Biomimetic Synthesis of Natural Products via Reactions of ortho-Quinone Methides

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B. Sc. (Hons.)

A thesis submitted in total fulfilment of the requirements for the degree of
Doctor of Philosophy

2016

Department of Chemistry
The University of Adelaide
For My Family
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........................................
Justin Spence

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........................................
Date
Acknowledgements

Firstly, I would like to thank my supervisor, Dr. Jonathan George for his guidance throughout my Ph.D. His advice and direction has been extremely valuable over the years. When I joined the George group during my honours year in 2011; Jonathan personally trained me in the lab and provided me with the essential synthetic labs skills and ethos that have held me in good stead for the duration of my Ph.D. and into the future. Jonathan’s passion for synthetic chemistry, as well as his keen eye for a potential biosynthesis of a natural product has always been a real inspiration to me. Finally, I am indebted to Jonathan, for allowing me to travel to all corners of the globe to present our research at international conferences. For these reasons I am grateful to Jonathan; converting this unworldly country boy into the professional synthetic chemist I am today.

I would also like to acknowledge the other members of the George group (Kevin Kuan, Henry Pepper, Michelle Cruickshank, Stephen Tulip, Hiu Lam and Adrian Markwell-Heys). Although we haven’t always seen eye to eye, it has been a pleasure traversing the postgraduate rollercoaster with you all. To my fellow lab mates (Lab 12), the weekly Wednesday lab lunch has left me with lasting memories that I will always cherish, and I hope the traditions continues on into the future. I would like to make a special mention to both Kevin and Hiu, who have assisted me greatly over the years and I wish both of them success and happiness. Furthermore, your company has been a pleasure, from all of the research discussions and brainstorming sessions going well into the evening, to the chats over beers on a Friday night.

To Jack Evans and Noby Leong it has been a pleasure and an honour to travel down this rocky road together. There have been ups and downs, but we were always there for one another, supporting each other through the tough times. Without you guys, this experience would have been considerably less enjoyable. I have particularly enjoyed the coffee breaks, Friday drinking sessions and weekly lunches. Although we may no longer all be on the same continent, I hope our friendship continues for many years to come. A special mention needs to go to Andrew Tarzia (TBT), although you were a late addition to ‘the club’ you are still a valued member. Furthermore, Hump day run club/Lofty crew (Sophie, Jack, Ren, Geno and Travis), the past year and half has been thrilling, thank you all for being delightful company.

To my Dad, whose support not only over the duration of my candidature but my entire life has been unwavering. You are my champion; picking me up from the bus on those late nights during undergrad and coming home from the lab. You have been a valuable source of
advice and a calming influence; when times are tough assuring me that everything is going to be OK. Your wisdom and calmness are traits I aspire to in my own life. And on the other hand there is never a dull moment in the Spence household, reminding me I must always be on my toes. To my dog Holly, your companionship has been most welcomed and has filled my life with joy from all of the cute photos and precious memories.

Finally, to my dearest Sophie, you are my best friend and I have cherished your patience, love and support over the past 4 years. You are the light of my life and I am excited to tackle the future by your side.
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Abstract

In recent times, natural product synthesis has become central to many scientific fields; from chemistry, through to biology and pharmacology. As synthetic chemists, natural products are attractive targets due to their interesting and complex structures, combined with some intriguing biological properties. One field that is of particular interest is the use of a biomimetic approach towards the synthesis of complex natural products. This thesis will describe the use ortho-quinone methides and cascade reactions towards the biomimetic synthesis of the penilactones A and B, the peniphenones A-D, virgatolide B and epicolactone.

The total synthesis of ent-penilactone A and penilactone B has been achieved via biomimetic Michael reactions between tetronic acids and o-quinone methides. A five-component cascade reaction between a tetronic acid, formaldehyde, and a resorcinol derivative that generates four carbon-carbon bonds, one carbon-oxygen bond and two stereocenters in a one-pot synthesis of penilactone A is also reported.

The total synthesis of peniphenones A-D has been achieved via Michael reactions between appropriate nucleophiles and a common ortho-quinone methide intermediate. This strategy, which was based on a biosynthetic hypothesis, minimised the use of protecting groups and thus facilitated concise syntheses of the natural products. The most complex target, the benzannulated spirokeetal peniphenone A, was synthesised enantioselectively in nine linear steps from commercially available starting materials.

A synthesis for the ortho-quinone methide precursor of virgatolide B has been developed. A simplified enol ether was employed for the biomimetic [4+2] cycloaddition reaction to afford a simplified virgatolide B analogue. An isomerised compound containing a cis fused ring junction, thought to arise via a [4+2] cycloaddition of an ortho-quinone methide and an endocyclic enol ether formed by acid catalysed tautomerisation in situ will also be reported.

Finally, preliminary studies towards the synthesis of epicolactone have been conducted. A synthesis of the proposed key proposed biosynthetic intermediate epicoccone B has been achieved in four steps. Efforts towards the synthesis of epicoccine via our proposed cycloetherification route proved to be challenging. Furthermore, the synthesis of epicolactone through our proposed biosynthesis was not viable, which was also observed by Trauner and co-workers in their 2014 synthesis of dibefurin.
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<table>
<thead>
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<th>Description</th>
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<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>Carbon-13</td>
</tr>
<tr>
<td>$^1$H</td>
<td>Hydrogen-1</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl, acetate</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BnBr</td>
<td>benzyl bromide</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration for specific rotation measurements</td>
</tr>
<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>CD</td>
<td>circular dichroism</td>
</tr>
<tr>
<td>cm$^{-1}$</td>
<td>wavenumbers</td>
</tr>
<tr>
<td>conc</td>
<td>concentrated</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazobicycloundec-7-ene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>ent</td>
<td>enantiomer</td>
</tr>
<tr>
<td>epi</td>
<td>epimer</td>
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<td>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HFIP</td>
<td>hexafluoroisopropanol</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation spectroscopy</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum correlation spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>hv</td>
<td>light</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>i-Pr₂NH</td>
<td>diisopropylamine</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>LiTMP</td>
<td>lithium tetramethylpiperidide</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Mz</td>
<td>megahertz</td>
</tr>
<tr>
<td>Min</td>
<td>minutes</td>
</tr>
<tr>
<td>Mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>nm</td>
<td>nanometre</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>o-QM</td>
<td>ortho-quinone methide</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on activated carbon</td>
</tr>
<tr>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>tetrakis(triphenylphosphine)palladium(0)</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>PIDA</td>
<td>phenyliodine diacetate ((diacetoxy)iodobenzene)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>S&lt;sub&gt;N&lt;/sub&gt;2</td>
<td>substitution nucleophilic bimolecular</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl (tosyl)</td>
</tr>
<tr>
<td>TsCl</td>
<td>tosyl chloride</td>
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</tbody>
</table>
1.1 Natural Products

The structural diversity and complexity of natural products has been of great interest to synthetic chemists over the years. This is in part due to their biological activity, but also their intriguing architectures, which appeals to a wide range of scientific fields. A large proportion of these natural compounds exhibit excellent therapeutic attributes against a range of diseases in the human body. Natural products can also be as lead compounds, which when used as a starting point can result in more effective and potent drugs. As a result, natural products have historically made up a significant portion of the pharmaceutical industry. Currently, over 40% of the pharmaceuticals on the market can be traced back to a natural product source.\textsuperscript{1-5} In recent years, natural products have found significant competition in combinatorial or target based screening approaches.

An example of a bioactive compound isolated from a soil micro-organism currently used therapeutically as a drug is \((\text{-})\text{-rapamycin (1.1), which was isolated from a soil sample collected from Easter Island (Figure 1.1).}\textsuperscript{6} \((\text{-})\text{-Rapamycin (1.1) is currently used as a post-transplant immunosuppressant, specifically in the treatment of kidney transplant patients.}\textsuperscript{7}

\[
\begin{align*}
\text{HO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{O} \\
\text{O} & \quad \text{OMe} \\
\text{HO} & \quad \text{OMe} \\
\text{1.1: \text{(-)-rapamycin}}
\end{align*}
\]

**Figure 1.1:** Structure of immunosuppressant \((-\text{-})\text{-rapamycin (1.1)}\)

Isolation of natural products from the natural source can be both expensive and inefficient, as the yield of such compounds after extraction can be very low when compared to the amount of biological material collected. Furthermore, extraction of these compounds is both time and technique demanding. Hence, if a simple synthetic route can be established, the
need for exhaustive mining of the natural supply can be eliminated. The aim of natural product synthesis is to be able to produce complex natural products in efficient and high yielding pathways, such that isolation from the natural source is no longer required. Furthermore, in some instances the quantities accessible in nature are infeasible from a pharmaceutical perspective, thus a chemical synthesis must be developed. An example of this is the anti-cancer drug eribulin an analogue of the complex natural product halichondrin, which is currently sourced synthetically in over 70 steps.8,9

1.2 Biomimetic Synthesis

Biomimetic synthesis is an approach to synthesis in which inspiration is taken from robust reactions that take place in nature. The key step in a biomimetic synthesis mimics a reaction that is presumed to occur in nature. The theory of biomimetic synthesis was first proposed by Robinson in his synthesis of tropinone (1.5).10,11 Although conducted in 1917 (many years before the actual biosynthesis of tropinone was elucidated), it remains an excellent example of a biomimetic synthesis due to the rapid increase in molecular complexity from the relatively simple starting materials succinaldehyde (1.2), methylamine (1.3) and acetonedicarboxylic acid (1.4), which gave tropinone (1.5) under very mild reaction conditions (Scheme 1.1).

\[ \text{CHO} + \text{H}_2\text{N-Me} + \text{COOH} \rightarrow \text{NMe} \]

\[ 1.2: \text{succinaldehyde} \quad 1.3: \text{methylamine} \quad 1.4: \text{acetonedicarboxylic acid} \quad 1.5: \text{tropinone} \]

Scheme 1.1: Robinson’s biomimetic synthesis of tropinone (1.5)³

The subject was further developed by van Tamelen under the title of biogenetic synthesis.12–14 Heathcock then proposed the following in 1996:

“The basic assumption of this approach is that nature is the quintessential process development chemist. We think that the molecular frameworks of most natural products arise by intrinsically favourable chemical pathways – favourable enough that the skeleton could have arisen by a non-enzymatic reaction in the primitive organism. If a molecule produced in this purely chemical manner was beneficial to the organism, enzymes would have evolved to facilitate the production of this useful material.”15
Introduction

Nature is the most advanced synthetic chemist, with millions of years of experience affording a toolbox of reactions that can be employed to synthesise complex molecules. Thus, biomimetic synthesis focuses on the reactions in nature that were once non-enzymatically driven to direct a synthesis. As these reactions occur readily in nature, it is reasonable to predict they will proceed in the reaction flask, and hence can be used to insightfully direct a synthesis. One particular area of interest in the field of biomimetic synthesis is nature’s use of cascade reactions to efficiently synthesise a variety of complex structures.

1.3 Biomimetic Cascade Reactions

Biomimetic cascade reactions are being increasingly employed toward the synthesis of complex natural products.\(^\text{16}\) Cascade reactions employ a predisposed selectivity of one reaction to generate a product that then possesses the required functionality to be converted into another species in the same pot. This allows for a large number of structural transformations to occur in the one reaction, thereby increasing efficiency and reducing time consumed by multiple purifications. By far the most valuable attribute of this methodology is the ability to rapidly generate molecular complexity, often with remarkable selectivity. The extreme diversity of natural products along with the synthetic chemist’s constant need to improve efficiency bodes well for this type of approach, inviting important development into this underutilised methodology. Prime examples of cascade reactions have been previously reviewed in the literature.\(^\text{16–19}\) As a result, an extensive review of this field will not be completed, instead two representative examples will be discussed.

Our group has made recent advances in the use of biomimetic cascade reactions, some of which will be reported in the upcoming chapters. Nonetheless, a salient example of the prowess of cascade reactions to install molecular complexity in a highly selective manner was reported in our groups synthesis of garcibracteatone (1.11).\(^\text{20,21}\) The biosynthesis of garcibracteatone was proposed to occur via a radical cyclisation cascade reaction. The first step involved a single electron oxidation of 1.6 to afford radical species 1.7. A 7-\textit{endo}-trig radical cyclisation onto the lavandulyl sidechain would afford 1.8, which would immediately undergo a 5-\textit{exo}-trig cyclisation onto the Δ\(^{7,8}\) enol to afford radical species 1.9. A secondary 5-\textit{exo}-trig radical cyclisation onto the Δ\(^{17,18}\) of the C-1 prenyl group of the tertiary radical of 1.9 would give 1.10. An intramolecular aromatic radical substitution would yield the desired natural product garcibracteatone (1.11) (Scheme 1.2). Successful transformation of 1.6 into the desired natural product would suggest that this is a plausible biosynthetic pathway for garcibracteatone (1.11).
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Scheme 1.2: Biomimetic radical cyclisation cascade of garcibracteateone (1.11)

The key intermediate 1.6 was synthesised in three steps from phloroglucinol (1.12) via a Friedel-Crafts reaction followed by prenylation and finally addition of the lavandulyl sidechain. Treatment of 1.16 with Mn(OAc)$_3$ and Cu(OAc)$_2$ in AcOH yielded garcibracteateone (1.11) as well as 5-epi-garcibracteateone (1.13) in 14% and 8% yield respectively (Scheme 1.3). This transformation introduces four new C-C bonds, five new stereocentres and four new carbocyclic rings in one step via a series of highly selective, predisposed radical cyclisations.

Scheme 1.3: George’s biomimetic synthesis of garcibracteateone (1.11)
Another pertinent example of the use of cascade reactions in the biomimetic synthesis of a natural product was reported in the total synthesis of (±)-endiandric acid A (1.19) firstly by Nicolaou in 1982,22 and then Lawrence and Sherburn in 2015.23 The biomimetic cascade approach employed by Lawrence and co-workers engaged a (Z,Z,Z,Z)-tetraene 1.15 (formed by cis selective reduction of tetryne 1.14), which first underwent an 8π-electrocyclisation to give 1.16, followed by a 6π-electrocyclisation to afford 1.17 (analogous to that reported by Nicolaou), which contains the 6,4-ring system of (±)-endiandric acid A (1.19). 1.19 was then primed to undergo an in situ intramolecular Diels-Alder reaction to yield 1.18, which after oxidation of the primary alcohol moiety completes the synthesis of (±)-endiandric acid A (1.19) (Scheme 1.4).

Scheme 1.4: Lawrence and Sherburn’s biomimetic synthesis of endiandric acid A (1.19)

Nicolaou’s 2003 review on their original synthesis of endiandric acids A-G elegantly summarised and emphasised the power of biomimetic cascade reactions: “The power of this cascade can only be fully appreciated when one recognizes that in a single operation a simple linear precursor had been converted into a complex tetracycle with complete relative control over the formation of eight stereocenters”.16 Whilst there are a plethora of methods towards biomimetic cascade reactions, an approach that is gaining momentum in this field is the use of ortho-quinone methides (o-QMs) to rapidly generate molecular complexity.
1.4 Biomimetic Reactions of ortho-Quinone Methides in Natural Product Synthesis

1.4.1 ortho-Quinone Methides

Ortho-quinone methides (o-QMs) such as 1.20 are highly reactive, transient species that Nature has harnessed to synthesise a vast range of complex natural products. Stable o-QMs are rare as a consequence of their extreme reactivity, where they are usually consumed rapidly in situ upon formation. However, the isolation of these highly reactive intermediates has recently been realised, as reported by Amouri et al. in their seminal work involving the complexation of o-QMs with transition metals.24,25 o-QMs can be represented by two resonance forms, a neutral heterodiene form 1.20 and a charged zwitterionic form 1.21 (Figure 1.2).

![Figure 1.2: Proposed o-QM resonance forms](image)

The reactivity of these intermediates has been harnessed by Nature over millions of years, where the reactivity of o-QMs as Michael acceptors is a quintessential defence mechanism.26 Furthermore, o-QMs play an important role in the biosynthesis of many complex natural products. For instance, Chapman’s biomimetic synthesis of (±)-carpanone (1.24) indicates the involvement of o-QMs in its biosynthesis.27 Oxidative coupling of two functionalised sesamol 1.22 molecules afforded o-QM 1.23, which simultaneously underwent a [4+2] cycloaddition to reveal the natural product (±)-carpanone (1.24) in 46% yield (Scheme 1.5). The total synthesis of (±)-carpanone (1.24) is a prime example of the reactivity of o-QMs, whereby simple starting materials can be transformed into complex structures to afford two new rings and five new stereocentres in the one step.

![Scheme 1.5: Chapman’s biomimetic synthesis of carpanone (1.24)](image)
1.4.2 Scope

This review will focus primarily on recent advances in the field of biomimetic $o$-QM reactions in natural product synthesis. Their importance in the biosynthesis of many natural products, via 4 main reaction pathways, including (a) [4+2] cycloadditions, (b) Michael reactions, (c) oxa-6π electrocyclisations and (d) 1,2-rearrangements (Scheme 1.6) will be discussed. An in depth review of $o$-QMs in the literature up to 2012 has been covered previously by Pettus 28,29 and Bray, 30 and therefore only select examples will be discussed in this section.

Scheme 1.6: Reaction pathways of $o$-QMs

1.4.3 Generation of ortho-Quinone Methides

Multiple pathways can be used to initiate the formation of an $o$-QM in situ, which include tautomerization 31–34, oxidation 35,36, thermolysis 37, photolysis 38, acid promotion 39 and base facilitation (Scheme 1.7). 40 Although nature does not utilise all these pathways, there are substantial options available to a synthetic chemist to synthesise these highly unstable intermediates.

Scheme 1.7: Methods for generating $o$-QMs
1.4.4 [4+2] Cycloadditions of ortho-Quinone Methides

ortho-QMs have recently entered an era of renaissance, whereby these reactive intermediates have been extensively utilised in [4+2] cycloaddition reactions to form new six-membered ring systems. As a result, there is a vast array of successful total syntheses reported in the literature involving [4+2] cycloaddition reactions with ortho-QMs.

A noteworthy example of [4+2] cycloadditions of ortho-QMs in the biomimetic synthesis of a natural product was in Baldwin’s synthesis of lucidene (1.28) published in 1999.\(^1\) ortho-QM 1.26 was thermally generated (from 1.25) in the presence of natural product α-humulene (1.27), which afforded lucidene (1.28) and iso-lucidene (1.29) in a 2.5:1 ratio with a combined yield of 17\% along with mono-adduct 1.30 in 28\% yield (Scheme 1.8). The proposed biosynthetic pathway originally reported was supported by Baldwin’s successful biomimetic synthesis of lucidene (1.28).

Studies in our own group have been prevalent, dating back to 2011 with our structural reassignment of the cytosporolide family of natural products.\(^3\) A simplified analogue 1.36 of our proposed structure of cytosporolide A (1.32) was synthesised in via a [4+2] cycloaddition between acid generated ortho-QM 1.35 (generated in situ from 1.33) and β-caryophyllene (1.34) (Scheme 1.9, part a). The revision was confirmed based on comparison of the spectral data of our simplified analogue to that reported in the isolation paper by Che and co-workers.\(^4\) Recently, Takao and co-workers reported a synthesis of our revised structure of (+)-cytosporolide A (1.32) through a [4+2] cycloaddition of thermally generated ortho-QM 1.39 (generated in situ from CJ-12,373 (1.37)) and diprotected fuscoatrol (1.38), followed by cleavage of the protecting groups (Scheme 1.9, part b).\(^5\) This biomimetic synthesis confirmed...
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our proposed structural reassignment, with the spectroscopic data of the synthesised compound matching that of the isolated compounds perfectly. This was a gratifying outcome, whereby biosynthetic speculation was employed to critique implausible structures in the literature.

Scheme 1.9: a) Our synthesis of simplified cytosporolide analogue 1.36; b) Takao’s synthesis of (+)-cytosporolide A (1.32)

Asai and co-workers published a prominent paper in 2015 investigating the key role that o-QMs played in the biosynthesis of some pseudo-natural fungal polyketides (1.40-1.52). The enzymatic synthesis of chaetophenol E (1.46) from chaetophenol B (1.42) was reported (Scheme 1.10). Furthermore, Asai and co-workers adopted a diversity oriented approach towards the conversion of 1.40 and 1.41 into several other potentially undiscovered natural products (1.47-1.52). Chaetophenol B (1.42) and its alkyl chain analogues 1.40 and 1.41 (R = H, Me) were enzymatically converted into o-QMs 1.43-1.45, subsequent in situ [4+2] cycloadditions afforded chaetophenol E (1.46) as well as 1.47-1.52. This single example
demonstrates the versatility of o-QMs, emphasising the variety of structures and backbones that can be obtained.

Scheme 1.10: Asai’s synthesis of chaetophenol E (1.47) and potentially undiscovered natural products 1.47-1.52

Pettus and co-workers also reported an enantioselective synthesis of (−)-medicarpin (1.57), (+)-sophoracarpan (1.58) and (±)-kushcarpin (1.59) via a diversity oriented approach, in which the key step involved the [4+2] cycloaddition of o-QM 1.54 with chiral enol ether 1.55 (Scheme 1.11). In this instance, o-QM 1.54 was generated under basic conditions from 1.53 (MeMgBr), and was immediately trapped by enol ether 1.55. A series of functional group transformations and finally oxidative dearomatisation, followed by in situ trapping with the phenol yielded the three natural products. This pathway represents a universal strategy towards almost all pterocarpan natural products in an enantioselective manner.
Scheme 1.11: Pettus’s synthesis of (−)-medicarpin (1.57), (+)-sophoracarpan (1.58) and (±)-kushcarpin (1.59)

The inherent utility of $\sigma$-QMs can be further expanded towards the formation of spirocyclic natural products, presumably via [4+2] cycloaddition reactions with the corresponding exocyclic alkenes. A pertinent example of this was reported De Brabander and co-workers in 2009, in which they observed a [4+2] cycloaddition of an $\sigma$-QM with a five-membered exocyclic enol ether in their elegant synthesis of the spirocyclic natural product berkelic acid (1.65)$^{46,47}$ The biomimetic synthesis was completed through a [4+2] cycloaddition of Lewis acid generated $\sigma$-QM 1.63 and exocyclic enol ether 1.62 (obtained by in situ cycloisomerisation of alkyne 1.60) to afford methyl berkelate 1.64 (Scheme 1.12). Finally, a regioselective hydrolysis of the ester moiety revealed the natural product when the reaction was interrupted at partial completion. Synthesis of both enantiomers of 1.65 allowed the unambiguous assignment of the absolute configuration of berkelic acid as $22S$ (1.65).
Another prominent example of [4+2] cycloadditions of $\sigma$-QMs was demonstrated by two groups with their biomimetic synthesis of spiroooliganones A and B (1.70 and 1.71).\textsuperscript{48} The groups of Tong\textsuperscript{49} and Yu\textsuperscript{50} both employed an $\sigma$-QM [4+2] cyloaddition strategy to furnish the desired natural products. The first approach published by Tong and co-workers utilised a simultaneous Claisen rearrangement-$\sigma$-QM formation reaction sequence under thermal conditions to first form $\sigma$-QM 1.67. This was followed by [4+2] cycloaddition of 1.67 with (−)-sabinene (1.68) to afford 1.69 in 79\% yield (Scheme 1.13, part a).\textsuperscript{50} Cycloadduct 1.69 was subsequently converted into spiroooliganones A and B (1.70 and 1.71) in six steps. Yu and co-workers make use of a slightly different $\sigma$-QM precursor 1.73, which was heated in the presence of (−)-sabinene (1.68) to afford cycloadduct 1.74 in 82\% yield (Scheme 1.13, part b).\textsuperscript{50} 1.74 was then transformed into the natural products in three steps via a method analogous to that reported by Tong to yield spiroooliganones A and B (1.70 and 1.71).
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Scheme 1.13: a) Tong's synthesis of spirooliganones A and B (1.70 and 1.71) (2014); b) Yu's synthesis of spirooliganones A and B (1.70 and 1.71) (2015)

Vitamins E and K are arguably the most well-known and studied antioxidants, mainly attributed to their ability to be oxidised into an o-QM, which would then subsequently undergo dimerisation and trimerisation reactions. This field of o-QM chemistry has been extensively studied in the literature due to its biological importance. More recently, Lei and co-workers have applied this methodology towards their biomimetic synthesis of (±)-schefflone (1.78), a trimeric natural product. Espinatol (1.75) was oxidised with Ag₂O to afford o-QM 1.76 in situ, which immediately underwent two successive [4+2] cycloadditions with two other molecules of o-QM 1.76 to afford (±)-schefflone (1.78) in 72% yield, as well as mono adduct 1.77 in 8% yield (Scheme 1.14). Furthermore, Lei and co-workers have also adopted this strategy towards the synthesis of several other previously isolated tocopherol trimers.

Scheme 1.14: Lei’s biomimetic synthesis of (±)-schefflone (1.78)
1.4.5 Oxa-6π Electrocyclisation of ortho-Quinone Methides

o-QMs have recently been observed to readily undergo oxa-6π electrocyclisation reactions. This pathway is believed to be key in the biosynthesis of several chromene natural products. A prime literature example of this was reported by George and co-workers in their synthesis of hyperguinone B (1.81) via the oxa-6π electrocyclisation of o-QM 1.80. In this instance, the o-QM 1.80 was generated via oxidation of 1.79 with PhI(OAc)_2 and TEMPO affording the natural product in 73% yield (Scheme 1.15).

Scheme 1.15: George’s synthesis of hyperguinone B (1.81)

In 2013, Hsung et al. reported a biosynthetically inspired synthesis of clusiacyclols A and B (1.87 and 1.88), iso-eriobrucinols A and B (1.89 and 1.90) and eriobrucinol (1.91), which employed an oxa-6π electrocyclisation of an o-QM as a vital step in synthesis of the natural products. This divergent strategy introduces the cyclol backbone 1.86 by first completing an electrophilic aromatic substitution of phloroglucinol (1.12) with citral (1.82) to afford benzyl alcohol 1.83. Benzyl alcohol 1.83 would then undergo a dehydration reaction to form o-QM 1.84, which is then primed to undergo an oxa-6π electrocyclisation to produce chromene 1.85. Chromene 1.85 then underwent an acid catalysed [2+2] cycloaddition between the chromene functionality and the prenol sidechain to yield the cyclol backbone 1.86 within the same pot (Scheme 1.16). Finally, Friedel-Crafts reaction with various acyl compounds then afforded natural products clusiacyclols A and B (1.87 and 1.88), iso-eriobrucinols A and B (1.89 and 1.90) and eriobrucinol (1.91).
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Scheme 1.16: Hsung’s biomimetic synthesis of clusiacyclols A and B (1.87 and 1.88), iso-eriobrucinols A and B (1.89 and 1.90) and eriobrucinol (1.91)

The Trauner group are heavyweights in the field of $o$-QM chemistry, which was emphasised by their use of oxa-6π electrocyclisations in their biomimetic synthesis of mollugin (1.94) and microphyllaquinone (1.97) in 2005. Trauner utilised a base initiated tautomerisation method for generating $o$-QMs 1.93 and 1.96, which underwent oxa-6π electrocyclisations to afford the natural products mollugin (1.94) and microphyllaquinone (1.97) in 81% and 70% yield respectively (Scheme 1.17).
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Scheme 1.17: Trauner’s biomimetic synthesis of mollugin (1.94) and microphyllaquinone (1.97)

1.4.6 Michael Reactions of ortho-Quinone Methides

Michael reactions of \( o \)-QMs represent an underdeveloped field, with relatively few literature examples of biomimetic Michael reactions being involved in the synthesis of natural products. The cause of this deficiency is likely due to the inherent reactivity of these species, where the conditions required to generate enolates (usually with strong bases) are incompatible with these highly reactive intermediates. These bases often partake in a competing reaction, generally sequestering the \( o \)-QM from the reaction mixture.\(^{40}\)

Advances in this field were first reported by Pettus and co-workers in their synthesis of rishirilide B (1.101), where they expanded the repertoire of \( o \)-QM reactions. \( o \)-QM 1.99 was generated from 1.98 under basic conditions using an excess of isobutyrylmagnesium bromide and subsequently trapped with the Grignard \textit{in situ} through a Michael reaction to furnish 1.100 (Scheme 1.18).\(^{59}\) This early intermediate was then transformed into the natural product rishirilide B (1.101) in 13 steps. Since Pettus’ approach utilised the Michael reaction on an early intermediate in the synthetic pathway, this route is not a true representation of a biomimetic Michael reaction of an \( o \)-QM.
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Scheme 1.18: Pettus’s synthesis of rishirilide B (1.101)

1.4.7 [1,2]-Rearrangements and *ortho*-Quinone Methides

Recent advances in *o*-QM chemistry have begun to incorporate [1,2]-rearrangements into its ever-expanding repertoire. An important example of the possibility [1,2]-rearrangements could be utilised with *o*-QMs was first reported in the proposed biosynthesis of the natural product (+)-liphagal (1.106), isolated by Andersen and later synthesised by George.\(^{60,61}\) Andersen proposed that (+)-liphagal (1.106) could arise in nature via epoxidation of the known natural product siphonodictyal B (1.102) (Scheme 1.19).\(^{62-64}\) Andersen proposed that the epoxide ring opening of 1.103 and ring expansion to occur via a carbocation intermediate, whereas George proposed this could alternatively take place via *o*-QM 1.104. Ring expansion of 1.104 from the most electron rich position followed by benzofuran formation would furnish the natural product liphagal (1.106) via ketone 1.105.

Scheme 1.19: Proposed biosynthesis of liphagal (1.106)
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The proposed biosynthesis was eventually realised by George and co-workers in their recent article outlining the structural reassignment of siphonodictyal B (1.102) to its C-8 epimer 1.107 and then its conversion into (+)-liphagal (1.106). The revised structure of siphonodictyal B (1.107) was treated with mCPBA and then in the same-pot acidified with TFA to initiate the epoxidation, o-QM formation, ring expansion and benzofuran formation cascade reaction to afford (+)-liphagal (1.106) in 42% yield (Scheme 1.20).

\[
\text{HO}_2\text{CHO} \quad \text{HO}_2\text{CHO} \quad \text{HO}_2\text{CHO}
\]

\[
1.102: \text{siphonodictyal B (proposed structure)} \quad 1.107: (-)-siphonodictyal B (revised structure) \quad 1.106: (+)-liphagal
\]

Scheme 1.20: George’s biomimetic synthesis of (+)-liphagal (1.106)

1.4.8 Outlook

This short literature review has outlined the pivotal role that o-QMs play in the biosynthesis of natural products, clearly demonstrating the versatility of these intermediates. The number of examples of o-QMs being used in biomimetic natural product synthesis is ever increasing, with new natural products potentially biosynthesised via these reactive intermediates isolated every day. This repertoire holds these intermediates in good stead, and forms a strong basis for further development in the future.

1.5 Project Aims

This thesis will focus on the biomimetic synthesis of several complex natural products. Chapter 2 will explore the biomimetic synthesis of penilactones A and B (2.7 and 2.8) via a Michael reaction of tetronic acids 2.10 and 2.11 with common o-QM 2.9 (Scheme 1.21). This novel pathway would feature an unprecedented biomimetic strategy towards the natural products, in which the key step involves the Michael reaction of a tetronic acid with an o-QM.
In chapter 3, the biomimetic synthesis of peniphenones A-D (3.1-3.4) will be described, with an aim to further expand the methodology previously developed in chapter 2. Peniphenone A (3.1) was targeted via a [4+2] cycloaddition of o-QM 2.9 with exocyclic enol ether 3.5 (Scheme 1.22), while the synthesis of peniphenones B-D (3.2-3.3) will harness the same o-QM 2.9 required for peniphenone A (3.1). A Michael reaction between this common o-QM intermediate with various nucleophilic coupling partners (3.6, 3.7 and 2.10) would then yield the corresponding natural products.

**Scheme 1.22**: Proposed biomimetic synthesis of peniphenones A-D (3.1-3.4)
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The goal of chapter 4 is to further build upon the concepts developed in chapters 2 and 3 and direct this towards the biomimetic synthesis of virgatolide B (4.2).\textsuperscript{68} Virgatolide B (4.2) will be targeted via a [4+2] cycloaddition of \(o\)-QM \textsuperscript{4.9} with exocyclic enol ether \textsuperscript{4.10} (Scheme 1.23).

![Scheme 1.23: Proposed biomimetic synthesis of (+)-virgatolide B (4.2)](image)

Finally, the objective of chapter 5 is to complete a synthesis of epicolactone (5.1) via a biomimetic cascade reaction.\textsuperscript{69,70} We propose that epicolactone (5.1) may arise from a heterodimerisation of \textsuperscript{5.9} and \textsuperscript{5.10} (oxidised forms of epicoccine (5.3) and epicoccone B (5.4)) via a [5+2] cycloaddition (Scheme 1.24). A subsequent hydrolysis-decarboxylation-lactonisation-vinylogous aldol cascade would afford epicolactone (5.1).

![Scheme 1.24: Proposed biomimetic synthesis of epicolactone (5.1) from epicoccine (5.3) and epicoccone B (5.4)](image)
1.6 References

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Chapter Two

The Biomimetic Total Synthesis of *ent*-Penilactone A and Penilactone B

2.1 Tetronic Acids

Tetronic acids are a common structural motif that are present in a variety of natural products. Tetronic acids are defined by having a 4-hydroxy-2(5H)-furanone ring and typically are functionalized at C-3 and C-5 or the C-4 hydroxy group (Figure 2.1). While ascorbic acid (2.2) is arguably the most well known tetronic acid, many other functionalized tetronic acids (2.3-2.6) have been isolated and have been of interest over the past 100 years for their varying structures and biological activities.2–7 This chapter focuses on two tetronic acid (2.1) derived fungal metabolites, penilactones A and B (2.7 and 2.8).

![](2.1: tetronic acid)  
![](2.2: ascorbic acid)  
![](2.3: papyracilic acid)  

Figure 2.1: Structure of 4-hydroxy-2(5H)-furanone core of tetronic acids

2.2 Isolation of Penilactones A and B

Penilactones A and B (2.7 and 2.8) are two tetracyclic polyketide natural products that were isolated in 2012 by Li and co-workers from the fungus *Penicillium crustosum* PRB-2 that was isolated from an Antarctic deep sea sediment (Figure 2.2).8 Microorganisms that live in extreme environments are often rich sources of complex and bioactive molecules. Penilactones A and B (2.7 and 2.8) are a testament to this, with the producing fungi living in a high pressure, low temperature and minimal light environment. In their isolation work, Li and co-workers cultured the fungus and the whole cell broth was then extracted with ethyl acetate and subjected to purification by flash chromatography and HPLC to give penilactones A and B (2.7 and 2.8).
It is of note that the penilactones A and B (2.7 and 2.8) have opposite absolute configurations, which implies that these natural products may be formed in nature under non-enzymatic conditions. The relative configuration of penilactone A (2.7) was determined through NOESY studies and the absolute configuration identified through X-ray crystallography, with a resultant Flack parameter of 0.03 providing a configuration of $3S, 4R, 5R$. The absolute configuration of penilactone B (2.8) was determined via comparison of its CD spectra with that of penilactone A, and as the spectrum was observed to be the inverse it was concluded that the configuration of penilactone B (2.8) was $3R, 4S, 5S$. The natural products were tested for their cytotoxicity against five different human tumour cell lines; although unfortunately neither of the penilactones exhibited inhibitory activity.

