannizzaro side products are detected. Trans-stilbenes are highly sought as they form the core in a range of valuable materials including pharmaceuticals, light emitting diodes and dye-sensitised photo-voltaic solar cells.

4.2.3 Scope and selectivity of the organocatalytic Wittig reaction employing stabilised ylids

We further extended the applicability of the organocatalytic Wittig reaction to include the generation and trapping of stabilised ylides derived from the (ethoxycarbonylmethyl)triisobutylphosphonium bromide 4-10. Employing L-proline as catalyst (10 mol%), olefination occurred smoothly under our standard aminocatalysis conditions with electron-rich and electron-deficient aldehydes yielding substituted cinnamate esters 4-11a to 4-11c in high yield and exclusive (E)-stereoselectivity (Table 4-3).

Table 4-3. Synthesis of cinnamate esters catalysed by L-proline or p-toluenesulfonamide

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>94</td>
</tr>
</tbody>
</table>

a. Tosylamide (0.1 eq.) replaces L-proline under otherwise identical conditions
4.3 Investigations into the mechanism of the organocatalytic Wittig

There are a vast number of natural products spanning countless ecological families which contain both 2- and 3- substituted indole moieties. Classically indole is synthesized through the Fischer indole synthesis or a Pictet-Spengler reaction but there is precedent for its formation using an intramolecular Wittig reaction. A few decades ago Le Corre and co-workers reported that indoles could be prepared from 2-acetamidobenzylphosphonium salts through an intramolecular Wittig reaction. More recently it has been reported that an intramolecular Wittig-type reaction on imines derived from aldehydes and o-aminobenzyltriphenylphosphonium salts resulted in 2-substituted indoles. We reasoned that such a process would be amenable to organocatalytic reaction conditions and were highly interested in using such a reaction to potentially validate our mechanistic hypothesis (see section 4.2.1, specifically Figure 4-1). In addition, we would be able to synthesize high-value substituted indoles. Indole formation could only proceed via imine/iminium formation and subsequent attack of the ylid onto the carbonyl surrogate in an intramolecular fashion (a formally Baldwin disallowed ring closure). Rearrangement of the π-system would presumably lead to expulsion of phosphine.

![Scheme 4-1](image)

Scheme 4-1. Experiment to prove the organocatalytic mechanism

We began by examining proposed routes to prepare our desired o-aminobenzylphosphonium salt. The most straightforward route began with the lithium aluminum hydride reduction of anthanilic acid to afford o-aminobenzyl alcohol which was subjected to PPr$_3$•HBr neat at 100 °C for 8 h. Unfortunately this was unsuccessful and performing the reaction in solvent gave the same result. o-Nitrobenzoic acid was therefore chosen as a more stable substitute (Scheme 4-2). Reduction using sodium borohydride with a substoichiometric amount of boron trifluoride diethyl etherate gave the corresponding benzyl alcohol which was used in subsequent reaction with minimal purification. Reaction with tripropylphosphine hydrobromide led to phosphonium salt formation though conversion to the benzyl bromide is required on a larger scale. The one-pot formation of PPr$_3$-HBr and subsequent phosphonium salt formation were attempted using 48% HBr$_{(aq)}$ and 33% HBr in acetic acid. Only the reaction performed in acetic acid led to complete conversion with no trace of phosphine oxide by NMR. Once formed the
phosphonium salt was reduced using 5% Pd/C under 1 atm H₂ overnight and the desired salt was obtained cleanly after vacuum filtration and concentration under reduced pressure.

\[
\begin{align*}
\text{4-14} & \xrightarrow{\text{NaBH₄, BF₃-OEt₂, THF, reflux, overnight}} \text{4-15} \\
\text{4-16} & \xrightarrow{5\% \text{ Pd/C, H}_2, \text{EtOH, rt}} \text{4-17}
\end{align*}
\]

**Scheme 4-2. Preparation of o-aminobenzyltripropylphosphonium bromide**

Initial attempts to prove the organocatalytic mechanism and produce high-value 2-substituted indole adducts led to formation of an unknown product which was slightly more polar than the desired indole by TLC. Isolation of the unknown spot by column chromatography led to its assignment as 2-amino-4’chlorostilbene. Repeated attempts to produce indole in a range of solvents and conditions led, in each case, to the stilbene product. While optimizing the process for the production of the stilbene, another less polar product was consistently being produced, even when done in water. This product was exceptionally difficult to obtain in high purity and would constantly co-elute with the aldehyde and and stilbene product. However we were able to isolate a small sample which revealed that a small but not insignificant portion of our stilbene product was being transformed into the imine. Stunningly this occurs even in aqueous solution. Our hypothesis is that as the stilbene begins to form into a biphasic system, which is visually confirmed, a small quantity of aldehyde is pulled into this developing phase and condenses with the product. Despite extending the reaction time no change in the intensity of the spot was observed.

\[
\begin{align*}
\text{4-17} & \xrightarrow{\text{NaHCO₃, H₂O, 24 h, 70 °C, 0 %}} \text{4-18} \\
\text{4-17} & \xrightarrow{\text{NaHCO₃, H₂O, L-Pro (10% mol), 24 h, 70 °C, 78%}} \text{4-9h}
\end{align*}
\]

**Scheme 4-3. Reaction salt 4-17 with p-chlorobenzaldehyde**
Though the initial intent of the project was to support the mechanism of the organocatalytic Wittig reaction and produce highly valuable 2-substituted indole adducts there is still a host of possibilities that exist with the protecting-group free preparation of \( o \)-aminostyryl units. There are numerous catalysts which exist, though mainly early transition metals, which will readily perform hydroaminations (scheme 4).\(^{23}\) Oxidative cyclisation of the amine onto the alkene is also a realistic possibility using electrophilic halogenating reagents or transition metals to access the initial target of the project, indoles.\(^{24}\) 2,3-subsituted quinolines are possible through imine formation followed by a 6\( \pi \)-electrocyclic rearrangement which should proceed through an intermediate not too dissimilar from a Pictet-Spengler reaction.\(^{25}\) If successful such a methodology could be applied to the total synthesis of Cryptosanguinolentine which was prepared by Fresneda and co-workers in 11 steps and 7% overall yield from 2-nitrobenzyltriphenylphosphonium bromide \(^{4-17}\). The proposed synthesis would prepare the natural product in as little as four steps from 2-aminobenzyltripropylphosphonium bromide. Stilbene formation with 2-fluoro- or 2-nitrobenzaldehyde and subsequent cyclisation would give the 3-substituted quinoline. Nucleophilic aromatic substitution of the fluoro- or nitro-group with sodium azide sets up the possibility of nitrene insertion. This is performed in tandem with activation of the 4-position of quinoline by alkylating with iodomethane to produce the natural product.

**4.5 Conclusion**

In conclusion, the first examples of organocatalytic Wittig olefination reactions involving an amine or sulfonamide catalysed olefination reaction of an aldehyde reacting with a phosphonium salt are described. A proposed catalytic cycle has been postulated involving either formation of an electrophilic iminium ion, in the case of weakly basic secondary amines, or an \( N \)-sulfonylimine, in the case of sulfonamide catalysis. Evidence in favour of a distinct iminium ion catalyzed pathway is presented. The reactions proceed solely in water involving the reaction of an \( in \, situ \) generated ylide with the iminium ion or sulfonylimine. Both intermediates are produced through a cascade process initiated through condensation of the catalytic amine and aldehyde, producing an iminium hydroxide, reacting with the phosphonium salt, producing the ylid, undergoing the Wittig reaction, producing the alkene and azaphosphorane which undergoes \( in \, situ \) hydrolysis completing the catalytic cycle. In particular, the use of salts derived from triethylphosphane allow for high \( (E) \)-olefin stereoselection straightforward product isolation. Substituted stilbenes and cinnamate esters are readily available in high yield and high \( (E) \)-olefin stereoselectivity using this protocol. No chromatography is required at any stage and organic solvent (Et\(_2\)O) is employed only for solvent extraction of two oils. This work opens a new reaction manifold within the field of organocatalysis.
Further, investigations into the scope of this organocatalytic aqueous Wittig reaction are under active investigation.

4.6 Experimental Section

4.6.1 General Considerations

Reactions were carried out under nitrogen or argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et$_2$O), tetrahydrofuran (THF), Toluene (PhMe) and triethylamine and N,N-diisopropylethylamine were distilled from Na$^+$ with benzophenone as an indicator. Dry dichloromethane (CH$_2$Cl$_2$) was distilled from calcium hydride while dry methanol (MeOH) was distilled from Mg$^0$. All fine chemicals were obtained from Sigma-Aldrich and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H-NMR) homogeneous materials, unless otherwise stated. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV. HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. NMR spectra were recorded on Bruker AV-600 and AV-700 spectrometers and calibrated using residual undeuterated solvent as an internal reference(CHCl$_3$ @ δ 7.26 ppm $^1$H NMR, δ 77.16 ppm $^{13}$C NMR; Acetone-d$_6$ @ δ 2.05, $^1$H NMR, δ 29.84 ppm $^{13}$C NMR ); $^{31}$P spectra were calibrated using an external reference of 85% H$_3$PO$_4$. Signal assignments were accomplished via analysis of HMBC, HMQC, COSY, NOESY experiments where necessary. The (E) to (Z) ratios were determined from the relative integration of the $^1$H spectra for the olefinic protons. All melting points are corrected.

4.6.2 Preparative Procedures

General experimental procedure for Catalyst Screening:

Into a flame-dried microwave vial, containing a magnetic stirring bar was weighed the corresponding trialkyl- or triphenylbenzyl phosphonium salt (2 mmol, 1 equiv). Water was added to make up a 2.0 M solution. To this were added the 4-chlorobenzaldehyde (2 mmol, 1 equiv), NaHCO$_3$ (4 mmol, 2 equiv), the corresponding catalyst (20% mol). The vial was then sealed and heated at 50 °C for 6 h. The oil bath was removed and the flask was left to attain room temperature. The mixture was then extracted with EtOAc (2 x 10 mL) and concentrated in vacuo. The residue which contained all organic soluble components was then taken up in CDCl$_3$ and an NMR recorded. Conversion was measured using the aldehyde peak and the olefinic peaks. E:Z ratios were determined by NMR integration of the olefinic doublets.
General experimental procedure for iminium Wittig synthesis:

\[ \text{Amine (10\% mol)} \quad \text{H}_2\text{O, NaHCO}_3 \quad 100 \^\circ\text{C} \]

To the trialkyl- or triphenylbenzyl phosphonium salt (2.2 mmol, 1.1 equiv) was added water (1 mL). To this were added the corresponding aldehyde (2 mmol, 1 equiv), NaHCO\(_3\) (4 mmol, 2 equiv) and L-Proline (10% mol). The vial was then sealed and heated at 105 °C for 18 - 72 hours. The oil bath was removed and the flask was left to attain room temperature. Water (15 mL) was added to the reaction mixture and the flask was stirred for a further 10 minutes. For solids, the resulting slurry was vacuum filtered and air dried to yield the title compound. In the case of oils, the title compound was taken up into ether and concentrated under reduce pressure to afford the corresponding product.

1-(4-chlorostyryl)benzene (4-4a)

Yield 93%, white Solid; Mp 122-124 °C; \(^1\)H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 7.05 (d, \(J = 16.2\) Hz, 1H), 7.09 (d, \(J = 16.2\) Hz, 1H), 7.28 (d, \(J = 7.4\) Hz, 1H), 7.32 (d, \(J = 8.5\) Hz, 2H), 7.37 (t, \(J = 7.4\) Hz, 2H), 7.74 (d, \(J = 8.5\) Hz, 2H), 7.51 (d, \(J = 7.4\) Hz, 2H); \(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 126.8, 127.5, 127.9, 128.1, 128.9, 129.0, 129.5, 133.4, 136.0, 137.2.

1-(4-methylstyryl)benzene (4-4b)

Yield 92%, white solid; Mp 112-114 °C; \(^1\)H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 2.37 (s, 3H), 7.06 (d, \(J = 16.1\) Hz, 1H), 7.09 (d, \(J = 16.5\) Hz, 1H), 7.18 (d, \(J = 7.9\) Hz, 2H), 7.09 (m, 1H), 7.36 (d, \(J = 7.6\) Hz, 2H), 7.42 (d, \(J = 7.9\) Hz, 2H), 7.51 (d, \(J = 7.9\) Hz, 2H); \(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 21.4, 126.54, 126.56, 127.6, 127.9, 128.8, 129.5, 134.7, 137.7.

5-styrylbenzo[d][1,3]dioxole (4-4c)

Yield 88%, white Solid; Mp 90-91 °C; \(^1\)H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 5.89 (s, 2H), 6.72 (d, \(J = 7.9\) Hz, 1H), 6.85 (m, 2H), 6.95 (d, \(J = 16.2\) Hz, 1H), 6.99 (d, \(J = 1.8\) Hz, 1H), 7.16 (m, 1H), 7.26 (t, \(J = 7.4\) Hz, 2H), 7.40 (d, \(J = 7.4\) Hz,
2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 101.3, 105.7, 108.6, 121.6, 126.5, 127.2, 127.5, 128.5, 128.8, 132.0, 137.6, 147.5, 148.3.

1-(4-nitrostyryl)benzene (4-4d)$^{27}$

![1-(4-nitrostyryl)benzene](image)

Yield 94%, yellow solid; Mp 154-155 °C; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.15 (d, $J = 16.2$ Hz, 1H), 7.27 (m, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.43 (t, $J = 7.0$ Hz, 2H), 7.58 (d, $J = 6.6$ Hz, 2H), 7.58 (d, $J = 7.2$ Hz, 2H), 7.58 (d, $J = 7.2$ Hz, 2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 124.3, 126.5, 127.0, 127.2, 129.0, 129.1, 133.5, 136.3, 144.0, 147.0.

1-methoxy-4-styrylbenzene (4-4e)$^{30}$

![1-methoxy-4-styrylbenzene](image)

Yield 91%, white solid; Mp 136-137 °C; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 3.84 (s, 3H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 16.3$ Hz, 1H), 7.07 (d, $J = 16.3$ Hz, 1H), 7.23 (t, $J = 7.3$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.48 (d, $J = 7.1$ Hz, 2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 55.5, 114.3, 126.4, 126.8, 127.4, 127.9, 128.4, 128.8, 130.3, 137.8, 159.5.

1,2,3-trimethoxy-5-styrylbenzene (4-4f)$^{27}$

![1,2,3-trimethoxy-5-styrylbenzene](image)

Yield 85%, light yellow solid; Mp 105-107 °C; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 3.91 (s, 3H), 3.95 (s, 6H), 6.78 (s, 2H), 7.04 (d, $J = 16.5$ Hz, 1H), 7.08 (d, $J = 16.5$ Hz, 1H), 7.29 (t, $J = 7.3$ Hz, 1H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.54 (d, $J = 7.3$ Hz, 2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 56.3, 61.1, 126.6, 127.7, 128.3, 128.77, 128.82, 133.2 137.3, 138.1, 153.5.

N,N-dimethyl-4-styrylbenzenamine (4-4g)$^{31}$

![N,N-dimethyl-4-styrylbenzenamine](image)

Yield 87%, yellow solid; Mp 146-147 °C; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 2.99 (s, 6H), 6.72 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 16.5$ Hz, 1H), 7.06 (d, $J = 16.5$ Hz, 1H), 7.20 (t, $J = 7.8$ Hz, 1H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 7.0$ Hz, 2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 40.6, 112.6, 124.6, 125.9, 126.2, 126.8, 127.7, 128.7, 128.9, 138.3, 150.3.
(E)-ethyl 3-(4-chlorophenyl)acrylate (4-6a)\textsuperscript{32}

Yield 96\%, colourless oil; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] \(\delta\) : 1.34 (t, \(J = 7.1\) Hz, 3H), 4.27 (q, \(J = 7.1\) Hz, 2H), 6.40 (d, \(J = 16.0\) Hz, 1H), 7.36 (m, 2H), 7.45 (m, 2H), 7.62 (d, \(J = 16.0\) Hz, 1H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \(\delta\) : 14.3, 60.6, 118.9, 129.18, 129.20, 133.0, 136.1, 143.1, 166.7.

(E)-ethyl 3-(benzo[d][1,3]dioxol-6-yl)acrylate (4-6c)\textsuperscript{33}

Yield 90\%, colourless oil; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] \(\delta\) : 1.34 (t, \(J = 7.2\) Hz, 3H), 4.26 (q, \(J = 7.1\) Hz, 2H), 6.00 (s, 2H), 6.27 (d, \(J = 15.8\) Hz, 1H), 6.80 (d, \(J = 8.1\) Hz, 1H), 6.99 (d, \(J = 8.0, 1.6\) Hz, 1H), 7.02 (d, \(J = 1.6\) Hz, 1H), 7.59 (d, \(J = 15.9\) Hz, 1H);
\textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \(\delta\) : 14.3, 60.3, 101.5, 106.4, 108.4, 116.1, 124.3, 128.8, 144.2, 148.3, 149.5, 167.0.

(E)-ethyl 3-(4-nitrophenyl)acrylate (4-6d)\textsuperscript{34}

Yield 94\%; light yellow solid; Mp 136-138 \{Lit.\textsuperscript{35} 138-139\}; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] \(\delta\) : 1.35 (t, \(J = 7.1\) Hz, 3H), 4.29 (q, \(J = 7.1\) Hz, 2H), 6.56 (d, \(J = 16.0\) Hz, 1H), 7.67 (d, \(J = 8.6\) Hz, 2H), 7.70 (d, \(J = 16.0\) Hz, 1H), 8.24 (d, \(J = 8.8\) Hz, 2H);
\textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \(\delta\) : 14.4, 61.1, 122.7, 124.3, 128.7, 140.7, 141.7, 148.6, 166.1.

4.7 Notes and References

The reaction was monitored by Kraus, G. A.; Guo, H.

The reaction was monitored by Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H.

The reaction was monitored by Sinclair, D. A.; Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M.  

The reaction was monitored by Aigrot, M. S.; Dolle, F.

The reaction was monitored by Miller, R. H.; Wang, Y.; Steward, W. P.; Gescher, A. J.

The reaction was monitored by Bureau, J. B.; Tomkinson, N. C. O.

The reaction was monitored by McNulty, J.; Das, P.

The reaction was monitored by McNulty, J.; Das, P.; McLeod, D.


Chapter 5

The Bio-orthogonal Wittig reaction: the Wittig reaction in biological systems under physiological conditions

5.1 Introduction

5.1.1 Literature Overview

The genomic era has augured unprecedented opportunities to elucidate the most fundamental aspects of biology. High-throughput gene sequencing methods have allowed the characterisation of organisms and mutations associated with human ailments while, in tandem, perturbations in gene regulation (deletion/overexpression) have revealed multiplex signalling networks beyond initial assumptions in breadth and complexity. Translating this wealth of genetically encoded information into biological function is a considerable and daunting task. Many biological processes are controlled by multiple genes which aren’t necessarily apparent through perturbations of individual gene expression; that is to say nothing of the possibility of chromatin or small RNA mediated epigenetic modification introducing the possibility of transient interactions. The crucial role of non-genetic biomolecules in regulating both cellular function and the biochemical activities of protein families further complicates matters. Clearly biological signalling is neither linear nor straightforward. Rather, what are required are complementary techniques which are able to elucidate the function and structure of an array of endogenous biomolecules.

Selective chemical reactions enacted within a cellular environment can be powerful tools for elucidating biological processes or engineering novel interactions. The ability of chemistry to modify biomolecules in vitro, thereby gaining insight into their structure and function has long been sought.\(^1,2\) To this end, bioorthogonal chemistry has emerged to allow study of biomolecular dynamics and function in living systems.\(^3\) In contrast to genetic tagging employing fluorescent proteins, bioorthogonal reactions are uniquely amenable to all classes of biomolecules including proteins, nucleic acids, lipids, glycans and certain regulatory processes such as posttranslational modifications.\(^4\) The high degree of flexibility/versatility in design of bioorthogonal probes offers the ability to study individual biomolecules at a cellular level or biological processes genome-wide.
The implementation of bioorthogonal chemistry comprises two distinct steps: the incorporation of a tailored/modified biomolecule—the bioorthogonal reporter—into the endogenous environment by either a native or an engineered biosynthetic pathway followed by bioorthogonal reaction of the reporter and an exogenous chemical probe. Reaction of the bioorthogonal reporter and cognate chemical probe must necessarily occur under physiological conditions in water at a neutral pH in the presence of myriad potentially reactive endogenous functional groups—a concept referred to as bioorthogonality—and must be non-toxic. Reactants and the reaction products should realistically be metabolically and thermally stable as well. Pragmatically, reactions should also be fast and high yielding at relatively low concentrations. Excess reagents may alter cellular physiology so high rate constants (0.001 to 1000 $M^{-1} s^{-1}$) are desirable.\(^5\)

Despite these constraints a number of bioorthogonal reactions have been developed which exhibit excellent selectivity in living systems.\(^6\) Broadly, these reactions can be classified as either polar reactions (Figure 5-1, A) or cycloadditions (Figure 5-1, B & C). Among the most widely employed polar reactions are condensations of aldehydes and ketones—which are rare on proteins and most biopolymers.\(^3c,7\) Bioorthogonal reactions which exploit the high reactivity of these functional groups with $\alpha$-effect nucleophiles (e.g., hydrazides, hydroxylamines)\(^8\) allow selective ligation of modified proteins\(^9\) and glycans\(^10\) and ultimately visualisation or retrieval of the target. Despite an inherent susceptibility to hydrolysis in cellular environments,\(^11\) the versatility of condensation strategies remains alluring and efforts have been made to develop more stable adducts.\(^12\) Inadvertent labeling of endogenous saccharides, microbial metabolites and mammalian hormones and other aldehyde/ketone containing metabolites remains a distinct possibility. To prevent undesirable background reactions and increase labeling selectivity, reactions of non-natural functional groups are of interest. The Staudinger ligation\(^13\) has thus become a stalwart of the field owing to its remarkable compatibility of cells, tissues and tolerance of biological functionality.\(^14,15\)
Figure 5-1. Archetypal bioorthogonal reaction motifs

Cycloadditions, meanwhile, are the largest class of bioorthogonal reactions; the most popular also exploit organo-azides as 1,3-dipoles in the Huisgen cycloaddition reaction. Indeed, the copper-catalyzed azide-alkyne cycloaddition has been used to visualise biomolecules in fixed cells, target retrieval, and monitoring the activity of small molecule enzyme inhibitors. While routinely employed in vitro, the cytotoxicity of Cu(I) has limited its application to in vivo studies. Bertozzi and coworkers ingeniously circumvented the need for copper by exploiting the ring strain present in cyclooctynes. It has since been used to tag azido-modified proteins, and other biomolecules in live cells and living organisms. In addition to azides, cyclooctynes also participate in 1,3-dipolar cycloadditions with nitrones, nitrile oxides, and diazo compounds. Strained alkenes have also been successfully employed in bioorthogonal reactions with nitrile imines, nitrile oxides and azides and most importantly in Diels-Alder chemistry. The inverse electron-demand Diels-Alder reaction between strained trans-cyclooctenes and tetrazines was first reported by Fox and coworkers in the presence of model proteins in aqueous media. The reaction exhibits impressive reactivity and has been employed in live animal imaging. The inherent reactivity of tetrazine to strained alkenes has also been exploited with norbornene and cyclopropene.

The means to chemically tag biomolecules—using cognate chemical reporters and probes—in their endogenous environment without significantly perturbing their native function has enabled visualisation/identification of biological targets. Myriad methods currently exist for introduction of chemical reporters—which must be incorporated into the native environment prior to reaction with a bioorthogonal probe—into biological systems; the incorporation of non-natural chemical reporters is typically performed via
native biosynthetic pathways modification of such pathways to tolerate aberrant substrates has been accomplished.\textsuperscript{37} Biomolecules have been labeled with bioorthogonal tags by: clickable covalent inhibitors, photoaffinity labelling with clickable photoprobes, ligation enzymes, metabolic labelling, and genetic encoding of unnatural amino acids.

The kinetics of the aforementioned reaction motifs are directly related to the concentration of chemical reagents; the overall reaction rate is proportional to both rate constant and reagent concentration. For slow reactions this typically requires a large excess of chemical probe for efficient labelling of the reporter-tagged biomolecule. Unfortunately, fluorescence microscopy—which allows spatiotemporal resolution—is typically employed requiring exhaustive washing steps to reduce background fluorescence and assure only the covalently linked probe remains. To circumvent such concerns, especially given low reaction rates or situations where removal of excess probe is difficult (\textit{in vivo} studies), activatable or “smart” probes are crucial.\textsuperscript{38} This class of reagent produces a detectable signal only upon bioorthogonal reaction (Figure 5-2). Covalent ligation induces an enhancement in fluorescence in luminescent (turn-on) probes.

**Figure 5-2.** Biorthogonal tagging of a biomolecule; A. Typical bioorthogonal tagging using a fluorescent probe; B. Bioorthogonal labelling employing a ‘smart’ probe

### 5.1.2 The Bioorthogonal Wittig

On initial consideration, the classical Wittig olefination reaction does not appear to be a suitable candidate for development as a potential physiological reaction manifold. The classic reaction\textsuperscript{39} requires the use of dry organic solvents—such as diethyl ether or tetrahydrofuran—and strong non-aqueous bases such as butyl lithium or lithium diisopropylamide. In addition, protecting groups are usually required on any exposed acidic hydrogens (alcohol, phenol, amino etc). Nonetheless, significant advantages can be envisioned for a process as outlined in Scheme 5-1. The coupling of a functionalised aldehyde 5-1 with a functionalised phosphonium salt 5-2 would produce the donor-
acceptor flanked “reporter” stilbene 5-3 which could be detected using standard analytical methods (NMR, MS, UV and/or fluorescence spectroscopy).

Thus, in addition to facilitating the conjugation of two functionalised units, such a process would simultaneously introduce a tunable, UV and/or visible fluorescent reporter stilbene. Stilbene units form the core of a range of valuable materials including pharmaceuticals, light emitting diodes and dye-sensitized photo-voltaic solar cells. Stilbene cores have been conjugated as structural and reporter units on varied materials including dendrimers, as well as to biological constructs such as nucleic acids, proteins (including lysozomes and antibody binding) and even to viral particles. Development of a mild olefination “click” process could thus prove of strategic value to the conjugation and detection of a wide range of materials, bioconjugates and other applications. We have investigated aqueous Wittig olefination reactions over the last few years under increasingly milder chemical conditions showing that stabilised and semi-stabilised ylides can be efficiently generated and trapped to give a range of useful alkenes, including stilbenes. More recently, we demonstrated the first organocatalytic aqueous Wittig olefination reactions using weakly and non-basic amines including L-proline, tosylamide and diphenylamine. We proposed a catalytic cycle for this process proceeding through an iminium ion intermediate as a carbonyl surrogate (see sections 4.2.1 & 4.2.2).

In order to extend these studies toward bioorthogonal applications we decided to investigate the critical issue of whether a Wittig olefination process is compatible and achievable under physiological conditions.

5.2 Development of a Bio-orthogonal Wittig process

5.2.1 Development of a suitable donor-acceptor stilbene system

We designed and prepared the amide-containing dual-functionalised test substrates 5-5 and 5-8 as reaction partners (Scheme 5-2). Wittig olefination was expected to yield the donor-acceptor flanked reporter stilbene 5-9. Amides were chosen to connect the functional groups on both the aldehyde and phosphonium salt reaction partners, suggesting immediate locations for alternative variations on this process on what is effectively a reporter amino acid derivative. The phosphonium salt reactivity is
intrinsically orthogonal, we elected to make this the “donor” substituent and settled on the 4-\(N\)-methylacetanilide \textit{5-8}.\textsuperscript{51} Aldehydes are known partners in bioorthogonal reactions\textsuperscript{[4a,b]} generally reacting reversibly with amines and hydroxylamines to generate imine or Schiff base adducts and hence this did not appear to be an issue. Aldehydes have also been used in the “aldehyde tag” process for site-specific protein encoding and subsequent bioorthogonal covalent labeling.\textsuperscript{[2b]} In order to limit possible oxido-reductase reactions and to increase electrophilicity of the aldehyde, we opted to functionalise the aldehyde with an \textit{ortho}-electron withdrawing group and thus settled on the morpholinamide derivative \textit{5-5}. The chemical synthesis of the initial reaction partners \textit{5-5} and \textit{5-8} is outlined in Scheme 5-2. Nucleophilic opening of phthalide \textit{5-4} with morpholine in the presence of a stoichiometric amount of AlCl\(_3\) gave the corresponding benzyl alcohol which was subject to a Swern oxidation providing a short entry to aldehyde \textit{5-5}. Acylation of 4-methylaniline \textit{5-6} proceeded smoothly and subsequent \(N\)-methylation using LiHMDS and iodomethane followed by benzylic bromination yielded the desired substituted benzyl bromide \textit{5-7}. Quaternisation with triphenylphosphine yielded the phosphonium salt \textit{5-8}. An alternative synthetic route to salt \textit{2a} was also developed (see section 5.5) from 4-aminobenzyl alcohol.

\[ \text{Scheme 5-2. Preparation of substrates 5-5 and 5-8} \]

\[
\begin{align*}
\text{A} & \quad \text{B} \\
\text{5-4} & \quad \text{5-5} \\
5-6 & \quad \text{5-7} \\
\text{5-8} & \quad \text{5-9}
\end{align*}
\]

\text{Scheme 5-2. Preparation of substrates 5-5 and 5-8}

\begin{itemize}
  \item a: morpholine, AlCl\(_3\), 1,2-DCE, 0 °C
  \item b: (COCl\(_2\)), DMSO, TEA, CH\(_2\)Cl\(_2\), -78 °C
  \item c: Ac\(_2\)O, CH\(_2\)Cl\(_2\), r.t.
  \item d: LiHMDS, CH\(_3\)I, THF, 0 °C
  \item e: NBS, BPO, PhH, reflux
  \item f: PPh\(_3\), PhMe, reflux
\end{itemize}

The Wittig olefination reaction of 5-5 and 5-8 was first investigated under a range of chemical conditions (Scheme 5-3, A). The reaction was observed to proceed slowly in water at 38 °C in the presence of sodium bicarbonate and a catalytic quantity of L-proline as the sole organic catalyst. This reaction was complete in 24 h and the donor-acceptor stilbene \textit{5-9} isolated in 87% yield as a 1:1 (\(E\)):(\(Z\)) mixture. The olefination reaction could also be completed more rapidly in water using the relatively stronger base potassium carbonate at 70 °C. Under these conditions, the reaction was complete within 3h yielding
the stilbene 5-9 in 76% isolated yield as a 65:35 (E):(Z) mixture, selectivity in accord with literature data. Full spectroscopic characterization of the (E) and (Z) isomers was accomplished, the NMR data of the olefinic protons of each isomer are clearly resolved. The mass spectrum (EI-TOF) gave the molecular ion 364 (87%) and readily identifiable fragments at 277 (100%) and 236/237 (48%/86%). The compounds could be readily detected at low concentrations using LC and LCMS and also via UV and fluorescence spectroscopy. The LC/MS (Phenomenex Luna C18, H2O, 0.1% formic acid/CH3CN gradient elution, see supplementary for full details) showed clear resolution of two distinct near-baseline resolved peaks for the (E)- and (Z)-stereoisomers (elution time 13.5 and 14.1 mins), each displaying a similar fragmentation pattern. LC/MS-MS analysis on 5-9 demonstrated clearly that the fragmentation at 277.9 led to the secondary fragmentation at 235.8, thus providing a definitive fingerprint for the identification of the stilbenes. In a similar fashion (Scheme 5-3, B), 4-cyanobenzaldehyde 5-10 reacted with phosphonium salt 5-11 yielding stilbene 5-12 which was likewise characterized. Fluorescence measurements on 5-9 using excitations at both 219 and 301 nm produced broad emission just outside the visible region at 395 nm.

Scheme 5-3. Model Bio-orthogonal Wittig performed in vitro

5.2.2 Identification of Bioorthogonal Wittig Products in vivo

As described above, the aqueous organocatalytic Wittig olefination reaction requires the presence of a catalytic quantity of a primary or secondary amine. Endogenous amines and nitrogen heterocycles are ubiquitous in living organisms, occurring as both primary and secondary metabolites (for examples, see Figure 5-3). We now focussed on testing the feasibility of conducting a Wittig-olefination reaction under purely physiological conditions in living tissue. We initially chose the plant Calystegia sepium (Convolvulaceae) as a vehicle for several reasons. The plant is a well-known member of the Convolvulaceae (bindweed or morning glory) family known to produce a
small assemblage of nortropane secondary-amine alkaloidal natural products known as the calystegines, Figure 5-3.\textsuperscript{53} Seeds of the plant are commonly available, are easily and rapidly germinated in water and can be cultivated in soil. or hydroponically under laboratory controlled conditions. Root and tissue cultures of the plant can also be prepared.\textsuperscript{53b,c}

![Calystegine A\textsubscript{3} and (-)-Adaline](image)

**Figure 5-3.** Examples of naturally occurring secondary amines in plants and animals. Calystegine A\textsubscript{3} a common ornithine-derived nortropane secondary amine metabolite from *Calystegia sepium.*\textsuperscript{53a} Adaline, a fatty-acid derived amine from the ladybird *Adalia 2-punctata.*\textsuperscript{53d}

![Confirmation of stilbenes via physiological Wittig-olefination](image)

**Figure 5-4.** Confirmation of the formation of stilbenes via a physiological Wittig-olefination in a living organism. A & D. LC trace showing the (E)- and (Z)-isomers scanning \textit{m/z} 278 & 365. B & E. fragmentation of the first eluting isomer (13.5 min) and C & F. the second isomer (14.1 min) showing the characteristic primary and secondary ion fragmentation fingerprint in each.
We investigated the germination of seedlings of *C. sepium* grown under hydroponic conditions, to minimise interference from soil-borne microorganisms, in a custom built growth chamber. Soaking in water allowed seedling germination to occur usually within 2-3 days. Plants were grown to a height of 3-4 cm under three conditions; in soil, in pure water and in a dilute aqueous NPK blend (total nitrogen 10%, available phosphoric acid (P$_2$O$_5$) 52%, soluble potash (K$_2$O) 10%, micronutrients 1%). Upon germination, the plant materials were irradiated with a sunlamp for 6 hours/day at a constant temperature of 25 ± 2 ºC. Seedlings were then injected separately with aqueous solutions of aldehyde 5-5 and phosphonium salt 5-8 (Scheme 3, B). Each solution was 2 mM in water; 100 μL of each were added twice a day. The growth of the plants was visually unaffected by treatment with compounds 5-5 and 5-8, relative to non-labelled controls, no evidence of herbicidal activity was observed. Non-labelled control and labelled plants were harvested after 8 days and the organic solubles extracted into methanol. LC/MS analysis of the control plant extracts (non-labelled) and control media, consisting of compounds 5-5 and 5-8 in pure water and compounds 5-5 and 5-8 in the NPK solution, showed conclusively that no olefination reaction occurs. Individual plants treated with 5-5 and 5-8 grown in soil (above ground leaves/stems) and under hydroponic conditions were carefully removed and washed thoroughly with water. The methanol extract of each was analyzed using the LC/MS-MS method described. The analysis showed conclusively formation of the reporter stilbenes (Figure 5-4) in labelled plants grown in soil and those grown hydroponically. Two peaks are observed with identical retention time in comparison to the synthetic controls (Figure 5-4, A). Detection of the fragment of m/z 278 was also in accord with the stilbene standards and the secondary fragmentation of each isomer (Z)- (Figure 5-4, B) and (E)-isomers (Figure 5-4, C). Similarly, separate feeding of 5-10 and 5-11 to hydroponically grown *C. sepium* resulted in formation of detectable quantities of stilbene 5-12, indicating that the Wittig chemistry reaction partners are more “orthogonal” under physiological conditions than initially anticipated. Deconvolution microscopic analysis of root, stem and leaf sections of *C. sepium* after feeding with compounds 5-5 and 5-8 showed accumualtion of stilbene 5-9 on the plant cell surface and/or intercellular media of the stem.

![Image](image_url)

**Figure 5-5.** Deconvolution micrographs of labelled (left) and unlabelled control (right) stems of *C. sepium* showing localization of the reporter stilbene on the membrane and/or intercellular media.
Lastly, since *C. sepium* is known to accumulate toxic secondary amines (see Figure 5-3) in addition to endogenous amino acids, it was of interest to investigate a possible physiological olefination in a more benign plant. The reaction of 5-5 and 5-8 was investigated in the pea plant *Pisum sativum*, an innocuous vehicle known mainly for primary amino acid production. Seeds of *P. sativum* are readily available and the plant is rapidly germinated in soil or under hydroponic conditions. Separate injection of compounds 5-5 and 5-8 into rapidly growing seedlings of *P. sativum* and harvesting of the plant tissue after 8 days followed by LCMS analysis as described above allowed unequivocal identification of stilbene 5-9 in stem and leaf tissue.

The synthesis of precursors 5-5 and 5-8 (Scheme 5-2) is rapid and its modular nature should enable application to analogous reaction partners in order to connect functional units of interest and to customise the properties of the chromophore. The initial process connects an amine to a carboxylic acid *via* amide bonds through an *in situ* and *in vivo* constructed reporter stilbene linkage. The technology to construct such a molecularly defined chromophore/fluorophore directly, while conjugating two differentially functionalised entities provides a new approach that is envisaged to be widely useful in installing such a *reporter* in these systems, including in living tissues. Stilbene 5-9 was chosen as a proof-of-principle for the physiological olefination process and not designed as a tissue specific target. It is not yet known if the olefination reaction occurs within the plant cell or the extracellular media promoted by endogenous amines. Nonetheless, it has now been demonstrated that Wittig-type olefination reactions are compatible under mild physiological conditions.

**5.3 Imaging Phase Transitions in Cell Membranes using a Bio-orthogonal Wittig Reaction**

Lipids control a vast array of cellular functions; their organisation into discrete membranes provides a signaling platform for protein complexes and is essential for the compartmentalisation of living matter. Perturbations in lipid composition of these membranes have a significant effect on organismal physiology. Lipid morphology controls membrane architecture and membrane-bound lipids act as site-specific ligands in the binding of protein effectors which consequently regulate both the function and localisation of bound proteins. It is no revelation, therefore, that aberrations of these signalling properties have been correlated with numerous diseases. The complexities associated with both the numerous protein targets as well as the lipids themselves, the structural variations of which are typically numerous, complicate the understanding of biological activities.
Lipid analysis has been accomplished in a few distinct ways: advances in chromatography and mass spectrometry have allowed large-scale lipidomic studies while radioactive tracers have traditionally been employed to monitor lipid uptake and metabolism. Though powerful, MS-based detection requires degrees of purification and even typically necessitates chemical derivatization to allow ionization. Radioactive tracers (³H or ¹⁴C lipid analogues), meanwhile, require long exposure to radiactivity for detection due to poor sensitivity—¹²⁵I may be used to improve sensitivity but it has a much shorter half-life—and represent a major detractor. Fluorescent-based approaches are a convenient alternative for detection of lipids in situ.

The complex and diverse mechanisms by which lipids control biological processes complicate the elucidation of their roles. Further, for a holistic understanding of lipid control of membrane trafficking and protein function, complementary approaches—including bioorthogonal reporters—are required. Design of lipid probes must be approached cautiously, as the location of derivatisation of lipid structures controls the presentation in the membrane.
5.3.1 Fluorescence requirements for an in vivo probe

Our initial bioorthogonal Wittig reaction furnished the donor-acceptor stilbene 5-9, which unfortunately did not possess the necessary photoexcitation/emission properties to be a useful probe. The excitation wavelength proved to be too low for effective excitation\(^6\) while the wavelength of emission suffered from the same problem, leading to poor contrast with background fluorescence.\(^7\) We did manage to effectively demonstrate the reaction using substrates 5-5 and 5-8 though; the resultant stilbene was readily visible by confocal microscopy (vide supra). While successful, the previous results had two major issues: the chemical probe wasn’t localised/targeted in any way and the starting materials weren’t amenable to variable functionalisation. We therefore wanted to design a targeted bioorthogonal probe with a high degree of synthetic flexibility which had the appropriate photochemical properties.

The nitrile group performed adequately as our acceptor in the model stilbene but lacked the ability to be functionalised while the triphenylamine donor is employed frequently in organic dyes used in solar cells due to its chemical stability—many dyes show a proclivity to bleaching—and large three-dimensional structure which discourages aggregation. It may be possible to change either of these functionalities and still retain the fluorescence properties necessary for use as an in vivo probe.

5.3.2 Structurally important aspects of a bioorthogonal lipid probe

In designing a targeted bioorthogonal probe, a few key structural and electronic specifications must be considered. Firstly, the limits of confocal fluorescence microscopy\(^6,7\) are such that only strong donors/acceptors can be considered; the formed stilbene must have a wavelength of emission greater than the background fluorescence and, ideally would also possess a wavelength of excitation which is outside the spectrum of its background. This limits the choices of acceptors to sulphonyls, nitriles and nitro-groups. A combination of the two in the form of a Michael acceptor might also satisfy the electronic specifications but would not be sufficiently chemically stable to be of any use in vivo. The donor should be an amine—an ether or phenol may also be suitable but the preponderance of dyes indicates amines should likely produce the best results electronically; each option allows for structural variability. The final key feature is the choice of tag which would allow labelling of the proper bimolecular structure. In our case a mono– or diglyceride–like structure (Figure 5-8) featuring one or two lipid tails to allow incorporation into a cell membrane. Preparation of a selection of stilbenes with the donors/acceptors described gave an indication which functional groups would be most suitable. For a variety of electronic and synthetic reasons the sulphonamide was chosen
as the preferable acceptor which should be placed opposite a benzylic phosphonium salt—a decision made after much consideration.

Figure 5-8. Target lipid reporter bearing a benzylicphosphonium salt

5.3.3 Constructing diglyceride lipid targets

We first decided to proceed from 3-amino-1,2-propanediol (Scheme 5-4) by tosylation in DMF/pyridine at room temperature. Previous radical brominations have shown that alkylation of the sulphonamide was necessary to prevent undesired N-Br bond formation. The next step, therefore, was to protect the vicinal alcohols as an acetonide, methylate with dimethyl sulphate followed by deprotection in methanol. It was found that using an excess of dimethyl sulphate followed by silica gel chromatography afforded the deprotected diol in one step. This is thought to be due to formation of acid doped silica as a result of partial or complete methylation. In a control reaction using exactly one equivalent of dimethylsulphate followed by silica gel chromatography no hydrolysis of the acetonide was observed. Esterification of the free diol was then attempted under two sets of conditions. The first attempt was through a Fischer esterification using pTSA and excess stearic acid in refluxing toluene. The result was, unfortunately, a mixture of mono- and bis-ester products as well as the excess stearic acid. The second attempt used stearoyl chloride with pyridine in DCM. To our disappointment this too produced a mixture of the mono- and bis-esters. Bromination of these products was attempted on a small scale but resulted in a complex mixture of poorly separable products.

Scheme 5-4. A bioorthogonal lipid probe constructed using 3-amino-1,2-propanediol
a: TsCl, py, DMF, r.t. b: pTSA, acetone, r.t. c: Me₂SO₄, K₂CO₃, acetone, reflux d: pTSA, MeOH, r.t. e: stearoyl chloride, TEA, CH₂Cl₂, r.t. f: NBS, BPO, PhH, reflux
Instead of installing the secondary amine or going back to the original synthesis which was flawed we opted to proceed with a route involving L-serine (Scheme 5-5) which would avoid the problem of forming a stearate ester on a secondary alcohol. Protection of L-serine as the methyl ester followed by tosylation, reduction of the ester, acetonide formation and alkylation afforded the intermediate 5-17. A more concise route to homologous compounds was also performed using the readily available amine 5-19 (Scheme 5-6) In all cases though the synthesis became lengthy and the radical bromination failed to give acceptable results.

Scheme 5-5. A bioorthogonal lipid probe constructed using L-serine
a: TsCl, NaOH, THF/H$_2$O (2:1), r.t. b: NaBH$_4$, BF$_3$•OEt$_2$, THF, reflux c: 2,2-DMP, pTSA, acetone, reflux
d: Me$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux e: pTSA, MeOH, r.t. f: stearoyl chloride, TEA, CH$_2$Cl$_2$, r.t.

5.3.4 Assembly of a fatty acid bioorthogonal probe

We shifted our attention to a route derived from L-proline because of the number of steps and difficulties in purification of the final compound in the previous diglyceride series. Formation of the methyl ester followed by tosylation led to the desired compound (Scheme 5-7). Reduction with LAH afforded the expected primary alcohol which was subsequently esterified with stearoyl chloride to give 5-23. Dilute concentrations were critical for the completion of the reaction. We were now at an intermediate which was ready for bromination in only four steps from a cheap chiral pool reagent. We had also avoided the need to methylate by starting from a secondary amine. The bromination was attempted numerous times with limited success. The reaction would never proceed to
completion and was usually approximately 50% complete. As a result of problems in bromination previously oxidized \( p \)-toluenesulphonyl groups were synthesized though these encountered other problems.\(^{69}\)

![Scheme 5-7](image)

**Scheme 5-7.** A bioorthogonal lipid probe constructed from L-proline

\( \text{a: } \text{SOCl}_2, \text{MeOH, reflux b: } \text{TsCl, NaOH, Et}_2\text{O/H}_2\text{O, r.t. c: } \text{LiAlH}_4, \text{THF, 0 }^\circ\text{C d: stearoyl chloride, TEA, CH}_2\text{Cl}_2, \text{r.t. e: } \text{NBS, BPO, CHCl}_3, \text{reflux} \)

After numerous routes to a desirable product we decided to simplify the molecule. Reductive amination of ethanolamine using cyclohexanone (or any ketone/aldehyde) afforded 2-cyclohexylaminoethanol (Scheme 5-8). Tosylation of this substrate afforded the product but suffered from poor yields as a result of \( O \)-tosylation and bis-\( N,O \)-tosylation. Two equivalents of tosyl chloride afforded the bis-tosylated product in excellent yield but hydrolysis of the \( O \)-tosylate proved more difficult than expected. Nucleophilic displacement using hydroxide in water or DMF left starting material or more than one product while cleavage using Mg in dry MeOH\(^{70}\) showed no conversion. Formation of the acetate though, followed by hydrolysis of the ester allowed for smooth conversion back to the alcohol. At this point ester formation using stearoyl chloride provided the desired product in moderate yield. Radical bromination of such substrates using BPO/NBS in benzene at elevated temperatures had not been working in previous examples. It was at this point a biphasic radical bromination with HOBr formed *in situ* from the reduction of NaBrO\(_3\) using NaHSO\(_3\) was performed. Using these more mild conditions bromination of these challenging substrates is possible, and most importantly allows for complete conversion. The final yield after column chromatography is much lower than the crude mass though. No other major side products are visible by TLC. Other ketones/aldehydes are possible allowing for a high degree of variability in future systems (Scheme 5-8).

![Scheme 5-8](image)

**Scheme 5-8.** A bioorthogonal lipid probe contructed using an ethanolamine linker
In conjunction with this successful route an alternative route from glycine was also explored (Scheme 5-9). Beginning with glycine, tosylation under aqueous conditions followed by methylation afforded the protected amine ester in good yields over two steps. Stearoyl, our prepared methyl ester, and an acid catalyst were heated neat to 80 °C for 6 h as a melt which solidified on cooling to give the trans-esterified product cleanly. Forseeably, bromination of the 5-5 furnished a number of products.

Scheme 5-9. A bioorthogonal lipid probe constructed using a glycine backbone

a: TsCl, NaOH, Et₂O/H₂O, r.t. b: Me₂SO₄, K₂CO₃, acetone, reflux c: C₁₈H₃₇OH, pTSA, neat, 80 °C d: many conditions

5.3.5 The in vitro bioorthogonal reaction of a lipid reporter

The in vitro bioorthogonal reaction of a lipid reporter

Phosphonium salt formation occurred smoothly to provide the salt seen below in good yield (Scheme 5-10). Reaction of this salt under bioorthogonal conditions in vitro afforded the desired donor-acceptor reporter stilbene in 89% yield as a bright yellow solid. Upon visualization of the compound in the column eluent (hexane/EtOAc, 8:2 v/v) under 364 nm light it was observed that the compound produced a blue fluorescence. When proper UV/Vis and fluorescence measurements were conducted in methanol to ascertain the absorption and emission λMAX it was noted that the emission wavelength was 520 nm or green light. It has been confirmed using fluorescence spectroscopy using 8 different solvents ranging from hexanes & toluene to DMF & methanol that the compound exhibits a solvachromic shift. The absorption wavelength of ~380 nm remains largely independent of solvent effects. The compound is highly fluorescent and has not been observed to suffer any photobleaching to date.
5.4 Conclusion

In summary, we report the synthesis of useful dual-functionalized donor-acceptor reporter stilbenes under extremely mild chemical organocatalytic olefination conditions and under physiological conditions within plant tissues. The reporter molecules can be isolated in large quantities using the chemical technique and can be readily identified at low concentrations via fluorescence or LC/MS-MS. The unprecedented chemoselectivity demonstrated here opens a new paradigm in olefination chemistry extending applicability to bioorthogonal applications. In addition, The core design elements of the ambiphilic phosphonium salt have been completed in a concise synthesis which is highly amenable to divergence of functionality. The reaction of this salt with TPA-CHO 5-31 under bioorthogonal conditions \textit{in vitro} has been accomplished and the properties have been confirmed to be adequate. The success of the chemical and bioorthogonal processes will suggest many applications for conjugation/detection in materials, biochemical and hybrid areas. Olefination chemistry continues to illuminate with new relevance a quarter century beyond Wittig’s passing.\textsuperscript{71}

5.5 Experimental Section

5.5.1 General Considerations

Reactions were carried out under nitrogen or argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et$_2$O), tetrahydrofuran (THF), Toluene (PhMe) and triethylamine and N,N-diisopropylethylamine were distilled from Na$^0$ with benzophenone as an indicator. Dry dichloromethane (CH$_2$Cl$_2$) was distilled from calcium hydride while dry methanol (MeOH) was distilled from Mg$^0$. All fine chemicals were obtained from Sigma-Aldrich and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H-NMR) homogeneous materials, unless otherwise stated. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV. HRMS (EI) were
performed with a Micromass Q-Tof Ultima spectrometer. NMR spectra were recorded on Bruker AV-600 and AV-700 spectrometers and calibrated using residual undeuterated solvent as an internal reference (CHCl$_3$ @ δ 7.26 ppm $^1$H NMR, δ 77.16 ppm $^{13}$C NMR; Acetone-d$_6$ @ δ 2.05, $^1$H NMR, δ 29.84 ppm $^{13}$C NMR); $^{31}$P spectra were calibrated using an external reference of 85% H$_3$PO$_4$. Signal assignments were accomplished via analysis of HMBC, HMQC, COSY, NOESY experiments where necessary. The (E) to (Z) ratios were determined from the relative integration of the $^1$H spectra for the olefinic protons. All melting points are corrected.

5.5.2 Preparative procedures

![Synthesis of SI-5-1](image)

Synthesis of SI-5-1: A solution of morpholine (436 mg, 5 mmol) in 1,2-dichloroethane (1 mL) was added to a suspension of AlCl$_3$ (347 mg, 2.6 mmol) in 1,2-dichloroethane (1 mL) with agitation and external cooling. The temperature was maintained at 15-25 °C during the addition and then allowed to warm to r.t. Phthalide (268 mg, 2 mmol) is added in one portion and the mixture stirred at r.t. for 2 h before quenching with a mixture of cold water (10 mL) and ice. The mixture is subsequently stirred for an additional 0.5 h and the organic phase separated. The aqueous phase is extracted with DCM (2 x 20 mL) and the organic phases combined, washed with brine and dried over anhydrous sodium sulphate (Na$_2$SO$_4$). After filtration and concentration under reduced pressure the crude product is pure enough for further reactions. Yield 88%, White powder; TLC (EtOAc, 100): R$_f$ = 0.18; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.43 (d, J = 7.2 Hz, 1H), 7.38 (td, J = 7.5, 1.2 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.19 (dd, J = 7.5, 0.8 Hz, 1H), 4.54 (s, 2H), 3.75 (s, 4H), 3.57 (s, 2H), 3.32 (s, 2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 170.4, 139.1, 134.5, 129.9, 129.7, 127.6, 126.3, 66.9, 66.8, 63.4, 48.0, 42.3; HREI MS (M)$^+$ calcd. for C$_{12}$H$_{15}$NO$_3$: 221.1052, found 221.1050.
Synthesis of **5-5**: To a solution of oxalyl chloride (0.1 mL) in DCM (0.54 mL) at -78 °C under an inert atmosphere in a 25 mL flame-dried round-bottomed flask was added dropwise over 15 min. a solution of DMSO (0.15 mL) in DCM (0.3 mL). The reaction was then left to stir at that temperature for 30 minutes after which time crude 2-(hydroxymethyl)morpholinobenzamide **SI-5-1** (221 mg, 1 mmol) was added in DCM (1 mL) dropwise over 15 min. The solution was then left for a further 40 min. before TEA (0.5 mL) was added and the reaction mixture was allowed to warm to room temperature over 2h. The mixture was subsequently dissolved in EtOAc and washed with NH₄Cl, followed by NaHCO₃, and Brine. The crude mixture was then column chromatographed with 70% EtOAc/Hexane over silica gel to yield pure aldehyde **5-5**. Yield 84%, White amorphous solid; Mp 77-80 °C {lit. 73 79-82 °C} TLC (EtOAc, 100): R_f = 0.36; ¹H-NMR [CDCl₃, 600 MHz] δ: 10.00 (s, 1H), 7.86 (dd, J = 7.7, 0.9 Hz, 1H), 7.60 (td, J = 7.5, 1.3 Hz, 1H), 7.52 (td, J = 7.6, 1.1 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 3.87 – 3.78 (m, 2H), 3.76 (d, J = 3.8 Hz, 2H), 3.56 – 3.41 (m, 2H), 3.19 – 3.00 (m, 2H); ¹³C-NMR [CDCl₃, 150 MHz] δ: 190.7, 168.3, 137.5, 134.3, 133.0, 131.4, 129.6, 127.2, 66.6, 66.5, 47.3, 42.2. HREI MS (M)⁺ calcd. for C₁₂H₁₃NO₃: 219.0895, found 219.0908.

