Novel methodology towards the total synthesis of Pseudopterogorgia metabolites

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Novel methodology towards the total synthesis of Pseudopterogorgia metabolites

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Department of Chemistry
Loughborough University
2013

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LE11 3TU
Dedicated to Angela O’Hora
Abstract

In 1982, routine screening of the *Pseudopterogorgia elizabethae* stirred the scientific community by showing the presence of cytotoxic metabolites with antimicrobial activity. Since this discovery a vast amount of research has been conducted in synthesising metabolites of the soft coral. Herein we report the developments towards the synthesis of two metabolites (+)-Erogorgiaene and (+)-Elisabethadione utilising three key reactions in setting up the molecules three chiral centres.

![Chemical structures of (+)-Erogorgiaene and (+)-Elisabethadione](image)

The use of asymmetric allylation, oxy-Cope rearrangement and cationic cyclisation was utilised to set up the desired stereocentres from a starting cinnamyl aldehyde. Natural elisabethadione was synthesised in a racemic form as a 2:1 mixture of diastereoisomers at the C-13 stereocentre.

![Chemical reaction](image)

Keywords

Pseudopterosin, ergorgiaene, elisabethadione, colombiasin A, asymmetric allylation, oxy-Cope, cationic cyclisation and natural product synthesis.
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I would like to acknowledge firstly my supervisor professor Andrei Malkov for the opportunity of studying towards my doctorate in philosophy and working in this extraordinary and (albeit frustrating at times) rewarding field of natural product synthesis. I am grateful for all the help and support over the past years both in and outside of the laboratories.

I would also like to thank Loughborough University and the Department of Chemistry not only for the funding for the project but also for many development opportunities and for the support in my time here as a student. To all the members of staff who have helped and guided me through my studies, I am grateful for your patience as I have turned up at your office doors with yet another problem, sample or query to answer and for the time in helping me.

To those that thought you were missed I would like to offer my appreciation to all researchers past and present that have helped make my time so enjoyable and memorable both in and outside of the department.

Finally I would like to thank all of my family for their support, motivation and inspiration throughout my studies and to my fiancée, your dedication and encouragement has been invaluable in helping me complete my time at Loughborough.
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Abbreviations

Å          Angstrom
Ac         Acetate
ACA        Asymmetric conjugate addition
AOC        Anionic oxy-Cope
AIBN       2,2’-Azobis(2-methylpropionitrile)
Aq         Aqueous
BARF       Tetrakis[3,5-bis(trifluoromethyl)phenyl]boron
BINAP      (2,2’-bis(diphenylphosphino)-1,1’-binaphthyl)
Bn         Benzyl
BPin       Boron pinacol ester
BZA        Benzoic Acid
t-Bu       Tertiary butyl
°C         Degrees centigrade
Cat        Catalytic
CAN        Cerium ammonium nitrate
Cb         Dimethylcarbamoyl
CFE        Cell free extracts
Cy         Cyclohexyl
d          Doublet (NMR spectroscopy)
DA         Diels Alder
DBU        1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC        Dicyclohexylcarbodiimide
DCE        Dichloroethane
DIBAL      Diisobutylaluminium hydride
DME        Dimethoxyethane
DMF  
$N,N$-Dimethylformamide

DMSO  
Dimethylsulfoxide

Dosp  
$(N$-dodecylbenzenesulfonyl)prolinate

DPPF  
$1,1'$-Bis(diphenylphosphino)ferrocene

dr  
Diastereomeric ratio

ee  
Enantiomeric excess

Eq/Equiv  
Equivalents

FT-IR  
Fourier Transform Infrared Spectroscopy

GC  
Gas chromatography

GGPP  
Geranylgeranyl diphosphate

h  
Hours

HMDS  
Hexamethyldisilazane

HMPA  
Hexamethylphosphoramide

HPLC  
High performance liquid chromatography

HRMS  
High resolution mass spectrometry

Hz  
Hertz

ipc  
Diisopinocampheylborane

$iPr$  
i-propyl

IR  
Infrared

LA  
Lewis acid

LAH  
Lithium aluminium hydride

LB  
Lewis base

LDA  
Lithium diisopropyl amine

M  
Molarity

m  
Multiplet (NMR spectroscopy)

MCPBA  
meta-Chloroperoxybenzoic acid
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms/mesyl</td>
<td>Methanesulfonate</td>
</tr>
<tr>
<td>min(s)</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>MS</td>
<td>Molecular sieves</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser effect (NMR spectroscopy)</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PLA2</td>
<td>Phospholipase A2</td>
</tr>
<tr>
<td>PMA</td>
<td>Polymolybdic acid</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>Ps</td>
<td>Pseudopterosin</td>
</tr>
<tr>
<td>q</td>
<td>Quartet (NMR spectroscopy)</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure activity relationship</td>
</tr>
<tr>
<td>t</td>
<td>Triplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBAF</td>
<td><em>Tetra-n-butylammonium fluoride</em></td>
</tr>
<tr>
<td>TBDMS</td>
<td><em>tert</em>-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TOCSY</td>
<td>Total Correlation Spectroscopy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Ts/Tosyl</td>
<td>4-Tolunesulfonate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin-resistant <em>Enterococcus faecium</em></td>
</tr>
<tr>
<td>18-c-6</td>
<td>18-crown-6</td>
</tr>
</tbody>
</table>
Preface

In the quest for new and novel drugs to combat the increasingly virulent strains of pathogens becoming ever resistant to known drugs and remedies, the scientific world is looking outside of the laboratory to the vast and yet to be discovered world of nature. It is here that scientists are using nature’s centuries of evolution to find novel metabolites and compounds that give potent activity without the normal cytotoxicity associated with drugs today.

An interesting area of research has been in the synthesis and evaluation of a family of diterpene marine natural products known as Pseudopterosins. Pseudopterosins are trace marine natural products from the sea whip known as Pseudopterogorgia elisabethae. This class of natural product has shown notable antimicrobial activity against Mycobacterium Tuberculosis with a commensurate lack of cytotoxicity. M. Tuberculosis is the causative agent of tuberculosis (TB), a disease which remains a serious threat to the global human population, causing nearly 2 million deaths and over 9 million new infections every year.\(^1\)

Existing antibiotic treatments can cure the majority of TB patients; however, several challenges still remain for the treatment of TB. The key drawbacks of current therapies are the lengthy duration (6-9 months) required to ensure complete eradication of the disease coupled with the associated toxicity of treatment. These factors result in poor patient compliance which contributes to the spread of the disease and increasing drug resistance. Increasing occurrences of strains resistant to multiple drugs is on the rise with approximately 5% of all TB cases being drug resistant or non-replicating persistent subpopulations of M. Tuberculosis.\(^2\)

Indeed with the growth in drug resistant forms of pathogens not only from M. Tuberculosis, new classes of molecules active against drug resilient strains are required and hence the vast amount of research that has been conducted in the area of marine natural products such as the pseudopterosins. Natural products have represented an obvious starting point on this path to drug candidates owing historically to the wealth of antibiotic lead compounds, which have been developed into successful drugs.\(^3\)
1.0 Introduction

(+)-Erogorgiaene 1, (-)-colombiasin A 2 and (+)-elisabethadione 3 (Figure 1.1) are members of the marine diterpenes isolated from the West Indian sea whip Pseudopterogorgia elizabethae. These marine soft corals are found in warm nutrient rich reefs and shallows of the Bahamas, Florida Keys and West Indian region. P. Elisabethae first came to light in 1982 when routine screening showed the presence of cytotoxic metabolites with antimicrobial activity.\(^4\),\(^5\) Since then a whole host of gorgonian sort corals have been sampled and extracted. The isolation of a wide family of metabolites has been achieved and they are collectively known as Pseudopterosins. Pseudopterosins are a family of diterpene pentosides which all share a hexahydro-1H-phenalene core skeleton with more than 26 variants of the core structure (Figure 1.2).