2.3 Proposed Biosynthesis of Penilactones A and B

Li and co-workers proposed a biosynthesis of penilactones A and B (2.7 and 2.8) that involved the unification of two molecules of $\alpha$-QM (2.9) with one molecule of (S)-5-methyltetronic acid (2.10) or (R)-5-carboxymethyltetronic acid (2.11) via a double Michael reaction followed by hemiacetal formation (Scheme 2.1). They proposed that the tetronic acids could be synthesised in nature from acetyl-coenzyme A and the $\alpha$-QM (2.9) could be accessed in the organism from clavatol (2.12), which is an aromatic polyketide previously isolated from *Aspergillus clavatus* in 1944. Tetronic acids 2.10 and 2.11 are common fungal metabolites and derivatives of 2.10 and 2.11 were also isolated alongside clavatol (2.12) in a related species of fungus *Penicillium griseoroseum*.12
Scheme 2.1: Proposed biosynthesis of penilactones A and B (2.7 and 2.8) by Li and co-workers

The proposed penilactone biosynthesis mechanism involves the oxidation of clavatol (2.12) in the organism to give the o-QM 2.9, which can undergo the first Michael reaction with 5-methyltetronic acid (2.10) to give mono-adduct 2.13 (Scheme 2.2). Compound 2.13 is a natural product, that was later isolated from a different organism (*Penicillium dipodomyicola*13) and is now known as peniphenone D (3.4) (see Chapter 3). Peniphenone D (3.4) can then undergo a second Michael reaction with another molecule of the o-QM 2.9 to give 2.14. While compound 2.14 has four available phenols that could potentially cyclise onto the C-4 ketone to give the hemiacetal, only one of these phenols was observed to undergo the hemiacetal formation in the natural organism, resulting in the formation of penilactone A (2.7). We believe this is attributed to two of the phenols C-2’ and C-2” being deactivated through hydrogen bonding to their adjacent aryl ketones, and the C-5 substituent directing C-4’ to preferentially cyclise over the C-4” position. A similar hemiacetal formation is also proposed to account for the biosynthesis of penilactone B (2.8), with the C-5 stereocentre in tetronic acid 2.11 dictating the absolute configuration of the natural product, which is opposite from that of penilactone A (2.7).
Scheme 2.2: Proposed biosynthesis mechanism of penilactone A (2.7)

The above proposed cascade reaction where two very simple starting materials could be employed to afford a complex natural product makes penilactones A and B (2.7 and 2.8) attractive targets for biomimetic synthesis.

2.4 Biomimetic Synthesis of ent-Penilactone A and Penilactone B

In order to gain insight into the biosynthesis of these natural products we planned to conduct a short biomimetic synthesis of the enantiomer of penilactone A (ent-2.7) and penilactone B (2.8). The synthesis of both the key precursors, namely o-QM 2.9 and the two chiral tetronic acids 2.10 and 2.11 were our top priority. Our biggest challenge was selecting an appropriate protocol for the generation of the desired o-QM 2.9. A truly biomimetic oxidative o-QM generation (such as the generation of 2.9 from clavatol (2.12)) is often very challenging and there are few natural products that have been successfully synthesised via this method. As a result, we opted for a more reliable series of o-QM precursors that could generate the o-QM under non-oxidative conditions, namely heat, acid or base (Figure 2.3). 2.15 and 2.16 were selected based on their literature precedence for o-QM formation, with each being able to generate the desired o-QM 2.9 under a variety of conditions.
2.4.1 Synthesis of o-QM Precursors 2.15 and 2.16

According to our retrosynthesis, each of the o-QM precursors (2.15 and 2.16) could be synthesised from 2-acetyl-4-methylresorcinol (2.17) via an addition of formaldehyde to the electron rich aromatic ring at C-6. 2-Acetyl-4-methylresorcinol (2.17) could be synthesised from 4-methylresorcinol (2.18) via a Friedel-Crafts acylation to install the acetyl group at the C-2 position (Scheme 2.3).

Scheme 2.3: Retrosynthetic analysis of key o-QM precursors 2.15-2.16

The synthesis of these key o-QM precursors was attempted, firstly by the Friedel-Crafts acylation of the commercially available starting material 4-methylresorcinol (2.18). Initial conditions of Ac₂O and BF₃·Et₂O failed to yield the desired product; instead the diester was isolated as the sole product. Successful acylation of 4-methylresorcinol (2.18) was achieved using modified conditions previously established by Gelb and co-workers.¹⁸ Treatment of 4-methylresorcinol (2.18) with BF₃·Et₂O and AcOH at 90 °C afforded 2.17 in 71% yield (Scheme 2.4).

Scheme 2.4: Friedel-Crafts acylation of 4-methylresorcinol

The success of this reaction was evident in the loss of one of the aromatic protons in the ¹H NMR spectrum and now affording two singlet aromatic resonances (δH 7.62 and 6.29),
and furthermore the observation of a carbonyl group in the $^{13}$C NMR spectrum ($\delta_C$ 203.0). The reaction immediately turned dark red upon the addition of 4-methylresorcinol (2.18) to the BF$_3$-Et$_2$O solution. Unfortunately, under the above reaction conditions the reaction failed to achieve completion, with a significant amount of starting material observed. Removal of the starting material proved to be a difficult endeavour, however under careful chromatographic purification the desired product was able to be obtained as a single compound.

An inspection of the literature reveals several potential pathways for installing the required o-QM functionality. The first analogue targeted was the benzylic alcohol 2.15 as this was the simplest to synthesise with a significant amount of literature precedence. The literature procedures employed the use of KOH/CaCl$_2$ with formaldehyde to afford the desired benzylic alcohol functionality of 2.15. Initial conditions were trialled, with KOH/CaCl$_2$ (0.4:0.4 molar ratio compared to the starting material) in MeOH. The progress of the reaction was monitored by TLC. A further equivalent of both KOH and CaCl$_2$ were added when no change to the TLC was observed after 16 hours (Scheme 2.5). The addition of excess KOH and CaCl$_2$ immediately revealed a less polar spot, which upon isolation and NMR elucidation, was determined to be diclavatol (2.19). H NMR revealed a signal at 3.92 ppm, which was too low for that of a benzylic alcohol. In addition, the integration of this resonance compared to that of the aryl methyl and acetyl protons was 1:3:3. Diclavatol (2.19) had been previously isolated from a related species of *Penicillium* fungus, and the formation of this product in our reaction demonstrated the feasibility of generating the desired o-QM (2.9) under these reaction conditions.

It became apparent that optimisation of the reaction conditions was required in order to obtain 2.15. Furthermore, the formation of the undesired compound diclavatol had to be minimised, if possible. Moreover, the $R_t$ value of the product is identical to that of the starting material, giving the appearance the reaction had failed to proceed. After several trials, it was found that the desired product 2.15 could be isolated in 89% yield if the reaction was performed under careful equivalency control of KOH/CaCl$_2$ (1:1 ratio, 0.4 molar respectively compared to the starting material) (Scheme 2.5).
We envisaged that $o$-QM 2.9 was first generated from 2.15 in situ under basic conditions. Subsequently, $o$-QM 2.9 could then undergo a Michael reaction with one molecule of 2-acetyl-4-methylresorcinol (2.17) to produce diclavatol (2.19) (Scheme 2.6).

**Scheme 2.6: Mechanism of the formation of diclavatol (2.19)**

Due to the propensity of $o$-QM precursor 2.15 to be converted into diclavatol (2.19) with an excess of base, we decided to focus our attention on $o$-QM precursor 2.16. We believed that formation of diclavatol (2.19) could be minimised under the conditions devised for the formation of $o$-QM precursor 2.16 and its subsequent reactions. There exists an extensive body of literature on reactions of electronic rich aromatics with formaldehyde under acid conditions to afford the benzyl alcohol functionality of 2.15.\(^{21, 22}\) We therefore devised a synthesis of 2.16 via acid catalysed addition of formaldehyde to form 2.15, which under the acidic conditions would subsequently undergo an in situ formation of $o$-QM 2.9, followed by a trapping with acetic acid to achieve our desired $o$-QM precursor 2.16. We modified the conditions reported by Baldwin and co-workers in their attempted one-pot formylation, $o$-QM formation and [4+2] cycloaddition synthesis of guajadial and psidial A with formaldehyde, AcOH and NaOAc.\(^{23}\) The absence of a dienophile in our case, afforded the desired acetoxy $o$-QM precursor 2.16 in 75% yield, along with a small quantity of diclavatol (2.19) (Scheme 2.7).
The reaction conditions yielded the desired acetoxy $o$-QM precursor $2.16$ in 75% yield along with 12% of diclavatol ($2.19$), the majority of which had precipitated out of the reaction upon cooling to room temperature, and the remainder could be triturated out after the work up. Due to the unstable nature of $2.16$ under silica gel chromatography, the crude product was carried through to the next step without purification. This pathway allowed access to gram scale quantities of $o$-QM precursor $2.16$, thus our attention now turned toward the synthesis of the two chiral tetronic acids $2.10$ and $2.11$.

### 2.4.2 Synthesis of (S)-5-Methyltetronic Acid

A synthesis of 5-methyltetronic acid ($2.10$) had previously been reported Baati and co-workers in a two step procedure starting from (S)-ethyl lactate ($2.20$). The conditions reported by Baati et al. were followed by first converting (S)-ethyl lactate ($2.20$) into its acetate ester $2.21$ under standard conditions ($\text{Ac}_2\text{O}$ and pyridine). Then, acetate ester $2.21$ was converted into 5-methyltetronic acid ($2.10$) with LiHMDS in THF at $-78 \degree C$ via an intramolecular Claisen condensation. 5-Methyltetronic acid ($2.10$) was isolated in 75% yield over the two steps as a 4:1 mixture of keto and enol tautomers and was readily purified by recrystallization from petroleum ether/EtOAc to give a white solid (Scheme 2.8). Notably, a synthesis of (+)-penilactone A ($2.7$) would require ($R$)-ethyl lactate. However, due to the lowered cost and greater availability of (S)-ethyl lactate ($2.20$) we decided to target the enantiomer of penilactone A ($\text{ent-}2.7$). Presumably, the desired biomimetic reaction would be synonymous with both enantiomers of tetronic acid $2.10$.

Scheme 2.7: Synthesis of $o$-QM precursor $2.16$

Scheme 2.8: Synthesis of (S)-5-methyltetronic acid ($2.10$)
2.4.3 Synthesis of Penilactone A via a Three-Component, One-Pot Cascade Reaction

Our primary objective was to complete the synthesis of penilactones A and B (2.7 and 2.8) utilising a biomimetic cascade reaction that is proposed to occur in the natural organism. With our two key precursors synthesised, we were now primed to attempt the key double Michael reaction followed by ketalisation reaction and investigate the predisposed reactivity of the system. Initial investigations employing o-QM precursor 2.15 failed to yield penilactone A (2.7) (Scheme 2.9).

As a result of the above observation, our attention was focused on acetoxy o-QM precursor 2.16. Acetoxy o-QM precursors such as 2.16 have largely been utilised to generate o-QMs under thermal conditions, hence this was determined to be a suitable starting point for trialling the biomimetic cascade reaction. Thus, acetoxy o-QM precursor 2.16 and (S)-5-methyltetronic acid (2.10) were dissolved in toluene and heated at 110 °C in a sealed tube. By TLC we observed the consumption of our two starting materials along with formation of a new product. Isolation of this compound by flash chromatography yielded our natural product ent-penilactone A (ent-2.7) (Scheme 2.10). Notably, the use of a sealed tube was pivotal; if the reaction was conducted under normal reflux conditions the yield was severely diminished. The spectroscopic data observed matched that reported in the literature by Li et al. (section 2.8.2). Importantly, the optical rotation of ent-2.7, \([\alpha]_D^{25} = -37.8\) (c 0.98, MeOH), showed good correlation with the literature value for 2.7, \([\alpha]_D^{25} = +45.1\) (c 0.1, MeOH), thus confirming the absolute stereochemical assignment of Li et al.
The above reaction proceeds in the excellent yield of 93%, and demonstrates the power of cascade reactions and o-QMs to generate molecular complexity very efficiently. Starting from two relatively simple starting materials, we ended up with a structurally complex natural product in one step via a three-component one-pot cascade reaction. In this reaction, we are forming two carbon-carbon bonds, one carbon-oxygen bond, one ring and two new stereocentres. This procedure has allowed access to ent-penilactone A (ent-2.7) in just three-steps from (S)-ethyl lactate (2.10) in 70% yield.

### 2.4.4 NMR Spectra of Penilactone A in Varying Deuterated Solvents

Penilactone A and B (2.7 and 2.8) were reportedly isolated as single diastereoisomers, however we observed that this was only the case when the NMR of the compounds were recorded in DMSO-d$_6$.\textsuperscript{8} When the compounds were characterised in any other deuterated NMR solvent, we found that the natural product no longer appeared as a single compound (Table 2.1). We propose that the reversible nature of the ketalisation step affords different proportions of products 2.7 and 2.22. Assignment of the major and minor diastereoisomers was extremely difficult due to the similarity of the two aromatic regions of the molecule. The NOESY data suggests that the major compound was ent-penilactone A (2.7) for acetone-d$_6$, C$_6$D$_6$ and CDCl$_3$. However, definitive evidence of this was impossible via 2D NMR experiments. Furthermore, as observed by Li et al., DMSO-d$_6$ was the only solvent where the natural product was observed to be a single diastereoisomer (2.7) (Figure 2.4). It is of note that in the solid state the equilibrium lies solely as penilactone A (2.7), as evidenced by Li et al. with the observed crystal structure.
Table 2.1: Diastereomeric ratio of penilactone A (2.7) in varying NMR Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Diastereomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO-d$_6$</td>
<td>1:0</td>
</tr>
<tr>
<td>Acetone-d$_6$</td>
<td>3:2</td>
</tr>
<tr>
<td>C$_6$D$_6$</td>
<td>9:1</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>9:1</td>
</tr>
</tbody>
</table>

Figure 2.4: Comparison of the NMR spectra of ent-penilactone A (ent-2.7) in different solvents
2.4.5 Synthesis of Penilactone A via a Five-Component, One-Pot Cascade Reaction

Penilactone A (2.7) was previously synthesised via a three-component one-pot cascade reaction, hence we wanted to investigate whether we could further push the boundaries of this reaction a little further. We wanted to attempt to incorporate the addition of formaldehyde to our electron rich aromatic ring into our cascade reaction. The goal was to simplify the previous route into a five-component, one-pot synthesis of a natural product. The reaction was initially trialled by combining 2-acetyl-4-methylresorcinol (2.17), (S)-5-methyltetronic acid (2.10) and formaldehyde in AcOH at the start of the reaction. However, we found that the reaction failed to yield the desired product, likely due to the competing nucleophilicity of the tetronic acid sequestering the available formaldehyde. We therefore decided to delay the addition of the (S)-5-methyltetronic acid (2.10). Hence, (S)-5-methyltetronic acid (2.10) was added after the mixture was stirred at 90 °C for 16 hours, which we deemed an ample amount of time for o-QM precursor 2.9 to form. The reaction mixture was then stirred at 110 °C for a further 24 hours and after careful column chromatography and recrystallisation we were able to isolate pure ent-penilactone A (ent-2.7) (Scheme 2.11).

\[
\text{Scheme 2.11: Five-component one-pot synthesis of ent-penilactone A (ent-2.7)}
\]

Ent-penilactone A (ent-2.7) was isolated in 45% yield, which is an impressive yield considering the complexity of the reaction. In this five-component, one pot reaction four carbon-carbon bonds, one carbon-oxygen bond, one ring and two stereocentres are formed, all in the one step. The synthesis of ent-penilactone A (ent-2.7) was achieved in 34% yield over three steps from (S)-ethyl lactate (2.20) (longest linear sequence). The most abundant by-product of this reaction was diclavatol (2.19), which made the purification of the natural product quite difficult. The presence of diclavatol (2.19) could account for the lower yield observed as the formation of diclavatol would irreversibly sequester the o-QM 2.9.
2.4.6 Two-step Synthesis of (±)-Penilactone

Having completed a three-component one-pot and a five-component one-pot synthesis of ent-penilactone A (ent-2.17) in a longest linear sequence of three steps, we next wanted to synthesise penilactone A (2.7) in two steps. Essential to this was the synthesis of (±)-5-methyltetronic acid (±-2.10) in one step, rather than the two step procedure previously completed. An inspection of the literature afforded a procedure by Garcia-Talledo and co-workers, who synthesised (±)-2.10 via a one-pot synthesis from methyl propiolate (2.23) and acetaldehyde (Scheme 2.12).\(^{25}\) A domino process was employed to first react methyl propiolate (2.23) with two molecules of acetaldehyde, and then subsequently heat the reaction mixture with conc. HCl to hydrolyse acetal 2.24 and cyclise the product to the desired (±)-5-methyltetronic acid (±-2.10).

![Figure 2.12: Synthesis of (±)-5-methyltetronic acid (±-2.10)](image)

(±)-Penilactone A (±-2.7) was then synthesised according to the previously established five-component one-pot procedure in 38% yield (Scheme 2.13). The synthesis of a complex natural product in two steps from very simple starting materials is noteworthy. This achievement demonstrates the power of biomimetic synthesis to generate molecular complexity in the most efficient way possible.

![Scheme 2.13: Five-component one-pot synthesis of (±)-penilactone A (±-2.7)](image)

Having demonstrated the feasibility of our biomimetic cascade reaction route with the synthesis of ent-penilactone A (ent-2.7), we proceeded to extend the above methodology
towards the synthesis of penilactone B (2.8). To achieve this, we directed our attention toward the synthesis of the desired tetronic acid, (S)-5-carboxymethyltetronic acid (2.11).

2.4.7 Synthesis of (S)-5-Carboxymethyltetronic Acid

(S)-5-carboxymethyltetronic acid (2.11) was synthesised following an adapted procedure by Schobert and co-workers (Scheme 2.14). Schobert and co-workers reacted (S)-dimethyl malate (2.25) with triphenylphosphoralideneketene (2.26) to form the tetronic acid backbone 2.30 in one step. The mechanism of this reaction proceeds firstly via nucleophilic attack of the hydroxyl group on the carbonyl of ketene 2.26 to afford 2.27, tautomerisation to 2.28 followed by a Wittig reaction with the adjacent methyl ester yielded 2.30 via 2.29.

![Scheme 2.14: Schobert and co-worker’s synthesis of tetronic acid 2.30](image)

A similar procedure was employed, substituting the methoxy protecting group strategy for a benzyl protecting group strategy. The removal of methyl ether protecting groups are often extremely difficult, therefore we decided a benzyl ether approach would likely be more successful. (S)-Malic acid (2.31) was converted into dibenzyl ester 2.32 under standard conditions of benzyl alcohol, p-toluenesulfonic acid and heated at reflux in toluene with a Dean-Stark apparatus. Dibenzyl ester 2.32 was then subjected to the conditions by Schobert et al., which employed triphenylphosphoralideneketene (2.26) and reflux in toluene. These conditions gave dibenzyl tetronic acid 2.33 in 52% yield (Scheme 2.15). The lower yield of this reaction could be due to some steric hindrance of the benzyl groups preventing the Wittig from proceeding. The reaction failed to go to completion, with 28% of the starting material being isolated from the reaction mixture.
The benzyl protecting groups were cleaved under standard hydrogenolysis conditions of hydrogen gas and 10% palladium on carbon (Scheme 2.16). This gave (S)-5-carboxymethyltetronic acid (2.11) in near quantitative yield. This reaction did not need to be purified, as hydrogenolysis of the benzyl ethers generates toluene as the sole by-product, which can be evaporated under reduced pressure. With the synthesis of this compound we were primed to complete a synthesis of penilactone B (2.8), using our previously developed three-component one-pot cascade conditions.

Scheme 2.16: Synthesis of (S)-5-carboxymethyltetronic acid (2.11) via hydrogenolysis

2.4.8 Synthesis of Penilactone B via a Three-Component, One-Pot Cascade Reaction

Penilactone B (2.8) was synthesised via a three-component one-pot cascade reaction of o-QM 2.9 and (S)-5-carboxymethyltetronic acid (2.11) (Scheme 2.17). The reaction was completed in dioxane due to the insolubility of polar tetronic acid 2.11 in toluene. Penilactone B (2.8) was isolated from the reaction mixture in 86% yield. The NMR spectra of the purified compound matched that perfectly of natural product (section 2.8.2), featuring two sets of aromatic signals and the presence of the carboxymethyl group from the tetronic acid. The optical rotation of 2.8, \([\alpha]_{D}^{25} = +27.1\) (c 1.0, MeOH), showed good correlation with the literature value for 2.8, \([\alpha]_{D}^{25} = +29.8\) (c 0.1, MeOH), obtained by Li et al., thereby confirming the absolute configuration of the natural product.
Scheme 2.17: Synthesis of penilactone B (2.8) via a three-component one-pot cascade reaction

Penilactone B (2.8) exhibited the same phenomenon in different solvents as penilactone A (2.7), exhibiting varying ratios of diastereoisomers based on which phenol completes the ketalisation step. Interestingly, like penilactone A (2.7), penilactone B (2.8) was also observed to be a single compound when the NMR was performed in DMSO-d_6.

2.5 Summary

The total synthesis of two complex natural products: ent-penilactone A (ent-2.7) and penilactone B (2.8) has been completed efficiently using a biomimetic approach. ent-Penilactone A (ent-2.7) was synthesised via two cascade approaches, primarily utilising a three-component one-pot synthesis using a synthesised o-QM precursor 2.16 and secondly via a five-component one-pot synthesis via forming the desired o-QM precursor 2.16 in situ. Both of these approaches yielded ent-penilactone A (ent-2.7) in the good yield of 75% and 34% respectively in three-steps from (S)-ethyl lactate (2.20). The step economy was improved further in our two-step synthesis of (+)-penilactone A (±-2.7), which proceeded in 26% overall yield from methyl propiolate (2.23) (Scheme 2.12). Penilactone B (2.8) was synthesised in 37% overall yield over 4 steps from (S)-malic acid (2.31) (Scheme 2.15).

The reported approach to synthesise the penilactones A and B (2.7 and 2.8) demonstrates the potency of biomimetic synthesis. The efficacy of the synthesis suggests that this o-QM double Michael reaction cascade process may be how these compounds are synthesised in nature. This success primes us to further adapt this methodology to target related families of natural products, and this will be reported in proceeding chapters in our attempts to synthesise peniphenones A-D (3.1-3.4) and virgatolides A-C (4.1-4.3).
2.6 Supporting Information

2.6.1 General Experimental

All commercially obtained chemicals were used without further purification. Solvents stated as dry, were either distilled under nitrogen and used immediately, or distilled under an atmosphere of nitrogen and stored over 4Å molecular sieves. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F\textsubscript{254} aluminium sheets and visualised under a UV lamp or with ceric ammonium molybdate (CAM), vanillin or potassium permanganate staining followed by heating. All $R_f$ values are rounded to the nearest 0.05. Davisil 43-60 micron chromatographic silica media was used for flash chromatography. $^1$H NMR spectra were recorded on a Varian Inova-600 spectrometer ($^1$H at 600 MHz, $^{13}$C at 150 MHz) in CDCl\textsubscript{3} as the solvent unless otherwise specified. $^1$H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and $^{13}$C NMR are reported in ppm relative to TMS (δ 0.0). All J values were quoted to the nearest 0.1 Hz. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sext) sextet and (m) multiplet. IR spectra were recorded on a Perkin-Elmer Fourier-Transform Infrared (FT-IR) spectrometer on a nickel-selenide crystal as neat compounds. High resolution mass spectra were obtained on a LTQ Orbitrap XL ETD (Thermo Fisher Scientific) mass spectrometer by Adelaide Proteomics Centre. Melting points were recorded on a Reichert electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on a P0A1 AR21 polarimeter for the compounds in CHCl\textsubscript{3}, and on an Atago AP-100 automatic polarimeter for the compounds in MeOH.
2.6.2 Experimental Procedures

4-Methyl-6-acetylresorcinol 2.17

To a solution of 4-methylresorcinol (2.18) (1.00 g, 8.10 mmol) in BF$_3$·Et$_2$O (10 mL) was added AcOH (0.92 mL, 16.1 mmol). The reaction mixture was heated to 90 °C and stirred for 16 hours. The reaction was quenched by the addition of H$_2$O (100 ml), then neutralised with sat. Na$_2$CO$_3$ and diluted with Et$_2$O (200 mL). The organic layer was separated, and the aqueous layer extracted with Et$_2$O (2 x 100 mL). The combined organics were dried over MgSO$_4$, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 10:1 - 4:1 gradient elution) to give 2.17 (943 mg, 71%) as a pale yellow solid.

R$_f$ = 0.50 (petroleum ether/EtOAc, 2:1)

Mp: 145-148 °C

IR (neat): 3288, 2967, 1630, 1587, 1497, 1368, 1322, 1270, 1056, 806 cm$^{-1}$

$^1$H NMR (600 MHz, DMSO-d$_6$) δ 12.47 (s, 1H), 7.62 (d, $J$ = 0.6 Hz, 1H), 6.29 (s, 1H), 2.51 (s, 3H), 2.06 (s, 3H).

$^{13}$C NMR (150 MHz, DMSO-d$_6$) δ 203.0, 163.6, 162.9, 133.7, 116.8, 112.9, 102.1, 26.8, 15.6.

HRMS (C$_9$H$_{10}$O$_3$, ESI): calculated [M-H]$^-$ 165.0557, found 165.0544
2-Methylenehydroxy-4-methyl-6-acetylresorcinol 2.15

To a solution of 4-methyl-6-acetylresorcinol 2.17 (500 mg, 3.01 mmol), KOH (135 mg, 2.41 mmol) and CaCl₂ (133 mg, 1.20 mmol) at 0 °C was added formaldehyde solution (37% in H₂O, 0.27 mL, 3.6 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 16 hours. The reaction was quenched by the addition of 1M HCl (10 mL) and the diluted with EtOAc (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated in vacuo to give 2-methylenehydroxy-4-methyl-6-acetylresorcinol 2.15 (526 mg, 89%) as an orange gum. This product was unable to be purified by column chromatography due to its instability on silica gel.

\[ R_f = 0.45 \text{ (petroleum ether/EtOAc, 1:1)} \]

**IR (neat):** 3300, 2970, 1624, 1593, 1486, 1369, 1330, 1238, 1187, 1090 cm⁻¹

**¹H NMR (600 MHz, CDCl₃)** δ 12.92 (s, 1H), 7.41 (s, 1H), 5.08 (s, 2H), 2.54 (s, 3H), 2.17 (s, 3H).

**¹³C NMR (150 MHz, CDCl₃)** δ 202.8, 162.3, 159.7, 131.7, 117.1, 112.6, 110.2, 58.8, 26.2, 15.3.

**HRMS (C₁₀H₉O₃, ESI):** calculated for o-quinone methide [M-H₂O⁺]⁺ 177.0557, found 177.0544
2-Methyleneacetoxy-4-methyl-6-acetylresorcinol 2.16

To a solution of 4-Methyl-6-acetylresorcinol 2.17 (795 mg, 4.80 mmol) and NaOAc (65 mg, 0.48 mmol) in AcOH (30 mL) was added formaldehyde solution (37 % in H₂O, 1.06 mL, 14.4 mmol). The reaction mixture was heated to 80 °C and stirred for 16 hours. The reaction was allowed to cool to room temperature and diclavatol 2.19 (102 mg, 12 %) was collected by vacuum filtration. The filtrate was poured carefully onto sat. NaHCO₃ (200 mL), then diluted with EtOAc (200 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organics were washed with sat. NaHCO₃, brine, dried over MgSO₄, filtered and concentrated in vacuo to give 2.16 (850 mg, 75 %) as a pale yellow solid, which was used in the next step without further purification.

Data for 2.16:

Rₓ = 0.50 (petroleum ether/EtOAc, 2:1)

Mp: 96-98 °C

IR (neat): 3360, 2921, 1698, 1618, 1375, 1335, 1283, 1239, 1181, 1101, 1018, 821 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 13.24 (s, 1H), 9.40 (s, 1H), 7.51 (s, 1H), 5.24 (s, 2H), 2.55 (s, 3H), 2.19 (d, J = 0.8 Hz, 3H), 2.14 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 202.6, 175.4, 162.8, 161.8, 133.5, 118.0, 112.8, 109.3, 56.9, 26.1, 20.9, 15.8.

HRMS (C₁₀H₉O₃, ESI): calculated for o-quinone methide [M-AcOH] 177.0557, found 177.0544
Data for 2.19:

\[ R_f = 0.60 \text{ (petroleum ether/EtOAc, 2:1)} \]

\textbf{Mp:} >260 °C

\textbf{IR (neat):} 3291, 1927, 1744, 1628, 1487, 1364, 1291, 1251, 1207, 1099, 874 cm\(^{-1}\)

\textbf{\(^1\)H NMR (600 MHz, CDCl}_3\)} \( \delta \) 14.50 (s, 2H), 9.39 (s, 2H), 7.41 (s, 2H), 3.92 (s, 2H), 2.56 (s, 6H), 2.18 (s, 6H).

\textbf{\(^{13}\)C NMR (150 MHz, CDCl}_3\)} \( \delta \) 203.2, 161.3, 159.0, 130.9, 118.7, 112.6, 112.3, 25.9, 16.1, 16.0.

\textbf{HRMS (C_{19}H_{20}O_6, ESI):} calculated [M-H] \(^{+}\) 343.1187, found 343.1164
(S)-Ethyl 2-acetoxypropanoate 2.21

\[ \text{HO-} \quad \text{AcO} \quad \text{AcO} \]

\[ 
\begin{array}{c}
\text{2.20: (S)-ethyl lactate} \\
\text{Ac}_2\text{O, pyridine} \\
\text{rt, 16 h} \\
(96\%) \\
\text{2.21} \\
\end{array}
\]

To a solution of (S)-ethyl lactate (2.20) (9.6 mL, 85 mmol) in pyridine (40 mL) was added Ac₂O (8.8 mL, 93 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured onto a mixture of ice (500 g) and conc. HCl (35 ml). Once the ice melted the mixture was diluted with Et₂O (250 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 x 250 mL). The combined organics were washed with 0.1N HCl (2 x 150 mL), brine, then dried over MgSO₄, filtered and concentrated \textit{in vacuo} to give 2.21 (13.0 g, 96%) as a colourless oil, which was used in the next step without further purification. Spectroscopic data is consistent with that in the literature.\textsuperscript{24}

\[ \text{R}_t = 0.75 \text{ (petroleum ether/EtOAc, 1:1)} \]

\[ [\alpha]_{D}^{25} = -40.6 \text{ (c 1.7, CHCl}_3) \]

\textbf{IR (neat):} 3225, 2989, 1782, 1740, 1620, 1450, 1372, 1236, 1199, 1102, 1053 cm\textsuperscript{-1}

\textbf{\textsuperscript{1}H NMR (600 MHz, CDCl}\textsubscript{3}) \delta 5.06 (q, \textit{J} = 7.1 \text{ Hz, 1H}), 4.21 (q, \textit{J} = 7.1 \text{ Hz, 2H}), 2.13 (s, 3H), 1.48 (d, \textit{J} = 7.1 \text{ Hz, 3H}), 1.28 (t, \textit{J} = 7.1 \text{ Hz, 3H}).

\textbf{\textsuperscript{13}C NMR (150 MHz, CDCl}\textsubscript{3}) \delta 170.8, 170.3, 68.6, 61.3, 20.6, 16.9, 14.0.
(S)-5-Methyl tetronic acid 2.10

To a solution of hexamethylidisilazane (39.0 mL, 187 mmol) in dry THF (200 mL) at 0 °C was added \( n \)-BuLi (2.5 M in hexane, 62.0 mL, 156 mmol) dropwise and stirred for 15 minutes. The reaction mixture was cooled to \(-78 °C\) and 2.21 (10.0 g, 62.4 mmol) in dry THF (100 mL) was added dropwise over 30 minutes. The reaction mixture was stirred at \(-78 °C\) for 1 hour. The reaction was quenched by pouring onto 2M HCl solution (100 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 150 mL), then dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The resultant residue was recrystallised from petroleum ether/EtOAc to give 2.10 (5.16 g, 75 %) as a white solid. Spectroscopic data was consistent with that in the literature.\(^{24}\)

\( R_f = 0.00 \) (petroleum ether/EtOAc, 2:1)

\( [\alpha]^{25}_D = +6.9 \) (c 1.6, CHCl\(_3\))

\textbf{IR (neat)}: 2918, 2707, 1782, 1701, 1592, 1480, 1320, 1279, 1237, 1178, 1056, 967 cm\(^{-1}\)

\textbf{\( ^1H \) NMR (600 MHz, CDCl\(_3\))} \( \delta \) 5.04 (s, 1H), 4.91 (q, \( J = 6.8 \) Hz, 1H), 4.86 (qd, \( J = 7.1, 1.1 \) Hz, 1H), 3.30 – 3.15 (m, 2H), 1.53 (d, \( J = 7.1 \) Hz, 3H), 1.53 (d, \( J = 6.8 \) Hz, 3H). Isolated as a mixture of keto and enol with ratio 5:4.

\textbf{\( ^{13}C \) NMR (150 MHz, CDCl\(_3\))} \( \delta \) 205.6, 184.89, 177.7, 169.7, 88.3, 82.7, 77.2, 37.0, 17.4, 16.6.
Ent-penilactone A ent-2.7

2-Methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (170 mg, 0.710 mmol) and tetronic acid 2.10 (27 mg, 0.24 mmol) were dissolved in toluene (15 mL) in a sealed tube. The tube was flushed with N₂, sealed and the reaction mixture heated at 110 °C for 16 hours. The reaction mixture was concentrated in vacuo, then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1 → 1:1 gradient elution) to give ent-penilactone A ent-2.7 (103 mg, 93%) as a white solid.

R₇ = 0.20 (petroleum ether/EtOAc, 2:1)

Mp: 237-239 °C

[α]D²⁵ = +37.8 (c 0.98, MeOH); lit for (−)-2.7 [α]D²⁵ = −45.1 (c 0.10, MeOH)

IR (neat): 3206, 2921, 1782, 1750, 1619, 1486, 1450, 1372, 1330, 1235, 1181, 1102 cm⁻¹

¹H NMR (600 MHz, DMSO-d₆) δ 13.01 (s, 1H), 12.83 (s, 1H), 9.79 (s, 1H), 8.16 (s, 1H), 7.61 (s, 1H), 7.58 (s, 1H), 5.00 (q, J = 6.2 Hz, 1H), 3.25 (d, J = 13.7 Hz, 1H), 3.13 (d, J = 13.7 Hz, 1H), 2.97 (d, J = 17.3 Hz, 1H), 2.79 (d, J = 17.3 Hz, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 1.51 (d, J = 6.3 Hz, 3H)

¹³C NMR (150 MHz, DMSO-d₆) δ 203.6, 203.3, 174.4, 161.7, 161.3, 159.0, 155.9, 132.2, 130.5, 116.0, 115.4, 112.6, 112.1, 109.2, 107.2, 102.8, 78.0, 48.7, 26.3, 26.2 (2C), 20.8, 16.4, 15.0, 11.8

HRMS (C₂₅H₂₆O₉, ESI): calculated [M+H]⁺ 471.1650, found 471.1642
Five-component one pot reaction

To a solution of 4-Methyl-6-acetylresorcinol 2.17 (500 mg, 3.0 mmol) and NaOAc (41 mg, 0.30 mmol) in AcOH (15 mL) was added formaldehyde solution (37% in H₂O, 0.27 mL, 3.6 mmol) and the reaction was heated at 90 °C in N₂ flushed sealed tube for 16 h. Tetronic acid 2.10 (103 mg, 0.900 mmol) was added and the mixture was heated at 110 °C for 24 h. The reaction mixture was cooled to room temperature and the resultant diclavatol 2.19 precipitate was filtered off. The filtrate was poured onto sat. NaHCO₃ (100 mL) and diluted with EtOAc (150 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organics were washed with sat. NaHCO₃ (200 mL), brine (200 mL) and then dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was recrystallised from methanol to give ent-penilactone A ent-2.7 (194 mg, 45 %) as a white crystalline solid.
To a solution of methyl propiolate 2.23 (500 mg, 5.96 mmol) and acetaldehyde (0.700 mL, 12.6 mmol) in CH$_2$Cl$_2$ (6 mL) at $-78^\circ$C was added Et$_3$N (0.08 mL, 0.60 mmol) and the reaction mixture was stirred for 2 hours. The reaction mixture was warmed to room temperature and conc. HCl (0.4 mL) and i-PrOH (100 mL) were added and the reaction was heated at 60 $^\circ$C for 24 hours. The solvent was removed in vacuo and the resultant residue purified by flash chromatography (SiO$_2$, petroleum ether/ EtOAc, 1:1 $\rightarrow$ 0:1 gradient elution) to give (±)-5-methyltetronic acid (±-2.10) (266 mg, 39%) as a white solid. Spectroscopic data was consistent with that in the literature.