Synthesis of **SI-5-2**: To a flame-dried 50 mL round-bottomed flask containing 4-methylaniline (1.07 g, 10 mmol) in dry dichloromethane (10 mL), was added triethylamine (1.4 mL) and acetic anhydride (1.0 mL). The solution was left to stir at room temperature overnight, after which a saturated solution of ammonium chloride was added and the mixture subsequently extracted with ethyl acetate (2 x 20 mL). When repeating the above it is not abnormal for product to crystallize out of solution. The
combined organic extracts were then washed with brine, dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the title compound. Yield 98%, reddish solid; Mp 144-145 °C {lit. $^{74}$ 150-152 °C} ; TLC (EtOAc, 100): R$_f$ = 0.24; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.81 (bs, 1H), 7.38 (d, $J$ = 8.4 Hz, 2H), 7.09 (d, $J$ = 8.2 Hz, 2H), 2.30 (s, 3H), 2.13 (s, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 168.8, 135.6, 134.0, 129.5, 120.3, 24.5, 20.9.

Synthesis of SI-5-3: To a flame-dried 50 mL round-bottomed flask containing 4-acetamidotoluene SI-5-2 (746 mg, 5 mmol) in dry THF (10 mL), was added LiHMDS (5.1 mL (1M solution in THF), 5.1 mmol) in one portion at 0 °C. The solution was left to stir at room temperature for 30 minutes over the course of which a gray precipitate formed. Methyl iodide (0.31 mL, 5.1 mmol) was subsequently added and the mixture left to stir overnight at which time the precipitate had given way to a homogeneous solution. A saturated solution of ammonium chloride was added and the mixture subsequently extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were then washed with brine, dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford SI-5-3. Yield 95%, Brown solid; Mp 78.1-79.3 °C {lit. $^{75}$ 80 °C} ; TLC (EtOAc, 100): R$_f$ = 0.27; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.19 (d, $J$ = 8.0 Hz, 2H), 7.05 (d, $J$ = 8.0 Hz, 2H), 3.22 (s, 3H), 2.36 (s, 3H), 1.84 (s, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 170.8, 142.2, 137.7, 130.4, 126.9, 37.3, 22.4, 21.1.

Synthesis of 5-7: To a flame-dried 25 mL round-bottomed flask fitted with a condenser containing 4-(N-methylacetamido)toluene SI-5-3 (326 mg, 2 mmol) in dry benzene (4
mL), was added N-bromosuccinimide (356 mg, 2 mmol) and benzoyl peroxide (99%) (48 mg, 0.2 mmol). The solution was brought to reflux and maintained for 3 h at which point the reaction was cooled to room temperature and the solvent removed under reduced pressure. The organic residue may then be used in the subsequent step or flash chromatographed over silica gel (EtOAc:Hexane 6:4 v/v) to afford the title compound. Yield 80%, White solid; TLC (EtOAc/Hexane, 6:4 v/v): Rf = 0.20; 1H-NMR [CDCl3, 600 MHz] δ: 7.44 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 4.50 (s, 2H), 3.26 (s, 3H), 1.88 (s, 3H); 13C-NMR [CDCl3, 150 MHz] δ: 170.6, 144.7, 137.5, 130.6, 127.6, 37.2, 32.5, 22.6.

Synthesis of 5-8: To a flame-dried 10 mL round-bottomed flask containing 5-7 (242 mg, 1 mmol) was added triphenylphosphine (262 mg, 1 mmol). Toluene (5 mL) was added and the mixture was heated to reflux for 8 h. The white solid which formed was vacuum filtered and washed with EtOAc (3 x 10 mL). Note an analytical quantity may be taken up in DCM and EtOAc added to recrystallize the title compound. Yield 96%, White solid. Mp 230-232 °C; TLC (CH2Cl2:MeOH, 9:1 v/v): Rf = 0.40; 1H-NMR [CDCl3, 600 MHz] δ: 7.82-7.74 (m, 9H), 7.64-7.59 (m, 6H), 7.30-7.25 (m, 2H), 6.95 (dd, J = 7.6 Hz, 2H), 5.63 (d, 2J(31P-1H) = 14.1 Hz, 2H), 2.98 (bs, 3H) 1.80 (bs, 3H); 13C-NMR [CDCl3, 150 MHz] δ: 170.2, 144.7, 135.2 (d, 4J(31P-13C) = 2.4 Hz), 134.5 (d, 2J(31P-13C) = 10.0), 133.1, 130.3 (d, 3J(31P-13C) = 12.6), 127.4, 117.8 (d, 1J(31P-13C) = 85.0), 37.2, 30.1 (d, 1J(31P-13C) = 46.6), 22.5; 31P-NMR [CDCl3, 80 MHz] δ: 24.0; HRES MS (M)+ calcd. for C28H27NOP: 424.1830, found 424.1813.
Synthesis of 5-9: To a flame-dried 10 mL round-bottomed flask containing a magnetic stir bar was weighed (4-(N-methylacetamido)benzyl)triphenylphosphonium bromide 5-8 (252 mg, 0.5 mmol), 2-formylmorpholinobenzamide 5-5 (110 mg, 0.5 mmol), and K$_2$CO$_3$ (276 mg, 2 mmol). Water (0.3 mL) was added and the reaction stirred at 70 °C for 3 h. Water (5 mL) was added and the reaction mixture extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude mixture was then column chromatographed (silica gel, EtOAc:Hexane 4:1 v/v) to afford 5-9 (x mg, 76%, 2:1 E/Z) as a white solid; the isomeric ratio which was inseparable by standard chromatography.

Synthesis of 5-9: To a flame-dried 10 mL round-bottomed flask containing a magnetic stir bar was weighed (4-(N-methylacetamido)benzyl)triphenylphosphonium bromide 5-8 (252 mg, 0.5 mmol), 2-formylmorpholinobenzamide 5-5 (110 mg, 0.5 mmol), NaHCO$_3$ (84 mg, 1 mmol), and L-proline (6 mg, 10% mol). Water (0.3 mL) was added and the reaction stirred at 37 °C overnight. Water (5 mL) was added and the reaction mixture extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude mixture was then column chromatographed (silica gel, EtOAc:Hexane 9:1 v/v) to afford 5-9 (x
mg, 87%, \( E/Z \approx 1:1 \) as white solid. Yield 87%, White solid; TLC (EtOAc, 100): \( R_f = 0.12 \); UV/Vis: \( \lambda_{\text{max}} \) 205, 207, 301 nm; Fluorescence (301 nm): \( \lambda_{\text{max}} \) 395 nm; HREI MS (M)\(^+\) calcd. for \( \text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 \): 364.1787, found 364.1795.

\[ (E) - \text{5-9} \]

\(^1\)H-NMR [CDCl\(_3\), 600 MHz] \( \delta \): 7.69 (d, \( J = 8.0 \) Hz, 1H), 7.51 (d, \( J = 8.0 \) Hz, 2H), 7.42 (t, \( J = 7.4 \) Hz, 1H), 7.33 (t, \( J = 7.4 \) Hz, 1H), 7.30-7.27 (m, 1H) 7.18 (d, \( J = 8.2 \) Hz, 2H), 7.15 (d, \( J = 15.0 \) Hz, 1H), 7.08 (d, \( J = 15.0 \) Hz, 1H), 3.94-3.83 (m, 2H), 3.82-3.71 (m, 2H), 3.58-3.46 (m, 2H), 3.28-3.22 (m, 5H), 1.92 (s, 3H, NC=OCH\(_3\)); \(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] \( \delta \):170.62, 169.74, 144.3, 136.4, 135.0, 134.0, 130.3, 129.6, 128.3, 128.0, 127.6, 126.9, 126.2, 125.9, 67.2, 67.1, 47.6, 42.3, 37.3, 22.6.

\[ (Z) - \text{5-9} \]

\(^1\)H-NMR [CDCl\(_3\), 600 MHz] \( \delta \): 7.30 (t, \( J = 7.8 \) Hz, 1H), 7.30-7.27 (m, 2H), 7.24-7.20 (m, 3H), 7.01 (d, \( J = 8.0 \) Hz, 2H), 6.67 (d, \( J = 12.3 \) Hz, 1H), 6.64 (d, \( J = 12.3 \) Hz, 1H), 3.82-3.71 (m, 4H), 3.58-3.46 (m, 2H), 3.23-3.18 (m, 5H), 1.86 (s, 3H, NC=OCH\(_3\)); \(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] \( \delta \):170.6, 169.5, 143.8, 136.0, 135.8, 134.5, 130.9, 130.3, 129.7, 129.0, 128.3, 128.0, 127.0, 126.8, 67.0, 67.0, 47.6, 42.2, 37.2, 22.5.

\[ \begin{array}{c}
\text{H}_2\text{N} \quad \text{OH} \\
\begin{array}{c}
\text{Ac}_2\text{O}, \text{TEA} \\
\text{CH}_3\text{Cl}_2, \text{r.t.} \quad 95\% \\
\end{array}
\end{array} \]

\[ \begin{array}{c}
\text{SI-5-4} \\
\begin{array}{c}
\text{O} \quad \text{N} \\
\text{OAc} \\
\end{array}
\end{array} \]

Synthesis of SI-5-4: To a flame-dried 50 mL round-bottomed flask containing 4-aminobenzyl alcohol (246 mg, 2 mmol) in dry dichloromethane (10 mL), was added triethylamine (1 mL) and acetic anhydride (1 mL). The solution was left to stir at room temperature overnight, at which point a saturated solution of ammonium chloride was added and the mixture subsequently extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were then washed with brine, dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to afford the title compound. Yield 95%, reddish solid; Mp 95.3-97.9 °C; TLC (EtOAc, 100): \( R_f = 0.48 \); \(^1\)H-NMR [CDCl\(_3\), 600 MHz] \( \delta \): 7.43 (d, \( J = 8.4 \) Hz, 2H), 7.25 (d, \( J = 8.4 \) Hz, 2H), 7.13 (s, 1H), 4.99 (s, 2H), 2.11 (s, 3H), 2.02 (s, 3H);
$^{13}\text{C-NMR} \quad [\text{CDCl}_3, \quad 150 \text{ MHz}] \quad \delta: \quad 170.90, \quad 168.22, \quad 137.89, \quad 131.83, \quad 129.26, \quad 119.80, \quad 65.90, \quad 24.66, \quad 21.04; \quad \text{HREI MS} \quad (\text{M}^+) \quad \text{calcd. for C}_{11}\text{H}_{13}\text{NO}_3: \quad 207.0895, \quad \text{found} \quad 207.0911.$

Synthesis of **SI-5-5**: To a flame-dried 25 mL round-bottomed flask containing **SI-5-4** (221 mg, 1 mmol) in dry THF (4 mL), was added NaH (60% dispersion in mineral oil) (42 mg, 1.05 mmol) in one portion at 0 °C. The solution was left to stir at room temperature until hydrogen evolution ceased, at which point methyl iodide (0.06 mL, 1 mmol) was added and the mixture left to stir for 30 min. A saturated solution of ammonium chloride was added and the mixture subsequently extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were then washed with brine, dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the title compound. Yield 80%, Colourless Oil; TLC (EtOAc, 100): $R_f = 0.50$; $^1\text{H-NMR} \quad [\text{CDCl}_3, \quad 600 \text{ MHz}] \quad \delta: \quad 7.34 \quad (d, \quad J = 8.1 \text{ Hz}, \quad 2\text{H}), \quad 7.12 \quad (d, \quad J = 8.1 \text{ Hz}, \quad 2\text{H}), \quad 5.06 \quad (s, \quad 2\text{H}), \quad 3.19 \quad (s, \quad 3\text{H}), \quad 2.06 \quad (s, \quad 3\text{H}), \quad 1.81 \quad (s, \quad 3\text{H}); \quad ^{13}\text{C-NMR} \quad [\text{CDCl}_3, \quad 150 \text{ MHz}] \quad \delta: \quad 169.8, \quad 169.5, \quad 143.4, \quad 134.6, \quad 128.5, \quad 126.2, \quad 64.5, \quad 36.1, \quad 21.4, \quad 20.0; \quad \text{HREI MS} \quad (\text{M})^+ \quad \text{calcd. for C}_{12}\text{H}_{15}\text{NO}_3: \quad 221.1052, \quad \text{found} \quad 221.1049.$

Synthesis of **SI-5-6**: To a flame-dried 25 mL round-bottomed flask containing 4-(N-methylacetamido)benzyl acetate **SI-5-5** (221 mg, 1 mmol) in wet MeOH (10 mL), was added K$_2$CO$_3$ (415 mg, 3 mmol) in one portion and the mixture left to stir at r.t. overnight. A saturated solution of ammonium chloride was added and the mixture subsequently extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were then washed with brine, dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the title compound. Yield 81%, White solid; Mp 84.8-85.3 °C; TLC (EtOAc, 100): $R_f = 0.21$; $^1\text{H-NMR} \quad [\text{CDCl}_3, \quad 600 \text{ MHz}] \quad \delta: \quad 7.42 \quad (d, \quad J = 8.0 \text{ Hz}, \quad 2\text{H}), \quad 7.19 \quad (d, \quad J = 8.0 \text{ Hz},
2H), 4.74 (s, 2H), 3.26 (s, 3H), 1.87 (s, 3H), 1.74 (bs, 1H); ¹³C-NMR [CDCl₃, 150 MHz] δ: 170.7, 144.1, 140.6, 128.3, 127.3, 64.8, 37.3, 22.6; HRES MS (M)⁺ calcd. for C₁₀H₁₃NO₂: 179.0946, found 179.0943.

Synthesis of 5-8: To a flame-dried 10 mL round-bottomed flask containing SI-5-6 (221 mg, 1 mmol) was added triphenylphosphine hydrobromide (343 mg, 1 mmol). The neat mixture was heated to 100 °C for 8 h. The yellow solid which formed was taken up in DCM/MeOH (9:1) and ethyl acetate added to recrystallize the title compound. Yield 81%, White solid. Mp 295-298 °C (decomp.); TLC (CH₂Cl₂:MeOH, 9:1 v/v): Rₚ = 0.35; ¹H-NMR [CDCl₃, 600 MHz] δ: 10.37 (s, 1H), 7.79 (td, J = 7.2, 1.4 Hz, 3H), 7.70 (d, J = 8.2 Hz, 2H), 7.66 – 7.61 (m, 8H), 7.60 (t, J = 5.3 Hz, 3H), 6.62 (dd, J = 8.6, 2.4 Hz, 2H), 4.91 (d, ²J(³¹P-¹H) = 13.7 Hz, 2H), 2.32 (s, 3H); ¹³C-NMR [CDCl₃, 150 MHz] δ: 171.7, 140.5 (d, ⁴J(³¹P-¹³C) = 3.0 Hz), 136.5, 135.4 (d, ²J(³¹P-¹³C) = 10.0 Hz), 132.6 (d, ²J(³¹P-¹³C) = 4.8 Hz), 131.3 (d, ³J(³¹P-¹³C) = 13.4 Hz), 123.6 (d, ³J(³¹P-¹³C) = 8.5 Hz), 121.2, 119.2 (d, ¹J(³¹P-¹³C) = 86.0 Hz), 30.3 (d, ¹J(³¹P-¹³C) = 47.4 Hz), 23.9; ³¹P-NMR [CDCl₃, 240 MHz] δ: 21.9; HRES MS (M)⁺ calcd. for C₂₇H₂₅NOP: 410.1674, found 410.1692.

Synthesis of SI-5-8: POCl₃ (4.47 mL) was added dropwise to DMF (8.5 mL) with stirring under absolutely dry conditions, and the temperature was kept below 10 °C. After
adding a mixture of triphenylamine (5.97 g, 24.34 mmol) and DMF (2 mL) to the reaction vessel at this temperature, the reaction mixture was maintained at 35 °C for 24 h. Subsequently, the reaction solution was poured into ice water and the precipitated mixture was filtered and washed with water. The crude product was purified by column chromatography (silica gel, dichloromethane) to afford SI-5-8. Yield 88%, yellow solid; Mp 129-130 °C{lit. 77 130-132 °C}; TLC (EtOAc:Hexanes, 3:7 v/v): R_f = 0.65; ^1H-NMR [CDCl_3, 200 MHz] δ: 9.81 (1H, s, CHO), 7.68 (2H, d, J = 8.6 Hz), 7.34 (4H, m), 7.16 (6H, m), 7.02 (2H, d, J = 8.6 Hz); ^13C-NMR [CDCl_3, 50 MHz] δ: 190.5, 153.4, 146.2, 131.4, 129.2, 126.4, 125.2, 119.4

Synthesis of SI-5-9: To a solution of NaBH_4 (25 mg, 0.67 mmol) in 30 ml dry dichloromethane and 10 ml anhydrous ethanol, SI-5-8 (183 mg, 0.67 mmol) was added rapidly and the bath was stirred at room temperature for 2 h. The solution was poured into 50 ml water with vigorously stirring and extracted with dichloromethane (15 ml x 3). The organic layer was dried with anhydrous sodium sulfate and then rotary evaporated to remove the solvent, gave SI-5-9. Yield 95%, white solid; Mp 98-99 °C{lit. 78 101-102 °C}; TLC (EtOAc:Hexanes, 3:7 v/v): R_f = 0.34; ^1H-NMR [CDCl_3, 600 MHz] δ: 7.26-7.22 (6H, m), 7.10-7.05 (6H, m), 7.00 (2H, t, J = 7.2 Hz), 4.64 (2H, s); ^13C-NMR [CDCl_3, 150 MHz] δ: 147.8, 147.5, 131.0, 129.3, 128.3, 124.3, 124.1, 122.9, 68.3.
Synthesis of 5-11: To a flame-dried 10 mL round-bottomed flask containing 4-((N,N-diphenylamino)benzyl alcohol SI-5-9 (275 mg, 1 mmol) was added triphenylphosphine hydrobromide (343 mg, 1 mmol). Acetonitrile (7 mL) was added and the mixture was heated to reflux for 3 h. The yellow solid which formed was vacuum filtered and washed with EtOAc (3 x 10 mL). Note an analytical quantity may be taken up in DCM and EtOAc added to recrystallize the title compound. Yield 98%, yellow solid; Mp 246-248 °C\textsuperscript{lit. 79 249 °C}; TLC (CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 9:1 v/v): R\textsubscript{f} = 0.62; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] δ: 7.80-7.73 (m, 9H), 7.63 (td, J = 7.8, 3.2 Hz, 6H), 7.22 (t, J = 7.8 Hz, 4H), 7.03-6.98 (m, 6H), 6.92 (dd, J = 9.0, 2.6 Hz, 2H), 6.79 (d, J = 8.1 Hz, 2H), 5.35 (d, J\textsubscript{31P-1H} = 13.7 Hz, 2H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] δ: 148.2 (d, J\textsubscript{31P-13C} = 3.3 Hz), 147.3, 135.1, 134.5 (d, J\textsubscript{31P-13C} = 9.4 Hz), 132.3 (d, J\textsubscript{31P-13C} = 5.4 Hz), 130.3 (d, J\textsubscript{31P-13C} = 12.8 Hz), 129.4, 124.7, 123.5, 123.2 (d, J\textsubscript{31P-13C} = 1.8 Hz), 120.0 (d, J\textsubscript{31P-13C} = 9.7 Hz), 118.2 (d, J\textsubscript{31P-13C} = 86.1 Hz), 30.6 (d, J\textsubscript{31P-13C} = 47.1 Hz); \textsuperscript{31}P-NMR [CDCl\textsubscript{3}, 240 MHz] δ: 22.5; HRES MS (M\textsuperscript{+}) calcd. for C\textsubscript{37}H\textsubscript{31}NP: 520.2194, found 520.2207.

![Chemical structure](image)

Synthesis of 5-12: To a flame-dried 10 mL round-bottomed flask containing a magnetic stir bar was weighed (4-((N,N-diphenylamine)benzyl)triphenylphosphonium bromide 5-11 (252 mg, 0.5 mmol), 4-formylbenzonitrile (110 mg, 0.5 mmol), NaHCO\textsubscript{3} (84 mg, 1 mmol), and L-proline (6 mg, 10% mol). Water (0.3 mL) was added and the reaction stirred at 37 °C overnight. Water (5 mL) was added and the reaction mixture extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude mixture was then column chromatographed over silica gel (EtOAc:Hexane 9:1 v/v) to afford resolved isomers (E)/(Z) 10:1. Yield 90%, bright yellow solid; Mp 142-144 °C\textsuperscript{lit. 80 151-152 °C};
TLC (EtOAc:Hexanes, 3:7 v/v): R_f = 0.70; UV/Vis: \( \lambda_{\text{max}} \) 203, 297, 384 nm; Fluorescence (384 nm): \( \lambda_{\text{max}} \) 528 nm; \(^1\)H-NMR [CDCl\(_3\), 600 MHz] \( \delta \): 7.61 (d, \( J = 8.4 \) Hz, 2H), 7.54 (d, \( J = 8.3 \) Hz, 2H), 7.39 (d, \( J = 8.7 \) Hz, 2H), 7.28 (t, \( J = 7.9 \) Hz, 4H), 7.14 (d, \( J = 16.3 \) Hz, 1H), 7.12 (d, \( J = 7.9 \) Hz, 4H), 7.08-7.03 (m, 4H), 6.95 (d, \( J = 16.3 \) Hz, 1H) \(^1\)C-NMR [CDCl\(_3\), 150 MHz] \( \delta \): 148.5, 147.4, 142.4, 132.6, 132.1, 130.1, 129.5, 128.0, 126.7, 125.0, 124.8, 123.6, 123.0, 119.3, 110.1; HREI MS (M)^+ calcd. for C\(_{27}\)H\(_{20}\)N\(_2\): 372.1626, found 372.1616.

5.6 Notes and References

Popular excitation sources are the argon ion laser that emits at 488 nm and 514 nm and the argon/krypton mixed gas laser that gives three useful spectral lines for excitation at 488 nm, 568 nm, and 647 nm.

No reaction occurs on attempted aqueous Wittig olefination (using either mild base or organocatalysis) under these conditions with salts such as 9a and aldoses such as D-glucose, indicating orthogonal reactivity to these common aldehydes.

Autofluorescence from naturally occurring fluorescent biomolecules limits in vivo fluorescence imaging below ~700 nm because of overlap between the fluorescent probe and the background emission spectra. Examples of autofluorescent molecules are NAD(P)H (ex. 340 nm, em. 450 nm), chlorophyll (ex. 465, 665 nm, em. 673, 726 nm), folic acid (em. 450), pyridoxine (em. 400 nm), tyrosine (em. 305). See: (a) Georgakoudi, I.; Jacobsen, B. C.; Müller, M. G.; Sheets, E. E.; Badizadegan, K.; Carr-Locke, D. L.;

Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
To begin, the phosphonium salt was placed opposite the acceptor so that the pK$_\text{a}$ of the benzylic protons might be lowered by consequence. This would allow the use of a tripropylphosphonium salt whose benefit is two-fold. A short-chain trialkylphosphine increases the solubility of the glyceride reagent in aqueous media helping uptake and, once in vivo, increases the likelihood the polar headgroup will be directed toward the extracellular matrix.

We attempted to use 4-carboxysulphonyl chloride derivatives, 4-carboxybenzenesulphonamide and related compounds to avoid late-stage oxidation of the toluyl-methyl but these introduced new problems. Many of these compounds were much more difficult to purify, led to lower yields, or were unstable to various reaction conditions which had previously been developed.
Chapter 6

Development of an efficient route to (E)-α,β-unsaturated aldehydes through two-carbon homologation of aldehydes and ketones

6.1. Background

6.1.1 Introduction

Alkenals (colloquially known as enals) are strategic intermediates in organic synthesis. Their importance is growing each year due to the expanding breadth of iminium\(^1\) and vinylogous enamine organocatalysis.\(^2\) The ability to rapidly increase molecular complexity using organocatalysis with the high degree of stereochemical control it affords has allowed for exceptional efficiency and a wealth of new reactions; iminium or vinylogous enamine promoted Diels-Alder reactions, specifically, have allowed for the stereoselective construction of bicyclic and/or fused ring systems. Though organocatalysis has led enals to prominence, they’ve always been a versatile reaction motif. Enals are ubiquitous as intermediates in the pharmaceutical and fine chemical industries. Classical aldol, Michael and Diels-Alder reactions (both catalyzed and absent a catalyst), Gilman reactions, etc. illustrate the abundance of chemistry surrounding α,β–unsaturated aldehydes.

6.1.2 Synthetic Studies Relating to the Preparation of α,β–Unsaturated Aldehydes from Aldehydes

One and two-carbon carbonyl homologation reactions are often employed as strategic transformations in organic synthesis. Many methods exist for the one carbon homologation of aldehydes to extended aldehydes or to the corresponding carboxylic acid derivative.\(^3\) The conversion of an aldehyde to the corresponding two-carbon homologated unsaturated aldehyde is a very desirable transformation often employed in fine chemical and pharmaceutical syntheses.\(^4,5\) However, the preparation of enals remains problematic requiring labour and reagent intensive multi-step sequences. They typically involve homologation to the unsaturated ester through a Horner–Wadsworth–Emmons (HWE) or related Wittig process, followed by DIBAL-H mediated reduction to the allylic alcohol and oxidation leading to the homologated alkenal. Mild oxidations suitable for such a process include: high-valent chromium reagents (PCC,\(^6\) PDC\(^7\) and the Collins\(^8\) reagent), dimethyl sulfoxide-promoted oxidations (Pfitzner-Moffatt,\(^9\) Swern,\(^10\) Parikh-Doering\(^11\) protocols), Hypervalent iodine reagents (IBX,\(^12\) DMP\(^13\)), Corey-Kim\(^14\) oxidation, Oppenhauer\(^15\) oxidation, Annelis\(^16\) oxidation (TEMPO), and reagents such as ammonium
perruthenate,\textsuperscript{17} and manganese dioxide.\textsuperscript{18} Alternatively, a one-pot reagent was developed by Wender \textit{et al.} in the synthesis of the Bryostatin anticancer agents\textsuperscript{19a} though it has found limited use.\textsuperscript{19}

Several methods have been developed to achieve this transformation in one or two steps using functionalised two-carbon phosphonium salts or phosphonate derivatives (Figure 6-1, 6-0, 6-1 & 6-2/6-3).\textsuperscript{20} Phosphorane 6-0, initially prepared by Trippett and Walker,\textsuperscript{21} displays good stereoselectivity on olefination but suffers from poor reactivity and myriad side reactions.\textsuperscript{22} Salts of type 6-2/6-3 derived from triphenylphosphine are most common but suffer from poor (\(E\)):\(Z\)) selectivity and removal of a stoichiometric amount of triphenylphosphine oxide is required. In addition, they exhibit low reactivity to some aldehydes and are non-reactive to enals.\textsuperscript{20l} By employing short-chain trialkylphosphines, the stereoselectivity increases, as does their reactivity and yields. Unsurprisingly, partial acetal hydrolysis is problematic, yet not infrequent\textsuperscript{20m} and may occur under surprisingly mild conditions.\textsuperscript{20m} Steric bulk is pivotal to retard hydrolysis of the resulting vinyl acetal as observed when comparing hydrolysis of 2-vinyl-1,3-dioxane/1,3-dioxolane acetals with the related 5,5-dimethyl-2-vinyl-1,3-dioxane.\textsuperscript{20m} We envisioned applying our experience in aqueous olefinations employing trialkylphosphoranylides of semi-stabilised ylids towards a ‘one-pot’ homologation protocol.

![Figure 6-1. A selection of acetaldehyde-derived phosphonium salts](image)

### 6.2. Aqueous Homologations

The use of water as solvent in the synthesis of fine chemicals and pharmaceuticals is highly desirable for environmental and economic reasons and has been discussed in numerous review articles.\textsuperscript{23} Our research group has been involved in the development of Wittig-type olefination reactions in aqueous media for several years, and we have highlighted the additional advantages gained employing ylides derived from short-chain trialkylphosphines.\textsuperscript{24} Ylids can be generated from these salts under mild conditions, and these react with a wide range of carbonyl compounds to deliver olefins with high (\(E\))-stereoselectivity. Additionally, short chain trialkylphosphine oxides are fully water soluble
and can easily be removed using a simple extraction protocol. In contrast, triarylphosphine oxides are notoriously difficult to remove.

6.2.1. Development of a suitable phosphonium salt

The aldehyde-to-alkenal homologation has been described using reagents such as 6-1 and 6-2/6-3 (Figure 6-1) several times in the literature. Our initial work generating and trapping ylides derived from salt 6-4 with aldehydes in water proved to be capricious, resulting in the formation of side products, which we attributed to the instability of the acetal under the reaction conditions. Bearing in mind the stability of cyclic acetals, and inspired by some of the recent chemistry documented for stable functionalised pinacolboranes, we considered a functionalised phosphonium salt of structural type 6-5 as a potentially ideal trialkylphosphonium salt that would be chemically robust and convey the advantages described above ((E)-stereoselectivity, allow generation and trapping of ylide in water and provide ease of purification). To this end, the tripropylphosphine derived pinacolacetal phosphonium salt 6-5 was synthesized from readily available 2-bromoethylacetaldehyde diethylacetal 6-6 and acetone-pinacol 6-7 (Scheme 6-1). The intermediate bromoacetal 6-8 was purified by distillation in high yield and reacted with tripropylphosphine to give the novel phosphonium salt 6-5, a colourless hygroscopic solid in 91% overall yield.

![Scheme 6-1. Preparation of phosphonium salt 6-5](image)

6.2.2 Development of Suitable Conditions for the Wittig Reaction

We next investigated the possibility of chemoselective olefination reaction of salt 6-5 under aqueous Wittig conditions using 4-chlorobenzaldehyde 6-9a as the initial substrate. It was determined that 6-9a reacted over 24h with aqueous solutions of 6-5 containing sodium hydroxide to produce the homologated acetal 6-10a in 87% yield. Prior to considering a one-flask process (vide infra), the acetals were partitioned into ethyl acetate from the aqueous phase at this stage, a process that also allows clean separation of water-soluble tripropylphosphine oxide, and isolated by filtration through a short silica-gel plug. The reaction proved to be quite general for aromatic aldehydes 6-10a to 6-10g (Table 6-1, entries 1-7) and the corresponding acetals were readily available in isolated yields of around 90%. The reaction was also successful with unsaturated aldehydes leading to the protected dienals 6-10h and 6-10i in moderate yield (Table 6-1, entries 8
and 9). This process is reportedly challenging, but has been achieved under non-aqueous conditions. Similarly, the new reagent allowed access to useful pyrene and pyridine analogs (Table 6-1, entries 10-12). The enolizable aliphatic aldehyde 3-phenylpropanal was also investigated, a challenging case given the possibility for aldol or Cannizarro side reactions that may be anticipated in aqueous basic conditions. The protected acetal 6-10m was isolated in a reasonable 48% yield.

### Table 6-1. Two-carbon homologation of aldehyds to acetals and hydrolysis to enals under aqueous Wittig conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Time (h)</th>
<th>Yield 6</th>
<th>Yield 7</th>
<th>(E):(Z)</th>
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<tr>
<td>1</td>
<td>6-9a</td>
<td>24</td>
<td>87</td>
<td>95&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>2</td>
<td>6-9b</td>
<td>24</td>
<td>91</td>
<td>93&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>6-9c</td>
<td>24</td>
<td>89</td>
<td>94&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>6-9d</td>
<td>24</td>
<td>90</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>96</td>
<td>95&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>72</td>
<td>90</td>
<td>88&lt;sup&gt;b&lt;/sup&gt;</td>
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#### Table 6-1 (continued)

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<th>Entry</th>
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<th>Yield 7</th>
<th>(E):(Z)</th>
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<td>76&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>83</td>
<td>nd</td>
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<tr>
<td>13</td>
<td>6-9m</td>
<td>48</td>
<td>48</td>
<td>82&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95:5</td>
</tr>
</tbody>
</table>

<sup>a</sup> 25% H<sub>3</sub>PO<sub>4</sub>, H<sub>2</sub>O, 65 °C

<sup>b</sup> IR120-H resin, H<sub>2</sub>O, 65 °C

6.2.3 Development of Suitable Conditions for Acetal Deprotection

We now turned our attention to the hydrolysis of the stable acetals 6-9a–m to allow access to the free α,β-unsaturated aldehydes 6-11a to m. Given the sensitivity of
the enal products, two methods were developed to allow for this acetal hydrolysis under mild conditions. The use of dilute phosphoric acid (25\% w/w) was initially found to be satisfactory (Table 1, method a) and allowed slow hydrolysis of the acetals. This hydrolysis was generally complete in 12h at 65 °C from which process the isolation of the product enals 6-11a to 6-11f was achieved in high yield (Table 6-1, entries 1-6). The use of solid-supported acid catalysts can provide additional flow and/or process-chemistry advantages and we were delighted to find that use of Amberlite-IR120 resin in its hydrogen form also allowed for the slow, chemoselective hydrolysis of the pinacolacetals to the corresponding α,β–unsaturated aldehydes in high isolated yields (Table 6-1, entries 7-10, 13). The unsaturated aldehydes were isolated by extraction into ethyl acetate and purification over a short silica gel column in each case. As we have noted previously concerning the use of ylides derived from trialkylphosphines,\textsuperscript{24} the unsaturated aldehydes are produced predominantly as the (E)-steroisomer with high selectivity.

![Scheme 6-2. One-flask operation for the aldehyde to (E)-α,β–unsaturated aldehydes two-carbon homologation using reagent 6-5](image)

We now investigated the development of a one-flask, two stage operation for the overall aldehyde to enal homologation without isolation of the intermediate pinacolactal, as shown in Scheme 6-2. The initial olefination reaction was conducted as before using 4-bromobenzaldehyde 6-9b as test subject. Upon completion, dichloromethane was added to the flask and the aqueous phase (containing salts and tripropylphosphine oxide) was removed from the flask. The dichloromethane solution of the pinacolactal was then directly treated with 25\% phosphoric acid solution and the hydrolysis reaction allowed to proceed. Isolation and purification as before now delivered the product enal in 93\% overall yield, compared with 84\% in the original two-flask process. Similarly, 4-methylbenzaldehyde 6-9c and piperonal 6-9e were converted to the cinnamaldehyde derivatives 6-11c and 6-11e also with greater efficiency employing the one-flask process. The conversion of piperonal to methylenedioxy-cinnamaldehyde 6-11e serves as an important example of the value of this one-flask aldehyde to enal conversion using the new salt 6-5. This aldehyde is a high value synthetic intermediate and demonstrates the value of this new homologation process in converting commodity aldehydes to high value intermediates through a mild process under aqueous conditions. In addition to their uses
in perfumery and as flavouring agents, functionalised cinnamaldehydes such as 6-11 serve as valuable building block in organic synthesis and as substrates for organocatalytic transformations.  

6.3 Aliphatic anhydrous Homologations

Though desirable, aqueous reaction media are not always amenable to complex molecular transformations. Advanced intermediates in total synthesis, typically adorned with myriad protecting groups and reactive sites, in particular, seem ill suited to the alkaline reaction conditions previously developed (vide supra). The multi-step approach to complex enal 6-14 from primary alcohol 6-12 by Paterson and coworkers in their total synthesis of (+)-discodermolide is a case in point. The marked decrease in yield observed for simple enolizable and α,β-unsaturated aldehydes and the poor reactivity of ketones (see Table 6-1) led us to develop a more classical method. This protocol was then adapted for the stereoselective preparation of alkenals from complex chiral aldehydes.

![Scheme 6-3. Total synthesis of (+)-discodermolide](image)

6.3.1. Optimisation of the pinacol salt DualPhos

We concurrently studied the large scale preparation and optimisation of the DualPhos salt (Scheme 6-4) and the subsequent Wittig reaction. A modified Whiting procedure was used to obtain the first batch of salt; high temperatures were required for phosphonium salt formation due to steric repulsion (Scheme 6-4, top). Whereas phosphonium salt formation with bromide 6-8 was sluggish, diethyl acetal salt 6-4 was easily prepared. Trans-acetalisation was then attempted using acetone-pinacol 6-7 with a catalytic amount of PTSA. All components were placed in a sealed tube under inert atmosphere and heated to produce a melt. While $^{31}$P-NMR indicated complete conversion to phosphonium salt 6-5 the reaction mixture had noticeably yellowed and would not crystallize even after multiple attempts. Activated charcoal failed to remove the coloured impurities and led to slight decomposition of the salt. We surveyed a variety of protic
acids, temperatures, solvents, etc. to no avail. The amount of excess pinacol seemed to play a large role in reaction rate, with around 1.5 equivalents being the best compromise between excess pinacol used and reaction times. Using straight toluene as the solvent had the same results as solvent mixtures.

![Scheme 6-4. Formation of pinacol-acetal phosphonium salt (DualPhos)](image)

By replacing both the solvent and acid catalyst with acetic acid, the reaction proceeded to completion in as little as 3 hours at 85 °C or higher, however at these temperatures a very polar, coloured impurity (cannot be removed by activated charcoal) also forms which in every instance appeared to prevent crystallisation. At 80 °C, no reaction or colouration occurred.

A one pot reaction was successful via two sets of conditions. There is a strict need for the presence of NaI, as the experiment without it displayed several phosphorus-containing impurities. These reactions also suffer from colouration and cannot be recrystallised. Flash column chromatography easily removes the impurities but is not suitable for a large scale preparation and yields suffered.

The side-reactions observed upon acetal transposition, though minimal, required re-evaluation of the original protocol. Preparation of bromide 6-8 is performed neat with a catalytic amount pTSA and is near quantitative following vacuum distillation (75 °C, 0.1 mbar). Quaternisation of the phosphine initially required temperatures in excess of 130 °C and led to slight colouration of the reaction. Purification by filtration was therefore required. The addition of (<0.1% mol) NaI allows the temperature to be lowered to ≤120 °C and the reaction time shortened slightly with no visible colouration. Importantly, the resulting viscous oil crystallises upon cooling to room temperature. The entire process is solvent free, produces ethanol as the sole by-product, and has been performed on scales as high as 60 grams.
To compare steric effects during the Wittig reaction and the stability of the resulting acyclic and cyclic acetals, we also prepared 1,3-dioxolane salt 6-16 on a large scale, in addition to pinacol salt 6-5 and diethyl salt 6-4 vide infra.

![Figure 6-2. Tripropylphosphine derived cyclic acetal salts](image)

6.3.2 Development of the Wittig protocol

The successful aqueous olefination of a diverse range of simple aldehydes employing salt 6-5 led us to consider developing a procedure for the olefination of complex high-value aldehydes under anhydrous reaction conditions which would complement the previous protocol. We began in a similar fashion, by attempting the olefination of 4-chlorobenzaldehyde. Analogous reports in the literature employing the triphenylphosphine variant of salt 6-16 consistently used NaH or KOTBu in THF\(^7\) as solvent. Optimization of the base, solvent, temperature and concentration with three distinct classes of aldehydes (aromatic, \(\alpha,\beta\)-unsaturated, enolizable aliphatic) led to the general olefination conditions below (Scheme 6-3). A small amount of DMF is required to solubilise the phosphonium salt affording a homogeneous solution. Potassium tert-butoxide or washed sodium hydride (NaH) produce the cleanest reactions and the highest yields of the homologated acetal. During deprotonation the reaction must not be allowed to warm above 30 °C or significant decomposition is observed.

![Scheme 3. General olefination procedure under anhydrous conditions](image)

The scope and selectivity of the olefination employing salts 6-4, 6-5 and 6-16 was investigated using simple representative aldehydes, the results of which are shown in Table 2. The corresponding diethyl acetals were not cleanly isolable and yields of the free enals suffered due to numerous side reactions. Both the 1,3-dioxolane and pinacol acetals derived from 6-5 & 6-16 were isolable, the latter being a much more labile protecting group. High \(E\)-selectivity was maintained upon switching the reaction medium from
water to organic solvents; this high \((E)\)-selectivity has previously been observed employing short-chain trialkylphosphine derived semi-stabilized ylids in organic media.\(^{28}\) The phosphine oxide byproduct was completely water soluble allowing for simple purification.

**Table 6-2.** Two-carbon homologation of aldehyds to acetals and hydrolysis to enals under anhydrous Wittig conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Intermediate(^a)</th>
<th>Hydrolysis Condition(^b)</th>
<th>Yield(^c)</th>
<th>Entry</th>
<th>Intermediate(^a)</th>
<th>Hydrolysis Condition(^b)</th>
<th>Yield(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-9a</td>
<td>6-17a</td>
<td>A</td>
<td>6-11a (93%)</td>
<td>6-11a</td>
<td>A</td>
<td>6-11m (51%)</td>
<td></td>
</tr>
<tr>
<td>6-9n</td>
<td>6-17n</td>
<td>A</td>
<td>6-11n (90%)</td>
<td>6-17r</td>
<td>A</td>
<td>6-11r (34%)</td>
<td></td>
</tr>
<tr>
<td>6-9o</td>
<td>6-17o</td>
<td>A</td>
<td>6-11o (89%)</td>
<td>6-17s</td>
<td>A</td>
<td>6-11s (52%)</td>
<td></td>
</tr>
<tr>
<td>6-9p</td>
<td>6-17p</td>
<td>A</td>
<td>6-11p (71%)</td>
<td>6-17t</td>
<td>A</td>
<td>6-11t (71%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-18q</td>
<td>A</td>
<td>6-11q (56%)</td>
<td>6-17u</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-18p</td>
<td>A</td>
<td>6-11q (84%)</td>
<td>6-18u</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-10q</td>
<td>B</td>
<td>6-11q (82%)</td>
<td>6-18v</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-10q</td>
<td>B</td>
<td>6-11q (80%)</td>
<td>6-10t</td>
<td>B</td>
<td>6-11t (84%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-10q</td>
<td>B</td>
<td>6-11q (80%)</td>
<td>6-10u</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

a. Diethyl acetals of this type are unstable and were characterized after hydrolysis
b. A. IR120H resin, acetone, r.t.; B. IR120H resin, H\(_2\)O, 65 °C
c. Isolated yields

Aliphatic and aromatic ketones such as cyclohexanone and acetophenone (Table 6-2, entries 6-9p,q) proceed smoothly. Citral (Table 6-2, entry 6-9r) underwent smooth olefination to give a mixture of four isomers; the starting aldehyde is a 95:5 mixture of geranial and neral. Simple aliphatic aldehydes with enolisable protons are also tolerated (Table 6-2, entry 6-9s,t). The reaction functions equally well employing either salt under the conditions outlined above with a notable exception, ketones. The yields of the corresponding acetal, while still good, are noticeably lower when comparing the reactions of salts 6-5 and 6-16 with both cyclohexanone and acetophenone. It seems sensible to assume this is likely the result of increased steric hindrance during reaction with salt 6-5.
6.3.3 Chiral Aldehydes

We wanted to further test the scope and selectivity of the anhydrous homologation protocol using representative functionalised aldehydes. It was important that all three aldehydes contained common protecting groups, were enolisable and, ideally, contained chiral centres. Thus we prepared three functionalised chiral aldehydes (Scheme 6-5). All three aldehydes were prepared according to literature procedure, and good yield. Aldehyde 6-20 is known to be unstable and was therefore used immediately without purification, save for aqueous/organic partition. Further, Garner’s aldehyde 6-23, prepared via DIBAL reduction of the corresponding methyl ester, was also used immediately as it has been reported that DIBAL can epimerise α-aminoaldehydes upon storage. With aldehydes 6-20, 6-21 6-23 & 6-25 in hand we worked on optimising the anhydrous Wittig protocol.

Gratifyingly, olefination of 6-20 with salt 6-5 under the previously developed conditions afforded unsaturated product 6-25, albeit in a paltry 32% yield. Initial experimentation revealed that NaH and KO\textsuperscript{t}Bu were both suitable bases. It is imperative that the temperature of the reaction remain below ~10 °C when adding the base, otherwise decomposition of the salt seems to occur during this process. The addition of a small amount of DMF helped to solubilise the phosphonium salt which improved the efficiency of deprotonation prior to addition of the aldehyde. The largest improvement in yield was observed when an excess of phosphonium salt/base were used. The use of 1.3 equivalents of salt/base provided reasonable yields (50-70%) whereas increasing the amount to 1.6 equivalents of salt/base typically provided the best results (60-85%). No additional benefit was observed by further increasing the proportion of salt/base.
Table 6-3. Homologation of chiral aldehydes using salt 6-5

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCHO</th>
<th>Latent Alkenal</th>
<th>Base</th>
<th>Eq. 7 Yield (%)</th>
<th>(E)/(Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-9a</td>
<td>6-10a</td>
<td>NaH</td>
<td>88</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>2</td>
<td>6-9m</td>
<td>6-10m</td>
<td>NaH</td>
<td>79</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>6-9r</td>
<td>6-10r</td>
<td>KOtBu</td>
<td>80</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>6-21</td>
<td>6-27</td>
<td>KOtBu</td>
<td>84</td>
<td>5:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>KOtBu</td>
<td>82</td>
<td>5:1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>KOtBu</td>
<td>86</td>
<td>5:1</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>KOtBu</td>
<td>80</td>
<td>5:1</td>
</tr>
</tbody>
</table>

6.3.4 Acetal hydrolysis

6.3.4.1 Simple aldehydes

The conditions required for hydrolysis of the acetals were dependent on the type of acetal as stability varied substantially. In addition to the erstwhile methods, two new methods were developed which allow for acetal hydrolysis under mild conditions, given the sensitivity of the enal products. Diethyl acetals 6-17a,m-u are quite sensitive and readily undergo hydrolysis in the presence of dilute AcOH or IR-120H resin (in acetone or water). The reactions were complete within 1 h at room temperature. Dioxolane acetals 6-18a,m-u are stable under neutral or basic conditions at room temperature but quite labile under acidic conditions; cleavage proceeds promptly with PTSA or IR-120H resin in acetone/water at room temperature. Cleavage of the pinacol acetals 6-10a,m-u has been demonstrated using the conditions above (see section 6.2.3) which use aqueous H$_3$PO$_4$ or IR-120H resin at 65 °C. Alternatively, IR-120H resin in refluxing acetone allows for the slow deprotection of the pinacol group. Under these conditions though, the yields for alkenal 6-10r suffer as a result of cationic side reactions.

6.3.4.2 Complex/Chiral aldehydes

The deprotection of the chiral acetals presented a unique challenge; developing suitable conditions for the chemoselective deprotection of acetals 6-26/6-27, 6-28 & 6-29
was essential. Our initial deprotection conditions (H$_3$PO$_4$ \textit{aq}) or IR120H resin, H$_2$O, 60 °C) were incompatible with the acid labile protecting groups present on each homologated acetal. The reactivity of the various acetals exhibited a useful contrariety. The ease with which enals $6$-$11a,m-u$ were liberated from derivatives $6$-$18a,m-u$ suggests that vinyl-1,3-dioxolane acetals are more labile than isopropylidene acetals. Indeed, enals $6$-$30$ and $6$-$31$ were formed cleanly using IR-120H resin or PTSA in acetone at room temperature from the corresponding dioxolane acetals.

Deprotection of pinacol acetals $6$-$26/7$, $6$-$28$ & $6$-$29$ required more forcing conditions. We quickly discovered that the acid labile isopropylidene acetals were incompatible with the aqueous conditions that allowed for removal of the pinacol, complicating matters. All attempts to cleave the pinacol acetal therefore required the use of acetone as solvent. Despite this constraint, there are still a variety of methods for acetal cleavage.\textsuperscript{32} We initially surveyed a variety of Brønsted acids. We began by screening weaker acids (i.e. AcOH, CSA, TFA, PTSA, MeSO$_3$H, 85% H$_3$PO$_4$); many simply would not furnish the free enal at any reasonable concentration. While a few were able to effect deprotection at reflux, the resultant enal proved unstable to these conditions decomposing nearly as quickly as it was formed. We were able to generate the free enal with strong acids (H$_2$SO$_4$, HCl) at varying concentrations at room temperature but degradation was prevalent and these reactions ultimately proved incompatible. We next attempted an iodine mediated acetal cleavage reported by Hu\textsuperscript{33}; this proved to be an unmitigated disaster. The sensitivity of starting materials and resultant enals to the harsh conditions required for deprotection led us to explore Lewis acids and non-acidic reagents for deprotection.

Over the past few years, milder protocols have emerged based upon the use of catalytic amounts of Lewis acids or of non-acidic reagents.\textsuperscript{34} Thus, we attempted deprotection with some basic Lewis acids. Strong Lewis acids (BF$_3$, AlCl$_3$) led to decomposition of the starting materials. Milder transition metal Lewis acids (MgBr$_2$•Et$_2$O, ZnBr$_2$, CuI$_2$, CuOAc$_2$, Yb(OTf)$_3$) showed no reaction. Luckily, FeCl$_3$•6H$_2$O and Bi(OTf)$_3$—Bi(NO$_3$)$_3$•5H$_2$O also worked but was less active—proved quite selective, allowing for clean deprotection of $6$-$29$ in acetone within 3 h at room temperature. When acetal $6$-$26$ was subjected to these same conditions cleavage of the TBS-ether was predominant. Conversely, use of a benzyloxy ether as in $6$-$27$ led to a large improvement in the yield of enal though the reaction was still capricious.
6.4 Conclusion

Two new phosphonium salts for the one pot homologation of aldehydes to $\alpha,\beta$-unsaturated aldehydes have been prepared from the inexpensive reagents bromoacetaldehyde dimethyl acetal, pinacol and ethylene glycol. These salts allow conversion of aldehydes to homologated acetals in good to excellent yield and high ($E$)-stereoselectivity under aqueous and/or anhydrous Wittig reaction conditions. The stability of the resulting vinyl acetals was then evaluated and compared. Two methods were developed for acetal hydrolysis of simple aldehydes under mild aqueous conditions leading to the two-carbon homologated aldehydes in high yield. Further, selected chiral aldehydes were reacted with these salts using classical Wittig conditions to give complex acetals. Chemoselective deprotection of these acetals to the homologated aldehydes was achieved using mild Lewis acids.

6.5 Experimental Section

6.5.1 General Considerations

Reactions were carried out under nitrogen or argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether ($\text{Et}_2\text{O}$), tetrahydrofuran (THF), Toluene (PhMe) and triethylamine and N,N-diisopropylethylamine were distilled from Na$^0$ with benzophenone as an indicator. Dry dichloromethane ($\text{CH}_2\text{Cl}_2$) was
distilled from calcium hydride while dry methanol (MeOH) was distilled from Mg\(^0\). All fine chemicals were obtained from Sigma-Aldrich and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (\(^1\)H-NMR) homogeneous materials, unless otherwise stated. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV. HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. NMR spectra were recorded on Bruker AV-600 and AV-700 spectrometers and calibrated using residual undeuterated solvent as an internal reference (CHCl\(_3\) @ \(\delta 7.26\) ppm \(^1\)H NMR, \(\delta 77.16\) ppm \(^{13}\)C NMR; Acetone-d\(_6\) @ \(\delta 2.05\), \(^1\)H NMR, \(\delta 29.84\) ppm \(^{13}\)C NMR); \(^31\)P spectra were calibrated using an external reference of 85% H\(_3\)PO\(_4\). Signal assignments were accomplished via analysis of HMBC, HMQC, COSY, NOESY experiments where necessary. The (\(E\)) to (\(Z\)) ratios were determined from the relative integration of the \(^1\)H spectra for the olefinic protons. All melting points are corrected.

### 6.5.2 Preparative Procedures

\[
\begin{align*}
\text{EtO} & \quad \text{PPr}_3 \\
\text{Br} & \quad \text{THF, 60 °C} \\
6-6 & \quad 95\% \\
\rightarrow
\end{align*}
\]

Synthesis of 6-4: A solution of bromoacetaldehyde diethyl acetal (9.60 g, 48.7 mmol) and tri-n-propylphosphine (8.58 g, 53.6 mmol) in THF (27 mL) was heated for 24 hours at 60 °C. After cooling, the reaction mixture was concentrated under reduced pressure to afford the desired phosphonium salt 6-4 (16.5 g, 95%) as a viscous oil which solidified to a white solid at 0 °C overnight. No further purification was necessary.

**Physical State:** white solid

\(R_f = 0.36\) (DCM/MeOH, 95:5 v/v; 2,4-DNP)

\(^1\)H NMR [CDCl\(_3\), 600 MHz] \(\delta\): 4.83 (dt, \(J = 16.6, 3.9\) Hz, 1H), 3.62 (dq, \(J = 9.1, 7.1\) Hz, 2H), 3.50 (dq, \(J = 9.2, 7.0\) Hz, 2H), 2.89 (dt, \(J = 10.8, 5.4\) Hz, 2H), 2.33 – 2.20 (m, 6H), 1.60 – 1.46 (m, 6H), 1.12 – 1.03 (m, 6H), 0.98 (td, \(J = 7.2, 1.4\) Hz, 9H)
13C NMR [CDCl₃, 150 MHz] δ: 99.1 (d, $^2$$J$(13C-31P) = 6.7 Hz), 64.1 (d, $^4$$J$(13C-31P) = 12.1 Hz), 25.9 (d, $^1$$J$(13C-31P) = 47.3 Hz), 22.3 (d, $^1$$J$(13C-31P) = 47.0 Hz), 15.4 (d, $^2$$J$(13C-31P) = 3.9 Hz), 15.2 (d, $^3$$J$(13C-31P) = 16.9 Hz), 14.8 (s)

31P NMR [CDCl₃, 240 MHz] δ 30.4

HRES MS (m/z): (M)$^+$ calcd. for C₁₅H₃₄O₂P 277.2296; found 277.2296.