![Diagram of molecular structures 1, 2, and 3]

**Figure: 1.1**

Due to the common biosynthetic ancestry of these natural products they all contain three distinctive stereocenters (Figure 1.2), with a proposed biosynthetic pathway from geranylgeranyl diphosphate (GGPP) \textit{vide intra} accounted for by the Kerr research group.\(^6\),\(^7\) Pseudopterosins represent an important structural class of non-steroidal anti-inflammatory, anti-tubercular, anticancer and analgesic metabolites and exhibit superior analgesic activity compared to industry standards such as Indomethacin. When applied to the skin of mice, Pseudopterosin A is significantly more potent than indomethacin in blocking phorbol myristate acetate (PMA) induced topical inflammation. (+)-Erogorgiaene has also shown promising activity against \textit{Mycobacterium tuberculosis} H\(_{37}\)Rv, the aetiological agent that causes tuberculosis.\(^8\)
In an overview of the inflammatory cascade (Figure 1.3), phospholipase A₂ (PLA₂) is an enzyme that specifically catalyses the hydrolysis of the ester at the Sn-2 position of a phospholipid to produce a free fatty acid. The release of arachidonic acid from the Sn-2 position of membrane phospholipids produces the substrate for the biosynthesis of eicosanoids. Inflammation is the result of the release of leukotrienes and histamine in the synthesis of eicosanoid, this causes the permeability of local venules and capillaries to be increased and as a result, fluid is leaked into the interstitial spaces causing edema. A variety of chemicals that modulate inflammation including eicosanoids, are released and migrate to the site of irritation. It is the inhibition of eicosanoid release by pseudopterosins that is thought to give these natural products their anti-inflammatory properties.⁹

**Figure: 1.2**

1. ergoglaene  pseudopteroxazole R=H  
   homopseudopteroxazole  R=pantol
   seco-pseudopteroxazole  lilebethin  
   pseudopterosin A-D  
   A - R₋₁=Ac, R₋₂=R₋₃=H  
   B - R₋₂=Ac, R₋₁=R₋₃=H  
   C - R₋₁=R₋₂=R₋₃=H  
   D - R₋₁=R₋₂=R₋₃=H

2. colombasin A  
   R=H, colombasin A  
   R=OH, colombasin B  
   elisapteosin B  
   elisabethin A  
   elisabethin B
Pseudopterosin A has been found to significantly inhibit phorbol myristate acetate induced topical inflammation in mice, with the methyl ether of pseudopterosin A showing promise as a treatment for contact dermatitis. In addition this class of natural products have a commercial market as ingredients in skin care products. Marine invertebrates such as corals and sponges have proven to be a prolific source of novel therapeutic agents often with biomedical action superior to that of existing pharmaceuticals. However, with the increased interest in pharmaceuticals and biotechnologies there is an increasing environmental and ethical problem associated with harvesting such organisms. A recent example is the isolation and extraction of sea algae *Bugula neritina*, which required 14 tonnes to produce just 18 grams for initial clinical studies.\(^\text{10}\) Even though Gorgonians known as sea whips, sea fans or sea plumes are prominent members of tropical and sub-tropical habitats, with over 195 documented species representing an estimated 38% of the known fauna, the gorgonian *Pseudopterogorgia elisabethae* is still only found in a few areas of the world and pseudopterosins A-Z are in most cases present in only 2-5% of the crude extract. As such, a need still continues to exist for synthetic methods in the preparation of erogorgiaene and other erogorgiaene congeners for clinical and structure activity relationship (SAR) studies.

Current nonsteroidal anti-inflammatory drugs inhibit cyclooxygenases and thus the biosynthesis of prostaglandins. While being efficient for short term pain relief and sporadic treatment of inflammation, their therapeutic use for long term inflammatory diseases such as rheumatism is problematic due to gastrointestinal side effects as well as adverse effects on blood formation and the function of the liver and kidney.
The pharmacologically most studied congeners, pseudopterosins A and E (PsA and PsE Figure: 1.4) have shown to be an attractive alternative in trials as they show potent analgesic and anti-inflammatory activities when applied topically or systemically, but only minor (PsA) to no (PsE, up to >300 mg/kg) toxicity in acute assays.\textsuperscript{12} This is important since positive results in anti-inflammatory assays often go along with undesired cytotoxicity.

\textbf{Figure:} 1.4

In vitro experiments conducted to understand the pharmacological mode of action have shown the natural products inhibit eicosanoid production. Inhibition of the eicosanoid biosynthesis by pseudopterosins is believed to happen by the inhibition of both PLA\textsubscript{2} and 5-lipoxygenase. A recent study has shown that o-quinone 4 (Figure 1.5) demonstrated to be a potent inhibitor of polymorph nuclear leukocyte (PMN)PLA\textsubscript{2} and bee venom.

\textbf{Figure:} 1.5
Recent research into the biosynthetic pathway of pseudopterosins made up of terpenes has been conducted by the Kerr research group.⁷ They have shown a possible mechanism for the formation of key intermediates in the biosynthesis of pseudopterosins. Compound 6 could be prepared from geranylgeranyl diphosphate (GGPP) ⁵ as shown in Schemes 1.1 and 1.2.

Scheme: 1.1

Scheme: 1.2
It is postulated that the mechanism of cyclisation can occur through 2 routes. In the first (Scheme 1.1), allylic cation derived from initial loss of the pyrophosphate group from GGPP 5 initiates a ring closure; GGPP undergoes an E-Z isomerisation followed by a ring closure to generate a six membered ring. Hydride shifts of α and β protons at C-12 and C-6, respectively, introduce the stereochemistry at C-13 and C-12 and subsequently form an allylic carbocation, which facilitates the second ring closure. Finally by proton abstraction at C-1 and rearrangement, bicyclic triene elisabethatriene 6 is formed. An alternative mechanism is shown in Scheme 1.2, in which intermediate 7 leads to a ten-membered ring being formed first. Hydride migration then leads to the bicyclic ring system, which undergoes proton abstraction and rearrangement to afford 6.