$R_f = 0.00$ (petroleum ether/ EtOAc, 2:1)

**IR (neat):** 2945, 1695, 1608, 1566, 1395, 1334, 1239, 1197, 1097, 1025 cm$^{-1}$

**$^1$H NMR (500 MHz, CDCl$_3$)** $\delta$ 5.04 (s, 1H), 4.91 (q, $J = 6.8$ Hz, 1H), 4.86 (qd, $J = 7.1$, 1.1 Hz, 1H), 3.30 – 3.15 (m, 2H), 1.53 (d, $J = 7.1$ Hz, 3H), 1.53 (d, $J = 6.8$ Hz, 3H). Isolated as a mixture of keto and enol with ratio 5:4.

**$^{13}$C NMR (125 MHz, CDCl$_3$)** $\delta$ 205.6, 184.89, 177.7, 169.7, 88.3, 82.7, 77.2, 37.0, 17.4, 16.6.
(±)-Penilactone A ±2.8

To a solution of 4-methyl-6-acetylresorcinol 2.17 (250 mg, 1.50 mmol) and NaOAc (20 mg, 0.15 mmol) in AcOH (15 mL) was added formaldehyde solution (37% in H₂O, 0.14 mL, 1.8 mmol) and the reaction was heated at 90 °C in N₂ flushed sealed tube for 16 hours. Tetronic acid ±2.10 (51 mg, 0.45 mmol) was added and the mixture was heated at 110 °C for 24 h. The reaction mixture was poured onto sat. NaHCO₃ (100 mL) and diluted with EtOAc (150 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with sat. NaHCO₃ (100 mL), brine (100 mL) and then dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/ EtOAc, 4:1 → 2:1 gradient elution) to give (±)-penilactone A ±2.7 (194 mg, 45 %) as a white crystalline solid.
Dibenzyl (S)-2-hydroxysuccinate 2.32

To a solution of (S)-malic acid (2.31) (5.0 g, 37 mmol) in toluene (100 mL) was added p-toluenesulfonic acid monohydrate (71 mg, 0.37 mmol) and benzyl alcohol (7.8 mL, 75 mmol). The reaction mixture was heated at reflux with a Dean-Stark apparatus for 6 h. The reaction mixture was cooled then washed with sat. NaHCO₃ (25 mL), brine (25 mL), then dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/ EtOAc, 4:1) to give dibenzyl (S)-2-hydroxysuccinate (2.32) (9.86 g, 84%) as a colourless oil. Spectroscopic data was consistent with that reported in the literature.²⁸

\[ R_f = 0.55 \text{ (petroleum ether/ EtOAc, 1:1)} \]

\[ [\alpha]_{D}^{25} = -14.6 \text{ (c 2.1, CHCl}_3) \]

**IR (neat):** 3477, 2952, 1735, 1498, 1455, 1383, 1355, 1264, 1162, 965 cm⁻¹

\[ ^1H \text{ NMR (600 MHz, CDCl}_3 \] \( \delta \) 7.40 – 7.21 (m, 10H), 5.13 (s, 2H), 5.07 (s, 2H), 4.52 (d, \( J = 5.2 \text{ Hz, 1H} \), 3.53 (s, 1H), 2.84 (ddd, \( J = 22.6, 16.4, 5.4 \text{ Hz, 2H} \)).

\[ ^{13}C \text{ NMR (150 MHz, CDCl}_3 \] \( \delta \) 172.9, 170.1, 135.3, 134.9, 128.41, 128.35, 128.33, 128.18, 128.13, 128.10, 127.3, 126.7, 67.4, 67.2, 66.5, 38.5.
Dibenzylated tetronic acid 2.33

Dibenzyl (S)-2-hydroxysuccinate 2.32 (500 mg, 1.59 mmol) and (triphenylphosphoranylidene)ketene (566 mg, 1.87 mmol) were dissolved in dry toluene (30 mL) and stirred at reflux for 24 hours. The reaction mixture was concentrated in vacuo, then purified by flash chromatography (SiO₂, petroleum ether/ EtOAc, 2:1) to give 2.33 (280 mg, 52 %) as a pale yellow oil.

\[R_f = 0.50\] (petroleum ether/ EtOAc, 1:1)

\([\alpha]^{25}_D = -4.0\) (c 1.0, CHCl₃)

**IR (neat):** 3034, 2945, 1756, 1736, 1627, 1314, 1232, 1153, 1041 cm⁻¹

\(^1H\ NMR (600 MHz, CDCl₃)\ δ 7.41 – 7.29 (m, 8H), 5.24 (dd, \(J = 7.7, 4.0\) Hz, 1H), 5.14 (s, 1H), 5.13 (s, 2H), 5.02 (m, 2H), 2.93 (dd, \(J = 16.2, 4.0\) Hz, 1H), 2.72 (dd, \(J = 16.2, 7.7\) Hz, 1H)

\(^13C\ NMR (150 MHz, CDCl₃)\ δ 179.6, 171.7, 168.6, 135.2, 133.6, 129.2, 128.9, 128.6, 128.5, 128.0, 90.1, 75.1, 74.7, 67.1, 37.2

**HRMS (C₂₀H₁₈O₅, ESI):** calculated [M+H]+ 339.1227, found 339.1217
To a solution of dibenzylated tetronic acid 2.33 (280 mg, 0.77 mmol) in MeOH (20 mL) was added 10% Pd/C (10 mg). The flask was evacuated, then flushed with N₂, then evacuated and flushed with H₂ gas (1 balloon). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered through a pad of Celite, which was then washed with MeOH (30 mL), then concentrated in vacuo to give (S)-5-carboxymethyl tetronic acid (2.11) (130 mg, 99%) as a pale yellow solid.

\[ R_f = 0.00 \text{ (petroleum ether/ EtOAc, 2:1)} \]

\[ [\alpha]_D^{25} = -2.8 \text{ (c 1.4, MeOH)} \]

**IR (neat):** 2945, 1695, 1608, 1566, 1395, 1334, 1239, 1197, 1097, 1025 cm⁻¹

**¹H NMR (600 MHz, CD₃OD)** \( \delta \) 5.13 (dd, \( J = 8.7, 3.8 \) Hz, 1H), 2.93 (dd, \( J = 16.5, 3.8 \) Hz, 1H), 2.54 (dd, \( J = 16.5, 8.7 \) Hz, 1H).

**¹³C NMR (150 MHz, CD₃OD)** \( \delta \) 184.4, 177.2, 173.0, 77.7, 37.9.

**HRMS (C₆H₆O₅, ESI):** calculated [M-H]⁻ 157.0142, found 157.0132
Penilactone B 2.8

2-Methyleneacetoxy-4-methyl-6-acetylresorcinol 2.16 (150 mg, 0.63 mmol) and tetronic acid 2.11 (33 mg, 0.21 mmol) were dissolved in anhydrous dioxane (13 mL) in a sealed tube. The tube was flushed with N₂, sealed and the reaction mixture heated at 110 °C for 5 hours. The reaction mixture was concentrated \textit{in vacuo}, then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1 → 0:1 gradient elution), then recrystallised from EtOAc/petroleum ether to give penilactone B 2.8 (92 mg, 86 %) as a pale yellow solid.

R₂ = 0.05 (CH₂Cl₂/MeOH, 10:1)

Mp: 86-89 °C

[α]²⁵D = +27.1 (c 1.0, MeOH); lit [α]²⁵D = +29.4 (c 0.10, MeOH);

IR (neat): 3286, 2951, 1783, 1711, 1625, 1482, 1371, 1186, 1089, 1023 cm⁻¹

¹H NMR (600 MHz, DMSO-d₆) δ 13.04 (s, 1H), 12.82 (s, 1H), 9.86 (s, 1H), 8.35 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 5.21 (d, J = 9.6 Hz, 1H), 3.25 (d, J = 13.7 Hz, 1H), 3.21 – 3.13 (m, 2H), 2.95 (d, J = 17.4 Hz, 1H), 2.81 (d, J = 17.4 Hz, 1H), 2.66 (dd, J = 16.8, 9.6 Hz, 1H), 2.56 (s, 3H), 2.53 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H)

¹³C NMR (150 MHz, DMSO-d₆) δ 203.7, 203.3, 174.0, 171.7, 161.7, 161.3 158.9, 155.5, 132.4, 130.5, 116.0, 115.4, 112.7, 112.1, 109.0, 107.0, 102.7, 78.7, 48.4, 32.8, 26.3, 26.2, 26.2, 20.6, 16.4, 15.0

HRMS (C₂₆H₂₆O₁₁, ESI): calculated [M-H]⁻ 513.1402, found 513.1347
2.7 References


2.8 Appendix One

2.8.1 NMR Spectra

\[ \text{\(1^H\) NMR} \\
\text{DMSO-\(d_6\)} \\
\text{600 MHz} \]

\[ \text{\(13^C\) NMR} \\
\text{DMSO-\(d_6\)} \\
\text{150 MHz} \]
2.15

$^1$H NMR
CDCl$_3$
600 MHz

2.15

$^{13}$C NMR
CDCl$_3$
150 MHz
Chapter 2

$^1$H NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
150 MHz
2.19

$^1$H NMR

CDCl$_3$

600 MHz

2.19

$^{13}$C NMR

CDCl$_3$

150 MHz
Chapter 2

2.21
$^1$H NMR
CDCl$_3$
600 MHz

2.21
$^{13}$C NMR
CDCl$_3$
150 MHz
Chapter 2

\[ ^{1}H\text{ NMR} \]
DMSO-\(d_6 \)
600 MHz

\[ ^{13}C\text{ NMR} \]
DMSO-\(d_6 \)
150 MHz

ent-2.7: ent-penilactone A

ent-2.7: ent-penilactone A
Chapter 2

$\text{H NMR}$

$\text{C}_6\text{D}_6$

600 MHz

\begin{center}
\textbf{ent-2.7: ent-penilactone A}
\end{center}

$\text{H NMR}$

acetone-$d_6$

600 MHz

\begin{center}
\textbf{ent-2.7: ent-penilactone A}
\end{center}
Chapter 2

$^1$H NMR
CDCl$_3$
600 MHz

ent-2.7: ent-penilactone A
Chapter 2

2.32

$^{1}H$ NMR
CDCl$_3$
600 MHz

2.32

$^{13}C$ NMR
CDCl$_3$
150 MHz
Chapter 2

$^{1}H$ NMR
CDCl$_3$
600 MHz

$^{13}$C NMR
CDCl$_3$
150 MHz
Chapter 2

\[ \text{2.11} \]

\(^1H\) NMR
\(CD_3OD\)
600 MHz

\[ \text{2.11} \]

\(^{13}C\) NMR
\(CD_3OD\)
150 MHz
Chapter 2

2.8: penilactone B

$^{1}H$ NMR
DMSO-$d_6$
600 MHz

$^{13}C$ NMR
DMSO-$d_6$
150 MHz

2.8: penilactone B
2.8.2 Penilactones A and B Assignment Tables

**Figure 2.18:** NMR comparison of synthetic and natural for penilactone A (*ent*-2.7)

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<th>Assignment</th>
<th>Natural, $^1$H NMR DMSO-$d_6$, 600 MHz</th>
<th>Synthetic, $^1$H NMR DMSO-$d_6$, 600 MHz</th>
<th>Natural, $^{13}$C NMR DMSO-$d_6$, 150 MHz</th>
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**Figure 2.19**: NMR comparison of synthetic and natural for (+)-penilactone B (2.8)

![Diagram of (+)-penilactone B](image)

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<th>Assignment</th>
<th>Natural, $^1$H NMR</th>
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<th>Natural, $^{13}$C NMR</th>
<th>Synthetic, $^{13}$C NMR</th>
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<td>9.86, s</td>
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</table>

*Isolation spectra incorrectly referenced to DMSO-d$_6$, all values consistently displaced by 0.6 ppm.*
Chapter Three

Total Synthesis of Peniphenones A-D via Biomimetic Reactions of a Common ortho-Quinone Methide Intermediate

3.1 Isolation of Peniphenones A-D

Peniphenones A-D (3.1-3.4) are a family of clavatol (2.12) derived natural products isolated from the mangrove fungus Penicillium dypodomyicola HN4-3A, collected from the South China Sea by Lu and She et al.\textsuperscript{1} The fungus was cultured on a potato dextrose agar medium and incubated for seven days, followed by extraction with EtOAc. The combined organic extracts were concentrated and the crude material was purified by flash chromatography, first over silica gel and later over Sephadex\textsuperscript{®} to give (±)-peniphenone A (±-3.1), a racemic benzannulated spiroketal natural product. Also obtained were three structurally related compounds containing a methylene bridge assigned as peniphenones B-D (3.2-3.4) and two previously isolated natural products clavatol (2.12) and 2-acetyl-4-methylresorcinol (2.17) (Figure 3.1).\textsuperscript{1,2} Peniphenones B and C (3.2 and 3.3) exhibit moderate inhibitory activity against MptpB (mycobacterium tuberculosis) with IC\textsubscript{50} values of 0.16 and 1.37 \textmu M respectively, whereas peniphenones A and D (3.1 and 3.4) were not tested for their inhibitory activity due to the insufficient amount of the natural products recovered after the isolation process.

![Chemical structures](image)

**Figure 3.1:** Peniphenones A-D (3.1-3.4) and biosynthetically related compounds clavatol (2.12) and 2-acetyl-4-methylresorcinol (2.17)
The structures of peniphenones A-D (3.1-3.4) were elucidated through 2D-NMR and then X-ray crystallography experiments. Peniphenone A (3.1) was found to have an optical rotation of zero, and was hence assigned as a racemic natural product. The two enantiomers were separated through chiral HPLC and characterised separately. Their absolute configurations were proposed based on comparison of their CD spectra to a predicted CD spectrum, and as a result (−)-peniphenone A ((−)-3.1) was assigned the absolute configuration of 8R,9R,10R,13R. The other chiral member of the family, (−)-peniphenone D (3.4) was assigned its absolute configuration of 10R based on the measured Flack parameter from X-ray crystallographic analysis.

The occurrence of peniphenone A (3.1) as a racemate is of particular interest to us as biomimetic chemists as this gives us an indication that it may be formed in nature via non-enzymatic reactions. Furthermore, peniphenone A (3.1) contains four stereocentres and we believe that there may be some inherent, predisposed selectivity in the biosynthesis of this molecule. We hoped to exploit this in our biomimetic synthesis.

3.2 Proposed Biosynthesis of Peniphenones A-D

Peniphenones A-D (3.1-3.4) can all be formed in nature via various reactions of nucleophiles with a common o-QM intermediate. Peniphenone A (3.1) for example, could be formed in nature via a [4+2] cycloaddition of racemic exocyclic enol ether 3.5 with o-QM 2.9 either by a stepwise or concerted process (Scheme 3.1). o-QM 2.9 could be generated from the direct oxidation of clavatol (2.12). It is worth noting that o-QM 2.9 is identical to that used in our synthesis of penilactones A and B (2.7 and 2.8) (Chapter 2). The resultant selectivity can be attributed to the [4+2] cycloaddition occurring with the Z-alkene of 3.5 via the endo transition state (assuming a concerted process).

Scheme 3.1: Proposed biosynthesis of (±)-peniphenone A (3.1)

Peniphenones B and D (3.2 and 3.4) could be synthesised in nature via a Michael reaction with o-QM 2.9. This pathway is similar to that reported in the biosynthesis of
penilactones A and B (2.7 and 2.8).\(^5\) Peniphenone B (3.2) could be synthesised by a Michael reaction between pyrone 3.6 and \(\alpha\)-QM 2.9 (Scheme 3.2), whereas peniphenone D (3.4) could arise from the mono-Michael addition of \((R)\)-5-methyltetronic acid (2.10) to \(\alpha\)-QM 3.9 (Scheme 3.2).\(^5\) The isolation of peniphenone D (3.4), a proposed biosynthetic precursor of penilactone A (2.7) from a related species of *Penicillium* fungus, adds validity to the proposed biosynthesis of the penilactone A and B (2.7 and 2.8) and also suggests a biosynthetic relationship between the two families of natural products.

Scheme 3.2: Proposed biosynthesis of peniphenones B and D (3.2 and 3.4)

Peniphenone C (3.3), unlike peniphenones B and D (3.2 and 3.4) could be synthesised in nature via an electrophilic aromatic substitution followed by an oxidation. Electrophilic aromatic substitution of phenol 3.7 with \(\alpha\)-QM 2.9 would afford biaryl hydroquinone 3.8, which upon aerobic oxidation would yield the *para*-quinone moiety and thus peniphenone C (3.3) (Scheme 3.3).

Scheme 3.3: Proposed biosynthesis of peniphenone C (3.3)
The primary goal of this project was to synthesise peniphenones A-D (3.1-3.4) utilising the \(\alpha\)-QM chemistry we have previously established in the synthesis of penilactones A and B (2.7 and 2.8) (Chapter 2). A biomimetic strategy will be employed using the common \(\alpha\)-QM 2.9 in order to shed some light on the biosynthesis of these fascinating compounds as well as expand the repertoire of these highly reactive intermediates \((\alpha\)-QMs). The participation of \(\alpha\)-QMs in Michael reactions, a pathway which is not prevalent in the literature with respect to total synthesis, will be probed.

Peniphenones B-D (3.1-3.4) are the simplest members of the peniphenone family of natural products. We therefore targeted the total synthesis of these using the methodology developed in chapter 2.

### 3.3 Synthesis of Peniphenone B

Peniphenone B (3.2) is a pyrone derived polyaromatic compound that could be synthesised in nature by the union of pyrone 3.6 and \(\alpha\)-QM 2.9 (\textit{vide supra}, Scheme 3.2). Having developed a methodology for enols and tetronic acids conducting Michael reactions with \(\alpha\)-QMs we wanted to expand this to pyrones. Firstly, we needed to complete a synthesis of the desired pyrone 3.12, which had previously been synthesised by Hua et al.\textsuperscript{6,7} Claisen condensation of methyl 3,4-dimethoxybenzoate 3.9 with the TMEDA/LDA initiated dianion of ethyl acetoacetate (3.10) afforded 3.11. Pyrone 3.12 was then furnished when 3.11 was heated under reduced pressure (160 °C, 5 mmHg) to initiate the cyclication-elimination event (Scheme 3.4).

![Scheme 3.4: Synthesis of pyrone 3.12](image)

With the key pyrone 3.12 in hand, the biomimetic cascade reaction was able to be attempted. Pyrone 3.12 and \(\alpha\)-QM precursor 2.16 were subjected to our previously optimised conditions for \(\alpha\)-QM generation (PhMe, 110 °C and a sealed tube), but unfortunately the reaction failed to proceed. Similarly, the coupling reaction in dioxane also failed to yield the desired compound. We concluded that the poor solubility of the pyrone 3.12 attributed to the
lack of formation of 3.13, with diclavatol 2.19 (Chapter 2) the only isolated product. The solvent was changed to acetic acid in order to prevent our o-QM precursor 2.16 from converting into diclavatol 3.19, thus allowing extra time for the pyrone to trap the o-QM. Pyrone 3.12 and o-QM precursor 2.16 in AcOH were heated at 120 °C in a sealed tube for 14 hours and upon cooling the desired peniphenone B dimethyl ether (3.13) precipitated from solution and was isolated by vacuum filtration in 66% yield (Scheme 3.5).

Scheme 3.5: Synthesis of peniphenone B dimethyl ether 3.13

The above reaction proceeds by firstly an in situ thermolytic formation of o-QM 2.9 followed by a Michael reaction with pyrone 3.12. The resultant product was confirmed by interpretation of the 1H NMR. The key resonance observed was the CH$_2$ ($\delta_H = 3.78$) bridging the two aromatic portions of the molecule, which had a similar chemical shift to the bridging CH$_2$ present in diclavatol (2.19) ($\delta_H = 3.92$).

Finally, peniphenone B (3.2) was furnished by standard demethylation conditions using BBr$_3$ in CHCl$_3$. The resultant product was recrystallised from acetone to afford peniphenone B (3.2) in 94% yield (Scheme 3.6). The spectroscopic data of synthetic peniphenone B (3.2) matched that reported in the literature (see Section 3.10.2).

Scheme 3.6: Demethylation of 3.13 to afford peniphenone B (3.2)
3.4 Synthesis of Peniphenone C

With peniphenone B (3.2) synthesised, the next member targeted was peniphenone C (3.3), which is a quinone natural product proposed to be formed in nature via an electrophilic aromatic substitution reaction followed by an oxidation. The pathway to peniphenone C is analogous to the formation of diclavatol (2.19), with a further oxidation step. In order to synthesise peniphenone C (3.3), we needed to complete a synthesis of the required triphenol 3.7 before we could trial the biomimetic reaction.

2,5-Dimethyl-1,4-benzoquinone (3.14) was treated with acetic anhydride and BF$_3$·Et$_2$O furnishing 3.15 in good yield. The triacetoxy esters were hydrolysed under acidic conditions to afford the desired 3,6-dimethyl-1,2,4-trihydroxybenzene (3.7) (Scheme 3.7).

\[
\text{BF}_3\cdot\text{Et}_2\text{O}, \text{Ac}_2\text{O} \quad 40^\circ\text{C}, 48\text{ h} \quad (95\%)
\]

3.14: 2,5-dimethyl-1,4-benzoquinone

\[
\text{AcO} \quad \text{AcO} \quad \text{AcO} \quad \text{OH} \quad \text{OH} \quad \text{OH}
\]

3.15 3.7

\[
\text{conc HCl, H}_2\text{O} \quad \text{reflux, 1 h} \quad \text{(quant.)}
\]

Scheme 3.7: Synthesis of 3,6-dimethyl-1,2,4-trihydroxybenzene (3.7)

With triphenol 3.7 and o-QM precursor 2.16 synthesised, we were primed to try the electrophilic aromatic substitution followed by oxidation sequence. Triphenol 3.7 and o-QM precursor 2.9 were dissolved in toluene and heated at 110 °C in a sealed tube (Scheme 3.8). The TLC of the reaction mixture demonstrated consumption of the triphenol starting material, with a new spot observed at $R_f = 0.35$ in 5:1 petrol/acetone. Isolation of this compound by column chromatography afforded a bright yellow, highly UV active compound. This was the first indication that the product may have undergone an autoxidation in air. This was confirmed by the NMR data, which matched the literature spectra of peniphenone C (3.3) perfectly (see Section 3.10.2).
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**Scheme 3.8:** One-pot synthesis of peniphenone C (3.3)

This one-pot two-component three-step cascade reaction proceeded in 72% yield, involving an \( o \)-QM formation, an electrophilic aromatic substitution and finally an autoxidation to furnish peniphenone C (3.3). This is an attractive reaction sequence as it further demonstrates the power of these \( o \)-QM intermediates and expands our methodology to encompass another molecular scaffold, namely an aromatic ring bridged to a quinone.

### 3.5 Synthesis of Peniphenone D

The final member of the peniphenones family to be synthesised was peniphenone D (3.3), which is a proposed biosynthetic intermediate in the biosynthesis of penilactone A (2.7) (Chapter 2). Peniphenone D (3.4) had previously been observed as a by-product of our synthesis of penilactone A (2.7), which we synthesised prior to the isolation of peniphenones A-D (3.1-3.4) in 2014. We observed that careful control of the equivalency of tetronic acid 2.10 to \( o \)-QM precursor 2.9 favoured the production of the mono-Michael reaction product peniphenone D (3.4) as opposed to penilactone A (2.7) (Scheme 3.9). Three equivalents of tetronic acid 2.10 were used under our standard conditions (PhMe and heat), yielding ent-peniphenone D (ent-3.4) as well as trace quantities of ent-penilactone A (ent-2.7).
Comparison of the spectral data revealed that we had indeed synthesised the desired product 3.4. However, an anomalous value was measured for the optical rotation; instead of observing $[\alpha]_{D}^{25} = +72$ expected for ent-peniphenone D (ent-3.4) (optical rotation for peniphenone D $[\alpha]_{D}^{25} = -72$) we observed $[\alpha]_{D}^{25} = -6.8$. The magnitude and sign of the optical rotation measured are both contradictory to what would be expected for our synthesised compound. A potential cause for this could be the small quantity of peniphenone D (1.2 mg) isolated by She and Liu, which introduced significant error in their measured optical rotation value. The X-ray crystallography data of She and Liu conclusively assigns the absolute configuration as 10R, whereas our enantiopure synthesis unambiguously affords an absolute configuration of 10S.

Finally, the isolation and synthesis of this biosynthetic intermediate adds some validity to the proposed biosynthesis of the penilactones. As peniphenone D (the mono Michael adduct) could potentially be further reacted with another molecule of the o-QM precursor 2.9 to afford penilactone A (2.7). This synthesis consolidates our proposed biosynthesis of both the penilactones and peniphenones involving Michael reactions of various nucleophiles with o-QMs. The successful synthesis of peniphenone D (3.4) rounds out the synthesis of the simpler peniphenones; providing a strong basis for tackling peniphenone A (3.1).
3.6 Synthesis of Peniphenone A

The primary target of this project was the most structurally complex member of the peniphenones family of natural products: (±)-peniphenone A (3.1). With its four stereocentres in a racemic natural product, we wanted to investigate the possibility of inherent selectivity associated with its biosynthesis. Our attempts to explore this notion and ultimately complete the synthesis of peniphenone A (3.1) will be reported herein.

3.6.1 Synthesis of a Simplified Peniphenone A Analogue

Exocyclic enol ether 3.5 (Scheme 3.1) was identified as a challenging synthetic target, hence we first aimed to synthesise a simplified analogue of peniphenone A (3.1). The goal of this was to attempt the biomimetic [4+2] cycloaddition with a simplified exocyclic alkene to gauge whether synthesising the functionalised structure would be worthwhile. We decided to synthesise the simplest exocyclic enol ether 3.17, which consists of a tetrahydropyran ring with an exocyclic alkene adjacent to the oxygen atom. This compound had been previously synthesised by Rizzacasa et al. through an elimination of 2-chloromethyltetrahydro-2H-pyran (3.16) with KOH (Scheme 3.10). Thus, (2-chloromethyl)tetrahydro-2H-pyran 3.16 was heated at reflux with solid KOH for 5 hours and the formed product was distilled to give exocyclic enol ether 3.17. The resultant exocyclic alkene 3.17 was extremely unstable and needed to be used immediately.

![Scheme 3.10: Synthesis of simplified exocyclic enol ether 3.17 reported by Rizzacasa](image)

With our α-QM precursor 2.16 and simplified exocyclic enol ether 3.17, we were primed to trial the model [4+2] cycloaddition. We therefore dissolved α-QM precursor 2.16 and simplified exocyclic enol ether 3.17 in toluene and heated the reaction at 110 °C for 16 hours in a sealed tube. TLC of the reaction mixture revealed consumption of the starting material and three new spots (two non-polar, one polar). Isolation of the products via flash chromatography revealed that the lower non polar compound was diclavatol (2.19), whereas the most non-polar product was an inseparable 9:1 mixture of compounds isolated in 26% yield. Interpretation of the 2D NMR data revealed the formation of isomerised compound 3.19 as the major product with our desired compound compound 3.18, isolated as the minor product.
Chapter 3

The lower more polar compound was isolated in 14% yield and observed to have two sets of peaks associated with the aromatic region of the molecule. Interpretation of the 2D NMR determined the structure to be 3.20, formed by the double addition of the isomerised endocyclic alkene 3.21 to two molecules of the o-QM 2.9 (Scheme 3.12).

![Scheme 3.11: Attempted synthesis of simplified peniphenone A (3.18) and the resultant by-products 3.19 and 3.20](image)

Presumably both products 3.19 and 3.20 arise in the reaction via acid catalysed tautomerisation of the exocyclic alkene 3.17 to the endocyclic alkene 3.21 (Scheme 3.12). An equivalent of AcOH was liberated in the formation of the o-QM 2.9, which was seemingly sufficient to initiate almost complete conversion of 3.17 to the endocyclic alkene 3.21. This isomerisation had been previously observed by Bray when working with acetoxy o-QM precursors similar to 2.16. With an abundance of endocyclic compound 3.21, a [4+2] cycloaddition with o-QM 2.9 gave the isolated major compound 3.19. Furthermore, we envisaged 3.20 might arise via a more stepwise approach, whereby there was an initial Michael reaction with o-QM 2.9 to afford 3.22, enolisation to 3.23 followed by another Michael reaction with o-QM 2.9 and finally ring closure yielded 3.20 (Scheme 3.12). This mechanistic pathway bears a similar resemblance to the synthesis of penilactones A and B (2.7 and 2.8) (Chapter 2).
Scheme 3.12: Initial observations in [4+2] cycloaddition reactions

The relative stereochemical outcome of both 3.19 and 3.20 was found to contain a cis-fused ring junction using 2D NOESY NMR. Strong cross peaks were observed for 3.19 between the C-6 methyl and the C-5 hydrogen (see Section 3.10.1). Compound 3.20 was observed to have a large amount of spectral overlap of the benzylic protons. The observed NOESY cross peaks between both C-8 and C-8' and the C-6 Me suggests a cis fused ring junction (Figure 3.2).

Figure 3.2: Observed NOESY cross peaks for 3.19 and 3.20

In order to achieve a better yield of our desired model peniphenone compound 3.18, we needed to prevent this isomerisation from proceeding. The main cause for the formation of the undesired endocyclic enol ether 3.21 can be attributed to the liberation of AcOH under the o-QM generation conditions. Thus, a logical approach forward would be to neutralise the acid generated in the reaction. Trialling the reaction with stoichiometric quantities of NaOAc and KOH marginally improved the ratio. Triethylamine was found to be the optimum base for
producing the desired model compound 3.18, and we propose in the reaction the base does two things. Firstly, it sequesters out the AcOH, and secondly it initiates the elimination of 2.16 to produce o-QM 2.9 (Scheme 3.13). Hence, this reaction proceeds at decreased temperatures, albeit in diminished yields.

![Scheme 3.13: Triethylamine buffered synthesis of model peniphenone A compound 3.18](image)

With the success of our model study, we believed the pursuit of peniphenone A (3.1) via our proposed biomimetic route was plausible. Thus, we endeavoured to synthesise exocyclic alkene 3.5 and hence peniphenone A (3.1).

### 3.6.2 Attempted Synthesis of Functionalised Exocyclic Enol Ether 3.5

The initial goal of this part of the project was to test whether we could synthesise the exocyclic alkene 3.5 in situ and subsequently trap it with o-QM 2.9 via a [4+2] cycloaddition. We targeted this methodology as we deemed installing the exocyclic alkene with a terminal methyl group to be a significant synthetic challenge. We proposed that if we could synthesise diketone 3.24 we could cyclise this linear compound and selectively eliminate the hemiacetal of 3.25 to give the desired exocyclic enol ether 3.5 (Scheme 3.14). We hoped that we may be able to control the elimination to selectively occur at the C-7 position, rather than the C-5 position of 3.25.

![Scheme 3.14: Proposed in situ elimination of 3.25 to produce exocyclic enol ether 3.5](image)

We first turned our attention toward the synthesis of diketone 3.24. (R)-Methyl 3-hydroxybutyrate 3.26 was selected as our starting material as large quantities of this compound were cheap and readily available. The secondary alcohol of 3.27 was protected with a TBS group under standard conditions (TBSCl, imidazole and DMF) to give 3.27 (Scheme 3.15). The ester moiety was then reduced carefully with DIBAL-H to give aldehyde 3.28. This
reaction proved to be very temperamental, as the reduction to the aldehyde only proceeded in 68% yield if a solution of DIBAL-H (1 M in cyclohexane) was used, whereas if a solution of DIBAL-H (1 M in THF) was used the sole product isolated was the primary alcohol. However, this primary alcohol could simply be oxidised with Dess-Martin periodinane to afford aldehyde **3.28** in 95% yield over the two steps.

**Scheme 3.15: Synthesis of aldehyde 3.28 via TBS protection and DIBAL-H reduction**

The aldol reaction of aldehyde **3.28** with the enolate of 3-pentanone (**3.29**) in THF at −78 °C afforded 1,3-hydroxyketone **3.30** as a complex mixture of diastereoisomers (Scheme 3.16). The resultant 1,3-hydroxyketone **3.30** contained two new stereocentres, which accounted for the observed complexity of the measured NMR spectra. This reaction proceeded in a good yield of 88% and the 1,3-hydroxyketone **3.30** was later oxidised with Dess-Martin periodinane to give diketone **3.24**. Whilst the diketone **3.24** was isolated as a 1:1 mixture of diastereoisomers, this ratio could potentially be improved further down the synthetic sequence as it is possible to epimerise at C-5.

**Scheme 3.16: Synthesis of diketone 3.24 via aldol product 3.30**

The above reaction sequence yielded our desired diketone **3.24** in just four steps from (R)-methyl 3-hydroxybutyrate (**3.26**), and could be used to test the key exocyclic enol formation. Unfortunately, treatment of **3.24** with acid formed the conjugated alkene **3.31** rather than the desired exocyclic alkene **3.5** (Scheme 3.17). We would expect this compound to be the more stable product due to the α,β-unsaturated carbonyl functionality. This molecule was isolated in good yield (89%). Cleavage of the silyl group with regular desilylating agents (e.g. TBAF) gave a complex mixture of products.
Scheme 3.17: Attempted tandem desilylation and cyclisation resulting in the undesired endocyclic alkene 3.31

As the elimination preferentially produced the conjugated endocyclic alkene 3.31 rather than the desired exocyclic alkene 3.5, we proposed that we may be able to deprotonate endocyclic alkene 3.31 under basic conditions to form a vinylogous enolate 3.32 that bears the desired exocyclic double bond (Scheme 3.18). A vinylogous Michael reaction of 3.32 with o-QM 2.9, followed by a cyclisation of intermediate 3.33 could allow access to peniphenone A (3.1).

Scheme 3.18: Proposed base induced vinylogous enolate 3.32 formation and [4+2] cycloaddition

3.6.3 Attempted Vinylogous Michael Reaction Towards Peniphenone A

For a relatively simple molecule, our synthetic approach towards endocyclic alkene 3.31 was relatively inefficient. Thus, a quick survey of the literature revealed a procedure reported by Burnell and co-workers. The authors demonstrated that an aldol reaction between 3-pentanone (3.29) and crotonaldehyde (3.34), followed by oxidation with Dess-Martin periodininane produced diketone 3.35, which upon treatment with p-toluenesulfonic acid afforded ±-3.31 (Scheme 3.19).
Scheme 3.19: Synthesis of conjugated endocyclic alkene 3.31 by Burnell

This method allowed access to large quantities (> 5 g) of the endocyclic alkene 3.31 (59% yield over 3 steps), which we adopted in the screening of vinylogous aldol reaction conditions. A series of reaction conditions were explored to attempt the desired deprotonation and vinylogous Michael reaction (Table 3.1).