Synthesis of 6-16: A solution of 2-bromomethyl-1,3-dioxolane (1.7 g, 10 mmol), sodium iodide (7.5 mg, 0.05 mmol and tri-n-propylphosphine (1.6 g, 10 mmol) in 1,4-dioxane (20 mL) was heated at 70 °C for 24 hours. After cooling, the reaction mixture was concentrated under reduced pressure to obtain the desired phosphonium salt 6-16 (3.27 g, 97%) as a white solid. No further purification was necessary.

Physical State: white solid

$R_f$ = 0.30 (DCM/MeOH, 95:5 v/v; 2,4-DNP)

1H NMR [CDCl₃, 600 MHz] δ: 5.14 (dt, $J$ = 11.1, 4.3 Hz, 1H), 4.03 – 3.92 (m, 2H), 3.85 – 3.76 (m, 2H), 2.93 (dd, $J$ = 13.0, 4.3 Hz, 2H), 2.41 – 2.27 (m, 6H), 1.59 – 1.51 (m, 6H), 1.00 (td, $J$ = 7.2, 1.2 Hz, 9H).

13C NMR [CDCl₃, 150 MHz] δ: 99.0 (d, $J$ = 4.8 Hz), 65.1 (s), 24.5 (d, $J$ = 48.0 Hz), 22.3 (d, $J$ = 46.8 Hz), 15.7 (d, $J$ = 4.3 Hz), 15.5 (d, $J$ = 16.8 Hz).

31P NMR [CDCl₃, 240 MHz] δ 30.4

HRES MS (m/z): (M)$^+$ calcd. for C₁₃H₂₈O₂P, 247.1827; found, 247.1834.
Synthesis of 6-8: Pinacol (6.94 g, 58.7 mmol), bromoacetaldehyde diethyl acetal (11.0 g, 55.9 mmol) and p-toluenesulphonic acid monohydrate (319 mg, 1.70 mmol) were combined and the mixture was heated to 100-110 °C for 15 minutes. Ethanol was then distilled at 100 °C at 32 mbar via a Vigreux column. The yellow residue was purified by distillation at 75 °C at 0.1 mbar to give the desired acetal 6-8 (11.2 g, 90%) as a colourless oil.

Physical State: colourless oil

\[ R_f = 0.53 \text{ (DCM/MeOH, 99.5:0.5 v/v; 2,4-DNP)} \]

\[ ^1H \text{ NMR [CDCl}_3, 600 MHz] \delta: 5.18 \text{ (t, } J = 4.9 \text{ Hz, 1H), 3.28 \text{ (d, } J = 4.9 \text{ Hz, 2H), 1.20 \text{ (s, 6H), 1.19 \text{ (s, 6H)}}. \]

\[ ^{13}C \text{ NMR [CDCl}_3, 150 MHz] \delta: 99.5, 83.2, 34.1, 24.1, 22.2. \]

Synthesis of 6-5: 2-(Bromomethyl-4,4,5,5-tetramethyl-1,3-dioxolane 6-8 (8.41 g, 37.7 mmol), tri-\text{-}n\text{-}propylphosphine (6.16 g, 38.4 mmol) and NaI (5.6 mg, 0.038 mmol) were heated for 24 hours at 125-130 °C. The resulting viscous oil solidifies to a white solid on cooling (14.2 g, 98%). No further purification was necessary.

Physical State: white solid

\[ R_f = 0.30 \text{ (DCM/MeOH, 95:5 v/v; 2,4-DNP)} \]

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$^1$H NMR [CDCl$_3$, 600 MHz] δ: 5.24 (td, $J = 5.6$, 2.3 Hz, 1H), 2.68 (dd, $J = 13.1$, 5.6 Hz, 2H), 2.46 – 2.38 (m, 6H), 1.57 (dt, $J = 11.3$, 7.6 Hz, 6H), 1.12 (s, 6H), 1.09 (s, 6H), 1.03 (td, $J = 7.2$, 1.5 Hz, 9H).

$^{13}$C NMR [CDCl$_3$, 150 MHz] δ: 94.8 (s), 83.2 (d, $^{2}J^{(13}C^{31}P) = 16.0$ Hz), 26.7 (d, $^{1}J^{(13}C^{31}P) = 46.3$ Hz), 23.9 (s), 21.8 (d, $^{1}J^{(13}C^{31}P) = 23.4$ Hz), 21.8 (s), 15.6 (d, $^{2}J^{(13}C^{31}P) = 4.0$ Hz), 15.3 (d, $^{3}J^{(13}C^{31}P) = 16.8$ Hz).

$^{31}$P NMR [CDCl$_3$, 240 MHz] δ: 29.9

HRES MS (m/z): (M)$^+$ calcd. for C$_{17}$H$_{36}$O$_2$P 303.2453; found 303.2458.

**General Preparation:** To a flask containing a magnetic stir bar was added phosphonium salt 6-5 (1.05 mmol, 1.05 equiv.) and water (1 mL) added to make a 1 M solution. Sodium hydroxide (3 mmol, 3 equiv.) was added followed by the corresponding aldehyde 6-9a-m (1 mmol, 1 equiv.). The flask was then sealed and heated to 100 °C in an oil bath with vigorous stirring for 1-3 days. The contents of the flask were subsequently transferred to an Erlenmeyer flask and water added to the mixture. The slurry was stirred for 10 minutes under open air before extraction with ethyl acetate (3 x 5 mL). The combined organic layers were then dried over sodium sulphate anhydrous and concentrated under reduced pressure. The crude mixture was then filtered through a silica plug to afford the title compound which was used without further purification.

**4,4,5,5-Tetramethyl-2-[(1E)-2-(4-chlorophenyl)ethenyl]-1,3-dioxolane (6-10a).**

Yield 87%, Colourless oil; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.35 (d, $J = 8.6$ Hz, 2H), 7.29 (d, $J = 8.6$ Hz, 2H), 6.68 (d, $J = 15.9$ Hz, 1H), 6.14 (dd, $J = 15.9$, 6.6 Hz, 1H), 5.54 (d, $J = 8.6$ Hz, 2H), 2.68 (dd, $J = 13.1$, 5.6 Hz, 2H), 2.46 – 2.38 (m, 6H), 1.57 (dt, $J = 11.3$, 7.6 Hz, 6H), 1.12 (s, 6H), 1.09 (s, 6H), 1.03 (td, $J = 7.2$, 1.5 Hz, 9H).
= 6.6 Hz, 1H), 1.29 (s, 6H), 1.28 (s, 6H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \( \delta \): 134.5, 133.8, 132.9, 128.6, 128.4, 128.1, 100.3, 82.4, 23.9, 21.9; HREI MS (M+H\textsuperscript{+}) calcd. for C\textsubscript{13}H\textsubscript{19}ClO\textsubscript{2}: 266.1074, found 266.1075

4,4,5,5-Tetramethyl-2-\[(1\text{E})-2-(4-bromophenyl)ethenyl\]-1,3-dioxolane (6-10b).

\[
\begin{align*}
\text{Yield 91\%, Colourless oil; } \textsuperscript{1}H-NMR & [CDCl\textsubscript{3}, 600 MHz] \( \delta \): 7.45 (d, \( J \) = 8.5 Hz, 4H), 7.29 (d, \( J \) = 8.5 Hz, 4H), 6.67 (d, \( J \) = 15.9 Hz, 2H), 6.16 (dd, \( J \) = 15.9, 6.7 Hz, 2H), 5.54 (d, \( J \) = 6.7 Hz, 2H), 1.29 (s, 13H), 1.28 (s, 12H); \\
\textsuperscript{13}C-NMR & [CDCl\textsubscript{3}, 150 MHz] \( \delta \): 134.9, 133.1, 131.6, 128.5, 128.4, 122.00, 100.3, 82.4, 23.9, 22.0; HRES MS (M+H\textsuperscript{+}) calcd. for C\textsubscript{15}H\textsubscript{18}BrO\textsubscript{2}: 309.0490, found 309.0490
\end{align*}
\]

4,4,5,5-Tetramethyl-2-\[(1\text{E})-2-(4-Methylphenyl)ethenyl\]-1,3-dioxolane (6-10c).

\[
\begin{align*}
\text{Yield 89\%, Colourless oil; } \textsuperscript{1}H-NMR & [CDCl\textsubscript{3}, 600 MHz] \( \delta \): 7.31 (d, \( J \) = 8.1 Hz, 2H), 7.12 (d, \( J \) = 8.0 Hz, 2H), 6.69 (d, \( J \) = 15.9 Hz, 1H), 6.11 (dd, \( J \) = 15.9, 6.8 Hz, 1H), 5.54 (d, \( J \) = 6.8 Hz, 1H), 2.34 (s, 3H), 1.28 (s, 6H), 1.27 (s, 6H); \\
\textsuperscript{13}C-NMR & [CDCl\textsubscript{3}, 150 MHz] \( \delta \): 137.9, 134.3, 133.2, 129.1, 126.8, 126.6, 100.8, 82.2, 24.00, 21.9, 21.2; HRES MS (M+H\textsuperscript{+}) calcd. for C\textsubscript{16}H\textsubscript{23}O\textsubscript{2}: 247.1698, found 247.1703
\end{align*}
\]

4,4,5,5-Tetramethyl-2-\[(1\text{E})-2-(1,3-benzodioxol-5-yl)ethenyl\]-1,3-dioxolane (6-10d).

\[
\begin{align*}
\text{Yield 90\%, Colourless oil; } \textsuperscript{1}H-NMR & [CDCl\textsubscript{3}, 600 MHz] \( \delta \): 7.52 – 7.47 (m, 6H), 7.22 – 7.11 (m, 22H), 6.96 (d, \( J \) = 15.7 Hz, 6H), 6.06 (dd, \( J \) = 15.7, 6.7 Hz, 6H), 5.58 (d, \( J \) = 6.7 Hz, 7H), 2.35 (s, 18H), 1.29 (s, 38H), 1.28 (s, 35H); \\
\textsuperscript{13}C-NMR & [CDCl\textsubscript{3}, 150 MHz] \( \delta \): 135.7, 135.1, 132.1, 130.1, 129.0, 127.9, 126.1, 125.9, 100.7, 82.2, 23.9, 21.9, 19.6; HRES MS (M+H\textsuperscript{+}) calcd. for C\textsubscript{16}H\textsubscript{23}O\textsubscript{2}: 247.1698, found 247.1687
\end{align*}
\]

4,4,5,5-Tetramethyl-2-\[(1\text{E})-2-(1,3-benzodioxol-5-yl)ethenyl\]-1,3-dioxolane (6-10e).
Yield 96%, Beige solid; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 6.94 (d, $J = 1.6$ Hz, 1H), 6.83 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.61 (d, $J = 15.8$ Hz, 1H), 5.97 (dd, $J = 15.97$, 6.84 Hz, 1H), 5.95 (s, 2H), 5.50 (d, $J = 6.8$ Hz, 1H), 1.27 (s, 6H), 1.25 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 147.9, 147.7, 134.1, 130.5, 125.8, 121.8, 108.2, 106.1, 101.1, 100.8, 82.3, 24.0, 22.0. HRES MS (M+H)$^+$ calcd. for C$_{16}$H$_{21}$O$_4$: 276.1964, found 276.1963.

4,4,5,5-Tetramethyl-2-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]-1,3-dioxolane (6-10f).

Yield 91%, Colourless Oil; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 6.63 (d, $J = 15.6$ Hz, 1H), 6.62 (s, 2H), 6.04 (dd, $J = 15.8$, 6.6 Hz, 1H), 5.52 (d, $J = 6.6$ Hz, 1H), 3.86 (s, 6H), 3.84 (s, 3H), 1.27 (s, 6H), 1.26 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 153.2, 138.2, 134.3, 131.8, 127.1, 104.0, 100.4, 82.3, 56.1, 24.0, 22.0; HRES MS (M+H)$^+$ calcd. for C$_{18}$H$_{27}$O$_5$: 324.1893, found 324.1898.

4,4,5,5-Tetramethyl-2-[2-(4-bromophenyl)ethenyl]-1,3-dioxolane (6-10g).

Yield 90%, Yellow oil; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.30 (d, $J = 8.8$ Hz, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 6.62 (d, $J = 15.8$ Hz, 1H), 5.94 (dd, $J = 7.0$, 15.8 Hz, 1H), 5.52 (d, $J = 7.0$ Hz, 1H), 2.95 (s, 6H), 1.28 (s, 6H), 1.26 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 150.5, 134.9, 128.2, 124.5, 123.1, 112.2, 101.5, 82.2, 40.5, 24.2, 22.1; HRES MS (M+H)$^+$ calcd. for C$_{17}$H$_{26}$NO$_2$: 278.1474, found 278.1482.

4,4,5,5-Tetramethyl-2-[(1E,3E)-4-penyl-1,3-butadien-1-yl]-1,3-dioxolane (6-10h).

Yield 36%, yellow oil; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.45 – 7.31 (m, 5H), 6.83 (dd, $J = 15.6$, 10.6 Hz, 1H), 6.64 (d, $J = 15.7$ Hz, 1H), 6.54 (dd, $J = 15.2$, 10.6 Hz, 1H),
5.82 (dd, \( J = 15.2, 6.8 \text{ Hz}, 1\text{H} \)), 5.50 (d, \( J = 6.8 \text{ Hz}, 1\text{H} \)), 1.29 (s, 6H), 1.29 (s, 6H); \(^{13}\text{C-}
\text{NMR [CDCl}_3, 150 \text{ MHz}] \delta: 136.8, 134.3, 134.3, 131.3, 128.5, 127.8, 127.5, 126.5, 100.2, 82.2, 23.9, 21.9; \text{HREI MS (M)}^+ \text{ calcd. for C}_{17}\text{H}_{22}\text{O}_2: 258.1620, \text{ found 258.1621.}

4,4,5,5-Tetramethyl-2-[(1\text{E,3E})-4-(1,3-benzodioxol-5-yl)-1,3-butadien-1-yl]-1,3-dioxolane (6i).

![4,4,5,5-Tetramethyl-2-[(1\text{E,3E})-4-(1,3-benzodioxol-5-yl)-1,3-butadien-1-yl]-1,3-dioxolane (6i).](image)

Yield 53\%, yellow; \(^1\text{H-NMR [CDCl}_3, 600 \text{ MHz}] \delta: 6.94 (d, \( J = 1.5 \text{ Hz}, 1\text{H} \)), 6.82 (dd, \( J = 8.0, 1.5 \text{ Hz}, 1\text{H} \)), 6.75 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 6.61 (dd, \( J = 15.5, 10.5 \text{ Hz}, 1\text{H} \)), 6.50 (d, \( J = 15.6 \text{ Hz}, 1\text{H} \)), 6.46 (dd, \( J = 15.1, 10.5 \text{ Hz}, 1\text{H} \)), 5.95 (s, 2H), 5.72 (dd, \( J = 15.1, 6.9 \text{ Hz}, 1\text{H} \)), 5.44 (d, \( J = 6.9 \text{ Hz}, 1\text{H} \)), 1.25 (s, 7H), 1.24 (s, 6H); \(^{13}\text{C-NMR [CDCl}_3, 150 \text{ MHz}] \delta: 148.0, 147.5, 134.5, 134.0, 131.5, 130.5, 126.0, 126.1, 108.4, 105.5, 101.1, 100.3, 82.2, 24.0, 22.0; \text{HRES MS (M+H)}^+ \text{ calcd. for C}_{18}\text{H}_{23}\text{O}_4: 304.1631; \text{ found 304.1656.}

4,4,5,5-Tetramethyl-2-[(1\text{E})-2-(1-pyrenyl)ethenyl]-1,3-dioxolane (6-10j).

![4,4,5,5-Tetramethyl-2-[(1\text{E})-2-(1-pyrenyl)ethenyl]-1,3-dioxolane (6-10j).](image)

Yield 92\%, Yellow solid; \(^1\text{H-NMR [CDCl}_3, 600 \text{ MHz}] \delta: 8.37 (d, \( J = 9.0 \text{ Hz}, 1\text{H} \)), 8.22 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 8.17 (d, \( J = 7.6 \text{ Hz}, 2\text{H} \)), 8.13 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 8.09 (d, \( J = 9.3 \text{ Hz}, 1\text{H} \)), 8.04 (d, \( J = 9.0 \text{ Hz}, 1\text{H} \)), 8.02 (d, \( J = 8.9 \text{ Hz}, 1\text{H} \)), 7.99 (t, \( J = 7.4 \text{ Hz}, 1\text{H} \)), 7.81 (d, \( J = 15.8 \text{ Hz}, 1\text{H} \)), 6.42 (dd, \( J = 6.7, 15.7 \text{ Hz}, 1\text{H} \)), 5.79 (d, \( J = 6.7 \text{ Hz}, 1\text{H} \)), 1.37 (s, 6H), 1.36 (s, 6H); \(^{13}\text{C-NMR [CDCl}_3, 150 \text{ MHz}] \delta: 131.7, 131.5, 131.3, 131.1, 131.0, 130.7, 128.5, 127.8, 127.6, 127.5, 126.1, 125.4, 125.2, 125.1, 125.0, 124.5, 123.1, 101.0, 82.6, 24.2, 22.2; \text{HRES MS (M+H)}^+ \text{ calcd. for C}_{25}\text{H}_{25}\text{O}_2: 357.1855, \text{ found 357.1867.}

4,4,5,5-Tetramethyl-2-[(1\text{E})-2-(3-pyridyl)ethenyl]-1,3-dioxolane (6-10k).
Yield 75%, Beige solid; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 8.61 (d, $J = 2.2$ Hz, 1H), 8.49 (dd, $J = 1.7$, 4.8 Hz, 1H), 7.73 (dt, $J = 1.9$, 7.9 Hz, 1H), 7.25 (dd, $J = 4.7$, 7.9 Hz, 1H), 6.71 (d, $J = 16.0$ Hz, 1H), 6.23 (dd, $J = 6.5$, 16.0 Hz, 1H), 5.54 (d, $J = 6.5$ Hz, 1H), 1.28 (s, 6H), 1.27 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 149.4, 148.9, 133.4, 131.8, 130.7, 130.3, 123.6, 100.2, 82.7, 24.1, 22.2; HRES MS (M+H)$^+$ calcd. for C$_{14}$H$_{20}$NO$_2$: 234.1493, found 234.1499.

$\textbf{4,4,5,5-Tetramethyl-2-[(1E)-2-(4-pyridyl)ethenyl]-1,3-dioxolane (6-10l).}$

Yield 83%, Beige solid; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 8.56 (dd, $J = 1.6$, 4.6 Hz, 2H), 7.27 (dd, $J = 1.6$, 4.6 Hz, 2H), 6.67 (d, $J = 16.0$ Hz, 1H), 6.36 (dd, $J = 6.2$, 16.0 Hz, 1H), 5.55 (d, $J = 6.2$ Hz, 1H), 1.29-1.27 (m, 12H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 150.3, 143.6, 132.7, 131.6, 121.4, 99.8, 82.8, 24.07, 22.1; HRES MS (M+H)$^+$ calcd. for C$_{14}$H$_{20}$NO$_2$: 234.1494, found 234.1499.

$\textbf{4,4,5,5-Tetramethyl-2-[(1E)-4-phenyl-1-buten-1-yl]-1,3-dioxolane (6-10m).}$

The parent compound was prepared using the general procedure. Yield 54%, Yellow oil; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.39 – 7.35 (m, 6H), 7.27 (s, 4H), 6.01 (dt, $J = 15.3$, 6.6 Hz, 2H), 5.64 (dd, $J = 15.4$, 7.2 Hz, 2H), 5.42 (d, $J = 7.2$ Hz, 2H), 2.82 – 2.79 (m, 5H), 2.51 – 2.44 (m, 4H), 1.32 (s, 12H), 1.32 (s, 12H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 141.6, 136.1, 129.2, 128.3, 125.8, 100.8, 82.1, 35.1, 33.8, 24.0, 21.9; HREI MS (M)$^+$ calcd. for C$_{17}$H$_{24}$O$_2$: 260.1776, found 260.1777.
General Procedure A: The reactions were performed in deionised water unless otherwise indicated. No special precautions were taken to exclude oxygen and standard vials were used. To 0.15 mmol of the acetal were added 1 mL of deionised water and 80 mg of Amberlite® IR120 hydrogen form. The vial was stirred at 700 rpm and heated to 60-70 °C for 12 – 18 hr. After that a filtration was performed to remove the Amberlite®, 1 mL of water was used to rinse the flask. Alternatively, if the product is a solid, ethyl acetate 1-2 mL could be used to dissolve and extract the product from the aqueous layer. Treatment with activated charcoal was performed at 40 °C during 3 hours to remove color impurities, filtration and evaporation of the solvent gives the product. When necessary, the crude product was purified by chromatography using ethyl acetate and hexane as the eluent.

General Procedure B: In a 1.5 mL vial equipped with a stirring bar, 0.15 mmol of the acetal were added to 1 mL of 25% H₃PO₄. Then the vial was closed and heated up to 60-70 °C for 12 – 18 hr. When the reaction was completed, the reaction mixture was cooled to room temperature. The pure product was isolated after a simple filtration. When necessary the crude product was purified by chromatography using ethyl acetate and hexane as the eluent.

General Procedure C: The corresponding acetal (0.5 mmol) was added to acetone (10 mL) and IR-120H Amberlite® resin (80 mg). The mixture was stirred until TLC showed complete consumption of the starting acetal (1-3 h) at which point the mixture was filtered through solid NaHCO₃ followed by anhydrous magnesium sulphate. Concentration under reduced pressure afforded the corresponding homologated aldehyde. When necessary, the crude product was purified by chromatography using ethyl acetate and hexane as the eluent.

(2E)-3-(4-Chlorophenyl)-2-propenal (6-11a).

The parent compound was prepared using the general procedure B. This compound is known and matches the reported spectroscopic data. Yield 95%, white solid; ¹H-NMR [CDCl₃,
600 MHz] δ: 9.70 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 15.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 6.69 (dd, J = 16.0, 7.6 Hz, 2H); 13C-NMR [CDCl₃, 150 MHz] δ: 193.3, 151.0, 137.3, 132.5, 129.6, 129.4, 129.0.

(2E)-3-(4-Bromophenyl)-2-propenal (6-11b).

The parent compound was prepared using the general procedure B. This compound is known and matches the reported spectroscopic data. 36,37 Yield 93%, white solid; 1H-NMR [CDCl₃, 600 MHz] δ: 9.71 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.5 Hz, 4H), 7.43 (d, J = 8.5 Hz, 5H), 7.42 (d, J = 15.6 Hz, 1H), 6.70 (dd, J = 16.0, 7.6 Hz, 2H); 13C-NMR [CDCl₃, 150 MHz] δ: 193.3, 151.1, 132.9, 132.4, 129.8, 129.0, 125.7.

(2E)-3-(4-Methylphenyl)-2-propenal (6-11c).

The parent compound was prepared using the general procedure B. This compound is known and matches the reported spectroscopic data. 38,39 Yield 94%, yellow solid; 1H-NMR [CDCl₃, 600 MHz] δ: 9.69 (d, J = 7.7 Hz, 2H), 7.47 (d, J = 8.1 Hz, 5H), 7.46 (d, J = 15.7 Hz, 1H), 7.24 (d, J = 8.0 Hz, 4H), 6.69 (dd, J = 15.9, 7.7 Hz, 2H), 2.40 (s, 6H); 13C-NMR [CDCl₃, 150 MHz] δ: 193.8, 152.9, 142.0, 131.3, 129.8, 128.5, 127.7, 21.6.

(2E)-3-(2-Methylphenyl)-2-propenal (6-11d).

The parent compound was prepared using the general procedure B. This compound is known and matches the reported spectroscopic data. 36,38 Yield 83%, yellow solid; 1H-NMR [CDCl₃, 600 MHz] δ: 9.73 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 15.8 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.27 – 7.24 (m, 1H), 6.67 (dd, J = 15.8, 7.7 Hz, 1H), 2.48 (s, 3H); 13C-NMR [CDCl₃, 150 MHz] δ: 193.9, 150.3, 137.9, 132.9, 131.1, 131.0, 129.6, 126.9, 126.6, 19.8.

(2E)-3-(1,3-benzodioxol-5-yl)-2-propenal (6-11e).
The parent compound was prepared using the general procedure B. This compound is known and matches the reported spectroscopic data.\textsuperscript{40,41} Yield 95%, beige solid; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] \(\delta\): 9.59 (d, \(J = 7.7\) Hz, 1H), 7.32 (d, \(J = 15.8\) Hz, 1H), 7.04 – 6.95 (m, 2H), 6.82 – 6.79 (m, 1H), 6.50 (dd, \(J = 15.8, 7.7\) Hz, 1H), 5.99 (s, 2H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \(\delta\): 193.6, 152.7, 150.6, 148.7, 128.6, 127.0, 125.4, 108.9, 106.9, 102.0.

\textit{(2E)-3-(3,4,5-trimethoxyphenyl)-2-propenal (6-11f).}

\textsuperscript{42,43} Yield 93%, translucent liquid; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] \(\delta\): 9.68 (d, \(J = 7.7\) Hz, 1H), 7.40 (d, \(J = 15.8\) Hz, 1H), 6.79 (s, 2H), 6.64 (dd, \(J = 15.8, 7.7\) Hz, 1H), 3.90 (s, 9H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \(\delta\): 193.4, 153.6, 152.7, 129.5, 128.0, 105.7, 61.0, 56.2.

\textit{(2E)-3-(4-(dimethylamino)phenyl)-2-propenal (6-11g).}

\textsuperscript{44} Yield 88%, yellow oil; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] \(\delta\): 9.59 (d, \(J = 7.9\) Hz, 1H), 7.45 (d, \(J = 8.9\) Hz, 2H), 7.37 (d, \(J = 15.6\) Hz, 1H), 6.68 (d, \(J = 8.9\) Hz, 2H), 6.54 (dd, \(J = 15.6, 7.9\) Hz, 1H), 3.05 (s, 6H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] \(\delta\): 193.67, 153.9, 152.4, 130.5, 123.8, 121.7, 111.7, 40.0.

\textit{(2E,4E)-5-Phenyl-2,4-pentadienal (6-11h).}
The parent compound was prepared using the general procedure A. This compound is known and matches the reported spectroscopic data.\textsuperscript{37,38} Yield 68%, yellow oil; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] δ: 9.56 (d, $J = 7.9$ Hz, 1H), 7.45 – 7.42 (m, 2H), 7.34 – 7.27 (m, 3H), 7.23 – 7.19 (m, 1H), 6.96 – 6.93 (m, 2H), 6.21 (dd, $J = 15.2$, 7.9 Hz, 1H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] δ: 193.6, 152.0, 142.4, 135.6, 131.7, 129.7, 129.0, 127.5, 126.2.

(2\textit{E},4\textit{E})-5-(1,3-Benzodioxol-5-yl)-2,4-pentadienal (6-11i).

The parent compound was prepared using the general procedure A. This compound is known and matches the reported spectroscopic data.\textsuperscript{45} Yield 76%, yellow oil; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] δ: 9.60 (d, $J = 8.0$ Hz, 1H), 7.23 (dd, $J = 15.2$, 10.8 Hz, 1H), 7.03 (d, $J = 1.6$ Hz, 1H), 6.97 (d, $J = 8.0$, 1.6 Hz, 1H), 6.93 (d, $J = 15.5$ Hz, 1H), 6.85 (d, $J = 10.7$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.23 (dd, $J = 15.2$, 7.9 Hz, 1H), 6.01 (s, 2H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] δ: 193.5, 152.3, 149.1, 148.4, 142.2, 130.9, 130.2, 124.5, 123.6, 108.6, 106.1, 101.5.

(2\textit{E})-3-(1-Pyrenyl)-2-propenal (6-11j).

The parent compound was prepared using the general procedure A. This compound is known and matches the reported spectroscopic data.\textsuperscript{46} Yield 81%, yellow solid; \textsuperscript{1}H-NMR [CDCl\textsubscript{3}, 600 MHz] δ: 9.95 (d, $J = 7.6$ Hz, 1H), 8.65 (d, $J = 15.7$ Hz, 1H), 8.50 (d, $J = 9.3$ Hz, 1H), 8.33 (d, $J = 8.1$ Hz, 1H), 8.27 (d, $J = 7.1$ Hz, 2H), 8.25 (d, $J = 9.2$ Hz, 1H), 8.21 (d, $J = 8.1$ Hz, 1H), 8.18 (d, $J = 8.8$ Hz, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 8.07 (t, $J = 7.6$ Hz, 1H), 7.04 (dd, $J = 15.6$, 7.6 Hz, 1H); \textsuperscript{13}C-NMR [CDCl\textsubscript{3}, 150 MHz] δ: 192.4, 148.1, 146.8, 130.8, 129.3, 128.2, 127.8, 127.6, 126.4, 126.2, 125.5, 125.2, 125.1, 125.0, 124.2, 123.5, 123.3, 122.5, 120.8.
(2E)-5-Phenyl-2-pentenal (6-11m).

The parent compound was prepared using the general procedure A. This compound is known and matches the reported spectroscopic data.\textsuperscript{47,48} Dichloromethane–hexane (1 : 1); Yield 82%, Yellow oil; \textsuperscript{1}H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 9.50 (d, \(J = 7.9\) Hz, 1H), 7.32 – 7.29 (m, 2H), 7.22 – 7.18 (m, 3H), 6.86 (dt, \(J = 15.6, 6.7\) Hz, 1H), 6.14 (ddt, \(J = 15.6, 7.8, 1.4\) Hz, 1H), 2.84 (t, \(J = 7.6\) Hz, 2H), 2.70 – 2.65 (m, 2H); \textsuperscript{13}C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 194.0, 157.3, 133.4, 129.4, 128.6, 128.3, 126.4, 34.2, 34.1.

(2E)-3-(4-methoxyphenyl)-2-propenal (6-11n)

The parent compound was prepared using the general procedure B. White solid; TLC (EtOAc:hexanes, 1:9 v/v): \(R_f = 0.23\); \textsuperscript{1}H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 9.68 (d, \(J = 7.7\) Hz, 1H), 7.55 (d, \(J = 8.8\) Hz, 2H), 7.45 (d, \(J = 15.8\) Hz, 1H), 6.97 (d, \(J = 8.8\) Hz, 2H), 6.64 (dd, \(J = 15.8, 7.7\) Hz, 1H), 3.89 (s, 3H); \textsuperscript{13}C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 193.70, 162.22, 152.70, 130.36, 126.82, 126.57, 114.59, 55.47. Its spectroscopic data were in accordance with those reported in the literature.\textsuperscript{49}

(2E)-3-(4-cyanophenyl)-2-propenal (6-11o)

The parent compound was prepared using the general procedure A. White solid; TLC (EtOAc:hexanes, 1:9 v/v): \(R_f = 0.10\); \textsuperscript{1}H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 9.79 (d, \(J = 7.5\) Hz, 1H), 7.80 – 7.73 (m, 2H), 7.69 (d, \(J = 8.3\) Hz, 2H), 7.50 (d, \(J = 16.1\) Hz, 1H), 6.80 (dd, \(J = 16.1, 7.5\) Hz, 1H); \textsuperscript{13}C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 192.86, 149.42, 138.17, 132.83, 131.21, 128.74, 118.13, 114.31. Its spectroscopic data were in accordance with those reported in the literature.

2-cyclohexylideneacetaldehyde (6-11p)
The parent compound was prepared using the general procedure A. Colourless oil; TLC (EtOAc:hexanes, 1:9 v/v): R_f = 0.17; ^1H-NMR [CDCl_3, 600 MHz] δ: 10.00 (d, J = 8.1 Hz, 1H), 5.80 (d, J = 8.2 Hz, 1H), 2.74 – 2.65 (m, 2H), 2.33 – 2.22 (m, 2H), 1.75 – 1.66 (m, 4H), 1.66 – 1.60 (m, 2H); ^13C-NMR [CDCl_3, 150 MHz] δ: 190.54, 168.07, 125.33, 38.08, 29.62, 28.42, 28.18, 26.18. Its spectroscopic data were in accordance with those reported in the literature.

3-phenyl-2-butenal (6-11q)

The parent compound was prepared using the general procedure A. Pale yellow oil; TLC (EtOAc:hexanes, 1:9 v/v): R_f = 0.10; ^1H-NMR [CDCl_3, 600 MHz] δ: 10.21 (d, J = 7.8 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.47 – 7.41 (m, 3H), 6.42 (dd, J = 7.8, 1.2 Hz, 1H), 2.60 (d, J = 1.2 Hz, 3H); ^13C-NMR [CDCl_3, 150 MHz] δ: 191.4, 157.7, 140.7, 130.2, 128.9, 127.4, 126.4, 16.5. Its spectroscopic data were in accordance with those reported in the literature.

(2E, 4E)-5,9-dimethyldeca-2,4,8-trienal (6-11r)

The parent compound was prepared using the general procedure A. Pale yellow oil (7:3, 4E:4Z); TLC (EtOAc:hexanes, 1:9 v/v): R_f = 0.20; ^1H-NMR [CDCl_3, 600 MHz] δ: 9.51 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 15.0, 11.5 Hz, 1H), 6.08 (d, J = 11.5 Hz, 1H), 6.02 (dd, J = 14.9, 8.0 Hz, 1H), 5.01 (t, J = 6.1 Hz, 1H), 2.14 – 2.09 (m, 4H), 1.88 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H); ^13C-NMR [CDCl_3, 150 MHz] δ: 194.09, 152.95, 148.58, 132.55, 130.01, 123.76, 123.05, 40.53, 26.26, 25.68, 17.72, 17.63. Its spectroscopic data were in accordance with those reported in the literature.

(2E)-2-hexenal (6-11s)

The parent compound was prepared using the general procedure A. Colourless oil (8:1, E/Z); TLC (EtOAc:hexanes, 1:9 v/v): R_f = 0.18; ^1H-NMR [CDCl_3, 600 MHz] δ: 9.43 (d, J = 7.9 Hz, 1H), 6.77 (dt, J = 15.6, 6.8 Hz,
$^1$H, 6.07 – 6.03 (m, 1H), 2.27 – 2.21 (m, 2H), 1.51 – 1.44 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 194.17, 158.73, 133.15, 34.69, 21.13, 13.63. Its spectroscopic data were in accordance with those reported in the literature.$^{53}$

(2$E$)-2-octenal (6-11t)

The parent compound was prepared using the general procedure A. Colourless oil (97:3, $E$/Z); TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.18$; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 9.41 (d, $J = 7.9$ Hz, 1H), 6.76 (dt, $J = 15.5$, 6.8 Hz, 1H), 6.03 (ddt, $J = 15.6$, 7.9, 1.4 Hz, 1H), 2.29 – 2.21 (m, 2H), 1.45 – 1.40 (m, 2H), 1.25 – 1.22 (m, 4H), 0.81 (t, $J = 7.0$ Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 194.14, 159.02, 132.99, 32.68, 31.28, 27.51, 22.38, 13.92. Its spectroscopic data were in accordance with those reported in the literature.$^{54}$

[Diagram]

**General Preparation:** To a microwave vial containing phosphonium salt 6-4 (180 mg, 0.75 mmol) is added THF (0.5 mL). The solution is then cooled to 0 °C for 15 minutes prior to the addition of KOtBu (56 mg, 0.75 mmol) portion-wise to afford an opaque orange mixture. It is critical on scaling up that the temperature does not rise substantially on addition of the base. The mixture containing the base was left to stir at 0 °C for 30 minutes before the corresponding aldehyde 6-9a,m-u (0.5 mmol) was subsequently added in one portion. The reaction mixture was allowed to warm to room temperature overnight before being quenched with water (10 mL). Standard extractive work-up with diethyl ether (2 x 10 mL) was followed by washing the combined organic fractions with water (10 mL). The combined organic extracts were then dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the corresponding acetals. Sodium hydride that has been washed with pentane produces similar results. In almost all cases the corresponding allylic diethyl acetals were unstable and readily hydrolyzed to the free
enal among other products, therefore, hydrolysis was performed on the crude acetals without prior characterization.

\[ \begin{array}{c}
\text{P} \\
\downarrow \\
\text{O} \\
\text{Br}
\end{array} \xrightarrow{\text{NaH or KOtBu, THF/DMF (4:1), 0 °C}} \begin{array}{c}
\text{O} \\
\downarrow \\
\text{RCHO 6-9a,m-u}
\end{array} \xrightarrow{\text{RCHO 6-9a,m-u}} \begin{array}{c}
\text{O} \\
\downarrow \\
\text{Cl}
\end{array}
\]

**General Preparation:** To a microwave vial containing phosphonium salt 6-16 (164 mg, 0.75 mmol) is added THF (0.4 mL) and DMF (0.1 mL). The solution is then cooled to 0 °C for 15 minutes prior to the addition of KOtBu (56 mg, 0.75 mmol) portion-wise to afford an opaque orange mixture. It is critical on scaling up that the temperature does not rise substantially on addition of the base. The mixture containing the base was left to stir at 0 °C for 30 minutes before the corresponding aldehyde 6-9a,m-u (0.5 mmol) was subsequently added in one portion. The reaction mixture was allowed to warm to room temperature overnight before being quenched with water (10 mL). Standard extractive work-up with diethyl ether (2 x 10 mL) was followed by washing the combined organic fractions with water (10 mL). The combined organic extracts were then dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the corresponding acetals. If required the acetals can be flash chromatographed over neutralized silica gel. Sodium hydride that has been washed with pentane produces similar results.

**(E)-2-(4-chlorostyryl)-1,3-dioxolane (6-18a)**

Yield 88%, White solid; TLC (EtOAc:hexanes, 1:4 v/v): \( R_f = 0.29 \); \(^1\text{H-NMR [CDCl}_3, 600 \text{ MHz]} \delta: 7.27 (d, J = 8.5 \text{ Hz}, 2H), 7.22 (d, J = 8.6 \text{ Hz}, 2H), 6.66 (d, J = 15.9 \text{ Hz}, 1H), 6.07 (dd, J = 16.0, 5.9 \text{ Hz}, 1H), 5.35 (dd, J = 5.9, 0.6 \text{ Hz}, 1H), 4.01 – 3.96 (m, 2H), 3.92 – 3.88 (m, 2H); \(^{13}\text{C-NMR [CDCl}_3, 150 \text{ MHz]} \delta: 133.52, 129.62, 129.46, 128.80, 128.14, 125.84, 103.62, 65.12; \text{HREI MS (M)}^+ \text{ calcd. for C}_{11}\text{H}_{11}\text{O}_2\text{Cl, 210.0448; found 210.0446.} \)
(E)-2-(4-chlorostyryl)-1,3-dioxolane (6-18n)

Yield 87%, White solid; TLC (EtOAc:hexanes, 1:4 v/v): Rf = 0.22; 1H-NMR [CDCl3, 600 MHz] δ: 7.38 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 16.0 Hz, 1H), 6.06 (dd, J = 16.0, 6.2 Hz, 1H), 5.43 (d, J = 6.2 Hz, 1H), 4.12 – 4.05 (m, 2H), 4.01 – 3.96 (m, 2H), 3.84 (s, 3H); 13C-NMR [CDCl3, 150 MHz] δ: 134.57, 130.36, 128.24, 122.79, 114.59, 113.99, 104.22, 65.05, 55.29; HREI MS (M)+ calcd. for C12H14O3, 206.0943; found 206.0969.

(E)-2-(4-chlorostyryl)-1,3-dioxolane (6-18o)

Yield 90%, White solid; TLC (EtOAc:hexanes, 1:4 v/v): Rf = 0.10; 1H-NMR [CDCl3, 600 MHz] δ: 7.64 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 6.81 (d, J = 16.0 Hz, 1H), 6.31 (dd, J = 16.0, 5.6 Hz, 1H), 5.48 (d, J = 5.6 Hz, 1H), 4.11 – 4.07 (m, 2H), 4.02 – 3.98 (m, 2H); 13C-NMR [CDCl3, 150 MHz] δ: 140.32, 132.64, 132.46, 129.16, 127.40, 118.74, 111.67, 103.01, 65.21; HREI MS (M)+ calcd. for C12H11NO2, 201.0790; found 201.0799.

2-(cyclohexylidenemethyl)-1,3-dioxolane (6-18p)

Yield 91%, colourless oil; TLC (EtOAc:hexanes, 1:9 v/v): Rf = 0.29; 1H-NMR [CDCl3, 600 MHz] δ: 5.45 (d, J = 7.3 Hz, 1H), 5.11 (d, J = 7.3 Hz, 1H), 3.97 – 3.89 (m, 2H), 3.84 – 3.76 (m, 2H), 2.19 (t, J = 5.5 Hz, 2H), 2.10 – 2.02 (m, 2H), 1.54 – 1.47 (m, 6H); 13C-NMR [CDCl3, 150 MHz] δ: 149.00, 118.07, 99.61, 64.88, 36.95, 29.43, 28.10, 27.72, 26.46. HREI MS (M)+ calcd. for C10H16O2, 168.1150; found 168.1139.

2-((E)-2-phenylprop-1-enyl)-1,3-dioxolane (6-18q)
Yield 84% (4:1, E/Z), Yellow oil; **E-Isomer**: TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.10$; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 7.46 (d, $J = 7.6$ Hz, 2H), 7.37 – 7.34 (m, 2H), 7.32 – 7.31 (m, 1H), 5.84 (dd, $J = 6.8, 1.1$ Hz, 1H), 5.71 (d, $J = 6.8$ Hz, 1H), 4.13 – 4.06 (m, 2H), 4.00 – 3.94 (m, 2H), 2.22 (d, $J = 1.1$ Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 142.40, 142.30, 128.27, 127.76, 125.95, 123.74, 100.54, 65.02, 16.52; **Z-Isomer**: TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.17$; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 7.40 – 7.36 (m, 2H), 7.33 – 7.31 (m, 2H), 7.29 (d, $J = 4.9$ Hz, 1H), 5.57 (dd, $J = 7.9, 1.2$ Hz, 1H), 5.15 (d, $J = 7.9$ Hz, 1H), 4.05 – 4.00 (m, 2H), 3.88 – 3.80 (m, 2H), 2.16 (d, $J = 1.3$ Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 145.03, 140.15, 128.10, 127.97, 127.52, 123.44, 101.07, 65.02, 25.49; HREI MS (M)$^+$ calcd. for C$_{12}$H$_{14}$O$_2$, 190.0994; found 190.0985.

2-((E)-4-phenylbut-1-enyl)-1,3-dioxolane (6-18m) Yield 76% (4:1, E/Z), colourless oil; TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.31$; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 7.20 (dd, $J = 10.4, 4.7$ Hz, 2H), 7.11 (t, $J = 8.1$ Hz, 3H), 5.91 (dt, $J = 15.5, 6.6$ Hz, 1H), 5.53 – 5.42 (m, 1H), 5.12 (d, $J = 6.4$ Hz, 1H), 3.93 – 3.90 (m, 2H), 3.82 – 3.79 (m, 2H), 2.67 – 2.64 (m, 2H), 2.33 (td, $J = 7.9, 1.3$ Hz, 2H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 141.51, 136.72, 128.39, 126.83, 125.96, 104.04, 64.96, 35.06, 33.85; HREI MS (M)$^+$ calcd. for C$_{13}$H$_{16}$O$_2$, 204.1150; found 204.1139.

2-((E,3E)-4,8-dimethylnona-1,3,7-trienyl)-1,3-dioxolane (6-18r)

Yield 70% (mixture of isomers A/B/C/D, 7:9:54:30), yellow oil; TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.40$; **Isomer C**: $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 6.57 (dt, $J = 15.2, 11.1$ Hz, 1H), 5.80 (d, $J = 11.0$ Hz, 1H), 5.45 (td, $J = 15.9, 6.3$ Hz, 1H), 5.23 (t, $J = 6.7$ Hz, 1H), 5.02 (dt, $J = 13.6, 6.9$ Hz, 1H), 3.94 (dd, $J = 6.3, 2.5$ Hz, 2H), 3.83 (dd, $J = 3.3, 2.2$ Hz, 2H), 2.05 – 1.99 (m, 4H), 1.70 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 142.17, 131.8, 131.60, 125.61, 123.75, 123.44, 104.1, 64.95, 39.92, 25.67, 26.41, 17.68, 16.76; **Isomer D**: $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 6.57 (dt, $J = 15.2, 11.1$ Hz, 1H), 5.80 (d, $J =$ 152
11.0 Hz, 1H), 5.45 (td, $J = 15.9, 6.3$ Hz, 1H), 5.23 (t, $J = 6.7$ Hz, 1H), 5.02 (dt, $J = 13.6, 6.9$ Hz, 1H), 3.94 (dd, $J = 6.3, 2.5$ Hz, 2H), 3.83 (dd, $J = 3.3, 2.2$ Hz, 2H), 2.05 – 1.99 (m, 4H), 1.72 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 142.40, 132.1, 131.32, 125.48, 124.24, 123.75, 104.2, 64.95, 32.50, 26.79, 25.67, 23.90, 17.68; HREI MS (M)$^+$ calcd. for C$_{14}$H$_{22}$O$_2$, 222.1620; found 222.1618.

2-((E)-pent-1-enyl)-1,3-dioxolane (6-18s)

Yield 76% (4:1, $E/Z$), pale yellow oil; TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.30$; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 5.84 (dt, $J = 15.4, 6.7$ Hz, 1H), 5.39 (dd, $J = 15.5, 6.5$ Hz, 1H), 5.09 (d, $J = 6.6$ Hz, 1H), 3.91 – 3.87 (m, 2H), 3.81 – 3.78 (m, 2H), 1.97 (td, $J = 7.9, 1.1$ Hz, 2H), 1.38 – 1.30 (m, 3H), 0.82 (t, $J = 7.3$ Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 137.73, 126.31, 104.24, 64.91, 34.06, 21.79, 13.65; HREI MS (M)$^+$ calcd. for C$_8$H$_{13}$O$_2$, 141.0916; found 141.0913.

2-((E)-hept-1-enyl)-1,3-dioxolane (6-18t)

Yield 82% (4:1, $E/Z$), pale yellow oil; TLC (EtOAc:hexanes, 1:9 v/v): $R_f = 0.30$; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 5.84 (dt, $J = 15.4, 6.7$ Hz, 1H), 5.38 (dd, $J = 15.5, 6.6$ Hz, 1H), 5.09 (d, $J = 6.6$ Hz, 1H), 3.94 – 3.87 (m, 2H), 3.83 – 3.76 (m, 2H), 1.98 (td, $J = 7.9, 1.2$ Hz, 2H), 1.34 – 1.30 (m, 2H), 1.21 – 1.18 (m, 4H), 0.80 – 0.78 (m, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 138.05, 126.09, 104.27, 64.92, 31.98, 31.34, 28.28, 22.47, 13.98; HREI MS (M)$^+$ calcd. for C$_{10}$H$_{18}$O$_2$, 170.1307; found 170.1316.

2-((1E,3E)-penta-1,3-dienyl)-1,3-dioxolane (6-18u)

Yield 72% (4:1, $E/Z$), yellow oil; TLC (EtOAc:hexanes, 1:4 v/v): $R_f$ = 0.48; $^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 6.27 (dd, $J = 15.4, 10.5$ Hz, 1H), 5.98 (ddd, $J = 14.9, 10.5, 1.5$ Hz, 1H), 5.71 (dd, $J = 15.0, 6.8$ Hz, 1H), 5.42 (dd, $J = 15.4, 6.2$ Hz, 1H), 5.17 (d, $J = 6.2$ Hz, 1H), 3.92 – 3.89 (m, 2H), 3.80 (dd, $J = 6.2, 2.7$ Hz, 2H), 1.68 (dd, $J = 6.7, 1.2$ Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150
MHz] δ: 135.30, 132.44, 130.18, 125.55, 103.83, 64.94, 18.16; HREI MS (M)+ calcd. for C₈H₁₂O₂, 140.0837; found 140.0833.

General Preparation: To a microwave vial containing phosphonium salt 6-5 (190 mg, 0.60 mmol) is added THF (0.4 mL) and DMF (0.1 mL). The solution is then cooled to 0 °C for 15 minutes prior to the addition of KOtBu (56 mg, 0.60 mmol) portion-wise to afford a light yellow mixture. It is critical on scaling up that the temperature does not rise substantially on addition of the base. The mixture containing the base was left to stir at 0 °C for 30 minutes before the corresponding aldehyde 6-9a,m-u (0.50 mmol) was subsequently added in one portion. The reaction mixture was allowed to warm to room temperature overnight before being quenched with water (10 mL). Standard extractive work-up with diethyl ether (2 x 10 mL) was followed by washing the combined organic fractions with water (10 mL). The combined organic extracts were then dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the corresponding acetals. If required the acetals can be column chromatographed over neutralized silica gel. Sodium hydride that has been washed with pentane produces similar results.

(E)-2-(4-chlorostyryl)-4,4,5,5-tetramethyl-1,3-dioxolane (6-10a)

Yield 88%, pale yellow oil; TLC (EtOAc:hexanes, 1:9 v/v): Rf = 0.40; ¹H-NMR [CDCl₃, 600 MHz] δ: 7.15 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 15.9 Hz, 1H), 5.95 (dd, J = 15.9, 6.6 Hz, 1H), 5.34 (d, J = 6.6 Hz, 1H), 1.10 (s, 6H), 1.09 (s, 6H); ¹³C-NMR [CDCl₃, 150 MHz] δ: 134.57, 133.84, 133.04, 128.71, 128.41, 128.14, 100.41, 82.43, 24.00, 22.01.
(E)-2-(4-chlorostyryl)-4,4,5,5-tetramethyl-1,3-dioxolane (6-10n)

Yield 83%, pale yellow oil; TLC (EtOAc:hexanes, 1:9 v/v): R_f = 0.29; ^1H-NMR [CDCl_3, 600 MHz] δ: 7.27 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 15.8 Hz, 1H), 5.94 (dd, J = 15.8, 6.9 Hz, 1H), 5.44 (d, J = 6.9 Hz, 1H), 3.73 (s, 3H), 1.20 (s, 6H), 1.19 (s, 6H); ^13C-NMR [CDCl_3, 150 MHz] δ: 159.64, 134.05, 128.22, 125.45, 113.90, 100.97, 82.24, 55.26, 24.04, 22.02; HREI MS (M)^+ calcd. for C_{16}H_{22}O_3, 262.1569; found 262.1571.

(E)-2-(4-chlorostyryl)-4,4,5,5-tetramethyl-1,3-dioxolane (6-10o)

Yield 91%, white solid; TLC (EtOAc:hexanes, 1:9 v/v): R_f = 0.17; ^1H-NMR [CDCl_3, 600 MHz] δ: 7.53 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.65 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 15.9, 6.3 Hz, 1H), 5.47 (d, J = 6.3 Hz, 1H), 1.20 (s, 12H); ^13C-NMR [CDCl_3, 150 MHz] δ: 140.57, 132.40, 132.17, 131.68, 127.38, 118.81, 99.82, 82.66, 23.96, 22.00; HREI MS (M)^+ calcd. for C_{16}H_{19}NO_2, 257.1416; found 257.1409.

2-(cyclohexylidenemethyl)-4,4,5,5-tetramethyl-1,3-dioxolane (6-10p)

Yield 77%, colourless oil; TLC (EtOAc:hexanes, 1:4 v/v): R_f = 0.73; ^1H-NMR [CDCl_3, 600 MHz] δ: 5.67 (d, J = 8.1 Hz, 1H), 5.05 (d, J = 8.1 Hz, 1H), 2.17 (d, J = 5.9 Hz, 2H), 2.06 – 1.99 (m, 2H), 1.51 – 1.42 (m, 6H), 1.14 (s, 6H), 1.13 (s, 6H); ^13C-NMR [CDCl_3, 150 MHz] δ: 147.56, 120.73, 95.45, 81.86, 37.16, 28.96, 27.99, 27.64, 26.56, 24.15, 21.99; HREI MS (M)^+ calcd. for C_{14}H_{24}O_2, 224.1776; found 224.1777.

4,4,5,5-tetramethyl-2-((E)-2-phenylprop-1-enyl)-1,3-dioxolane (6-10q)

Yield 70% (13:7, E/Z), colourless oil; TLC (EtOAc:hexanes, 1:4 v/v): R_f = 0.70; (E)-Isomer: ^1H-NMR [CDCl_3, 600 MHz]
δ: 7.34 – 7.29 (m, 2H), 7.23 – 7.22 (m, 1H), 7.18 – 7.15 (m, 2H), 5.77 (d, J = 7.5 Hz, 1H), 5.64 (dd, J = 7.5, 1.3 Hz, 1H), 2.07 (d, J = 1.3 Hz, 3H), 1.17 (s, 6H), 1.16 (s, 6H), 1.04 (s, 3H); 13C-NMR [CDCl₃, 150 MHz] δ: 142.78, 141.19, 128.18, 127.54, 126.57, 126.04, 96.49, 82.12, 24.11, 22.03; (Z)-Isomer: 1H-NMR [CDCl₃, 600 MHz] δ: 7.25 – 7.23 (m, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.18 – 7.16 (m, J = 2.5, 1.4 Hz, 2H), 5.42 (dd, J = 8.3, 1.3 Hz, 1H), 5.21 (d, J = 8.3 Hz, 1H), 2.00 (d, J = 1.3 Hz, 3H), 1.16 (s, 6H), 1.04 (s, 6H); 13C-NMR [CDCl₃, 150 MHz] δ: 143.74, 140.07, 128.11, 127.99, 127.37, 125.88, 97.21, 82.08, 25.52, 16.26; HREI MS (M)+ calcd. for C₁₆H₂₂O₂, 246.1620; found 246.1618.