The significance of intermediate 6 comes from extensive isolation and extractions of the crude natural product, which has been doped with radiolabeled $^3$H-GGPP and $^{14}$C-xylose by adsorbing the radiolabeled compounds onto food particles for the ingestion via the filter feeding gorgonian. This allowed the determination of intermediates in the biosynthetic pathway and allows the attempt of a biosynthesis in the laboratory from the commercially available GGPP. The next transformation of elisabethatriene 6 to erogorgiaene was via a dehydrogenation and aromatization process (Scheme 1.3). Incubation with cell free extracts (CFEs) of P. Elisabethae produced the radiolabeled pseudopterosins and where characterised via HPLC and NMR spectroscopy. Intermediates 8a and 8b were confirmed by incubating isolated radioactive samples 8a and 8b with CFEs and monitoring for the production of the $^3$H-labled pseudopterosin 9a and 9b. The ring closure/ hydrolysis revealed that the origin of the α- and β-isobutenyl groups is due to the selective ring closure of the cis- and trans-amphilectosins.
In a summary of the findings, the pseudopterosins are postulated to be produced by a cyclisation of GGPP to elisabethatriene followed by aromatization to erogorgiaene 1. Two successive oxidations to 7,8-dihydroxyerogorgiene and glycosylation afford seco-pseudopterosin as a key intermediate. Dehydrogenation then leads to amphilectosins which undergoes ring closure to yield the pseudopterosins F and Y.
Due to the biological activity and commercial potential, researchers have been interested in total synthetic strategies in developing *P. Elisabethae*. In the production of (+)-erogorgiaene most synthetic routes start with ring A followed by the construction of B (Scheme 1.4).\textsuperscript{14-18} In the synthesis of pseudopterosins A - D (Scheme 1.5)\textsuperscript{19-37} the adoption of the chiral pool route, starting with ring system B in the form of a monoterpenue (+)-menthol, (-)-limonene or (-)-isopulegol, with subsequent forming of ring A and final construction of ring C has yielded the natural product.

In the synthesis of (-)-colombiasin A, routes start with mixtures of ring A and ring B followed by stereoselective Diels-Alder cycloaddition to complete the tetracyclic skeleton (Scheme 1.6).\textsuperscript{38-45} An interesting feature of colombiasin A is its tetracyclic carbon framework which is decorated with four methyl groups, two carbonyl functions, two double bonds and a hydroxyl group, which are in conjunction with six stereogenic centres, of which two are adjacent to quaternary carbon atoms. Colombiasin A and its sister compound elisapterosin B (Figure 1.2) are only recent additions to the diterpene family. Colombiasin A was discovered by Rodríguez\textsuperscript{46} in 2000 and first synthesised by Nicolaou in 2001.\textsuperscript{42} It was noted that its sister compound, (-)-elisapterosin B, has shown strong antiplasmodial activity against *plasmodium falciparum*, a parasite responsible for the most severe forms of malaria.

Recently a new metabolite (+)-elisabethadione has been synthesised by Davies\textsuperscript{47} and they to date remain the only group to have made this compound.

\textbf{Scheme: 1.4}
Scheme: 1.5
In a review of literature on the total synthesis of (+)-erogorgiaene, (-)-colombiasin A and the closely related pseudopterosins A and E it is apparent a variety of methods are employed in the development of the stereocentres. A major challenge associated with the synthesis of this class of natural product is the control of the three stereocentres. It is further complicated with the lack of functional groups near the stereogenic carbons. Applications in controlling the stereocentres can be divided into two distinct paths; those that use the chiral pool approach, utilising stereocentres already present in a molecule and building onto the skeleton and those that create stereogenic centres through a chiral auxiliary and asymmetric synthesis. Although not extensive, the review outlines the most common synthetic routes to the pseudopterosins in each category and highlights key intermediates used by research groups in their formal or total synthesis.
1.1 Synthetic methods towards (+)-erogorgiaene

At first glance, (+)-erogorgiaene would appear to be the simplest in the family of pseudopterosins to synthesise, yet research teams lead by Davies, Hoveyda, Harmata and Yadav have found this molecule to be challenging due to its lack of functional groups and ultimately the directing abilities of such groups. Erogorgiaene was first synthesised by Hoveyda in 2004, was shown to inhibit 96% of *Mycobacterium tuberculosis* H₃₇Rv growth at 12.5μg/mL which has made it an interesting lead in the synthesis of new anti-tubercular agents. The overview below will be split into two parts. The first will be on synthesis developed through the chiral auxiliary (stoichiometric) methods and the second on catalytic asymmetric synthesis.
Asymmetric syntheses with stoichiometric chiral auxiliaries

In this example of asymmetric synthesis, Yadav\textsuperscript{17} employed Evans’ stoichiometric diastereoselective alkylation protocol to introduce the stereogenic centre at the benzylic position. The Crimmins’ protocol\textsuperscript{48} for the aldol coupling and intramolecular Friedel-Crafts reaction of oxetane finishes the other stereocentres (Scheme 1.7).

Scheme: 1.7

The synthesis begins with the coupling of the Evans chiral auxiliary to the readily available acid 10 producing 11. Alkylation of 11 with Mel affords 12 with a 99% diastereoselectivity. Removal of the auxiliary through reduction and three more steps produce the aldehyde 13 which undergoes aldol coupling under Crimmins protocol giving 14 in a 93% yield and 49:1 dr.

The intramolecular Friedel-Crafts reaction of oxetane 15 was carried out following the reaction employed for epoxides resulting in one diastereomer 16. (+)-Erogorgiaene 1 was then obtained in a 8.2% overall yield within 3 more steps.
Harmata’s key reaction utilises the synthesis of benzothiazine 17 which produces the required stereocenter C-13 through intramolecular cyclisation (Scheme 1.8).

Scheme: 1.8

The synthesis begins by the Horner-Wadsworth-Emmons reaction of commercially available o-bromotolualdehyde. Coupling with (S)-S-methyl-S-phenylsulfoximine using the Buchwald-Hartwig reaction gave the sulfoximine 17 in an 89% yield. Aniline 18 was then obtained in three steps by reduction, protection and reductive desulfurization giving 18 with complete diastereoselectivity in an 85% yield.

The elaboration of aniline 18 into erogorgiaene starts with the construction of the trans-substituted ring system. This began by producing iodide 19, which upon radical cyclisation produces two compounds 20a and 20b in a 1:7.4 ratio of stereoisomers. The mixture is confirmed as a kinetic product and favours the undesired product. At this point the alkylation and reduction of esters 20 gives an inseparable mixture of diastereoisomers with the favoured unwanted isomer. From this step it is 12 steps via a route developed by Hoveyda to erogorgiaene.
In a recent publication by Aggarwal, (+)-erogorgiaene was synthesised in 8 steps by a lithiation/borylation/proto-deboronation methodology.  

**Scheme: 1.9**

The synthesis starts with the Noyori reduction of $p$-methylacetophenone followed by carbamoylation with $\text{CbCl}$ to furnish the carbamate 21 in a 93% yield and 99:1 er. Treatment with $s$-BuLi and addition of boronic ester yielded 22, which on treatment of TBAF gave ester 23 with retention of stereochemistry. In order to gain the desired carbamate, ester 23 was treated with PPA followed by the reduction to trans alcohol with a $(S,S)$-Noyori catalyst in a high yield and excellent diastereoselectivity (>99:1 er, 98:2 dr). This was followed by carbamoylation to 26.

**Scheme: 1.10**
The synthesis of the (S)-borane 28 followed Scheme 1.10 whereby the stereogenic centre was provided by the lithiation of N,N-diisopropyl ethylcarbamate in the presence of O’Brien’s (+)-sparteine surrogate followed by the addition of the boron substrate. The final reaction in establishing erogorgiaene was completed in a single reaction by addition of the borane 28 to the lithiated carbamate gaining the natural product in a 73% yield and a 13:1 dr.
Catalytic asymmetric syntheses

This section starts with Hoveyda’s\(^\text{15}\) approach using chiral phosphine ligands derived from amino acids that they developed to accomplish a 1,4 addition with excellent stereocontrol. The ligands are able to effect Cu-catalyzed asymmetric conjugate additions (ACA) of alkylzinc reagents to acyclic enones in high enantioselectivity (Scheme 1.11).