Table 3.1: Attempted conditions for vinylogous enolate formation and [4+2] cycloaddition

<table>
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<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>DBU, CH3CN, reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>DBU, PhMe, 110 °C, sealed tube</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>LDA, THF, -78 to rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Et3N, PhMe, 110 °C, sealed tube</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>AcOH, 120 °C, sealed tube</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>hv, PhMe, rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>PhMe, 110 °C, sealed tube</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Disappointingly, the reaction failed to proceed under basic conditions with isolation of the starting material (Entries 1-4). This suggested that the desired vinylogous enolate intermediate 3.32 was not forming in situ, or undergoing undesired side reactions. To further investigate the formation of 3.32 we screened a series of non-basic conditions (Entries 5-8); disappointingly these also failed to yield peniphenone A (3.1). In order to probe the viability of this reaction, we investigated a reaction of 3.31 with iodomethane. The attachment of the
methyl group would clearly reveal the most favourable deprotonation site of 3.31 to afford either 3.36 or 3.37 (Table 3.2).

\[
\begin{array}{ccc}
\text{conditions} & \text{3.36} & \text{3.37} \\
\pm 3.31 & & \\
\end{array}
\]

Table 3.2: Attempted vinylogous enolate reactions with iodomethane

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI, Et$_3$N, PhMe, rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>MeI, LDA, THF, $-78 , ^\circ\text{C}$</td>
<td>3.35</td>
</tr>
<tr>
<td>3</td>
<td>MeI, NaHMDS, THF, $-78 , ^\circ\text{C}$ to rt</td>
<td>3.35</td>
</tr>
<tr>
<td>4</td>
<td>MeI, $t$-BuOK, DMF, 0 $^\circ\text{C}$</td>
<td>3.31 and 3.35</td>
</tr>
</tbody>
</table>

Unfortunately, under basic conditions with iodomethane (Entries 1-4), endocyclic alkene 3.31 reverted back to 3.35, presumably via a retro-6$\pi$-electrocyclisation of undesired enolate 3.38 (Scheme 3.20). This observation suggests that deprotonation is preferentially occurring at C-3 position rather than the C-9 position, and once C-3 deprotonation occurs the retro-6$\pi$ electrocyclisation consumes the starting material. It quickly became apparent that the isolation of 3.35 suggested that this pathway would prevent access to peniphenone A (3.1) by this strategy.

\[
\begin{array}{ccc}
\text{deprotonation} & \text{3.38} & \text{retro-6$\pi$ electrocyclisation} \\
\pm 3.31 & & 3.35 \\
\end{array}
\]

Scheme 3.20: Undesired retro-6$\pi$ producing 3.35

3.6.4 One-pot Synthesis of a Peniphenone A Analogue

It was observed that diketone 3.24 preferentially cyclised to endocyclic alkene 3.31 under acidic conditions. Therefore, we wanted to investigate the outcome of the elimination if the C-4 ketone was removed (i.e. reduced to the alcohol). We wanted explore a one-pot synthesis of peniphenone A (3.1) under acidic conditions using 1,3-hydroxyketone 3.30 (the precursor to 3.24), to investigate whether the absence of the ketone could trigger selective
elimination to produce the desired exocyclic alkene 3.39. Exocyclic alkene 3.39 would then be primed to undergo a [4+2] cycloaddition with \( \sigma \)-QM precursor 2.16 to afford 2.40 (Scheme 3.21).

![Scheme 3.21: Proposed one pot acid catalysed synthesis of 3.40](image)

Secondary alcohol 3.30 and \( \sigma \)-QM 2.16 were dissolved in AcOH and heated in a sealed tube for 16 hours. TLC analysis revealed a non-polar spot above the starting materials. Isolation by flash chromatography revealed a 3:1 ratio of diastereoisomers of spirocycle compound 3.41, which was elucidated by NMR (Scheme 3.22). However, the relative configuration of the diastereoisomers of 3.41 were unable to be determined. The key resonances observed were the appearance of a \( \delta_H \) 5.85 (d, 2H) and a quaternary \( \delta_C \) 100.3 that corresponded to the \( \Delta^{10,11} \) alkene hydrogen and C-9 acetal quaternary carbon respectively. Furthermore, the observation of two methyl doublets C-17 and C-19 (\( \delta_H \) 1.08 and 0.98) as well as a downfield methyl singlet C-18 (\( \delta_H \) 1.76) was important for the structural elucidation of 3.41. This culminates in a compound that has the backbone of peniphenone A (3.1), however instead of the expected hydroxy group at C-11, elimination afforded an alkene between the C-10 and C-11 carbons.

![Scheme 3.22: One-pot synthesis of eliminated compound 3.41](image)

We envisaged that desilylation of 3.30 followed by cyclisation of the newly generated 3.42 under the acidic reaction conditions occurred first to give hemiacetal 3.43. Hemiacetal 3.43 would then subsequently undergo two sequential eliminations at C-5 and C-7, presumably via the oxonium ion, to afford conjugated exocyclic alkene 3.45 (via 3.44). 3.45 could then undergo a [4+2] cycloaddition with thermally induced \( \sigma \)-QM 2.9 formed in situ to produce 3.41, which is structurally analogous to peniphenone A (3.1) (Scheme 3.23).
Scheme 3.23: Proposed mechanism for the formation of eliminated analogue 3.41

The relative configuration of the two compounds could not be determined; predominantly due to the lack of NOESY cross peaks across the acetal group. The only interactions observed were between the C-17 and C-18 methyl groups, however due to the planarity of the $\Delta^{10,11}$ alkene, the relative stereochemistry could not be assigned (Figure 3.3). Interestingly, only two compounds are observed yet there are three stereocentres (two uncontrolled), allowing up to four diastereoisomers. The observation of only two diastereoisomers in a 3:1 ratio suggests some order of selectivity; likely controlled by the E/Z nature of the exocyclic alkene of 3.45. Presumably, the acetal stereocentre can be equilibrated to the most stable relative configuration, likely affording 3.41 where the C-19 methyl would be oriented in the marginally more favoured pseudo-equatorial position.

Figure 3.3: NOESY correlations of 3.41

The synthesis of an analogous backbone for peniphenone A bearing the desired spirocyclic framework was a promising result, as we could potentially hydroborate 3.41 into secondary alcohol 3.40, thus allowing access to peniphenone A. Hydroboration reactions preferentially oxygenate at the least substituted carbon, which upon oxidation would hopefully afford peniphenone A (3.1), depending on the relative configuration of 3.40. Hydroboration
under standard conditions (BH₃, then H₂O₂ and NaOH) was attempted on 3.41, however instead of a hydroboration of the alkene a reduction of the aryl ketone to 3.46 was observed. This was supported by the loss of a carbonyl peak in the carbon NMR spectrum and disappearance of the δ_H 2.54 (s, 3H), and the appearance of δ_H 1.58 (d, J = 6.5 Hz).

Scheme 3.24: Attempted hydroboration of 3.41

Attempts to hydroborate with various other hydroboration reagents (9-BBN, Me₂S·BH₃) did not prove to be fruitful in yielding the desired alcohol 3.40. Similarly, they caused the reduction of the aryl ketone, with excess equivalents failing to achieve reaction with the alkene of 3.41. The reactivity of the endocyclic alkene of 3.41 was further tested via an epoxidation reaction. Standard epoxidation conditions of mCPBA in CH₂Cl₂ were trialled and it was observed that the reaction proceeded, albeit in a very poor yield of 13% to afford 3.47 (Scheme 3.25). The reaction failed to proceed to completion, with a large portion of starting material isolated after purification.

Scheme 3.25: Epoxidation of endocyclic alkene 3.41 with mCPBA

Epoxide 3.47 was isolated as a single compound. However, due to the small quantities of material isolated and difficulty in observing NOESY cross peaks between the two halves of the molecule, the relative configuration was unable to be assigned. Furthermore, the poor yield as well as the difficulty of selectively ring opening epoxides from the most hindered position brings this pathway towards the synthesis of peniphenone A (3.1) to a close.
3.6.5 A More Pragmatic Approach Towards Peniphenone A

We initially surveyed a variety of reactions that could potentially yield peniphenone A (3.1) via a [4+2] cycloaddition of an exocyclic enol ether 3.5 and an o-QM 2.9. However, we observed that this pathway to the natural product peniphenone A (3.1) was extremely challenging, therefore an alternate method would be required to synthesise the natural product. We therefore embarked on a more pragmatic approach to synthesise the peniphenone A (3.1), whereby we would attach a linear fragment 3.48 with o-QM 2.9 through a Michael reaction and subsequently cyclise 3.49 to achieve the backbone of peniphenone A (3.1) (Scheme 3.26). Notably, this late stage spiroketalisation approach affording the acetal moiety has been employed by a number of research groups using catalytic quantities of acid\(^{15}\), for example Brimble et al. in their synthesis of the chaetoquadrins\(^{16}\) and virgatolide B\(^{17,18}\).

![Scheme 3.26: Proposed alternative synthesis of peniphenone A (3.1)](image)

The presence of the free hydroxyl group in 3.48 would likely interfere with the coupling reaction under basic conditions. Therefore, the previously synthesised TBS protected analogue 3.24 was used. This is an ideal choice of protecting group, since simultaneous deprotection and spirocyclisation in one step under acidic conditions, could afford the natural product. Diketone 3.24 was enolised with LDA, then o-QM precursor 2.9 was added at \(-78^\circ\text{C}\) and the reaction mixture was stirred at this temperature for two hours (Scheme 3.27). A new spot on the TLC was observed below 3.24, which upon isolation and interpretation of the 2D NMR was not the desired compound 3.50. The key resonances of the expected structure were not observed; potentially a product associated with deprotonation at the most acidic position could be envisaged.

![Scheme 3.27: Attempted synthesis of 3.50](image)
A new approach to avoid this unknown side product was investigated. We decided to remove the diketone functionality, and solely aim for selective deprotonation at C-7 induced by the steric bulk of the TMS protecting group. We decided to employ 1,3-hydroxy ketone 3.30 in the coupling reaction, but we deemed that the best course of action was to protect the hydroxyl moiety. Thus, trimethylsilyl protection of 3.30 with TMSCl and pyridine gave ketone 3.51 as a complex mixture of diastereoisomers (Scheme 3.28).

Scheme 3.28: Synthesis of mixed TMS-TBS protected compound 3.51

With 3.51 in hand, we were primed to trial the key Michael reaction with o-QM 2.16 under basic conditions and subsequently cyclise this product under acidic conditions in order to achieve the backbone of peniphenone A (3.1). However, these types of transformations are rare in the literature; this is largely attributed to the highly basic nature of lithiated bases. Often their conjugate acids are highly nucleophilic and can irreversibly bind to the o-QM intermediate, thus preventing reaction with the enolate.\textsuperscript{19} Despite this, a series of reaction conditions were tested for the coupling of diprotected compound 3.51 and o-QM 2.16 (Table 3.3).
Table 3.3: Screened conditions for coupling of 3.51 and α-QM 2.16

<table>
<thead>
<tr>
<th>Entry</th>
<th>3.51:2.16</th>
<th>Conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2</td>
<td>LDA (2.1 equiv), THF, −78 °C, 3 h</td>
<td>13%</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>LDA (3 equiv), THF, −78 °C, 3 h</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>3:1</td>
<td>LDA (4.5 equiv), THF, −78 °C to rt, 3 h</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>4</td>
<td>1:1</td>
<td>KHMDS (2.2 equiv), THF, −78 °C, 2 h</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>1:1</td>
<td>LiTMP (3 equiv), THF, −78 °C, 7 h</td>
<td>32%</td>
</tr>
<tr>
<td>6</td>
<td>1:1</td>
<td>LiTMP (3 equiv), THF, −78 °C to rt, 4 h</td>
<td>20%</td>
</tr>
<tr>
<td>7</td>
<td>1:1</td>
<td>LiTMP (6 equiv), THF, −78 °C, 7 h</td>
<td>13%</td>
</tr>
<tr>
<td>8a</td>
<td>1:1</td>
<td>LiTMP, THF, −78 °C</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>1:1</td>
<td>Et3N (2 equiv), PhMe, 110 °C, 16 h</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>1:1</td>
<td>DBU, PhMe, 110 °C, 16 h</td>
<td>0%</td>
</tr>
<tr>
<td>11</td>
<td>1:1</td>
<td>NaH, THF, 0 °C to 60 °C, 5 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>12</td>
<td>1:1</td>
<td>t-BuOK, DMF, 0 °C to rt, 3 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

*3 equiv of LiTMP was added to a solution of 3.51 and 2.16

The optimised conditions for the coupling of 3.51 and α-QM precursor 2.16 were found to be a stoichiometric ratio of the reactants (1:1) with 3 equivalents of LiTMP in THF at −78 °C for 7 hours (Entry 5). It is of note, the use of LiTMP instead of LDA or KHMDS led to an increased yield (Entries 1-4), which we attribute to the more hindered nature of conjugate acid 2,2,6,6-tetramethylpiperidine (vide supra). It is observed that a change to the ratios of starting materials (Entries 2 and 3), as well as an increase in the amount of base (Entry 7) used leads to a diminished yield. Furthermore, the modification of the addition pattern (Entry 8) by addition of the base to a combined solution of 3.51 and 2.16 failed to yield the desired compound. The use of non-metalated bases (Entries 9 and 10) failed to yield any of the desired compound 3.52.

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Furthermore, the use of NaH (Entry 11) and alkoxide bases (such as t-BuOK, Entry 12) caused the starting materials to decompose.

The products isolated could not unambiguously be assigned due to the complexity of the $^1$H NMR spectrum, with now three uncontrolled stereocentres and a possibility of eight diastereoisomers. As a result, compound 3.52 was carried through to the next step. A tandem double desilylation-cyclisation using stoichiometric quantities of acid was attempted. Interestingly, conditions reported by Brimble et al. (CSA in CH$_2$Cl$_2$) (Entry 1) in her synthesis of spiroketal natural product virgatolide B failed to yield the desired acetal 3.53 in a significant yield.$^{17,18}$ The major compound isolated was eliminated compound 3.41, which had been previously synthesised in Scheme 3.22. Therefore, we screened a series of acidic conditions with a goal to minimise the formation of this undesired product 3.41 (Table 3.4).

![Chemical Structure](image)

**Table 3.4: Screened conditions for acid spiroketalisation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product ratio 3.53:3.41</th>
<th>Yield of 3.53</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CSA, CH$_2$Cl$_2$, rt, 24 h</td>
<td>1:3</td>
<td>13%</td>
</tr>
<tr>
<td>2</td>
<td>$p$-TsOH, CH$_2$Cl$_2$, rt, 5 h</td>
<td>1:2</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>AcOH, CH$_2$Cl$_2$, rt, 6 h</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>PPTS, CH$_2$Cl$_2$, rt, 16 h</td>
<td>-</td>
<td>TMS cleavage</td>
</tr>
<tr>
<td>5</td>
<td>AcOH, H$_2$O, rt, 5 min</td>
<td>-</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>$p$-TsOH (cat), CH$_2$Cl$_2$, rt, 16 h</td>
<td>0:1</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>3 M HCl, THF, rt, 3 h</td>
<td>-</td>
<td>decomposition</td>
</tr>
<tr>
<td>8</td>
<td>3 M HCl, CH$_3$CN, rt, 15 min</td>
<td>1:0</td>
<td>53%</td>
</tr>
</tbody>
</table>

As shown in Table 3.4, aqueous acid (3 M HCl) with CH$_3$CN as the solvent (Entry 8) proved to be the ideal conditions to complete the spiroketalisation, whilst also minimising the undesired eliminated compound 3.41. The aqueous solvent was pivotal in this reaction as it prevents the loss of water observed under anhydrous acidic conditions. The desired spiroketal
3.53 was isolated as a complex mixture of compounds, with compounds observed by TLC. However, both compounds were isolated as complex mixtures. These mixtures were carried on to the oxidation reaction, which reduced the number stereocentres by one, allowing a clear representation of the diastereomeric ratio relative to peniphenone A (3.1). As a result, spiroketal 3.53 was oxidised with Dess-Martin periodinane to hopefully produce peniphenone A (3.1) (Scheme 3.29). The reaction yielded three products that were difficult to purify by flash chromatography. $^1$H NMR analysis of 3.54 revealed a 1:2:4 ratio of diastereoisomers, with peniphenone A (3.1) observed as the minor product. This suggested that this route favours the incorrect relative stereochemistry across C-8, C-9 and C-10.

Scheme 3.29: Dess-Martin oxidation of spiroketal 3.53 to peniphenone A (3.1) and it’s diastereoisomers

The last hope for synthesising peniphenone A (3.1) involved the exploration of methods for altering the ratio of this complex mixture of diastereoisomers. The proton at C-10 (α to the carbonyl group) and the acetal at C-9 have the potential to be epimerised. We therefore explored the epimerisation of the complex mixture 3.54 using strong acids, which gave some interesting results. 3.54 was stirred in an excess of $p$-TsOH, which caused the ratio of diastereoisomers to gradually favour peniphenone A (3.1) over a period of several days (Scheme 3.30). The ratio was observed to progressively changed from a 1:2:4 ratio of three diastereoisomers (peniphenone A (3.1) as the minor product) towards a ratio of 3:3:1 with peniphenone A (3.1) as the co-major product after 7 days. We therefore envisaged the three compounds to be 3.1 (peniphenone A), 3.55 (8-epi-peniphenone A) and an unknown diastereoisomer 3.56 (Scheme 3.30). Peniphenone A (3.1) and 8-epi-peniphenone A (3.55) can both adopt a conformation where all substituents are in the equatorial position on the pyranone ring. The structures of 3.1 and 3.55 were confirmed by comparison of the NMR data to the natural product and synthesised 8-epi-peniphenone A (3.55) (vide infra, Scheme 3.36). We were unable to determine the structure of 3.56.
The separation of these three compounds by flash chromatography proved to be a challenging task, with only trace quantities of pure compounds able to be isolated. The bulk of the material co-eluted resulting in a mixture similar to that observed in the crude NMR. At this stage, the outlook for isolating a pure sample of peniphenone A (3.1) was bleak; our only likely avenue being to use HPLC to separate the complex mixture. Instead of attempting to separate this complex mixture, we deemed a stereocontrolled synthesis a more apt endeavour.

We therefore set our sights towards an enantioselective synthesis of peniphenone A (3.1).

### 3.6.6 Enantioselective Synthesis of Peniphenone A

Enantioselective polyketide synthesis has been widely researched over the past 30 years, with a number of different chiral auxiliary approaches developed. Evans employed the use of chiral oxazolidinones in aldol reactions\textsuperscript{20}, alkylation\textsuperscript{21} and [4+2] cycloadditions.\textsuperscript{22,23} The use of chiral boronates has also been extensively studied in the literature, which reduces the number of steps required as the auxiliary can be attached and removed in the one pot. This work was pioneered by Paterson and co-workers with their extensive studies on IPC\textsubscript{2}BOTf (diisopinocampheylboron trifluoromethanesulfonate).\textsuperscript{24–26}

We initially investigated the most direct route to our chiral 1,3-hydroxyketone 3.57, which was using Paterson’s conditions.\textsuperscript{26} Unfortunately, IPC\textsubscript{2}BOTf was not commercially available, and needed to be synthesised from (-)-\alpha-pinene and borane. The resultant IPC\textsubscript{2}BH was then treated with TfOH to generate a stock solution of IPC\textsubscript{2}BOTf that could be used following Paterson’s methodology.\textsuperscript{26} With this solution in hand, 3-pentanone (3.29) and aldehyde 3.28 were treated with IPC\textsubscript{2}BOTf/iPr\textsubscript{2}NEt under Paterson’s conditions to potentially form the syn aldol product (Scheme 3.31). Disappointingly, the desired syn aldol product was not observed. Instead, the reaction failed to proceed, with slow decomposition observed over an extended period of time.
It is likely that the extreme moisture sensitivity of the IPC₂BOTf led to the failure of this pathway, with the IPC₂BOTf likely quenched by small quantities of water. This setback forced us to reconsider our approach. Specifically, we turned our attention towards using an Evans’ auxiliary to control the stereoselectivity of the aldol reaction. In order to achieve the desired relative stereochemistry across the three stereocentres of 3.60, (R)-4-benzyl-2-oxazolidinone (3.58) was chosen as the starting material. The oxazolidinone was first converted into the propionyl amide 3.59 under the standard conditions ($n$-BuLi, propionyl chloride)²⁷ and subsequently subjected to Evan’s aldol conditions to generate the desired aldol product 3.60 (Scheme 3.32).

The stereoselectivity of this reaction was very good, with no other peaks observed in the NMR spectrum of 3.60. We would expect to see multiple compounds if the selectivity was poor, with C-2 a fixed stereocentre. The aldol product 3.60 was observed to have an identical R$_f$ value to the starting material 3.59, thus the fact that the reaction failed to go to completion made purification extremely difficult. As a result, the aldol product 3.60 was carried through as a mixture to the next step and was not fully characterised.

The chiral auxiliary attached to 3.60 was cleaved by converting the structure into a Weinreb amide using MeONHMe.HCl and AlMe₃, which afforded 3.61 in 65% yield over the two steps.²⁸ Weinreb amide 3.61 was then treated with ethylmagnesium bromide to afford ketone 3.57. This provided a single enantiomer of our previously synthesised hydroxyketone 3.30 (Scheme 3.33).
With hydroxyketone 3.57 in hand, we could now protect the C-5 hydroxy group and subsequently couple this compound with o-QM precursor 2.16. The C-5 hydroxy group was protected using TMSCl and pyridine to afford 3.62 in 81% yield (Scheme 3.34). The polarity of this compound made it particularly difficult to separate from the TMS hydrolysis products. Furthermore, a TBS group was also attached to the C-5 hydroxyl group, with a goal to test the effect of having greater steric hindrance on the Michael reaction with o-QM precursor 2.16. This was completed using the more reactive silylating agent TBSOTf, as use of TBSCI failed to deliver the desired product 3.63.

Having optimised the enolate coupling with an o-QM (reported in Section 3.6.5, Table 3.3), we were in the perfect position to perform our key coupling reaction. Thus, the two silyl protected ketones 3.62 and 3.63 were reacted with o-QM precursor 2.16, in the presence of LiTMP at −78 °C over 7 hours to afford linear coupled intermediates 3.64 and 3.65 in 17% and 27% yield respectively (Scheme 3.35). A series of spots were observed by TLC. Again, these were not separated but were carried through to the next step where a clear representation of diastereomeric ratio could be observed. This involved stirring the coupled products 3.64 and 3.65 in 3M HCl in CH₃CN for 15 minutes, which afforded an inseparable mixture of 3.66 and 3.67 in a 4.5:1 ratio (TMS pathway) and a 2.4:1 ratio (TBS pathway). Purification and NMR analysis allowed for the relative stereochemistry and ratios to be determined. The spiroketalisation proceed in a modest yield of 69% (TMS pathway) and 67% (TBS pathway), predominantly due to the propensity of the C-11 hydroxy group towards elimination.
Scheme 3.35: TMS and TBS ketone coupling with $\alpha$-QM precursor 2.16 and spiroketalisation

The major product of both of these reactions was determined by interpretation of the 2D NMR, specifically analysis of the NOESY data, where the key couplings assign the major product as having the $S$ configuration at C-8 (3.66) rather than the required $R$ configuration at C-8 (3.67). Notably, the NMR analysis was performed in C$_6$D$_6$ due to a significant amount of spectral overlap when CDCl$_3$ was employed as the solvent. A key correlation between the C-8 and C-10 hydrogens confirmed C-8 was in the $S$ configuration and a correlation between C-11 and C-13 hydrogens confirmed the conformation of the 6-membered ring. This axial-axial correlation demonstrated that the C-18, C-11 OH and C-19 are all in the equatorial position as we would expect energetically (Figure 3.4).

The observed ratios of 3.66 to 3.67 demonstrate that the di-TBS derivative slightly favours the formation of peniphenone A (3.1) with a 2.4:1 (3.66:3.67) ratio compared to TMS-TBS derivative (4.5:1 of 3.66:3.67 ratio). Unfortunately, the two diastereoisomers were
inseparable by flash chromatography. We therefore decided to carry the mixture through to the next step, hoping that the two compounds may become separable. Spiroketals 3.66 and 3.67 were ultimately subjected to Ley oxidation conditions (TPAP, NMO, 4Å mol. sieves) to afford 8-epi-peniphenone A (3.55) and peniphenone A (3.1) in a 2.35:1 diastereomeric ratio (from the TBS route) (Scheme 3.36). The more favourable ratio of peniphenone A (3.1) to 8-epi-peniphenone A (3.55) (1:2.35) associated with the TBS pathway prompted the utilisation of the di-TBS protected compound 3.63 for all future reactions.

![Scheme 3.36: Ley oxidation of C-11 hydroxyl group](image)

Ideally, a more stereocontrolled route towards peniphenone A, with inversion of the C-8 stereocentre from S to R would be desirable. We suspect that this stereocentre can ultimately be governed by the E/Z character of the enolate intermediate 3.68, generated in situ. It is of note that deprotonation of ketones with lithiated bases preferentially form E-enolates. However, certain additives are able to reverse this phenomenon to afford the Z-enolate. The most common reagents used are boron reagents (IPC₂BOTf, Bu₂BOTf) that preferentially induce formation of the Z-boron enolate. After having limited success with non-lithiated bases we opted for a different additive, namely HMPA. HMPA has been observed to invert the relative E/Z ratio of lithiated enolates, in favour of the Z-enolate. This is proposed to occur via HMPA solubilising and stabilising the transition state associated with formation of the Z-enolate. Considering, our success with the di-TBS protected system towards formation of peniphenone A (3.1), we focused our attention towards the coupling of 3.63 with o-QM precursor 2.16 in the presence of HMPA. Formation of the enolate 3.68 under HMPA-THF mediated conditions followed by addition of o-QM precursor 2.16 afforded 3.69 in 27% yield. Unfortunately, the major spot isolated contained an extremely complex ¹H NMR spectrum, with what appeared to be a mixture of products. Nevertheless, 3.69 was subsequently subjected to our previously optimised double desilylation-spirocyclisation conditions (3M HCl in CH₃CN), and to our delight, yielded the desired spiroketal 3.67 in 23% yield over the two steps (Scheme 3.37). As expected the stereochemistry at the C-8 position was inverted from S to R,
with a diastereomeric ratio of 16:1 in favour of 8R in contrast to 1:2.4 ratio in the absence of HMPA.

Scheme 3.37: HMPA mediated coupling followed by spirocyclisation

Interestingly, we observed that spiroketal 3.67 was less prone to elimination at C-11 compared with its C-8 epimer 3.66 when the reaction time was extended from 15 minutes to 16 hours. This tactic assisted in the removal of the undesired epimer through elimination at C-11, culminating in an overall 16:1 diastereomeric ratio in favour of 3.67.

Furthermore, the C-8 configuration was confirmed via interpretation of the 2D NOESY data and determined as 8R (Figure 3.5). We observed key cross peaks between the hydrogen at C-10 and methyl group at C-17, and the hydrogen at C-8 and the methyl of C-18 (see Section 3.10.1 for spectra).

Figure 3.5: NOESY correlations of 3.67

The final step in the synthesis of peniphenone A (3.1) was the Ley oxidation of the C-11 hydroxyl group, revealing the ketone functionality in 60% yield (Entry 1). Attempts to optimise this oxidation toward peniphenone A is depicted in Table 3.5. Ley oxidation proved to be the most reliable, with PCC and NaHCO$_3$ buffered Dess-Martin periodinane (Entry 2 and 3) giving similar yields. Furthermore, spiroketal 3.67 was most stable under the Ley oxidation conditions, where 3.67 could be stirred overnight with the majority of the starting material consumed and minimal decomposition observed, as opposed to unbuffered DMP oxidation (Entry 4).
Table 3.5: Screened conditions for oxidation to peniphenone A (3.1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 3.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TPAP, NMO, 4Å mol. sieves, CH₂Cl₂, 0 °C to rt, 16 h</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, 0 °C to rt, 2 h</td>
<td>59%</td>
</tr>
<tr>
<td>3</td>
<td>PCC, CH₂Cl₂, rt 16 h</td>
<td>57%</td>
</tr>
<tr>
<td>4</td>
<td>Dess-Martin periodinane, CH₂Cl₂, 0 °C to rt, 2 h</td>
<td>15%</td>
</tr>
</tbody>
</table>

The spectroscopic data of peniphenone A matched that reported by She and Liu, with the exception of the optical rotation value. Isolated (−)-peniphenone A (3.1) was assigned as 8R,9R,10R,13R with an optical rotation value of $[\alpha]_{D}^{25} = -172$, whereas our synthesis definitively afforded 8R,9R,10R,13R-peniphenone A with an observed optical rotation value of $[\alpha]_{D}^{25} = +85.6$. This value is half of that reported by She and Liu and also is the opposite sign. Our synthesis unambiguously assigns the absolute configuration of (+)-peniphenone A ((+)-3.1) as 8R,9R,10R,13R, which is opposite to that reported in the isolation paper. The lower value observed could be attributed to a large degree of error in the optical rotation measurement conducted by the isolation chemists on a very small quantity of material (1.4 mg of (±)-peniphenone A was isolated and the enantiomers separated by chiral HPLC).

In summary, peniphenone A (3.1) was successfully synthesised in 9 steps (longest linear sequence) in 6% overall yield from cheap and readily available starting materials. The key highlights of our approach involved HMPA mediated coupling of a Z-enolate with an o-QM followed by an acid catalysed double desilylation-spiroketalisation reaction resulting in good diastereoselectivity. Although a truly biomimetic synthesis was not achieved, the groundwork has been put in place for this to be completed, provided the desired exocyclic enol ether 3.5 can be synthesised.
3.7 Summary

In conclusion, we have completed the first total synthesis of the entire family of natural products peniphenones A-D (3.1-3.4) via Michael reactions of enols or enolates with a common \( o\)-QM 2.9. Although peniphenone A was not unveiled by a completely biomimetic route involving exocyclic enol ether 3.5, we were still able to complete the total synthesis through a more pragmatic approach. The remaining members, peniphenones B-D (3.2-3.4), were synthesised via a bioinspired cascade reactions akin to the methodology developed in Chapter 2. The scope of these very reactive intermediates (\( o\)-QMs) was further expanded through this novel synthetic approach, where we have developed a very strong basis for the synthesis of other complex spiroketal natural products, such as the virgatolides\(^{34}\) (Chapter 4) and the chaetoquadrins.\(^{35,36}\)
3.8 Supporting Information

3.8.1 General Experimental

All commercially obtained chemicals were used without further purification. Solvents stated as dry, were either collected from a solvent purification system (THF or DMF), or distilled under an atmosphere of nitrogen and stored over 4Å molecular sieves. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F$_{254}$ aluminium sheets and visualised under a UV lamp or with ceric ammonium molybdate (CAM), vanillin or potassium permanganate staining followed by heating. All R$_f$ values are rounded to the nearest 0.05. Davisil 43-60 micron chromatographic silica media was used for flash chromatography. $^1$H NMR spectra were recorded on an Agilent 500 spectrometer ($^1$H at 500 MHz, $^{13}$C at 125 MHz) in CDCl$_3$ as the solvent unless specified otherwise. $^1$H chemical shifts are reported in ppm relative to TMS (δ 0.0) and $^{13}$C NMR are reported in ppm relative to TMS (δ 0.0). All J values were quoted to the nearest 0.1 Hz. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sext) sextet and (m) multiplet. IR spectra were recorded on a Perkin-Elmer Fourier-Transform Infrared (FT-IR) spectrometer on a nickel-selenide crystal as neat compounds. High resolution mass spectra were obtained on an Agilent ESI high resolution mass spectrometer. Melting points were recorded on a Reichert electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on an Anton Paar MCP 100 polarimeter in either CHCl$_3$ or MeOH.
3.8.2 Experimental Procedures

**ethyl 5-(3,4-dimethoxyphenyl)-3,5-dioxopentanoate 3.11**

To a solution of i-Pr$_2$NH (3.60 mL, 25.5 mmol) in dry Et$_2$O (50 mL) at −78 °C was added n-BuLi (1.0 M hexanes, 10.2 mL, 25.5 mmol) and the mixture was then stirred at 0 °C for 30 minutes. The solution was cooled to −78 °C and ethylacetoacetate (3.10) (1.30 mL, 10.2 mmol) and TMEDA (1.53 mL, 10.2 mmol) was added dropwise. Then the solution was warmed to 0 °C and stirred for 3 hours. To this solution was added methyl 3,4-dimethoxybenzoate (3.9) (2.00 g, 10.2 mmol) in dry Et$_2$O (40 mL) and the reaction was warmed to rt and stirred for 2 days. Acetic acid (2 mL) was added and the mixture was stirred for 10 minutes. The resultant precipitate was collected by vacuum filtration and washed with Et$_2$O (50 mL). The filtrate was set aside, and the precipitate was taken up in 1M HCl (100 mL) and CH$_2$Cl$_2$ (150 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The set aside filtrate was washed with 1M HCl (100 mL), and the aqueous extracted with Et$_2$O (2 x 100 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo. The two crude residues were purified by flash chromatography (SiO$_2$, petroleum ether/ EtOAc, 4:1) to give 3.11 (1.25 g, 42%) as a yellow oil. The spectroscopic data was consistent with that reported in the literature. 

- **R$_f$** = 0.35 (petroleum ether/ EtOAc, 2:1)

- **IR (neat):** 2978, 1735, 1595, 1513, 1463, 1263, 1136, 1021 cm$^{-1}$

- **$^1$H NMR (500 MHz, CDCl$_3$) δ 7.51 (dd, $J$ = 8.4, 2.0 Hz, 1H), 7.45 (d, $J$ = 2.0 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.23 (s, 1H), 4.22 (q, $J$ = 7.1 Hz, 2H), 3.94 (s, 6H), 3.44 (s, 2H), 1.30 (t, $J$ = 7.1 Hz, 3H).

- **$^{13}$C NMR (125 MHz, CDCl$_3$) δ 186.2, 184.1, 167.8, 153.1, 149.1, 127.2, 121.4, 110.5, 109.7, 96.1, 61.5, 56.09, 56.04, 45.2, 14.2.
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6-(3,4-dimethoxyphenyl)-4-hydroxy-2H-pyran-2-one 3.12

![Chemical Structure]

Ethyl 5-(3,4-dimethoxyphenyl)-3,5-dioxopentanoate 3.11 (1.77 g, 6.02 mmol) was heated at 160 °C under vacuum (55 mmHg) for 2 hours. The reaction was cooled and Et₂O (10 mL) was added. The resultant precipitate was collected by vacuum filtration and washed with Et₂O (10 mL) to give 3.12 (654 mg, 44%) as a brown solid. The spectroscopic data was consistent with that reported in the literature.⁶

R_f = 0.0 (petroleum ether/ EtOAc, 1:1)

Mp: 223-225 °C

IR (neat): 2958, 1622, 1585, 1558, 1512, 1437, 1405, 1233, 1143, 1023 cm⁻¹

^1H NMR (500 MHz, DMSO) δ 11.73 (s, 1H), 7.44 (dd, J = 8.5, 2.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 6.72 (s, 1H), 5.34 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H).

^13C NMR (125 MHz, DMSO) δ 170.8, 163.1, 160.3, 151.2, 148.9, 123.5, 118.8, 111.7, 108.5, 97.0, 88.7, 55.67, 55.64.
2-Methylenecetoxo-4-methyl-6-acetylresorcinol 2.16 (48 mg, 0.20 mmol) and pyrone 3.12 (50 mg, 0.20 mmol) were dissolved in AcOH (10 mL) in a sealed tube. The tube was flushed with N₂, sealed and the reaction mixture heated at 120 °C for 16 hours. The reaction mixture was then cooled and the formed precipitate collected via vacuum filtration, to give 3.13 (57 mg, 66 %) as a brown solid, which was used without further purification.

\[ \text{Rf} = 0.20 \text{ (petroleum ether/ EtOAc, 1:1)} \]

**Mp:** 158-160 °C

**IR (neat):** 3215, 2940, 1667, 1625, 1568, 1517, 1377, 1274, 1149 cm⁻¹

**¹H NMR (500 MHz, CDCl₃)** \( \delta \) 10.34 (s, 1H), 9.74 (s, 1H), 7.43 (s, 1H), 7.39 (d, \( J = 8.5 \text{ Hz} \), 1H), 7.28 (s, 1H), 6.91 (d, \( J = 8.5 \text{ Hz} \), 1H), 6.50 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.78 (s, 2H), 2.57 (s, 3H), 2.22 (s, 3H).

**¹³C NMR (125 MHz, CDCl₃)** \( \delta \) 203.3, 167.9, 162.0, 159.4, 158.7, 151.7, 149.3, 130.9, 123.4, 119.6, 119.2, 112.51, 112.39, 111.1, 108.2, 102.0, 98.2, 56.13, 56.06, 25.9, 17.5, 16.1.