4,4,5,5-tetramethyl-2-((E)-4-phenylbut-1-enyl)-1,3-dioxolane (6-10m)

Yield 79% (4:1, E/Z), pale yellow oil; TLC (EtOAc:hexanes, 1:4 v/v): R₇ = 0.68; ¹H-NMR [CDCl₃, 600 MHz] δ: 7.17 (dt, J = 11.2, 3.7 Hz, 2H), 7.09 (dd, J = 12.6, 5.4 Hz, 3H), 5.82 (dt, J = 15.3, 6.6 Hz, 1H), 5.45 (dd, J = 15.4, 7.2 Hz, 1H), 5.23 (d, J = 7.2 Hz, 1H), 2.63 – 2.60 (m, 2H), 2.29 (td, J = 7.8, 1.1 Hz, 2H), 1.13 (s, 6H), 1.12 (s, 6H); ¹³C-NMR [CDCl₃, 150 MHz] δ: 141.66, 136.13, 129.30, 128.37, 125.90, 100.86, 82.11, 24.02, 21.98; HREI MS (M)+ calcd. for C₁₆H₂₄O₂, 260.1776; found 260.1776.

4,4,5,5-tetramethyl-2-((1E,3E)-4,8-dimethylnona-1,3,7-trienyl)-1,3-dioxolane (6-10r)

Yield 80% (mixture of isomers A/B/C/D, 8:8:42:42), colourless oil; TLC (EtOAc:hexanes, 1:9 v/v): R₇ = 0.39; Isomer C: ¹H-NMR [CDCl₃, 600 MHz] δ: 6.59 (dd, J = 15.1, 10.9 Hz, 1H), 5.88 (d, J = 11.0 Hz, 1H), 5.54 (dd, J = 15.0, 7.1 Hz, 1H), 5.44 (d, J = 7.3 Hz, 1H), 5.14 – 5.07 (m, 1H), 2.15 – 2.07 (m, 4H), 1.76 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.25 (s, 12H); ¹³C-NMR [CDCl₃, 150 MHz] δ:
141.53, 131.7, 130.73, 128.23, 123.82, 123.56, 100.95, 82.07, 39.91, 26.84, 25.68, 23.99, 23.89, 21.98, 17.68, 16.69; **Isomer D:** $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 6.59 (dd, $J$ = 15.1, 10.9 Hz, 1H), 5.88 (d, $J$ = 11.0 Hz, 1H), 5.54 (dd, $J$ = 15.0, 7.1 Hz, 1H), 5.44 (d, $J$ = 7.3 Hz, 1H), 5.14 – 5.07 (m, 1H), 2.15 – 2.07 (m, 4H), 1.82 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.25 (s, 12H);

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 141.53, 131.7, 130.73, 128.23, 123.82, 123.56, 100.95, 82.07, 39.91, 26.84, 25.68, 23.99, 23.89, 21.98, 17.68, 16.69; HRES MS (M)$^+$ calcd. for C$_{18}$H$_{30}$O$_2$, 278.2246; found 278.2239.

**4,4,5,5-tetramethyl-2-((E)-pent-1-enyl)-1,3-dioxolane (6-10s)**

Yield 74% (6:1, E/Z), colourless oil; TLC (EtOAc:hexanes, 1:4 v/v): $R_f$ = 0.77; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.87 (dd, $J$ = 15.2, 6.8 Hz, 1H), 5.48 (dd, $J$ = 15.3, 7.3 Hz, 1H), 5.34 (d, $J$ = 7.3 Hz, 1H), 2.06 (td, $J$ = 7.9, 1.1 Hz, 2H), 1.48 – 1.38 (m, 2H), 1.25 (s, 6H), 1.24 (s, 6H), 0.92 (t, $J$ = 7.4 Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 137.09, 128.85, 101.04, 82.01, 34.07, 24.01, 21.95, 21.92, 13.73; HREI MS (M)$^+$ calcd. for C$_{12}$H$_{22}$O$_2$, 198.1620; found 198.1622.

**4,4,5,5-tetramethyl-2-((E)-hept-1-enyl)-1,3-dioxolane (6-10t)**

Yield 76% (17:3, E/Z),, colourless oil; TLC (EtOAc:hexanes, 1:4 v/v): $R_f$ = 0.80; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.76 (dt, $J$ = 15.2, 6.7 Hz, 1H), 5.41 – 5.33 (m, 1H), 5.23 (d, $J$ = 7.3 Hz, 1H), 1.96 (td, $J$ = 8.0, 1.3 Hz, 2H), 1.30 (dt, $J$ = 14.5, 7.3 Hz, 2H), 1.22 – 1.16 (m, 4H), 1.13 (s, 6H), 1.12 (s, 6H), 0.78 (t, $J$ = 5.4 Hz, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 137.49, 128.77, 101.18, 82.12, 32.10, 31.52, 28.52, 24.13, 22.61, 22.08, 14.11; HREI MS (M)$^+$ calcd. for C$_{14}$H$_{26}$O$_4$, 226.1933; found 226.1935.

**4,4,5,5-tetramethyl-2-((1E,3E)-penta-1,3-dienyl)-1,3-dioxolane (6-10u)**

Yield 72% (7:1, E/Z), colourless oil; TLC (EtOAc:hexanes, 1:4 v/v): $R_f$ = 0.75; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 6.31 (dd, $J$ = 15.2, 10.5 Hz, 1H), 6.11 – 6.04 (m, 1H), 5.78 (dq, $J$ = 13.6, 6.7 Hz, 1H).
Hz, 1H), 5.53 (dd, $J = 15.3, 6.9$ Hz, 1H), 5.39 (d, $J = 7.0$ Hz, 1H), 1.78 (d, $J = 6.7$ Hz, 3H), 1.25 (s, 6H), 1.24 (s, 6H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 134.7, 131.9, 130.3, 128.2, 100.6, 82.1, 24.0, 22.0, 18.2; HREI MS (M)$^+$ calcd. for C$_{12}$H$_{20}$O$_2$, 196.1463; found 196.1469.

Synthesis of 6-11r: To 6-10r in acetone (24 mg, 0.086 mmol) in acetone (2.1 mL) at room temperature was added iron trichloride hexahydrate (1.2 mg, 4.3x10$^{-3}$ mmol). The yellow solution was stirred for 16 h, at which point water (5 mL) was added and volatile organic compounds were removed under reduced pressure. The remaining aqueous mixture was extracted with hexanes (3 x 5 mL) and the combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give 6-11r (14 mg, 88%, ~7:3 E/Z) as a yellow oil.

Physical State: yellow oil

$R_f = 0.20$ (EtOAc/hexanes, 1:9 v/v; 2,4-DNP)

$^1$H NMR [CDCl$_3$, 600 MHz] δ: 9.51 (d, $J = 8.0$ Hz, 1H), 7.33 (dd, $J = 15.0, 11.5$ Hz, 1H), 6.08 (d, $J = 11.5$ Hz, 1H), 6.02 (dd, $J = 14.9, 8.0$ Hz, 1H), 5.01 (t, $J = 6.1$ Hz, 1H), 2.14 – 2.09 (m, 4H), 1.88 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H)

$^{13}$C NMR [CDCl$_3$, 150 MHz] δ: 194.1, 153.0, 148.6, 132.6, 130.0, 123.8, 123.1, 40.5, 26.3, 25.7, 17.7, 17.6.
Synthesis of **SI-6-1**: DMP (6.0 mL, 48 mmol) and TsOH (64 mg, 0.325 mmol) were added to a solution of dimethyl L-tartrate (5.8 g, 32 mmol) in PhMe (38 mL). The resultant mixture was fitted with a Dean-Stark apparatus and heated at reflux for 16 h. The reaction mixture was then cooled to r.t. and saturated aqueous NaHCO$_3$ (25 mL) added. The resultant mixture was stirred at r.t. for 15 min then the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were sequentially washed with H$_2$O (20 mL) and brine (20 mL), then dried over anhydrous sodium sulphate and concentrated *in vacuo* to give **SI-6-1** (6.00 g, 86%) as a pale yellow oil.

**Physical State**: pale yellow oil

R$_f$ = 0.40 (EtOAc:hexanes, 1:4 v/v; KMnO$_4$)

[α]$_D$ = −59.9° (MeOH, c 0.98)  (lit. 55 [α]$_D$ = −58.7° (MeOH, c 0.86))

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 4.77 (d, $J = 1.7$ Hz, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 170.0, 113.8, 76.9, 52.7, 26.2.

Its spectroscopic data were in accordance with those reported in the literature. 56

Synthesis of **SI-6-2**: A solution of dimethyl (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **SI-6-1** (1.00 g, 4.58 mmol) in THF (10 mL) was slowly added drop-wise to a suspension of LiAlH$_4$ (0.348 g, 9.16 mmol) in THF (15 mL) at 0 °C. The resulting mixture was heated under reflux for 30 min to complete the reduction. The reaction was carefully quenched with aq. NaOH (15% w/w, 2 mL) and the resulting suspension was stirred for 1 h before it was filtered through a pad of celite washing with ethyl acetate.
The filtrate was dried over anhydrous sodium sulphate, the solvent was evaporated to afford diol **SI-6-2** (0.609 g, 82%) as a colourless oil.

**Physical State:** colourless oil

\[ R_f = 0.60 \text{ (EtOAc; KMnO}_4) \]

\[ [\alpha]_D = -6.3^\circ \text{ (MeOH, c 0.74)} \quad \text{(lit.}^{57} [\alpha]_D = -8.2^\circ \text{ (MeOH, c 1.0))} \]

**H-NMR** \([\text{CDCl}_3, 600 \text{ MHz}] \delta: 4.04 - 3.99 \text{ (m, 2H), 3.81 (ddd, } J = 11.8, 2.5, 1.3 \text{ Hz, 2H), 3.70 (ddd, } J = 11.8, 2.4, 1.3 \text{ Hz, 2H), 2.00 (br s, 2H), 1.43 (s, 6H).} \]

**C-NMR** \([\text{CDCl}_3, 150 \text{ MHz}] \delta: 109.3, 77.8, 61.9, 27.1. \]

Its spectroscopic data were in accordance with those reported in the literature.56

Synthesis of **SI-6-3**: NaH (60% in mineral oil, 400 mg, 10 mmol) was washed with pentane (10 mL), then vigorously stirred in THF (30 mL) at 0 °C. Diol **SI-6-2** (1.6 g, 10 mmol) in THF (20 mL) was then added dropwise and the resulting solution stirred at room temperature for 45 min before addition of TBSCl (1.5 g, 10 mmol) in a single portion. The reaction mixture was then left to stir at r.t. for 16 h. The mixture was diluted with diethyl ether (50 mL) and washed with saturated aq. NH\(_4\)Cl (50mL) and the aqueous layer further extracted with Et\(_2\)O (3 x 20 mL). The organic extracts were then dried over magnesium sulphate anhydrous, filtered and concentrated under reduced pressure to afford **SI-6-3** (2.32 g, 92%) as a pale yellow oil which is pure enough to proceed to the next step.

**Physical State:** colourless oil

\[ R_f = 0.51 \text{ (EtOAc:hexanes, 1:2 v/v; vanillin)} \]
$[\alpha]_D = +17.8^\circ$ (CHCl$_3$, c 2.32)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 4.00 – 3.95 (m, 1H), 3.90 – 3.83 (m, 2H), 3.76 (dd, $J = 11.5, 4.7$ Hz, 1H), 3.70 (dd, $J = 11.5, 4.4$ Hz, 1H), 3.68 – 3.63 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 109.2, 80.3, 78.3, 63.9, 62.9, 27.2, 27.0, 26.0, 18.4, -5.4, -5.4.

Synthesis of 6-26: To SI-6-3 (1.42 g, 5.14 mmol) in CH$_2$Cl$_2$ (32 mL) at room temperature were added DMSO (2.9 mL) and TEA (7.5 mL). The solution was then cooled to 0 °C prior to the addition of a solution of SO$_3$·py (3.27 g, 20.5 mmol) in DMSO (12.4 mL) dropwise over 20 minutes and stirring continued for 4 h at this temperature. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (50 mL) prior to extraction with Et$_2$O (3 x 50 mL). The combined organic fractions were dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. The crude aldehyde 6-20 was placed under high vacuum for 1 h and carried on directly to the next step.

To phosphonium salt 6-5 (2.96 g, 7.71 mmol) was added THF (4.0 mL) and DMF (1.6 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KOtBu (864 mg, 7.71 mmol) portion-wise to afford a light yellow mixture. Slow addition of the base is required to prevent local heating which causes degradation of the phosphonium salt. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 6-20 in THF (3.0 mL) was subsequently added dropwise. The reaction mixture was allowed to warm to room temperature overnight before being quenched with a
saturated NH₄Cl solution (20 mL). Standard extractive work-up with diethyl ether (3 x 20 mL) was followed by washing the combined organic fractions with brine (10 mL). The combined organic extracts were then dried over anhydrous MgSO₄ and concentrated under reduced pressure to give crude 6-26 which was flash chromatographed (silica gel, EtOAc:hexanes, 1:19 → 1:9 v/v) to give pure 6-26 (1.59 g, 77% two steps, 5:1 E/Z) as a light yellow oil.

**Physical State:** light yellow oil

R<sub>f</sub> = 0.21 (EtOAc:hexanes, 1:9 v/v; vanillin)

[α]<sub>D</sub> = −4.7 ° (CHCl₃, c 2.10)

**¹H-NMR** [CDCl₃, 600 MHz] δ: 5.90 (dd, J = 15.6, 5.9 Hz, 1H), 5.80 (ddd, J = 15.6, 6.2, 1.1 Hz, 1H), 5.38 (d, J = 6.2 Hz, 1H), 4.41 (t, J = 6.2 Hz, 1H), 3.77 – 3.70 (m, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.22 (s, 9H), 1.21 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

**¹³C-NMR** [CDCl₃, 150 MHz] δ: 132.7, 131.4, 109.4, 99.9, 81.4, 77.7, 62.6, 27.2, 27.1, 26.1, 24.1, 24.0, 22.1, -5.2, -5.3.

**HREI MS (m/z):** (M)<sup>+</sup> calcd. for C<sub>21</sub>H<sub>40</sub>O₅Si, 400.2645; found 400.2640.

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Synthesis of **SI-6-4**: To SI-6-3 (278 mg, 1.01 mmol) in CH₂Cl₂ (6.5 mL) at room temperature were added DMSO (0.6 mL) and TEA (1.5 mL). The solution was then cooled to 0 °C prior to the addition of a solution of SO₃·py (645 mg, 4.05 mmol) in DMSO (2.5 mL) dropwise over 10 minutes and stirring continued for 4 h at this temperature. The reaction was quenched with a saturated aqueous solution of NH₄Cl (50 mL) prior to extraction with EtOAc (3 x 10 mL). The combined organic fractions were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford
a yellow oil. The crude aldehyde 6-20 was placed under high vacuum for 1 h and carried on directly to the next step.

To phosphonium salt 6-16 (632 mg, 1.65 mmol) was added THF (1.3 mL) and DMF (0.3 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KO\textsubscript{t}Bu (185 mg, 1.65 mmol) portion-wise to afford a light yellow mixture. Slow addition of the base is required to prevent local heating which causes degradation of the phosphonium salt. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 6-20 was subsequently added neat and the residual added in THF (1.0 mL). The reaction mixture was allowed to warm to room temperature overnight before being quenched with a saturated NH\textsubscript{4}Cl solution (10 mL). Standard extractive work-up with diethyl ether (3 x 20 mL) was followed by washing the combined organic fractions with brine (10 mL). The combined organic extracts were then dried over anhydrous MgSO\textsubscript{4} and concentrated under reduced pressure to give crude SI-6-4 which was flash chromatographed (silica gel, EtOAc:hexanes, 1:19 → 1:9 v/v) to give pure SI-6-4 (282 mg, 81% two steps, 5:1 E/Z) as a light yellow oil.

**Physical State:** yellow oil

*R* = 0.36 (EtOAc:hexanes, 1:4 v/v)

[α]\textsubscript{D} = +8.6° \( \text{(CHCl}_{3}, c \ 1.27) \)

\(^1\text{H NMR} \) \([\text{CDCl}\textsubscript{3}, 600 \text{ MHz}] \delta: 5.90 (dd, J = 15.6, 6.1 \text{ Hz}, 1\text{H}), 5.74 (ddd, J = 15.6, 5.5, 1.1 \text{ Hz}, 1\text{H}), 5.22 (d, J = 5.0 \text{ Hz}, 1\text{H}), 4.34 (t, J = 6.3 \text{ Hz}, 1\text{H}), 3.95 – 3.89 (m, 3\text{H}), 3.86 – 3.81 (m, 3\text{H}), 3.80 – 3.76 (m, 1\text{H}), 3.71 – 3.67 (m, 3\text{H}), 3.67 – 3.61 (m, 1\text{H}), 1.35 (s, 3\text{H}), 1.34 (s, 3\text{H}), 0.83 (s, 12\text{H}), -0.00 (s, 3\text{H}), -0.00 (s, 3\text{H}).

\(^{13}\text{C NMR} \) \([\text{CDCl}\textsubscript{3}, 600 \text{ MHz}] \delta: 133.13, 128.95, 109.28, 102.86, 81.22, 77.67, 64.96, 64.89, 62.46, 26.99, 26.91, 25.89, -5.36, -5.44.

**HREI MS** \((m/z)\): \((M)^+\) calcd. for C\textsubscript{17}H\textsubscript{32}O\textsubscript{5}Si, 344.1997; found 344.2019.
Synthesis of **SI-6-5**: Homologated acetal **SI-6-4** (172 mg, 0.5 mmol) was added to acetone (10 mL) and IR-120H Amberlite® resin (50 mg). The mixture was stirred for 1 h at which point the mixture was filtered through solid NaHCO₃, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the corresponding homologated aldehyde (126 mg, 84%, 9:1, E/Z) as a pale yellow oil. The crude product was column chromatographed over silica gel (EtOAc/Hex, 1:9 v/v).

**Physical State**: colourless oil

\[R_f = 0.43\] (EtOAc:hexanes, 1:4 v/v)

[α]₀ = +2.5° (CHCl₃, c 0.99) (lit.⁵⁸ for enantiomer [α]₀ = −3.0° (CHCl₃, c 1.0))

**¹H NMR** [CDCl₃, 600 MHz] δ: 9.51 (d, \(J = 7.9\) Hz, 1H), 6.75 (dd, \(J = 15.7, 4.8\) Hz, 1H), 6.31 (ddd, \(J = 15.7, 7.9, 1.4\) Hz, 1H), 4.59 – 4.51 (m, 1H), 3.80 – 3.75 (m, 2H), 3.70 – 3.66 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 0.82 (s, 9H), 0.01 (s, 3H), -0.00 (s, 3H).

**¹³C NMR** [CDCl₃, 600 MHz] δ: 193.14, 153.39, 131.90, 110.25, 80.64, 78.15, 62.95, 26.90, 26.71, 25.84, 18.28, -5.41, -5.47.

**HREI MS (m/z)**: (M-CH₃)⁺ calcd. for C₁₄H₂₅O₄Si, 285.1522; found 285.1519.
Synthesis of 6-27: To SI-6-18 (1.01 g, 4.00 mmol) in CH₂Cl₂ (24 mL) at room temperature were added DMSO (2.0 mL) and TEA (6.0 mL). The solution was then cooled to 0 °C prior to the addition of a solution of SO₃∙py (2.55 g, 16.0 mmol) in DMSO (8 mL) dropwise over 20 minutes and stirring continued for 4 h at this temperature. The reaction was quenched with a saturated aqueous solution of NH₄Cl (50 mL) prior to extraction with Et₂O (3 x 50 mL). The combined organic fractions were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford a yellow oil. The crude aldehyde 6-21 was placed under high vacuum for 2 h and carried on directly to the next step.

To phosphonium salt 6-5 (2.45 g, 6.40 mmol) was added THF (5.1 mL) and DMF (1.3 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KO'Bu (718 mg, 6.40 mmol) portion-wise to afford a light yellow mixture. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 6-21 in THF (3.0 mL) was subsequently added dropwise. The reaction mixture was allowed to warm to room temperature overnight before being quenched with a saturated NH₄Cl solution (20 mL). Standard extractive work-up with diethyl ether (3 x 20 mL) was followed by washing the combined organic fractions with brine (10 mL). The combined organic extracts were then dried over anhydrous MgSO₄ and concentrated under reduced pressure to give crude 6-27 which was chromatographed (silica gel, EtOAc:hexanes, 1:19 → 1:9 v/v) to give pure 6-27 (1.16 g, 77% two steps, 5:1 E/Z) as a light yellow oil.

**Physical State:** colourless oil

\[ R_f = 0.25 \text{ (EtOAc:hexanes, 1:4 v/v; vanillin)} \]

\[ [\alpha]_D = -11.9^\circ \text{ (CHCl₃, c 1.05)} \]

**¹H-NMR [CDCl₃, 600 MHz]** \( \delta: 7.29 - 7.24 \text{ (m, 5H)}, 5.80 \text{ (dd, } J = 15.6, 6.3 \text{ Hz, 1H)}, 5.70 \text{ (ddd, } J = 15.5, 6.1, 0.9 \text{ Hz, 1H)}, 5.30 \text{ (d, } J = 6.1 \text{ Hz, 1H)}, 4.54 - 4.50 \text{ (m, 2H)}, 4.22 \text{ (ddd, } J = 8.2, 6.3, 0.8 \text{ Hz, 1H)}, 3.88 - 3.82 \text{ (m, 1H)}, 3.52 \text{ (qd, } J = 10.5, 4.6 \text{ Hz, 2H)}, 1.36 \text{ (s, 3H)}, 1.36 \text{ (s, 3H)}, 1.14 \text{ (s, 6H)}, 1.13 \text{ (s, 3H)}, 1.13 \text{ (s, 3H)} \).
$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 138.0, 132.2, 131.9, 128.4, 127.7, 127.7, 109.6, 99.5, 82.3, 80.0, 77.7, 73.6, 69.5, 27.0, 26.9, 23.9, 23.9, 22.0.

HRES MS (m/z): (M+H)$^+$ calcd. for C$_{22}$H$_{33}$O$_5$, 377.2328; found 377.2318.

Synthesis of 6-30: To benzyl ether 6-27 (52 mg, 0.14 mmol) in dry acetone was added FeCl$_3$$\cdot$6H$_2$O (3.7 mg, 14 μmol). The mixture was stirred for 12 h at which point water (5 mL) was added and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude oil was column chromatographed (silica gel, EtOAc:hexanes, 1:6 v/v) to afford 6-30 (24 mg, 64%) as a colourless oil.

Physical State: colourless oil

$R_f = 0.21$ (EtOAc:hexanes, 1:9 v/v; vanillin)

$[\alpha]_D = -14.5^\circ$ (CHCl$_3$, c 0.36)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 9.58 (d, $J = 7.9$ Hz, 1H), 7.38 – 7.35 (m, 2H), 7.34 – 7.31 (m, 3H), 6.79 (dd, $J = 15.7$, 5.0 Hz, 1H), 6.36 (ddd, $J = 15.7$, 7.9, 1.5 Hz, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.59 (d, $J = 12.1$ Hz, 1H), 4.56 (ddd, $J = 8.3$, 5.0, 1.5 Hz, 1H), 3.98 (dt, $J = 8.3$, 5.0 Hz, 1H), 3.70 (dd, $J = 10.2$, 4.8 Hz, 1H), 3.63 (dd, $J = 10.2$, 5.2 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 193.2, 152.8, 137.7, 132.4, 128.7, 128.1, 127.9, 110.7, 79.5, 78.1, 73.9, 69.6, 27.1, 26.8.

HREI MS (m/z): (M+Na)$^+$ calcd. for C$_{16}$H$_{20}$O$_4$Na, 299.1259; found 299.1261.
Synthesis of SI-6-7: To methyl serinate hydrochloride (1.56 g, 10.0 mmol) suspended in THF (50 mL) at 0 °C was added triethylamine (3.0 mL) followed by Boc₂O (2.20 g, 10.1 mmol) in THF (20 mL) dropwise over a period of 30 minutes. After 10 min of additional stirring, the ice-water bath was removed and the suspension stirred overnight at room temperature, then warmed at 50°C for a further 3 hr. The solvent was removed under reduced pressure and the residue partitioned between diethyl ether (20 mL) and a saturated NaHCO₃ solution. After further extraction with diethyl ether (3 x 20 mL) the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to give SI-6-7 (2.10 g, 96%) as a colourless oil.

**Physical State:** colourless oil

\[ R_f = 0.21 \text{ (EtOAc:hexanes, 3:7 v/v)} \]

\[ [\alpha]_D = -16.7^\circ \text{ (MeOH, } c \ 4.74) \] (lit.\(^59\) \([\alpha]_D = -17.0^\circ \text{ (MeOH, } c \ 4.41))\]

\(^1\text{H NMR [CDCl}_3, 600 \text{ MHz]} \delta: 5.37 \text{ (s, 1H), 4.33 (s, 1H), 3.93 – 3.87 (m, 1H), 3.87 – 3.82 (m, 1H), 3.72 (s, 3H), 2.19 (s, 1H), 1.39 (s, 9H).}\]

\(^13\text{C NMR [CDCl}_3, 150 \text{ MHz]} \delta: 171.3, 155.8, 80.4, 63.6, 55.7, 52.7, 28.3.\]

Its spectroscopic data were in accordance with those reported in the literature.\(^60\)

Synthesis of SI-6-8: To a solution of SI-6-7 (1.0 g, 4.56 mmol) in acetone (20 mL) is added 2,2-dimethoxypropane (5 mL, 40.0 mmol) and boron trifluoride etherate (0.035
mL, 0.28 mmol). The resulting orange solution was stirred at room temperature for 2.5 hr at which point the reaction mixture was treated with triethylamine (0.2 mL) and the solvent removed under reduced pressure. The residual brown syrup is partitioned between diethyl ether (20 mL) and saturated NaHCO$_3$ solution (40 mL). The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give crude oxazolidine methyl ester SI-6-8 (1.06 g, 90%). The product was used without further purification.

**Physical State**: pale yellow oil

$R_f = 0.34$ (EtOAc:hexanes, 1:9 v/v)

$[\alpha]_D = -51.7^\circ$ (CHCl$_3$, c 1.13) (lit.$^{61}$ $[\alpha]_D = -54.0^\circ$ (CHCl$_3$, c 1.30))

**Major Rotamer:**

$^1$H NMR [CDCl$_3$, 600 MHz] $\delta$: 4.31 (dd, $J = 7.0$, 3.0 Hz, 1H), 4.10 – 4.07 (m, 1H), 3.96 (dd, $J = 9.2$, 3.0 Hz, 1H), 3.69 (s, 3H), 1.60 (s, 3H), 1.47 (s, 3H), 1.35 (s, 9H).

$^{13}$C NMR [CDCl$_3$, 150 MHz] $\delta$: 171.7, 151.2, 95.0, 80.3, 66.3, 59.3, 52.3, 28.3, 24.9, 24.4.

**Minor Rotamer:**

$^1$H NMR [CDCl$_3$, 600 MHz] $\delta$: 4.42 (dd, $J = 6.8$, 2.4 Hz, 1H), 4.06 (dd, $J = 7.9$, 5.8 Hz, 1H), 3.99 (dd, $J = 9.2$, 2.5 Hz, 1H), 3.69 (s, 3H), 1.57 (s, 3H), 1.43 (s, 12H).

$^{13}$C NMR [CDCl$_3$, 150 MHz] $\delta$: 171.3, 152.1, 94.4, 80.9, 66.0, 59.2, 52.4, 28.3, 26.0, 25.2.

Its spectroscopic data were in accordance with those reported in the literature.$^{60}$
Synthesis of 6-23: To SI-6-8 (520 mg, 2.0 mmol) in dry toluene (4 ml) at -78 °C was added a -78 °C solution of DIBAL-H (1.0 M in toluene, 2.3 ml) dropwise via cannula. After addition, the reaction mixture was stirred for an additional 2.5 h at –78 °C. The reaction was quenched by slowly adding cold CH₃OH (2 mL at -78 °C) making sure the internal temperature did not rise above –60 °C. The resulting white emulsion was slowly poured into 15 ml of ice-cold 1 N HCl with stirring over 15 min, and the aqueous mixture was then extracted with EtOAc (3 × 10 ml), dried with MgSO₄, filtered and concentrated under reduced pressure to give crude product 6-23 as a yellow oil, which was subsequently flash column chromatographed (silica gel, EtOAc/Hexanes, 1:9 v/v) to afford Garner’s aldehyde 6-23 (377 mg, 82%) as a colourless oil.

**Physical State:** colourless oil

\[ R_f = 0.30 \text{ (EtOAc:hexanes, 1:9 v/v)} \]

\[ [\alpha] = -90.0^\circ \text{ (CHCl}_3, \ c 1.72) \text{ (lit.}^{62} [\alpha] = -91.7^\circ \text{ (CHCl}_3, \ c 1.34)) \]

**Major Rotamer:**

\[^1H\text{ NMR [CDCl}_3, \ 600\text{ MHz}] \delta: 9.48 \text{ (d, } J = 2.3 \text{ Hz, } 1H), 4.13 \text{ (dd, } J = 6.5, 3.1 \text{ Hz, } 1H), 4.03 \text{ (t, } J = 8.1 \text{ Hz, } 2H), 1.59 \text{ (s, } 3H), 1.49 \text{ (s, } 3H), 1.37 \text{ (s, } 9H).\]

\[^{13}C\text{ NMR [CDCl}_3, \ 150\text{ MHz}] \delta: 198.5, 150.3, 94.1, 80.1, 63.7, 62.9, 27.3, 24.8, 22.8.\]

**Minor Rotamer:**

\[^1H\text{ NMR [CDCl}_3, \ 600\text{ MHz}] \delta: 9.54 \text{ (s, } 1H), 4.28 \text{ (d, } J = 6.4 \text{ Hz, } 1H), 4.00 \text{ (dd, } J = 9.1, 3.0 \text{ Hz, } 3H), 1.53 \text{ (s, } 3H), 1.45 \text{ (s, } 3H), 1.45 \text{ (s, } 9H).\]

\[^{13}C\text{ NMR [CDCl}_3, \ 150\text{ MHz}] \delta: 198.5, 151.6, 93.3, 80.4, 63.8, 62.5, 27.3, 25.7, 23.7.\]

Its spectroscopic data were in accordance with those reported in the literature. \(^{63}\)
Synthesis of 6-28: To phosphonium salt 6-5 (619 mg, 1.61 mmol) was added THF (0.8 mL) and DMF (0.2 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KOtBu (182 mg, 1.61 mmol) portion-wise to afford a light yellow mixture. Slow addition of the base is required to prevent local heating which causes degradation of the phosphonium salt. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 6-23 (231 mg, 1.01 mmol) was subsequently added dropwise. The reaction mixture was allowed to warm to room temperature overnight before being quenched with a saturated NH₄Cl solution (10 mL). Standard extractive work-up with diethyl ether (3 x 5 mL) was followed by washing the combined organic fractions with brine (10 mL). The combined organic extracts were then dried over anhydrous MgSO₄ and concentrated under reduced pressure to give crude 6-28 which was flash chromatographed (silica gel, EtOAc:hexanes, 1:19 → 1:9 v/v) to give pure 6-28 (309 mg, 86%) as a colourless oil.

**Physical State:** colourless oil

$R_f = 0.32$ (EtOAc:hexanes, 1:4 v/v)

$[\alpha]_D^0 = +6.8^\circ$ (CHCl₃, c 1.15)

$^1H$ NMR [Tol-d₈, 500 MHz, 70 °C] $\delta$: 5.80 (dd, $J = 15.3, 7.2$ Hz, 1H), 5.72 (dd, $J = 15.3, 4.5$ Hz, 1H), 5.40 (d, $J = 5.5$ Hz, 1H), 4.16 (s, 1H), 3.72 (dd, $J = 8.6, 6.3$ Hz, 1H), 3.51 (dd, $J = 8.8, 2.1$ Hz, 1H), 1.69 (s, 3H), 1.54 (s, 3H), 1.47 (s, 9H), 1.13 (s, 6H), 1.09 (d, $J = 2.0$ Hz, 6H).

$^{13}C$ NMR [Tol-d₈, 500 MHz, 70 °C] $\delta$: 152.2, 133.7, 132.3, 100.5, 94.5, 82.3, 79.7, 68.5, 59.2, 28.8, 27.3, 24.4, 24.3, 22.4.
HREI MS \((m/z)\): \((\text{M}-\text{CH}_3)^+\) calcd. for \(\text{C}_{18}\text{H}_{30}\text{NO}_5\), 340.2124; found 340.2133.

Synthesis of SI-6-9: To phosphonium salt 6-16 (619 mg, 1.61 mmol) was added THF (0.8 mL) and DMF (0.2 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KO\(_\text{tBu}\) (182 mg, 1.61 mmol) portion-wise to afford a light yellow mixture. Slow addition of the base is required to prevent local heating which causes degradation of the phosphonium salt. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 6-23 (231 mg, 1.01 mmol) was subsequently added dropwise. The reaction mixture was allowed to warm to room temperature overnight before being quenched with a saturated NH\(_4\)Cl solution (10 mL). Standard extractive work-up with diethyl ether (3 x 5 mL) was followed by washing the combined organic fractions with brine (10 mL). The combined organic extracts were then dried over anhydrous MgSO\(_4\) and concentrated under reduced pressure to give crude SI-6-9 which was flash chromatographed (silica gel, EtOAc:hexanes, 1:19 → 1:9 v/v) to give pure SI-6-9 (235 mg, 78%) as a colourless oil.

**Physical State**: yellow oil

\(R_f = 0.26\) (EtOAc:hexanes, 1:4 v/v)

\([\alpha]_D = +4.4^\circ\) (CHCl\(_3\), c 1.02)

\(^1\text{H NMR}\) [Tol-d\(_8\), 500 MHz, 70 °C] \(\delta\): 5.84 (dd, \(J = 15.4, 7.3\) Hz, 1H), 5.68 (dd, \(J = 15.4, 4.8\) Hz, 1H), 5.18 (d, \(J = 5.4\) Hz, 1H), 4.14 (s, 1H), 3.71 (dd, \(J = 8.8, 6.3\) Hz, 1H), 3.63 – 3.59 (m, 2H), 3.50 – 3.46 (m, 3H), 1.67 (s, 3H), 1.53 (s, 3H), 1.46 (s, 9H), 1.44 (s, 3H)

\(^{13}\text{C NMR}\) [Tol-d\(_8\), 125 MHz, 70 °C] \(\delta\): 152.21, 134.80, 129.60, 103.77, 94.61, 79.77, 68.42, 65.19, 65.15, 59.10, 28.77, 27.29, 24.60
HREI MS \((m/z)\): \((M)^+\) calcd. for C\(_{15}\)H\(_{25}\)NO\(_5\), 299.1733; found 299.1745.

![Chemical structure of SI-6-9 and SI-6-10](image)

Synthesis of SI-6-10: Homologated acetal SI-6-9 (60 mg, 0.2 mmol) was added to acetone (10 mL) and IR-120H Amberlite\textsuperscript{®} resin (20 mg). The mixture was stirred for 1 h at which point the mixture was filtered through solid NaHCO\(_3\), dried over MgSO\(_4\), filtered and concentrated under reduced pressure to afford the corresponding homologated aldehyde (44 mg, 86%) as a pale yellow oil.

**Physical State**: pale yellow oil

\(R_f = 0.28\) (EtOAc:hexanes, 1:4 v/v)

\([\alpha]_D = -19.6^\circ\) (CHCl\(_3\), c 0.83)

\(^1\text{H NMR} [\text{Tol-d}_8, 500 \text{ MHz, } 70 \text{ °C}] \delta: 9.30 (d, J = 7.4 \text{ Hz, } 1 \text{H}), 6.20 (dd, J = 15.6, 6.8 \text{ Hz, } 1 \text{H}), 6.02 (dd, J = 15.4, 6.8 \text{ Hz, } 1 \text{H}), 4.09 (\text{broad s, } 1 \text{H}), 3.63 (dd, J = 9.0, 6.5 \text{ Hz, } 1 \text{H}), 3.34 (dd, J = 9.1, 2.6 \text{ Hz, } 1 \text{H}), 1.60 (s, 3 \text{H}), 1.48 (s, 3 \text{H}), 1.35 (s, 9 \text{H})

\(^{13}\text{C NMR} [\text{Tol-d}_8, 125 \text{ MHz, } 70 \text{ °C}] \delta: 190.89, 152.56, 132.68, 79.63, 66.90, 57.94, 27.87

HREI MS \((m/z)\): \((M−\text{CH}_3)^+\) calcd. for C\(_{12}\)H\(_{18}\)NO\(_4\), 240.1236; found 240.1236

![Chemical structure of SI-6-11](image)

Synthesis of SI-6-11: To (S)-glutamic acid (0.99 g, 6.7 mmol) in water (10 mL) was added 2 N HCl (4 mL), and the solution is cooled to 0 °C. A solution of sodium nitrite (0.55 g, 8.0 mmol) in water (4 mL) was added dropwise at a rate that maintains the temperature of the reaction solution below 4 °C. The ice bath was removed and the
mixture stirred for an additional 2 h, during which time the opaque mixture warmed to room temperature and became clear and colourless. The reaction solution was concentrated under reduced pressure to a viscous syrup containing white solid. To this was added acetonitrile (8 mL) and anhydrous Na$_2$SO$_4$. The mixture is stirred magnetically for fifteen minutes, filtered and concentrated under reduced pressure to yield a pale yellow syrup which was purified by recrystallisation from benzene/diethyl ether (1:1 v/v) to give SI-6-11 (650 mg, 74%) as a white crystalline solid.

**Physical State**: white crystalline solid

$R_f = 0.29$ (EtOAc:hexanes, 1:9 v/v)

$[\alpha]_D = +14.9^\circ$ (95% EtOH, $c$ 1.87) (lit.$^{64}$ $[\alpha]_D = +15.6^\circ$ (EtOH, $c$ 2))

$^1$H NMR [Acetone-d$_6$, 600 MHz] $\delta$: 5.03 (dd, $J = 8.6$, 4.8 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.58 – 2.53 (m, 2H), 2.39 – 2.31 (m, 1H).

$^{13}$C NMR [Acetone-d$_6$, 150 MHz] $\delta$: 176.9, 171.9, 76.3, 27.3, 26.6.

Synthesis of SI-6-12: To a cooled (0 °C) suspension of LiAlH$_4$ (1.48 g, 39.0 mmol) in THF (30 ml) was added dropwise a solution of 5-oxotetrahydrofuran-2-carboxylic acid SI-6-11 (1.95 g, 15.0 mmol) in THF (20 ml). After complete addition, the reaction mixture was refluxed for 20 h, cooled to room temperature and neutralized with 20% H$_2$SO$_4$. The inorganic salts were filtered off and washed with THF (10 ml). After
concentration of the filtrate under reduced pressure the remaining water was distilled off in high vacuo \((5 \times 10^{-2} \text{ mbar}, 60 \, ^\circ\text{C})\) to give the pure \textbf{SI-6-12} \((1.50 \, \text{g}, 83\%)\) as a pale yellow oil.

**Physical State**: pale yellow oil

\(R_f = 0.32\) (EtOAc:MeOH, 6:1 v/v)

\([\alpha]_D = -11.1^\circ\) (MeOH, \(c\ 3.43\)) \((\text{litr.} 65\) \([\alpha]_D = -12.5^\circ\) (MeOH, \(c\ 1\)).

\(^1\text{H NMR}\) [CD\(_3\)OD, 600 MHz] \(\delta:\ 3.64 – 3.57\) (m, 3H), 3.50 (dd, \(J = 11.1, 4.6\) Hz, 1H), 3.46 (dd, \(J = 11.1, 6.5\) Hz, 1H), 1.77 – 1.68 (m, 1H), 1.65 – 1.58 (m, 2H), 1.48 – 1.36 (m, 1H).

\(^{13}\text{C NMR}\) [CD\(_3\)OD, 150 MHz] \(\delta:\ 73.1, 67.4, 63.1, 30.9, 29.8\).

Synthesis of \textbf{SI-6-13}: To a solution of the \textbf{SI-6-12} \((1.03 \, \text{g}, 8.57 \, \text{mmol})\) and 2,2-dimethoxypropane \((8.25 \, \text{ml}, 66.9 \, \text{mmol})\) in acetone \((45 \, \text{ml})\) was added (+)-camphorsulfonic acid \((206 \, \text{mg}, 0.885 \, \text{mmol})\) and the reaction mixture stirred for 16 h at room temperature. The reaction was quenched by addition of triethylamine \((1.2 \, \text{ml})\) before the solvent was removed under reduced pressure. The residue was dissolved in EtOAc \((10 \, \text{ml})\), the ammonium salt filtered off and washed with EtOAc \((10 \, \text{ml})\). To the combined filtrate was added (+)-camphorsulphonic acid \((252 \, \text{mg}, 1.09 \, \text{mmol})\) and the mixture stirred for 10 minutes to cleave any mixed acetal present at the primary hydroxyl. The reaction was quenched by addition of a 10% K\(_2\)CO\(_3\) solution \((40 \, \text{ml})\). The layers were separated and the aqueous layer was extracted with EtOAc \((20 \, \text{ml})\). The combined organic layers were dried with MgSO\(_4\), filtered, and concentrated under reduced pressure to give \textbf{SI-6-13} \((1.14 \, \text{g}, 83\%)\) as a pale yellow oil.

**Physical State**: pale yellow oil

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$R_f = 0.19$ (EtOAc:hexanes, 1:1 v/v; vanillin)

$[\alpha]_D = +20.6^\circ$ (CHCl$_3$, c 0.60) (lit. $[\alpha]_D = +14.2^\circ$ (CHCl$_3$, c 2.2))

$^1$H NMR [CDCl$_3$, 600 MHz] $\delta$: 4.06 (tdd, $J = 7.2, 4.8, 2.2$ Hz, 1H), 3.99 (dd, $J = 7.9, 6.0$ Hz, 1H), 3.61 (s, 2H), 3.47 (t, $J = 7.6$ Hz, 1H), 1.68 – 1.53 (m, 4H), 1.36 – 1.33 (s, 3H), 1.29 (s, 3H).

$^{13}$C NMR [CDCl$_3$, 150 MHz] $\delta$: 109.0, 76.0, 69.5, 62.7, 30.3, 29.2, 26.9, 25.7.

Synthesis of 6-25: To a suspension of SI-6-13 (702 mg, 4.38 mmol) and NaHCO$_3$ (3.38 g, 40.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added Dess-Martin periodinane (2.23 g, 5.26 mmol). The reaction mixture was stirred for an hour, diluted with diethyl ether (12 mL) and hexanes (12 mL), filtered through celite, and stirred over freshly ground K$_2$CO$_3$ (1 g) for 30 min. After filtration through celite and solvent evaporation, there was isolated 6-25 (603 mg, 87%) as a pale yellow oil which was used without further purification.

Physical State: pale yellow oil

$R_f = 0.45$ (EtOAc:hexanes, 1:1 v/v; vanillin)

$[\alpha]_D = -2.6^\circ$ (CHCl$_3$, c 2.14) (lit. $[\alpha]_D = -2.2^\circ$ (CHCl$_3$, c 3.46))

$^1$H NMR [CDCl$_3$, 600 MHz] $\delta$: 9.74 (t, $J = 1.3$ Hz, 1H), 4.18 – 4.12 (m, 1H), 4.07 (dd, $J = 8.0, 6.1$ Hz, 1H), 3.57 (dd, $J = 7.8, 7.1$ Hz, 1H), 2.73 – 2.52 (m, 2H), 1.95 (dd, $J = 12.2, 7.1, 4.4$ Hz, 1H), 1.85 (td, $J = 14.2, 7.8$ Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

$^{13}$C NMR [CDCl$_3$, 150 MHz] $\delta$: 201.7, 109.1, 74.9, 69.1, 40.1, 26.9, 26.0, 25.5.
Synthesis of 6-29: To phosphonium salt 6-5 (810 mg, 2.11 mmol) was added THF (0.8 mL) and DMF (0.2 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KOtBu (237 mg, 2.11 mmol) portion-wise to afford a light yellow mixture. Slow addition of the base is required to prevent local heating which causes degradation of the phosphonium salt. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 6-25 (209 mg, 1.32 mmol) in THF (0.2 mL) was subsequently added dropwise. The reaction mixture was allowed to warm to room temperature overnight before being quenched with a saturated NH₄Cl solution (20 mL). Standard extractive work-up with diethyl ether (3 x 20 mL) was followed by washing the combined organic fractions with brine (10 mL). The combined organic extracts were then dried over anhydrous MgSO₄ and concentrated under reduced pressure to give crude 6-29 which was flash chromatographed (silica gel, EtOAc:hexanes, 1:19 → 1:9 v/v) to give pure 6-29 (301 mg, 80%, 5:1 E/Z) as a colourless oil.

Physical State: colourless oil

\[ R_f = 0.29 \text{ (EtOAc:hexanes, 1:9 v/v; vanillin)} \]

\[ [\alpha]_D = +9.5^\circ \text{ (CHCl}_3, c 0.93) \]

\[^{1}H \text{ NMR [CDCl}_3, 600 \text{ MHz}] \delta: 5.88 \text{ (dt, } J = 15.3, 6.6 \text{ Hz, } 1H), 5.52 \text{ (ddt, } J = 15.4, 7.2, 1.4 \text{ Hz, } 1H), 5.34 \text{ (d, } J = 7.2 \text{ Hz, } 1H), 4.10 \text{ (ddd, } J = 12.9, 7.0, 6.0 \text{ Hz, } 1H), 4.04 \text{ (dd, } J = 7.8, 6.0 \text{ Hz, } 1H), 3.52 \text{ (t, } J = 7.5 \text{ Hz, } 1H), 2.26 - 2.18 \text{ (m, } 1H), 2.16 - 2.08 \text{ (m, } 1H), 1.75 \text{ (dddd, } J = 12.8, 9.8, 7.0, 5.7 \text{ Hz, } 1H), 1.62 \text{ (ddt, } J = 13.5, 9.8, 5.8 \text{ Hz, } 1H), 1.41 \text{ (s, } 3H), 1.36 \text{ (s, } 3H), 1.24 \text{ (s, } 6H), 1.23 \text{ (s, } 6H). \]

\[^{13}C \text{ NMR [CDCl}_3, 150 \text{ MHz}] \delta: 135.8, 129.5, 108.8, 100.8, 82.1, 75.4, 69.3, 32.7, 28.2, 26.9, 25.7, 24.0, 22.0. \]
HRES MS ($m/z$): (M+H)$^+$ calcd. for C$_{16}$H$_{29}$O$_4$, 285.2066; found 285.2060.

Synthesis of 6-29: To protected diol 6-29 (63 mg, 0.22 mmol) in dry acetone was added FeCl$_3$•6H$_2$O (6.0 mg, 22 μmol). The mixture was stirred for 2 h at which point water (5 mL) was added and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude oil was column flash chromatographed (silica gel, EtOAc:hexanes, 1:6 v/v) to afford 6-29 (36 mg, 88%) as a colourless oil.

**Physical State**: colourless oil

$R_f$ = 0.29 (EtOAc:hexanes, 1:9 v/v)

$[\alpha]_D = +9.5^\circ$ (CHCl$_3$, c 0.93)

$^1$H NMR [CDCl$_3$, 600 MHz] $\delta$: 9.45 (d, $J$ = 7.8 Hz, 1H), 6.80 (dt, $J$ = 15.6, 6.7 Hz, 1H), 6.08 (ddt, $J$ = 15.6, 7.8, 1.5 Hz, 1H), 4.06 (dt, $J$ = 7.1, 6.0 Hz, 1H), 4.00 (dd, $J$ = 7.9, 6.0 Hz, 1H), 3.49 (dd, $J$ = 7.9, 7.0 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.39 – 2.31 (m, 1H), 1.77 – 1.63 (m, 2H), 1.35 (s, 3H), 1.29 (s, 3H).


HREI MS ($m/z$): (M)$^+$ calcd. for C$_{10}$H$_{17}$O$_3$, 185.1178; found 185.1177.
Synthesis of **SI-6-14**: Solid P₂O₅ (2.34 g, 16.5 mmol) was added in several portions over 2 h to a stirring solution of dimethyl L-tartrate (2.49 g, 12.1 mmol) and dimethoxymethane (2.5 mL) in CH₂Cl₂ (25 mL). After an additional 1 h, the reaction mixture was poured into saturated NaHCO₃ solution (30 mL) and extracted with CH₂Cl₂ (4 x 10 mL). The combined organic phase was washed with H₂O (2 x 10 mL) and dried over MgSO₄. The solvent was removed under reduced pressure to afford **SI-6-14** (2.61 g, 81%) as a colourless oil.

**Physical State**: colourless oil

\[ R_f = 0.32 \text{ (EtOAc:hexanes, 1:4 v/v; vanillin)} \]

\[ [\alpha]_D = +159.1^\circ \text{ (CHCl}_3, \ c \ 1.02) \text{ (lit.}^{68} \ [\alpha]_D = +155.9^\circ \text{ (CHCl}_3, \ c \ 1.00)) \]

\(^1\text{H-NMR [CDCl}_3, \ 600 \text{ MHz]} \delta: 4.79 \text{ (d, } J = 7.1 \text{ Hz, } 1\text{H}), 4.72 \text{ (s, } 1\text{H}), 4.67 \text{ (d, } J = 7.1 \text{ Hz, } 1\text{H}), 3.80 \text{ (s, } 3\text{H}), 3.35 \text{ (s, } 3\text{H}).\]

\(^{13}\text{C-NMR [CDCl}_3, \ 150 \text{ MHz]} \delta: 169.34, 96.43, 75.45, 56.23, 52.28.\]

Synthesis of **SI-6-15**: A stirred suspension of LiAlH₄ (640 mg, 16.9 mmol) in Et₂O (30 mL) was treated with a solution of the above bis-MOM ester **SI-6-14** (2.14 g, 8.03 mmol) in Et₂O (15 mL) dropwise over 1 h and the resulting mixture was refluxed for 2 h at which point it was cooled to 0-5 °C and quenched with successive H₂O (1.83 mL), 15% NaOH (1.83 mL), and H₂O (5.49 mL). The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting crude oil was purified by flash chromatographed (silica gel, EtOAc/hexane, 4/1) to afford diol **SI-6-15** (1.52, 90%) as a colourless oil.

**Physical State**: colourless oil
\( R_f = 0.32 \) (EtOAc; vanillin)

\([\alpha]_D = -40.4^\circ \) (CHCl\(_3\), c 1.18) (lit. \( [\alpha]_D = -42.0^\circ \) (CHCl\(_3\), c 1.00))

\(^1\text{H-NMR}\) [CDCl\(_3\), 600 MHz] \( \delta: 4.78 \) (d, \( J = 6.8 \) Hz, 1H), 4.73 (d, \( J = 6.8 \) Hz, 1H), 3.82 – 3.71 (m, 3H), 3.45 (s, 3H).

\(^{13}\text{C-NMR}\) [CDCl\(_3\), 150 MHz] \( \delta: 97.41, 80.26, 61.88, 55.96. \)

Synthesis of SI-6-16: NaH (60% in mineral oil, 200 mg, 4.99 mmol) was washed with pentane (10 mL), then vigorously stirred in THF (15 mL) at 0 \(^\circ\)C. Diol SI-15 (1.05 g, 4.99 mmol) in THF (10 mL) was then added dropwise and the resulting solution stirred at room temperature for 45 min before addition of TBSCl (750 mg, 4.99 mmol) in a single portion. The reaction mixture was then left to stir at room temperature for 16 h. The mixture was diluted with diethyl ether (25 mL) and washed with saturated aq. NH\(_4\)Cl (30 mL) and the aqueous layer further extracted with Et\(_2\)O (3 x 10 mL). The organic extracts were then dried over magnesium sulphate anhydrous, filtered and concentrated under reduced pressure to afford SI-6-16 (1.36 g, 84%) as a colourless oil which is pure enough to proceed to the next step.

**Physical State**: colourless oil

\( R_f = 0.32 \) (EtOAc:hexanes, 1:4 v/v; vanillin)

\([\alpha]_D = +3.2^\circ \) (CHCl\(_3\), c 1.13)

\(^1\text{H-NMR}\) [CDCl\(_3\), 600 MHz] \( \delta: 4.69 \) (dd, \( J = 8.3, 6.9 \) Hz, 2H), 4.61 (dd, \( J = 20.6, 6.8 \) Hz, 2H), 3.75 – 3.63 (m, 6H), 3.37 (s, 3H), 3.34 (s, 3H), 0.83 (s, 9H), -0.00 (s, 6H).
13C-NMR [CDCl₃, 150 MHz] δ: 97.75, 97.26, 80.58, 78.42, 62.68, 62.10, 55.88, 55.86, 25.82, 18.18, -5.47, -5.52

HREI MS (m/z): (M+Na)+ calcd. for C₁₄H₃₂O₆NaSi, 347.1866; found 347.1855.

Synthesis of SI-6-17: To a flame-dried two-necked round-bottomed flask was added freshly distilled oxalyl chloride (0.35 mL, 4.0 mmol) in CH₂Cl₂ (10 mL). The flask was then cooled to -78 °C prior to the drop-wise addition of DMSO (0.5 mL) in CH₂Cl₂ (2 mL). After 5 minutes of stirring at -78 °C mono-silyl alcohol SI-6-16 (650 mg, 2.0 mmol) in CH₂Cl₂ (1 mL) was added drop-wise and, after 15 minutes at this temperature, triethylamine (1 mL) was subsequently added. The reaction was allowed to then slowly warm to room temperature over the next 3 hours at which point a saturated aqueous solution of NH₄Cl (15 mL) was added. Extraction with diethyl ether (30 mL) and subsequent washing of the organic layer with saturated aqueous NaHCO₃ and brine followed by drying over anhydrous MgSO₄ and concentration under reduced pressure afforded the crude aldehyde (570 mg, 88%) as a colourless oil. No further purification was necessary.