Scheme: 1.11

The synthesis starts with the treatment of enone 29 with 3 equivalents of Me\(_2\)Zn in the presence of 2.4 mol\% chiral phosphine 34 and 1.0 mol\% (CuOTf\(_2\))\(_2\)C\(_6\)H\(_6\) to produce β-methyl ketone 30 in 94% yield and >98% ee. Later in the sequence, the same reaction was used again. Diastereoselective conjugate addition of Me\(_2\)Zn to enone 31 this time was carried out in the presence of 12 mol\% chiral phosphine 35 and 5 mol\% (CuOTf\(_2\))\(_2\)C\(_6\)H\(_6\) and Me\(_2\)Zn. The reaction shows that in the Cu-catalyzed ACA to acyclic enones, the stereocchemical outcome may not be affected by stereogenic centres present in the substrate but is largely dictated by the chiral ligand; 32 was obtained in 50% yield and 97:3 diastereoselectivity ratio. Reduction of 32 to the alcohol followed by reduction of the double bond using Li/liquid NH\(_3\) at -78°C and reinstalling of the ketone through Dess–Martin oxidation to give 33 in an 85:15 diastereoselectivity. The synthesis of (+)-erogorgiaene was completed in 5 more steps from 33 yielding the enantiomerically pure product.
Davies\textsuperscript{14} envisaged that (+)-erogorgiaene could be accessed from two precursors dihydronaphthalene (S)-36 and vinyldiazoacetate 37. The key enantioselective step would be a combined alkylation via C-H activation/Cope rearrangement catalyzed by dirhodium tetraprolinate $[\text{Rh}_2(\text{dosp})_4]$ (dosp=(N-dodecylbenzenesulfonyl)prolinate). It was noted that only (S)-36 would perform the required C-H activation/Cope rearrangement to form 38 whereas (R)-36 would undergo cyclopropanation forming 40, thus a racemic mixture of 36 could be used (Scheme 1.12).

The reaction catalyzed by $[\text{Rh}_2(\text{R-dosp})_4]$ performed excellently resulting in an 48:48:4 mixture of the combined C-H alkylation rearrangement product 38 (90% ee) and the cyclopropane 40 and only a small trace of the opposite cyclopropane diastereomer, with a combined yield of 76%. The ester 38 was reduced to alcohol 39 which was isolated through chromatography in a 31\% overall yield. Oxidation of 39 to the aldehyde with PCC followed by Wittig chain extension completes the total synthesis of (+)-erogorgiaene.

\begin{center}
\textbf{Scheme: 1.12}
\end{center}
1.2 Synthetic methods towards Pseudopterosins

In contrast to the synthesis of (+)-erogorgiaene, the synthesis of pseudopterosins includes methods utilising the chiral pool. Notably, the research group of Corey\textsuperscript{21} employed several strategies using various monoterpenes, the earliest syntheses of this group of natural products dating back to 1989. All of these natural products have shown anti-inflammatory activity. The following section shows work by Corey\textsuperscript{21}, Kocienski\textsuperscript{15} and Rajanbabu\textsuperscript{34} in developing the synthetic approaches towards the tricyclic framework of pseudopterosins A-J and is divided into the strategies based on chiral pool, chiral reagents and catalytic methods.
**Chiral pool methods**

The use of chiral pool reagents by Corey\(^3\) is illustrated by his synthesis using inexpensive (S)-(−)-limonene and its widely known hydroboration product 41 (Scheme 1.13).

![Scheme 1.13](image)

Diol 41 was obtained from (S)-(−)-limonene as an inseparable 1:1 mixture of diastereomers. By exposing 41 to sodium hypochlorite in aqueous acetic acid, product 42 is formed in excellent yield. Treatment of this mixture with isopropenyl acetate in isopropyl ether using Amano PS lipase as the catalyst resulted in selective acetylation of the (13S)-hydroxy ketone producing the desired (13R)-alcohol 43 with the ratio of 13R/13S = 99:1, which can be easily separated using flash chromatography. Construction of the aromatic ring was completed in 6 steps to produce 44 with three of the four stereogenic centres already set up. The highly diastereoselective cationic cyclization of 44 to 45 (25:1) took place using CH\(_3\)SO\(_3\)H in high yields. The synthesis is completed in two more steps through debenzylation to form pseudopterosin aglycone a key intermediate in the production of pseudopterosins A and E.
Corey’s\textsuperscript{30} revised total synthesis of pseudopteroxazole takes 16 steps, producing two stereoisomers, neither of which corresponds to the natural product pseudopteroxazole (Scheme 1.14) due to the inability to control the C-9 methyl.

Scheme: 1.14

The synthesis starts with the coupling of (R)-carboxylic acid 46 and amino phenol 47 using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole producing 48 cleanly in 84\% yield. The formation of the next two stereocentres utilises lead tetraacetate, generating the quinone mono imide, which subsequently undergoes intramolecular Diels-Alder (DA) addition forming the endo product 49 in 69\% yield and an endo:exo ratio of 8:1. This cleverly designed DA reaction completes the introduction of three of the four stereocentres to the molecule. With a further 9 steps compound 50 is isolated, which as previously discussed undergoes cationic cyclisation to form a 1:2 ratio of diastereomers 51a + 51b. It is from this point the two isomers are separated and in 4 more steps taken through to the analogues of natural pseudopteroxazole. Further synthetic efforts have utilised the chiral pool approach in gaining the natural product pseudopteroxazole.
Buszek’s synthesis of pseudopterosin A and E aglycon was achieved through an intramolecular benzyne DA cycloaddition with a substituted cyclohexadiene (Scheme 1.15).

Scheme: 1.15

The synthesis begins with compound 52 produced from commercially available (R)-(-)-2-phenylpropionic acid. Coupling of 52 and 53 produced compound 54 which was subjected to LDA to produce the benzyne which undergoes the DA to produce 55a and 55b in a 58:42 mixture of diastereoisomers which could be separated by chromatography. Oxidative cleavage of the ethylene bridge gave diol 56 which after selective protection of the less hindered alcohol was oxidised to the aldehyde. Decarbonylation with Wilkinson’s regent gave 57 as a single diastereomer. Simple functional group interconversion takes the tosylate group to a methyl group by nucleophilic hydride displacement with excess LAH, this then completes a formal synthesis of the aglycon by the method already developed by Corey.
Synthetic approaches based on the use of chiral reagents

In 1998 Kocienski\textsuperscript{23} developed a route to pseudopterosin G (a stereochemically related metabolite) using the reaction of a dimethoxy arene with allylic cation equivalents, starting from 2,3-dimethoxy-4-methyl-1-iodobenzene 59 (Scheme 1.16).

\begin{center}
\textbf{Scheme: 1.16}
\end{center}

The first stereo centre was achieved in a 60\% yield with an enantiomeric ratio of greater than 95:5 by regio- and enantiofacially-selective addition of zinc-cuprate reagent 60 to the homochiral iron complex yielding compound 61. The construction of the second ring and consequently the second stereo centre employed an intramolecular Nicholas reaction involving electrophilic aromatic substitution, using a cobalt stabilised propargylic cation equivalent as an electrophile. The second stereocentre was formed in high diastereomeric ratio of 95:5 and in 65\% yield. The final stereocentre was installed by simple alkylation of ester 62 using LDA and iodomethane, producing 63 in 85\% yield and a diastereomeric ratio of 10:1. Pseudopterosin G is then synthesised in 4 more steps.
Catalytic asymmetric approaches

The use of ethylene in the synthesis of pseudopterosin has been reported by Rajanbabu and co-workers. The group utilises the C-C bond forming asymmetric hydrovinylation reaction, in which ethylene is added to a vinyl group (Scheme 1.17).