**HRMS (C₂₃H₂₂O₈, ESI):** calculated [M-H]⁻ 425.1242, found 425.1245
Peniphenone B 3.2

To a solution of dimethoxy peniphenone B 3.13 (58 mg, 0.14 mmol) in CHCl₃ (3 mL) was added BBr₃ (1.0 M in CH₂Cl₂, 1.36 mL, 1.36 mmol) dropwise and the reaction mixture was heated at reflux for 1.5 hours. The reaction mixture was quenched with 1M HCl (5 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The resultant solid was recrystallised from acetone to give peniphenone B 3.2 (51 mg, 94%) as a yellow solid.

Rₚ = 0.05 (petroleum ether/ EtOAc, 1:1)

Mp: 255-260 °C

IR (neat): 3329, 2924, 1655, 1605, 1555, 1526, 1369, 1289, 1182, 1138 cm⁻¹

¹H NMR (500 MHz, DMSO) δ 13.10 (s, 1H), 9.65 (s, 1H), 9.40 (s, 1H), 7.55 (s, 1H), 7.14 (d, J = 2.2 Hz, 1H), 7.09 (dd, J = 8.4, 2.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.52 (s, 1H), 3.68 (s, 2H), 2.53 (s, 3H), 2.11 (s, 3H).

¹³C NMR (125 MHz, DMSO) δ 203.1, 169.2, 167.3, 167.0, 161.3, 160.9, 158.1, 148.6, 145.7, 130.9, 121.7, 117.4, 116.6, 116.1, 112.8, 112.23, 112.18, 100.1, 96.4, 26.3, 16.9, 16.0.

HRMS (C₂₁H₁₈O₈, ESI): calculated [M+H]⁺ 399.1090, found 399.1087
1,3,4-triacetoxy-2,5-dimethylbenzene 3.15

To a solution of 2,5-dimethyl-1,4-benzoquinone (3.13) (1.00 g, 7.34 mmol) in Ac₂O (8 mL) was added BF₃·OEt₂ (0.40 mL, 3.1 mmol) dropwise and the mixture was heated at 40 °C for 48 hours. The reaction mixture was then poured onto ice water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to give 3.15 (1.96 g, 95%) as a yellow solid, which was carried onto the next step without further purification. The spectroscopic data was consistent with that reported in the literature.⁸

Rᵣ = 0.60 (petroleum ether/EtOAc, 1:1)

IR (neat): 2933, 1757, 1367, 1195, 1171, 1074, 1008, 926, 867 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 6.85 (s, 1H), 2.29 (s, 6H), 2.29 (s, 3H), 2.15 (s, 3H), 1.96 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 168.8, 167.9, 167.7, 146.8, 141.8, 139.2, 129.5, 122.5, 121.5, 20.7, 20.28, 20.27, 16.0, 10.2.
1,3,4-trihydroxy-2,5-dimethylbenzene 3.7

To a solution of 1,3,4-triacetoxy-2,5-dimethylbenzene 3.15 (1.0 g, 3.6 mmol) in H$_2$O (80 mL) was added conc. HCl (80 mL) and the reaction mixture was stirred at reflux for 1 hour until the starting material dissolved. The reaction mixture was cooled and diluted with H$_2$O (50 mL) and Et$_2$O (100 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (2 x 50 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo to give 3.7 (550 mg, quantitative) as an off white solid, which was carried on to the next step without further purification. The spectroscopic data was consistent with that reported in the literature.$^9$

$^8$R$_f$ = 0.50 (petroleum ether/EtOAc, 1:1)

**IR (neat):** 3373, 3257, 2927, 1716, 1521, 1473, 1370, 1301, 1222, 1192, 1066 cm$^{-1}$

**$^1$H NMR (500 MHz, DMSO) $\delta$** 8.33 (s, 1H), 7.90 (s, 1H), 7.41 (s, 1H), 6.02 (s, 1H), 2.02 (s, 3H), 1.91 (s, 3H).

**$^{13}$C NMR (125 MHz, DMSO) $\delta$** 148.3, 144.7, 135.3, 121.8, 108.6, 106.9, 16.2, 9.1.
Peniphenone C 3.3

![Chemical Structure](image)

2-Methylenacetoxy-4-methyl-6-acetylresorcinol (2.16) (100 mg, 0.420 mmol) and 1,3,4-trihydroxy-2,5-dimethylbenzene (3.7) (59 mg, 0.38 mmol) were dissolved in toluene (10 mL) in a sealed tube and heated at 110 °C for 2 hours. The reaction mixture was cooled and the solvent was removed in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/Acetone, 5:1) to give the auto-oxidised product peniphenone C 3.3 (92 mg, 72%) as a bright yellow solid.

R<sub>f</sub> = 0.35 (petroleum ether/acetone, 5:1)

Mp: 212-216 °C

IR (neat): 3320, 2926, 1655, 1625, 1603, 1284, 1253, 1156, 1083 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, CDCl₃) δ 13.18 (s, 1H), 9.57 (s, 1H), 7.41 (s, 1H), 3.74 (s, 2H), 2.53 (s, 3H), 2.37 (s, 3H), 2.22 (s, 3H), 1.91 (s, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl₃) δ 202.7, 191.2, 183.7, 161.8, 161.1, 151.6, 143.4, 139.8, 131.1, 118.4, 116.8, 112.8, 110.6, 26.2, 22.0, 16.1, 12.5, 8.2.

HRMS (C₁₈H₁₈O₆, ESI): calculated [M+H]<sup>+</sup> 331.1176, found 331.1181
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(-)-Peniphenone D 3.4

2-Methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (100 mg, 0.42 mmol) and (R)-5-methyltetronic acid (2.10) (144 mg, 1.26 mmol) were dissolved in toluene (10 mL) in a sealed tube. The tube was flushed with N₂, sealed and then the reaction mixture was heated at 110 °C for 16 hours. The reaction mixture was concentrated in vacuo, then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 4:1 → 2:1 gradient elution) to give (-)-3.4 (63 mg, 51%) as a white solid.

R f = 0.05 (petroleum ether/EtOAc, 2:1)

[α]₂⁵ = -6.8 (c 1.0, MeOH),

Mp: 175-177 °C

IR (neat): 3159, 2916, 2583, 1714, 1655, 1576, 1322, 1233, 1099, 1055, 808 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 13.97 (br s, 1H), 8.58 (br s, 1H), 8.24 (br s, 1H), 7.41 (d, J = 0.5 Hz, 1H), 4.84 (q, J = 6.8 Hz, 1H), 3.48 (d, J = 15.1 Hz, 1H), 3.43 (d, J = 15.1 Hz, 1H), 2.57 (s, 3H), 2.21 (d, J = 0.5 Hz, 3H), 1.46 (d, J = 6.8 Hz, 3H)

¹³C NMR (150 MHz, CDCl₃) δ 203.5, 177.2, 175.8, 160.2, 158.8, 130.7, 119.5, 113.3, 112.8, 101.5, 76.2, 26.0, 17.2, 15.9, 14.5.

HRMS (C₁₅H₁₈O₆, ESI): calculated [M-H] 291.0874, found 291.0871
2-methylenetetrahydro-2H-pyran \( \text{3.17} \)

\[
\begin{align*}
\text{3.16: 2-(chloromethyl)tetrahydro-2H-pyran} & \quad \text{KOH, reflux, 3.5 h} & \quad \text{3.17} \\
\end{align*}
\]

2-(Chloromethyl)-tetrahydro-2H-pyran \( \text{3.16} \) (2.8 mL, 22.3 mmol) and powdered KOH (2.5 g, 44.6 mmol) were heated at reflux for 4 hours. The resultant mixture was then distilled at 190 °C onto KOH pellets to give \( \text{3.17} \) (1.47 g, 67%) as a colourless oil. The spectroscopic data was consistent with that reported in the literature.\(^{10} \) \( \text{3.17} \) was observed to be unstable, as a consequence \( \text{3.17} \) was synthesised fresh each time and immediately carried through to the next step.

Partial data for \( \text{3.17} \):

\(^1\text{H NMR (500 MHz, CDCl}_3\)} \delta 4.29 (s, 1H), 4.02 (s, 1H), 3.87 (br s, 2H), 2.22 (br s, 2H), 1.70-1.71 (m, 4H).
Isomeric compound 3.19 and double Michael reaction product 3.20

2-Methylenecetoxy-4-methyl-6-acetylresorcinol (2.16) (100 mg, 0.42 mmol) and 2-methylenetetrahydro-2H-pyran (3.17) (38 mg, 0.38 mmol) in toluene (5 mL) were heated at 110 °C in a sealed tube for 16 hours. The solvent was removed in vacuo and the residue purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 10:1 → 1:1 gradient elution) to give 3.19 (28 mg, 26%) as a colourless oil as an 9:1 mixture of isomers (3.19 : 3.18), further elution afforded 3.20 (13 mg, 14%) as a colourless oil.

Data for 3.19:

Rᵣ = 0.45 (petroleum ether/EtOAc, 5:1)

IR (neat): 2931, 1738, 1620, 1478, 1373, 1282, 1232, 1193, 1116, 1074, 997 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 12.93 (s, 1H), 7.36 (s, 1H), 3.99 – 3.92 (m, 1H), 3.78 (dd, J = 11.2, 4.8 Hz, 1H), 2.83 (dd, J = 17.5, 6.5 Hz, 1H), 2.62 (d, J = 17.5 Hz, 1H), 2.54 (s, 3H), 2.17 (s, 3H), 2.06 – 1.97 (m, 1H), 1.81 – 1.72 (m, 1H), 1.58-1.54 (m, 2H), 1.41 (s, 3H), 1.38 – 1.27 (m, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 202.6, 161.3, 158.3, 129.6, 117.2, 112.4, 106.5, 100.9, 62.1, 34.4, 26.2, 25.2, 25.09, 25.07, 25.05, 15.7.

HRMS (C₁₆H₂₀O₄, ESI): calculated [M-H]⁻ 275.1289, found 275.1278

Data for 3.20:

Rᵣ = 0.10 (petroleum ether/EtOAc, 5:1)

IR (neat): 3357, 2946, 1626, 1480, 1444, 1380, 1286, 1190, 1114 cm⁻¹
$^1$H NMR (500 MHz, CDCl$_3$) 13.07 (s, 1H), 12.88 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 6.04 (br s, 1H), 4.17 (td, $J = 11.9$, 3.3 Hz, 1H), 3.85 (dd, $J = 12.2$, 5.6 Hz, 1H), 3.19 (d, $J = 14.0$ Hz, 1H), 2.95 (d, $J = 14.9$ Hz, 1H), 2.91 (d, $J = 18.6$ Hz, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 2.46 (d, $J = 17.8$ Hz, 1H), 2.42 – 2.28 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.54 (s, 3H), 1.53 – 1.49 (m, 1H), 1.48 – 1.4 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 202.8, 202.6, 162.7, 161.1, 160.2, 157.4, 131.1, 129.5, 116.8, 114.6, 113.6, 112.51, 112.44, 108.2, 104.5, 62.0, 37.4, 26.9, 26.5, 26.35, 26.2, 22.0, 20.7, 15.8, 15.7.

HRMS ($C_{26}H_{30}O_7$, ESI): calculated [M-H]$^-$ 453.1919, found 453.1916
Simplified peniphenone A analogue 3.18

To a solution of 2-methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (50 mg, 0.21 mmol) and 2-methylenetetrahydro-2H-pyran (3.17) (98 mg, 1.0 mmol) in toluene (5 mL) was added Et$_3$N (0.06 mL, 0.42 mmol). The reaction was heated at 110 °C in a sealed tube for 16 hours. The solvent was removed in vacuo and the residue purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 10:1) to give 3.18 (31 mg, 53%) as a pale yellow oil.

$R_f = 0.45$ (petroleum ether/EtOAc, 5:1)

IR (neat): 2942, 2872, 1619, 1478, 1438, 1369, 1331, 1266, 1230, 1177, 1145, 1070 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.84 (s, 1H), 7.36 (s, 1H), 3.72 (td, $J = 11.8, 2.8$ Hz, 1H), 3.65 (dd, $J = 11.1, 4.7$ Hz, 1H), 2.75 – 2.69 (m, 2H), 2.54 (s, 3H), 2.21 (s, 3H), 2.09 – 2.01 (m, 2H), 1.92 (d, $J = 13.4$ Hz, 1H), 1.80 – 1.58 (m, 5H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 202.7, 160.5, 156.9, 129.4, 117.3, 112.7, 110.4, 96.8, 62.2, 34.5, 31.0, 26.2, 25.1, 18.6, 15.4, 15.1.

HRMS (C$_{16}$H$_{20}$O$_4$, ESI): calculated [M+H]$^+$ 277.1434, found 277.1440
To a solution of \((R)\)-methyl 3-hydroxybutyrate (3.26) (4.00 g, 33.9 mmol) in DMF (50 mL) was added imidazole (4.61 g, 67.8 mmol), followed by TBSCl (5.31 g, 35.5 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched with sat. NH$_4$Cl (100 mL) and diluted with Et$_2$O (150 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (2 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over MgSO$_4$, filtered and concentrated \textit{in vacuo}. The resultant residue was purified by flash chromatography (SiO$_2$, petroleum ether/Et$_2$O, 8:1) to give 3.27 (7.69 g, 98%) as a colourless oil. The spectroscopic data was consistent with that reported in the literature.$^{12}$

\[ R_f = 0.55 \text{ (petroleum ether/EtOAc, 5:1)} \]

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.28 (dq, $J = 12.3$, 6.0 Hz, 1H), 3.66 (s, 3H), 2.48 (dd, $J = 14.5$, 7.7 Hz, 1H), 2.38 (dd, $J = 14.5$, 5.2 Hz, 1H), 1.19 (d, $J = 6.1$ Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.1, 65.9, 51.4, 44.8, 25.7, 24.0, 18.0, -4.5, -5.1.
(R)-3-((tert-butyldimethylsilyl)oxy)butanal 3.28

To a solution of (R)-methyl 3-((tert-butyldimethylsilyl)oxy)butanoate (3.27) (7.60 g, 32.7 mmol) in CH₂Cl₂ (300 mL) at −78 °C was added diisobutylaluminium hydride (1.0 M in cyclohexane, 45.7 mL, 45.7 mmol) dropwise over 1 hour and the reaction mixture stirred at −78 °C for 2 hours. The reaction was quenched with 1M HCl (100 mL) and stirred for 10 minutes. The organic layer was separated, and the aqueous layer extracted with CH₂Cl₂ (2 x 150 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, Petroleum ether/EtOAc, 50:1 - 20:1 gradient elution) to give 3.28 (4.42 g, 68%) as a colourless oil. The spectroscopic data was consistent with that reported in the literature.¹²,¹³

Rₐ = 0.45 (petroleum ether/EtOAc, 5:1)

[α]ᵢ²⁵ = −8.1 (c 1.1, CHCl₃)

IR (neat): 2957, 2930, 1728, 1473, 1376, 1255, 1098, 1028, 834 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 9.80 (s, 1H), 4.35 (dq, J =12.3, 6.2 Hz, 1H), 2.55 (ddd, J = 15.1, 7.0, 2.2 Hz, 1H), 2.46 (dd, J = 15.7, 4.9 Hz, 1H), 1.24 (d, J = 6.2 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 202.2, 64.6, 53.0, 25.7, 24.2, 18.0, -4.4, -4.9.
(7R)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-4-methyloctan-3-one 3.30

\[
\text{3.29: 3-pentanone} \quad \xrightarrow{\text{LDA, THF, } -78^\circ C, 1 \text{ h}} \quad \text{3.30}
\]

To a solution of diisopropylamine (2.23 mL, 16.3 mmol) in THF (200 mL) at −78 °C was added n-BuLi (2M in cyclohexane, 7.45 mL, 14.9 mmol) and the mixture stirred at 0 °C for 20 minutes. The reaction mixture was cooled to −78 °C and 3-pentanone (3.29) (1.44 mL, 13.6 mmol) was added dropwise and then stirred for 20 minutes. To this solution was added (R)-3-((tert-butyldimethylsilyl)oxy)butanal (3.28) (2.75 g, 13.6 mmol) in THF (5 mL) dropwise, and then the reaction mixture was stirred at −78 °C for 1 hour. The reaction was quenched with sat NH₄Cl (100 mL) and diluted with Et₂O (200 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated \textit{in vacuo}. The resultant residue was then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 8:1) to give 3.30 (3.44 g, 88%) as a pale yellow oil as a complex mixture of diastereoisomers. Due to the complexity of the spectra this compound was not fully characterised.

Partial data for 3.30:

\[
\text{R} \text{f} = 0.30 \text{ (petroleum ether/EtOAc, 5:1)}
\]

\[\text{IR (neat): 3497, 2931, 2858, 1707, 1463, 1377, 1256, 1068, 1005, 908, 836 cm}^{-1}\]

\[\text{HRMS (C}_{15}\text{H}_{32}\text{O}_{3}\text{Si, ESI): calculated [M+Na]}^+ 311.2013, \text{ found 311.2014} \]
(7R)-7-((tert-butyldimethylsilyl)oxy)-4-methyloctane-3,5-dione 3.24

To a solution of 3.30 (110 mg, 0.48 mmol) in CH$_2$Cl$_2$ (10 mL) was added NaHCO$_3$ (81 mg, 0.96 mmol) and Dess-Martin periodinane (204 mg, 0.48 mmol) at 0 °C and the reaction was then stirred gradually warming to room temperature for 1 hour. The reaction mixture was concentrated in vacuo, and then purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 3:1) to give 3.24 (98 mg, 90%) as a colourless oil as a 1:1 mixture of diastereoisomers.

Partial Data for 3.24:

$R_F = 0.40$ (petroleum ether/EtOAc, 5:1)

IR (neat): 2931, 1728, 1702, 1462, 1376, 1255, 1134, 1086 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.33-4.28 (m, 2H), 3.67 (dd, $J = 12.9, 6.4$ Hz, 2H), 2.71 (dd, $J = 16.5, 6.8$ Hz, 1H), 2.65 (dd, $J = 15.9, 7.6$ Hz, 1H), 2.57 – 2.41 (m, 4H), 1.36 – 1.22 (m, 6H), 1.21 – 1.11 (m, 6H), 1.04 (q, $J = 7.1$ Hz, 6H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 207.9, 207.5, 205.9, 205.7, 66.8, 65.9, 65.3, 64.7, 61.5, 61.3, 51.4, 51.2, 51.0, 44.8, 44.5, 35.1, 34.9, 24.0, 23.8, 17.97, 17.93, 12.5, 12.3, -4.6, -4.86, -4.93, -5.1.
Conjugated endocyclic alkene 3.31

To a solution of diketone 3.24 (50 mg, 0.17 mmol) in CH₂Cl₂ (3 mL) was added p-TsOH (36 mg, 0.19 mmol) and the reaction was stirred at room temperature for 16 hours. The reaction mixture was quenched with sat. NaHCO₃ (10 mL) and diluted with CH₂Cl₂ (15 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 5:1) to give 3.31 (24 mg, 89%) as a colourless oil. Data was consistent with that reported in the literature.¹⁴

\[ R_f = 0.20 \text{ (petroleum ether/EtOAc, 5:1)} \]

\[ \text{IR (neat): } 2978, 1724, 1661, 1606, 1458, 1385, 1367, 1220, 1181 \text{ cm}^{-1} \]

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{) } \delta 4.44-4.33 \text{ (m, 1H), 2.41 (d, } J = 7.7 \text{ Hz, 2H), 2.34 (qd, } J = 14.2, 7.0 \text{ Hz, 2H), 1.73 (s, 3H), 1.41 (d, } J = 6.3 \text{ Hz, 3H), 1.13 (t, } J = 7.6 \text{ Hz, 3H).} \]

\[ ^{13}C \text{ NMR (125 MHz, CDCl}_3\text{) } \delta 193.0, 174.1, 109.0, 74.5, 42.9, 25.7, 20.5, 10.9, 9.0. \]
Eliminated product 3.41

\[
\begin{align*}
\text{2.16} & \quad \text{OAc} \\
\text{3.30} & \quad \text{TBS} \quad \text{AcOH, 120 °C, 3 days} \quad \rightarrow \\
\text{3.41} & \quad \text{(23%)}
\end{align*}
\]

2-Methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (121 mg, 0.42 mmol) and 3.30 (100 mg, 0.42 mmol) were dissolved in AcOH (10 mL) in a sealed tube and heated at 120 °C for 3 days. The reaction mixture was poured onto sat. NaHCO₃, which was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. NaHCO₃, brine, dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 20:1) to give 3.41 (31 mg, 23%) as a yellow oil that solidifies in the freezer. Product isolated as a 3:1 ratio of two diastereoisomers.

\[R_f = 0.50\] (petroleum ether/acetone, 5:1)

**IR (neat):** 2969, 2927, 1626, 1477, 1381, 1332, 1278, 1189, 1067, 951, 907 cm⁻¹

**Major diastereoisomer:**
**¹H NMR (500 MHz, CDCl₃)** δ 12.86 (s, 1H), 7.33 (s, 1H), 5.83 (d, \(J = 5.9\) Hz, 1H), 4.01 – 3.91 (m, 1H), 2.76 (dd, \(J = 16.4, 5.5\) Hz, 1H), 2.54 (s, 3H), 2.50 – 2.44 (m, 1H), 2.12 (s, 3H), 2.10 – 2.04 (m, 1H), 2.01 – 1.86 (m, 2H), 1.76 (s, 3H), 1.08 (d, \(J = 6.2\) Hz, 3H), 0.98 (d, \(J = 6.6\) Hz, 3H).

**¹³C NMR (125 MHz, CDCl₃)** δ 202.6, 160.2, 157.8, 132.6, 129.1, 126.0, 117.3, 112.4, 110.9, 100.3, 64.4, 32.5, 31.0, 26.2, 23.0, 20.9, 17.9, 15.8, 15.2.

**Minor diastereoisomer:**
**¹H NMR (500 MHz, CDCl₃)** δ 12.85 (s, 1H), 7.33 (s, 1H), 5.81 (d, \(J = 6.8\) Hz, 1H), 4.21 (qnt, \(J = 6.6\) Hz, 1H), 2.69 (dd, \(J = 9.5, 7.4\) Hz, 1H), 2.54 (s, 3H), 2.50 – 2.44 (m, 1H), 2.10 (s, 3H), 2.10 – 2.04 (m, 1H), 2.01 – 1.86 (m, 2H), 1.80 (s, 3H), 1.28 (d, \(J = 6.8\) Hz, 3H), 0.95 (d, \(J = 6.6\) Hz, 3H).
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 202.5, 160.2, 157.8, 132.0, 129.2, 123.2, 117.2, 112.4, 110.6, 98.6, 67.0, 31.8, 29.6, 25.8, 23.2, 20.6, 18.1, 15.8, 15.1.

HRMS (C$_{19}$H$_{24}$O$_4$, ESI): calculated [M+H]$^+$ 317.1747, found 317.1732
To a solution of 3.41 (30 mg, 0.095 mmol) in THF (3 mL) at 0 °C was added BH$_3$·THF (1.0 M in THF, 0.12 mL, 0.12 mmol) and the reaction mixture was stirred for 30 minutes. The reaction mixture was warmed to room temperature and stirred for 16 hours. H$_2$O$_2$ (30%, 1 mL) and 3 M NaOH (1 ml) were added and the reaction mixture stirred at room temperature for 2 hours. The reaction mixture was diluted with Et$_2$O (10 mL) and H$_2$O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 10:1 → 5:1 gradient elution) to afford 3.46 (5 mg, 16%) as a colourless oil as a mixture of diastereoisomers.

Partial Data for 3.46

R$_f$ = 0.45 (petroleum ether/EtOAc, 5:1)

IR (neat): 3370, 2970, 1623, 1477, 1381, 1261, 1191, 1127, 1065 cm$^{-1}$

Major compound:

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 (s, 1H), 6.59 (s, 1H), 5.79 (d, J = 5.9 Hz, 1H), 5.02 – 4.96 (m, 1H), 3.97 (ddd, J = 10.1, 6.2, 3.8 Hz, 1H), 2.74 (dd, J = 16.2, 5.5 Hz, 1H), 2.50 (dd, J = 16.2, 12.7 Hz, 1H), 2.22 (d, J = 4.0 Hz, 1H), 2.12 (dd, J = 13.9, 7.9 Hz, 1H), 2.08 (s, 3H), 1.99 – 1.85 (m, 2H), 1.75 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 6.2 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.0, 133.4, 125.4, 124.8, 118.7, 116.5, 111.7, 99.2, 83.2, 71.7, 63.9, 32.7, 31.1, 23.7, 23.5, 20.9, 18.1, 15.5, 15.3.
Epoxide 3.47

To a solution of 3.41 (15 mg, 0.047 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added mCPBA (32 mg, 0.15 mmol). The reaction mixture was gradually warmed to room temperature and then stirred for 6 hours. The crude mixture was loaded directly onto a column and purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 8:1) to give epoxide 3.47 (2 mg, 13 %) as a colourless oil.

Partial data for 3.47

Rᵣ = 0.40 (petroleum ether/EtOAc, 5:1)

IR (neat): 2926, 2855, 1628, 1455, 1383, 1333, 1279, 1191, 974 cm⁻¹

¹H NMR (500 MHz, CDCl₃)  δ 12.85 (s, 1H), 7.35 (s, 1H), 4.17 – 4.06 (m, 1H), 3.25 (d, J = 2.6 Hz, 1H), 2.77 (dd, J = 16.4, 5.6 Hz, 1H), 2.55 (s, 3H), 2.46 – 2.37 (m, 2H), 2.20 (s, 3H), 2.08 – 2.04 (m, 2H), 2.01 (dd, J = 12.4, 6.3 Hz, 1H), 1.64 – 1.57 (m, 1H), 1.45 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃)  δ 202.7, 159.9, 152.7, 129.2, 117.8, 112.6, 110.3, 62.2, 58.5, 33.0, 32.2, 30.9, 29.7, 26.2, 23.4, 20.5, 19.5, 15.9, 15.6.
Chapter 3

(7R)-7-((tert-butyldimethylsilyl)oxy)-4-methyl-5-((trimethylsilyl)oxy)octan-3-one 3.51

![Chemical structure of 3.30 and 3.51](image)

To a solution of ketone 3.30 (100 mg, 0.35 mmol) in CH$_2$Cl$_2$ (5 mL) at room temperature was added pyridine (0.085 mL, 1.05 mmol) and TMSCl (0.05 mL, 0.38 mmol) and the reaction mixture was stirred for 2 hours. The reaction mixture was quenched with sat. NH$_4$Cl (10 mL) and diluted with CH$_2$Cl$_2$ (15 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 10:1) to give 3.51 (114 mg, 91%) as a colourless oil, isolated as a complex mixture of diastereoisomers. For data of a single diastereoisomer see 3.62.

Partial data for 3.51

$R_f = 0.70$ (petroleum ether/EtOAc, 5:1)

**IR (neat):** 2958, 1711, 1462, 1377, 1252, 1055, 908 cm$^{-1}$
**Adduct 3.52**

To a solution of 2,2,6,6-tetramethylpiperidine (0.14 mL, 0.84 mmol) in THF (6 mL) at −78 °C was added $n$-BuLi (2.0 M in cyclohexane, 0.42 mL, 0.84 mmol) and the mixture was stirred for 20 minutes. Compound 3.51 (100 mg, 0.28 mmol) in THF (2 mL) was then added dropwise at −78 °C and the mixture was stirred for 20 minutes. 2-Methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (66 mg, 0.28 mmol) in THF (2 mL) was then added dropwise at −78 °C and the reaction mixture was stirred for 5 hours. The reaction was quenched with sat. NH$_4$Cl (15 mL) and diluted with EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The major spots on the TLC were separated by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 50:1 → 10:1) to give 3.52 (48 mg, 32%) as a colourless that was a complex and inseparable mixture of up to 8 diastereoisomers.

Partial data for 3.52:

$$R_f = 0.60 \text{ (petroleum ether/EtOAc, 5:1)}$$

**IR (neat):** 2993, 2857, 1689, 1626, 1461, 1373, 1253, 1184, 1075 cm$^{-1}$

**HRMS ($C_{28}H_{50}O_6Si_2$, ESI):** calculated [M-H] $537.3073$, found 537.3062
Spiroketal 3.53

3.52 (51 mg, 0.095 mmol) was dissolved in CH₃CN (8 mL) and 3M HCl (4 mL) was added. The reaction mixture was stirred at room temperature for 15 minutes. The reaction was diluted with H₂O (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1) to give 3.53 (16.7 mg, 53%) as a colourless oil as an inseparable mixture of diastereoisomers.

Partial data for 3.53:

R<sub>f</sub> = 0.05 (petroleum ether/EtOAc, 5:1)

IR (neat): 3413, 2928, 1738, 1627, 1478, 1382, 1333, 1280, 1189, 1066 cm<sup>-1</sup>

HRMS (C<sub>19</sub>H<sub>26</sub>O<sub>5</sub>, ESI): calculated [M-H]<sup>-</sup> 333.1707, found 333.1702
Mixture of peniphenone A diastereoisomers 3.54

To a solution of spiroketal 3.53 (38 mg, 0.11 mmol) in CH₂Cl₂ (10 mL) was added Dess-Martin periodinane (73 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched by the addition of sat. NaHCO₃ (5 mL) and sat. Na₂S₂O₃ (5 mL) and then stirred for 5 minutes. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 3:1) to give 3.54 (21.5 mg, 57%) as a colourless oil as a 1:2:4 ratio of peniphenone A (3.1) to two of its diastereoisomers.

Partial data for 3.54:

**Rf** = 0.25 (petroleum ether/EtOAc, 5:1)

**IR** (neat): 2928, 1725, 1629, 1383, 1333, 1276, 1188, 1074 cm⁻¹

**HRMS** (C₁₉H₂₄O₅, ESI): calculated [M-H]⁻ 331.1551, found 331.1562
To a solution of 3.54 (21.5 mg, 0.065 mmol) in CH$_2$Cl$_2$ (3 mL) was added p-TsOH (25 mg, 0.13 mmol). The reaction mixture was stirred at room temperature for 7 days. The reaction mixture was concentrate in vacuo and the residue was purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 8:1) to give an inseparable mixture (13 mg, 60%) of peniphenone A (3.1), 8-epi-peniphenone A (3.55) and 3.56 as a colourless oil. Data for synthetic peniphenone A matched that reported in the literature.\(^\dagger\)

Partial data for 3.1/3.55/3.56:

\(R_f = 0.25\) (petroleum ether/EtOAc, 5:1)

\[\text{IR (neat): } 2925, 1726, 1630, 1454, 1382, 1332, 1278, 1187, 1076 \text{ cm}^{-1}\]

\[\text{HRMS (C}_{19}\text{H}_{24}\text{O}_5, \text{ESI): } \text{calculated [M-H]} 331.1551, \text{found } 331.1562\]
(R)-4-benzyl-3-((2R,3S,5R)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxy-2-methylhexanoyl)oxazolidin-2-one 3.60

To a solution of (R)-(−)-4-Benzyl-3-propionyl-2-oxazolidinone (3.59) (1.00 g, 4.3 mmol) in CH₂Cl₂ (50 mL) at −78 °C was added dibutylboron trifluoromethanesulfonate (1.0 M in CH₂Cl₂, 6.43 mL, 6.43 mmol) dropwise over 30 min. Et₃N (1.2 mL, 8.6 mmol) was added immediately once the addition was complete and the reaction mixture was stirred at −78 °C for 10 minutes and then warmed to 0 °C and stirred for 1 hour. The solution was cooled to −78 °C and 3.28 (1.3 g, 6.43 mmol) in CH₂Cl₂ (10 mL) was added dropwise and stirred at −78 °C for 20 minutes. The reaction mixture was then warmed to 0 °C and stirred for 3 hours. pH 7 buffer (5 mL), MeOH (20 mL) and H₂O₂ (30% in H₂O, 10 mL) were added and the mixture stirred at 0 °C for 2 hours. The reaction mixture was then diluted with CH₂Cl₂ (100 mL) and H₂O (100 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 5:1) to give 3.60 (1.70 g) as a colourless oil that was an inseparable mixture with the starting material and was carried through to the next step without further characterisation.

Partial data for 3.60:

IR (neat): 3519, 2956, 2930, 1781, 1700, 1384, 1209, 1112, 1007, 836 cm⁻¹

HRMS (C₂₃H₃₇NO₅Si, ESI): calculated [M+Cl⁻] 470.2135, found 470.2133
Weinreb amide 3.61

To a solution of \( N,O \)-dimethylhydroxylamine hydrochloride (1.46 g, 15.0 mmol) in \( CH_2Cl_2 \) (100 mL) was added trimethylaluminium (2.0 M in hexane, 7.50 mL, 15.0 mmol) dropwise at 0 °C over 30 minutes and the mixture was stirred for 1 hour. The reaction mixture was cooled to -20 °C and 3.60 (1.70 g, 3.75 mmol) in \( CH_2Cl_2 \) (10 mL) was added dropwise and the reaction was then warmed to room temperature and stirred for 3 hours. Sat. aq. Rochelle’s salt (25 mL) was added dropwise (strong effervescence) at 0 °C and then stirred for 1 hour. The organic layer was separated and the aqueous layer was extracted with \( CH_2Cl_2 \) (2 x 100 mL). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The resultant residue was purified by flash chromatography (SiO\(_2\), petroleum ether/EtOAc, 5:1 \( \rightarrow \) 2:1 gradient elution) to give 3.61 (902 mg, 65% over 2 steps) as a colourless oil.

\( \text{R}_f = 0.15 \) (petroleum ether/EtOAc, 2:1)

\([\alpha]^{25}_D = -10.1 \) (c 0.70, CHCl\(_3\))

\textbf{IR (neat):} 3472, 2957, 2931, 2857, 1638, 1461, 1381, 1255, 1059, 993, 836 cm\(^{-1}\)

\textbf{\( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \):} 4.18 – 4.14 (m, 1H), 4.13 – 4.09 (m, 1H), 4.00 (br s, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.86 (s, 1H), 1.65 (ddd, \( J = 13.6, 10.2, 3.1 \) Hz, 1H), 1.43 – 1.36 (m, 1H), 1.21 (d, \( J = 1.1 \) Hz, 3H), 1.19 (d, \( J = 2.2 \) Hz, 3H), 0.89 (s, 9H), 0.085 (s, 3H), 0.081 (s, 3H).

\textbf{\( ^13C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \):} 68.6, 66.5, 61.5, 42.9, 40.2, 32.0, 25.9, 23.7, 18.0, 11.6, -4.5, -4.9.

\textbf{HRMS (C\(_{15}\)H\(_{33}\)NO\(_4\)Si, ESI):} calculated [M+H]\(^+\) 320.2252, found 320.2244
To a solution of Weinreb amide 3.61 (1.62 g, 5.07 mmol) in Et₂O (100 mL) was added ethylmagnesium bromide (3.0 M in Et₂O, 5.07 mL, 15.2 mmol) dropwise at room temperature and then the reaction mixture was stirred for 1 hour. Ethylmagnesium bromide (3.0 M in Et₂O, 2.53 mL, 7.6 mmol) was added to the mixture at room temperature and then stirred for 3 hours. The reaction was quenched with sat. NH₄Cl (100 mL) and then diluted with Et₂O (100 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (2 x 100 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 8:1) to give 3.57 (1.15 g, 79 %) as a colourless oil.

\[ R_f = 0.30 \text{ (petroleum ether/EtOAc, 5:1)} \]

\[ [\alpha]_{D}^{25} = -21.8 \text{ (c 0.92, CHCl}_3\text{)} \]

**IR (neat):** 3491, 2930, 1700, 1463, 1377, 1255, 1066, 1006, 836 cm⁻¹

**¹H NMR (500 MHz, CDCl₃)** δ 4.21 – 4.16 (m, 1H), 3.53 (br s, 1H), 2.63 – 2.58 (m, 1H), 2.56 – 2.51 (m, 2H), 1.61 (ddd, \( J = 13.8, 10.4, 3.3 \) Hz, 1H), 1.37 (ddd, \( J = 14.1, 6.2, 1.6 \) Hz, 1H), 1.22 (d, \( J = 6.3 \) Hz, 3H), 1.14 (d, \( J = 7.1 \) Hz, 3H), 1.06 (t, \( J = 7.3 \) Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H).