Physical State: colourless oil

Rf = 0.32 (EtOAc:hexanes, 1:4 v/v; vanillin)

[α]D = +24.9° (CHCl₃, c 1.18)

1H-NMR [CDCl₃, 600 MHz] δ: 9.71 (d, J = 0.6 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.9 Hz, 1H), 4.55 (d, J = 6.9 Hz, 1H), 4.14 (d, J = 2.8 Hz, 1H), 3.97 (ddd, J = 7.4, 5.2, 3.2 Hz, 1H), 3.71 (qd, J = 10.1, 6.3 Hz, 2H), 3.38 (s, 3H), 3.27 (s, 3H), 0.82 (s, 9H), -0.00 (s, 3H), -0.00 (s, 3H).
$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 202.30, 97.60, 96.87, 81.30, 77.89, 60.92, 56.19, 55.83, 25.80, 18.17, -5.47, -5.55.

**HREI MS (m/z):** (M+H)$^+$ calcd. for C$_{14}$H$_{31}$O$_6$NaSi, 323.1890; found 323.1893.

![Synthesis of SI-6-18](image)

Synthesis of **SI-6-18**: NaH (60% in mineral oil, 400 mg, 10 mmol) was washed with pentane (10 mL), then vigorously stirred in THF (30 mL) at 0 °C. Diol **SI-6-2** (1.6 g, 10 mmol) in THF (20 mL) was then added dropwise and the resulting solution stirred at room temperature for 45 min before addition of benzyl bromide (1.7 g, 10 mmol) in a single portion. The reaction mixture was then left to stir at r.t. for 16 h. The mixture was diluted with diethyl ether (50 mL) and washed with saturated aq. NH$_4$Cl (50 mL) and the aqueous layer further extracted with Et$_2$O (3 x 20 mL). The organic extracts were then dried over magnesium sulphate anhydrous, filtered and concentrated under reduced pressure to afford **SI-6-18** (2.32 g, 92%) as a colourless oil which is pure enough to proceed to the next step.

**Physical State:** colourless oil

$R_f = 0.22$ (EtOAc:hexanes, 3:7 v/v; vanillin)

$[\alpha]_D = +9.2^\circ$ (CHCl$_3$, c 1.71) (lit.$^{70}$ $[\alpha]_D = +9.1^\circ$ (CHCl$_3$, c 1.))

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.40 – 7.28 (m, 5H), 4.59 (s, 2H), 4.09 – 4.03 (m, 1H), 3.95 (dt, $J = 8.4$, 4.4 Hz, 1H), 3.78 (dd, $J = 11.7$, 4.5 Hz, 1H), 3.69 (dd, $J = 9.8$, 5.0 Hz, 2H), 3.56 (dd, $J = 9.8$, 5.8 Hz, 1H), 2.20 (bs, 1H), 1.42 (s, 3H), 1.42 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 137.7, 128.6, 128.0, 127.9, 109.5, 79.8, 76.7, 73.9, 70.5, 62.6, 27.1, 27.1.

6.6 Notes and References
For reviews on iminium catalysis, see: Erkkilä, A.; Majander, I; Pihko, P. M. Chem. Rev. 2007, 107, 5416


Chapter 7

The Total Synthesis of Phomolides G & H

7.1 Background

The following section describes the biological activity and biosynthesis of the decanolides with a particular emphasis on those whose structures resemble 7-3 & 7-4.

7.1.1 Introduction

Endophytes are microorganisms that live in the internal tissues of living plants.\(^1\) Investigation of an endophytic fungi *Phomopsis* sp. of the mangrove species, *Kandelia candel*, collected from the Fugong Mangrove Conservation Area in Fujian, China led to the identification of five novel nonenolides (phomolides D-H) among other natural products.\(^2\) Though antibacterial assays exhibited no inhibition in the growth of bacteria and yeast, they remain an interesting target for total synthesis due to their scarcity and their similarity to structurally related biologically active natural products such as penicillinolide A,\(^3\) the putaminoxins,\(^4\) pinolide,\(^5\) pinolidoxins,\(^6\) decarestrictines\(^7\) and Seimatopolides A & B.\(^8\)

![Related decanolides of the subclass of polykides](image)

**Figure 7-1.** Related decanolides of the subclass of polykides
7.1.2 Biological activity

The decanolides, to which phomolides G and H belong, are a diverse subset of naturally occurring 10-membered lactones. The first reported isolation of naturally occurring decanolides was by Ishiba and Wada, who isolated diplodialides A-D from *Diplodia pinea*. Since then more than fifty different decanolides have been isolated from microorganisms (mostly fungi), plants and both marine and terrestrial animals. The ubiquity of these compounds and the diverse collection of organisms which produce them as secondary metabolites presumes diverse biological activity.

Indeed, though there is little biological data available for phomolides G and H, the biological data reported for structures within this class of polyhydroxylated macrolide cannot be restricted to a common mode of biological action. Herbarumin I, herbarumin II, putaminoxin, and pinolidoxin have been shown to exhibit potent phytotoxic effects. The decarestrictines showed interesting activity in cell line tests with HEP-G2 liver cells due to an inhibitory effect on cholesterol biosynthesis whereas microcarpalide, isolated from *Ficus microcarpa* L., showed strong antimicrofilament activity. Diplodialide A inhibits progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer*. The subgroup of simple 10-membered lactones exhibit no significant antibacterial, antifungal, antiprotozoal or antiviral activity.

7.1.3 Biosynthesis

The biosynthesis of the decanolides, as a class, has not been studied in detail. However, feeding experiments using $^{13}$C-labelled acetates to *Achaetomium cristalliferum* confirmed the carbon skeleton of achaetolide A was assembled via the polyketide pathway from eight acetate building blocks. The decarestrictines, meanwhile, are the only simple decanolide to have been studied in detail. Stable isotope labeling studies conducted on *Penicillium simplicissimum* using $^{13}$C-labelled acetate and malonic acid confirmed an analogous biosynthetic pathway. The carbon skeleton of the ten-membered lactones are derived from an acetyl CoA starter unit (C-10/C-9), which is elongated by four malonyl CoA units. Cyclisation then occurs via the acetate oxygen to form common pentaketide precursor which undergoes post-polyketide modifications by ‘tailoring enzymes’ in an operon-like gene cluster. Studies in an $^{18}$O enriched environment found that the epoxide in decarestrictine $A_1/A_2$ is derived from oxygen. Interestingly, decarestrictines D, N & O are the product of a non-enzymatic conversion from decarestrictines $A_1$ and $A_2$, likely through acid catalysed regio- and stereoselective ring opening.
In contrast, the eicosanoid-like marine metabolites have been suggested to arise from C20 fatty acid precursors and fatty acid metabolism in general.\textsuperscript{20}

7.2 Approaches to the core

The phomolides are polyketide natural products and are characterized by a ten-membered macrocyclic lactone core. At the onset of our studies, there were two related total syntheses towards phomolides G & H. It is noteworthy that both Seimatopolide A\textsuperscript{8} and decarestrictine O possess an identical core, varying only in the length of the aliphatic side-chain.

7.2.1 First approach to phomolide G

The first stereoselective total synthesis of phomolide G (and its methylated analogue phomolide H) was claimed by Meshram and co-workers in 15 steps and 7.3\% overall yield though lacked any experimental data—not even for the final synthetic material.\textsuperscript{21} Regardless, the natural product was allegedly prepared as two separate fragments from (R)-epichlorohydrin 7-13, which were coupled with retention of configuration under Yamaguchi\textsuperscript{22} conditions. The macrocycle 7-16 was then completed by a ring closing metathesis (RCM) approach with Grubbs II catalyst.\textsuperscript{23}
7.2.2 Second approach to phomolide G

The second total synthesis was completed one year later by Yadav and co-workers in 15 steps and 17.6% overall yield. The natural product was again prepared as two separate fragments from dimethyl L-tartrate and 1,4-butanediol respectively. Both the C-3 and C-9 stereocenters were set using an organocatalytic one-pot epoxidation developed by MacMillan. Though the starting materials differed, the natural product was completed by coupling identical fragments in an identical sequence of steps. The synthetic macrolide was said to be identical spectroscopically to the natural material despite differences in deuterated NMR solvent.

7.2.3 Routes to the related Seimatopolide A

Seimatopolide A 7-1 was isolated from the culture broth of *Seimatosporium discosioides* and the absolute stereochemistry (3R,6R,7R,9S) was assigned by modified Mosher’s method before being corrected by total synthesis (3S,6S,7S,9R). More recently, (−)-seimatopolide A was prepared from undecanal in 20 linear steps using...
Kita’s ruthenium catalysed lactonisation while Nanda and co-workers applied a cross metathesis/Yamaguchi lactonisation strategy from an L-tartaric acid derivative. The most thorough examination of seimatopolide A was carried out by Schmidt who prepared both the laevorotatory and dextrorotatory products. Both enantiomers were produced following an identical synthetic route (see Scheme 7-4). Allylic alcohol 7-25 was prepared via a cross metathesis from diol 7-24. Sharpless asymmetric epoxidation followed by regioselective opening of the resultant epoxide with Red-Al affords 7-26 after protecting group interconversions. The second fragment was prepared by enzymatic kinetic resolution of rac-7-29 to afford 7-28 at which point 7-28 was protected as its TBS ether then coupled with retention of configuration by Shiina’s esterification. Ring closing metathesis with Grubbs II to form the lactone followed by global deprotection gave seimatopolide A 7-1.

In contrast to the same tired metathesis strategies Prasad and Revu leveraged a furan ring as an (E)-but-2-ene-1,4-dione surrogate. Furfural was used in an aldol with ethyl acetate and the resulting racemic β-hydroxy ester was enriched by Sharpless kinetic resolution. Conversion of the ester to the Weinreb amide and alkylation with nonylmagnesium bromide followed by reduction of the ketone with tetramethylammonium triacetoxyborohydride furnished diol 7-32. Oxidation of the furan with NBS proceeded smoothly to give ketone 7-33 which converted to the allylic diol by Leuchte reduction. Protecting group interconversion, oxidation of the primary alcohol to the enal and Nagao acetate aldol provided acid 7-34 after oxidative cleavage of the thiazolidine-2-thione auxiliary. The macrolactone was then completed by Shiina lactonisation in good yield. Deprotection of the acetonide proved facile, giving (+)-7-1 in 14 steps and 7.8% overall yield.
Two further syntheses of Seimatopolide A have been completed by Yadav and co-workers.\textsuperscript{31} Although the authors claimed to have prepared (−)-seimatopolide A, this work was clearly erroneous but was never retracted.

### 7.2.4 Routes to Decarestrictines O & D

Decarestrictine O \textsuperscript{7-40} is a polyketide natural product isolated from \textit{Penicillium simplicissimum} (strain FH-A6090) and biosynthetically derived from decarestrictine A\textsubscript{1}/A\textsubscript{2} \textsuperscript{7-9,7-10}. It possesses an identical lactone core to phomolides G/H \textsuperscript{7-3,7-4} and seimatopolide A \textsuperscript{7-1}. Despite its similarities to related biologically active decanolides, it has been the target of total synthesis a mere three times.\textsuperscript{32} Krishna and Rao\textsuperscript{32a} reported the first enantioselective synthesis from achiral starting materials \textsuperscript{7-36} and \textsuperscript{7-38}. Lactone formation was performed in two steps, in a like manner to the natural products above, by ester formation followed by RCM with Grubbs II. The precursor alcohol \textsuperscript{7-39} was prepared using a Sharpless asymmetric dihydroxylation to construct the 1,2-\textit{syn} diol which was then protected as the acetonide. Formation of the macrocycle using Grubbs II led to an inseparable mixture of \((E)\)/(\(Z\)) isomers (8:2). The second total synthesis of decarestrictine O was completed two years after the first in a near identical manner by Yadav and coworkers.\textsuperscript{32b} The lactone was constructed from the TBS-protected \textsuperscript{7-37} and \textsuperscript{7-39} using a Yamaguchi/RCM protocol, though each precursor was prepared \textit{via} distinct starting materials.
Scheme 7-6. Total synthesis of decarestrictine O 7-40 by Krishna and co-workers

Decarestrictine D 7-12, isolated from *Penicillium simplicissimum*, *Polyporus tuberaster* & *Penicillium corylophilum*, is derived from the same biosynthetic precursor as decarestrictine O 7-40 and has been identified as a potent inhibitor of *de novo* cholesterol biosynthesis. Consequently, 7-12 and its seco acid have become an attractive target for total synthesis (Figure 7-2). Its relative stereochemistry was confirmed by single crystal X-ray diffraction, while Andrus’ total synthesis was used to establish its absolute configuration. Andrus and Kobayashi prepared identical seco intermediates but used two distinct lactonization reactions. Andrus found the optimal conditions for cyclisation were those of Corey and Nicolau (AgClO₄, PPh₃, (2-pyr-S)₂), whereas Kobayashi used the more typical Yamaguchi lactonisation. Aggarwal, meanwhile, used a novel strategy to construct the 1,4-diol containing the (E)-olefin, stereoselectively preparing the allylsilane through borylation of lithiated carbamates prior to epoxide formation and Petersen elimination. The synthesis was completed by constructing the previously prepared tribenzyl-protected seco-acid.

Figure 7-2. Total syntheses of decarestrictine D 7-12 classified by ring-closing step

The synthetic approach to lactones has typically focused on the use of fragmentation/ring expansion reactions and on lactonisation strategies. Despite the rise
of metathesis (specifically RCM), there exists a paucity of reports wherein the lactone is formed via construction of a C-C bond. Pilli and Victor, in synthesising decaerestrictine D, deftly applied an intramolecular Nozaki-Hiyama-Kishi (NHK) reaction to finish their synthesis.\textsuperscript{39} Kumar\textsuperscript{40} and Srihari\textsuperscript{32c} both applied an esterification/RCM approach typical of the synthesis of the decanolides described above.

\subsection*{7.2.5 Miscellaneous syntheses of similar decanolides}

Selected examples of decanolide syntheses are described herein; those with unique/distinct syntheses or ring closure protocols are highlighted.

Kibayashi published the first preparation of decaerstrictines C\textsubscript{1}/C\textsubscript{2} as an epimeric mixture at C-3 starting from (S,S)-dioxirane 7-41.\textsuperscript{41} The carbon skeleton of the natural product was constructed before they shrewdly applied an intramolecular Reformatsky reaction to close the ring, providing both epimers in a 1:1 mixture. The synthetic material was found to be identical with a diastereomeric mixture of natural decaerstrictines C\textsubscript{1}/C\textsubscript{2} on \textsuperscript{1}H and \textsuperscript{13}C NMR spectral comparison. Yamada and co-workers used a similar SmI\textsubscript{2}-mediated Reformatsky\textsuperscript{42} to complete the total synthesis of decaerestrictine J, though the absolute configuration of the natural product has yet to be determined.\textsuperscript{43}

\begin{equation}
\text{Scheme 7-7. First total synthesis of decaerstrictine } \text{C}_1/\text{C}_2
\end{equation}

In addition to the preparation of the epimeric mixture prepared above, Kibayashi has also reported the stereoselective synthesis of 7-44.\textsuperscript{44} Starting from C\textsubscript{2}-symmetric tetrol 7-45 derived from D-Mannitol, 7-46 is prepared in 10 steps, most of which are protecting group manipulation. Interestingly though, a Wittig reaction with unprotected (2-oxoethyl)triphenylphosphonium chloride is used to form the enal of 7-46. The stereocenter at C-3 was introduced by a diastereoselective aldol using a tin(II)-enolate. The total synthesis was then finished by removal of the chiral auxiliary and Yamaguchi lactonization. Though originally presumed to be diastereomers which are epimeric at C-3, Mohapatra suggested that decaerstrictines C\textsubscript{1}/C\textsubscript{2} 7-43,7-44 are in fact equilibrating conformers of decaerestrictine C\textsubscript{2} 7-44 based on variable temperature NMR studies.\textsuperscript{45} Furthermore, NMR spectra of decaerestrictine C\textsubscript{2} prepared by total synthesis are incongruous with those of decaerestrictine C from natural sources.
Related, a pair of 3,6-dihydroxydecanolides (C-3/C-6 diastereomers of 7-43 & 7-44), one of which was isolated from the entomopathogenic fungus Cordyceps militaris BCC 2816, were prepared by Willis and co-workers. In contrast to the RCM approach undertaken for the construction of the C-4/C-5 alkene in related compounds (vide supra), they proposed a NHK reaction to complete the nonenolide ring, similar to that performed by Pilli towards Decarestrictine D. Fragments 7-51 & 7-52 were prepared from diol 7-50 & acetylene 7-49 respectively. Yamaguchi esterification followed by deprotection and oxidation with Dess-Martin periodinane gave aldehyde 7-53 which, on treatment with CrCl$_2$ and NiCl$_2$ in DMF, gave a 3:1 mixture of epimers at C-6 (decanolide numbering) in reasonable yield. The (3$S$)-diastereomer was also subjected to identical conditions giving a 5:1 mixture of epimers at C-6 in an 87% yield. It is interesting to note that the NHK coupling with each diastereomer preferentially gives the (R)-alcohol as the major product.

7.3 Retrosynthetic analysis

We became interested in the total synthesis of phomolide G because it possesses an ‘interrupted’ triol moiety; a group which we felt would aptly demonstrate the utility of the Wittig aldehyde homologation. Thus, the total synthesis would consist of four key steps: a Wittig reaction, an alkylation, an auxiliary-directed acetate aldol, and a
lactonisation. Two retrosynthetic strategies for the synthesis of phomolides G & H are depicted in Figure 7-3. Disconnection of the lactone would provide a β-hydroxy seco acid which would be formed through an asymmetric auxiliary directed acetate aldol, *vide infra*, on enal 7-55. We then targeted 7-55 through two complementary routes: *i*) early introduction of the latent enal and *ii*) the late-stage introduction of the enal through sequential oxidation/Wittig/deprotection. In approach *i*, the latent enal is introduced onto the L-tartaric acid derived backbone prior to synthesis of the C₄–alcohol. In approach *ii*, by contrast, the contiguous alcohol and alkyl chain would be installed prior to the Wittig reaction to prepare the α,β–unsaturated aldehyde. Both routes are, unfortunately, entirely linear.

![Figure 7-3. Key disconnections towards Phomolide G](image)

Of the four key reactions, the acetate aldol with densely functionalised enal 7-55 presented—at least initially—the most formidable challenge; stereochemical control of the acetate aldol reaction has historically been quite difficult. Be that as it may, *N*-acetyl thiazolidinethiones have found regular use in natural product synthesis displaying unprecedented stereoselectivity for the non-Evans diastereomer (Figure 7-4). Typically, Evans auxiliaries (N-acyloxazolidinones), which are incredibly reliable, would be suitable but boron enolates from *N*-acyloxazolidinone provide only marginal selectivity.
7.4 The Total Synthesis of (–)-Phomolide G

7.4.1 Synthesis of the required enal through early introduction of pinacol acetal

The synthesis was initiated from the commercially available and inexpensive starting material dimethyl L-tartrate. The protected aldehyde 6-20 was obtained in four steps and 51% overall yield. Homologation with phosphonium salt 6-5 worked equally well employing NaH or KOTBu but required a slight excess of the salt for improved efficiency. Importantly, the Wittig reaction occurs with a reasonable degree of stereoselectivity (E:Z, 5:1). With the latent enal installed, removal of the silyl-protecting group was carried out with TBAF followed by the Appel reaction to form primary iodide 7-58. Nucleophilic substitution with KCN proved challenging as iodide 7-58 was un-reactive to substitution in most solvents, even at reflux. Admittedly, we had to settle on using DMSO as the solvent; the reaction proved sluggish, requiring 3 days at room temperature. Moreover, we initially activated the alcohol by forming the mesylate (tosylate formation proved sluggish due to steric encumbrance) but it proved un-reactive to cyanide substitution under all conditions attempted.

With nitrile 7-56 in-hand we began to construct the side-chain and contiguous chiral alcohol. Unfortunately, the reaction of nitrile 7-56 with n-propylmagnesium chloride resulted in deprotonation of the starting material followed by decomposition of the acetonide-protected tartrate backbone. A substitute reagent was not immediately obvious as we needed to maintain a high degree of nucleophilicity while tempering the basicity. We thus began to explore alkylzinc reagents but only allylzinc bromide was nucleophilic enough for alkylation of a nitrile. The propensity of the resulting allyl ketone 7-59 to isomerisation necessitated the succeeding step to be reduction of the ketone rather than hydrogenation of the terminal olefin.
Myriad methods exist for the diastereoselective reduction of β-alkoxy ketones to 1,3-diols. Typically, though, hydroxyl-directed chelation-assisted substrate control is employed leading to syn-1,3-diols, with zinc\textsuperscript{55} or boron\textsuperscript{56} (other metals such as aluminium have also been studied but are much less common) intermediates playing an important role in determining the stereoselectivity. Chelation-assisted diastereoselective reduction of β-alkoxy ketones in which the alkoxy-oxygen is protected as an acetal is more difficult due to delocalisation and reports are fewer.\textsuperscript{57} It is noteworthy that chelation-assisted reduction of allyl ketone \textsuperscript{7-59} would lead to the (S)-alcohol, whereas the absolute configuration of C9 in the natural product is (R). Further, chiral-reducing agents, such as the Corey (R)- or (S)-oxaborilidine\textsuperscript{58} are commonly employed and provide a high degree of selectivity; the stereochemical configuration of the resulting alcohol is dependent upon the chirality of the catalyst.

We ruminated on the choice of reducing agent, considering the absolute configuration of the natural product and the efficiency of the process. Allyl ketone \textsuperscript{7-59} was thus dissolved in diethyl ether with a ten-fold excess of LiI at -100 °C prior to the addition of LAH. The reduction afforded homo-allyl alcohol \textsuperscript{7-60} in excellent yield with good stereoselectivity (≥9:1 d.r.).
Chemoselective reduction of the terminal alkene proved capricious. We initially attempted hydrogenation with Pd/C (5% w/w) at 1 atm H₂. Toluene was chosen as the solvent to attenuate the reactivity of the catalyst. At a catalyst loading of 5 mol% complete reduction was observed within half an hour. Decreasing the loading of the catalyst to 3 mol% Pd/C (5% w/w) under identical conditions afforded a 3:1 mixture of the mono-reduced to completely reduced product which were inseparable by standard chromatographic techniques. Decreasing the catalyst loading further, to 2 mol% Pd/C (5% w/w) produced a 1:7:1 mixture of starting material to mono-reduced product to complete reduction. The lack of chemoselectivity observed using Pd/C led us to consider further attenuating the reactivity of our heterogeneous palladium catalyst (Pd/BaSO₄⁵⁹ or Pd/CaCO₃⁶₀) or alternatively using homogeneous transition metal catalysis.

We decided to explore the literature for chemoselective homogeneous metal catalysts due to their high degree of reproducibility—likely a result of defined structures and known mechanisms. Two catalysts were selected as candidates: the Shrock-Osbourne catalyst which is the (1,5-cyclooctadiene)bis(triphenylphosphine)rhodium (I) cation⁶¹ sold as the hexafluorophosphate dichloromethane complex (1:1) and tris(triphenylphosphine)ruthenium (II) dichloride.⁶² We attempted hydrogenation of homo-allyl alcohol 7-60 with the Shrock-Osbourne catalyst varying the loading in CH₂Cl₂ and CHCl₃ under a hydrogen atmosphere (1 atm) but no reduction was seen. It appears the catalyst is highly moisture sensitive.⁶³ Fortunately, (PPh₃)₃RuCl₂ (1 mol%) in EtOH:Benzene (1:1 v/v) under H₂(g) (1 atm) gave chemoselective reduction of the
terminal olefin in 6 h. No reduction of the internal alkene was observed even with higher loadings of the catalyst.

The C₄-alcohol finished, it was necessary to orthogonally protect the secondary alcohol to ensure, prior to removal, regioselective lactone formation. We initially surveyed a variety of protection schemes in order to assess their suitability. It was quickly established that methoxybenzyl ethers provided the best stability while allowing for removal under mild conditions (see section 7.4.3). p-Methoxybenzyl chloride was prepared fresh from the corresponding benzyl alcohol and thionyl chloride. Classical Williamson ether synthesis using NaH in THF failed to give any product, despite additives such as KI⁶⁴ and TBAI⁶⁵. Silver ions are well known to accelerate the rate at which alkyl halides react⁶⁶ and silver oxide (Ag₂O), in particular, has been reported to facilitate benzyl ether formation.⁶⁷ Unfortunately, Ag₂O failed to give benzyl ether formation with this particular substrate; incidentally, neither did any other silver sources. Benzyl perfluoro-⁶⁸a-c and perchloroimidates⁶⁸d-g have been used for benzyl ether formation under acidic conditions and were contemplated but weren’t attempted. We instead reexamined the Williamson ether synthesis; to our delight, the reaction proceeded smoothly pre-forming the alkoxide using NaH in a mixture of THF/DMF (1:1 v/v) prior to addition of p-methoxybenzyl chloride as a neat liquid.

Deprotection of the pinacol moiety presented a unique challenge. As the isopropylidene acetal is more labile than the pinacol acetal the deprotection must be performed in acetone (see section 6.3.4.2 above). Enal 7-61 was unmasked in a reasonable yield using Iron(III) chloride hexahydrate and used immediately.
7.4.2 Synthesis of the necessary enal employing a late stage olefination

The prolonged difficulty finding the appropriate conditions necessary to chemoselectively remove the pinacol acetal led us to consider an alternate route to phomolide G through a common intermediate 7-61. As above, the synthesis began with dimethyl L-tartrate. Protected alcohol 7-62 was prepared in three steps and 65% yield according to ref. 29. Following the identical synthetic sequence, Appel reaction to form the primary iodide and cyanide substitution followed by alkylation of the resulting nitrile with allyl zinc bromide at room temperature afforded allyl ketone 7-63 which was diastereoselectively reduced (≥9:1 d.r.) and protected with para-methoxybenzyl chloride to furnish 7-64. Chemoselective hydrogenolysis of the benzyloxy ether was accomplished using H₂(g) and Raney nickel as demonstrated by Terashima and co-workers on a structurally similar intermediate in the synthesis of anti-tumour agent (+)-FR900482. Parikh-Doering oxidation of the resultant primary alcohol followed by Wittig reaction with salt 6-16 and acid catalyzed hydrolysis afforded enal 7-61 as a common intermediate.

The dichotomous reactivity observed between the dioxolane acetal derived from salt 6-16 and the more sterically hindered pinacol acetals is quite remarkable. Whereas the dioxolane acetal was able to be removed chemoselectively under mildly acidic conditions, the pinacol acetal required strongly acidic aqueous acids or, as we developed
(see section 6.4.2), FeCl₃-promoted Lewis acidic cleavage. Moreover, the pinacol-masked enal was inert to multiple transformations, including: iodine/PPh₃, KCN substitution in DMSO, organometallic reagents (allyl zinc bromide), homogeneous/heterogeneous transition metal catalysed hydrogenations and strongly basic alkylations.

![Scheme 7-13. Alternate route to enal 7-61](image)

### 7.4.3 Completion of relay 7-23 and the formal total synthesis of Phomolide G

A TiCl₄-mediated Nagao acetate aldol reaction employing thiazolidinethione (−)-7-47 and enal 7-61 gave allylic alcohol 7-67 as the non-Evans product; the yield was 82% (~4:1 d.r.). Unfortunately these diastereomers proved inseparable by chromatographic purification so they were carried forward for separation later in the synthesis. The mixture was subsequently protected (TBSOTf, 2,6-lutidine in CH₂Cl₂ at −0 °C) and the auxiliary imide was oxidatively cleaved to the corresponding carboxylic acid. We had initially attempted protection with TBSCl under a variety of conditions but it was simply not reactive enough for silylation of alcohol 7-67. Treatment of acid 7-69 with DDQ in CH₂Cl₂ allowed selective deprotection of the methoxybenzyl ether; no side reactions were observed, whereas attempted oxidative cleavage of the PMB-ether with
CAN led to degradation of the starting acid. Mitsonobu lactonisation (triphenylphosphine, DIAD in PhMe) followed to invert the alcohol at C9 and close the ring which should have provided relay 7-23; in fact, the Mitsunobu was much more complicated than expected (see section 7.4.4). The final steps in the synthesis of phomolide G and H will be discussed there.

Scheme 7-14. Final steps to Phomolide G

7.4.4 Confirmation of the Absolute Stereochemistry of Phomolide G: ‘the end game’

Mitsunobu esterification, oft used because of its high stereoselectivity, mild reaction conditions and functional group tolerance, generally affords inversion of secondary alcohols. Indeed, when performed in non-polar solvents (toluene, CH₂Cl₂, THF) the reaction commonly affords stereospecific inversion. Unsurprisingly, the Mitsunobu has found particular importance in total synthesis where quick configurational manipulation of complex intermediates and the opportunity for late stage inversion of configuration allow for flexibility in the design of a total synthesis. Appropriately, therefore, it has been conspicuously exploited for the construction of lactones and key ring junctions including a number of 11- to 16-membered macrolactone natural products and even a few strained 9-membered lactones.⁷²
Classical conditions employing DEAD-PPh$_3$ in toluene, benzene or THF at room temperature suffer from notable drawbacks including but not limited to formation of hydrazide by-products. Evans attenuated this problem by using the more hindered DIAD in toluene during the total synthesis of lonomycin A. The original mechanistic hypothesis proposed by Mitsunobu and Yamada wherein the reaction proceeds, through ylid 7-73, directly to alkoxyphosphonium 7-75 has been shown to be simplistic. Evidence for the existence of acyloxyphosphonium intermediates 7-76 began to emerge sporadically in the decades since the initial investigations by Mitsunobu. The isolation of acid anhydrides from carboxylic acids and DEAD, followed several years later by reports from De Brabander, Smith, DeShong and Hughes in which the Mitsunobu reaction proceeded with retention of configuration seem to confirm the existence of intermediate 7-76. More thorough mechanistic investigations using BPO/PBu$_3$ showed unambiguously that acyloxyphosphonium 7-76 forms prior to base catalyzed equilibration to the alkoxyphosphonium 7-75 followed by nucleophilic displacement (S$_{N2}$) by the carboxylate anion to afford inversion. Interestingly, reactions performed in the absence of a base and/or in N,N-dimethylformamide proceeded with a high degree of retention of configuration.

Scheme 7-15. Mechanism of the Mitsunobu reaction

Initial attempts at Mitsunobu lactonization (7-70, PPh$_3$ in PhMe (50 mL mmol$^{-1}$) to which DIAD was added) furnished a single major product whose spectral data were similar but inconsistent with the literature data reported for relay 7-23. The similarity of the $^1$H- and $^{13}$C-NMR suggested that it was probably an isomer of 7-23. We hoped to grow a crystal of the 4-bromobenzoyl ester to elucidate the absolute stereochemistry of the product. Cleavage of the TBS-ether was attempted with TBAF but the basicity proved problematic leading to hydrolysis of the lactone. Global deprotection with TFA in CH$_2$Cl$_2$ removed the acetonide but left the TBS-ether intact while 2N HCl (aq) in THF led to complete decomposition of the starting lactone. Concurrently, mass spectrometry using ESI$^+$ and EI indicated that the Mitsunobu had yielded the macrodilide 7-80 in spite of the
high dilution of the reaction. Though dilide formation had been considered a possibility, in fact, the Mitsunobu reaction initially furnished dilides as the major product of medium-sized lactones. Methanalysis of macrodilide 7-80 \((K_2CO_3/MeOH)\) indicated the reaction had proceeded with inversion of configuration. The conditions of the reaction were thus adjusted (7-70, \(PPh_3\), in PhMe \((200 \text{ mL mmol}^{-1})\) to which DIAD was added) to furnish the lactone as the major product, though with a significant amount of the dilide still present; despite fervent attempts, no conditions were found which did \textit{not} afford dilide.

\[
\begin{align*}
\text{7-60} & \xrightarrow{\text{TiCl}_4, \text{DIPEA}} \text{PMBO} \\
\text{CH}_2\text{Cl}_2, -78 \degree \text{C} & \quad \text{82\%}
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{H} & \quad \text{7-67} \\
\text{R} = \text{TBS} & \quad \text{7-68} \\
\text{R} = \text{PMB} & \quad \text{7-69} \\
\text{R} = \text{H} & \quad \text{7-70} \\
\end{align*}
\]

\[
\begin{align*}
\text{TBSOTf, 2,6-lutidine} & \quad \text{CH}_2\text{Cl}_2, 0 \degree \text{C to r.t.} \\
\text{89\%} & \\
\text{THF/H}_2\text{O (4:1), r.t.} & \quad \text{89\%}
\end{align*}
\]

\[
\begin{align*}
\text{DDQ} & \quad \text{CH}_2\text{Cl}_2, \text{r.t.} \\
\text{81\%} & \\
\text{PPh}_3, \text{DIAD} & \quad \text{PhMe, 0 \degree \text{C}}
\end{align*}
\]

Scheme 7-16. Synthesis of the putative structure of phomolide G 7-3
Stepwise removal of the protecting groups was achieved by removal of the TBS group using TBAF to give 7-71, the acetonide derivative of 7-3, and finally acidic hydrolysis using TFA in wet-acetonitrile to yield macrolactone 7-3, the putative structure assigned to natural Phomolide G.\(^2\) Inspection of the NMR data for natural Phomolide G in comparison to our synthetic material 7-3 revealed the overall data to be similar in many respects, but not identical. The \(^{13}\)C-NMR data were particularly indicative with respect to the chemical shift values for the secondary alcohol carbons (71.6, 72.5, 76.0, 78.1 for the natural product\(^2\) as compared to 67.6, 73.0, 76.9, 79.7 for 7-3; see appendix eight). In order to confirm the structure of compound 7-3, the late-stage alcohol 7-71 was converted to its corresponding 4-bromobenzoate derivative 7-79 which fortunately proved to be crystalline. A single-crystal X-ray structural determination on compound 7-79 confirmed the absolute and relative stereochemistry as depicted in 7-3 (CCDC #1439915, Scheme 7-16). In order to further prove that the Mitsunobu reaction 7-70 to 7-23 proceeded with inversion of stereochemistry, the pre-Mitsunobu intermediate 7-69 was converted to 7-81 as before, and intermediate 7-81 converted to the methyl ester 7-82. The Mitsunobu product macrolactone 7-23 was independently subjected to methanolysis to yield the acyclic methyl ester 7-83 (Scheme 7-17). Comparison of the NMR data of compounds 7-82 and 7-83 revealed them to be epimeric at the secondary alcohol position C9, confirming the inversion of configuration during the Mitsunobu process (Figure 7-6).\(^80\) Overall, the X-ray structure of 7-79 and chemical correlations affirm the stereochemical outcomes of the 1,3-ketone reduction, acetate aldol and Mitsunobu reactions as described. The data\(^2\) point to the likelihood that natural phomolide G is a diastereomer of the reported structure 7-3.
Figure 7-6. Comparison of synthetic 7-82 and the product of methanolysis 7-83

The synthetic strategy devised for the construction of 7-3 was designed to allow access to epimeric derivatives at C9 through Yamaguchi-type macrolactonization reactions on an intermediate such as 7-70, or to C3 epimeric compounds from acetate aldol reactions of the alkenal 7-61 with the thiazolidinethione antipode (S)-7-47. We fortuitously elected to next pursue the latter strategy as outlined in Scheme 7-18 based on the Δδ (ppm) of the 13C-NMR signal of C3. The Nagao acetate aldol reaction of 7-61 with antipode (S)-7-47 now provided the syn-aldol intermediate 7-84 as essentially a single diasteromer (>20:1), indicating this to be the stereochemically matched-pair. Intermediate 7-84 was protected as its TBS-ether, the auxiliary rapidly cleaved selectively with basic peroxide and the PMB-ether then removed oxidatively using DDQ, providing the seco-acid derivative 7-87. This compound was subjected to the standard Mitsunobu reaction73 conditions employing DIAD as before, to yield the macrolactone 7-88. Stepwise removal of the protecting groups was also achieved in this case by removal of the TBS group using TBAF to give 7-89, followed by acidic hydrolysis using TFA in wet-acetonitrile to afford macrolactone 7-90, the C3-epimer of the structure assigned to natural phomolide G.2 As before (Scheme 7-17) the Mitsunobu reaction was proven to proceed via inversion at C9 by conversion of intermediate 7-86 to 7-93, and comparison of 7-93 with 7-92 (the product obtained from 7-88) which proved to be the C9-epimer of 7-93 (see supporting information, Figure 7-7).
The $p$-bromobenzoate derivative 7-91 was also prepared as an oil resisting all attempts at crystallization to date. Inspection of the $^1$H and $^{13}$C-NMR data (Table 7-1) for natural phomolide G in comparison to the synthetic material 7-90 revealed an identical match in the same solvents and conditions as reported for the natural product. Natural phomolide G was reported as levorotatory with a specific rotation of $-10.4^\circ$ in methanol.²
Synthetic phomolide G of absolute stereochemistry depicted in 7-90 also proved to be levorotatory but exhibited a higher magnitude of rotation of -65° to -69° at the same concentration in methanol.

There are two previous reports\textsuperscript{21,24} on the total synthesis of phomolide G (see section 6.4.2.1 & 6.4.2.2) as structure 7-3 in the literature. The first publication\textsuperscript{21} contains no procedural or spectroscopic information. The second report which follows an overall similar strategy to the first contains a supplemental section with select $^1$H and $^{13}$C-NMR data. Inspection of this data reveals that the synthetic data do not match that reported for natural Phomolide G.\textsuperscript{2} We have run the spectra of both compounds 7-3 and 7-90 in the original medium,\textsuperscript{2} as well as that reported by Reddy and co-workers,\textsuperscript{24} confirming the mis-match. The NMR data of compounds 7-3 and 7-90 do not match the data reported by Reddy and co-workers, while that of compound 7-90 is identical to the natural product (Table 7-1). Additionally, compound 7-23 reported above (Scheme 7-16), the structure of which is secured following the sequence 7-23$\rightarrow$7-72$\rightarrow$7-79 (X-ray) is also reported as a late stage intermediate in the synthesis of Reddy and co-workers, the $^1$H and $^{13}$C-NMR data of which do not match with these structures. It is most difficult to rationalise the claims made in these two prior publications with the synthetic schemes and data that are presented.

**Table 7-1. Comparison of NMR data for compounds 7-3 and 7-90**

<table>
<thead>
<tr>
<th>Atom</th>
<th>$^1$H</th>
<th>$^{13}$C</th>
<th>$^1$H</th>
<th>$^{13}$C$^b$</th>
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<td>169.4</td>
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<td>169.8</td>
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<td>45.2</td>
<td>2.44 (dd, $J = 11.8$, 3.3)</td>
<td>43.6</td>
<td>2.21 (t, $J = 10.4$)</td>
<td>45.2</td>
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<tr>
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<td>2.50 (dd, $J = 101.1$, 5.6)</td>
<td></td>
<td>2.55 (dd, $J = 11.8$, 3.9)</td>
<td></td>
<td>2.51 (dd, $J = 10.2$, 5.8)</td>
<td></td>
</tr>
<tr>
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<td>4.21 (q, $J = 8.7$)</td>
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<td>4.67 (m)</td>
<td>66.7</td>
<td>4.22 (dd, $J = 15.6$, 9.3)</td>
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</tr>
<tr>
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<td>5.88 (dd, $J = 15.8$, 3.1)</td>
<td>135.4</td>
<td>5.61 (dd, $J = 15.8$, 8.6)</td>
<td>136.4</td>
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<td>128.1</td>
<td>5.50-5.64 (m)</td>
<td>126.3</td>
<td>5.06 (dd, $J = 15.8$, 9.4)</td>
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<tr>
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<td>78.1</td>
<td>3.74 (dd, $J = 12.2$, 5.9)</td>
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<td>3.57 (t, $J = 9.1$ Hz)</td>
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<td>3.17-3.28 (m)</td>
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<td>4.64-4.72 (m)</td>
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<td>0.79 (t, $J = 7.4$)</td>
<td>13.2</td>
</tr>
</tbody>
</table>

a. Acetone-d$_6$ (600 MHz, δ in ppm, $J$ in Hz)
b. The (CD$_3$)$_2$CO peak was calibrated to 28.9 rather than 29.84 due to systemic shift differences
7.4.7 The total synthesis of phomolide H

Having completed the total synthesis of phomolide G and reassigned its absolute stereochemical configuration, we decided to investigate the total synthesis of phomolide H 7-4, the C3 methoxy analogue of phomolide G. The spurious nature of the reports concerning the total synthesis of phomolide G led us to presume that the two prior total syntheses of phomolide H were specious. Logically, phomolide H should possess the same absolute stereochemical configuration as phomolide G, having been isolated from the same species of fungi; that phomolide H would possess a different core is highly improbable. We thus began by methylating lactone 7-89, a compound one step away from phomolide G (Scheme 7-19). Methylation proceeded smoothly using silver(I) oxide and iodomethane in THF with dimethylsulphide to give methyl ether 7-94. Deprotection of the acetonide under identical conditions to those employed previously afforded the C3 methoxy analogue of phomolide G 7-95 in good yield. Inspection of the \(^1\)H and \(^{13}\)C-NMR data of synthetic 7-95 showed it to be quite different than that reported for natural phomolide H (Table 7-2). Consequently, we synthesised the originally proposed structure of phomolide H 7-4 in the hopes that its initial stereochemical assignment was accurate (Scheme 7-20). Unfortunately, the spectroscopic data for this compound were also not in agreement for that originally reported for the natural product (Table 7-2).

\[\text{Scheme 7-19. Completion of the revised structure of phomolide H}\]

\[\text{Scheme 7-20. Completion of the original putative structure of phomolide H}\]

The controversy surrounding the NMR data of diastereomeric methyl ethers 7-95 and 7-4 as compared that reported for the natural material was exacerbated by the lack of spectra published alongside the chemical shifts. A careful examination of the NMR data (\(\Delta\delta \text{ ppm}\)) for all three compounds elucidated a few key differences. The \(^{13}\)C-NMR
signals associated with the C3 carbon in the diasteromeric methyl ethers were both deshielded by 9.0+ ppm as compared with the natural product (Table 7-2). Further, the $^{13}$C-NMR signals associated with the methyl ether were themselves at an identical shift in each diastereomer located 7.0 ppm higher than the methyl ether of the natural material. The natural material also exhibited a characteristic set of signals in the $^1$H-NMR which corresponded to the $^1$H-atoms attached to C3 and C9 located immediately beside one another. Examination of the prepared diasteromers revealed neither diastereomer exhibited this pattern; in fact, both showed increased shielding of the C3 protons as compared to the free hydroxyl (Table 7-1 and Table 7-2). Finally, the $^{13}$C-NMR signals corresponding to C6-C9 display little variance from those reported for the natural material. Inspection of both the $^1$H and $^{13}$C NMR signals corresponding to the natural material reveal them to likely be a result of methanol contamination. Together, these data indicate that phomolide H is not a methyl ether at all and after comparison of the NMR data is, in fact, the original structure of phomolide G\textsuperscript{7-3} (Table 7-2).

**Table 7-2.** Comparison of NMR data for compounds 7-95, 7-4 and 7-3

<table>
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<tr>
<th>Atom</th>
<th>Natural Product</th>
<th>Compound 7-95</th>
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<th>Compound 7-3</th>
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<td>$^1$H</td>
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<td>169.7</td>
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</tr>
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<td>9</td>
<td>1.30-1.32 (m)</td>
<td>18.0</td>
<td>1.34-1.25 (m)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>0.91 (t, $J = 7.4$)</td>
<td>13.3</td>
<td>0.88 (t, $J = 7.4$)</td>
<td>13.3</td>
</tr>
<tr>
<td>10</td>
<td>3.31 (s)</td>
<td>48.8</td>
<td>3.29 (s)</td>
<td>55.8</td>
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<td>3.29 (s)</td>
</tr>
</tbody>
</table>

a. Acetone-$d_6$ (600 MHz, $\delta$ in ppm, $J$ in Hz).

b. The (CD$_3$)$_2$CO peak was calibrated to 28.9 rather than 29.84 due to systemic shift differences.
7.4.8 Investigation of diasteromers of phomolide G

The lack of clarity initially associated with the Mitsunobu macrolactonisation prompted us to investigate epimerisation of the stereocenter at C9 earlier in the total synthesis. In an identical route, (+)-dimethyl L-tartrate 7-17 was converted to nitrile 7-57 which was then converted to the same 1,3-syn alcohol 7-95 prior to a Mitsunobu reaction with p-nitrobenzoic acid to invert the stereocenter at C9 (Scheme 7-21). Hydrolysis of the resulting ester using K₂CO₃/MeOH prior to PMB-ether formation led to 9-epi-7-65 which could then proceed via same protocol discussed in section 7.4.2/7.4.3 to complete the macrolactone. The issues surrounding the Mitsunobu were resolved though and the absolute configuration of the 1,3-syn reduction, aldol and Mitsunobu were confirmed by single crystal x-ray analysis of 7-79. This particular avenue towards diasteromers of the phomolide core was therefore abandoned though may be useful as a platform towards biologically active homologs/stereoisomers.

While preparation of 7-96 & 9-epi-7-65 allowed for confirmation of the success of the chelation controlled 1,3-syn reduction, it wasn’t the most convenient method for the preparation of diastereomers of the phomolide core. Rather a method permitting late-stage diversification of one or two compounds into a number of analogue scaffolds is appealing. We therefore decided to attempt epimerisation of the C9 alcohol on seco acids 7-70 & 7-87 using the Mitsunobu reaction with p-nitrobenzoic acid (analogous sequence as above). Unfortunately the hydrazide by-products of the reaction prevented isolation of the inverted PNB-ester, eluding all attempts at purification by standard chromatographic techniques. Consequently, we subjected methyl esters 7-82 & 7-93 to identical conditions to give PNB-esters 7-97 & 7-98, both of which proved separable from the hydrazide by-products. Stepwise cleavage starting with the PNB-ester using K₂CO₃ in dry MeOH afforded methyl esters 7-99 & 7-100 followed by conversion to the seco acids using K₂CO₃ in MeOH/H₂O (1:1). Though these epi-seco acid will be redundant if conditions can be found which allow for macrolactonisation of the original seco acids 7-70 & 7-87 it isn’t necessarily a formality; these transformations have been shown to be non-trivial, especially with the rigidity of the trans-acetonide.34,35b

![Scheme 7-21. Preparation of 9-epi-synthons towards diastereomers of phomolides G & H]
Macrolactonisations are typically carried out on quite advanced substrates, consequently, methodological studies are rare. It is therefore rather difficult to realize the best conditions for cyclisation. Initial attempts towards the macroide employing a Yamaguchi esterification failed to furnish product (Scheme 7-23). Formation of the mixed anhydride using 2,4,6-trichlorobenzoyl chloride was evident by TLC but cyclization upon exposure to 4-DMAP in toluene at high dilution (~2 μM) proved elusive, even upon slow addition of the mixed anhydride by syringe pump at several temperatures (25 °C, 60 °C, 80 °C). Generally, filtration of the NEt₃•HCl salt isn’t crucial, but Evans showed it was necessary to prevent acid-promoted decomposition of the seco acid during the total synthesis of roxaticin. Despite this modification to the Yamaguchi procedure, no macroide was observed in the present case. The Yonemitsu variation of the Yamaguchi reaction has yet to be attempted but it allowed Kobayashi to cyclise a similar substrate though in only a paltry 17% yield. Further, Keck-Boden modified Steglich esterifcation (DCC, 4-DMAP•HCl) and Shiina macrolactonisation have also been unsuccessful as yet. The mild reaction conditions typical of a Shiina lactonisation offer an encouraging outlook though. Further studies towards 9-epi macrolides are still under investigation.
7.5 Conclusion

The anhydrous homologations using salts 6-5 and 6-16 were applied to the asymmetric synthesis of the macrolactone 7-3, the putative structure originally assigned to the natural nonenolide (−)-phomolide G,\(^2\) the \(^1\)H and \(^{13}\)C-NMR data of which do not match that of the natural product. The asymmetric synthesis of the C3-epimeric nonenolide 7-90, the data of which proved to be an identical match to natural (−)-phomolide G was also synthesized. This work, therefore, represents the first report on the total synthesis and unambiguous stereochemical assignment of the structure of this natural decanolide. Phomolide H was also prepared in two steps from the late stage intermediate 6-89. The spurious nature of the original syntheses has been demonstrated making this the first total synthesis of phomolide H as well. The general synthetic strategy reported permits synthesis of all diastereomers of the phomolide nonenolide core at positions 3 and 9, while use of D-tartrate or other carbohydrate-derived C4-chirons should allow access to diastereomers equivalent to 7-62. The pivotal terminal olefin introduced here as in 7-60/7-63 is designed to allow access to homologous analogs such as seimatopolide A 7-1 and (−)-achaetolide\(^88\) via cross-metathesis or hydroboration/cross-coupling sequences. The synthesis of a series of diastereomers and homologs based on this general synthetic strategy and detailed investigation of their biological activities is under active investigation.

7.6 Experimental Section

7.6.1 Materials & Methods

General Considerations. Reactions were carried out under nitrogen or argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et\(_2\)O), tetrahydrofuran (THF), Toluene (PhMe) and triethylamine and N,N-diisopropylethylamine were distilled from Na\(^0\) with benzophenone as an indicator. Dry dichloromethane (CH\(_2\)Cl\(_2\)) was distilled from calcium hydride while dry methanol (MeOH) was distilled from Mg\(^0\). All fine chemicals were obtained from Sigma-Aldrich and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (\(^1\)H-NMR) homogeneous materials, unless otherwise stated. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV. HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. NMR spectra were recorded on Bruker AV-600 and AV-700 spectrometers and calibrated using residual undeuterated solvent as an internal reference(CHCl\(_3\)) @ δ 7.26 ppm \(^1\)H NMR, δ 77.16 ppm \(^{13}\)C NMR; Acetone-d\(_6\)) @ δ 2.05, \(^1\)H NMR, δ 29.84 ppm \(^{13}\)C NMR ); \(^{31}\)P spectra were calibrated using an external reference of 85% H\(_3\)PO\(_4\). Signal assignments were accomplished via
analysis of HMBC, HMQC, COSY, NOESY experiments where necessary. The (E) to (Z) ratios were determined from the relative integration of the $^1$H spectra for the olefinic protons. All melting points are corrected.

7.6.2 Preparative Procedures

\[ \text{CO}_2\text{H} \quad \text{LAH, THF} \quad 0 \degree \text{C to reflux} \quad 74\% \quad \text{SI-7-1} \]

Synthesis of SI-7-1: To a suspension of LiAlH$_4$ (2.40 g, 63 mmol) in THF (60 mL) at 0 °C was added D-valine (5.00 g, 42.5 mmol) in five portions over 30 minutes at which point the reaction mixture was allowed to stir at 0 °C for 1 h prior to removal of the ice bath. After attaining room temperature the suspension was brought to gentle reflux for 16 h at which point the oil bath was removed and the reaction mixture allowed to cool to room temperature. Dilution with diethyl ether (50 mL) followed by subsequent additions of water (2.5 mL), aqueous 15% NaOH (2.5 mL) and finally by the further addition of water (10 mL) afforded a stark white suspension which stirred for a further 30 minutes at which point the suspension was filtered. The precipitate was washed with three aliquots of ethyl ether (20 mL) and the combined organic layers concentrated under reduced pressure. The resulting slightly yellow oil was then distilled under vacuum (bp 63-64 °C, 1 mmHg) to give D-valinol SI-7-1 (3.26 g, 74%) as a colourless oil which solidified to a white solid upon standing.

**Physical State:** white solid

$R_f = 0.40$ (MeOH/CH$_2$Cl$_2$, 1:4 v/v; ninhydrin)

$[\alpha]_D = -17.1^\circ$ (EtOH, $c 2.77$) (lit.$^{89} -16.6^\circ$ (EtOH, $c 0.09$))
**1H-NMR** [CDCl₃, 600 MHz] δ: 3.63 (dd, J = 10.5, 4.0 Hz, 1H), 3.28 (dd, J = 10.5, 8.8 Hz, 1H), 2.55 (dd, J = 8.8, 6.4, 4.0 Hz, 1H), 1.91 (br s, 3H), 1.66 – 1.46 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H)

**13C-NMR** [CDCl₃, 150 MHz] δ: 64.9, 58.6, 31.7, 19.4, 18.5.

Synthesis of **SI-7-2**: To a solution of D-valinol (3.02 g, 29.3 mmol) in EtOH (9 mL) was added carbon disulfide (5.3 mL, 76.2 mmol). A 2.25 M solution of KOH (4.45 g, 79.0 mmol) in EtOH/H₂O (1:1 v/v, 35 mL) was then added dropwise at room temperature over 30 min. The homogeneous red solution is then heated to reflux for 72 h under an argon atmosphere. The flask was then cooled, the volatiles removed under reduced pressure and the mixture slowly acidified with 0.5 M HCl (160 mL). The aqueous solution is then extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic extracts dried over MgSO₄. Concentration under reduced pressure afforded a yellow oil which was purified by column chromatography (silica gel, hexanes/EtOAc, 1:4 → 3:7) to give **SI-7-2** (3.64 g, 77%) as a colourless crystalline solid.