Scheme: 1.17

In the three key steps from starting material 2,3-dimethoxy-4-methylstyrene, an excellent yield and stereoselectivity was observed. Ni catalyzed asymmetric hydrovinylation of styrene 64 using ligand L1 gave 65 in 99% yield and er 98:2 setting up the C-9 stereocenter with the correct configuration. Simple steps afforded the 1,3-diene 66. Hydrovinylation of the 1,3-diene sets up the second stereocentre at C-13 in a 92% yield and a dr 92:8. Interestingly using chiral ligand L2 can give you the opposite stereocenter at the C-3 position. Alcohol 67 was produced in a series of high yielding reactions followed by a Li/liquid NH₃ reduction, this yields the correct stereocentre at C-12 with a dr >20:1. The final reaction sets up the third stereocentre in 99% yield and dr > 99:1. From this, pseudopterosin aglycon was synthesised by cross-metathesis.
1.3 Synthetic methods towards Colombiasin A

The final in the series of pseudopterosins to be discussed is that of colombiasin A. This complex natural product has a tetracyclic framework and six stereocentres. Like other members of this family of pseudopterosins it was shown to exhibit potent activity towards *Mycobacterium tuberculosis*. The first total synthesis was reported by Nicolaou\textsuperscript{42} in 2001 and makes use of the Diels-Alder reaction in the final cyclisation step to construct rings C and D. Since first publication, the Diels-Alder reaction has become a common key step in synthesising colombiasin A.
Racemic approach

Scheme: 1.18

Nicolaou’s\textsuperscript{42} construction of colombiasin A starts with a DA reaction of \textbf{68} and \textbf{69} which yields the desired endo cycloadduct as a sole product. The product is then converted to the aromatic derivative \textbf{70} through exposure to K\textsubscript{2}CO\textsubscript{3} and MeI followed by deprotection of the TBS group completing the AB ring system. Formation of enol ester \textbf{71} followed by palladium(0) catalysed intramolecular allylic substitution produced the required C-C bond in \textbf{72}. Unfortunately there was a mixture of the \(\alpha\)-allylated ketone \textbf{72a} + \textbf{72b} in an 1:4 ratio (Scheme 1.18).

Scheme: 1.19
A series of transformations from 72a affords aldehyde 73 which still contains the incorrect C-13 stereocentre. The reaction to invert the C-13 stereocenter was accomplished by treatment of 73 with NaOMe in MeOH/THF, this resulted in an equilibrium of epimerized aldehyde and starting material in a 2:1 ratio. The desired epimer was separated from the starting material and taken through another series of reactions to form diene 74. A challenging oxidation of the aromatic moiety of diene 74 was achieved through formation of a sulfone followed by oxidation of the sulfone with AgO/HNO₃. Previous attempts to perform the oxidation had failed in what is believed to be the diene further reacting. By protecting the diene as a cyclic sulfone 75 the oxidation preceded smoothly affording a chromatographically separable dione 76 (1:3.1 mixture of C-16 epimers) (Scheme 1.19).

Scheme: 1.20

Heating of 76 in toluene to 180 °C led to the single endo cycloadduct through a cheletropic extrusion of SO₂ followed by [4+2] cycloaddition. Deprotection of the methoxy group gives the natural product 2 as a racemic mixture (Scheme 1.20).
Asymmetric approaches based on chiral pool

In Harrowven’s\textsuperscript{43} pathway to colombiasin A, a Moore rearrangement and intramolecular [4+2] and [5+2] cycloadditions aid setting up the stereocentres found in the molecule. The synthesis utilises the chiral pool of (−)-dihydrocarvone as a starting building block (Scheme 1.21).

\begin{align*}
\text{Colombiasin A} & \rightarrow \text{81} \\
77 & \xrightarrow{\text{H}_{2}O_{2}, \text{NaN}} \xrightarrow{\text{2:5 separable}} \xrightarrow{\text{Microwave THF, 110°C}} \text{79} \\
& \xrightarrow{\text{Air, rt}} \text{80} \\
& \xrightarrow{\text{Microwave THF, 110°C}} \text{81} \\
& \xrightarrow{\text{Air, rt}} \text{80}
\end{align*}

\textbf{Scheme: 1.21}

The synthesis starts by the hydroboration with ((−)ipc\textsubscript{2})BH of reduced (−)-dihydrocarvone 77 followed by an oxidative workup to set up the C-13 stereocenter as a 2:5 mixture of diastereomers which is separated by chromatography. Multiple steps afford 78 on which an \textit{in-situ} variant of the Shapiro reaction was performed for the addition of the squarate to 78 yielding the vinyl cyclobutene 79, although in a low yield (36%). It is from 79 by microwave irradiation the Moore rearrangement gave hydroquinone 80. After cooling to ambient temperature and stirring in air, quinone 81 was isolated. The final step was to induce the DA cycloaddition to the (−)-colombiasin A \textit{tert}-butyl ether which after deprotection gave the natural product.
Asymmetric approach based on chiral auxiliaries

As has been previously shown, the DA reaction has been utilised wildly in setting up the final core ring. In Flynn’s\textsuperscript{45} work it was proposed a tandem enantioselective Diels-Alder/elimination/intramolecular DA sequence could provide the main structural core of the natural product (Scheme 1.22). The sulfoxide group is the key component in this synthesis as it acts as a multifunctional substituent that controls the regio and facial selectivity of the DA before eliminating to produce the dienophile for the intramolecular DA reaction.

\begin{equation}
\begin{align*}
\text{Scheme: 1.22} \\
\text{The synthesis starts with bromophenol 82 which is reacted with (S,S)-mentyl-p-toluene sulfinate 83 yielding 84. Oxidation with cerium ammonium nitrate (CAN) to 85 was achieved in an excellent yield (90%). DA reaction of diene 86 and 85 gave the respective product 87 in a 51% yield which undergoes the intramolecular DA upon heating. This gives the adduct 88 in an excellent yield and enantioselectivity (91%, er 94:6).}
\end{align*}
\end{equation}
The synthesis by Rychnovsky\textsuperscript{40} explores the route to elisapterosin and colombiasin A through an intramolecular [4+2] cycloaddition (Scheme 1.23).