**¹³C NMR (125 MHz, CDCl₃)** δ 215.6, 68.5, 67.0, 51.1, 41.9, 35.5, 25.8, 23.1, 18.0, 11.4, 7.6, -4.5, -5.0.

**HRMS (C₁₅H₃₂O₃Si, ESI):** calculated [M+Na]+ 311.2013, found 311.2019
Chapter 3

(4R,5S,7R)-7-((tert-butyldimethylsilyl)oxy)-4-methyl-5-((trimethylsilyl)oxy)octan-3-one 3.62

To a solution of ketone 3.57 (480 mg, 1.66 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) at room temperature was added pyridine (0.40 mL, 5.0 mmol) and TMSCl (0.32 mL, 2.5 mmol) and the reaction mixture was stirred for 2 hours. The reaction mixture was quenched with sat. NH\textsubscript{4}Cl (25 mL) and diluted with CH\textsubscript{2}Cl\textsubscript{2} (50 mL). The organic layer was separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 25 mL). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered and concentrated \textit{in vacuo}. The resultant residue was purified by flash chromatography (SiO\textsubscript{2}, petroleum ether/ Et\textsubscript{2}O, 10:1) to give 3.62 (486 mg, 81%) as a colourless oil.

R\textsubscript{f} = 0.70 (petroleum ether/EtOAc, 5:1)

\textbf{IR} (\textit{neat}): 2957, 2931, 1719, 1462, 1376, 1251, 1114, 1052, 976, 836 cm\textsuperscript{-1}

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \delta 4.03 (dt, J = 7.9, 3.9 Hz, 1H), 3.89 – 3.81 (m, 1H), 2.66 – 2.55 (m, 2H), 2.41 (dq, J = 18.2, 7.2 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.32 (ddd, J = 14.1, 8.1, 3.8 Hz, 1H), 1.15 (d, J = 6.1 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.13 (s, 9H), 0.07 (s, 6H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 213.5, 71.8, 66.1, 52.1, 45.1, 36.1, 25.9, 24.7, 18.1, 11.8, 7.5, 0.6, -3.4, -4.3.

\textbf{HRMS} (C\textsubscript{18}H\textsubscript{40}O\textsubscript{3}Si\textsubscript{2}, ESI): calculated [M+Na]\textsuperscript{+} 383.2408, found 383.2403
(4R,5S,7R)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-methyloctan-3-one 3.63

![Chemical Structure](image)

To a solution of ketone 3.57 (250 mg, 0.87 mmol) in CH₂Cl₂ (10 mL) at room temperature was added pyridine (0.07 mL, 0.9 mmol) and TBSOTf (0.22 mL, 0.95 mmol) and the reaction mixture was stirred for 2 hours. The reaction mixture was quenched with sat. NH₄Cl (25 mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/Et₂O, 10:1) to give 3.63 (343 mg, 98%) as a colourless oil.

Rᵣ = 0.70 (petroleum ether/EtOAc, 5:1)

[α]²⁵ <sup>D</sup> = −39.0 (c 1.05, CHCl₃)

IR (neat): 2956, 2930, 1712, 1473, 1462, 1377, 1253, 1052, 833 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 4.07 – 4.02 (m, 1H), 3.85 (m, 1H), 2.65 – 2.60 (m, 2H), 2.42 (dq, J = 18.1, 7.2 Hz, 1H), 1.67 – 1.62 (m, 1H), 1.34 (ddd, J = 14.0, 6.9, 4.4 Hz, 1H), 1.16 (d, J = 6.1 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 213.2, 71.6, 66.2, 51.7, 45.1, 35.8, 25.90, 25.85, 24.6, 18.07, 18.05, 11.1, 7.5, -2.9, -3.5, -4.24, -4.29.

HRMS (C₂₁H₄₆O₃Si₂, ESI): calculated [M+Na]⁺ 425.2883, found 425.2881
Spiroketal 3.66

To a solution of 2,2,6,6-tetramethylpiperidine (0.13 mL, 0.74 mmol) in THF (6 mL) at −78 °C was added n-BuLi (2.5 M in hexanes, 0.30 mL, 0.74 mmol) and the mixture was stirred for 20 minutes. Di-TBS compound 3.63 (100 mg, 0.25 mmol) in THF (2 mL) was then added dropwise at −78 °C and the mixture was stirred for 20 minutes. 2-Methyleneacetoxy-4-methyl-6-acetyresorcinol (2.16) (60 mg, 0.25 mmol) in THF (2 mL) was then added dropwise at −78 °C and the reaction mixture was stirred for 5 hours. The reaction was quenched with sat. NH₄Cl (25 mL) and diluted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The major spots on the TLC were separated by flash chromatography (SiO₂, petroleum ether/EtOAc, 50:1 → 10:1) and the major compound (39.1 mg) was dissolved in CH₃CN (2 mL) and 3M HCl (2 mL) was added. The reaction mixture was stirred at room temperature for 15 minutes. The reaction was diluted with H₂O (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1) to give 3.66 (15.1 mg, 18% over the two steps) as a colourless oil as a 2.4:1 ratio of diastereoisomers.

Data for 3.66

Rₚ = 0.30 (petroleum ether/EtOAc, 2:1)

¹H NMR (500 MHz, CDCl₃) δ 12.86 (br s, 1H), 7.34 (s, 1H), 3.92 (dq, J = 12.5, 6.2, 2.2 Hz, 1H), 3.84 (td, J = 10.9, 4.7 Hz, 1H), 3.03 (dd, J = 16.7, 6.5 Hz, 1H), 2.54 (s, 3H), 2.40 (dd, J = 16.7, 6.3 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.16 (s, 3H), 2.04 (ddd, J = 12.4, 4.8, 2.2 Hz, 1H), 1.73 (dd, J = 9.7, 6.6 Hz, 1H), 1.33 (q, J = 11.5 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H).
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 202.7, 160.7, 157.2, 129.4, 116.6, 112.8, 109.4, 103.2, 70.9, 65.1, 44.5, 41.9, 35.4, 30.5, 26.2, 25.9, 21.6, 17.2, 15.6, 12.5.

HRMS (C$_{19}$H$_{26}$O$_5$, ESI): calculate [M-H]$^-$ 333.1707, found 333.1704
Spiroketal 3.66

To a solution of 2,2,6,6-tetramethylpiperidine (0.28 mL, 1.7 mmol) in THF (15 mL) at –78 °C was added n-BuLi (2.5 M in hexanes, 0.67 mL, 1.7 mmol) and the mixture was stirred for 20 minutes. Compound 3.62 (200 mg, 0.55 mmol) in THF (5 mL) was then added dropwise at –78 °C and the mixture was stirred for 20 minutes. 2-Methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (131 mg, 0.55 mmol) in THF (5 mL) was then added dropwise at –78 °C and the reaction mixture was stirred for 5 hours. The reaction was quenched with sat. NH₄Cl (25 mL) and diluted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The major spots on the TLC were separated by flash chromatography (SiO₂, petroleum ether/EtOAc, 50:1 → 10:1) and the major compound (51.8 mg) was dissolved in CH₃CN (5 mL) and 3M HCl (5 mL) was added. The reaction mixture was stirred at room temperature for 15 minutes. The reaction was diluted with H₂O (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1) to give 3.66 (22.3 mg, 13% over the two steps) as a colourless oil as a 4.5:1 ratio of diastereoisomers.
To a solution of spiroketal 3.66 (15.1 mg, 0.0451 mmol) in CH$_2$Cl$_2$ (2 mL) was added 4Å molecular sieves (3 balls), $n$-tetrapropylammonium perruthenate (0.79 mg, 0.0023 mmol) and $N$-methylmorpholine $N$-oxide (6.5 mg, 0.054 mmol) at 0 °C and the reaction was gradually warmed to room temperature and then stirred for 16 hours. The reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 4:1 → 2:1 gradient elution) to give 8-epi-peniphenone A 3.55 (9.1 mg, 61%) as a colourless film as a 2.35:1 mixture of diastereoisomers.

**Major compound 3.55:**

R$_f$ = 0.25 (petroleum ether/EtOAc, 5:1)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.85 (s, 1H), 7.34 (s, 1H), 4.20 (dqd, $J$ = 12.1, 6.1, 2.9 Hz, 1H), 3.07 (dd, $J$ = 16.7, 6.4 Hz, 1H), 2.77 (dd, $J$ = 13.6, 6.3 Hz, 1H), 2.58-2.54 (m, 1H), 2.54 (s, 3H), 2.45 (dd, $J$ = 16.8, 5.7 Hz, 1H), 2.37-2.32 (m, 2H), 2.09 (s, 3H), 1.22 (d, $J$ = 6.4 Hz, 6H), 1.15 (d, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.8, 205.5, 163.2, 159.0, 132.2, 119.4, 115.8, 111.8, 107.1, 69.0, 53.6, 50.6, 37.8, 28.9, 28.1, 24.5, 19.3, 18.0, 12.7.

**HRMS (C$_{19}$H$_{24}$O$_5$, ESI):** calculated [M-H]$^-$ 331.1551, found 331.1547
Spiroketal 3.67

To a solution of 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.60 mmol) in THF (10 mL) at −78 °C was added n-BuLi (2.5 M in hexanes, 0.64 mL, 1.60 mmol) and the mixture was stirred for 20 minutes. Di-TBS compound 3.63 (215 mg, 0.533 mmol) in THF (2 mL) was then added dropwise at −78 °C and the mixture was stirred for 20 minutes. 2-Methyleneacetoxy-4-methyl-6-acetylresorcinol (2.16) (127 mg, 0.533 mmol) in THF (2 mL) was then added dropwise at −78 °C and the reaction mixture was stirred for 5 hours. The reaction was quenched with sat. NH₄Cl (25 mL) and diluted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The major spots on the TLC were separated by flash chromatography (SiO₂, petroleum ether/EtOAc, 50:1 → 10:1) and the major compound (79.1 mg) was dissolved in CH₃CN (8 mL) and 3M HCl (4 mL) was added. The reaction mixture was stirred at room temperature for 16 hours. The reaction was diluted with H₂O (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1) to give 3.67 (41.2 mg, 23% over the two steps) as a colourless oil.

Rₙ = 0.30 (petroleum ether/EtOAc, 2:1)

[α]₀°²⁵ = +63.5 (c 0.65, CHCl₃)

IR (neat): 3392, 2936, 1627, 1478, 1383, 1333, 1281, 1189, 1065, 916 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 12.83 (s, 1H), 7.33 (s, 1H), 4.01 (td, J = 10.7, 4.6 Hz, 1H), 3.71 (dqd, J = 12.4, 6.2, 2.3 Hz, 1H), 2.68 (dd, J = 16.4, 5.5 Hz, 1H), 2.54 (s, 3H), 2.44 (dd, J = 16.4, 12.6 Hz, 1H), 2.13 (s, 3H), 2.10 (dd, J = 12.8, 6.2 Hz, 1H), 2.04 (ddd, J = 12.5, 4.7, 2.4
Hz, 1H), 1.76 (dq, $J = 10.0, 6.7$ Hz, 1H), 1.31 (q, $J = 11.6$ Hz, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H), 1.06 (d, $J = 6.2$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) 202.7, 160.1, 156.5, 129.2, 116.9, 112.8, 111.3, 102.9, 69.6, 65.5, 42.7, 42.5, 30.5, 26.2, 23.4, 21.4, 15.5, 15.0, 10.6.

HRMS ($C_{19}H_{26}O_5$, ESI): calculated [M-H] $^\dagger$ 333.1707, found 333.1711
To a solution of spiroketal 3.67 (35 mg, 0.11 mmol) in CH$_2$Cl$_2$ (3 mL) was added 4Å molecular sieves (3 balls), $n$-tetrapropylammonium perruthenate (1.8 mg, 0.052 mmol) and $N$-methylmorpholine $N$-oxide (13.5 mg, 0.116 mmol) at 0 °C and the reaction was gradually warmed to room temperature and then stirred for 16 hours. The reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 4:1 → 2:1 gradient elution) to give (+)-peniphenone A ((+)-3.1) (20.8 mg, 60%) as a colourless film.

$R_f = 0.25$ (petroleum ether/EtOAc, 5:1)

$[\alpha]_D^{25} = +85.6$ (c 0.88, MeOH)

**IR (neat):** 2976, 2939, 1725, 1629, 1479, 1455, 1382, 1332, 1278, 1188, 1076, 933 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl$_3$) δ 12.82 (s, 1H), 7.32 (s, 1H), 3.93 (dqd, $J = 12.3$, 6.2, 3.1 Hz, 1H), 2.87 (q, $J = 6.8$ Hz, 1H), 2.77 (dd, $J = 16.5$, 5.6 Hz, 1H), 2.54 (s, 3H), 2.53 (dd, $J = 16.5$, 3.0 Hz, 1H), 2.50 (dd, $J = 14.0$, 3.0 Hz, 1H), 2.34 (dd, $J = 13.3$, 11.8 Hz, 1H), 2.09 (dt, $J = 10.1$, 6.0 Hz, 1H), 2.04 (s, 3H), 1.23 (d, $J = 6.8$ Hz, 3H), 1.19 (d, $J = 6.2$ Hz, 3H), 1.14 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 206.5, 202.9, 160.0, 155.6, 129.5, 117.0, 113.2, 111.1, 105.0, 67.5, 49.2, 48.7, 30.8, 26.3, 23.5, 21.8, 15.19, 15.09, 7.6.

**HRMS (C$_{19}$H$_{24}$O$_5$, ESI):** calculated [M-H] 331.1551, found 331.1554
Chapter 3

3.9 References

(26) Paterson, I.; Goodman, J. M.; Anne Lister, M.; Schumann, R. C.; McClure, C. K.;
Commun.* 1987, 21, 1625.
Chapter 3

3.10 Appendix Two

3.10.1 NMR Spectra

![NMR Spectra Image]

3.11

$^1$H NMR
CDCl$_3$
500 MHz

3.11

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.12

$^1$H NMR
DMSO
500 MHz

3.12

$^{13}$C NMR
DMSO
125 MHz
Chapter 3

3.13
$^1$H NMR
CDCl$_3$
500 MHz

3.13
$^{13}$C NMR
CDCl$_3$
125 MHz
3.2: peniphenone B

$^1$H NMR
CDCl$_3$
500 MHz

3.2: peniphenone B

$^{13}$C NMR
DMSO
125 MHz
Chapter 3

3.15

$^1$H NMR
CDCl$_3$
500 MHz

3.15

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.3: peniphenone C

$^1$H NMR
CDCl$_3$
500 MHz

$^{13}$C NMR
CDCl$_3$
125 MHz
3.4: peniphenone D

$^1$H NMR
CDCl$_3$
500 MHz

$^{13}$C NMR
CDCl$_3$
125 MHz
3.17
$^1$H NMR
CDCl$_3$
500 MHz
Chapter 3

3.19
$^1$H NMR
CDCl$_3$
500 MHz

3.19
$^{13}$C NMR
CDCl$_3$
125 MHz
3.20
\( ^1H \text{ NMR} \)
CDCl₃
500 MHz

3.20
\( ^{13}C \text{ NMR} \)
CDCl₃
125 MHz
Chapter 3

3.18

$^1$H NMR
CDCl$_3$
500 MHz

3.18

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.27

$^1$H NMR
CDCl$_3$
500 MHz

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.30
$^1$H NMR
CDCl$_3$
500 MHz

3.30
$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.24

$^1$H NMR
CDCl$_3$
500 MHz

3.24

$^{13}$C NMR
CDCl$_3$
125 MHz
3.31
$^1$H NMR
CDCl$_3$
500 MHz

3.31
$^{13}$C NMR
CDCl$_3$
125 MHz
3.41

**$^1$H NMR**

CDCl$_3$

500 MHz

---

3.41

**$^{13}$C NMR**

CDCl$_3$

125 MHz
Chapter 3

3.47
$^1$H NMR
CDCl$_3$
500 MHz

3.47
$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.51

$^1$H NMR
CDCl$_3$
500 MHz

3.51

$^{13}$C NMR
CDCl$_3$
125 MHz
isolated as a 3:1:3 ratio of 3.1 : 3.55 : 3.56

Mixture 3.54

3:1:3 ratio peniphenone A (3.1) : 8-epi-peniphenone A (3.55) : unknown (3.56)

2.35:1 ratio 8-epi-peniphenone A (3.55) : peniphenone A (3.1)

(Scheme 3.36)
Chapter 3

3.61

$^1$H NMR
CDCl$_3$
500 MHz

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.57
$^1$H NMR
CDCl$_3$
500 MHz

3.57
$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.63

$^1\text{H NMR}$

CDCl$_3$

500 MHz

3.63

$^{13}\text{C NMR}$

CDCl$_3$

125 MHz
Chapter 3

$^{1}$H NMR
CDCl$_3$
500 MHz

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.66
2.4:1 dr
$\text{^1H NMR}$
CDCl$_3$
500 MHz

3.66
2.4:1 dr
$\text{^{13}C NMR}$
CDCl$_3$
125 MHz
3.66
$^1$H NMR
C$_6$D$_6$
500 MHz

3.66
$^{13}$C NMR
C$_6$D$_6$
500 MHz
Chapter 3

3.66 NOESY
C₆D₆
500 MHz

3.66 NOESY
C₆D₆
500 MHz
Chapter 3

3.55
2.35:1 dr
$^1$H NMR
CDCl$_3$
500 MHz

3.55
2.35:1 dr
$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 3

3.67
$^1$H NMR
$C_6D_6$
500 MHz

3.67
$^{13}$C NMR
$C_6D_6$
125 MHz
Chapter 3

3.1: Peniphenone A
18:1 dr
$^1$H NMR
CDCl$_3$
500 MHz

3.1: Peniphenone A
18:1 dr
$^{13}$C NMR
CDCl$_3$
125 MHz
3.10.2 Tables of $^1$H and $^{13}$C NMR Data for Peniphenones A-D

**Figure 3.6:** Comparison of the $^1$H and $^{13}$C spectra of natural and synthetic peniphenone A (3.1)\(^1\)

![Diagram of peniphenone A](image)

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Natural, $^1$H spectrum, CDCl$_3$, 400 MHz</th>
<th>Synthetic, $^1$H spectrum, CDCl$_3$, 500 MHz</th>
<th>Natural, $^{13}$C spectrum, CDCl$_3$, 100 MHz</th>
<th>Synthetic, $^{13}$C spectrum, CDCl$_3$, 125 MHz</th>
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*Correction to natural product isolation data.
**Figure 3.7:** Comparison of the $^1$H and $^{13}$C spectra of natural and synthetic peniphenone B (3.2)\(^1\)

![peniphenone B](image)

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<th>Assignment</th>
<th>Natural, $^1$H spectrum, DMSO, 400 MHz</th>
<th>Synthetic, $^1$H spectrum, DMSO, 500 MHz</th>
<th>Natural, $^{13}$C spectrum, DMSO, 100 MHz</th>
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**Figure 3.8:** Comparison of the $^1$H and $^{13}$C spectra of natural and synthetic peniphenone C (3.3)$^1$

![Chemical structure of peniphenone C]

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OH-5 and OH-1 indicate hydroxyl groups.
Figure 3.9: Comparison of the $^1$H and $^{13}$C spectra of natural and synthetic peniphenone D (3.4)\textsuperscript{1}

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*Correction to natural product isolation data.
Chapter 3
Chapter Four

Progress Towards the Biomimetic Synthesis of Virgatolide B

4.1 Isolation of Virgatolides A-C

Virgatolides A-C (4.1-4.3) are a family of enantiopure benzanulated spiroketal natural products isolated from the endophytic fungi *Pestalotiopsis virgatula*, which was harvested from the leaves of Chinese medicinal plant *Dractomelum duperreanum*.\(^1\) The leaves were subjected to solid substrate fermentation, and the resultant cultures were extracted with EtOAc and fractionated to reveal virgatolides A-C (4.1-4.3) along with biosynthetically related compounds pestaphthalides A and B (4.4 and 4.5) (Figure 4.1). Virgatolide A (4.1) is the most structurally complex member of the family with two spirocycle moieties, whereas virgatolide B and C (4.2 and 4.3) contain a single spirocycle and are C-4 epimers. Co-isolated compounds pestaphthalides A and B (4.4 and 4.5) were previously isolated from a related species of fungus *Pestalotiopsis foedan* and contain the aromatic functionality of the virgatolides A-C (4.1-4.3).\(^2\)

The crude EtOAc extract was biologically tested and observed to exhibit cytotoxicity toward HeLa (cervical epithelium) cells.

**Figure 4.1:** Structures of virgatolides A-C (4.1-4.3) and biosynthetic precursors pestaphthalides A and B (4.4 and 4.5)

The structure of virgatolides A-C (4.1-4.3) were elucidated using 2D NMR studies, with the relative configuration confirmed based on the X-ray crystallographic data of virgatolide A (4.1). The absolute configuration was originally determined through CD spectral comparison.
of virgatolide A (4.1) with that of known compounds pestaphthalides A and B (4.4 and 4.5), and it was observed that virgatolide A (4.1) contained the backbone of pestaphthalide A (4.4). Based on this key piece of information the absolute configuration of virgatolide A was assigned as 2'R, 4'S, 10'S, 11'R, 13'R, 15'S, 16'S. The structures of virgatolides B and C (4.2 and 4.3) were then elucidated by comparison of the 2D NMR data with virgatolide A (4.1) and were found to contain identical relative configuration of the cyclohexane portion of the molecule. The configuration of the aromatic region was determined by comparison of the CD spectra to pestaphthalides A and B (4.4 and 4.5) and it was observed that virgatolide B and C (4.2 and 4.3) contained the backbones of pestaphthalide A (4.4) and pestaphthalide B (4.5) respectively.

### 4.2 Proposed Biosynthesis of Virgatolides A-C

Che and co-workers proposed a biosynthesis of the virgatolides A-C (4.1-4.3) that involves an electrophilic aromatic substitution of 4.6 with coenzyme-A bound fragment 4.7 (Scheme 4.1). Che proposed that the resultant compound could be cyclised to form the spiroketal 4.8, which after a series of stereospecific hydrogenations and reductions would afford virgatolide B (4.2). Virgatolide B (4.2) could then be converted into virgatolide A (4.1) by installing the C-13 lactone functionality.

![Scheme 4.1: Biosynthesis of virgatolide B (4.2) proposed by Che and co-workers](image)

The above biosynthesis is rather implausible, with many potential selectivity issues around the formation of the key stereocentres. Therefore, we proposed an alternative biosynthesis of the virgatolides that employs the co-isolated compounds pestaphthalides A and B (4.4 and 4.5). We hypothesise that the virgatolides A-C (4.1-4.3) could be synthesised in nature via a [4+2] cycloaddition of an o-QM generated through oxidation of either pestaphthalide A or B (4.4 or 4.5) and the relevant chiral exocyclic enol ether. For example, this biosynthesis can be observed on the least structurally complex natural product, virgatolide B (4.2), where o-QM 4.9 (generated from pestaphthalide A (4.4)) could undergo a [4+2] cycloaddition with chiral exocyclic enol ether 4.10 (Scheme 4.2). Presumably, the observed relative stereochemistry across the C-10 and C-11 stereocentres would be determined based on the geometry of the exocyclic alkene as well as the steric associated with the chirality present.
in both 4.9 and 4.10. Virgatolide C (4.3) could be biosynthesised through the same pathway as virgatolide B, this time using the $o$-QM generated from oxidation of pestaphthalide B (4.5).

![Scheme 4.2: Our proposed biosynthesis of virgatolide B (4.2)](image)

Virgatolide A (4.1) contains an extra spirocycle moiety, but the biosynthesis can be envisaged to involve the coupling of a bicyclic enol ether 4.11 with $o$-QM 4.9 derived from pestaphthalide A (4.4) (Scheme 4.3). The goal of this project was to synthesise virgatolide B (4.2) the simplest member of the virgatolide family.

![Scheme 4.3: Proposed biosynthesis of virgatolide A (4.1)](image)

### 4.3 Previous Work on the Virgatolides A-C

Since the isolation of virgatolides A-C (4.1-4.3), there has been one total synthesis of virgatolide B reported in the literature.\(^3\)\(^4\) Brimble and co-workers adopted an approach towards the synthesis of virgatolide B (4.2) that afforded the natural product in 15 steps (longest linear sequence) with an overall yield of 4.7% (Scheme 4.4).

Brimble and co-workers converted 3,5-dihydroxybenzoic acid (4.12) into BOM protected bromobenzaldehyde 4.13 via a bromination, protection, reduction and oxidation sequence. Bromobenzaldehyde 4.13 was then treated with ethyltriphénylphosphonium iodide under Wittig conditions which afforded the arylpropene moiety as an inseparable mixture of $E/Z$ isomers, which was isomerised with Ru(CO)ClH(PPh₃)₃ under reflux in toluene to exclusively deliver the $E$ isomer 4.12. Coupling of the aryl bromide moiety of 4.12 with chiral boronate 4.15 via a Suzuki reaction followed by cleavage of the chiral auxiliary with MeLi revealed compound 4.16. Sharpless asymmetric dihydroxylation with AD-mix $\alpha$ formed diol...
4.17 as a single diastereoisomer. The lactone functionality was then introduced by iodination, followed by palladium catalysed CO insertion to afford 4.18. Concomitant TMS enol formation and TMS alcohol protection with TMSOTf, followed by a BF₃·Et₂O mediated Mukaiyama aldol reaction with a chiral aldehyde and finally TMS ether cleavage furnished a single diastereoisomer of 4.20. Finally, virgatolide B (4.2) was realized by global deprotection of 4.20 under hydrogenolysis conditions, followed by acid catalysed spiroketalisation with CSA. The highlights of the synthesis are Suzuki coupling of a chiral trifluoroborionate with an aryl bromide, followed by a Sharpless asymmetric dihydroxylation and finally a spiroketalisation to furnish virgatolide B.

![Chemical structure](image)

**Scheme 4.4:** Brimble’s synthesis of (+)-virgatolide B (4.2)

The above result by Brimble and co-workers was reported mid-way through our synthetic studies on the virgatolides. However, we proposed that our approach would be complementary and afford virgatolide B (4.2) via a shorter route. Hence, if we could achieve our desired [4+2] cycloaddition of a heavily functionalised o-QM with a chiral exocyclic enol ether, a more efficient synthesis of the virgatolides would be showcased.
4.4 Studies Towards the Total Synthesis of Virgatolide B

We envisaged the most significant challenge resides in the synthesis of the chiral exocyclic enol ether 4.10. Thus, before a significant amount of synthetic effort was invested, we wanted to develop the [4+2] cycloaddition chemistry on a simplified model system (i.e. the synthesis of 4.21) (Scheme 4.4). In order to do so, we first needed to establish a synthesis of our desired o-QM 4.9. This was no trivial matter, and numerous pathways had previously been attempted. The successful synthesis of the chiral aromatic o-QM precursor 4.9 and subsequent [4+2] cycloadditions with a simplified exocyclic enol ether 3.17 (Chapter 3) will be reported herein.

Scheme 4.4: Targeted [4+2] cycloaddition towards simplified virgatolide B analogue 4.21

4.4.1 Retrosynthetic Analysis of o-QM Precursor 4.9

From a retrosynthetic perspective, we foresaw that the spirocycle moiety of 4.21 could be installed by a [4+2] cycloaddition of an o-QM 4.9 and exocyclic alkene 3.17 (3.17 from Chapter 3) (Scheme 4.5). Conceivably, the desired o-QM precursor 4.22 could be synthesised via a similar pathway that we have reported in chapters 2 and 3 in our total synthesis of penilactones A and B and peniphenones A-D. This would involve a reaction of chiral aryl compound 4.6 with formaldehyde under acidic conditions, which would allow for a thermally generated o-QM. Lactone 4.6 could be synthesised via a Sharpless asymmetric dihydroxylation of arylpropene 4.23. The aryl carbonyl group of 4.23 could be installed via a Vilsmeier-Haack formylation followed by a Pinnick oxidation protocol. Finally, the trans alkene moiety of 4.24 could be installed through a Grignard addition of ethylmagnesium bromide to aldehyde 4.24, followed by an acid catalysed dehydration.
A suitable protecting group strategy may be required to mask the phenol moiety of 4.25. This would guarantee the success of the Grignard addition and the Sharpless asymmetric dihydroxylation. As a result, a benzyl protecting group was chosen as an ideal protecting group strategy, due to its relative ease of installation and removal.

4.4.2 Synthesis of the Key o-QM Precursor

The starting point of our synthesis was the synthesis of 3,5-dibenzylxybenzaldehyde 4.28, as large quantities were not commercially available. Thus, methyl 3,5-dihydroxybenzoate 4.26 was protected as the di-benzyl ether under standard benzylation conditions (BnBr, K₂CO₃) to afford the diprotected ester 4.27. The ester moiety was then reduced with LiAlH₄ and immediately oxidised with PCC to reveal the desired dibenzylxybenzaldehyde 4.29 in 93% yield over 3 steps (Scheme 4.6).

With our desired starting material in hand, we then devised a plan for installing the arylpropene functionality. As pointed out by Brimble and co-workers, a Wittig reaction would likely produce an inseparable mixture of E/Z isomers, which they later isomerised with a ruthenium catalyst to afford the E alkene. Ideally, direct installation of the trans alkene without
the need for using expensive catalysts would be desirable. A literature procedure by Pincock reports that treatment of dimethoxy aryl aldehyde 4.30 with ethylmagnesium bromide yielded the benzyl alcohol 4.31, which when heated at reflux in benzene with catalytic $p$-TsOH under Dean-Stark conditions yielded predominantly the desired $E$ alkene 4.32 in a 97:3 isomeric ratio ($E/Z$) (Scheme 4.7). With this precedence, we were well placed to complete the identical chemistry on our dibenzyloxybenzaldehyde 4.29. Treatment of 4.29 with ethylmagnesium bromide in Et$_2$O furnished the desired benzylic alcohol 4.33 in the excellent yield of 88%; subsequent elimination with catalytic $p$-TsOH in toluene yielded the desired $E$-alkene of arylpropene 4.34. The NMR revealed the predominant formation of the $E$-alkene as seen by the coupling constant of 15.8 Hz, which is characteristic of a vicinal trans coupling constant. Arylpropene 4.34 was isolated in 81% yield, which when paralleled to the work by Brimble et al. furnishes the desired compound in comparable yield. This pathway allows for multigram scale quantities of aryl propene 4.34 to be prepared, without the use of expensive catalysts.

![Scheme 4.7: Pincock’s synthesis of 4.32, paralleled with our synthesis of 4.34](image)

Synthesis of arylpropene 4.34 was deemed as the most significant challenge in the synthesis of the key $o$-QM precursor 4.22. Hence, with a successful synthesis achieved, we were well situated to now install the lactone moiety onto the aromatic ring. The first step was to attach a carbonyl group to the C-6 position via a Vilsmeier-Haack formylation reaction. Thus, arylpropene 4.34 was treated with POCl$_3$ in DMF and the subsequent iminium ion formed was hydrolysed with H$_2$O to afford the desired benzaldehyde 4.35 (Scheme 4.8). Formylation at the C-4 position was not observed due to the steric bulk of the benzyl protecting groups. The synthesis of 4.35 was confirmed by the observed asymmetry in the $^1$H NMR of the product; if the C-4 position were formylated, a single aromatic signal would be expected, instead of the two separate signals that were observed.
With the desired carbonyl functionality adjacent to the trans alkene installed, an oxidation state transformation was necessary to introduce the lactone moiety. Hence, an oxidation of the aryl aldehyde 4.35 to the aryl carboxylic acid 4.36 was required. A Pinnick oxidation (NaClO₄, NaH₂PO₄ and 2-methyl-2-butene) was implemented to convert aldehyde 4.35 into carboxylic acid 4.36 (scheme 4.9). The resultant carboxylic acid 4.36 was then carried through to the next step without purification and was converted into methyl ester 4.37 under standard methylating conditions (MeI, K₂CO₃) in 84% yield over the two steps.

The Sharpless asymmetric dihydroxylation of 4.27 was completed under standard methanesulfonamide promoted AD-mix α conditions in t-BuOH-H₂O, which furnished the desired chiral lactone 4.38 in 82% yield (Scheme 4.10). This reaction achieved the desired lactone moiety of 4.38 via the proposed dihydroxylation and lactonisation cascade in the one pot under ambient conditions as evidenced by the loss of the methyl ester moiety in the ¹H NMR. However, an excess of AD-mix α was required to drive the reaction towards completion in 30 hours. When Sharpless’ original quantities were employed (1.4 g/mmol of 4.37), a significant portion of the starting material was isolated. The benzyl ethers were then cleaved under hydrogenolysis conditions (H₂, 10 % Pd/C) to afford the desired phenol product 4.6 in quantitative yield.
Scheme 4.10: Sharpless asymmetric dihydroxylation of arylpropene 4.37 followed by benzyl ether cleavage

Phenol 4.6 was converted into o-QM precursor 4.22 according to our previously established conditions reported in chapters 2 and 3. As expected, there was no observed change in the TLC over the course of the reaction, and thus the reaction had to be monitored by $^1$H NMR at regular intervals. We found that if the reaction was allowed to stir at 90 °C overnight 50% consumption of 4.6 was observed (Scheme 4.11). Alteration of the reaction time and the use of excess reagents appeared to have minimal effect on the observed ratio. As a result, further optimisation of this reaction is necessary. However, for preliminary studies we decided to carry this crude mixture through to the [4+2] cycloaddition reaction.

Scheme 4.11: Synthesis of o-QM precursor 4.22

The formation of the desired o-QM precursor 4.22 was determined via $^1$H NMR, with new signals observed at $\delta_H$ 5.02 and 1.99 ppm. The collected crude $^1$H NMR spectrum was very impure, with significant decomposition contributing a large quantity of spectral noise and broadening. The purity observed for this reaction was poor compared to that of our previous o-QM precursor 2.16 (chapters 2 and 3), however this may be expected due to the more sensitive functionality present in 4.22, namely the lactone and secondary alcohol moieties.
4.4.3 Model [4+2] Cycloadditions of an o-QM with an Exocyclic Enol Ether

With the synthesis of the key o-QM precursor 4.22 completed, we focussed on the biomimetic [4+2] cycloaddition reaction of o-QM 4.9 with simple exocyclic enol ether 3.17. Enol ether 3.17 was utilised in Chapter 3 to complete a similar model [4+2] cycloaddition for the synthesis of a simplified analogue of peniphenone A (Scheme 3.13). However, the o-QM employed in that case was a significantly more easily synthesised (available in two steps from 4-methylresorcinol), whereas o-QM precursor 4.22 was a much more laborious endeavour, obtained in eight steps from commercially available starting materials.

o-QM precursor 4.22 and the simplified exocyclic enol ether 3.17 (Chapter 3) were heated in toluene in a sealed tube overnight (Table 4.1, Entry 1). As expected, the outcome observed was similar to that of the peniphenones project, with liberation of acetic acid in the o-QM formation step of the cascade reaction resulting in an isomerisation of the exocyclic enol ether 3.17 to endocyclic isomer 3.21 (Scheme 4.12). Hence, this resulted in the formation of the undesired [4+2] cycloaddition adducts, diastereoisomers 4.39 and 4.40 in 19% yield as a 1:1 ratio, with trace quantities of the desired spiroketal product 4.41. 4.39 and 4.40 were assigned using 2D NMR. The presence of 2 x CH₃ resonances at δH 1.42 and 1.45 ppm (C-16 and C-17) and one CH resonance at δH 2.03 (C-10) in the HSQC unambiguously identifies isomerised the products 4.39 and 4.40.

\[
\begin{align*}
\text{3.17} & \xrightarrow{\text{H}^+} \text{3.21} \quad \text{[4+2] cycloaddition (19%)} \\
\end{align*}
\]

**Scheme 4.12:** [4+2] Cycloaddition of endocyclic alkene 3.21 with in situ generated o-QM 4.9

A change of solvent from toluene to dioxane (Entry 2), led to isolation of the desired spiroketal product 4.41, albeit in the unsatisfactory yield of 12% in a 1:1.2 ratio of C-11 epimers. The product was assigned based on the 2D HSQC data with now only one CH₃ resonance observed and six CH₂ resonances. Interestingly, when exocyclic enol ether 3.17 was introduced in a large excess in toluene (Entry 3) the observed ratio of 4.41:4.39/4.40 favoured the desired compound 4.41 in a 4:1 ratio.
Table 4.1: Conditions screened for the [4+2] cycloaddition of \( o \)-QM precursor 4.22 and exocyclic enol ether 3.17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (equiv)</th>
<th>Conditions</th>
<th>4.41</th>
<th>4.39 and 4.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.22 and 3.17 (1:1)</td>
<td>PhMe, 110 °C, 16 h</td>
<td>trace</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>4.22 and 3.17 (1:3)</td>
<td>dioxane, 110 °C, 16 h</td>
<td>12%</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>4.22 and 3.17 (1:10)</td>
<td>PhMe, 110 °C, 16 h</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>4.22 and 3.17</td>
<td>Et(_3)N, PhMe, 100 °C, 16 h</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

In pursuit of the desired spiroketal 4.41, we needed to limit the acid-catalysed isomerisation reaction. The strategy developed in Chapter 3 was trialled, where Et\(_3\)N was used as a buffer, which consumed the liberated acetic acid associated with \( o \)-QM formation. However, we proposed the secondary alcohol moiety may inhibit the coupling of the exocyclic alkene 3.17 to the \( o \)-QM precursor 4.22. This prediction holds true, as we observed the addition of Et\(_3\)N to the reaction mixture failed to yield 4.41 (Entry 4), with decomposition of the starting material ensuing. Therefore, further conditions to this end need to be explored, more specifically in screening a series of milder bases to act as a buffer in the reaction.