**Physical State**: colourless crystalline solid

R₉ = 0.34 (EtOAc:hexanes, 3:7 v/v; KMnO₄)

[α]D = +37.4° (CHCl₃, c 0.78) (for enantiomer, lit.⁹⁰ [α]D = –34.8° (CHCl₃, c 1.11))

**1H-NMR** [CDCl₃, 600 MHz] δ: 7.83 (br s, 1H), 4.04 (td, J = 8.3, 6.7 Hz, 1H), 3.50 (dd, J = 11.1, 8.2 Hz, 1H), 3.32 (dd, J = 11.1, 8.4 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H)
\textbf{Synthesis of (R)-7-47}: To a suspension of 60\% NaH (0.546 g, 13.64 mmol) in dry THF (10 mL) at 0 °C was added a solution of (4\textit{R})-isopropyl-1,3-thiazolidine-2-thione (2.00 g, 12.40 mmol) in dry THF (10 mL). The mixture was stirred at 0 °C for 10 min, and acetyl chloride (0.98 mL, 13.64 mmol) was injected into the solution and stirred at 0 °C for 10 min and then at room temperature for 1 h. 5\% Hydrochloric acid was added, and the mixture was extracted with EtOAc, washed with brine, and worked up. Purification of the crude product so obtained by flash column chromatography (silica gel, hexanes/EtOAc, 1:9 v/v) afforded (S)-7-47 (2.32 g, 92\%) as a bright yellow oil.

\textbf{Physical State}: bright yellow oil

\(R_f = 0.21\) (EtOAc:hexanes, 1:9 v/v)

\[\alpha\]_D = -431.1° (CHCl\textsubscript{3}, c 0.93) (For enantiomer, lit.\textsuperscript{91} \[\alpha\]_D = +448.9° (CHCl\textsubscript{3}, c 0.51))

\textbf{1H-NMR} [CDCl\textsubscript{3}, 600 MHz] δ: 5.15 (t, \(J = 7.1\) Hz, 1H), 3.50 (dd, \(J = 11.5, 8.0\) Hz, 1H), 3.02 (dd, \(J = 11.5, 1.0\) Hz, 1H), 2.77 (s, 3H), 2.42 – 2.30 (m, 1H), 1.06 (d, \(J = 6.8\) Hz, 3H), 0.98 (d, \(J = 6.9\) Hz, 3H).

\textbf{13C-NMR} [CDCl\textsubscript{3}, 150 MHz] δ: 203.4, 170.9, 71.4, 30.9, 30.5, 27.1, 19.2, 17.9.
Synthesis of **SI-7-3**: To a suspension of LiAlH₄ (2.40 g, 63 mmol) in THF (60 mL) at 0 °C was added L-valine (5.00 g, 42.5 mmol) in five portions over 30 minutes at which point the reaction mixture was allowed to stir at 0 °C for 1 h prior to removal of the ice bath. After attaining room temperature the suspension was brought to gentle reflux for 16 h at which point the oil bath was removed and the reaction mixture allowed to cool to room temperature. Dilution with diethyl ether (50 mL) followed by subsequent additions of water (2.5 mL), aqueous 15% NaOH (2.5 mL) and finally by the further addition of water (10 mL) afforded a stark white suspension which stirred for a further 30 minutes at which point the suspension was filtered. The precipitate was washed with three aliquots of ethyl ether (20 mL) and the combined organic layers concentrated under reduced pressure. The resulting slightly yellow oil was then distilled under vacuum (BP 63-65 °C, 1 mmHg) to give L-valinol **SI-7-3** (3.08 g, 70%) as a colourless oil.

**Physical State**: colourless oil

\[ R_f = 0.40 \text{ (MeOH:CH}_2\text{Cl}_2, 1:4 \text{ v/v; ninhydrin) } \]

\[ [\alpha]_D^\circ = +17.5^\circ \text{ (EtOH, } c 1.14) \text{ (lit.}^92 [\alpha]_D^\circ = +18.4^\circ \text{ (EtOH, } c 2.01)) \]

**¹H-NMR** [CDCl₃, 600 MHz] \( \delta \): 3.63 (dd, \( J = 10.5, 4.0 \text{ Hz, } 1\text{H} \)), 3.27 (dd, \( J = 10.4, 8.8 \text{ Hz, } 1\text{H} \)), 2.54 (ddd, \( J = 8.8, 6.4, 4.0 \text{ Hz, } 1\text{H} \)), 1.59 – 1.51 (m, 1H), 0.92 (d, \( J = 6.9 \text{ Hz, } 3\text{H} \)), 0.90 (d, \( J = 6.9 \text{ Hz, } 3\text{H} \))

**¹³C-NMR** [CDCl₃, 150 MHz] \( \delta \): 65.0, 58.6, 31.8, 19.4, 18.5.
Synthesis of SI-7-4: To a solution of L-valinol SI-7-3 (3.02 g, 29.3 mmol) in EtOH (9 mL) was added carbon disulfide (5.3 mL, 76.2 mmol). A 2.25 M solution of KOH (4.45 g, 79.0 mmol) in EtOH/H$_2$O (1:1 v/v, 35 mL) was then added dropwise at room temperature over 30 min. The homogeneous red solution is then heated to reflux for 72 h under an argon atmosphere. The flask was then cooled, the volatiles removed under reduced pressure and the mixture slowly acidified with 0.5 M HCl (160 mL). The aqueous solution is then extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic extracts dried over MgSO$_4$. Concentration under reduced pressure afforded a yellow oil which was purified by column chromatography (silica gel, hexanes/EtOAc, 1:4 → 3:7) to give SI-7-4 (3.96 g, 84%) as a colourless crystalline solid.

**Physical State**: colourless crystalline solid

R$_f$ = 0.34 (EtOAc:hexanes, 3:7 v/v; KMnO$_4$)

[α]$_D$ = $-33.0^\circ$ (CHCl$_3$, c 1.02) (lit.$^{90}$ [α]$_D$ = $-34.8^\circ$ (CHCl$_3$, c 1.11))

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.91 (br s, 1H), 4.07 (td, $J$ = 8.3, 6.7 Hz, 1H), 3.53 (dd, $J$ = 11.1, 8.2 Hz, 1H), 3.35 (dd, $J$ = 11.1, 8.4 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.06 (d, $J$ = 6.8 Hz, 3H), 1.02 (d, $J$ = 6.8 Hz, 3H)

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 201.3, 70.1, 36.2, 32.2, 19.0, 18.4.
Synthesis of (S)-7-47: To a suspension of 60% NaH (0.546 g, 13.64 mmol) in dry THF (10 mL) at 0 °C was added a solution of (4S)-isopropyl-1,3-thiazolidine-2-thione SI-7-4 (2.00 g, 12.40 mmol) in dry THF (10 mL). The mixture was stirred at 0 °C for 10 min, and acetyl chloride (0.98 mL, 13.64 mmol) was injected into the solution and stirred at 0 °C for 10 min and then at room temperature for 1 h. 5% Hydrochloric acid was added, and the mixture was extracted with EtOAc, washed with brine, and worked up. Purification of the crude product so obtained by flash column chromatography (silica gel, hexanes/EtOAc, 1:9 v/v) afforded (S)-7-47 (2.27 g, 90%) as a bright yellow oil.

**Physical State**: bright yellow oil

\[ R_f = 0.21 \text{ (EtOAc:hexanes, 1:9 v/v)} \]

\[ [\alpha]_D = +465.3^\circ \text{ (CHCl}_3, c 0.48) \text{ (lit.}^{91} [\alpha]_D = +448.9^\circ \text{ (CHCl}_3, c 0.51)) \]

\(^1\text{H-NMR [CDCl}_3, 600 \text{ MHz]} \delta: 5.17 – 5.13 \text{ (m, 1H), 3.50 (dd, } J = 11.5, 8.0 \text{ Hz, 1H), 3.02 (dd, } J = 11.5, 1.1 \text{ Hz, 1H), 2.77 (s, 3H), 2.41 – 2.32 \text{ (m, 1H), 1.06 (d, } J = 6.8 \text{ Hz, 3H), 0.98 (d, } J = 6.9 \text{ Hz, 3H).} \]

\(^{13}\text{C-NMR [CDCl}_3, 150 \text{ MHz]} \delta: 203.4, 170.9, 71.4, 30.9, 30.5, 27.1, 19.2, 17.9.\]

Synthesis of SI-7-5: NaH (60% in mineral oil, 400 mg, 10 mmol) was washed with pentane (10 mL), then vigorously stirred in THF (30 mL) at 0 °C. Diol SI-6-2 (1.6 g, 10 mmol) in THF (20 mL) was then added dropwise and the resulting solution stirred at room temperature for 45 min before addition of benzyl bromide (1.7 g, 10 mmol) in a
single portion. The reaction mixture was then left to stir at r.t. for 16 h. The mixture was diluted with diethyl ether (50 mL) and washed with saturated aq. NH₄Cl (50mL) and the aqueous layer further extracted with Et₂O (3 x 20 mL). The organic extracts were then dried over magnesium sulphate anhydrous, filtered and concentrated under reduced pressure to afford 7-62 (2.32 g, 92%) as a pale yellow oil which is pure enough to proceed to the next step.

To a stirred solution of 7-62 (602 mg, 2.09 mmol) in dry THF (10 mL) were added successively, at 0 °C, 1H-imidazole (301 mg, 4.42 mmol), Ph₃P (604 mg, 2.30 mmol), and I₂ (585 mg, 2.30 mmol, in THF (2 mL)). The resulting mixture was stirred for 2 h at r.t. and then quenched by H₂O (10 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were then washed with brine and dried over anhydrous MgSO₄ prior to concentration under reduced pressure. The crude mixture was column chromatographed over silica gel (Et₂O/Hexanes, 1:9 v/v) to afford iodide SI-7-5 (3.33 g, 82% over two steps) as a colourless oil.

**Physical State**: colourless oil

Rf = 0.70(Et₂O:hexanes, 1:4 v/v; vanillin)

[α]D = −8.7° (CHCl₃, c 2.32)

¹H-NMR [CDCl₃, 600 MHz] δ: 7.39 – 7.35 (m, 5H), 4.63 – 4.61 (m, 2H), 4.00 (dt, J = 6.9, 5.1 Hz, 1H), 3.92 – 3.87 (m, 1H), 3.68 (qd, J = 10.1, 4.9 Hz, 2H), 3.38 (dd, J = 10.5, 5.1 Hz, 1H), 3.31 (dd, J = 10.6, 5.3 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H).

¹³C-NMR [CDCl₃, 150 MHz] δ: 137.8, 128.5, 127.8, 127.7, 109.8, 80.1, 77.7, 73.6, 70.5, 27.4, 27.3, 6.4.

HRES MS (m/z): (M+Na)⁺ calcd. for C₁₄H₁₉O₃NaI, 385.0277; found 385.0288.
Synthesis of 7-57: To iodide SI-7-5 (2.96 mg, 8.17 mmol) were added DMSO (8 mL), tetrabutylammonium iodide (0.296 mg, 0.817 mmol) and powdered KCN (1.06 mg, 16.3 mmol). The slightly yellow mixture was allowed to stir for 3 d at room temperature after which water (30 mL) was added to quench the reaction. Extraction with Et₂O (3 x 30 mL) followed by drying of the combined organic extracts with anhydrous MgSO₄ and concentration under reduced pressure gave the crude nitrile as a brown oil. Purification over silica gel (EtOAc/Hexanes, 1:4 v/v) afforded nitrile 7-57 (1.93 g, 91%) as a colourless oil.

Physical State: colourless oil

Rf = 0.39 (EtOAc:hexanes, 3:7 v/v; vanillin)

[α]D = −3.8° (CHCl₃, c 2.70)

¹H-NMR [CDCl₃, 600 MHz] δ: 7.41 – 7.36 (m, 2H), 7.34 (dd, J = 6.8, 4.2 Hz, 3H), 4.59 (s, 2H), 4.09 – 4.02 (m, 3H), 3.76 (dd, J = 9.8, 4.3 Hz, 1H), 3.59 (dd, J = 9.8, 5.9 Hz, 1H), 2.82 (dd, J = 17.0, 4.2 Hz, 1H), 2.67 (dd, J = 17.0, 4.9 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H).

¹³C-NMR [CDCl₃, 150 MHz] δ: 137.5, 128.6, 128.0, 127.7, 116.6, 110.3, 78.1, 74.4, 73.8, 69.9, 27.0, 26.9, 21.8.

HRES MS (m/z): (M+H)⁺ calcd. for C₁₅H₂₀NO₃, 262.1443; found 262.1445.
Synthesis of **7-63**: Allylzinc bromide was prepared under a nitrogen atmosphere by using Knochel’s procedure\(^93\), which was slightly modified. In a flame-dried round-bottom flask fitted with magnetic bar and dropping funnel was placed zinc powder (0.78 g, 12 mmol), and the flask was flushed with dry nitrogen. Zinc powder was heated to 60–70 °C. 1,2-Dibromoethane (100 μL, 1.2 mmol) and THF (2 mL) was added, and the temperature was maintained for 10 min. The reaction mixture was then cooled to room temperature. Trimethylsilyl chloride (100 μL, 0.8 mmol) and THF (1 mL) was added. The mixture was stirred at room temperature for 15 min. After this step, allyl bromide (1.2 g, 10 mmol) in THF (5 mL) was added dropwise over 30 min, and the mixture was stirred for 2 min. The resulting opaque white solution was used immediately.

To a stirred solution of nitrile **7-57** (1.80 mg, 6.89 mmol) in THF (5 mL) at room temperature was added allylzinc bromide (6 mL, 1.4 M in THF) dropwise. The reaction was observed to be complete after 1 h, as monitored by TLC, at which time a 10% aqueous solution of citric acid (30 mL) was added. The aqueous phase was extracted with Et\(_2\)O (4 x 10 mL) and the combined organic extracts dried over anhydrous magnesium sulphate prior to concentration under reduced pressure. The crude oil was then flash chromatographed over silica gel (Et\(_2\)O/Hexanes, 1:4 v/v) to afford the allyl ketone **7-63** (1.76 g, 84%) as a colourless oil.

**Physical State**: colourless oil

\(R_f = 0.21\) (EtOAc:hexanes, 1:4 v/v; vanillin)

\([\alpha]_D = -13.1^\circ\) (CHCl\(_3\), c 0.90)
$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.39 – 7.29 (m, 5H), 5.93 (ddt, $J = 17.1, 10.2, 6.9$ Hz, 1H), 5.21 (d, $J = 10.2$ Hz, 1H), 5.16 (d, $J = 17.1$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 4.57 (d, $J = 12.1$ Hz, 1H), 4.29 (td, $J = 7.9$, 4.2 Hz, 1H), 3.89 (dt, $J = 8.1$, 5.2 Hz, 1H), 3.67 (dd, $J = 10.0$, 5.4 Hz, 1H), 3.59 (dd, $J = 10.0$, 5.1 Hz, 1H), 3.25 (d, $J = 6.9$ Hz, 2H), 2.80 (dd, $J = 16.2$, 7.8 Hz, 1H), 2.72 (dd, $J = 16.2$, 4.2 Hz, 1H), 1.42 (s, 6H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 205.9, 137.9, 130.2, 128.4, 127.7, 119.1, 109.3, 79.5, 74.6, 73.6, 70.4, 48.4, 45.7, 27.2, 26.9.

**HRES MS (m/z):** (M+H)$^+$ calcd. for C$_{18}$H$_{25}$O$_4$, 305.1753; found 305.1749.

Synthesis of SI-7-6: To a stirred solution of 7-63 (1.67 g, 5.49 mmol) in ether (60 mL), LiI (2.20 g, 16.5 mmol) was added, and the resulting mixture was stirred at -40 °C for 10 minutes. The reaction mixture was then cooled to -100 °C and LiAlH$_4$ (0.625 g, 16.5 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at this temperature for 2 h and quenched with saturated aqueous sodium sulphate (1.5 mL). The crude suspension was then filtered through celite, water (50 mL) added and extracted with ether (3 x 20 ml). The combined organic layers were dried over anhydrous MgSO$_4$, concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexanes/EtOAc 4:1) to afford alcohols SI-7-6 (1.55 g, 92%, 9:1 d.r.) as an inseparable colourless oil.

**Physical State:** colourless oil

$R_f = 0.38$ (EtOAc:hexanes, 3:7 v/v; vanillin)

$[\alpha]_D = -7.0^\circ$ (CHCl$_3$, $c$ 3.63)
$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 7.40 – 7.30 (m, 5H), 5.85 (ddt, $J = 17.3, 10.2, 7.1$ Hz, 1H), 5.16 – 5.09 (m, 2H), 4.61 (s, 2H), 4.04 – 3.98 (m, 1H), 3.94 – 3.86 (m, 2H), 3.66 (dd, $J = 10.2, 5.2$ Hz, 1H), 3.59 (dd, $J = 10.2, 4.8$ Hz, 1H), 3.13 (d, $J = 1.2$ Hz, 1H), 2.34 – 2.22 (m, 2H), 1.83 (dt, $J = 14.2, 2.7$ Hz, 1H), 1.66 (dt, $J = 14.2, 9.5$ Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 137.8, 134.7, 128.4, 127.8, 127.7, 117.6, 109.4, 80.2, 78.5, 73.7, 70.3, 70.2, 41.8, 39.4, 27.2, 27.0.

HRES MS ($m/z$): (M+H)$^+$ calcd. for C$_{18}$H$_{27}$O$_4$, 307.1909; found 307.1908.

Synthesis of 7-64: Sodium hydride (60% dispersion in mineral oil (236 mg, 5.89 mmol) in dry DMF (4 mL) was added dropwise to a stirred solution of alcohol SI-7-6 (1.53 g, 5.00 mmol) in dry THF (8 mL) at 0 °C, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the mixture was diluted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL), brine (20 mL), and then dried over Na$_2$SO$_4$. Concentration of the solvent under reduced pressure gave a residue, which was purified by column chromatography (hexane/ethyl acetate, 9:1→4:1 v/v) to give 7-64 (1.66 g, 78%) as a colourless oil.

Physical State: colourless oil

$R_f = 0.64$ (EtOAc:hexanes, 3:7 v/v; vanillin)

$[\alpha]_D = +3.1^\circ$ (CHCl$_3$, $c$ 0.91)
$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.35 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 5.88 – 5.78 (m, 1H), 5.07 (t, $J = 14.0$ Hz, 2H), 4.57 (d, $J = 12.2$ Hz, 1H), 4.53 (d, $J = 12.2$ Hz, 1H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.36 (d, $J = 11.1$ Hz, 1H), 3.94 (td, $J = 7.7$, 4.2 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.79 (s, 3H), 3.62 (p, $J = 5.8$ Hz, 1H), 3.53 (ddd, $J = 14.3$, 10.3, 4.8 Hz, 2H), 2.44 – 2.36 (m, 1H), 2.36 – 2.29 (m, 1H), 1.89 (dt, $J = 13.7$, 6.7 Hz, 1H), 1.84 – 1.76 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 159.3, 138.2, 134.7, 130.9, 129.4, 128.5, 127.8, 117.4, 113.9, 109.0, 80.3, 75.5, 73.6, 70.7, 70.4, 55.4, 38.1, 37.1, 27.5, 27.2.

HRES MS (m/z): (M+H)$^+$ calcd. for C$_{26}$H$_{35}$O$_5$, 427.2484; found 427.2486.

Synthesis of 7-65: A mixture of 7-64 (1.56 mg, 3.66 mmol) and W-4 Raney nickel (excess) in ethanol (15 mL) was stirred for 2 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off under argon, washed with EtOAc (3 x 10 mL) and the filtrate concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate, 3:1 → 1:1 v/v) to afford 7-65 (1.08 g, 87%) as a colourless oil.

Physical State: colourless oil

$R_f = 0.23$ (EtOAc:hexanes, 2:3 v/v; vanillin)

$[\alpha]_D^{\circ} -15.6^\circ$ (CHCl$_3$, c 1.02)

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.26 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 4.45 (d, $J = 11.1$ Hz, 1H), 4.42 (d, $J = 11.1$ Hz, 1H), 4.00 (td, $J = 7.6$, 4.7 Hz, 1H), 3.81 – 3.72
(m, 5H), 3.59 (tdd, J = 14.6, 9.5, 5.0 Hz, 2H), 2.01 – 1.94 (m, 2H), 1.79 – 1.71 (m, 1H),
1.57 – 1.53 (m, 2H), 1.46 – 1.34 (m, 8H), 0.92 (t, J = 7.3 Hz, 3H).

\(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 159.3, 130.9, 129.5, 113.9, 108.7, 81.6, 75.9, 74.4, 70.4,
62.2, 55.4, 37.2, 36.0, 27.5, 27.2, 18.6, 14.4.

HRES MS \((m/z)\): (M+Na)\(^+\) calcd. for C\(_{19}\)H\(_{30}\)O\(_5\)Na, 361.1991; found 361.1989.

Synthesis of SI-7-7: To 7-65 (2.92 g, 8.63 mmol) in CH\(_2\)Cl\(_2\) (52 mL) at room temperature
were added DMSO (5 mL) and TEA (12.0 mL). The solution was then cooled to 0 °C prior to the addition of a solution of SO\(_3\)∙py (6.87 g, 43.1 mmol) in DMSO (20 mL) dropwise over 20 minutes and stirring continued for 4 h at this temperature. The reaction was quenched with a saturated aqueous solution of NH\(_4\)Cl (100 mL) prior to extraction with Et\(_2\)O (3 x 50 mL). The combined organic fractions were dried over anhydrous MgSO\(_4\), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude aldehyde 7-66 was placed under high vacuum for 1 h and carried on directly to the next step.

To phosphonium salt 6-16 (4.24 g, 12.9 mmol) was added THF (12 mL) and DMF (3 mL). The solution was cooled to 0 °C for 15 minutes prior to the addition of KO\(^{t}\)Bu (1.45 g, 12.9 mmol) portion-wise to afford a light yellow mixture. Slow addition of the base is required to prevent local heating which causes degradation of the phosphonium salt. The mixture containing the base was left to stir at 0 °C for 1 h before the corresponding aldehyde 7-66 in THF (3 mL) was subsequently added dropwise. The reaction mixture
was allowed to warm to room temperature overnight before being quenched with a saturated NH₄Cl solution (10 mL). Standard extractive work-up with diethyl ether (3 x 20 mL) was followed by washing the combined organic fractions with water (10 mL). The combined organic extracts were then dried over anhydrous MgSO₄ and concentrated under reduced pressure to give crude SI-7-7 (2.87 g, 82% two steps, 20:1 E/Z) as a light yellow oil. The crude oil was used in the next step without further purification. An analytical quantity was flash chromatographed (silica gel, EtOAc:hexanes, 1:9 to 1:4 v/v) to give pure SI-7-7.

**Physical State:** light yellow oil

\[ R_f = 0.20 \text{ (EtOAc:hexanes, 1:4 v/v; vanillin)} \]

\[ [\alpha]_D = -2.9^\circ \text{ (CHCl}_3, c 1.05) \]

\[ ^1\text{H-NMR} \text{ [CDCl}_3, 600 MHz] \delta: 7.26 \text{ (d, } J = 8.7 \text{ Hz, 2H)}, 6.87 \text{ (d, } J = 8.7 \text{ Hz, 2H)}, 5.89 \text{ (ddd, } J = 15.6, 6.6, 0.5 \text{ Hz, 1H)}, 5.80 \text{ (ddd, } J = 15.5, 5.3, 0.7 \text{ Hz, 1H)}, 5.27 \text{ (d, } J = 5.3 \text{ Hz, 1H)}, 4.42 \text{ (s, 2H)}, 4.11 - 4.06 \text{ (m, 1H)}, 3.99 - 3.94 \text{ (m, 2H)}, 3.92 - 3.87 \text{ (m, 2H)}, 3.84 - 3.76 \text{ (m, 4H)}, 3.56 \text{ (p, } J = 5.9 \text{ Hz, 1H)}, 1.90 \text{ (ddd, } J = 13.9, 7.6, 6.0 \text{ Hz, 1H)}, 1.73 \text{ (ddd, } J = 14.2, 6.0, 4.2 \text{ Hz, 1H)}, 1.55 - 1.50 \text{ (m, 2H)}, 1.46 - 1.32 \text{ (m, 8H)}, 0.91 \text{ (t, } J = 7.3 \text{ Hz, 3H)}. \]

\[ ^{13}\text{C-NMR} \text{ [CDCl}_3, 150 MHz] \delta: 159.1, 132.4, 131.0, 130.2, 129.4, 113.7, 108.8, 102.7, 81.1, 77.8, 75.7, 70.3, 65.0, 64.9, 55.3, 36.1, 27.3, 26.9, 18.4, 14.2. \]

**HRES MS (m/z):** \((M+Na)^+\) calcd. for C₂₃H₃₄NaO₆, 429.2248; found 429.2247.
Synthesis of \textbf{SI-6-6}: To \textbf{6-26} (1.56 g, 3.66 mmol) in THF (15 mL) was added TBAF at 0 °C. The mixture was stirred for 1 h at this temperature. The mixture was concentrated \textit{in vacuo} to remove the solvent and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 4:1 → 7:3 v/v) to afford \textbf{SI-6-6} (1.08 g, 87%) as a colourless oil.

Spectroscopic data for (\textit{E})-\textbf{18}:

\textbf{Physical State}: colourless oil

\( R_f = 0.08 \) (EtOAc:hexanes, 3:7 v/v; vanillin)

\([\alpha]_D^{\circ} = −5.72 ^\circ \) (CHCl\(_3\), c 1.02)

\( ^1\text{H-NMR} \ [\text{CDCl}_3, \ 600 \text{ MHz}] \delta: 5.86 \) (dd, \( J = 15.5, 6.3 \text{ Hz}, 1\text{H} \)), 5.81 \( \text{ (dd, } J = 15.6, 5.5 \text{ Hz, } 1\text{H) } \), 5.37 \( \text{ (d, } J = 5.7 \text{ Hz, } 1\text{H) } \), 4.38 \( \text{ (dd, } J = 8.4, 6.2 \text{ Hz, } 1\text{H) } \), 3.83 \( \text{ (dd, } J = 12.1, 3.0 \text{ Hz, } 1\text{H) } \), 3.81 – 3.77 \( \text{ (m, } 1\text{H) } \), 3.60 \( \text{ (dd, } J = 12.1, 3.8 \text{ Hz, } 1\text{H) } \), 1.42 \( \text{ (s, } 6\text{H) } \), 1.21 \( \text{ (s, } 9\text{H) } \), 1.20 \( \text{ (s, } 3\text{H) } \).

\( ^{13}\text{C-NMR} \ [\text{CDCl}_3, \ 150 \text{ MHz}] \delta: 132.91, 131.80, 109.57, 99.60, 82.51, 81.16, 76.73, 60.85, 27.13, 27.08, 24.03, 24.00, 22.08. \)

\textbf{HREI MS (m/z)}: (M)\(^+\) calcd. for C\(_{15}\)H\(_{26}\)O\(_5\), 286.1780; found 286.1770.

Spectroscopic data for (\textit{Z})-\textbf{18}:

\textbf{Physical State}: colourless oil

\( R_f = 0.18 \) (EtOAc:hexanes, 3:7 v/v; vanillin)

\([\alpha]_D^{\circ} = −5.72 ^\circ \) (CHCl\(_3\), c 1.02)
$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.77 – 5.73 (m, 2H), 5.73 – 5.66 (m, 1H), 4.70 (t, $J$ = 8.6 Hz, 1H), 3.84 – 3.72 (m, 3H), 2.89 (dd, $J$ = 8.5, 5.7 Hz, 1H), 1.43 (s, 6H), 1.23 (s, 6H), 1.22 (s, 3H), 1.19 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 133.83, 132.30, 109.37, 95.47, 82.99, 82.86, 80.86, 74.39, 61.24, 27.13, 27.09, 24.11, 23.78, 22.05, 21.99.

HREI MS ($m/z$): (M)$^+$ calcd. for C$_{15}$H$_{26}$O$_5$, 286.1780; found 286.1770.

Synthesis of 7-58: To a stirred solution of SI-6-6 (593 mg, 2.07 mmol) in dry THF (10 mL) were added successively, at 0 °C, $1H$-imidazole (284 mg, 4.14 mmol), Ph$_3$P (652 mg, 2.48 mmol), and I$_2$ (628 mg, 2.48 mmol, in THF (2 mL)). The resulting mixture was stirred for 2 h at r.t. and then quenched by a 10% Na$_2$S$_2$O$_3$ solution (10 mL) and extracted with Et$_2$O (3 x 10 mL). The combined organic layers were then washed with brine and dried over anhydrous MgSO$_4$ prior to concentration under reduced pressure. The crude mixture was column chromatographed (silica gel, Et$_2$O/Hexanes, 1:9 v/v) to afford iodide 7-58 (738 mg, 90%) as a colourless oil.

Physical State: colourless oil

$R_f$ = 0.32 (EtOAc:hexanes, 1:9 v/v; vanillin)

$[\alpha]_D$ = -23.9° (CHCl$_3$, c 3.73)
$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.83 (dd, $J = 15.5$, 6.2 Hz, 1H), 5.78 (dd, $J = 15.6$, 5.6 Hz, 1H), 5.32 (d, $J = 5.7$ Hz, 1H), 4.15 (dd, $J = 7.5$, 6.3 Hz, 1H), 3.57 (dt, $J = 7.7$, 4.9 Hz, 1H), 3.27 (dd, $J = 10.8$, 4.7 Hz, 1H), 3.16 (dd, $J = 10.8$, 5.2 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.15 (s, 12H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 133.14, 131.46, 109.92, 99.50, 82.56, 81.27, 79.51, 27.41, 27.37, 24.05, 22.10, 4.98.

HREI MS (m/z): (M–CH$_3$)$^+$ calcd. for C$_{14}$H$_{22}$IO$_4$, 381.0563; found 381.0562.

Synthesis of 7-56: To iodide 7-58 (280 mg, 0.71 mmol) were added DMSO (1 mL), tetrabutylammonium iodide (26 mg, 0.07 mmol) and powdered KCN (92 mg, 1.41 mmol). The slightly yellow mixture was allowed to stir for 3 d at room temperature after which water (10 mL) was added to quench the reaction. Extraction with Et$_2$O (3 x 10 mL) followed by drying of the combined organic extracts with anhydrous MgSO$_4$ and concentration under reduced pressure gave the crude nitrile as a brown oil. Purification via column chromatography (silica gel, EtOAc/Hexanes, 1:4 v/v) afforded nitrile 7-56 (136 mg, 67%) as a colourless oil.

Physical State: colourless oil

$R_f = 0.##$ (EtOAc:hexanes, 3:7 v/v; vanillin)

$[\alpha]_D = -25.6 \degree$ (CHCl$_3$, c 1.30)
$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.92 (dd, $J = 15.6$, 5.7 Hz, 1H), 5.86 (dd, $J = 15.6$, 6.5 Hz, 1H), 5.41 (d, $J = 5.6$ Hz, 1H), 4.32 (dd, $J = 8.2$, 6.6 Hz, 1H), 3.87 (dt, $J = 8.4$, 4.7 Hz, 1H), 2.78 (dd, $J = 17.1$, 4.6 Hz, 1H), 2.60 (dd, $J = 17.1$, 4.9 Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.25 (s, 12H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 134.30, 129.73, 116.17, 110.34, 99.10, 82.53, 79.91, 75.41, 27.03, 26.86, 23.89, 21.95, 20.42.

HREI MS ($m/z$): (M–CH$_3$)$^+$ calcd. for C$_{15}$H$_{22}$NO$_4$, 280.1549; found 280.1555.

Synthesis of 7-59: Allylzinc bromide was prepared using Knochel’s procedure, which was slightly modified. In a flame-dried round-bottom flask fitted with magnetic bar and dropping funnel was placed zinc powder (0.78 g, 12 mmol), and the flask was flushed with dry nitrogen. Zinc powder was heated to 60–70 °C. 1,2-Dibromoethane (100 μL, 1.2 mmol) and THF (2 mL) was added, and the temperature was maintained for 10 min. The reaction mixture was then cooled to room temperature. Trimethylsilyl chloride (100 μL, 0.8 mmol) and THF (1 mL) was added. The mixture was stirred at room temperature for 15 min. After this step, allyl bromide (1.2 g, 10 mmol) in THF (5 mL) was added dropwise over 30 min, and the mixture was stirred for 2 min. The resulting opaque white solution was used immediately.
To a stirred solution of nitrile 7-56 (1.21 g, 4.10 mmol) in THF (3 mL) at room temperature was added allylzinc bromide (6.0 mL, 1.4 M in THF) dropwise. The reaction was observed to be complete after 1 h, as monitored by TLC, at which time a 10% aqueous solution of citric acid (30 mL) was added. The aqueous phase was extracted with Et₂O (4 x 10 mL) and the combined organic extracts dried over anhydrous magnesium sulphate prior to concentration under reduced pressure. The crude oil was then flash chromatographed over silica gel (Et₂O/Hexanes, 1:4 v/v) to afford the allyl ketone 7-59 (1.16 g, 84%) as a colourless oil.

Physical State: colourless oil

R<sub>f</sub> = 0.26 (EtOAc:hexanes, 1:4 v/v; vanillin)

[α]<sub>D</sub> = −17.3 ° (CHCl₃, c 2.12)

<sup>1</sup>H-NMR [CDCl₃, 600 MHz] δ: 5.90 (ddt, J = 17.2, 10.2, 6.9 Hz, 1H), 5.83 (dd, J = 15.5, 5.6 Hz, 1H), 5.79 (dd, J = 15.5, 5.3 Hz, 1H), 5.35 (d, J = 5.3 Hz, 1H), 5.18 (ddd, J = 10.2, 2.8, 1.3 Hz, 1H), 5.13 (dddd, J = 17.2, 3.0, 1.5 Hz, 1H), 4.12 – 4.06 (m, 2H), 3.22 (dt, J = 6.9, 1.2 Hz, 2H), 2.68 (dd, J = 16.0, 7.7 Hz, 1H), 2.60 (dd, J = 16.0, 3.3 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.20 – 1.19 (m, 12H).

<sup>13</sup>C-NMR [CDCl₃, 150 MHz] δ: 205.70, 133.41, 131.10, 130.28, 119.29, 109.54, 99.47, 82.52, 82.49, 80.68, 76.34, 48.53, 44.29, 27.27, 27.05, 24.04, 24.03, 22.09.

HREI MS (m/z): (M–CH₃)<sup>+</sup> calcd. for C<sub>18</sub>H₂₇O₅, 323.1858; found 323.1843.
Synthesis of 7-60: To a stirred solution of 7-59 (860 mg, 2.54 mmol) in ether (38 mL), LiI (2.20 g, 16.5 mmol) was added, and the resulting mixture was stirred at -40 °C for 10 minutes. The reaction mixture was then cooled to -100 °C and LiAlH₄ (0.625 g, 16.5 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at this temperature for 2 h and quenched with saturated aqueous sodium sulphate (1.5 mL). The crude suspension was then filtered through celite, water (50 mL) added and extracted with ether (3 x 20 ml). The combined organic layers were dried over anhydrous MgSO₄, concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexanes/EtOAc 4:1) to afford alcohols 7-60 (798 mg, 92%, 9:1 d.r.) as an inseparable colourless oil.

**Physical State:** colourless oil

Rᵣ = 0.17 (EtOAc:hexanes, 1:4 v/v; vanillin)

[α]ᵣ = −5.3 ° (CHCl₃, c 1.19)

**¹H-NMR** [CDCl₃, 600 MHz] δ: 5.89 – 5.77 (m, 3H), 5.38 (dd, J = 3.5, 1.8 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.08 (ddd, J = 8.4, 3.7, 2.0 Hz, 1H), 3.86 (ddddd, J = 9.0, 6.2, 5.9, 2.5 Hz, 1H), 3.81 (ddd, J = 9.8, 8.5, 2.8 Hz, 1H), 3.05 (bs, 1H), 2.32 – 2.18 (m, 2H), 1.77 (dt, J = 14.2, 2.7 Hz, 1H), 1.59 (dt, J = 14.2, 9.7 Hz, 1H), 1.41 (s, 6H), 1.22 (s, 12H).

**¹³C-NMR** [CDCl₃, 150 MHz] δ: 134.74, 133.20, 131.19, 117.80, 109.65, 99.56, 82.55, 81.50, 80.62, 70.43, 41.91, 38.10, 27.34, 27.12, 24.06, 24.02, 22.11.

**HREI MS** (m/z): (M)⁺ calcd. for C₁₉H₃₂O₅, 340.2250; found 340.2253.
Synthesis of **SI-7-9**: To **7-60** (1.21 g, 3.55 mmol) in benzene/ethanol (1:1 v/v, 20 mL) under an atmosphere of H₂ (1 atm) was added tris(triphenylphosphine)ruthenium dichloride (68 mg, 0.071 mmol). The violet reaction was stirred for 1 h at which point the hydrogen was allowed to dissipate and the reaction turned green, indicating deactivation of the catalytic species. The reaction was concentrated under reduced pressure and flash chromatographed (silica gel, EtOAc/hexanes, 1:4 v/v) to afford **SI-7-9** (1.12 g, 92%) as a colourless oil.

**Physical State**: colourless oil

Rₓ = 0.19 (EtOAc:hexanes, 1:4 v/v; vanillin)

[α]D = −5.0 ° (CHCl₃, c 0.74)

**¹H-NMR** [CDCl₃, 600 MHz] δ: 5.85 – 5.77 (m, 2H), 5.38 (dd, J = 3.3, 2.0 Hz, 1H), 4.13 – 4.00 (m, 1H), 3.84 – 3.73 (m, 2H), 1.73 (dt, J = 14.2, 2.5 Hz, 1H), 1.56 (dt, J = 14.2, 9.8 Hz, 1H), 1.51 – 1.42 (m, 2H), 1.41 (s, 6H), 1.21 (s, 12H), 0.92 (t, J = 7.1 Hz, 3H).

**¹³C-NMR** [CDCl₃, 150 MHz] δ: 133.18, 131.26, 109.63, 99.56, 82.53, 81.60, 80.94, 70.96, 39.72, 38.81, 27.32, 27.10, 24.04, 24.01, 22.09, 18.74, 14.21.

**HRES MS (m/z)**: (M+H)⁺ calcd. for C₁₉H₃₅O₅, 343.2484; found 343.2481.
Synthesis of SI-7-10: Sodium hydride (60% dispersion in mineral oil (5.6 mg, 0.14 mmol) was added to a stirred solution of alcohol SI-7-9 (40 mg, 0.12 mmol) and \textit{p}-methoxybenzyl chloride (22 mg, 0.14 mmol) in THF (0.6 mL) and DMF (0.4 mL) at 0 °C, and stirring was continued for 16 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the mixture was diluted with diethyl ether (10 mL). The organic layer was washed with brine (5 mL), and then dried over Na$_2$SO$_4$. Concentration of the solvent under reduced pressure gave a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate, 9:1 v/v) to give SI-7-10 (56 mg, 78%) as a colourless oil.

**Physical State**: colourless oil

$R_f = 0$. (EtOAc:hexanes, 1:4 v/v; vanillin)

$[\alpha]_D^\circ = -5.0 ^\circ$ (CHCl$_3$, c 0.62)

$^1$H-NMR [CD$_2$Cl$_2$, 600 MHz] $\delta$: 7.25 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.81 – 5.72 (m, 2H), 5.32 (m, 1H), 4.40 (d, $J = 11.0$ Hz, 1H), 4.38 (d, $J = 11.0$ Hz, 1H), 4.07 – 4.03 (m, 1H), 3.78 (s, 3H), 3.76 (td, $J = 8.0$, 4.0 Hz, 1H), 3.53 (p, $J = 5.9$ Hz, 1H), 1.84 (ddd, $J = 13.8$, 7.8, 5.8 Hz, 1H), 1.71 (ddd, $J = 14.3$, 6.1, 4.0 Hz, 1H), 1.54 – 1.49 (m, 2H), 1.43 – 1.33 (m, 8H), 1.19 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 0.91 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR [CD$_2$Cl$_2$, 150 MHz] $\delta$: 159.2, 133.2, 131.6, 131.3, 129.4, 113.6, 108.6, 99.5, 82.2, 81.3, 77.9, 75.8, 70.2, 55.3, 36.1, 36.0, 27.1, 26.7, 23.8, 21.8, 18.4, 14.1.
HRES MS (m/z): (M+Na)+ calcd. for C_{27}H_{42}O_{6}Na, 485.2879; found 485.2887.

Synthesis of 7-61: Crude acetal SI-7-10 (51 mg, 0.11 mmol) was dissolved in acetone (5 mL) and Iron(III) chloride hexahydrate (3.0 mg, 0.011 mmol) added with vigorous stirring. After stirring at room temperature for 10 h the reaction was quenched with a saturated NaHCO₃ solution. The reaction mixture was extracted with diethyl ether (3x 5 mL) and the combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to afford crude 7-61 (25 mg, 63%) which was used without further purification.

Synthesis of 7-61: Crude acetal SI-7-7 (2.84 g, 6.51 mmol) was dissolved in acetone (30 mL) and p-toluenesulphonic acid (112 mg, 0.589 mmol) added with vigorous stirring. After stirring at room temperature for 1 h the reaction was quenched with a saturated NaHCO₃ solution. The reaction mixture was concentrated under reduced pressure (<30 °C), the residue dissolved in diethyl ether (30 mL), the suspension dried with MgSO₄, the
solids filtered and the mother liquor concentrated under reduced pressure to afford crude 7-61 (2.36 mg, 93%) which was used without further purification.

**Physical State**: light yellow oil

$R_f = 0.24$ (EtOAc:hexanes, 1:4 v/v; vanillin)

$[\alpha]_D = -9.6^\circ$ (CHCl$_3$, c 2.60)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 9.43 (d, $J = 7.9$ Hz, 1H), 7.16 (d, $J = 8.7$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 6.63 (dd, $J = 15.7$, 5.4 Hz, 1H), 6.27 (ddd, $J = 15.7$, 7.9, 1.4 Hz, 1H), 4.40 (d, $J = 11.2$ Hz, 1H), 4.30 (d, $J = 11.2$ Hz, 1H), 4.27 (ddd, $J = 8.3$, 5.4, 1.3 Hz, 1H), 3.85 – 3.82 (m, 1H), 3.73 (s, 3H), 3.51 (p, $J = 5.8$ Hz, 1H), 1.90 (dt, $J = 14.4$, 6.4 Hz, 1H), 1.74 (dt, $J = 14.4$, 5.1 Hz, 1H), 1.52 – 1.44 (m, 2H), 1.38 (s, 3H), 1.35 – 1.31 (m, 5H), 0.85 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 193.1, 159.2, 152.5, 132.7, 130.6, 129.3, 113.8, 109.6, 80.2, 77.7, 75.3, 70.3, 55.3, 36.1, 35.8, 27.3, 26.6, 18.4, 14.2.

**HRES MS** ($m/z$): (M+Na)$^+$ calcd. for C$_{21}$H$_{30}$NaO$_5$, 385.1986; found 385.1984.

> PMBO
> O
> O
> H$_3$C
> CH$_3$
> "(R)-7-47"
> TiCl$_4$, DIPEA
> CH$_2$Cl$_2$, -78 °C
> 82%

![Chemical Structures](image)

Synthesis of 7-67: To a 0 °C solution of Nagao auxillary (−)-7-47 (0.51 g, 2.5 mmol) in CH$_2$Cl$_2$ (19 mL) was added TiCl$_4$ (1.0 $M$ in CH$_2$Cl$_2$, 2.8 mL, 2.8 mmol) and the resulting solution was stirred for 5 min. before cooling to −78 °C. DIPEA ($N,N$-Diisopropylethylamine) (0.48 mL, 2.8 mmol) was then added dropwise, and the resulting
enolate solution was stirred for 2 h at $-78 \, ^\circ\text{C}$. Aldehyde 7-61 (530 mg, 1.5 mmol) in CH$_2$Cl$_2$ (5 mL) was then added dropwise to the reaction mixture, and the resulting solution stirred at $-78 \, ^\circ\text{C}$ for an additional 15 min. The reaction was quenched with 10 mL of saturated NH$_4$Cl solution, diluted with 20 mL CH$_2$Cl$_2$ and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were then washed with brine (10 mL), dried over MgSO$_4$ and concentrated. Flash chromatography (silica gel, hexanes/EtOAc 5:1 → 4:1 → 2:1 → 1:1) afforded allylic alcohol 7-67 (680 mg, 82%, 4:1 d.r.) as a vibrant yellow oil.

**Physical State**: yellow oil

$R_f = 0.14$ (EtOAc:hexanes, 3:7 v/v; vanillin)

$[\alpha]_{D}^\circ = -183.0^\circ$ (CHCl$_3$, c 0.63)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 7.27 (d, $J = 9.8$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.91 – 5.84 (m, 1H), 5.74 (ddd, $J = 15.4$, 7.5, 1.4 Hz, 1H), 5.14 (dd, $J = 10.4$, 3.8 Hz, 1H), 4.68 (ddd, $J = 5.2$, 3.1, 1.3 Hz, 1H), 4.42 (s, 2H), 4.05 (t, $J = 7.9$ Hz, 1H), 3.83 – 3.79 (m, 4H), 3.63 (dd, $J = 17.7$, 2.9 Hz, 1H), 3.57 – 3.50 (m, 2H), 3.26 (dd, $J = 17.7$, 8.7 Hz, 1H), 3.02 (dd, $J = 11.5$, 0.9 Hz, 1H), 2.39 – 2.32 (m, 1H), 1.89 (ddd, $J = 13.9$, 7.5, 6.2 Hz, 1H), 1.72 (ddd, $J = 14.2$, 6.0, 4.4 Hz, 1H), 1.56 – 1.51 (m, 2H), 1.44 – 1.34 (m, 8H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.91 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 203.1, 172.5, 159.2, 135.6, 131.2, 129.5, 128.1, 113.9, 108.7, 82.0, 78.0, 75.9, 71.5, 70.4, 68.0, 55.5, 45.3, 36.3, 36.2, 31.0, 30.8, 27.5, 27.1, 19.2, 18.5, 18.0, 14.4.

HRES MS (m/z): (M+Na)$^+$ calcd. for C$_{29}$H$_{43}$NNaO$_6$S$_2$, 588.2424; found 588.2427.
Synthesis of 7-68: To a solution of alcohol 7-67 (608 mg, 1.07 mmol) and 2,6-lutidine (249 µL, 2.15 mmol) in CH₂Cl₂ (5 mL) was added dropwise TBSOTf (232 µL, 1.28 mmol) at 0 °C. After stirring for 1 h at room temperature, saturated NaHCO₃ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc, 9:1) to afford silyl ether 7-68 (658 mg, 90%) as a yellow oil.

Physical State: yellow oil

Rᶠ = 0.40 (EtOAc:hexanes, 1:4 v/v; vanillin)

[α]D = −180.9° (CHCl₃, c 0.60)

¹H-NMR [CD₂Cl₂, 600 MHz] δ: 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.86 (ddd, J = 15.4, 6.2, 0.7 Hz, 1H), 5.65 (ddd, J = 15.4, 7.5, 1.1 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.81 – 4.75 (m, 1H), 4.42 (d, J = 11.0 Hz, 1H), 4.38 (d, J = 11.0 Hz, 1H), 4.01 (t, J = 7.8 Hz, 1H), 3.79 (s, 3H), 3.73 (td, J = 8.3, 3.4 Hz, 1H), 3.64 (dd, J = 16.6, 8.1 Hz, 1H), 3.55 – 3.51 (m, 1H), 3.49 (dd, J = 11.5, 7.9 Hz, 1H), 3.16 (dd, J = 16.6, 4.4 Hz, 1H), 3.03 (dd, J = 11.5, 1.0 Hz, 1H), 2.37 (dq, J = 13.6, 6.8 Hz, 1H), 1.83 (ddd, J = 14.0, 8.4, 5.5 Hz, 1H), 1.68 (ddd, J = 14.2, 6.6, 3.4 Hz, 1H), 1.53 – 1.48 (m, 2H), 1.45 – 1.40 (m, 1H), 1.40 – 1.34 (m, 7H), 1.04 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.92 – 0.89 (m, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).
$^{13}$C-NMR [CD$_2$Cl$_2$, 150 MHz] δ: 203.6, 171.2, 159.5, 137.4, 131.7, 129.7, 128.0, 113.9, 108.87, 82.3, 78.4, 76.4, 72.3, 70.6, 69.9, 55.6, 46.8, 36.5, 36.5, 31.3, 27.5, 27.1, 26.0, 19.3, 18.8, 18.3, 17.9, 14.4, -4.0, -4.8.

HRES MS (m/z): (M+H)$^+$ calcd. for C$_{35}$H$_{58}$NO$_6$SiS$_2$, 680.3475; found 680.3448.

Synthesis of 7-69: To a stirred solution of the above TBS ether 7-68 (1.73 g, 2.54 mmol) in THF:H$_2$O (4:1) (10 mL) at room temperature, LiOH·H$_2$O (327 mg, 7.77 mmol) and H$_2$O$_2$ (30% in H$_2$O, 0.75 mL) were added sequentially. The yellow color of the reaction mixture gradually disappeared over the course of 20 min. The reaction mixture was then concentrated and directly loaded into a flash column chromatograph (20% EtOAc in hexane as eluant) to afford pure acid 7-69 (1.12 g, 82%) as a colourless oil.

Physical State: colourless oil

$R_f = 0.24$ (EtOAc:hexanes, 1:4 v/v; vanillin)

$[\alpha]_D = -19.1^\circ$ (CHCl$_3$, c 0.62)

$^1$H-NMR [CD$_2$Cl$_2$, 600 MHz] δ: 7.25 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.82 (ddd, $J = 15.4$, 6.0, 0.7 Hz, 1H), 5.68 (ddd, $J = 15.4$, 7.0, 1.1 Hz, 1H), 4.61 (dd, $J = 11.3$, 5.2 Hz, 1H), 4.43 (d, $J = 11.0$ Hz, 1H), 4.39 (d, $J = 11.0$ Hz, 1H), 4.03 (t, $J = 7.7$ Hz, 1H), 3.78 (s, 3H), 3.72 (td, $J = 8.3$, 3.3 Hz, 1H), 3.57 – 3.52 (m, 1H), 2.56 (dd, $J = 15.2$, 5.0 Hz, 1H), 2.51 (dd, $J = 15.2$, 6.6 Hz, 1H), 1.83 (ddd, $J = 13.9$, 8.4, 5.4 Hz, 1H), 1.69 (ddd, $J = 14.2$, 6.6, 3.3 Hz, 1H), 1.55 – 1.48 (m, 2H), 1.44 – 1.40 (m, 1H), 1.39 (s, 3H), 1.36 (q, $J = 4.3$ Hz, 4H), 0.93 – 0.87 (m, 12H), 0.09 (s, 3H), 0.08 (s, 3H).
$^{13}$C-NMR [CD$_2$Cl$_2$, 150 MHz] $\delta$: 172.6, 159.5, 135.4, 131.6, 129.7, 128.9, 114.0, 109.0, 81.9, 78.4, 76.3, 70.5, 69.9, 55.6, 42.9, 36.4, 36.3, 27.5, 27.1, 25.9, 18.8, 18.3, 14.4, -4.2, -5.0.

HRES MS ($m/z$): (M-H) calcd. for C$_{29}$H$_{47}$O$_7$Si, 535.3091; found 535.3029.

Synthesis of 7-70: To 7-69 (267 mg, 0.497 mmol) in CH$_2$Cl$_2$ (10 mL) at room temperature was added DDQ (124 mg, 0.547 mmol) in one portion. The initially dark green mixture was allowed to stir for 1 h at which point it was an opaque yellow suspension. TLC showed complete consumption of the starting material. The heterogeneous mixture was then concentrated under reduced pressure and the crude residue suspended in hexane (10 mL) and filtered through sand to remove insoluble material. After exhaustive washing the combined organic extracts where concentrated under reduced pressure and column chromatographed to afford seco acid 7-70 (174 mg, 84%) as a colourless oil.

Physical State: colourless oil

$R_f$ = 0.28 (EtOAc:hexanes, 3:7 v/v; vanillin)

$[\alpha]_D$ = $-6.8^\circ$ (CHCl$_3$, $c$ 0.35)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 5.84 (dd, $J = 15.4$, 6.0 Hz, 1H), 5.68 (ddd, $J = 15.4$, 7.4, 0.9 Hz, 1H), 4.62 (q, $J = 5.6$ Hz, 1H), 4.03 (t, $J = 7.8$ Hz, 1H), 3.84 – 3.74 (m, 2H), 2.56 (d, $J = 6.0$ Hz, 2H), 1.71 (dt, $J = 14.2$, 2.5 Hz, 1H), 1.58 (dt, $J = 14.2$, 9.6 Hz, 1H), 1.53 – 1.47 (m, 1H), 1.46 – 1.33 (m, 8H), 0.93 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).
$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 174.2, 136.1, 127.8, 109.6, 82.1, 80.8, 71.0, 69.5, 42.9, 39.7, 38.7, 27.3, 27.1, 25.8, 18.8, 18.2, 14.2, -4.2, -4.9.

**HRES MS (m/z):** (M+Na)$^+$ calcd. for C$_{21}$H$_{40}$NaO$_6$Si, 439.2486; found 439.2484.

Synthesis of 7-23: Triphenylphosphine (74 mg, 0.273 mmol) was added to a cooled solution (0 °C) of seco acid 7-70 (31 mg, 0.124 mmol) in dry toluene (x mL) under a nitrogen atmosphere. To this mixture, a solution of diisopropyl azodicarboxylate (x mL) was added dropwise over ten minutes. The resulting mixture was then allowed to stir at room temperature overnight. Removal of the solvent followed by purification on silica gel column chromatography (hexanes/EtOAc, 9:1 v/v) afforded lactone 7-23 (19 mg, 63%) and diolide 7-80 (6.5 mg, 11%).