Scheme: 1.23

The synthesis to set up the cis-decaline serrulatin skeleton used a DA addition of 92 and 91 prepared with the aid of the Myers pseudoephedrine auxiliary. The Myers auxiliary was employed to produce the enantiomerically pure aldehyde 89. Wittig olefination of 89 gave the ester 90 which is converted to the diene 91. The DA reaction gave a 1.7:1 inseparable mixture of diastereomers 93a/93b. The major isomer was confirmed as the correct isomer and its stereoselectivity is proposed to arise from a Felkin-Ahn like approach of the dienophile to the diene. The acetate substituent on the diene also controls the regioselectivity in the cycloaddition which in turn is replaced by a methyl group by treatment with lithium dimethylcuprate and took place via a $S_N2$ displacement of the acetate group. A series of reactions formed 94 which after heating, the [4+2] intramolecular cyclisation gave colombiasin A as a 1.7:1 mixture of diastereomers which were separated by chromatography.
Catalytic asymmetric formation of stereogenic centres

The work of Jacobson\textsuperscript{39} completed the total synthesis of colombiasin A in 12 steps. The approach uses the Cr catalysed asymmetric quinone DA reaction to set up the C-9 stereocentre (Scheme 1.24).

\[
\begin{align*}
\text{CHO} + \text{OEt} & \xrightarrow{95} \text{CHO} \text{OEt} & \xrightarrow{i) \text{LiBu}, \text{THF}} & \text{CHO} \text{OEt} \\
& \xrightarrow{\text{MS 4A}} & \xrightarrow{\text{ii) ZnCl}_2, \text{THF}} & \xrightarrow{\text{iii) PtCl}_2, \text{MeCN}} \text{CH}_2\text{Cl_2} \\
& & \xrightarrow{\text{iv) KHMDMS, THF}} \xrightarrow{\text{v) TESCl}} & \text{CHO} \\
& & \xrightarrow{\text{g) BrCH}_2\text{PhH}_2} & \text{OMe} \\
& & \xrightarrow{\text{h) KHMDS, THF}} & \text{CHO} \\
& & \xrightarrow{\text{i) LiCl, MeCN}} & \text{CHO} \\
& & \xrightarrow{\text{j) PTSA, MeCN}} & \text{CHO} \\
& & \xrightarrow{\text{k) TESCl}} & \text{CHO} \\
& & \xrightarrow{\text{l) HCl, MeOH}} & \text{CHO} \\
& & \xrightarrow{\text{m) NaBH_4, MeOH}} & \text{CHO} \\
& & \xrightarrow{\text{n) PPh}_3, \text{PdCl}_2(\text{dpdf})} & \text{CHO} \\
\end{align*}
\]

Scheme: 1.24

The synthesis begins by inverse electron demand hetero DA reaction catalysed by dimeric chromium complex \textit{95} to gain the cyclo adduct \textit{96} in good yield and high enantioselectivity (93% ee) setting up the C-13 stereocentre. Lithiation, transmetalation with ZnCl\textsubscript{2} followed by Negishi coupling with 1-bromopropene afforded keto aldehyde \textit{97}. Wittig olefination and conversion of the ketone to silyl enol ether gave diene \textit{98}. The key quinone DA reaction with chromium complex \textit{95} exerted a high level of stereocontrol producing \textit{99} with a d.r. 17:1 and a regioselectivity of 10:1. Treatment of \textit{99} with HCl and methanol deprotected the silyl enol ether and after tautomerization and epimerization the desired diastereomer was attained with d.r. >10:1. This then yields a key intermediate in the synthesis of the natural product which is completed in 6 more steps.
The final synthesis to be described in this chapter is the work of Davies (Scheme 1.25).\textsuperscript{38} The key reaction step utilising a C-H activation/Cope rearrangement was already touched on in the synthesis of ergorgiaene (Section 1.1).

\textbf{Scheme: 1.25}

The Rh\textsubscript{2}(R-dosp)\textsubscript{4} catalysed reaction of 101 and 102 gave a 1:1 mixture of the C-H functionalised product and cyclopropane in a 41% yield and 92% ee. Hydrogenation and reduction to alcohol 103 proceeded in a 96% yield. Alcohol 103 is a common intermediate and from this point the synthesis can be taken onto 4 natural products. A further 5 steps closely following the synthesis by Nicolaou afforded the natural product colombiasin A.
1.4 Structure activity relationship studies

Despite the amazing ability of the sea whip to re-grow after harvesting, this natural resource would not sustain large scale pharmaceutical exploitation. Even after extensive research into the total synthesis of pseudopterosins A and E or their aglycons there has been no commercial exploitation towards pharmacological studies, possibly due to the complexity of the natural structure or the availability of raw material. The supply of promising natural product based lead compounds is also an issue when the natural source is limited. Lengthy synthetic routes have also led to delays in medicinal chemistries efforts to generate analogues for structure activity relationship (SAR) studies. In an attempt to simplify the generation of pharmacological active materials, analogues of pseudopterosins have been prepared and their biological activity studied. Interesting developments have been found when looking at the key functional areas of the pseudopterosin skeleton whereby the aromatic moiety and functional groups hold the key to the activity of the natural product. The following section describes these analogues and the active functional groups of the skeleton.

To explore the activity and SAR of the natural products and analogues, a rapid access to non-natural congeners on a several hundred milligram scale was desired for SAR testing. A recent publication by Kerr\textsuperscript{50} has shown an efficient one-pot synthesis of various analogues of pseudopteroxazole via a silver(I)-mediated catechol to benzoazole transformation. Pseudopteroxazole was chosen as it showed promising antibiotic activity against \textit{Mycobacterium tuberculosis}, the causative agent of tuberculosis, with commensurate low toxicity. The one-pot synthesis draws on the ability to synthesise 105 and its derivatives from aglycone 104 which has the same backbone as the pseudopterosin family of natural products (Scheme 1.26). Two methods have been devised and both yield the desired pseudopteroxazoles with different C-21 substituents.
**Scheme: 1.26**

Method A (Scheme 1.27) proceeds by oxidation of the catechol 104 into the ortho-quinone 106, subsequent nucleophilic attack of the ammonia onto one of the ortho-quinone carbonyls gives an imine on the less sterically hindered carbonyl. Redox cycling followed by condensation with an aldehyde yields imine 107, this then undergoes cyclisation and oxidation to the benzoxazole product.
**Scheme: 1.27**

Method B (Scheme 1.28) proceeds by heating aglycone 104 with Ag₂O and an amino acid. It is thought the reaction proceeds much the same as in method A with the attack of the nitrogen from the amino acid yielding imine 108. Decarboxylation yields the imine 109 which then undergoes cyclisation and oxidation to the benzoxazole product. In both methods A and B there is a preference for the nucleophile to attack the less hindered C-3 carbonyl, with a greater preference in method B due to the greater steric bulk surrounding the nitrogenous nucleophile.

**Scheme: 1.28**
The following products (entries 1-14) were synthesised and tested against six microorganisms. Pseudopteroxazole, isopsuedopteroxazole and several analogues (entry 7, 9 & 11 Table 1.1) exhibited activity at a similar potency to that exhibited by the drug rifampicin used clinically against *M. Smegmatis* and *M. diernhoferi*. The compounds were also tested against vancomycin-resistant *Enterococcus faecium* (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and *Candida albicans*. While no activity was shown against the latter two pathogens, entry’s 1, 3, 7, 9, & 11 showed strong activity against VRE and entries 7, 9 & 11 showed strong activity against MRSA. From these findings it shows that analogues with a more lipophilic side chain are less active to the natural product. Those with a relatively polar C-21 substituent showed a stronger activity than the natural pseudopteroxazole against MRSA.