The relative stereochemistry of the diastereomeric mixture of 4.39/4.40 was determined through the 2D NOESY data. This was made slightly more difficult by the fact that the spectrum was complicated by the presence of two diastereoisomers. However, a cross peak between the C-17 methyl group and the C-10 hydrogen atom suggests these two functional groups are on the same side, which is characteristic of a \( cis \) fused ring junction (Figure 4.2, section 4.9.1).
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Figure 4.2: Key NOESY cross peak assigning the relative configuration across C-10 and C-11 of 4.39/4.40

Alternatively, a differing protecting group strategy could be chosen where the secondary alcohol could be protected (with an acid stable protecting group) thus eliminating its inhibitory activity on the [4+2] cycloaddition.

4.5 Summary

A synthesis of chiral lactone 4.6 was reported in 7 steps in 35% yield from commercially available starting materials, and we subsequently converted this compound into our desired o-QM precursor 4.22. Furthermore, model [4+2] cycloaddition conditions have been trialled with promising results, demonstrating that a [4+2] cycloaddition is possible with our synthesised o-QM precursor 4.22. In order to achieve this, two key challenges need to be overcome, the first being optimised conditions for the synthesis of o-QM precursor 4.22 from 4.6, as the formaldehyde reaction currently only allows access to a small amount of impure material. Secondly, a method for preventing the isomerisation of the exocyclic enol ether 3.17 to the endocyclic alkene 3.21 needs to be developed. Studies to this effect and efforts towards the synthesis of virgatolide B (3.2) are currently ongoing in our research group.

4.6 Future Directions

In the future, the primary goal will be to develop a synthesis of virgatolide B (4.2) via our proposed [4+2] cycloaddition of o-QM 4.9 and exocyclic enol ether 4.10. Firstly, an avenue towards the synthesis of o-QM 4.9 needs to be devised, with a potential change of strategy required. Acetoxy o-QM precursor 4.22 was synthesised as a 1:1 mixture with its starting material, which suggests this may not be a suitable pathway to yield o-QM 4.9. Alternatively, a procedure involving the methylation of 4.6 to afford pestaphthalide A (4.4) can be conceived; subsequent oxidation would yield the desired o-QM 4.9 (Scheme 4.13). Exocyclic enol ether 4.10 may then be introduced in situ, which would allow the biomimetic [4+2] cycloaddition
reaction to occur affording virgatolide B (4.2). This pathway would furnish a truly biomimetic approach towards virgatolide B (4.2).

**Scheme 4.13:** Future directions towards the synthesis of virgatolide B (4.2)
4.7 Supporting Information

4.7.1 General Experimental

All commercially obtained chemicals were used without further purification. Solvents stated as dry, were either collected from a solvent purification system (THF or DMF), or distilled under an atmosphere of nitrogen and stored over 4Å molecular sieves. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F_{254} aluminium sheets and visualised under a UV lamp or with ceric ammonium molybdate (CAM), vanillin or potassium permanganate staining followed by heating. All R_f values are rounded to the nearest 0.05. Davisil 43-60 micron chromatographic silica media was used for flash chromatography. \(^1\)H NMR spectra were recorded on a Varian Inova-600 spectrometer (\(^1\)H at 600 MHz, \(^{13}\)C at 150 MHz) or an Agilent 500 spectrometer (\(^1\)H at 500 MHz, \(^{13}\)C at 125 MHz) in CDCl\(_3\) as the solvent unless specified otherwise. \(^1\)H chemical shifts are reported in ppm relative to TMS (δ 0.0) and \(^{13}\)C NMR are reported in ppm relative to TMS (δ 0.0). All J values were quoted to the nearest 0.1 Hz. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sxt) sextet and (m) multiplet. IR spectra were recorded on a Perkin-Elmer Fourier-Transform Infrared (FT-IR) spectrometer on a nickel-selenide crystal as neat compounds. High resolution mass spectra were obtained on an Agilent ESI high resolution mass spectrometer. Melting points were recorded on a Reichert electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on an Anton Paar MCP 100 polarimeter in either CHCl\(_3\) or MeOH.
4.7.2 Experimental Procedures

**methyl 3,5-dibenzyloxybenzoate 4.27**

![Chemical Structure](image)

To a solution of methyl 3,5-dihydroxybenzoate (4.26) (20.0 g, 119 mmol) and K$_2$CO$_3$ (34.5 g, 250 mmol) in acetone (200 mL) was added benzyl bromide (29.7 mL, 250 mmol) and the mixture was heated under reflux for 24 h. The K$_2$CO$_3$ was then filtered off, and the filtrate concentrated in vacuo. The resultant residue was diluted with EtOAc (250 mL) and H$_2$O (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo to give methyl 3,5-dibenzyloxybenzoate 4.27 (41.4 g) which was carried onto the next step without purification. Spectroscopic data matched that reported in the literature.$^5$

$^{R_f} = 0.5$ (petroleum ether/EtOAc, 2:1)

**Mp:** 68-71 °C

**IR (neat):** 2950, 1720, 1594, 1443, 1347, 1324, 1299, 1234, 1156, 1055 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.42 (d, $J = 7.1$ Hz, 4H), 7.38 (t, $J = 7.4$ Hz, 4H), 7.34 (d, $J = 7.1$ Hz, 2H), 7.30 (d, $J = 2.3$ Hz, 2H), 6.80 (t, $J = 2.3$ Hz, 1H), 5.06 (s, 4H), 3.90 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.7, 159.8, 136.5, 132.1, 128.6, 128.1, 127.6, 108.4, 107.3, 70.3, 52.3.
3,5-dibenzylxoybenzyl alcohol 4.28

To a suspension of LiAlH₄ (3.27 g, 86.2 mmol) in Et₂O (200 mL) at 0 °C was added methyl 3,5-dibenzylxoybenzoate 4.27 (15.0 g, 43.1 mmol) in Et₂O (100 mL) dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the careful addition of H₂O (4 mL) and stirred for 5 min, followed by 15% NaOH solution (4 mL), H₂O (8 mL) and then stirred for 15 minutes. The formed alumina was the filtered, and the filtrate concentrated in vacuo to give 3,5-dibenzylxoybenzyl alcohol 4.28 (12.8 g) as a white solid, which was used in the next step without purification. Spectroscopic data matched that reported in the literature.⁵

Rᶠ = 0.25 (petroleum ether/EtOAc, 2:1)

Mp: 78-80 °C

IR (neat): 3314, 2904, 1592, 1443, 1369, 1351, 1285, 1152, 1023, 988 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, J = 7.2 Hz, 4H), 7.37 (t, J = 7.6 Hz, 4H), 7.31 (t, J = 7.2 Hz, 2H), 6.60 (s, 2H), 6.54 (s, 1H), 5.01 (s, 4H), 4.59 (d, J = 5.7 Hz, 2H), 1.80 (t, J = 5.7 Hz, 1H).

¹³C NMR (150 MHz, CDCl₃) δ 160.2, 143.4, 136.8, 128.6, 128.0, 127.5, 105.7, 101.3, 70.1, 65.3.
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3,5-dibenzylxybenzaldehyde 4.29

![Structural formula](image)

To a solution of 3,5-dibenzylxybenzyl alcohol 4.28 (13.8 g, 43.1 mmol) in CH$_2$Cl$_2$ (250 mL) was added pyridinium chlorochromate (11.1 g, 51.7 mmol) and then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (SiO$_2$, Petroleum ether/ EtOAc, 4:1) to give 3,5-dibenzylxybenzaldehyde (4.29) (12.7 g, 93% over 3 steps) as a white solid. Spectroscopic data matched that reported in the literature.$^5$

$R_f = 0.60$ (petroleum ether/EtOAc, 2:1)

Mp: 79-80 °C

IR (neat): 3032, 1687, 1593, 1448, 1383, 1351, 1297, 1172, 1049 cm$^{-1}$

$^1$H NMR (600 MHz, CDCl$_3$) δ 9.89 (d, $J = 0.5$ Hz, 1H), 7.42 (d, $J = 7.5$ Hz, 4H), 7.39 (t, $J = 7.5$ Hz, 4H), 7.34 (t, $J = 7.1$ Hz, 2H), 7.10 (d, $J = 1.6$ Hz, 2H), 6.86 (s, 1H), 5.08 (s, 4H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 191.8, 160.4, 138.4, 136.2, 128.7, 128.2, 127.6, 108.7, 108.3, 70.4.
1-(3,5-dibenzzyloxyphenyl)propan-1-ol 4.33

A solution of bromoethane (4.5 mL, 60 mmol) in dry Et₂O (150 mL) was slowly added to magnesium turnings (2.0 g, 80 mmol) and stirred under self sustained reflux until the majority of the magnesium turnings had been consumed. 3,5-Dibenzzyloxybenzaldehyde 4.29 (12.7 g 40.0 mmol) in Et₂O (150 mL) was then added dropwise, and the reaction mixture was then stirred at reflux for 1 h. The reaction was quenched with sat. NH₄Cl (100 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (2 x 150 mL). The combined organics were dried over MgSO₄, filtered and concentrated in vacuo. The crude product was then purified by flash chromatography (SiO₂, Petroleum ether/EtOAc, 4:1) to give 1-(3,5-dibenzzyloxyphenyl)propan-1-ol 4.33 (12.3 g, 88%) as a white solid.

\[ R_f = 0.45 \text{ (petroleum ether/EtOAc, 2:1)} \]

\[ \text{Mp: 72}-73 \degree \text{C} \]

\[ \text{IR (neat): 3257, 2967, 1739, 1609, 1593, 1446, 1357, 1291, 1159, 1039, 833 cm}^{-1} \]

\[ ^1H \text{ NMR (500 MHz, CDCl}_3) \delta 7.42 \text{ (d, } J = 7.4 \text{ Hz, 4H}), 7.38 \text{ (t, } J = 7.5 \text{ Hz, 4H}), 7.32 \text{ (t, } J = 7.1 \text{ Hz, 2H}), 6.61 \text{ (d, } J = 2.2 \text{ Hz, 2H}), 6.54 \text{ (t, } J = 2.0 \text{ Hz, 1H}), 5.03 \text{ (s, 4H)}, 4.53 \text{ (td, } J = 6.6, 3.5 \text{ Hz, 1H}), 1.79 \text{ (d, } J = 3.7 \text{ Hz, 1H}), 1.84 - 1.67 \text{ (m, 2H)}, 0.91 \text{ (t, } J = 7.4 \text{ Hz, 3H}). \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3) \delta 160.0, 147.2, 136.9, 128.58, 128.56, 128.0, 127.58, 127.56, 105.1, 101.1, 76.0, 70.1, 31.8, 10.1. \]

\[ \text{HRMS (C}_{23}\text{H}_{24}\text{O}_3, \text{ ESI): calculated [M+H]* 349.1798, found 349.1810} \]
(E)-(3,5-dibenzylxoyphenyl)prop-2-ene 4.34

To a solution of 1-(3,5-dibenzylxoyphenyl)propan-1-ol 4.33 (6.00 g, 17.2 mmol) in toluene (250 mL) was added p-TsOH.H₂O (328 mg, 1.72 mmol) and the mixture was heated at reflux with a Dean-Stark apparatus for 1.5 hours. The reaction mixture was cooled and washed with sat. NaHCO₃ (100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude product was the purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 4:1) to give (E)-(3,5-dibenzylxoyphenyl)prop-2-ene 4.34 (4.63 g, 81%) as a pale yellow oil.

Rᵣ = 0.60 (petroleum ether/EtOAc, 2:1)

IR (neat): 3030, 1584, 1453, 1437, 1374, 1282, 1155, 1048, 960 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 7.42 (d, J = 7.4 Hz, 4H), 7.38 (t, J = 7.5 Hz, 4H), 7.36 – 7.29 (m, 2H), 6.59 (d, J = 2.1 Hz, 2H), 6.48 (t, J = 2.1 Hz, 1H), 6.32 (d, J = 15.8 Hz, 1H), 6.20 (dq, J = 15.6, 6.5 Hz, 1H), 5.03 (s, 4H), 1.86 (d, J = 6.5 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 160.1, 140.1, 137.0, 130.9, 128.6, 128.0, 127.6, 127.5, 126.4, 105.2, 100.7, 70.1, 18.4.

HRMS (C₂₃H₂₂O₂, ESI): calculated [M+H]⁺ 331.1693, found 331.1692
(E)-2,4-dibenzyloxy-6-(prop-1-en-1-yl)benzaldehyde 4.35

To a solution of (E)-(3,5-dibenzyloxyphenyl)prop-2-ene 4.34 (2.0 g, 6.1 mmol) in DMF (30 mL) at 0 °C was added POCl₃ (0.85 mL, 9.1 mmol) and the mixture was stirred for 30 min. The reaction was then heated at 90 °C and stirred for 1 h. H₂O (30 mL) was added and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 4:1) to give (E)-2,4-dibenzyloxy-6-(prop-1-en-1-yl)benzaldehyde 4.35 (1.53 g, 71%) as a white solid.

Rₖ = 0.50 (petroleum ether/EtOAc, 4:1)

Mp: 82-83 °C

IR (neat): 2897, 1683, 1593, 1567, 1417, 1336, 1277, 1149, 1039, 964 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 10.56 (s, 1H), 7.45 – 7.30 (m, 11H), 6.68 (d, J = 1.9 Hz, 1H), 6.49 (d, J = 2.1 Hz, 2H), 6.14 (dq, J = 15.5, 6.6 Hz, 1H), 5.10 (s, 2H), 5.09 (s, 2H), 1.91 (dd, J = 6.7, 1.4 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 190.6, 163.9, 163.5, 143.6, 136.01, 135.99, 130.05, 129.98, 128.73, 128.69, 128.3, 128.2, 127.6, 127.3, 116.3, 105.3, 98.6, 70.7, 70.2, 18.7.

HRMS (C₂₄H₂₂O₃, ESI): calculated [M+H]⁺ 359.1642, found 359.1653
(E)-2,4-bis(benzyloxy)-6-(prop-1-en-1-yl)benzoic acid 4.36

To a solution of aldehyde 4.35 (1.45 g, 4.05 mmol) in DMSO (30 mL) and Acetone (30 mL) at 0 °C was added 2-methyl-2-butene (2.60 mL, 24.3 mmol). A solution of NaH₂PO₄ (2.92 g, 24.3 mmol) and NaClO₂ (2.20 g, 24.3 mmol) in H₂O (30 mL) was added and the reaction was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for 2 hours. The reaction mixture was diluted with H₂O (100 mL) and EtOAc (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over MgSO₄, filtered and concentrated in vacuo to give crude carboxylic acid 4.36 (1.54 g), which was carried through to the next step without further purification.

Rₜ = 0.05 (petroleum ether/EtOAc, 4:1)
(E)-methyl 2,4-bis(benzyloxy)-6-(prop-1-en-1-yl)benzoate 4.37

To a solution of carboxylic acid 4.36 (1.51g, 4.03 mmol) in DMF (30 mL) was added K$_2$CO$_3$ (1.1 g, 8.1 mmol) at room temperature and the mixture was stirred for 2 hours. Iodomethane (0.50 mL, 8.1 mmol) was added and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction was quenched with sat. NH$_4$Cl (100 mL) and diluted with EtOAc (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over MgSO$_4$, filtered and concentrated **in vacuo**. The resultant residue was purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 4:1) to give methyl ester 4.37 (1.32 g, 84% over 2 steps) as a yellow solid.

R$_f$ = 0.45 (petroleum ether/EtOAc, 4:1)

Mp: 90-92 °C

IR (neat): 2947, 1725, 1597, 1580, 1433, 1377, 1263, 1167, 1092, 1040 cm$^{-1}$

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.41 – 7.27 (m, 10H), 6.69 (s, 1H), 6.45 (s, 1H), 6.39 (d, J = 15.5 Hz, 1H), 6.19 (dq, J = 15.4, 6.5 Hz, 1H), 5.04 (d, J = 5.1 Hz, 4H), 3.87 (s, 3H), 1.86 (d, J = 6.6 Hz, 3H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 168.6, 160.4, 157.1, 138.1, 136.6, 136.5, 129.3, 128.6, 128.5, 128.12, 128.09, 127.79, 127.76, 127.65, 127.52, 127.40, 126.9, 116.05, 103.1, 99.6, 70.5, 70.2, 52.2, 18.7.

HRMS (C$_{25}$H$_{24}$O$_4$, ESI): calculated [M+H]$^+$ 389.1747, found 389.1745
To a solution of ester 4.37 (1.32 g, 3.46 mmol) and methanesulfonamide (0.39 g, 4.1 mmol) in t-BuOH (40 mL), H₂O (40 mL) and THF (20 mL) at 0 °C was added AD-mix α (9.7 g). The reaction mixture was gradually warmed to room temperature and then stirred for 30 hours. Sodium sulfite (10 g) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was diluted with H₂O (100 mL) and EtOAc (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 1:1) to give lactone 4.38 (1.09 g, 82%) as a white solid.

Rᶠ = 0.20 (petroleum ether/EtOAc, 1:1)

[α]²⁵₀ = −32.1 (c 1.0, CHCl₃)

Mp: 110-112 °C

IR (neat): 3415, 2927, 1738, 1603, 1451, 1334, 1210, 1161, 1064, 1021 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 7.47 (d, J = 7.7 Hz, 2H), 7.43 - 7.34 (m, 7H), 7.31 (t, J = 7.3 Hz, 1H), 6.60 (s, 1H), 6.54 (s, 1H), 5.25 (s, 2H), 5.17 (d, J = 4.1 Hz, 1H), 5.07 (s, 2H), 4.14 - 4.05 (m, 1H), 1.89 (d, J = 6.0 Hz, 1H), 1.34 (d, J = 6.3 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 167.7, 165.6, 158.7, 151.6, 135.9, 135.6, 128.79, 128.72, 128.5, 128.0, 127.6, 126.8, 108.1, 101.5, 99.9, 82.6, 70.8, 70.6, 68.9, 18.7.

HRMS (C₂₄H₂₂O₅, ESI): calculated [M+Na]⁺ 413.1359, found 413.1365
(S)-5,7-dihydroxy-3-((S)-1-hydroxyethyl)isobenzofuran-1(3H)-one 4.6

Lactone 4.38 (1.05 g, 2.68 mmol) was dissolved in MeOH (100 mL) and the flask was purged with N\textsubscript{2}. Pd/C (100 mg) was added and the flask was purged with H\textsubscript{2} (1 balloon). The reaction was stirred at room temperature for 2 hours. The reaction mixture was then filtered through a pad of Celite and washed with MeOH. The filtrate was concentrate in vacuo to give deprotected compound 4.6 (567 mg, quant.) as a colourless crystalline solid that was of significant purity to be used without further purification.

\[ R_f = 0.05 \text{ (petroleum ether/EtOAc, 1:1)} \]

\[ [\alpha]_D^{25} = +44.9 \text{ (c 1.0, MeOH)} \]

\[ \text{Mp: 195-197 °C} \]

\[ \text{IR (neat): 3146, 1720, 1686, 1606, 1478, 1352, 1216, 1162, 1062, 980 cm}^{-1} \]

\[ ^1H \text{ NMR (500 MHz, CD}_3\text{OD) } \delta 6.44 (s, 1H), 6.28 (d, J = 1.5 Hz, 1H), 5.23 (d, J = 3.2 Hz, 1H), 4.13 (qd, J = 6.5, 3.4 Hz, 1H), 1.23 (d, J = 6.5 Hz, 3H). \]

\[ ^13C \text{ NMR (125 MHz, CD}_3\text{OD) } \delta 172.2, 167.2, 159.6, 153.0, 105.4, 103.8, 102.5, 84.7, 68.8, 18.6. \]

\[ \text{HRMS (C}_{10}\text{H}_{10}\text{O}_5, \text{ESI): calculated [M+H]}^+ 211.0601, \text{found 211.0600} \]
Ortho-quinone methide precursor 4.22

To a solution of benzofuran 4.6 (100 mg, 0.48 mmol) and NaOAc.3H₂O (7 mg, 0.048 mmol) in AcOH (5 mL) was added formaldehyde solution (37% in H₂O, 0.03 mL, 0.95 mmol) and the reaction mixture was heated at 80 °C for 16 hours. The reaction mixture was poured onto sat. NaHCO₃ (25 mL) and diluted with EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with sat. NaHCO₃ (25 mL), brine (25 mL), dried over MgSO₄, filtered and concentrated in vacuo to give o-QM precursor 4.22 (93 mg) as a yellow brown solid as an inseparable mixture with the starting material. This was carried on to the next step without purification.
[4+2] Isomerized compound 4.39/4.40

\[
\begin{array}{c}
\text{4.22} \quad \text{3.17} \\
\text{PhMe, 110 °C, 16 h} \\
\end{array}
\]

\[
1:1 \text{ ratio of 4.39/4.40}
\]

\( o\)-QM precursor 4.22 (50 mg, 0.18 mmol) and exocyclic enol ether 3.17 (20 mg, 0.20 mmol) were dissolved in toluene (10 mL) and heated at 110 °C in a sealed tube for 16 hours. The reaction mixture was concentrated \textit{in vacuo} and purified by flash chromatography (SiO\textsubscript{2}, petroleum ether/EtOAc, 1:1) to give [4+2] isomerized compounds 4.39/4.40 (11 mg, 19\%) as a colourless oil, which was isolated as an inseparable 1:1 mixture of diastereoisomers.

\( R_f = 0.40 \) (petroleum ether/EtOAc, 1:1)

\textbf{IR (neat):} 3421, 2931, 1726, 1630, 1606, 1453, 1381, 1224, 1114, 1071, 996 cm\(^{-1}\)

\textbf{\(^1H\) NMR (600 MHz, CDCl\textsubscript{3})} \( \delta \) 7.82 (s, 2H), 6.52 (s, 1H), 6.51 (s, 1H), 5.24 (d, \( J = 4.9 \) Hz, 1H), 5.23 (d, \( J = 5.1 \) Hz, 1H), 4.07 (dd, \( J = 12.9, 6.4 \) Hz, 2H), 3.98 – 3.88 (m, 2H), 3.82 – 3.77 (m, 2H), 2.88 (t, \( J = 6.3 \) Hz, 1H), 2.85 (t, \( J = 6.2 \) Hz, 1H), 2.67 (d, \( J = 8.0 \) Hz, 1H), 2.64 (d, \( J = 8.1 \) Hz, 1H), 2.03 (ddd, \( J = 16.1, 10.9, 3.3 \) Hz, 2H), 1.85 – 1.71 (m, 2H), 1.65 – 1.54 (m, 6H), 1.45 (s, 3H), 1.43 (s, 3H), 1.42 (d, \( J = 3.6 \) Hz, 3H), 1.41 (d, \( J = 3.6 \) Hz, 3H).

\textbf{\(^{13}C\) NMR (150 MHz, CDCl\textsubscript{3})} \( \delta \) 171.80, 171.79, 161.16, 161.15, 155.63, 155.61, 145.48, 145.45, 107.03, 106.98, 103.82, 103.82, 103.27, 103.18, 101.14, 101.13, 85.38, 85.32, 68.99, 68.92, 62.23, 62.22, 34.20, 34.16, 25.18, 25.04, 24.99, 24.97, 24.95, 24.74, 24.64, 18.62, 18.57.

\textbf{HRMS (C\textsubscript{17}H\textsubscript{20}O\textsubscript{6}, ESI):} calculated [M+H]\(^+\) 321.1333, found 321.1336
Spiroketal 4.41

{o-QM precursor 4.22 (138 mg, 0.490 mmol) and exocyclic enol ether 3.17 (142 mg, 1.44 mmol) were dissolved in dioxane (10 mL) and heated at 110 °C in a sealed tube for 16 hours. The reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO2, petroleum ether/EtOAc, 1:1) to give spiroketal 4.41 (19 mg, 12%) as a colourless oil, which was isolated as an inseparable 1:1 mixture of diastereoisomers.}

\[ \text{R}_f = 0.40 \text{ (petroleum ether/EtOAc, 1:1)} \]

\[ \text{IR (neat): 3425, 2942, 1726, 1637, 1606, 1454, 1375, 1226, 1146, 1031, 968 cm}^{-1} \]

\[ ^1H \text{ NMR (500 MHz, CDCl}_3) \delta 7.79 \text{ (s, 2H), 6.54 \text{ (s, 1H), 6.52 \text{ (s, 1H), 5.25 \text{ (d, J = 4.7 Hz, 1H), 5.24 \text{ (d, J = 4.7 Hz, 1H), 4.06 \text{ (br s, 2H), 3.80 - 3.72 \text{ (m, 2H), 3.68 - 3.62 \text{ (m, 2H), 2.76 - 2.73 \text{ (m, 4H), 2.12 - 1.95 \text{ (m, 4H), 1.89 \text{ (d, J = 13.1 Hz, 2H), 1.78 - 1.60 \text{ (m, 10H), 1.39 \text{ (d, J = 6.4 Hz, 6H).}}}}}}}} \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3) \delta 171.90, 171.89, 159.95, 159.85, 154.85, 144.97, 144.95, 111.05, 110.96, 104.07, 104.04, 103.46, 103.33, 97.16, 97.09, 85.30, 85.25, 69.04, 68.98, 62.24, 62.16, 34.36, 34.32, 30.71, 30.68, 24.94, 24.93, 18.41, 18.38, 18.26, 18.25, 14.84, 14.83. \]

\[ \text{HRMS (C}_{17}\text{H}_{20}\text{O}_{6}, \text{ ESI): calculated [M+H]}}^+ 321.1333, \text{ found 321.1345} \]
4.8 References

4.9 Appendix Three

4.9.1 NMR Spectra

**4.27**

$^1$H NMR
CDCl$_3$
500 MHz

**4.27**

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 4

4.28

$^1$H NMR
$^1$C NMR
CDCl$_3$
CDCl$_3$
600 MHz
150 MHz
Chapter 4

4.29

$^1$H NMR
CDCl$_3$
600 MHz

4.29

$^{13}$C NMR
CDCl$_3$
150 MHz
Chapter 4

4.33

$\text{^1H NMR} \quad \text{CDCl}_3 \quad 500 \text{ MHz}$

$\text{^13C NMR} \quad \text{CDCl}_3 \quad 125 \text{ MHz}$
Chapter 4

4.34
$^1$H NMR
CDCl$_3$
600 MHz

$^1$C NMR
CDCl$_3$
150 MHz
4.35

**$^1$H NMR**

CDCl$_3$

600 MHz

4.35

**$^{13}$C NMR**

CDCl$_3$

150 MHz
Chapter 4

4.37

$^1$H NMR
CDCl$_3$
600 MHz

4.37
$^{13}$C NMR
CDCl$_3$
150 MHz
4.38

$^1$H NMR
CDCl$_3$
600 MHz

4.38

$^{13}$C NMR
CDCl$_3$
150 MHz
Chapter 4

4.27
$^1$H NMR
CD$_3$OD
500 MHz

4.6
$^{13}$C NMR
CD$_3$OD
125 MHz
Chapter 4

4.39/4.40
$^1$H NMR
CDCl$_3$
600 MHz

4.39/4.40
$^{13}$C NMR
CDCl$_3$
150 MHz
Chapter 4

4.41
$^1$H NMR
CDCl$_3$
500 MHz

4.41
$^{13}$C NMR
CDCl$_3$
125 MHz
4.41
HSQC
CDCl₃
500 MHz
Chapter Five

Progress Towards the Biomimetic Synthesis of Epicolactone

5.1 Isolation of Epicolactone

Epicolactone (5.1) is a polycyclic natural product first isolated in 2012 by Marsaioli and co-workers from the endophytic fungus Epicoccum nigrum wild type P16, found in sugarcane (Figure 5.1).\(^1\) The second isolation of epicolactone (5.1) was reported in 2013 by Laatsch and co-workers, from the endophytic fungi Epicoccum sp. CAFTBO that was collected from Theobroma cacao L. (the cocoa tree).\(^2\) In both instances, the fungi was cultured and the resultant whole cell broth was extracted with ethyl acetate, concentrated and purified to give the natural product epicolactone (5.1). Epicolactone (5.1) was found to possess antimicrobial and antibacterial activity. However, extensive biological testing of the molecule was not performed.

![Figure 5.1: The structure of epicolactone (5.1) from three different perspectives](image)

The structure of epicolactone (5.1) was elucidated based on 2D NMR studies and X-ray crystallography, with the relative configuration first assigned via the NOESY spectra and later confirmed from the X-ray crystal structure. The observed optical rotation of \(\sim -2.5\) suggested that epicolactone could be a near racemic natural product. Further evidence was obtained from the X-ray crystal data, as determined from the \(\text{P}1\text{̅}\) space group, which suggested an inversion element in the crystal morphology. This implied that both enantiomers were present in the natural organism.

5.2 Proposed Biosynthesis of Epicolactone

Interestingly, Laatsch and co-workers also co-isolated two other known natural products epicoccine (5.3)\(^3,4\) and epicoccone B (5.4)\(^4\), previously isolated from a related
Epicoccum species of fungus (Figure 5.2). Epicolactone (5.1) appears to be derived from the oxidised backbone of these two molecules. The highly oxygenated seven-membered ring fused to a six-membered ring of epicolactone (5.1) was also observed in the structurally related benzotropolone natural product purpurogallin (5.2). The proposed biosynthesis of purpurogallin (5.2) has not been fully established, with the mechanism of its formation still the subject of some debate.5–7 However, the pathway that is favoured amongst the research community involves a [5+2] cycloaddition of two o-quinones followed by a hydrolytic cleavage to achieve the seven-membered ring. In addition, this biosynthetic pathway is identical to that proposed for many benzotropolone natural products.8

Figure 5.2: Structure of purpurogallin (5.2), epicoccine (5.3) and epicoccone B (5.4)

The biosynthesis of purpurogallin (5.2) begins with the oxidation of pyrogallol (5.5) to o-quinone 5.6, which then undergoes a [5+2] cycloaddition dimerisation with another molecule of 5.6 to afford bridged bicyclic 5.7 (Scheme 5.1). This reaction is likely to be a stepwise process consisting of a Michael reaction followed by a nucleophilic attack of the enolate formed on the adjacent carbonyl group to achieve the bridged structure of 5.7.5,7 Hydrolytic ring opening of the bridge ring system by a molecule of water would give carboxylic acid 5.8, which upon oxidation and decarboxylation would afford purpurogallin (5.2).

Scheme 5.1: proposed biosynthesis of purpurogallin (5.2)
Turning our attention to epicolactone (5.1), we presume that this natural product could be synthesised via similar pathway. However, instead of a dimerization of pyrogallol (5.2), a [5+2] cycloaddition between 5.9 and 5.10 (the oxidised forms of epicoccine (5.3) and epicoccone B (5.4)) would furnish the benzotropolone framework (compound 5.11) (Scheme 5.2). Ring opening of the lactone moiety with water would yield carboxylic acid 5.12, which can undergo instantaneous decarboxylation to afford intermediate 5.13. The primary alcohol moiety could then ring open the bridged ketone, forming lactone 5.14. Finally, a vinylogous aldol reaction with the ketone at C-14 of 5.15 would yield epicolactone (5.1).

**Scheme 5.2: Proposed biosynthesis of epicolactone (5.1)**

The synthesis of epicolactone (5.1) would first require the synthesis of both epicoccine (5.3) and epicoccone B (5.4). Oxidation to their corresponding o-quinones (5.9 and 5.10) would hopefully yield epicolactone (5.1) by the above cascade reaction. Additionally, initial studies by Nakatsuka et al. in their synthesis of benzotropolone derivative 5.20, showed that it was possible to form the benzotropolone backbone under oxidative coupling conditions (Scheme 5.3). Excess o-quinone 5.17 was employed to initiate the oxidation of 5.16, which underwent a [5+2] cycloaddition to afford 5.18. The addition of water to the reaction mixture yielded the
benzotropolone scaffold 5.20, via a hydrolysis-oxidation-decarboxylation cascade presumably via 5.19. This evidence was a promising starting point for our synthetic approach.

Scheme 5.3: Nakatsuka’s synthesis of benzotropolone derivative 5.20

With this in mind, the aim of this project is to first synthesise both epicoccine (5.3) and epicoccone B (5.4), then screen conditions for the oxidation of each compound into their corresponding \( \alpha \)-quinones, and finally complete a synthesis of epicolactone (5.1).

5.3 Synthesis of Epicoccone B

The first goal of this project was to synthesise what we deemed as the more easily obtainable precursor: epicoccone B (5.4). The key to the synthesis was to control the installation of the C-6 methyl group \( \textit{meta} \) to the C-2 carbonyl group. As a result, a plan to differentiate between the C-2 and C-6 positions was devised. We decided to start from a protected form of gallic acid (methyl 3,4,5-trimethoxybenzoate (5.21)) and take advantage of its inherent symmetry to introduce formaldehyde at the C-2 and C-6 positions. We employed a procedure developed in 1942 by King and King, whereby methyl 3,4,5-trimethoxybenzoate (5.21) was heated at reflux in concentrated HCl in the presence of formalin to afford benzyl chloride lactone 5.22 (Scheme 5.4). The reaction presumably proceeds via a double electrophilic aromatic substitution reaction with formaldehyde to first give the dibenzyl alcohol, which then undergoes an \textit{in situ} lactonisation as well as a simultaneous substitution reaction to install the benzyl chloride moiety. The reaction proceeded in excellent yield (95%), and the desired product was recrystallised from ethanol.
Scheme 5.4: Electrophilic aromatic substitution with formaldehyde followed by LiAlH$_4$ reduction to afford 5.23

A reduction of the benzoyl chloride moiety to an aryl methyl group as well as a simultaneous lactone reduction to the diol with LiAlH$_4$ afforded compound 5.23 (Scheme 5.4) according to Popp and co-workers.\(^\text{10}\) The desired benzyl alcohol product 5.23 was obtained in 72% yield after flash chromatography. We hypothesised this to be our key intermediate toward the synthesis of both epicoccone B (5.4) via an oxidation, and epicoccine (5.3) via a cycloetherification reaction (Scheme 5.5).