Spectroscopic data for 7-23:

**Physical State:** colourless oil

$R_f = 0.28$ (EtOAc:hexanes, 1:9 v/v, vanillin)

$\lbrack \alpha \rbrack_d = -15.2^\circ$ (CHCl$_3$, c 0.38)
1H-NMR [CDCl₃, 600 MHz] δ: 5.91 (dd, J = 15.4, 2.5 Hz, 1H), 5.67 (ddd, J = 15.4, 9.4, 1.5 Hz, 1H), 4.98 – 4.91 (m, 1H), 4.72 – 4.64 (m, 1H), 4.14 – 4.03 (m, 1H), 3.63 (dd, J = 13.3, 4.6 Hz, 1H), 2.51 – 2.43 (m, 2H), 2.06 (d, J = 15.3 Hz, 1H), 1.88 (dt, J = 15.3, 10.1 Hz, 1H), 1.54 – 1.48 (m, 1H), 1.48 – 1.43 (m, 1H), 1.41 (s, 3H), 1.41 (s, 3H), 1.29 (dd, J = 15.0, 7.5 Hz, 2H), 0.93 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H).

13C-NMR [CDCl₃, 150 MHz] δ: 168.7, 137.8, 123.3, 108.1, 84.4, 81.9, 72.4, 67.9, 45.4, 38.4, 37.0, 27.2, 27.1, 25.9, 18.7, 18.4, 14.1, -4.8, -5.0.

HRES MS (m/z): (M+Na)⁺ calcd. for C_{21}H_{38}O_{5}SiNa, 421.2386; found 421.2399

Spectroscopic data for 7-80:

Physical State: colourless oil

R_f = 0.12 (EtOAc:hexanes, 1:9 v/v, vanillin)

[α]D = −11.1° (CHCl₃, c 0.91)

1H-NMR [CDCl₃, 600 MHz] δ: 5.88 (dd, J = 15.4, 3.7 Hz, 1H), 5.72 (ddd, J = 15.3, 7.8, 1.4 Hz, 1H), 4.91 (dt, J = 8.2, 5.7 Hz, 1H), 4.60 (dt, J = 6.2, 4.6 Hz, 1H), 4.01 (t, J = 8.1 Hz, 1H), 3.60 (td, J = 7.8, 4.0 Hz, 1H), 2.45 (d, J = 6.3 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.63 – 1.57 (m, 1H), 1.53 – 1.47 (m, 1H), 1.43 – 1.38 (m, 4H), 1.37 (s, 3H), 1.34 – 1.27 (m, 1H), 0.93 – 0.88 (m, 12H), 0.08 (s, 3H), 0.08 (s, 3H).

13C-NMR [CDCl₃, 150 MHz] δ: 170.0, 136.2, 126.9, 109.0, 82.0, 77.8, 72.6, 68.5, 44.4, 36.9, 36.7, 27.4, 27.0, 26.0, 18.6, 18.3, 14.2, -4.4, -4.9.

HRES MS (m/z): (M+Na)⁺ calcd. for C_{42}H_{76}O_{10}Si_{2}Na, 819.4875; found 819.4882
Synthesis of 7-71: To lactone 7-23 (15 mg, 38 µmol) in THF (3 mL) at 0 °C was added TBAF (1 M in THF, 42 µL) at 0 °C and the resulting slightly yellow solution was stirred for 1 h. The reaction was quenched with acetic acid (20 µL) and concentrated under reduced pressure. The crude oil was then column chromatographed (silica gel, hexanes:EtOAc 6:4) to furnish 7-71 (9.9 mg, 92%) as a colourless oil.

**Physical State**: colourless oil

\[ R_f = 0.12 \text{ (EtOAc:hexanes, 4:6 v/v; vanillin)} \]

\[ [\alpha]_D -27.5^\circ \text{ (CHCl}_3, c 0.42) \]

\textbf{H-NMR} [CDCl\textsubscript{3}, 600 MHz] \( \delta \): 5.92 (dd, \( J = 15.8, 2.5 \text{ Hz, 1H} \)), 5.63 (ddd, \( J = 15.8, 9.3, 1.5 \text{ Hz, 1H} \)), 5.09 (ddd, \( J = 9.6, 7.8, 5.5 \text{ Hz, 1H} \)), 4.72 (br s, 1H), 4.07 (t, \( J = 8.8 \text{ Hz, 1H} \)), 3.70 – 3.61 (m, 1H), 2.63 (dd, \( J = 12.1, 3.4 \text{ Hz, 1H} \)), 2.55 (dd, \( J = 12.1, 3.8 \text{ Hz, 1H} \)), 2.40 (br t, 1H), 2.07 (d, \( J = 15.6 \text{ Hz, 1H} \)), 1.90 (dt, \( J = 15.6, 9.9 \text{ Hz, 1H} \)), 1.57 – 1.51 (m, 2H), 1.49 – 1.44 (m, 1H), 1.40 (s, 6H), 1.30 (dq, \( J = 14.7, 7.4 \text{ Hz, 2H} \)), 0.90 (t, \( J = 7.4 \text{ Hz, 3H} \)).

\textbf{C-NMR} [CDCl\textsubscript{3}, 150 MHz] \( \delta \): 170.2, 137.0, 123.3, 108.3, 84.1, 81.9, 72.9, 67.5, 44.5, 38.3, 37.1, 27.2, 27.1, 18.6, 13.9.

\textbf{HRES MS (m/z)}: (M+NH\textsubscript{4})\textsuperscript{+} calcd. for C\textsubscript{15}H\textsubscript{28}NO\textsubscript{5}, 302.1967; found 302.1956.
Synthesis of 7-79: To a solution of 7-71 (5.0 mg, 18 µmol) in CH₂Cl₂ (0.5 mL) were added TEA (10 µL, 70 µmol), 4-DMAP (0.2 mg, 1.8 µmol) and 4-bromobenzoyl chloride (4.7 mg, 21 µmol) at room temperature. The reaction mixture was stirred for 6 h prior to quenching with saturated aqueous NH₄Cl (1 mL). Standard extractive work-up with Et₂O (3 x 1 mL), drying over MgSO₄, and concentration under reduced pressure afforded a light yellow residue which was purified by column chromatography (silica gel, hexanes:EtOAc 19:1 v/v) to give 7-79 (7.0 mg, 86%) as a colourless oil.

**Physical State:** White crystalline solid

R<sub>f</sub> = 0.38 (EtOAc:hexanes, 1:9 v/v)

[α]<sub>D</sub> = +24.7° (CHCl₃, c 0.41)

<sup>1</sup>H-NMR [CD₂Cl₂, 600 MHz] δ: 7.97 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 6.01 (dd, J = 15.8, 2.9 Hz, 1H), 5.86 – 5.75 (m, 1H), 5.60 (ddd, J = 15.8, 9.3, 1.4 Hz, 1H), 5.07 – 5.00 (m, 1H), 4.06 (t, J = 8.8 Hz, 1H), 3.65 (t, J = 8.9 Hz, 1H), 2.78 (dd, J = 12.8, 3.0 Hz, 1H), 2.67 (dd, J = 12.8, 4.1 Hz, 1H), 2.07 (d, J = 15.4 Hz, 1H), 1.93 (dt, J = 15.5, 10.0 Hz, 1H), 1.59 – 1.45 (m, 2H), 1.36 (s, 3H), 1.35 (s, 3H), 1.33 – 1.26 (m 2H), 0.90 (t, J = 7.4 Hz, 3H).

<sup>13</sup>C-NMR [CD₂Cl₂, 150 MHz] δ: 168.7, 164.7, 132.9, 132.3, 131.7, 129.3, 128.7, 124.7, 108.5, 84.3, 82.1, 73.1, 69.6, 42.4, 38.5, 37.1, 27.2, 27.1, 18.9, 14.0.

**HRES MS (m/z):** (M+NH₄)<sup>+</sup> calcd. for C₂₂H₃₁NO₆Br, 484.1335; found 484.1328.
Synthesis of 7-3: To a solution of 7-71 (5.0 mg, 0.018 mmol) in acetonitrile/water (4:1 v/v, 0.3 mL) was added TFA (21 µl) at room temperature. The reaction mixture was stirred at this temperature for 16 h, at which point NaHCO₃ (23 mg) was added and the reaction allowed to stir for 15 min. The solvent was removed under a stream of nitrogen, the residue taken up in EtOAc (1 mL) and the suspension filtered through Na₂SO₄ which was subsequently rinsed with EtOAc (2x 1 mL). The combined organic extracts were concentrated and the crude residue purified by column chromatography (silica gel, EtOAc → DCM/MeOH 19:1 v/v) to afford 7-3 (3.6 mg, 83%) as a white solid.

**Physical State:** white solid

$R_f = 0.28$ (DCM:MeOH, 9:1 v/v; vanillin)

$[\alpha]_D = -20.4^\circ$ (MeOH, c 0.19)

$^1$H-NMR [Acetone-d₆, 600 MHz] $\delta$: 5.88 (dd, $J = 15.8, 3.1$ Hz, 1H), 5.64 – 5.50 (m, 1H), 4.74 (dt, $J = 12.2, 6.0$ Hz, 1H), 4.67 (s, 1H), 4.19-4.19 (m, 1H), 3.91-3.85 (m, 1H), 3.83 (d, $J = 1.9$ Hz, 1H), 3.74 (dd, $J = 12.2, 5.9$ Hz, 1H), 3.35 (d, $J = 2.4$ Hz, 1H), 2.55 (dd, $J = 11.8, 3.9$ Hz, 1H), 2.44 (dd, $J = 11.8, 3.3$ Hz, 1H), 1.85 – 1.81 (m, 2H), 1.56 – 1.42 (m, 2H), 1.33 – 1.27 (m, 2H), 0.89 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR [Acetone-d₆, 150 MHz] $\delta$: 170.3, 136.3, 127.2, 79.7, 76.9, 73.1, 67.7, 44.5, 42.0, 39.9, 30.2, 19.0, 14.0.

**HRES MS (m/z):** (M+Na)$^+$ calcd. for C₁₂H₂₀O₅Na, 267.1208; found 267.1208
Synthesis of 7-81: To a solution of 7-69 (38.1 mg, 0.071 mmol) in acetone (3 mL) was added K$_2$CO$_3$ (19.6 mg, 0.142 mmol) at room temperature and the suspension stirred for 15 min at this temperature at which point iodomethane (5.3 µL, 0.085 mmol) was added dropwise. The suspension was stirred for 1 h before quenching with saturated aqueous NH$_4$Cl (1 mL). The mixture was extracted with Et$_2$O (3 x 2 mL) and the combined organic layers dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, hexanes/EtOAc 9:1) furnished 7-81 (35 mg, 89%) as a colourless oil.

**Physical State**: colourless oil

$R_f = 0.26$ (EtOAc:hexanes, 1:9 v/v; vanillin)

$[\alpha]_D = -19.8^\circ$ (CHCl$_3$, c 0.55)

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.27 (d, $J = 9.2$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.81 (dd, $J = 15.4$, 6.1 Hz, 1H), 5.64 (ddd, $J = 15.4$, 7.3, 1.1 Hz, 1H), 4.65 – 4.60 (m, 1H), 4.45 (d, $J = 11.0$ Hz, 1H), 4.42 (d, $J = 11.1$ Hz, 1H), 4.03 (t, $J = 7.7$ Hz, 1H), 3.80 (s, 3H), 3.73 (td, $J = 8.4$, 3.2 Hz, 1H), 3.66 (s, 3H), 3.60 – 3.55 (m, 1H), 2.50 (dd, $J = 14.6$, 8.4 Hz, 1H), 2.43 (dd, $J = 14.6$, 4.7 Hz, 1H), 1.87 (ddd, $J = 14.0$, 8.4, 5.3 Hz, 1H), 1.69 (ddd, $J = 14.2$, 6.8, 3.2 Hz, 1H), 1.55 – 1.48 (m, 2H), 1.45 – 1.34 (m, 8H), 0.90 (t, $J = 7.3$ Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 171.5, 159.2, 136.8, 131.2, 129.5, 127.5, 113.9, 108.8, 81.8, 78.2, 76.1, 70.5, 69.9, 55.4, 51.7, 43.7, 36.3, 27.5, 27.1, 25.8, 18.5, 18.2, 14.4, -4.1, -5.0.
HRES MS (m/z): (M)$^+$ calcd. for $C_{30}H_{50}O_7Si$, 550.3326; found 550.3324.

Synthesis of 7-82: To a solution of 7-81 (31.1 mg, 0.056 mmol) in CH$_2$Cl$_2$ (5 mL) was added DDQ (14.1 mg, 0.062 mmol) in one portion at room temperature. The solution was allowed to stir for 1 h changing from dark green to beige. The solvent was removed under reduced pressure and the residue suspended in hexanes (10 mL), filtered through celite and the precipitate washed with hexanes (3 x 5 mL). The combined organic extracts were concentrated in vacuo and the resulting yellow oil purified by column chromatography (silica gel, hexanes/EtOAc 9:1 v/v) to afford 7-82 (21.2 mg, 87 %) as a colourless oil.

Physical State: colourless oil

$R_f$ = 0.09 (EtOAc:hexanes, 1:9 v/v)

$[\alpha]_D = -14.3^\circ$ (CHCl$_3$, c 0.63)

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.85 – 5.80 (m, 1H), 5.64 (ddd, $J = 15.5$, 7.5, 1.0 Hz, 1H), 4.62 (td, $J = 6.4$, 3.0 Hz, 1H), 4.02 (t, $J = 7.9$ Hz, 1H), 3.83 – 3.75 (m, 2H), 3.67 (s, 3H), 2.52 (dd, $J = 14.6$, 8.2 Hz, 1H), 2.46 (dd, $J = 14.6$, 4.9 Hz, 1H), 1.72 (dt, $J = 14.2$, 2.4 Hz, 1H), 1.58 – 1.50 (m, 3H), 1.45 – 1.36 (m, 8H), 0.93 (t, $J = 7.1$ Hz, 3H), 0.86 (q, $J = 2.5$ Hz, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 171.4, 137.2, 127.2, 109.6, 82.2, 81.0, 71.1, 69.9, 51.7, 43.6, 39.7, 38.8, 27.4, 27.1, 25.8, 18.8, 18.2, 14.2, -4.2, -4.9.
HRES MS \((m/z)\): (M+K)\(^+\) calcd. for C\(_{22}\)H\(_{42}\)KO\(_6\)Si, 469.2382; found 469.2381.

Synthesis of 7-83: To a solution of 7-23 (2.3 mg, 5.8 µmol) in MeOH (0.2 mL) was added K\(_2\)CO\(_3\) (4 mg, 22 µmol) at room temperature. The suspension was allowed to stir for 18 h before quenching with acetic acid (20 µL). The solvent was removed at 0 °C under a light stream of nitrogen and the residue purified by column chromatography (silica gel, hexanes/EtOAc 9:1) to afford 7-83 (1.5 mg, 61%) as a colourless oil.

Physical State: colourless oil

\(R_f = 0.21\) (EtOAc:hexanes, 1:4 v/v)

\([\alpha]_D = -35.7^\circ\) (CHCl\(_3\), c 0.15)

\(^1\)H-NMR [CDCl\(_3\), 600 MHz] \(\delta\): 5.81 (dd, \(J = 15.4, 6.2\) Hz, 1H), 5.64 (dd, \(J = 15.4, 7.4\) Hz, 1H), 4.66 – 4.60 (m, 1H), 4.07 (t, \(J = 7.9\) Hz, 1H), 3.93 (td, \(J = 8.0, 3.7\) Hz, 1H), 3.89 – 3.83 (m, 1H), 3.67 (s, 3H), 2.52 (dd, \(J = 14.5, 8.1\) Hz, 1H), 2.46 (dd, \(J = 14.5, 4.8\) Hz, 1H), 1.68 (ddd, \(J = 9.2, 7.9, 3.3\) Hz, 2H), 1.47 – 1.38 (m, 10H), 0.93 (t, \(J = 7.1\) Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

\(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] \(\delta\): 171.4, 137.1, 127.3, 109.1, 81.3, 78.2, 69.9, 68.7, 51.7, 43.6, 39.9, 37.8, 27.4, 27.0, 25.8, 19.0, 18.2, 14.2, -4.2, -5.0.

HRES MS \((m/z)\): (M+Na)\(^+\) calcd. for C\(_{22}\)H\(_{42}\)O\(_6\)NaSi, 453.2648; found 453.2635.
Synthesis of 7-84: To a 0 °C solution of Nagao auxillary (+)-7-47 (1.34 g, 5.91 mmol) in CH₂Cl₂ (45 mL) was added TiCl₄ (1.0 M in CH₂Cl₂, 6.60 mL, 6.60 mmol) and the resulting solution was stirred for 5 min. before cooling to −78 °C. DIPEA (N,N-Diisopropylethylamine) (1.15 mL, 6.60 mmol) was then added dropwise, and the resulting enolate solution was stirred for 2 h at −78 °C. Aldehyde 7-61 (1.26 g, 3.48 mmol) in CH₂Cl₂ (10 mL) was then added dropwise to the reaction mixture, and the resulting solution stirred at −78 °C for an additional 15 min. The reaction was quenched with 10 mL of saturated NH₄Cl solution, diluted with 20 mL CH₂Cl₂ and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated. Flash chromatography (5:1 to 1:1 = hex:EtOAc) afforded allylic alcohol 7-84 (1.69 g, 86%, >20:1 d.r.) as a bright yellow oil.

Physical State: bright yellow oil

R<sub>f</sub> = 0.10 (EtOAc:hexanes, 3:7 v/v; vanillin)

[α]₀°₂⁺ = +164.6° (CHCl₃, c 0.34)

<sup>1</sup>H-NMR [CDCl₃, 600 MHz] δ: 7.27 (d, J = 7.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.87 (dd, J = 15.5, 5.2 Hz, 1H), 5.74 (ddd, J = 15.5, 7.4, 1.4 Hz, 1H), 5.16 – 5.11 (m, 1H), 4.69 – 4.65 (m, 1H), 4.45 – 4.39 (m, 2H), 4.05 (t, J = 7.9 Hz, 1H), 3.82 – 3.77 (m, 4H), 3.62 (dd, J = 17.6, 2.9 Hz, 1H), 3.58 – 3.50 (m, 2H), 3.28 (dd, J = 17.6, 8.9 Hz, 1H), 3.02 (d, J = 11.5 Hz, 1H), 2.36 (dq, J = 13.5, 6.8 Hz, 1H), 1.89 (ddd, J = 13.8, 7.4, 6.1 Hz, 1H), 1.71 (ddd, J = 14.2, 6.0, 4.2 Hz, 1H), 1.56 – 1.49 (m, 2H), 1.44 – 1.35 (m, 8H), 1.06 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H).
\[ {_{13}C}\text{-NMR } [\text{CDCl}_3, 150 \text{ MHz}] \delta: 203.1, 172.4, 159.2, 135.4, 131.1, 129.6, 129.5, 128.0, 113.9, 108.8, 82.0, 78.0, 75.9, 71.5, 70.4, 68.0, 55.5, 45.3, 36.2, 36.2, 31.0, 30.8, 27.5, 27.1, 19.2, 18.5, 18.0, 14.4. \]

**HRES MS (m/z):** (M+H)+ calcd. for C\(_{29}\)H\(_{44}\)NO\(_6\)S\(_2\), 566.2610; found 566.2600.

Synthesis of \(7\text{-85}\): To a solution of alcohol \(7\text{-84}\) (1.36 g, 2.41 mmol) and 2,6-lutidine (0.56 mL, 4.81 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added dropwise TBSOTf (0.52 mL, 2.89 mmol) at 0 °C. After stirring for 1 h at room temperature, saturated NaHCO\(_3\) solution (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). The combined organic layers were dried with MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to afford silyl ether \(7\text{-85}\) (1.45 g, 89%) as a yellow oil.

**Physical State:** bright yellow oil

\( R_f = 0.38 \) (EtOAc:hexanes, 1:9 v/v)

\( [\alpha]_D = +128.8^\circ \) (CHCl\(_3\), c 0.27)

\[^1^H\text{-NMR } [\text{CD}_2\text{Cl}_2, 600 \text{ MHz}] \delta: 7.25 (d, J = 8.7 \text{ Hz}, 2\text{H}), 6.85 (d, J = 8.7 \text{ Hz}, 2\text{H}), 5.86 (ddd, J = 15.4, 6.0, 0.8 \text{ Hz}, 1\text{H}), 5.65 (ddd, J = 15.4, 7.3, 1.2 \text{ Hz}, 1\text{H}), 5.06 – 5.00 (m, 1\text{H}), 4.79 – 4.72 (m, 1\text{H}), 4.42 (d, J = 11.1 \text{ Hz}, 1\text{H}), 4.38 (d, J = 11.1 \text{ Hz}, 1\text{H}), 4.01 (t, J = 7.8 \text{ Hz}, 1\text{H}), 3.79 (s, 3\text{H}), 3.70 (td, J = 8.3, 3.5 \text{ Hz}, 1\text{H}), 3.63 (dd, J = 16.6, 8.1 \text{ Hz}, 1\text{H}), 3.54 – 3.47 (m, 2\text{H}), 3.13 (dd, J = 16.6, 4.1 \text{ Hz}, 1\text{H}), 3.04 (dd, J = 11.5, 0.9 \text{ Hz}, 1\text{H}), 2.37 (dq, J = 13.6, 6.8 \text{ Hz}, 1\text{H}), 1.82 (dd, J = 13.9, 8.3, 5.4 \text{ Hz}, 1\text{H}), 1.68 (ddd, J = 14.2, 6.7, 2.3 Hz), 0.27 (dq, J = 13.6, 6.8 Hz, 1H), 1.82 (ddd, J = 13.9, 8.3, 5.4 Hz, 1H), 1.68 (ddd, J = 14.2, 6.7,
3.5 Hz, 1H), 1.53 – 1.48 (m, 2H), 1.45 – 1.39 (m, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.35 – 1.30 (m, 1H), 1.04 (d, \( J = 6.8 \) Hz, 3H), 0.96 (d, \( J = 6.9 \) Hz, 3H), 0.90 (t, \( J = 7.3 \) Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

\(^{13}\)C-NMR \([\text{CD}_2\text{Cl}_2, 150 \text{ MHz}]\) δ: 203.6, 171.2, 159.5, 137.0, 131.7, 129.6, 127.8, 113.9, 108.9, 82.2, 78.3, 76.3, 72.2, 70.5, 69.9, 55.6, 46.7, 36.4, 36.2, 31.3, 27.5, 27.1, 26.0, 19.3, 18.8, 18.3, 17.9, 14.4, -4.0, -4.8.

HRES MS \((m/z)\): \((\text{M}+\text{H})^+\) calcd. for \(\text{C}_{35}\text{H}_{58}\text{NO}_6\text{SiS}_2\), 680.3475; found 680.3499.

**Synthesis of 7-86:** To a stirred solution of the above TBS ether 7-85 (1.56 g, 2.29 mmol) in THF:H\(_2\)O (4:1) (10 mL) at room temperature, LiOH·H\(_2\)O (295 mg, 7.02 mmol) and a 30% aqueous solution of H\(_2\)O\(_2\) (0.70 mL) were added sequentially. The yellow color of the reaction mixture disappeared gradually. A TLC after 10 min indicated the completion of the reaction. The reaction mixture was then concentrated and the residue purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1 v/v) to afford pure acid 7-86 (1.09 g, 89%) as a light yellow oil.

**Physical State:** light yellow oil

\(R_f = 0.41\) (EtOAc:hexanes, 3:7 v/v)

\([\alpha]_D = -7.5^\circ\) (CHCl\(_3\), c 0.38)
**1H-NMR** [CDCl₃, 600 MHz] δ: 7.26 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.82 (dd, J = 15.5, 5.9 Hz, 1H), 5.68 (ddd, J = 15.4, 6.9, 1.1 Hz, 1H), 4.58 (dd, J = 11.6, 5.8 Hz, 1H), 4.04 (t, J = 7.6 Hz, 1H), 3.80 (s, 3H), 3.70 (td, J = 8.2, 3.4 Hz, 1H), 3.59 – 3.54 (m, 1H), 2.54 (dd, J = 15.2, 7.0 Hz, 1H), 2.50 (dd, J = 15.2, 5.2 Hz, 1H), 1.86 (ddd, J = 13.8, 8.1, 5.3 Hz, 1H), 1.69 (ddd, J = 14.3, 6.6, 3.4 Hz, 1H), 1.55 – 1.49 (m, 2H), 1.48 – 1.31 (m, 8H), 0.90 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

**13C-NMR** [CDCl₃, 150 MHz] δ: 173.8, 159.2, 135.3, 131.1, 129.5, 128.2, 113.9, 108.9, 81.5, 78.1, 75.9, 70.4, 69.6, 55.4, 42.9, 36.0, 35.9, 27.5, 27.0, 25.9, 18.5, 18.2, 14.4, -4.1, -5.0.

**HRES MS (m/z):** (M+Na)+ calcd. for C₉₂H₄₈NaO₇Si, 559.3067; found 559.3060.

Synthesis of **7-87**: To **7-86** (102 mg, 0.190 mmol) in CH₂Cl₂ (8 mL) was added DDQ (47.4 mg, 0.209 mmol) in one portion at room temperature. The opaque mixture was allowed to stir for 1 h at which point TLC showed complete consumption of the starting material. The heterogeneous mixture was then concentrated under reduced pressure and the crude residue suspended in hexanes (10 mL) and filtered through sand to remove insoluble material. After exhaustive washing with hexanes (5 x 5 mL) the combined organic extracts where concentrated under reduced pressure the residue purified by column chromatography (silica gel, hexanes:EtOAc 9:1→ 4:1) to afford seco-acid **7-87** (64.1 mg, 81%) as a colourless oil.

**Physical State:** colourless oil

R<sub>f</sub> = 0.27 (EtOAc:hexanes, 3:7 v/v)
\([\alpha]_D = +2.4^\circ \text{ (CHCl}_3, \ c \ 0.92)\]

**\(^1\)H-NMR** [CDCl\(_3\), 600 MHz] \(\delta\): 5.85 (dd, \(J = 15.5, 6.0 \text{ Hz}, 1\)H), 5.67 (ddd, \(J = 15.5, 7.4, 1.1 \text{ Hz}, 1\)H), 4.60 (q, \(J = 6.0 \text{ Hz}, 1\)H), 4.02 (t, \(J = 7.9 \text{ Hz}, 1\)H), 3.83 – 3.73 (m, 2H), 2.58 (dd, \(J = 14.9, 7.1 \text{ Hz}, 1\)H), 2.50 (dd, \(J = 14.9, 5.8 \text{ Hz}, 1\)H), 1.69 (dt, \(J = 14.2, 2.7 \text{ Hz}, 1\)H), 1.58 (dt, \(J = 14.3, 9.4 \text{ Hz}, 1\)H), 1.52 – 1.34 (m, 10H), 0.92 (t, \(J = 7.0 \text{ Hz}, 3\)H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

**\(^{13}\)C-NMR** [CDCl\(_3\), 150 MHz] \(\delta\): 175.2, 136.3, 127.6, 109.6, 82.0, 80.5, 70.9, 69.6, 43.4, 39.6, 38.5, 27.3, 27.1, 25.9, 18.8, 18.2, 14.2, -4.2, -5.0.

**HRES MS** (\(m/z\)): (M+Na)\(^+\) calcd. for C\(_{21}\)H\(_{40}\)NaO\(_6\)Si, 439.2486; found 439.2484.

\(|\alpha|_D = -28.6^\circ \text{ (CHCl}_3, \ c \ 0.24)\)

**Synthesis of 7-88**

: To a solution of triphenylphosphine (176 mg, 0.672 mmol) in PhMe (7 mL) at 0 °C was added diisopropyl azodicarboxylate (130 \(\mu\)L, 0.672 mmol) dropwise over five minutes. To this mixture was added 7-87 (28.1 mg, 0.067 mmol) in dry toluene (3 mL) over fifteen minutes. The resulting mixture was then allowed to stir at room temperature for 2 h. Removal of the solvent afforded a viscous yellow oil which was column chromatographed (silica gel, hexanes/EtOAc, 9:1) afforded lactone 7-88 (15.8 mg, 59%) as a colourless oil.

**Physical State**: colourless oil

\(R_f = 0.28 \text{ (EtOAc:hexanes, 1:9 v/v)}\)

\(|\alpha|_D = -28.6^\circ \text{ (CHCl}_3, \ c \ 0.24)\)
$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 5.84 (dd, $J = 15.8$, 9.1 Hz, 1H), 5.30 (dd, $J = 15.8$, 9.3 Hz, 1H), 5.02 (ddd, $J = 10.2$, 8.1, 5.6 Hz, 1H), 4.46 (td, $J = 9.6$, 6.1 Hz, 1H), 3.97 (t, $J = 8.8$ Hz, 1H), 3.60 (t, $J = 8.8$ Hz, 1H), 2.69 (dd, $J = 10.7$, 6.1 Hz, 1H), 2.39 (t, $J = 10.4$ Hz, 1H), 2.04 (d, $J = 15.4$ Hz, 1H), 1.89 (dt, $J = 15.4$, 10.0 Hz, 1H), 1.56 – 1.49 (m, 1H), 1.48 – 1.42 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.32 – 1.24 (m, 2H), 0.89 (t, $J = 7.4$ Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 170.1, 139.0, 124.4, 108.4, 83.6, 81.7, 72.4, 72.2, 46.8, 38.2, 37.0, 27.2, 27.0, 25.9, 18.6, 18.2, 14.0, -4.4, -4.8.

HRES MS ($m/z$): (M+Na)$^+$ calcd. for C$_{21}$H$_{38}$O$_5$SiNa, 421.2386; found 421.2395.

![Chemical Structure](image)

Synthesis of 7-89: To lactone 7-88 (12.3 mg, 0.031 mmol) in THF (3 mL) was added TBAF (1 M in THF, 34 μL) at 0 °C and the resulting slightly yellow solution was stirred for 1 h. The reaction was quenched with acetic acid (20 μL) and concentrated under reduced pressure. The crude oil was then column chromatographed (silica gel, hexanes:EtOAc 6:4) furnished 7-89 (7.6 mg, 87%) as a colourless oil.

**Physical State**: colourless oil

$R_f = 0.18$ (EtOAc:hexanes, 4:6 v/v)

$[\alpha]^0_d = -27.5^\circ$ (CHCl$_3$, $c$ 0.37)
$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 5.86 (dd, $J = 15.8, 9.2$ Hz, 1H), 5.36 (dd, $J = 15.8, 9.3$ Hz, 1H), 5.02 (ddd, $J = 10.2, 8.1, 5.7$ Hz, 1H), 4.53 (td, $J = 9.9, 6.0$ Hz, 1H), 3.97 (t, $J = 8.8$ Hz, 1H), 3.60 (t, $J = 8.9$ Hz, 1H), 2.80 (dd, $J = 10.5, 6.0$ Hz, 1H), 2.39 (t, $J = 10.5$ Hz, 1H), 2.05 (d, $J = 15.4$ Hz, 1H), 1.91 (dt, $J = 15.5, 10.0$ Hz, 1H), 1.57 – 1.49 (m, 1H), 1.49 – 1.42 (m, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 1.29 (dq, $J = 14.8, 7.4$ Hz, 2H), 0.89 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 169.9, 137.8, 126.1, 108.6, 83.5, 81.7, 72.7, 71.5, 45.7, 38.2, 36.9, 27.2, 27.0, 18.6, 14.0.

HRES MS (m/z): (M+Na)$^+$ calcd. for C$_{15}$H$_{24}$O$_5$Na, 307.1521; found 307.1525.

Synthesis of 7-91: To a solution of 7-89 (5.0 mg, 18 µmol) in CH$_2$Cl$_2$ (0.5 mL) were added TEA (10 µL, 70 µmol), 4-DMAP (0.2 mg, 1.8 µmol) and 4-bromobenzoyl chloride (4.7 mg, 21 µmol) at room temperature. The reaction mixture was stirred for 6 h prior to quenching with saturated aqueous NH$_4$Cl (1 mL). Standard extractive work-up with Et$_2$O (3 x 1 mL), drying over MgSO$_4$, and concentration under reduced pressure afforded a light yellow residue which was purified by column chromatography (silica gel, hexanes:EtOAc 19:1 v/v) to give 7-91 (7.4 mg, 90%) as a colourless oil.

Physical State: colourless oil

R$_f$ = 0.47 (EtOAc:hexanes, 1:9 v/v; vanillin)
$[\alpha]_D = -76.3^\circ$ (CHCl$_3$, c 0.50)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 7.87 (d, $J = 8.6$ Hz, 2H), 7.58 (d, $J = 8.6$ Hz, 2H), 5.97 (dd, $J = 15.8$, 9.5 Hz, 1H), 5.67 (td, $J = 10.2$, 6.1 Hz, 1H), 5.59 (dd, $J = 15.8$, 9.3 Hz, 1H), 5.09 (ddd, $J = 10.1$, 7.9, 5.7 Hz, 1H), 4.00 (t, $J = 8.8$ Hz, 1H), 3.66 (t, $J = 8.8$ Hz, 1H), 3.04 (dd, $J = 10.5$, 6.1 Hz, 1H), 2.55 (t, $J = 10.6$ Hz, 1H), 2.09 (d, $J = 15.5$ Hz, 1H), 1.93 (dt, $J = 15.6$, 10.0 Hz, 1H), 1.59 – 1.53 (m, 2H), 1.52 – 1.45 (m, 1H), 1.39 (s, 6H), 1.32 (dt, $J = 15.1$, 7.4 Hz, 2H), 0.91 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 168.9, 164.7, 133.0, 132.0, 131.3, 128.8, 128.6, 128.3, 108.7, 83.5, 81.5, 73.1, 73.1, 42.8, 38.2, 37.0, 27.1, 27.0, 18.7, 14.0.

HRES MS ($m/z$): (M+Na)$^+$ calcd. for C$_{22}$H$_{27}$O$_6$BrNa, 489.0889; found 489.0892.

Synthesis of 7-90: To a solution of 7-89 (6.2 mg, 0.02 mmol) in acetonitrile/water (4:1 v/v, 0.4 mL) was added TFA (25 µl) at room temperature. The reaction mixture was stirred at this temperature for 16 h, at which point NaHCO$_3$ (27 mg) was added and the reaction allowed to stir for 15 min. The solvent was removed under a stream of nitrogen, the residue taken up in EtOAc (1 mL) and the suspension filtered through Na$_2$SO$_4$ which was subsequently rinsed with EtOAc (2x 1 mL). The combined organic extracts were concentrated and the crude residue purified by column chromatography (silica gel, EtOAc → DCM/MeOH 19:1 v/v) to afford 7-90 (4.5 mg, 84%) as a white solid.

Physical State: white solid
\( R_f = 0.31 \) (DCM:MeOH, 9:1 v/v; vanillin)

\([\alpha]_D = -69.9^\circ \) (MeOH, \( c 0.32 \)) (lit. \([\alpha]_D = -10.4^\circ \) (MeOH, \( c 0.24 \))

**Corrected to Acetone**

\(^1\)H-NMR [Acetone-\( d_6 \), 600 MHz] \( \delta: 5.71 \) (dd, \( J = 15.8, 8.6 \) Hz, 1H), 5.16 (dd, \( J = 15.8, 9.4 \) Hz, 1H), 4.82 – 4.74 (m, 1H), 4.47 (br s, 1H), 4.32 (dd, \( J = 15.6, 9.3 \) Hz, 1H), 4.24 (br s, 1H), 3.84 (br s, 1H), 3.67 (t, \( J = 9.1 \) Hz, 1H), 3.38 – 3.27 (m, 1H), 2.61 (dd, \( J = 10.2, 5.8 \) Hz, 1H), 2.31 (t, \( J = 10.4 \) Hz, 1H), 1.88 – 1.82 (m, 2H), 1.55 – 1.43 (m, 2H), 1.33 – 1.25 (m, 2H), 0.89 (t, \( J = 7.4 \) Hz, 3H).

\(^{13}\)C-NMR [Acetone-\( d_6 \), 150 MHz] \( \delta: 170.7, 137.3, 129.0, 79.0, 76.9, 73.4, 72.5, 46.1, 42.0, 39.9, 19.0, 14.1 \).

**Corrected to the Natural Product:**

\(^1\)H-NMR [Acetone-\( d_6 \), 600 MHz] \( \delta: 5.61 \) (dd, \( J = 15.8, 8.6 \) Hz, 1H), 5.06 (dd, \( J = 15.8, 9.4 \) Hz, 1H), 4.72 – 4.64 (m, 1H), 4.37 (br s, 1H), 4.22 (dd, \( J = 15.6, 9.3 \) Hz, 1H), 4.14 (br s, 1H), 3.74 (br s, 1H), 3.57 (t, \( J = 9.1 \) Hz, 1H), 3.28 – 3.17 (m, 1H), 2.51 (dd, \( J = 10.2, 5.8 \) Hz, 1H), 2.21 (t, \( J = 10.4 \) Hz, 1H), 1.72 – 1.69 (m, 2H), 1.45 – 1.33 (m, 2H), 1.23 – 1.15 (m, 2H), 0.79 (t, \( J = 7.4 \) Hz, 3H).

\(^{13}\)C-NMR [Acetone-\( d_6 \), 150 MHz] \( \delta: 169.9, 136.4, 128.1, 78.1, 76.0, 72.5, 71.6, 45.2, 41.1, 39.0, 18.1, 13.2 \).

**HRES MS (m/z):** \((M+Na)^+\) calcd. for \( C_{12}H_{20}O_5Na \), 267.1208; found 267.1209.
Synthesis of SI-7-11: To a solution of 7-86 (26.8 mg, 0.050 mmol) in acetone (5 mL) was added K$_2$CO$_3$ (13.9 mg, 0.101 mmol) at room temperature and the suspension stirred for 15 min at this temperature at which point iodomethane (3.7 µL, 0.060 mmol) was added dropwise. The suspension was stirred for 1 h before quenching with saturated aqueous NH$_4$Cl (1 mL). The mixture was extracted with Et$_2$O (3 x 3 mL) and the combined organic layers dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, hexanes/EtOAc 9:1) furnished SI-7-11 (24.7 mg, 90%) as a colourless oil.

**Physical State:** colourless oil

$R_f = 0.58$ (EtOAc:hexanes, 1:4 v/v; vanillin)

$[\alpha]_D = -0.9^\circ$ (CHCl$_3$, c 0.65)

$^1$H-NMR [CDCl$_3$, 600 MHz] δ: 7.23 (d, $J = 6.8$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.79 (dd, $J = 15.3$, 5.7 Hz, 1H), 5.67 – 5.59 (m, 1H), 4.57 (dd, $J = 13.2$, 5.3 Hz, 1H), 4.42 (d, $J = 11.1$ Hz, 1H), 4.39 (d, $J = 11.1$ Hz, 1H), 4.00 (t, $J = 7.7$ Hz, 1H), 3.77 (s, 3H), 3.68 – 3.64 (m, 1H), 3.62 (s, 3H), 3.56 – 3.51 (m, 1H), 2.48 (dd, $J = 14.7$, 8.3 Hz, 1H), 2.38 (dd, $J = 14.7$, 5.0 Hz, 1H), 1.82 (ddd, $J = 13.8$, 8.3, 5.2 Hz, 1H), 1.65 (ddd, $J = 14.1$, 6.9, 3.2 Hz, 1H), 1.54 – 1.46 (m, 2H), 1.44 – 1.30 (m, 8H), 0.87 (t, $J = 7.3$ Hz, 3H), 0.83 (s, 9H), -0.00 (s, 3H), -0.02 (s, 3H).

$^1$H-NMR [CDCl$_3$, 150 MHz] δ: 171.5, 159.2, 136.4, 131.1, 129.4, 127.3, 113.8, 108.8, 81.7, 78.2, 76.0, 70.5, 69.6, 55.4, 51.7, 43.6, 36.1, 36.0, 27.5, 27.1, 25.8, 18.5, 18.2, 14.4, -4.2, -5.0.

**HRES MS (m/z):** (M+Na)$^+$ calcd. for C$_{30}$H$_{50}$O$_7$NaSi, 573.3224; found 573.3218.
Synthesis of 7-93: To a solution of SI-7-11 (16.4 mg, 0.03 mmol) in CH₂Cl₂ (3 mL) was added DDQ (7.4 mg, 0.03 mmol) in one portion at room temperature. The solution was allowed to stir for 1 h changing from dark green to beige. The solvent was removed under reduced pressure and the residue suspended in hexanes (5 mL), filtered through celite and the precipitate washed with hexanes (3 x 5 mL). The combined organic extracts were the concentrated in vacuo and the resulting yellow oil purified by column chromatography (silica gel, hexanes/EtOAc 9:1 v/v) to afford 7-93 (10.6 mg, 83 %) as a colourless oil.

Physical State: colourless oil

R<sub>f</sub> = 0.33 (EtOAc:hexanes, 1:4 v/v; vanillin)

[α]<sub>D</sub> = +7.3° (CHCl₃, c 0.73)

<sup>1</sup>H-NMR [CDCl₃, 600 MHz] δ: 5.85 (ddd, J = 15.4, 5.7, 0.7 Hz, 1H), 5.66 (ddd, J = 15.4, 7.4, 1.2 Hz, 1H), 4.61 (dtd, J = 6.9, 5.6, 1.1 Hz, 1H), 4.01 (t, J = 7.9 Hz, 1H), 3.79 (ddddd, J = 9.5, 7.2, 4.7, 2.4 Hz, 1H), 3.75 (dddd, J = 9.8, 8.5, 2.8 Hz, 1H), 3.66 (s, 3H), 2.55 (dd, J = 14.7, 7.8 Hz, 1H), 2.44 (dd, J = 14.7, 5.5 Hz, 1H), 1.68 (dt, J = 14.2, 2.6 Hz, 1H), 1.55 (dt, J = 14.2, 9.7 Hz, 1H), 1.51 – 1.35 (m, 10H), 0.93 (t, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

<sup>13</sup>C-NMR [CDCl₃, 150 MHz] δ: 171.5, 137.0, 126.9, 109.5, 82.1, 80.9, 70.9, 69.6, 51.7, 43.7, 39.7, 38.7, 27.4, 27.1, 25.8, 18.8, 18.2, 14.2, -4.2, -5.0.

HRES MS (m/z): (M+Na)<sup>+</sup> calcd. for C₂₂H₄₂O₆NaSi, 453.2648; found 453.2630.
Synthesis of 7-92: To a solution of 7-88 (1.7 mg, 4.3 µmol) in MeOH (0.2 mL) was added K₂CO₃ (4 mg, 22 µmol) at room temperature. The suspension was allowed to stir for 18 h before quenching with acetic acid (20 µL). The solvent was removed at 0 °C under a light stream of nitrogen and the residue purified by column chromatography (silica gel, hexanes/EtOAc 9:1) to afford 7-92 (1.3 mg, 72%) as a colourless oil.

Physical State: colourless oil

$R_f = 0.21$ (EtOAc:hexanes, 1:4 v/v; vanillin)

$[\alpha]_D = -5.2^\circ$ (CHCl₃, c 0.15)

$^1$H-NMR [CDCl₃, 600 MHz] δ: 5.82 (ddd, $J = 15.5, 5.9, 0.7$ Hz, 1H), 5.65 (ddd, $J = 15.5, 7.3, 1.1$ Hz, 1H), 4.61 (dt, $J = 12.3, 3.5$ Hz, 1H), 4.06 (t, $J = 8.0$ Hz, 1H), 3.91 – 3.82 (m, 2H), 3.66 (s, 3H), 2.55 (dd, $J = 14.5, 7.8$ Hz, 1H), 2.44 (dd, $J = 14.5, 5.7$ Hz, 1H), 1.65 (dt, $J = 7.2, 3.6$ Hz, 2H), 1.48 (ddddd, $J = 12.5, 9.2, 5.0, 2.8$ Hz, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.38 – 1.33 (m, 1H), 1.31 – 1.28 (m, 1H), 0.94 (t, $J = 7.1$ Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

$^{13}$C-NMR [CDCl₃, 150 MHz] δ: 171.5, 136.8, 127.2, 109.1, 81.3, 78.2, 69.8, 68.8, 51.8, 43.8, 39.9, 37.7, 27.4, 27.0, 25.9, 19.0, 18.2, 14.2, -4.2, -5.0.

HRES MS (m/z): (M+Na)$^+$ calcd. for C$_{22}$H$_{42}$O$_6$NaSi, 453.2648; found 453.2635.
Synthesis of 7-94: To a solution of 7-89 (15 mg, 0.053 mmol) were added sequentially silver(I) oxide (18.3 mg, 0.079 mmol), iodomethane (22 mg, 0.16 mmol) and dimethyl sulphide (1 drop). The reaction was stirred at room temperature for 4 h at which point the solvent was removed and the crude residue column chromatographed (silica gel, hexanes/EtOAc 9:1) to afford 7-94 (13 mg, 86%) as a colourless oil.

**Physical State:** colourless oil

$R_f = 0.21$ (EtOAc:hexanes, 1:4 v/v; vanillin)

$[\alpha]_{D} = -13.8^\circ$ (CHCl$_3$, c 0.42)

$^1$H-NMR [CDCl$_3$, 600 MHz] $\delta$: 5.80 (dd, $J = 15.8, 9.3$ Hz, 1H), 5.47 (dd, $J = 15.9, 9.3$ Hz, 1H), 5.06 – 4.99 (m, 1H), 4.07 – 3.99 (m, 2H), 3.62 (t, $J = 8.7$ Hz, 1H), 3.32 (s, 3H), 2.81 (dd, $J = 10.6, 5.8$ Hz, 1H), 2.35 (t, $J = 10.6$ Hz, 1H), 2.06 (d, $J = 15.4$ Hz, 1H), 1.91 (dt, $J = 15.5, 10.0$ Hz, 1H), 1.57 – 1.51 (m, 2H), 1.49 – 1.43 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.30 (dt, $J = 15.0, 7.5$ Hz, 2H), 0.90 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR [CDCl$_3$, 150 MHz] $\delta$: 170.0, 137.3, 128.1, 108.6, 83.5, 81.6, 79.8, 72.7, 57.2, 43.7, 38.2, 36.9, 27.2, 27.0, 18.7, 14.0.

**HRES MS (m/z):** (M+Na)$^+$ calcd. for C$_{16}$H$_{26}$O$_5$Na, 321.1678; found 321.1671.
Synthesis of 7-95: To a solution of 7-94 (6.2 mg, 0.02 mmol) in acetonitrile/water (4:1 v/v, 0.4 mL) was added TFA (25 µl) at room temperature. The reaction mixture was stirred at this temperature for 16 h, at which point NaHCO$_3$ (27 mg) was added and the reaction allowed to stir for 15 min. The solvent was removed under a stream of nitrogen, the residue taken up in EtOAc (1 mL) and the suspension filtered through Na$_2$SO$_4$ which was subsequently rinsed with EtOAc (2x 1 mL). The combined organic extracts were concentrated and the crude residue purified by column chromatography (silica gel, hexanes/EtOAc 6:4 → 4:6 v/v) to afford 7-95 (4.5 mg, 85%) as a white solid.

**Physical State**: white solid

$R_f$ = 0.12 (EtOAc:hexanes, 1:1 v/v; vanillin)

$[\alpha]_D = -25.0^\circ$ (CHCl$_3$, c 0.16)

$^1$H-NMR [Acetone-d$_6$, 600 MHz] δ: 5.67 (dd, $J = 15.9$, 8.7 Hz, 1H), 5.32 (dd, $J = 15.9$, 9.4 Hz, 1H), 4.85 – 4.79 (m, 1H), 4.34 (d, $J = 3.2$ Hz, 1H), 3.93 (ddd, $J = 10.7, 9.1, 5.8$ Hz, 1H), 3.90 (d, $J = 2.5$ Hz, 1H), 3.78 – 3.71 (m, 1H), 3.39 – 3.33 (m, 1H), 3.31 (s, 3H), 2.68 (dd, $J = 10.3$, 5.7 Hz, 1H), 2.27 (t, $J = 10.5$ Hz, 1H), 1.89 – 1.81 (m, 2H), 1.57 – 1.46 (m, 2H), 1.35 – 1.28 (m, 3H), 0.91 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR [Acetone-d$_6$, 150 MHz] δ: 170.6, 135.3, 132.0, 132.0, 81.1, 78.9, 78.8, 76.8, 76.6, 73.6, 56.7, 43.3, 42.0, 42.0, 39.8, 19.0, 14.1.

**HRES MS (m/z)**: (M+Na)$^+$ calcd. for C$_{13}$H$_{22}$O$_5$Na, 281.1365; found 281.1368.
Synthesis of 7-96: To a solution of 7-72 (21 mg, 0.074 mmol) were added sequentially silver(I) oxide (26 mg, 0.11 mmol), iodomethane (31 mg, 0.22 mmol) and dimethyl sulphide (1 drop). The reaction was stirred at room temperature for 4 h at which point the solvent was removed and the crude residue column chromatographed (silica gel, hexanes/EtOAc 9:1) to afford 7-96 (18 mg, 83%) as a colourless oil.

Physical State: colourless oil

R\text{f} = 0.21 \text{ (EtOAc:hexanes, 1:4 v/v; vanillin)}

[\alpha]_D = -47.7^\circ \text{ (CHCl}_3, c 0.25)

$^1$H-NMR $[CDCl_3, 600 MHz]$ $\delta$: 5.83 (dd, $J = 15.8$, 2.6 Hz, 1H), 5.65 (ddd, $J = 15.8$, 9.4, 1.3 Hz, 1H), 5.08 – 4.97 (m, 1H), 4.16 (td, $J = 2.7$, 1.3 Hz, 1H), 4.09 – 4.02 (m, 1H), 3.65 (t, $J = 8.9$ Hz, 1H), 3.40 (s, 3H), 2.72 (dd, $J = 12.3$, 3.0 Hz, 1H), 2.45 (dd, $J = 12.3$, 4.2 Hz, 1H), 2.06 (d, $J = 15.3$ Hz, 1H), 1.88 (dt, $J = 15.4$, 10.1 Hz, 1H), 1.55 – 1.43 (m, 2H), 1.41 (t, $J = 7.4$ Hz, 6H), 1.29 (dq, $J = 15.1$, 7.4 Hz, 2H), 0.89 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR $[CDCl_3, 150 MHz]$ $\delta$: 169.0, 134.7, 124.0, 108.2, 84.3, 81.7, 76.1, 72.5, 57.6, 42.6, 38.3, 36.8, 27.2, 27.1, 18.6, 14.0.

HRES MS ($m$/z): (M+Na)$^+$ calcd. for C$_{16}$H$_{26}$O$_5$Na, 321.1678; found 321.1671.
Synthesis of 7-4: To a solution of 7-96 (6.2 mg, 0.02 mmol) in acetonitrile/water (4:1 v/v, 0.4 mL) was added TFA (25 µl) at room temperature. The reaction mixture was stirred at this temperature for 16 h, at which point NaHCO₃ (27 mg) was added and the reaction allowed to stir for 15 min. The solvent was removed under a stream of nitrogen, the residue taken up in EtOAc (1 mL) and the suspension filtered through Na₂SO₄ which was subsequently rinsed with EtOAc (2x 1 mL). The combined organic extracts were concentrated and the crude residue purified by column chromatography (silica gel, hexanes/EtOAc 6:4 → 4:6 v/v) to afford 7-4 (4.5 mg, 82%) as a white solid.

Physical State: white solid

R_f = 0.12 (EtOAc:hexanes, 1:1 v/v; vanillin)

[α]_D = −18.0° (CHCl₃, c 0.15)

1H-NMR [Acetone-d₆, 600 MHz] δ: 5.79 (dd, J = 15.9, 3.3 Hz, 1H), 5.46 (ddd, J = 15.9, 9.5, 1.3 Hz, 1H), 4.71 (dd, J = 12.5, 8.0, 4.7 Hz, 1H), 4.22 (d, J = 3.2 Hz, 1H), 4.17 (dt, J = 4.4, 3.2, 1.4 Hz, 1H), 3.82 (d, J = 2.3 Hz, 1H), 3.74 (td, J = 9.1, 3.0 Hz, 1H), 3.38 – 3.33 (m, 1H), 3.29 (s, 3H), 2.59 (dd, J = 12.2, 3.0 Hz, 1H), 2.46 (dd, J = 12.2, 4.2 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.51 – 1.45 (m, 2H), 1.34 – 1.25 (m, 3H), 0.88 (t, J = 7.4 Hz, 3H).

13C-NMR [Acetone-d₆, 150 MHz] δ: 169.6, 133.2, 128.5, 79.6, 76.9, 76.7, 72.9, 56.7, 41.8, 41.4, 39.8, 19.0, 14.2.

HRES MS (m/z): (M+Na)^+ calcd. for C_{13}H_{22}O_{5}Na, 281.1365; found 281.1368.
7.7 Notes and References

10. For examples of decanolides isolated from microorganisms see:


(a) Natural product thiazolidine thione use


64 For an example, see: Declamp, J. H.; Gormisky, P. E.; White, M. C. J. Am. Chem. Soc. 2013, 135, 8460-8463.
82 The $^1$H and $^{13}$C NMR data of the methyl ether on phomolide H $\delta3.31$ (s) and 49.8 (ref. 2) correspond with methanol contamination. Methanol in acetone-$d_6$ appears at $\delta$ 3.31 (s) and 49.8. While the $^{13}$C-NMR signals differ by ~1 ppm, this is the same systemic difference observed throughout the NMR data supplied by the original paper.

CONCLUSION

Employing semi-stabilised trialkylphosphoranylides, generated in water using mild carbonate bases, we were able to synthesise an array of functionalised styrenes and 1,3-terminal dienes through the aqueous Wittig reaction with aqueous formalin. In particular, halogenated styrenes were prepared which are challenging to synthesise by classical methods. Using an analogous process (aqueous Wittig reaction) we were also able to synthesise pterostilbene. During the synthesis we encountered an interesting meta-directing effect which eroded stereoselectivity of the Wittig reaction and required the opposite Wittig disconnection.

The first organocatalytic Wittig reaction was described in which we used weakly basic secondary amines/sulphonamides to promote the Wittig reaction between semi-stabilised trialkyl- or triarylphosphoranylides with a range of aromatic aldehydes. This process then led to the development of the Wittig reaction as a bio-orthogonal manifold. Critically, we’ve shown that the Wittig reaction can be performed in living systems!