**Table: 1.1 – Antimicrobial evaluation of semi synthetic pseudopterosin congeners**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th><em>M. smegmatis</em>, MIC µg.mL</th>
<th><em>M. diernhoferi</em>, MIC µg.mL</th>
<th>VRE, IC&lt;sub&gt;50&lt;/sub&gt; µg.mL</th>
<th>MRSA, IC&lt;sub&gt;50&lt;/sub&gt; µg.mL</th>
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<tbody>
<tr>
<td>1</td>
<td>(Ptx-H)</td>
<td>2</td>
<td>4</td>
<td>13</td>
<td>&gt;128</td>
</tr>
<tr>
<td>2</td>
<td>(Ptx(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>3</td>
<td>(Ptx-CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>8</td>
<td>4</td>
<td>2.5</td>
<td>&gt;128</td>
</tr>
<tr>
<td>4</td>
<td>(Ptx-CH(CH&lt;sub&gt;3&lt;/sub&gt;)CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>5</td>
<td>(Ptx-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;SCH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>16</td>
<td>16</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>6</td>
<td>(Ptx-CH&lt;sub&gt;3&lt;/sub&gt;Ph)</td>
<td>&gt;64</td>
<td>4</td>
<td>&gt;128</td>
<td>&gt;128</td>
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<tr>
<td>7</td>
<td>(Ptx-CH&lt;sub&gt;3&lt;/sub&gt;CONH&lt;sub&gt;2&lt;/sub&gt;)</td>
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<td>2</td>
<td>3</td>
<td>3</td>
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<td>8</td>
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<td>16</td>
<td>8</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>9</td>
<td>(Ptx-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CONH&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>(Ptx-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>11</td>
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<td>8</td>
<td>4</td>
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<td>12</td>
<td>(iso-Ptx-H)</td>
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<td>8</td>
<td>13</td>
<td>&gt;128</td>
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<td>13</td>
<td>(Ptx-(2-CH&lt;sub&gt;3&lt;/sub&gt;0-Ph))</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>14</td>
<td>(Ptx-(4-F-Ph))</td>
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<td>&gt;64</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>15</td>
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<td>4</td>
<td>8.75</td>
<td>NT</td>
</tr>
</tbody>
</table>
To further the SAR studies on the C-21 substituents, an analogue 110’ (Scheme 1.29) with an imidazole moiety was synthesised which showed to be more potent than natural products pseudopterosin and pseudopteroxazole and showed equipotent activity against both replicating and non-replicating persistent forms of *M. Tuberculosis* with a near absence of in vitro cytotoxicity.\(^5\) The synthesis took place following the previous Scheme 1.27 from aglycone 104, Ag₂O and histidine.

**Scheme: 1.29**

In a recent study by F. Flachsmann et al\(^1\) on pseudopterosins analogues, a flexible and efficient synthetic scheme was developed for the preparation of 10 simplified analogues. The molecules devised included structural modifications of the hexahydrophenalenalene core with different C(2,9) configurations as well as variations of the sugar moiety and the glycosidation. Key to the synthetic route was the ability for multigram scale up required for biological testing. The analogues were tested for their ability to reduce PMA induced mouse ear edema when administered topically in a single dose study (25 \(\mu\)g/ear in acetone solution). Compounds 111 to 117 (Figure 1.6) were tested and with the exception of compound 115, all showed statistically significant reduction of edema relative to the PMA control. Ketone 115 was found to be completely inactive and is thought to be because of an enhanced chemical reactivity related to the acidity of the HO-C(4) group or the presence of tautomeric quinone-methide structures. Comparative studies using aglycons 111-114 showed no significant differences when D-xylosides and L-fucosides are used and changes between O-C(4) and O-C(3) glycosides. A comparison of the addition of substituents at either C(2) or C(9) does not strongly alter the activity of the compounds as seen by no statistical differences in edema reduction seen in compounds 116-120. It is believed the non-glycosylated hydroxyl functional group is needed to competitively bind to the adenosine receptor A₂A in human embryonic kidney cells in order to inhibit *T. Thermophile*.\(^5\)
In conclusion to this section on non-natural analogues and SAR studies it can be found that the major activity comes from the C-3 and C-4 substituents off the natural pseudopterosin scaffold. Varying the substituents in this region can lead to retained activity against *M. Tuberculosis* H37Rv and other Gram positive pathogens such as MRSA and VRE and in some cases an improved potency. Whilst an efficient medicinal synthetic route is still out of reach, this efficient one-pot synthesis can provide a whole host of derivatives to conduct SAR studies and attempt to develop simplified and more potent drug candidates.
1.5 Conclusions

In this brief overview it is clear that the developments towards natural products have been extremely varied in approaches: from chiral pool methods exercised by Corey to highly enantioselective synthetic routes by Davies utilising catalytic methods. Many methods focus on setting up the core skeleton and cyclic ring systems before they elaborate on the construction of side chains or aromatic functionality. It is from this method that many groups have found they converge on a key intermediate and follow the best descriptions in the literature in achieving the total synthesis of any given natural product. In many cases, as has been highlighted, formation of inseparable mixtures of isomers have been observed, which have to be taken onto further steps increasing the difficulty in purifying and characterising the later products. Moreover, those who can isolate pure products do so at a high cost of labour (extensive HPLC chromatography requiring multiple runs to separate product) or kinetic resolution of racemic intermediates which, as seen in work by Davies, can result in reduced yields. However, in some cases is has been possible to resolve stereocentres by base catalysed epimerisation as seen in the synthesis of colombiasin A by Nicolaou. These can alleviate problems of mixtures of certain stereocentres. In a round off of the characterisations of these classes of natural products it has been clear the vast amount of work that has been carried out by various research groups, noticeably that of Kerr and Rychnovsky. Many metabolites of the sea whip have been isolated and characterised by intensive NMR and mass spectroscopy, the latter being used to determine the absolute configuration of the stereocentres. In the future it is hoped a suitable sample for x-ray crystallography will be prepared in order to enhance our knowledge of the pseudopterosins stereocentres. In light of the current synthetic methodologies in producing these classes of natural products, a sub-region of natural product analogues have been synthesised and SAR studies conducted to show the key components of the structure to be the C-3 and C-4 substituents. With these major breakthroughs in the synthesis of the pseudopterosin family, the fight against ever virulent forms of pathogens continues to gather strength.
2.0 - Aims and objectives

The development of a novel, short and efficient synthetic route towards diterpene natural products from the family of marine pseudopterogorgia metabolites based on key stereoselective bond forming reactions: asymmetric allylation, Cope rearrangement and cationic cyclisation (Scheme 2.1).