Scheme 5.5: Proposed conversion of diol 5.23 into epicoccone B (5.4) and epicoccine (5.3)

With this key intermediate 5.23 in hand, we first attempted the synthesis of epicoccone B (5.4). However, there is a significant regioselectivity problem that needed to be addressed, as we required the oxidation to occur at the C-8 primary alcohol instead of the C-7 primary alcohol. While we hoped that the electronics of the molecule would favour our desired oxidation, we theorised that a mixture of the oxidation products could potentially occur. Unfortunately, this statement held true, with oxidation of the diol 5.23 affording approximately a 2:1 ratio in favour of the undesired lactone 5.25 to the desired lactone 5.24. A series of oxidants were screened in order to optimise the yield and to attempt to improve the ratio with respect to our desired lactone 5.24 (Table 5.1).
Table 5.1: Optimised oxidation conditions to form lactone 5.24

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product (ratio)</th>
<th>Total Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCC, CH2Cl2, 0 °C to rt, 16 h</td>
<td>5.24 and 5.25 (1:1.8)</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>PDC, CH2Cl2, 0 °C to rt, 4 h</td>
<td>5.24 and 5.25 (1:2.2)</td>
<td>N.D. ( ^a )</td>
</tr>
<tr>
<td>3</td>
<td>MnO(_2), CHCl(_3), reflux, 3 days</td>
<td>5.24 and 5.25 (1:1.6)</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>TPAP, NMO, CH2Cl2, 4 Å mol. sieves, rt, 30 min</td>
<td>5.24 and 5.25 (1:5)</td>
<td>22%</td>
</tr>
<tr>
<td>5</td>
<td>(COCl)(_2), DMSO, Et(_3)N, CH2Cl2, −78 °C to rt, 2 h</td>
<td>5.26</td>
<td>28%</td>
</tr>
</tbody>
</table>

\( ^a \) ratio determined from the crude NMR

Varying the oxidant affected the product distribution drastically. The yield for all of the oxidation reactions was modest (Entries 1-4) (less than 50%), which could be attributed to the formation of dialdehyde 5.26, which we found to be extremely unstable when isolated from the Swern oxidation (Entry 5). Dialdehyde 5.26 readily decomposed over a matter of hours, with various decomposition products observed in the NMR spectrum. The optimised oxidation conditions were obtained using MnO\(_2\) in chloroform and the reaction heated at reflux for 3 days (Entry 4), which yielded our desired lactone 5.24 as the minor product in a 1:1.6 ratio. The two lactones 5.24 and 5.25 had almost identical R\(_f\) values, but with careful chromatography, the desired lactone 5.24 was isolated in 19% yield.

Finally, to complete the synthesis of epicoccone B (5.4) a deprotection of the three methyl ethers was required. Lactone 5.24 was stirred in a dispersion of AlCl\(_3\) in CH\(_2\)Cl\(_2\) at room temperature for three days, which afforded epicoccone B (5.4) in a good yield (88%), along with trace quantities of monomethyl and dimethyl protected analogues (Scheme 5.6). The purification of the mixed deprotected species proved to be troublesome, however a simple solution to this was developed. Trituration of the resultant reaction mixture with chloroform afforded almost pure epicoccone B (5.4) after isolation by vacuum filtration. The data collected matched that of the natural product, thus confirming the synthesis of our first intermediate towards epicolactone (5.1).
Scheme 5.6: Deprotection of methyl ethers to reveal epicoccone B (5.4)

5.4 Attempted Oxidation of Epicoccone B

With the key intermediate epicoccone B (5.4) in hand, we attempted to oxidise the triphenol moiety to the corresponding \( o \)-quinone 5.10. If this reaction was facile, it would overcome the first hurdle in the synthesis of epicolactone (5.1). A regioselectivity issue arising from the presence of the triphenol moiety could prove problematic, with two possible quinone tautomers that could be obtained 5.10 and 5.27 (Figure 5.3). Furthermore, the \( para \) aryl methyl and benzyl position are also potential oxidation sites.

Figure 5.3: Two possible \( o \)-quinones 5.10 and 5.27 from the oxidation of epicoccone B (5.4)

The oxidation of epicoccone B (5.4) was attempted under a variety of reaction conditions (Table 5.2). The oxidative outcome would be the first major test of our biomimetic synthesis. To our dismay, under all of the tested conditions, the starting material merely decomposed without any quinone products observed.
Table 5.2: Attempted oxidation of epicoccone B (5.4) to $o$-quinone 5.10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>chloranil, CH$_2$Cl$_2$, rt, 3 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>chloranil, CH$_3$CN-H$_2$O, rt, 16 h</td>
<td>lactol 5.29</td>
</tr>
<tr>
<td>3</td>
<td>chloranil, Et$_2$O, –20 °C, 20 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>DDQ, MeOH, 0 °C to rt, 1 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>Ag$_2$O, Et$_2$O, rt, 1 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>Ag$_2$O, THF, rt, 4 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>CAN, MeOH, 0 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>8</td>
<td>PhI(OAc)$_2$, HFIP, 0 °C, 10 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>9</td>
<td>NaIO$_4$, CH$_2$Cl$_2$, H$_2$O, 0 °C to rt, 1 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>10</td>
<td>FeCl$_3$-6H$_2$O, MeOH-H$_2$O, rt, 5 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>11</td>
<td>MnO$_2$, THF, 60 °C, 2 h</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

The synthesis of desired $o$-quinone 5.10 proved to be a challenging task. The only reaction to afford a product used aqueous oxidation conditions with chloranil as the oxidant to afford lactol 5.29 (Entry 2), presumably via para-quinone methide 5.28, which was then trapped with water (Scheme 5.7). This emphasises the regioselectivity issues of the oxidation, with a preference for the benzylic oxidation rather than the desired oxidation to $o$-quinone 5.10. Lactol 5.29 was assigned based on the presence of a new signal at $\delta_H$ 6.37 in the $^1$H NMR spectrum, which is a heavily downfield signal due to the two adjacent electronegative atoms as well as the electron rich aromatic ring.

Scheme 5.7: Aqueous chloranil oxidation affording lactol 5.29
We still held some hope for the total synthesis of epicolactone (5.1) if we could synthesise the other key precursor epicoccine (5.3). A successful oxidation of epicoccine (5.3) and subsequent reaction to afford a benzotropolone type backbone would strongly suggest a potential biosynthetic link with epicolactone (5.1).

5.5 Towards a Synthesis of Epicoccine

We now focussed our attention towards the synthesis of epicoccine (5.3), and wanted to find a suitable protecting group strategy as we were unsure if the cyclic ether of 5.3 would be stable to harsh Lewis acidic demethylation conditions. We therefore devised tandem methyl and benzyl protecting group strategies towards benzyl alcohols 5.23 and 5.30 (Figure 5.4). Trimethyl ether 5.22 is an advanced intermediate in the synthesis of epicoccone B (5.4), thus the main goal of this part of the project was to synthesise tribenzyl ether 5.30.

Figure 5.4: Target benzyl alcohols 5.23 and 5.30

Initial studies into the protection of gallic acid, and the subsequent reaction of the tribenzylated compound with formalin and concentrated HCl proved to be unsuccessful. The reaction with formaldehyde failed to proceed, with only starting material isolated. We therefore devised an alternate plan, whereby we converted the undesired product 5.25 from our optimised oxidation reaction of diol 5.23. The three methyl ethers of lactone 5.25 (undesired product from the MnO₂ oxidation) were cleaved with AlCl₃, which afforded epicoccone A 5.31 (co-isolated with epicoccone B⁴,¹¹) in moderate yield (Scheme 5.8). The deprotection reaction was slow, with a significant portion of the mono and di-demethylated compounds observed. The phenols of 5.31 were then protected with benzyl groups under standard conditions (BnBr, K₂CO₃, DMF) to afford the tribenzyl ether 5.32, which was then reduced with LiAlH₄ to the desired benzyl alcohol compound 5.30.

Scheme 5.8: Synthesis of benzyl alcohol 5.30
Cycloetherification of the diols \(5.23\) and \(5.30\) was explored next. A look into the literature revealed two possible methods for the conversion of \(5.23\) and \(5.30\) into the corresponding furan ring observed in epicoccine \(5.3\). The first method reported by Hart and co-workers\(^\text{12}\) involved heating benzyl alcohol \(5.33\) at 60 °C in \(p\)-TsOH and dichloroethane to afford cycloether \(5.34\) in 30% yield (Scheme 5.9). The NMR of \(5.34\) was compared to that of the starting material, the authors observed a shift in the benzyl protons, which confirmed a transformation to the cycloether compound \(5.34\) had occurred.

\[
\begin{align*}
\text{Scheme 5.9: Acid catalysed cycloetherification} \\
\text{These conditions were mimicked on our benzyl alcohol } 5.23, \text{ with little success (Scheme 5.10). The reaction mixture formed two inseparable compounds that were slightly less polar than the starting material on the TLC plate, while the NMR spectra demonstrated that the starting material was consumed and was converted into a 2:1 mixture of unknown compounds. The fact that the two compounds were inseparable suggested that this was not a suitable pathway to cycloether 5.35, and an alternative procedure needed to be explored.}
\end{align*}
\]

The second method reported in the literature was described by Malacria and co-workers,\(^\text{13}\) whereby \(5.36\) was treated with \(n\)-BuLi and TsCl, which upon mono tosyl protection followed by a nucleophilic substitution reaction yielded the desired cycloether \(5.37\) in 80% yield (Scheme 5.11).

\[
\begin{align*}
\text{Scheme 5.11: Base initiated cycloetherification} \\
\end{align*}
\]
This methodology was applied to our substrate, with the addition of trimethyl ether 5.23 to a cooled solution of n-BuLi. TsCl was then added and the reaction mixture was gradually warmed to room temperature. The resultant yield of product was 55%, but the NMR of the isolated compound appeared to be a single compound. Analysis of the 2D NMR data failed to provide a clear identification of the product. However, when the $^{13}$C NMR spectrum of the isolated compound was compared to that of epicoccine (5.3) a discrepancy was observed. The $^1$H NMR of epicoccine (5.3) and 5.38 were consistent, however inspection of the $^{13}$C NMR demonstrated a large irregularity with the key cycloether peaks of our synthesised compound appearing much further upfield at $\delta_H$ 40.0 and 37.4 ppm instead of $\delta_H$ 73.6 and 72.6 ppm observed in epicoccine (5.3). We rationalised that the drastic change in chemical shift was due to a less electronegative atom attached at the benzylic position. Considering the reaction conditions, it appears that instead of a cycloetherification, we have instead observed a di-substitution of chloride for the tosylate moieties, resulting in dichloro compound 5.38 (Scheme 5.12). This chemical shift correlates to that observed in many common benzyl chlorides.\(^{14}\)

![Scheme 5.12: Attempted synthesis of cycloether 5.35](image)

A similar result was obtained when the trimethyl protected compound 5.23 was treated with thionyl chloride in an attempt form cycloether 5.35 (Scheme 5.13). Instead of a single chlorination reaction, dichlorination of 5.23 was favoured. When one equivalent of thionyl chloride was used, dichlorinated compound 5.38 was obtained in 50% yield along with 50% of the starting material 5.23. Addition of an extra equivalent of thionyl chloride part way through the reaction consumed the rest of the starting material to produce dichlorinated compound 5.38 in 95% yield. This pathway confirmed the formation of 5.38, reinforcing the observation that the TsCl and n-BuLi reaction failed to yield the desired cycloether compound 5.35, but instead afforded dichlorinated compound 5.38.

![Scheme 5.13: Thionyl chloride dichlorination of 5.23](image)
Up unto this point the synthesis of epicoccine (5.3) had eluded us, but there were still a large number of avenues to explore for installing the furan ring of epicoccine (5.3). Unfortunately, this was where our adventure toward the synthesis of epicolactone (5.1) ended. In late 2014 Trauner and co-workers publish a synthesis of dibefurin (5.39)\textsuperscript{15} and a year later (late 2015) they succeeded in their mission to synthesise epicolactone (5.1) via an eight step biosynthetically inspired synthesis.\textsuperscript{16}

5.6 Trauner’s Synthesis of Dibefurin and Epicolactone

Trauner and co-workers completed a synthesis of epicoccine (5.3) and epicoccone B (5.4) in their 2014 synthesis of dibefurin (5.39).\textsuperscript{15} Dibefurin (5.39) is a dimeric fungal metabolite isolated in 1996, which was observed to have calcineurin phosphatase inhibition. Dibefurin (5.39) is proposed to arise in nature via a homodimerization of \( \text{o-quinone 5.9} \) formed by oxidation of epicoccine (5.3) (Scheme 5.14).\textsuperscript{17}

![Scheme 5.14: Proposed biosynthesis of dibefurin (5.39) via homodimerisation of 5.9](image)

Epicoccine (5.3) was synthesised in five steps from eudesmic acid (5.40), with the key reactions involving a two-step reduction of a lactone (5.25) to a lactol with DIBAL-H, followed by acid catalysed triethylsilane reduction of the lactol revealing the cyloether of 5.3 (Scheme 5.15). Similarly, epicoccone B (5.4) was synthesised via a six step sequence from 2,3,4-trimethoxybenzoic acid (5.41), where the key steps involved selective demethylation at the C-2 and C-3 methyl ethers, followed by formylation to afford 5.42. Finally, reduction of the formyl moiety to the aryl methyl group, followed by cleavage of the C-4 methyl ether revealed epicoccone B (5.3) (Scheme 5.15).
Similarly, Trauner and co-workers were also unsuccessful in their attempts to oxidise epicoccone B (5.4) to \(o\)-quinone 5.10. In order to achieve regioselective oxidation, the final deprotection of the C-4 methyl ether was not performed. This allowed for oxidation of 5.43 with chloranil to afford \(o\)-quinone 5.44 in reasonable yield (78%) (Scheme 5.16).

Scheme 5.16: Chloranil oxidation of mono-methyl epicoccone B (5.42)

Epicoccine (5.3) was much more receptive to oxidation with a variety of oxidants able to be employed; \(K_3[Fe(CN)_{6}]\) proved to be the ideal oxidant for this type of transformation. Interestingly, the desired \(o\)-quinone 5.9 was never observed. Instead a dimerised compound was isolated from the oxidation reaction, which was determined to be the natural product dibefurin (5.39) (Scheme 5.17).

Scheme 5.17: Trauner’s synthesis of dibefurin (5.39)
This was an undesired result considering the target of the synthesis was epicolactone (5.1), however it sheds some light on the biosynthesis of dibefurin (5.39) and the possibility of a biosynthetic link to epicolactone (5.1). In order to counter the formation of dibefurin (5.39) and thus investigate the biosynthesis of epicolactone (5.1), Trauner and co-workers employed two equivalents of o-quinone 5.44, where one equivalent initiates the oxidation of epicoccine (5.3) and the second is available for the heterodimerisation (Scheme 5.18). Unfortunately, the reaction failed to yield epicolactone (5.1) instead an alternative heterodimerisation reaction was observed affording 5.45, which was characterised by trapping the hemiacetal of 5.45 with acetic anhydride and pyridine to provide 5.46. Isolation of intermediate 5.45 was impossible, as attempted crystallisation simply converted the structure back to dibefurin (5.39), presumably via a retro-Diels-Alder reaction.

\[
\text{Scheme 5.18: [4+2] Cycloaddition observed when attempting to mimic biosynthesis of epicolactone (5.1)}
\]

Trauner and co-workers proposed the above reaction proceeded via the desired o-quinone 5.44, however this then undergoes a tautomerisation to the p-quinone methide, which completed the [4+2] cycloaddition with o-quinone 5.9. This outcome eliminates the hypothesised biosynthesis of epicolactone (5.1) proceeding via the heterodimerisation of the two quinones of epicoccine (5.3) and epicocone B (5.4).

Interestingly, the following year in 2015 Trauner and co-workers solved this problem by suggesting a slightly modified biosynthesis of epicolactone (5.1). It was reported that in the biosynthesis there might be a decarboxylation of epicocone B (5.4) to benzyl alcohol 5.47. This pathway would remove the need for a decarboxylation step in the middle of the biosynthetic cascade. The primary alcohol present in 5.48 would allow immediate ring opening of the bridge ketone 5.13 to afford the benzotropolone backbone 5.15, whereby a subsequent vinylogous aldol would afford the natural product 5.1 (Scheme 5.19).
This hypothesis was tested, with the minor adjustment of removing the carbonyl functionality from epicoccone B (5.4) allowing access to the desired natural product epicolactone (5.1). The monomethyl ether of the precursor 5.49 was synthesised in six steps from vanillyl alcohol (5.47).\(^{16,18}\) With 5.49 in hand the [5+2] cycloaddition was completed by stirring 5.49 and epicoccine (5.3) with \(K_3[Fe(CN)_6]\) and NaHCO\(_3\) in CH\(_3\)CN/H\(_2\)O to give epicolactone mono methyl ether 5.50 as well as structural isomer 5.51 (Scheme 5.20). Finally, to furnish the natural product the methyl ether of 5.50 was cleaved with MgI\(_2\) to afford epicolactone (5.1) in eight steps in exceptional yield.

**Scheme 5.20:** Trauner’s synthesis of epicolactone (5.1)
5.7 Summary

In conclusion, the synthesis of epicoccone B (5.4), one of our proposed biosynthetic precursors to epicolactone (5.1) was completed. Unfortunately, all attempts to oxidise epicoccone B (5.4) to its corresponding o-quinone 5.10 were unsuccessful. A similar observation was also made by Trauner and co-workers in their synthesis of dibefurin (5.39). While significant progress towards the synthesis of epicoccine (5.3) was made, we were unable to complete the desired cycloetherification to furnish epicoccine (5.3). In 2014 and 2015, two papers by the Trauner research group were published, proving that our proposed biosynthesis of epicolactone (5.1) does not involve the heterodimerisation of epicoccine (5.3) and epicoccone B (5.4), but instead is more likely to occur via the heterodimerisation of epicoccine (5.3) and a decarboxylated version of epicoccone B 5.49. The publication of these findings discontinued our efforts towards the biomimetic synthesis of epicolactone (5.1).
5.8 Supporting Information

5.8.1 General Experimental

All commercially obtained chemicals were used without further purification. Solvents stated
as dry, were either distilled under nitrogen and used immediately, or distilled under an
atmosphere of nitrogen and stored over 4Å molecular sieves. Thin-layer chromatography
(TLC) was conducted on Merck silica gel 60 F<sub>254</sub> aluminium sheets and visualised under a UV
lamp or with ceric ammonium molybdate (CAM), vanillin or potassium permanganate staining
followed by heating. All R<sub>f</sub> values are rounded to the nearest 0.05. Davisil 43-60 micron
chromatographic silica media was used for flash chromatography. <sup>1</sup>H NMR spectra were
recorded on an Agilent 500 spectrometer (<sup>1</sup>H at 500 MHz, <sup>13</sup>C at 125 MHz) in CDCl<sub>3</sub> as the
solvent unless specified otherwise. <sup>1</sup>H chemical shifts are reported in ppm relative to TMS (δ
0.0) and <sup>13</sup>C NMR are reported in ppm relative to TMS (δ 0.0). All J values were quoted to the
nearest 0.1 Hz. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q)
quartet, (qnt) quintet, (sxt) sextet and (m) multiplet. IR spectra were recorded on a Perkin-
Elmer Fourier-Transform Infrared (FT-IR) spectrometer on a nickel-selenide crystal as neat
compounds. High resolution mass spectra were obtained on an Agilent ESI high resolution
mass spectrometer. Melting points were recorded on a Reichert electrothermal melting point
apparatus and are uncorrected.
5.8.2 Experimental Procedures

7-(chloromethyl)-4,5,6-trimethoxyisobenzofuran-1(3H)-one 5.22

To a solution of 3,4,5-trimethoxybenzoic acid (5.21) (20 g, 94 mmol) in conc. HCl (140 mL) was added formaldehyde solution (37% in H₂O, 100 mL) and the mixture was heated at reflux for 1 hour. The reaction mixture was cooled to 0 °C and the resultant precipitate was collected via vacuum filtration. The crude product was recrystallised from EtOH to give lactone 5.22 (24.5 g, 95%) as a white solid. The spectroscopic data matched that reported in the literature.⁹

Rᵣ = 0.45 (petroleum ether/EtOAc, 1:1)

Mp: 79-80 °C

IR (neat): 2950, 1738, 1608, 1579, 1482, 1456, 1341, 1127, 1003 cm⁻¹

¹H NMR (500 MHz, CDCl₃)  δ 5.25 (s, 2H), 5.07 (s, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.98 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 169.5, 154.3, 150.1, 148.0, 134.2, 126.1, 118.4, 67.1, 61.9, 61.1, 60.4, 34.0.
To a dispersion of LiAlH₄ (10.2 g, 270 mmol) in Et₂O (500 mL) at 0 °C was added lactone 5.22 (24.5 g, 89.9 mmol) portionwise and the reaction mixture was stirred at 0 °C for 1 hour and then warmed to room temperature and stirred for 1 hour. The reaction was quenched by the dropwise addition of H₂O (10 mL) at 0 °C, followed by 15% NaOH solution (10 mL) and then H₂O (30 mL). The solution was stirred at room temperature for 10 minutes. The resultant alumina formed was removed by vacuum filtration and washed with Et₂O (250 mL). The filtrate was concentrated in vacuo and the residue purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 1:2 → 1:3 gradient elution) to give diol 5.23 (16.4 g, 72%) as a white solid. The spectroscopic data matched that reported in the literature.¹⁰

\( R_f = 0.05 \) (petroleum ether/EtOAc, 1:1)

\( \text{Mp: } 55\text{-}58 °C \)

\( \text{IR (neat): } 3358, 3254, 1583, 1462, 1412, 1334, 1103, 1074, 882 \text{ cm}^{-1} \)

\( ^1H \text{ NMR (500 MHz, CDCl}_3 \) \( \delta 4.81 \text{ (s, 2H)}, 4.74 \text{ (s, 2H)}, 3.90 \text{ (s, 3H)}, 3.87 \text{ (s, 3H)}, 3.83 \text{ (s, 3H)}, 2.71 \text{ (s, 1H)}, 2.63 \text{ (s, 1H)}, 2.31 \text{ (s, 3H)}. \)

\( ^{13}C \text{ NMR (125 MHz, CDCl}_3 \) \( \delta 152.0, 150.2, 146.0, 134.3, 129.3, 127.3, 62.9, 60.75, 60.65, 59.3, 56.8, 11.6. \)

\( \text{HRMS (C}_{12}\text{H}_{18}\text{O}_5, \text{ ESI): } \) calculated [M+Na]^+ 265.1046, found 265.1053
3,4,5-trimethoxy-6-methylphthalaldehyde 5.26

To a solution of DMSO (0.17 mL, 2.46 mmol) in CH₂Cl₂ (10 mL) at −78 °C was added oxalyl chloride (0.10 mL, 1.23 mmol) and the mixture was stirred at −78 °C for 10 minutes. To this solution was added diol 5.23 (100 mg, 0.41 mmol) in CH₂Cl₂ (1 mL) and the reaction mixture was stirred at −78 °C for 20 minutes. Triethylamine (0.52 mL, 3.69 mmol) was added and the mixture was stirred at −78 °C for 1 hour and then warmed to room temperature and stirred for 1 hour. The reaction was quenched with sat. NH₄Cl (10 mL) and diluted with CH₂Cl₂ (25 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL). The combined organics were dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 2:1) to give dialdehyde 5.26 (28 mg, 28%) as a deep red-black gum. The formed compound was unstable and slowly decomposed over time in the NMR tube.

**Rt = 0.30** (petroleum ether/EtOAc, 2:1)

**IR (neat):** 2939, 1687, 1611, 1478, 1354, 1197, 1116, 979, 874 cm⁻¹

**¹H NMR (500 MHz, CDCl₃)** δ 10.35 (s, 1H), 10.22 (s, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 2.28 (s, 3H).

**¹³C NMR (125 MHz, CDCl₃)** δ 194.0, 190.3, 157.6, 155.2, 148.0, 134.1, 127.9, 126.0, 62.7, 60.98, 60.85, 11.8.

**HRMS (C₁₂H₁₄O₅, ESI):** calculated [M+H]^+ 239.0914, found 239.0913
5,6,7-trimethoxy-4-methylisobenzofuran-1(3H)-one 5.24

To a solution of diol 5.23 (5.00 g, 20.6 mmol) in CHCl₃ (200 mL) was added MnO₂ (3.60 g, 41.3 mmol) and the reaction mixture was heated at reflux for 1 day. To this solution was added extra MnO₂ (1.80 g, 20.7 mmol) and then the reaction was stirred for a further 2 days. The reaction mixture was then filtered through a plug of SiO₂ and then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 4:1) to give undesired lactone 5.25 (1.45 g, 29%) as a white solid, further elution also produced the lactone 5.24 (920 mg, 19%) as a white solid.

Data for 5.24

Rᵣ = 0.30 (petroleum ether/EtOAc, 2:1)

Mp: 83-86 °C

IR (neat): 2981, 2946, 1750, 1599, 1482, 1447, 1357, 1335, 1286, 1114, 1040 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 5.11 (s, 2H), 4.11 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 2.13 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 168.8, 157.7, 151.3, 146.0, 142.1, 120.0, 112.4, 68.1, 62.5, 61.4, 60.9, 11.2.

HRMS (C₁₂H₁₄O₅, ESI): calculated [M+Na]⁺ 265.1046, found 265.1053

Data for undesired 5.25

Rᵣ = 0.35 (petroleum ether/EtOAc, 2:1)

Mp: 75–78 °C
IR (neat): 2943, 1743, 1590, 1484, 1455, 1340, 1192, 1122, 996 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.21 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.85 (s, 3H), 2.54 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.7, 153.4, 150.4, 145.2, 134.2, 128.3, 118.6, 66.7, 61.1, 60.8, 60.5, 10.0.

HRMS ($C_{12}H_{14}O_5$, ESI): calculated [M+H]$^+$ 239.0914, found 239.0924
Epicoccone B 5.4

To a dispersion of AlCl$_3$ (10.1 g, 75.6 mmol) in CH$_2$Cl$_2$ (200 mL) was added lactone 5.24 (2.0 g, 8.4 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and then stirred for 2 days. The reaction was carefully quenched by the addition of 1M HCl (100 mL), the mixture was stirred for 10 minutes and the CH$_2$Cl$_2$ was removed in vacuo. The resultant aqueous layer was extracted with Et$_2$O (3 x 150 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The resultant residue was triturated with CHCl$_3$ to give epicoccone B (5.4) (1.45 g, 88%) as a white cream solid.

R$_f$ = 0.15 (petroleum ether/EtOAc, 1:1)

Mp: 228-230 °C

IR (neat): 3511, 3438, 3335, 2981, 1736, 1634 1519, 1455, 1381, 1222, 1018 cm$^{-1}$

$^1$H NMR (500 MHz, DMSO-d$_6$) δ 9.29 (br s, 2H), 8.76 (br s, 1H), 5.10 (s, 2H), 1.97 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 169.9, 151.2, 143.1, 138.1, 132.9, 109.2, 102.8, 67.8, 10.8.

HRMS (C$_9$H$_8$O$_5$, ESI): calculated [M+H]$^+$ 197.0444, found 197.0449
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3,5,6,7-tetrahydroxy-4-methylisobenzofuran-1(3H)-one 5.29

To a solution of epicoccone B (5.4) (100 mg, 0.51 mmol) in CH$_3$CN (3mL) and H$_2$O (3 mL) was added chloranil (125 mg, 0.51 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with H$_2$O (15 mL) and Et$_2$O (25 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (2 x 15 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo.

The resultant residue was purified by flash chromatography (SiO$_2$, petroleum ether/EtOAc, 2:1 → 0:1 gradient elution) to give lactol 5.29 (77 mg, 71%) as a colourless oil.

Partial data for 5.29

$R_f = 0.05$ (petroleum ether/EtOAc, 1:1)

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.34 (br s, 1H), 9.28 (br s, 1H), 8.88 (br s, 1H), 7.60 (d, $J$ = 7.8 Hz, 1H), 6.37 (d, $J$ = 6.4 Hz, 1H), 2.06 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 167.8, 151.2, 142.6, 137.6, 134.2, 111.8, 104.0, 96.2, 10.6.
To a dispersion of AlCl$_3$ (15.1 g, 113 mmol) in CH$_2$Cl$_2$ (250 mL) was added lactone 5.25 (3.00 g, 12.6 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and then stirred for 2 days. The reaction was carefully quenched by the addition of 1M HCl (100 mL), the mixture was stirred for 10 minutes and the CH$_2$Cl$_2$ was removed in vacuo. The resultant aqueous layer was extracted with Et$_2$O (3 x 150 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The resultant residue was triturated with CHCl$_3$ to give epicoccone A (5.31) (1.50 g, 61%) as a dark grey solid.

$R_f = 0.15$ (petroleum ether/EtOAc, 1:1)

**Mp:** >260 °C

**IR (neat):** 3341, 3187, 1725, 1611, 1523, 1453, 1313, 1270, 1103, 1004 cm$^{-1}$

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.15 (s, 3H), 5.08 (s, 2H), 2.33 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 171.8, 145.3, 140.2, 137.3, 126.6, 116.4, 112.9, 66.8, 10.0.

**HRMS (C$_9$H$_8$O$_5$, ESI):** calculated [M+H]$^+$ 197.0444, found 197.0449
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4,5,6-tris(benzyloxy)-7-methylisobenzofuran-1(3H)-one 5.32

![Reaction Scheme](image)

To a solution of epicoccone A (5.31) (1.5 g, 7.65 mmol) in DMF (40 mL) was added K₂CO₃ (4.20 g, 30.6 mmol) and benzyl bromide (3.64 mL, 30.6 mmol) and the reaction mixture was stirred at room temperature for 36 hours. The reaction mixture was then diluted with H₂O (150 mL) and EtOAc (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine (3 x 150 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 8:1) to give tribenzylated compound 5.32 (2.15 g, 60%) as colourless oil.

Rᵣ = 0.65 (petroleum ether/EtOAc, 2:1)

**IR (neat):** 3032, 2941, 1752, 1605, 1476, 1453, 1334, 1112, 979 cm⁻¹

**¹H NMR (500 MHz, CDCl₃)** δ 7.47 – 7.26 (m, 15H), 5.19 (s, 2H), 5.13 (s, 2H), 5.03 (s, 2H), 4.85 (s, 2H), 2.48 (s, 3H).

**¹³C NMR (125 MHz, CDCl₃)** δ 170.7, 152.2, 150.2, 144.0, 136.7, 136.65, 136.61, 136.0, 129.4, 128.70, 128.66, 128.57, 128.54, 128.53, 128.51, 128.44, 128.39, 118.9, 75.9, 75.4, 75.2, 66.8, 10.5.

**HRMS (C₃₀H₂₆O₅, ESI):** calculated [M+H]⁺ 467.1853, found 467.1860
(3,4,5-tris(benzyloxy)-6-methyl-1,2-phenylene)dimethanol 5.30

![Chemical Structure](image)

To a dispersion of LiAlH₄ (350 mg, 9.22 mmol) in Et₂O (100 mL) at 0 °C was added tribenzyloxy lactone 5.32 (2.15 g, 4.61 mmol) and the reaction was warmed to room temperature and stirred for 2 hours. The reaction was quenched by the dropwise addition of H₂O (0.35 mL) at 0 °C, followed by 15% NaOH solution (0.35 mL) and then H₂O (1 mL). The solution was stirred at room temperature for 30 minutes. The resultant alumina formed was removed by vacuum filtration and washed with Et₂O (250 mL). The filtrate was concentrated in vacuo to give diol 5.30 (1.82 g, 84%) as a white solid that was of sufficient purity to carry through to the next step.

Rᵣ = 0.10 (petroleum ether/EtOAc, 2:1)

Mp: 82-85 °C

IR (neat): 3318, 2914, 1582, 1453, 1367, 1331, 1103, 977 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 7.48 – 7.42 (m, 4H), 7.40 – 7.32 (m, 11H), 5.12 (s, 2H), 5.10 (s, 2H), 5.05 (s, 2H), 4.70 (s, 2H), 4.70 (s, 2H), 2.72 (br s, 1H), 2.34 (s, 3H), 1.69 (br s, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 151.2, 148.7, 145.3, 137.37, 137.34, 137.1, 135.1, 130.0, 128.9, 128.60, 128.48, 128.46, 128.45, 128.43, 128.35, 128.11, 128.04, 76.3, 75.7, 75.3, 59.4, 57.2, 12.0.

1,2-bis(chloromethyl)-3,4,5-trimethoxy-6-methylbenzene 5.38

To a solution of diol 5.23 (100 mg, 0.41 mmol) in THF (10 mL) was added n-BuLi (2.5 M in hexanes, 0.34 mL, 0.86 mmol) at −78 °C and the reaction mixture was stirred for 30 minutes. The reaction was gradually warmed to 0 °C and TsCl (94 mg, 0.49 mmol) was added and the reaction gradually warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with sat. NH₄Cl (10 mL) and then diluted with EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2x10 mL), washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 8:1) to give dichlorinated compound 5.38 (51 mg, 55%) as a colourless oil that solidified in the freezer.

R_f = 0.50 (petroleum ether/EtOAc, 10:1)

Mp: 38-40 °C

IR (neat): 2942, 1579, 1460, 1409, 1336, 1249, 1100, 1062, 971 cm⁻¹

^1H NMR (500 MHz, CDCl₃) δ 4.80 (s, 2H), 4.74 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 2.30 (s, 3H).

^13C NMR (125 MHz, CDCl₃) δ 152.9, 150.7, 146.8, 130.8, 128.1, 126.3, 126.3, 61.7, 60.71, 60.68, 40.0, 37.4, 11.4.
To a solution of diol 5.23 (1.00 g, 4.13 mmol) in THF (60 mL) was added SOCl₂ (0.36 mL, 4.96 mmol) at 0 °C. The reaction was gradually warmed to room temperature and stirred for 1 hour. In order to drive the reaction to completion SOCl₂ (0.36 mL, 4.96 mmol) was added at room temperature and then stirred for 1 hour. The reaction mixture was concentrated in vacuo and then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 10:1) to give dichlorinated compound 5.38 (1.09 g, 95%) as a colourless oil that solidified in the freezer.
5.9 References

(9) King, F. E.; King, T. J. J. Chem. Soc. 1942, 0, 726.
5.10 Appendix Four

5.10.1 NMR Spectra

5.22
\[ ^1H \text{ NMR} \]
\[ \text{CDCl}_3 \]
\[ 500 \text{ MHz} \]

5.22
\[ ^13C \text{ NMR} \]
\[ \text{CDCl}_3 \]
\[ 125 \text{ MHz} \]
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5.23
$^1$H NMR
CDCl$_3$
500 MHz

5.23
$^{13}$C NMR
CDCl$_3$
125 MHz
5.26
$^{1}H$ NMR
CDCl$_3$
500 MHz

5.26
$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 5

5.24

$^1$H NMR
CDCl$_3$
500 MHz

5.24

$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 5

5.25
$^1$H NMR
CDCl$_3$
500 MHz

5.25
$^{13}$C NMR
CDCl$_3$
125 MHz
Chapter 5

5.4
$^1$H NMR
DMSO-$d_6$
500 MHz

5.4
$^{13}$C NMR
DMSO-$d_6$
125 MHz
5.29

$^1$H NMR
DMSO-$d_6$
500 MHz

5.29

$^{13}$C NMR
DMSO-$d_6$
125 MHz
Chapter 5

5.31
$^1$H NMR
DMSO-$d_6$
500 MHz

5.31
$^{13}$C NMR
DMSO-$d_6$
125 MHz
5.32

$^1$H NMR

CDCl$_3$

500 MHz

5.32

$^{13}$C NMR

CDCl$_3$

125 MHz
Chapter 5

5.30
\(^1 \text{H NMR}\)
\(\text{CDCl}_3\)
500 MHz

5.30
\(^{13} \text{C NMR}\)
\(\text{CDCl}_3\)
125 MHz
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5.38

$^1$H NMR
CDCl$_3$
500 MHz

5.38

$^{13}$C NMR
CDCl$_3$
125 MHz