Finally, new reagents for the two carbon homologation of aldehydes to α,β-unsaturated aldehydes were explored. The pinacol-acetal tripropylphosphine-derived salt, DualPhos, proved stable enough to allow olefination under aqueous conditions. Isolation of the latent alkenals proved facile, while hydrolysis was performed using aqueous acid. A non-aqueous version of this olefination was also developed which allowed the olefination of chiral aldehydes possessing diverse functionality. One in particular, a tartrate derivative, was carried forward in the total synthesis of phomolides G and H. The latent alkenal was installed early in the synthesis and proved inert under multiple reaction conditions until chemoselective deprotection to the α,β-unstaurated aldehyde was necessitated. Both natural products required structural and/or stereochemical reassignment.
Appendix One

Spectra Relevant to Chapter Three:

Development of a scaleable route towards Pterostilbene and related hydroxyl-stilbenes
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1H-NMR CDCl3

f1 (ppm)

f2 (ppm)

OCH3

H3CO

O

H3

OCH3

OCH3

3-12
May04-2013
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3,5-dimethoxybenzyl alcohol
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 36
3,5-dimethoxybenzyl alcohol

C13SN CDCl3

May04-2013
Account McNulty

C13SN CDCl3 /USERdata/mcnulty mcleod2 36
3,5-dimethoxybenzyl chloride

$\text{H}_3\text{C} \quad \text{Cl} \quad 3\text{-14}$

$\text{OCH}_3$

$\text{f1 (ppm)}$
3,5-dimethoxybenzyl chloride
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 45
(3,5-dimethoxybenzyl)tripropylphosphonium chloride

1H-NMR CDCl3 /USERdata/mcnulty mcleod2 48
Dec17-2012
Account McNulty
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C13SN CDCl3 /USERdata/mcnulty mcleod2 48
Dec17-2012
Account McNulty
(3,5-dimethoxybenzyl)tripropylphosphonium chloride
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Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
OTHP benzaldehyde

1H-NMR CDCl₃ / USERdata/mcnulty_mcleod2 37

May05-2013

Account McNulty

THPO 3-19

CHO
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1H-NMR MeOD /USERdata/mcnulty mcleod2 55
4-Hydroxybenzytriphosphonium bromide

\[
\text{HO} \quad \text{PPr}_3^+ \quad \text{Cl}^- 
\]

\[
\begin{align*}
15.99 & \quad 16.10 & \quad 16.56 & \quad 16.59 & \quad 21.41 & \quad 21.72 & \quad 26.55 & \quad 26.85 \\
117.69 & \quad 119.86 & \quad 119.91 & \quad 132.45 & \quad 132.48 & \quad 159.45 & \quad 199.45
\end{align*}
\]
4-hydroxybenzyltripropylphosphonium bromide
1d_31P_Hdec MeOD /USERdata/mcnulty mcleod2 55
May 05-2013
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1H-NMR CDCl3 /USERdata/mcnulty mcleod2 3S

3-26

CHO

TsO
OTs benzaldehyde

C13SN CDCl3 /USERdata/mcnulty mcleod2 35

21.89 123.23 128.62 130.10 131.41 132.21 134.98 146.03 154.03 190.77

TsO

CHO

3-26
3-30

TsO

PPr₃⁺Cl⁻
May 04, 2013
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3-24

MeO

CHO

OMe
Appendix Two

Development of a mild method for the preparation of $N$-sulphonyl imines
A2.1 Background

N-Sulphonyl imines are valuable synthons in organic synthesis and are capable of undergoing many unique transformations. Although analogous to N-Acyl imines, N-sulphonyl imines are generally much more stable and typically isolable. Both act as electron-deficient imines and undergo a diverse array of synthetically useful reactions including various types of cycloadditions, nucleophilic additions amidoalkylations, and ene reactions.

The first reported synthesis of aryl N-sulphonyl imines by Lichtenberger and co-workers utilized ZnCl$_2$ as a Lewis acid. Within two years, the Russian group of Kretow and Abrazhanova had found the use of AlCl$_3$ instead of ZnCl$_2$ improved yields. The yields of N-tosyl aldimines were greatly improved by direct reaction of the corresponding diethyl acetal with tosyl amide, but the overall yield suffered due to poor isolated yields of the starting acetals. In 1988, Jennings and Lovely reported a milder and higher yielding variation of the Lewis acid catalyzed reactions which used titanium tetrachloride/triethylamine at 0 °C. Lewis acid routes towards these compounds require that a non-enolizable aldehyde is used and as such limits their utility.

Kresze and coworkers also pioneered the use of N-sulphinyl sulphonamides in the generation of N-sulphonyl imines. Conversion to the N-sulphonyl imine is carried out with a catalytic amount of AlCl$_3$ and probably involves a [2+2] cycloaddition to form the four membered intermediate below (Scheme 2). Aliphatic aldimines are possible from N-sulphinyl sulphonamides with boron trifluoride diethyl etherate as catalyst. Aromatic aldehydes may also be used with this method. An improved preparation of N-tosyl aldimines was reported by Love- and co-workers which uses Si(OEt)$_4$ to effect the desired transformation.

Numerous other ways exist for the formation of N-sulphonyl imines but do not start with an aldehyde, these include: from oximes, from sulphonylation of imines, from oxidation of sulphonamides, and from reduction of N-sulphonyl lactams.

N-Sulphonyl imines have proven to be a synthetically useful class of compounds, most notably as precursors for Davis reagents (N-sulphonyl oxaziridines). Importantly, these oxidants are chemoselective towards oxygen transfer. N-sulphonyl imines are also used in cycloaddition chemistry as well as aldol and Mannich type reactions. Recently, Tian and co-workers reported the use of N-sulphonyl imines as carbonyl equivalents in the Wittig reaction of semi-stabilized ylids and in so doing was able to obtain high stereoselectivity towards either the E or Z product.
A2.2 Scope and Selectivity of imine formation

The investigation of amine and sulphonamide promoted Wittig reactions in water\(^{19}\) led to an intriguing method of preparing N-sulphonyl imines. The synthesis of sulfonyl imines generally requires the use of dehydrating agents and anhydrous conditions (as described above). Hence it did not seem probable that aqueous NaHCO\(_3\) would allow generation of these intermediates. Nonetheless, control experiments conducted in dry toluene have shown that the \(N\)-tosyl imine derived from 4-chlorobenzaldehyde and tosylamide is formed quantitatively under NaHCO\(_3\) catalysis. The reaction requires a Dean-Stark apparatus and temperatures above 120 °C for full conversion and requires a simple filtration to remove the solid catalyst when complete. The scope and limitations of the reaction were investigated using tosylamide and numerous aromatic aldehydes containing electron-releasing and –withdrawing groups (Table A2-1).

**Table A2-1.** Synthetic preparation of \(N\)-tosylimines

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Yield(^a)</th>
<th>((E):(Z))</th>
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<tbody>
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<td>95</td>
<td>99:1</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CHO})</td>
<td>93</td>
<td>99:1</td>
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<td>(\text{CHO})</td>
<td>96</td>
<td>99:1</td>
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<tr>
<td>4</td>
<td>(\text{CHO})</td>
<td>95</td>
<td>99:1</td>
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<tr>
<td>5</td>
<td>(\text{CHO})</td>
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<td>7</td>
<td>(\text{CHO})</td>
<td>81</td>
<td>65:35</td>
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\(\text{a. Isolated Yields}\)

The reaction time increased as the electron releasing capability of the substituent increased as can be expected based on the proposed mechanism. Nucleophilic attack of the tosyl anion will be greatly attenuated by the decreased reactivity of the aldehyde. The
reaction is not solely thermal though as Wynne and co-workers\textsuperscript{21} showed only benzaldehyde and 4-chlorobenzaldehyde may be formed thermally. The reaction seems to be limited to aromatic aldehydes though, as acetophenone and decanal showed no conversion to the N-tosyl imine. In both cases starting material was recovered with no trace of product visible. No Cannizarro or homo-aldol products were observed for any of the reactions. Gratifyingly, the method proved useful in the preparation of the N-sulphonyl imine derivative of indole-3-carbaldehyde without the need for protecting groups (entry 6). The product was quite reactive though and prone to hydrolysis if not handled under inert conditions.

**Table A2-2.** Synthesis of N-sulphonylimines of 4-chlorobenzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulphonyl Amine</th>
<th>Tosyl-Imine</th>
<th>Yield\textsuperscript{a}</th>
<th>((E):(Z))</th>
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<td>(\text{H}_3\text{C})(\text{SO}_2\text{NH}_2)</td>
<td>(\text{Cl} \text{N} \text{S} \text{O}_2 \text{R} \text{N})</td>
<td>95</td>
<td>\text{99:1}</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Cl} \text{SO}_2 \text{NH}_2)</td>
<td>(\text{Cl} \text{N} \text{S} \text{O}_2 \text{R} \text{N})</td>
<td>92</td>
<td>\text{99:1}</td>
</tr>
<tr>
<td>3</td>
<td>(\text{H}_3\text{C})(\text{SO}_2\text{NH}_2)</td>
<td>(\text{Cl} \text{N} \text{S} \text{O}_2 \text{R} \text{N})</td>
<td>93</td>
<td>\text{99:1}</td>
</tr>
<tr>
<td>4</td>
<td>(\text{H}_3\text{C})(\text{SO}_2\text{NH}_2)</td>
<td>(\text{Cl} \text{N} \text{S} \text{O}_2 \text{R} \text{N})</td>
<td>93</td>
<td>\text{99:1}</td>
</tr>
</tbody>
</table>

\textsuperscript{a.} Isolated Yields
The scope and limitations of the sulphonamide moiety were also investigated and successfully extended to a range of substituted sulphonamides. Both aliphatic and aromatic sulphonamides are tolerated. The steric bulk presented by the trisyl-substituted example (Table A2-2, Entry 4) was a relative non-factor as the N-sulphonyl imine formed without issue in good yield. In all cases isolation merely requires filtration to remove NaHCO₃ followed by concentration in vacuo. Once isolated N-sulphonyl imines are air stable for short periods but for prolonged storage an inert atmosphere at low temperatures is necessary.

**General Procedure for the synthesis of N-Tosyl Imines**

\[
\begin{align*}
&\text{CHO} & \text{R} & \text{TsNH} & \text{2}, \text{NaHCO}_3 & \text{PhMe, reflux} \\
&\quad & & & & \\
&\text{R} & \text{N} & \text{Ts} \\
\end{align*}
\]

Into a flame-dried flask fitted with a Dean-Stark trap, and a condenser, containing a magnetic stirring bar was weighed the corresponding aldehyde (2 mmol), tosyl amide (2 mmol) and NaHCO₃ (20% mol). Dry Toluene (10 mL mmol⁻¹) was added and the mixture was allowed to reflux overnight. Approximately half of toluene was removed through the Dean-Stark trap. The product was then allowed to cool, taken up into ethyl acetate and washed with brine. The organic extract was concentrated in vacuo to afford the title compound.

**(E)-phenyl-N-tosylmethanimine (A2-3a)**

Yield 85%, white solid. Mp 112-113 °C (Lit.20 114 °C); \(^1\)H-NMR [CDCl₃, 600 MHz] \(\delta\): 8.96 (s, 1H), 7.89 – 7.84 (m, 2H), 7.82 (d, \(J = 8.3\) Hz, 2H), 7.54 (d, \(J = 7.5\) Hz, 1H), 7.42 (t, \(J = 7.8\) Hz, 2H), 7.28 (d, \(J = 8.0\) Hz, 2H), 2.37 (s, 3H); \(^{13}\)C-NMR [CDCl₃, 150 MHz] \(\delta\): 170.15, 144.62, 135.17, 134.94, 132.41, 131.33, 129.82, 129.16, 128.12, 21.66.

**Yield 92%, white solid. Mp 114-115 °C (Lit.20 116-118 °C); \(^1\)H-NMR [CDCl₃, 600 MHz] \(\delta\): 8.91 (s, 1H), 7.80 (d, \(J = 8.3\) Hz, 1H), 7.73 (d, \(J = 8.2\) Hz, 1H), 7.26 (d, \(J = 8.0\) Hz, 1H), 7.20 (d, \(J = 8.0\) Hz, 1H), 2.35 (s, 1H), 2.35 (s, 1H); \(^{13}\)C-NMR [CDCl₃, 150 MHz] \(\delta\): 169.98, 146.40, 144.45, 135.43, 131.44, 129.94, 129.88, 129.77, 128.03, 22.00, 21.64.
(E)-(4-chlorophenyl)-N-tosylmethanimine (A2-3c)

Yield 96%, white solid. Mp 169-170 °C (Lit. 172-173 °C); \( ^1 \)H-NMR \([\text{CDCl}_3, 600 \text{ MHz}]\) \( \delta \): 2.34 (s, 3H), 7.26 (d, \( J = 8.4 \) Hz, 2H), 7.36 (d, \( J = 8.6 \) Hz, 2H), 7.77 (d, \( J = 8.6 \) Hz, 2H), 7.79 (d, \( J = 8.6 \) Hz, 2H), 8.90 (s, 1H); \( ^{13} \)C-NMR \([\text{CDCl}_3, 150 \text{ MHz}]\) \( \delta \): 168.8, 144.9, 141.5, 135.0, 132.4, 130.9, 129.7, 128.2, 126.5, 21.7; HRES MS (M+Na\(^+\)) calcd. for C\(_{14}\)H\(_{12}\)NO\(_2\)NaClS: 316.0175, found 316.0168.

(E)-(4-nitrophenyl)-N-tosylmethanimine (A2-3d)

Yield 94%, yellow solid. Mp 200-201 °C (Lit. 205 °C); \( ^1 \)H-NMR \([\text{CDCl}_3, 600 \text{ MHz}]\) \( \delta \): 2.46 (s, 3H), 7.38 (d, \( J = 8.1 \) Hz, 2H), 7.91 (d, \( J = 8.3 \) Hz, 2H), 8.11 (d, \( J = 8.8 \) Hz, 2H), 8.33 (d, \( J = 8.8 \) Hz, 2H), 9.11 (s, 1H); \( ^{13} \)C-NMR \([\text{CDCl}_3, 150 \text{ MHz}]\) \( \delta \): 167.42, 151.34, 145.50, 137.60, 134.31, 132.01, 130.17, 128.56, 124.34, 21.87; HRES MS (M+H\(^+\)) calcd. for C\(_{14}\)H\(_{12}\)N\(_2\)O\(_4\)S: 305.0596, found 305.0585.

(E)-(4-methoxyphenyl)-N-tosylmethanimine (A2-3e)

Yield 84%, white solid. Mp 120-122 °C (Lit. 128-129 °C); \( ^1 \)H-NMR \([\text{CDCl}_3, 600 \text{ MHz}]\) \( \delta \): 2.46 (s, 3H), 7.91 (d, \( J = 6.2 \) Hz, 2H), 7.90 (d, \( J = 5.6 \) Hz, 2H), 7.36 (d, \( J = 8.0 \) Hz, 2H), 6.99 (d, \( J = 8.9 \) Hz, 2H), 3.91 (s, 3H), 2.45 (s, 3H); \( ^{13} \)C-NMR \([\text{CDCl}_3, 150 \text{ MHz}]\) \( \delta \): 169.20, 165.29, 144.25, 135.77, 133.73, 129.73, 127.91, 125.25, 114.68, 55.68, 21.63.

(E)-(3,4,5-trimethoxyphenyl)-N-tosylmethanimine (A2-3f)

Yield 79%, amorphous yellow solid; \( ^1 \)H-NMR \([\text{CDCl}_3, 600 \text{ MHz}]\) \( \delta \): 8.94 (s, 1H), 7.90 (d, \( J = 8.3 \) Hz, 2H), 7.90 (d, \( J = 8.3 \) Hz, 2H), 7.37 (d, \( J = 8.0 \) Hz, 2H), 7.19 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 2.46 (s, 3H); \( ^{13} \)C-NMR \([\text{CDCl}_3, 150 \text{ MHz}]\) \( \delta \): 169.8, 153.5, 144.5, 135.4, 129.8, 128.1, 128.1, 127.4, 126.5, 108.5, 61.1, 56.4, 21.7; HRES MS (M+H\(^+\)) calcd. for C\(_{17}\)H\(_{20}\)NO\(_5\)S: 350.1062, found 350.1052.

N,N-dimethyl-4-((E)-tosyliminomethyl)benzenamine (A2-3g)

Yield 82% (E/Z, 65:35), yellow solid; Mp 128-130 °C; \( ^1 \)H-NMR \([\text{CDCl}_3, 600 \text{ MHz}]\) \( \delta \): 8.73 (s, 1H), 7.77 (d, \( J = 8.3 \) Hz, 2H), 7.73 (d, \( J = 8.3 \) Hz, 2H), 7.37 (d, \( J = 8.3 \) Hz, 2H), 7.19 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 2.46 (s, 3H); \( ^{13} \)C-NMR \([\text{CDCl}_3, 150 \text{ MHz}]\) \( \delta \): 169.8, 153.5, 144.5, 135.4, 129.8, 128.1, 127.4, 126.5, 108.5, 61.1, 56.4, 21.7; HRES MS (M+H\(^+\)) calcd. for C\(_{17}\)H\(_{20}\)NO\(_5\)S: 350.1062, found 350.1052.
= 8.3 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.58 (d, J = 9.0 Hz, 2H), 3.02 (s, 6H), 2.34 (s, 3H) ; $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 169.2, 155.0, 143.6, 136.9, 129.8, 129.7, 127.7, 126.5, 111.5, 40.2, 21.6.

(E)-(1H-indol-3-yl)-N-tosylmethanimine (A2-3h)$^{24}$

Yield 91%, amorphous orange solid; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 9.19 (s, 1H), 8.92 (s, 1H), 8.13 – 8.08 (m, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.72 (s, 1H), 7.32 (dd, J = 6.4, 2.5 Hz, 1H), 7.16 (d, J = 8.1 Hz, 2H), 7.09 (dd, J = 5.5, 3.6 Hz, 2H), 2.25 (s, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 163.4, 143.7, 137.1, 136.9, 129.6, 129.1, 128.2, 127.5, 124.9, 124.7, 123.4, 122.8, 114.0, 111.9, 21.6.

**General Procedure for the synthesis of N-Sulphonyl Imines**

![Chemical reaction diagram]

Into a flame-dried flask fitted with a Dean-Stark trap, and a condenser, containing a magnetic stirring bar was weighed 4-chlorobenzaldehyde (2 mmol), the corresponding sulphonamide (2 mmol) and NaHCO$_3$ (20% mol). Dry Toluene (10 mL mmol$^{-1}$) was added and the mixture was allowed to reflux 18-24 h. Approximately half the toluene was removed through the Dean-Stark trap. The product was then allowed to cool and was taken up into ethyl acetate and washed with brine. The organic extract was concentrated *in vacuo* to afford the title compound.

N-(4-Chlorobenzylidene)methanesulfonamide (A2-5a)

Yield 95%, Amorphous white solid; $^1$H-NMR [CDCl$_3$, 600 MHz] δ: 8.93 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 3.08 (s, 3H); $^{13}$C-NMR [CDCl$_3$, 150 MHz] δ: 170.24, 141.79, 132.38, 130.55, 129.78, 40.30. HRES MS (M+H)$^+$ calcd. for C$_{17}$H$_{20}$NO$_5$S: 350.1062, found 350.1052.

N-(4-Chlorobenzylidene)-2-methylbenzenesulfonamide (A2-5b)$^{25}$

Yield 93%, White solid. Mp 115-116 °C (Lit.25 118-120 °C); $^1$H-NMR [CDCl$_3$, 600 MHz] δ 8.97 (s, 1H), 8.00 (d, J
= 8.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.43 (dt, J = 7.5, 3.7 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.27 (dd, J = 14.9, 7.6 Hz, 2H), 2.65 (s, 3H); \(^{13}\)C-NMR [CDCl\(_3\), 150 MHz] δ: 169.28, 141.50, 138.87, 136.27, 133.80, 132.52, 132.39, 130.85, 129.65, 129.28, 126.41, 20.63.

2,4,6-triisopropyl-N-(4-chlorobenzylidene)-benzenesulphonamide (A2-5c)\(^{26}\)

Yield 89%, Amorphous white solid; 1H-NMR [CDCl\(_3\), 600 MHz] δ: 8.91 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.13 (s, 2H), 4.25 (hept, J = 6.7 Hz, 2H), 2.84 (hept, J = 6.9 Hz, 1H), 1.21 (d, J = 6.8 Hz, 12H), 1.18 (d, J = 6.9 Hz, 6H); 13C-NMR [CDCl\(_3\), 150 MHz] δ: 166.26, 152.81, 150.23, 140.11, 131.09, 130.16, 129.71, 128.61, 128.45, 122.89, 33.25, 28.79, 23.75, 22.52; HRES MS (M+H)+ calcd. for C\(_{22}\)H\(_{28}\)ClNO\(_5\)S: 406.1608, found 406.1607.

Notes and References

1 For some reviews of the chemistry of N-acyl imines, see (a) Zaug, H. E. *Synthesis* 1982, 85, 181. (b) Scola, P. M.; Weinreb, S. M. *Chem. Rev.* 1989, 89, 1525.


Appendix Three

Spectra Relevant to Chapter Four:

Development of an amine and sulphonamide promoted Wittig reaction
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SpinWorks 3: Account McNulty

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4-11c

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4-11c

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Appendix Four

Spectra Relevant to Chapter Five:

The Bio-orthogonal Wittig reaction: the Wittig reaction in biological systems under physiological conditions
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|----------|------------------|
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| SI-5-2   | $^1$H-NMR        |
|          | page SI-334      |
| SI-5-2   | $^{13}$C-NMR     |
|          | page SI-335      |
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|          | page SI-336      |
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|          | page SI-337      |
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|          | page SI-338      |
| 5-7      | $^{13}$C-NMR     |
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|          | page SI-340      |
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|          | page SI-346      |
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|          | page SI-348      |
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|          | page SI-349      |
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|          | page SI-350      |
| SI-5-7   | $^1$H-NMR        |
|          | page SI-351      |
| SI-5-7   | $^{13}$C-NMR     |
|          | page SI-352      |
| SI-5-7   | $^{31}$P-NMR     |
|          | page SI-353      |
| SI-5-8   | $^1$H-NMR        |
|          | page SI-354      |
| SI-5-8   | $^{13}$C-NMR     |
|          | page SI-355      |
| SI-5-9   | $^1$H-NMR        |
|          | page SI-356      |
| SI-5-9   | $^{13}$C-NMR     |
|          | page SI-357      |
| 5-11     | $^1$H-NMR        |
|          | page SI-358      |
| 5-11     | $^{13}$C-NMR     |
|          | page SI-359      |
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|          | page SI-360      |
| 5-12     | $^1$H-NMR        |
|          | page SI-361      |
| 5-12     | $^{13}$C-NMR     |
|          | page SI-362      |
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Ph.D. Thesis – D. McLeod, McMaster University – Chemistry

SpinWorks 3: Account McNulty

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SpinWorks 3: Account McNulty

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SpinWorks 3: Account McNulty

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SI-5-7

SpinWorks 3: Account McNulty

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Appendix Five

Spectra Relevant to Chapter Six: Development of an efficient route to (E)-α,β-unsaturated aldehydes
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6-8

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O
H
3
C
CH₃
CH₃
CH₃
Br

6-8

1H-NMR CDCl₃ /USER/data/mcnulty mcleod2 6C

Jun28-2014
Account McNulty
Bromoacetaldehyde pinacol acetate
Pinacol Phosphonium salt \([\text{PPr}_3]\)

\[6-5\]
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Figure 6-5: 

[Diagram of the molecule with labels: Br, H₃C, CH₃, and symbols for carbon and hydrogen atoms.]
cyclohexanone homologation (dioxolane)

[Diagram showing chemical structure labeled as 6-18p]
DHC homologation (dioxolane)
NaH (washed)/THF:DMF (4:1)
1H-NMR CDCl3 /USERdata/mchnulty mceod2 60

6-18m

Jan30-2014
Account/Mchnulty

2.04 0.55 2.62 2.68 2.66 1.00 0.25 0.25 0.99 0.26 1.00
3.87 2.63

2.31 2.32 2.33 2.34 2.35 2.35 2.42 2.42 2.43 2.44 2.45 2.46 2.46 2.63 2.64 2.65 2.67 3.81 3.82 3.92 3.92 3.93 5.12 5.13 5.43 5.45 5.46 5.48 5.48 5.49 7.10 7.11 7.12 7.19 7.20 7.21 7.22

O

O

385
6-18m
4-chlorobenzaldehyde homologation (dioxolane)

1H-NMR CDCl3 /USERdata/mcnnity.mcleod2 57

6-18s
6-18s
Crotonal homologation (dioxolane)

[Diagram of chemical structure]
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6-10a

H₃C

CH₃

CH₃

Cl

[Chemical Structure Image]
H-methoxybenzaldehyde homologation (pinacol)

Structural formula:

\[ 
\text{H}_3\text{CO} \quad 6-10\text{n} 
\]
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Feb09-2014
Account McNulty
Citral homologation (pinacol)

1d_13C_carbon_CDC3JUSERdata/mcnulty/mcLeod2.56
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H₃C

O

CH₃

O

CH₃

6-10u

1H NMR CDCl₃ /USERdata/mcnulty mcleod2.56

February 2004

Account McNaught

crotonaldehyde homologation (pinacol)

6-10u
crotonaldehyde homologation (pinacol)

$\text{H}_{3}\text{C}$

$\text{CH}_{3}$

$\text{O}$

$\text{H}_{3}\text{C}$

$\text{O}$

$\text{CH}_{3}$

$\text{O}$

$\text{CH}_{3}$

6-10u
TBSO

6-26

H₃C

O

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₃

O

H₃C

CH₳
TBSO

\[
\begin{align*}
\text{H}_3\text{C} & - \text{CH}_3 \\
\text{TBSO} & \\
\text{CH}_3 & - \text{O} - \text{O} - \text{H}_3\text{C} - \text{CH}_3 \\
6-26 & 
\end{align*}
\]
3-[(4-methoxyphenyl)prop-2-enal
1H-NMR CDCl3 /USER/data/mcnulty/mcleod2 SS

H₃CO

6-11n
3-(4-methoxyphenyl)prop-2-enal

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6-11q
5-phenylpent-2-ena
1H-NMR CDCl3 /USERdata/mcnulty/mcleod2-4E

6-11m
6-11t
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Mar11-2014
Account McNulty
Tartrate Hornologiation Aldehyde
1H-NMR CDCl3 /USERdata/mcnulty.mcleod2.5%

H₃C
\[\text{TBSO} \]
\[\text{SI-6-5} \]

\[\text{CH}_3\]

\[\text{O} \]

\[\text{O} \]

\[\text{H} \]

\[\text{3} \]

\[\text{C} \]

\[\text{CH} \]

\[\text{3} \]
Glu-Hom-Pir
Deprotection:
FeCl₃, H₂O, 2 h
1H-NMR (CDCl₃; JUSERdata/mcnulty.mcleod2.57)
Ph.D. Thesis – D. McLeod; McMaster University – Chemistry

6-benzylxox-4, 5-diisopropylidene-hex-2-en pinacol acetate
1H-NMR (CDCl3) /USER/data/mcnulty/mcleod23E
2,3-acetone L-tartrate diol
1H-NMR CDCl3 (USERdata/mcnulty/mcleod2.57)
May 16-2016
Account McNulty
Phomolide G
OBn-Acet-OH
1H-NMR CDCl3 /USERdata/mcnulty mcleod 60

457
HO
NH\text{Boc}
\text{OCH}_3

\text{SI-6-7}
HO
NHBoc
OCH₃

SI-6-7

Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
N-Boc Methyl 5-carboxy-2,2-dimethyl-1,3-oxazolidine
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 56
N-Boc Methyl 3-carboxy-2,2-dimethyl-1,3-oxazolidine
C13SN CDCl3 /USERdata/mcnully/mcleod2.5k
OMOM

HO

OMOM

SI-6-15
2-carboxy-gammabutyrolactone
1H-NMR Acetone /USERdata/mcnulty.mcleod2.59
SI-6-11

2-carboxy-gamma-methylbutyrolactone
HO

SI-6-12

HO

SI-6-12

HO

SI-6-12
3-\{(S)-2,2-dimethyl-1,3-dioxolan-4-yl\}propan-1-ol
C13H16O3

SIG-6-13
Appendix Six

Synthetic Summary for Phomolides G & H
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\[
\begin{align*}
\text{MeO}_2C\text{C}OH & \xrightarrow{\text{PhMe, reflux}} \text{MeO}_2C\text{C}O\text{Me} \\
6-19 & \xrightarrow{\text{THF, reflux}} \text{Si-6-1} \\
\text{LiAlH}_4 & \xrightarrow{\text{THF, reflux}} \text{Si-6-2} \\
\text{NaH, TBSCI} & \xrightarrow{\text{THF, 0 °C to r.t.}} \text{Si-6-3} \\
\text{SO}_{2}\text{py}, \text{TEA, DMSO} & \xrightarrow{\text{THF, reflux}} \text{Si-6-4} \\
\text{Pr}_3\text{P} & \xrightarrow{\text{KOTBu}} \text{6-5} \\
\text{TBSO} & \xrightarrow{\text{THF/DMF (4:1), 0 °C to r.t.}} \text{6-20} \\
\text{KOH} & \xrightarrow{\text{THF, 0 °C}} \text{6-26} \\
\text{PPH}_3, \text{I}_2 & \xrightarrow{\text{THF, 0 °C}} \text{7-58} \\
\text{KCN, TBAI} & \xrightarrow{\text{DMSO, r.t.}} \text{7-56} \\
\text{ZnBr} & \xrightarrow{\text{THF, r.t.}} \text{7-59} \\
\text{PPH}_3, \text{RuCl}_2, \text{H}_2 & \xrightarrow{\text{PhH/EtOH (1:1) r.t.}} \text{7-60} (\geq 9:1 \text{ d.r.}) \\
\text{PMBOCl, NaH} & \xrightarrow{\text{THF/DMF (2:1), r.t.}} \text{84%} \\
\text{FeCl}_3 \cdot \text{H}_2\text{O} & \xrightarrow{\text{Acetone, r.t.}} \text{PMBO} \\
\text{Si-7-10} & \xrightarrow{\text{Si-7-11}} \text{7-61} \text{CHO}
\end{align*}
\]
Ph.D. Thesis – D. McLeod; McMaster University – Chemistry

\[ \text{PMBO} \quad \text{CHO} \quad \text{PMBO} \quad \text{CHO} \]

\[ \begin{align*}
\text{7-61} & \quad \text{CHO} \quad \text{7-67} \\
\text{TiCl}_4, \text{DIPEA} & \quad \text{PMBO} \quad \text{CHO} \\
\text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} & \quad 82\% \\
\end{align*} \]

\[ \begin{align*}
\text{7-69} & \quad \text{TBSO}^{-} \quad \text{OH} \\
\text{LiOH, H}_2\text{O}_2 & \quad \text{THF/H}_2\text{O} (4:1), \text{r.t.} \\
\text{82}\% & \\
\end{align*} \]

\[ \begin{align*}
\text{7-70} & \quad \text{TBSO}^{-} \quad \text{OH} \\
\text{DDQ, CH}_2\text{Cl}_2, \text{r.t.} & \quad \text{84}\% \\
\end{align*} \]

\[ \begin{align*}
\text{7-68} & \quad \text{TBSO}^{-} \quad \text{N} \quad \text{O} \\
\text{Ph}_3\text{P}, \text{DIAD} & \quad \text{PhMe, 0 \text{C} to r.t.} \\
\text{83}\% & \\
\end{align*} \]

\[ \begin{align*}
\text{7-71} & \quad \text{OH} \\
\text{TBAF} & \quad \text{THF, 0 \text{C} to r.t.} \\
\text{92}\% & \\
\end{align*} \]

\[ \begin{align*}
\text{7-80} & \quad \text{OH} \\
\text{TFA} & \quad \text{MeCN/H}_2\text{O} (3:1), \text{r.t.} \\
\text{83}\% & \\
\end{align*} \]
PMBO

H₃C

O

O

H₃C

CH₃

CO₂R

OTBS

DDQ

CH₂Cl₂, r.t.

87%

R= H  7-69  →  Mel, K₂CO₃

Acetone, r.t.

93%

R=Me  7-81  ←

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

7-82

Me₂CO, r.t.

87%

PMBO

H₃C

O

O

H₃C

CH₃

CO₂R

OTBS

K₂CO₃

MeOH, r.t.

61%

7-23

7-83

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

R= H  7-86  →  Mel, K₂CO₃

Acetone, r.t.

90%

R=Me  7-88  ←

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

7-92

MeOH, r.t.

72%

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

R= H  7-86  →  Mel, K₂CO₃

Acetone, r.t.

90%

R=Me  7-88  ←

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

7-93

MeOH, r.t.

83%

R= H  7-69  →  Mel, K₂CO₃

Acetone, r.t.

93%

R=Me  7-81  ←

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

7-82

Me₂CO, r.t.

87%

PMBO

H₃C

O

O

H₃C

CH₃

CO₂R

OTBS

K₂CO₃

MeOH, r.t.

61%

7-23

7-83

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

R= H  7-86  →  Mel, K₂CO₃

Acetone, r.t.

90%

R=Me  7-88  ←

H₃C

O

O

H₃C

CH₃

CO₂Me

OTBS

7-92

MeOH, r.t.

72%
Appendix Seven

Spectra Relevant to Chapter Seven:

The Total Synthesis of Phomolides G & H
### SUPPORTING INFORMATION

#### Table of Contents

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<td>C-NMR page</td>
<td>SI-514</td>
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<td>H-NMR page</td>
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<td>SI-7-9</td>
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<td>H-NMR page</td>
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Compound SI-7-6 $^{13}$C-NMR................................................. page SI-528
Compound 7-64 $^1$H-NMR........................................ page SI-529
Compound 7-64 $^{13}$C-NMR........................................ page SI-530
Compound 7-65 $^1$H-NMR........................................ page SI-531
Compound 7-65 $^{13}$C-NMR........................................ page SI-532
Compound SI-7-7 $^1$H-NMR........................................ page SI-533
Compound SI-7-7 $^{13}$C-NMR........................................ page SI-534
Compound 7-61 $^1$H-NMR........................................ page SI-535
Compound 7-61 $^{13}$C-NMR........................................ page SI-536
Compound 7-67 $^1$H-NMR........................................ page SI-537
Compound 7-67 $^{13}$C-NMR........................................ page SI-538
Compound 7-68 $^1$H-NMR........................................ page SI-539
Compound 7-68 $^{13}$C-NMR........................................ page SI-540
Compound 7-69 $^1$H-NMR........................................ page SI-541
Compound 7-69 $^{13}$C-NMR........................................ page SI-542
Compound 7-70 $^1$H-NMR........................................ page SI-543
Compound 7-70 $^{13}$C-NMR........................................ page SI-544
Compound 7-23 $^1$H-NMR........................................ page SI-545
Compound 7-23 $^{13}$C-NMR........................................ page SI-546
Compound 7-80 $^1$H-NMR........................................ page SI-547
Compound 7-80 $^{13}$C-NMR........................................ page SI-548
Compound 7-71 $^1$H-NMR........................................ page SI-549
Compound 7-71 $^{13}$C-NMR........................................ page SI-550
Compound 7-79 $^1$H-NMR........................................ page SI-551
Compound 7-79 $^{13}$C-NMR........................................ page SI-552
Compound 7-3 $^1$H-NMR........................................ page SI-553
Compound 7-3 $^{13}$C-NMR........................................ page SI-554
Compound 7-3 $^{13}$C-NMR........................................ page SI-555
Compound 7-3 COSY............................................. page SI-556
Compound 7-3 HSQC................................................ page SI-557
Compound 7-81 $^1$H-NMR........................................ page SI-558
Compound 7-81 $^{13}$C-NMR........................................ page SI-559
Compound 7-82 $^1$H-NMR........................................ page SI-560
Compound 7-82 $^{13}$C-NMR........................................ page SI-561
Compound 7-82 and 7-83 Stacked $^1$H-NMR................. page SI-562
Compound 7-83 $^1$H-NMR........................................ page SI-563
Compound 7-83 $^{13}$C-NMR........................................ page SI-564
Compound 7-84 $^1$H-NMR........................................ page SI-565
Compound 7-84 $^{13}$C-NMR........................................ page SI-566
Compound 7-85 $^1$H-NMR........................................ page SI-567
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Compound 7-85 \(^{13}\)C-NMR................................................ page SI-568
Compound 7-86 \(^{1}\)H-NMR................................................ page SI-569
Compound 7-86 \(^{13}\)C-NMR................................................ page SI-570
Compound 7-87 \(^{1}\)H-NMR................................................ page SI-571
Compound 7-87 \(^{13}\)C-NMR................................................ page SI-572
Compound 7-88 \(^{1}\)H-NMR................................................ page SI-573
Compound 7-88 \(^{13}\)C-NMR................................................ page SI-574
Compound 7-89 \(^{1}\)H-NMR................................................ page SI-575
Compound 7-89 \(^{13}\)C-NMR................................................ page SI-576
Compound 7-90 \(^{1}\)H-NMR................................................ page SI-577
Compound 7-91 \(^{13}\)C-NMR................................................ page SI-578
Compound 7-90 \(^{1}\)H-NMR................................................ page SI-579
Compound 7-90 \(^{13}\)C-NMR................................................ page SI-580
Compound 7-90 COSY................................................ page SI-581
Compound 7-90 HSQC................................................ page SI-582
Compound SI-7-11 \(^{1}\)H-NMR................................................ page SI-583
Compound SI-7-11 \(^{13}\)C-NMR................................................ page SI-584
Compound 7-93 \(^{1}\)H-NMR................................................ page SI-585
Compound 7-93 \(^{13}\)C-NMR................................................ page SI-586
Compound 7-93 and 7-92 Stacked \(^{1}\)H-NMR........................................ page SI-587
Compound 7-92 \(^{1}\)H-NMR................................................ page SI-588
Compound 7-92 \(^{13}\)C-NMR................................................ page SI-589
Compound 7-94 \(^{1}\)H-NMR................................................ page SI-590
Compound 7-94 \(^{13}\)C-NMR................................................ page SI-591
Compound 7-95 \(^{1}\)H-NMR................................................ page SI-592
Compound 7-95 \(^{13}\)C-NMR................................................ page SI-593
Compound 7-95 COSY........................................ page SI-594
Compound 7-95 HSQC................................................ page SI-595
Compound 7-96 \(^{1}\)H-NMR................................................ page SI-596
Compound 7-96 \(^{13}\)C-NMR................................................ page SI-597
Compound 7-4 \(^{1}\)H-NMR................................................ page SI-598
Compound 7-4 \(^{13}\)C-NMR................................................ page SI-599
Compound 7-4 COSY................................................ page SI-600
Compound 7-4 HSQC................................................ page SI-601
Nov04-2015
Account: McNulty
D: Valino
1H-NMR CDCl3 /USERdata/mcnulty/mealod2.5E

Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
Nov04-2015
Account McNulty
D-Valinol
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 S8

SI-7-1
(+)-isopropyl-1,3-thiazolidin-2-thione

13C_{carbon} CDCl3 /USER/data/MCNulty-mcleod2-58
N-Acyl 4-isopropyl-1,3-thiazolidin-2-thione
1H-NMR CDCl3 /USERdata/mcnulty/macleod2.5

(S)-7-47
N-Acyl 4-isopropyl-1,3-thiazolidin-2-thione

1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 S9

(N)-7-47
Jan 15-2016
Account McNulty
Phomolide G:
TBS-Acet-Pin
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 37
Phomolide G:
OH-Acet-Pin (E)

Jan15-2016
Account McNulty

Phomolide G: OH-Acet-Pin (E)
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 36
OH-Acet-Pin (Z)
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 31

(Z)-SI-6-6
Phomolide G:

1H-NMR CDCl3 /USERdata/mcnulty.mcleod2 12

Jan17-2016
Account McNulty

I-Acet-Pin

H₃C
O
O
H₃C
O
O

CH₃

7-58

f1 (ppm)
Phomolide G: E-Allyl Ketone

1H-NMR CDCl3 /USERdata/mcnulty mcleod2 60

Jun04-2014
Account McNulty

513
Phomolide G: Allyl-OH-Acet-Pin
1H-NMR CDCl3 USERdata/mcnulty mcleod2 59

Jan19-2016
Account McNulty

HO

H3C

CH3

CH3

7-60

CH3

CH3

f1 (ppm)
Ph.D. Thesis – D. McLeod; McMaster University – Chemistry

Account McNulty
Phomolide G:
Propyl-OH-Acet-Pin
1H-NMR CDCl3 / USERdata/mcnulty mcleod 60

\[ \text{HO} \]

\[ \text{H}_3\text{C} \]

\[ \text{CH}_3 \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{H} \]

\[ \text{C} \]

\[ \text{CH}_3 \]

\[ \text{Si}-7.9 \]

\[ \text{H}_3\text{C} \]

\[ \text{CH}_3 \]

\[ \text{CH}_3 \]

\[ \text{CH}_3 \]

\[ \text{HO} \]
Ph.D. Thesis – D. McLeod; McMaster University – Chemistry

Jan19-2016
Account McNulty
Phomolide G
Propyl-OH-Acet-Pin
C13SN CDCl3 /USERdata/mcnulty mcleod2 60

SI-7-9

\[
\text{fL (ppm)}
\]

\[
\text{fL (ppm)}
\]
Phomolide G: Bn-Acet-I

![NMR spectrum of Phomolide G: Bn-Acet-I](image)

**Chemical Shifts:**
- 6.52 ppm
- 27.42 ppm
- 27.50 ppm
- 70.64 ppm
- 73.75 ppm
- 77.79 ppm
- 80.23 ppm
- 109.97 ppm
- 127.83 ppm
- 127.92 ppm
- 128.59 ppm
- 137.94 ppm

**Structure:**
- H3C
- CH3
- O
- O
- O
- O
- OBn

**Comment:**
- SI-7-5

**Technical Details:**
- Nov04-2015
- Account McNulty
- Phomolide G: Bn-Acet-I
- 1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 60
Phomolide G:
PMB-Aldol-TBS-Aux
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 60
Phomolide G: D-Seco Acid
1H-NMR CDC\textsubscript{3} \textbackslash USERdata/mcnulty mcleod2 59
Phomolide G: D-Seco Acid

Nov27-2015
Account McNulty
Phomolide G: D-Seco Acid
1d_13C_carbon CDC13 /USERdata/mcnulty mcleod2 59

H3C
\[
\text{CH}_3
\]
\[
\text{O}
\]
\[
\text{O}
\]
\[
\text{TBSO}
\]
\[
\text{OH}
\]
\[
\text{TBSO}
\]
\[
\text{OH}
\]
\[
\text{TBSO}
\]
\[
\text{OH}
\]
\[
\text{TBSO}
\]
\[
\text{OH}
\]

7-70
Phomolide G: Acet-Lactone

1H-NMR CDCl3 /USERdata/mcnulty mcleod2 54
Ph. D. Thesis – D. McLeod; McMaster University – Chemistry

Sep21-2015

File: McNulty_mcleod2 54

Acet-Lactone

13C_carbon CDCl3/

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<td>108.34</td>
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<td>94.09</td>
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<td>83.86</td>
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<td>72.91</td>
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<td>44.53</td>
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<td>38.63</td>
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<td>37.14</td>
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<td>36.63</td>
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<td>27.06</td>
<td></td>
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<tr>
<td>27.20</td>
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</tr>
<tr>
<td>17.94</td>
<td></td>
</tr>
<tr>
<td>15.09</td>
<td></td>
</tr>
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</table>
Phomolide G: p-bromobenzoate Acet Lactone
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 54

7-79
Phomolide G: Lactone (D-Mitsunobu) 
Acetone-D6 + CD3OD 
1H-NMR Acetone /USERdata/mcnulty-mcleod2 60
Phomolide G: TFA Cleavage of Acet-Lactone (D-mitsu)

Oct 22-2015
Account: McNulty
Phomolide G: TFA Cleavage of Acet-Lactone (D-mitsu)
C13SN Acetone /USERdata/mcnulty mcleod2 S3
Oct 22-2015
Account McNulty
Phomolide G:
TFA Cleavage of Acet-Lactone (D-mitsu)
2d_hsqC HCg Acetone /USERdata/mcnulty mcleod2 53

[Chemical structure diagram]

Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
Phomolide G
PMBO-Acet-TBS-Methyl ester
1H NMR CDCl₃ /USERdata/mcLeod2 SC
Ph.D. Thesis – D. McLeod; McMaster University – Chemistry

Nov 12 2015

Phomolide G:

D-9epi-Acet-TBS-Methyl Ester

1d_13C_carbon CDCl3 /USER/datalab/mcnulty mcleod2 60

Phomolide G: D-9epi-Acet-TBS-Methyl Ester

1d_13C_carbon CDCl3 /USER/datalab/mcnulty mcleod2 60

Phomolide G:

D-9epi-Acet-TBS-Methyl Ester

1d_13C_carbon CDCl3 /USER/datalab/mcnulty mcleod2 60
Phomolide G:
L-Aldol
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 59
[Image of an NMR spectrum with chemical shifts labeled. The spectrum shows various peaks at different ppm values, corresponding to different chemical structures in the sample.]
Phomolide G:
PMB-Acet-TBS-Acid
L-Series
C13SN CDCl3 /USERdata/mcnulty mcleod2 5B
Oct23-2015
Account McNulty
Phomolide G: Acet-Lactone (Mitsunobu)
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 55

![1H-NMR spectrum of Phomolide G: Acet-Lactone (Mitsunobu)](image)

---

Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
Phomolide G:
Acet-Lactone (L-Mitsunobu)

Oct 23-2015
Account McNulty
Phomolide G:
Acet-Lactone (L-Mitsunobu)
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 S5

Oct 23-2015
Account McNulty
Phomolide G:
Acet-Lactone (L-Mitsunobu)
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 S5
Phomolide G:
Acet-4BrBz-Lactone (L-Mitsunobu)
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 60
Phomolide G:
Lactone (L-Mitsunobu)
C13SN Acetone /USERdata/mcnulty mcleod2 59

δ 169.83, 136.38, 128.11, 78.11, 75.96, 72.51, 71.62, 45.18, 41.09,
39.02, 18.13, 13.23
Phomolide G:
PMB-Acet-TBS-Methyl Ester (L)
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 60
Nov06-2015
Account McNulty
Phomolide G:
(L)-PMB-Acet-TBS-Methyl Ester
C13SN CDCl3 /USERdata/mcnulty mcleod2 60

-5.15
-4.28
14.23
18.04
18.35
25.71
26.92
27.36
35.87
36.00
43.50
51.55
55.29
69.51
70.33
75.83
108.70
113.74
127.18
129.31
130.99
136.26
159.09
171.39
171.39
159.09
PMBO
O
O
H
3
C
CH
3
T
B
S
O
CO
2
Me

Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
Phomolide G:
L-Acet-TBS-Methyl Ester
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 56
Phomolide G: L-Acet-TBS-Methyl Ester

1d _13C_carbon CDCl3 /USERdata/mcnulty mcleod256

-4.99 -4.23 14.21 18.20 18.76 25.84 27.11 27.35 38.65 39.71 43.65 51.72 69.57 70.93 80.88 82.12 109.52 126.94 137.01 171.48

OH
O
O
H
3
C
CH
3
TBSO

CO
2
Me

7-93
Phomolide G: Lactone Methanolysis
Acet-TBS-Methyl Ester (L)
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 59

Sep21-2015
Account McNulty
Phomolide G:
Lactone Methanolysis
Acet-TBS-Methyl Ester (L)
1H-NMR CDCl3 /USERdata/mcnulty mcleod2 59

OH
O
O
H
3
C
CH
3
TBSO
CO
2
Me

7-92 (Red)
TBSO
CO
2
Me

7-93 (Blue)
TBSO

Phomolide G:
Lactone Methanalysis
Acet-TBS-Methyl Ester (L)
$^1$H-NMR CDCl$_3$ JUSB4data/mcLeod2.5S
Ph.D. Thesis – D. McLeod; McMaster University – Chemistry
Phomolide H: L-Acet-Lactone Methyl Ether

C13SN CDCl3 /USERdata/mcnulty mcleod2 58

Feb 12-2016
Account McNulty

1.00 137.24 128.10 108.57 57.17 43.70 38.22 43.12 57.91 27.02 27.92 22.29 13.96

13.96 18.66 27.02 27.19 36.94 38.22 43.70 57.17 43.70 38.22 36.94 27.19

H3C CH3

O

O

O

OCH3

7-94

O

O

H3C CH3

O

O

O

OCH3

7-94

f1 (ppm)
Phomolide H: L-OMe-Lactone
1H-NMR Acetone /USERdata/mcnulty mcleod2 60

![NMR Spectrum](image-url)
Phomolide H: L-OMe-Lactone

2d_hsqcHCg Acetone /USERdata/mcnulty.mcleod2 60
Phomolide H: D-Acet-OMe-Lactone

1H-NMR CDCl3 /USERdata/mcnulty mcleod2 60

Apr21-2016
Account McNulty
Phomolide H:

D-Acet-OMe-Lactone

1H-NMR CDCl3 /USERdata/mcnulty mcleod2 60
Phomolide H:
D-Acet-OMe-Lactone
1d_13C_carbon CDCl3 /USERdata/mcnulty mcleod2 60

Apr21-2016
Account McNulty

14.01 18.60 27.06 27.21 36.84 38.26 42.58
57.58 72.47 76.12 81.68 84.30 108.23 123.99 134.68 169.02

O
OCH3
O
O
O
C
CH3
H3C

7-96
Phomolide H: D-O-Me-Lactone
1H-NMR Acetone /USERdata/mcnulty mcleod2 35
Phomolide H: D-OMe-Lactone
C13SN Acetone /USERdata/mcnulty mcleod2 35
Jun08-2016
Account McNulty
Phomolide H:
D-OMe-Lactone
2d_COSY_dqf Acetone /USERdata/mcnulty mcleod2 35
Phomolide H: D-OMe-Lactone
Appendix Eight

Comparison of NMR data
Table A8-1. $^{13}$C NMR spectral data for phomolide G and compounds 7-3 and 7-90

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<th>Position</th>
<th>phomolide G (ppm)</th>
<th>7-3 (ppm)</th>
<th>$\Delta \delta$ (ppm)</th>
<th>7-90 (ppm)</th>
<th>$\Delta \delta$ (ppm)</th>
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</tr>
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<td>13.3</td>
<td>0.1</td>
<td>13.2</td>
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Figure A8-1. Plots depicting the difference between the chemical shift of selected resonances in the $^{13}$C NMR spectra of 7-3 and 7-90
Table A8-1. $^{13}$C NMR spectral data for phomolide G and compounds 7-95, 7-4 & 7-3

<table>
<thead>
<tr>
<th>Position</th>
<th>Phomolide H (ppm)</th>
<th>7-95 (ppm)</th>
<th>Δδ (ppm)</th>
<th>7-4 (ppm)</th>
<th>Δδ (ppm)</th>
<th>7-3 (ppm)</th>
<th>Δδ (ppm)</th>
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</thead>
<tbody>
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<td>-0.3</td>
<td>168.6</td>
<td>-1.4</td>
<td>169.4</td>
<td>-0.6</td>
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<td>42.4</td>
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<td>134.4</td>
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<td>NA</td>
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</table>

Figure A8-2.
Figure A8-3. Description

Figure A8-4. Plot depicting the difference between the chemical shift of selected resonances in the $^{13}$C NMR spectra of 7-95, 7-4 & 7-3
Appendix Nine

X-ray Crystallographic Data for Compound 7-79
Figure A9-1. X-ray structure for 7-79

Table A9-1. Crystal data and structure refinement for 7-79.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>CCDC #1439915</th>
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</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C22 H27 Br O6</td>
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<tr>
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<tr>
<td>Temperature</td>
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</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
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<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2_12_12_1</td>
</tr>
</tbody>
</table>
Unit cell dimensions  
\[ a = 6.8825(6) \, \text{Å} \quad a = 90^\circ. \]
\[ b = 10.4082(8) \, \text{Å} \quad b = 90^\circ. \]
\[ c = 31.020(3) \, \text{Å} \quad g = 90^\circ. \]

Volume  
\[ 2222.1(3) \, \text{Å}^3 \]

Z  
4

Density (calculated)  
\[ 1.397 \, \text{Mg/m}^3 \]

Absorption coefficient  
\[ 1.884 \, \text{mm}^{-1} \]

F(000)  
968

Crystal size  
\[ 0.371 \times 0.161 \times 0.122 \, \text{mm}^3 \]

Theta range for data collection  
\[ 3.032 \text{ to } 30.540^\circ. \]

Index ranges  
\[ -9 \leq h \leq 9, \quad -14 \leq k \leq 14, \quad -43 \leq l \leq 39 \]

Reflections collected  
\[ 30432 \]

Independent reflections  
\[ 6730 \quad [R(\text{int}) = 0.0270] \]

Completeness to theta = 26.000°  
\[ 99.6 \% \]

Absorption correction Numerical

Max. and min. transmission  
\[ 0.8860 \text{ and } 0.6609 \]

Refinement method  
Full-matrix least-squares on F2

Data / restraints / parameters  
\[ 6730 / 1 / 270 \]

Goodness-of-fit on F2  
\[ 1.062 \]

Final R indices [I>2\sigma(I)]  
\[ R1 = 0.0346, \quad wR2 = 0.0780 \]

R indices (all data)  
\[ R1 = 0.0443, \quad wR2 = 0.0808 \]

Absolute structure parameter  
\[ 0.016(7) \]

Extinction coefficient n/a

Largest diff. peak and hole  
\[ 0.691 \text{ and } -0.459 \, \text{e.Å}^{-3} \]