2.1 - Project overview

Scheme: 2.1

The synthetic strategy in the development of a novel approach towards the class of natural products known as pseudopterosins, focused on three key steps in setting up the three desired stereocentres (C-9, C-12, C-13) all contained in this class of natural products discussed. The three key reactions are an asymmetric allylation, anionic oxy-Cope rearrangement and cationic cyclisation. Once these stereocenters are set up, it is possible to access multiple pseudopterosins. As will be discussed, the synthetic route starts with asymmetric crotylation of cinnamaldehyde 124 to produce syn alcohol 123. This in turn is subjected to the anionic oxy-Cope rearrangement setting up the desired stereocentre at C-12 and the required olefin in an E configuration 122. Extension of the aldehyde followed by cationic cyclisation finishes the core skeleton 121 with correct stereochemical configurations for these complex natural products and accesses a formal synthesis, as reported by Davies.47 Within 5 steps the total synthesis of (±)-elisabethadione 3 is achieved. During the course of the synthesis development of enantioselective variant has not been complete, therefore only a racemic total synthesis has been carried out.
2.2 - Key synthetic strategies

In the synthesis of natural products elisabethadione and erogorgiaene we have explored the combination of three key reactions which work to afford the desired stereocentres. The advantage of our route over those already described in the literature is that a single stereogenic centre, introduced early in the synthesis by catalytic asymmetric allylation, efficiently controls formation of the remaining stereocentres by the subsequent Cope rearrangement and cationic cyclisation. This method uses no alternative directing bodies such as chiral auxiliaries or the need for complex resolution techniques and does not require costly protecting groups to be used during the synthesis. To further elaborate these three key reactions and their abilities to induce the desired configurations of stereocentres, a brief overview of literature will be described below.

In explaining the stereochemistry of the C-9, C-12 and C-13 stereocentres and their relation to each other, the following system will be used as per Harmata’s paper on erogorgine. The C-12(H) and C-13(Me) will be referred to as syn to each other whilst the C-12 and C-9 centres will be viewed as trans to each other (Figure 2.1).

![Figure 2.1](image-url)
2.2.1 - Cationic cyclisation

The topic of cationic cyclisation has had little mention in the literature over the past 25 years. Indeed, a lot of the problems arise from the lack of control of stereoselectivity involved in the cyclisation and thus the lack of control needed in synthesising natural products and analogues. In a paper by Casey it was reported that the diastereoselective cationic cyclisation was initiated by addition of an electrophile $X^+$ to an alkene $125$, followed by electrophilic attack on the arene. Nucleophilic substitution of the heteroatom has the added benefit of giving you extra functionality such as methylation $126$ (Scheme 2.2). The studies have shown that tetralins can be attained via endo or exo cationic cyclisations by addition of $I^-$ to alkenyl arenes followed by reductive deiodination.

![Scheme 2.2]

To highlight the ability of gaining the desired stereoselectivity during the cationic cyclisation, the following section describes why it is crucial to have control of the $E/Z$ ratios prior to cyclisation in order to gain the desired selectivity (Scheme 2.3).

![Scheme 2.3]
Cyclisation of alkene 127a (c.a E/Z 1:5 ratio) yielded iodotetralin 128a in a mixture of three diastereoisomers (6:1:1). Subsequent reductive deiodination under radical conditions yielded the sesquiterpene calamenene 129a as a mixture of cis/trans isomers 3.5:1. The analogous trans alkene 127b (c.a. 6:1 E/Z) gave the iodotetralin 128b albeit in a lower yield and with a substantial amount of side products, reduction of the crude product gave 129b with a 6:1 ratio of trans to cis.

Scheme: 2.4

It is postulated that the observed diastereoselectivity is imparted from a reversible iodonium ion formation on which the cyclisation is faster for the diastereomer with the benzylic methyl substituent in the pseudoequatorial orientation (Scheme 2.4).

An interesting development of the cationic cyclisation of pseudopteroxazole was discovered by the Corey research group,31 it was found that by changing the reaction conditions of the cyclisation, two stereoisomers 133 + 135 could be isolated (Scheme 2.5). When acetic acid was used as solvent with methanesulfonic acid, a 4:1 ratio of the desired 135 with (S) configuration at C(16) was obtained. Use of CH₂Cl₂ and methanesulfonic acid obtained the diastereomer of 133 with a 4:1 ratio. Mechanistically this can be considered by the protonation of the 1,3-diene subunit 130 by methanesulfonic acid which initiates the cyclisation in the form of a stabilized allylic carbocation. The (S) stereochemistry at C(16) of 134 is favoured over the (R) arrangement of 132 because of the lack of steric repulsion from the isobutenyl group. A 1,2-shift of C(16) in 134 to the next position on the benzenoid ring and subsequent deprotonation produces 135 stereoselectively when acetic acid is used as solvent. In CH₂Cl₂ as solvent with methane sulfonic acid as catalyst, the balance is shifted in favour of the alternative direct six-membered cyclisation pathway 131-133 as shown. In this
ring closure, the (R) configuration at C(16) is favoured for steric reasons and so the final product is the C(16)-(R) diastereomer 133. The reason for preferential formation of 135 with HOAc as solvent versus 133 with CH₂Cl₂ as solvent may simply be greater stabilisation of the transition state for cyclisation of 134-135 by hydrogen bonding of the carbamate NH to the solvent acetic acid.

Scheme: 2.5

In the Kerr research group, ongoing experiments to understand the biosynthetic pathway to the isolated natural products have been conducted with the radiolabeling of amphilectosins. The group has found that ring closure of these amphilectosins under enzymatic control has produced the required pseudopterosins. The observations are analogous with the work conducted by Corey in the synthesis of seco-pseudopterosin J. Also concluded by the group is the α/β position of the isobutenyl group is due to the selective ring closure of E/Z alkenes of the amphilectosins (Scheme 2.6).
The highly diastereoselective 6-endo-trig cyclisation of 2-alkenyl-1,3-dithiolanes 136 has been developed yielding trans-decalins. Baati and workers have produced an important scaffold present in numerous di- and triterpenes. The novelty of this 6-endo-trig cyclisation comes from the stepwise mechanism involving 2-alkenyl-1,3-dithiolane 136, acting as a novel latent initiator (Scheme 2.7). The group proposes the thio-ketal opens temporarily under the influence of TMSOTf, triggering the cationic 6-endo-trig cyclisation, and closes after C-C bond formation and diastereoselective protonation to terminate the process. The reaction tolerates a wide range of functionalities and nucleophilic partners within the substrate with 8 examples being provided. The paper shows the shortest total synthesis of triptophenolide and the shortest formal synthesis of triptolide.

From this review of synthetic strategies it can be concluded that to introduce the desired stereocentre at C-9, a trans alkene is required.
2.2.2 - Anionic oxy Cope rearrangement

The oxy–Cope rearrangement (AOC) in its simplest form is a [3,3]-sigmatropic rearrangement, first introduced in 1964; its early landmarks include the preparation of acoragermacrone and (-)-periplanone B.\textsuperscript{56,57} Since then it has been established as a powerful tool to the synthetic chemist in the construction of complex organic molecules. The rearrangement has vast rate acceleration ($10^{10-17}$)\textsuperscript{58} under milder conditions relative to the neutral version, forming new carbon skeletons.

The oxyanionic rate accelerating phenomenon, which has been observed in the gas phase and in solution stems from a charge induced weakening of the C(3)-C(4) bond. Since the donor properties of an oxygen substituent increases substantially in the order of OH > O\textsuperscript{–}M\textsuperscript{+} > O\textsuperscript{–}, the electrostatic effects of the metal ion and the degree of its separation from the alkoxide will impact directly on the extent of orbital destabilization in the reactant.\textsuperscript{59} Theorectical and experimental results show the AOC is characterised by a highly dissociative transition state whereby the C3 – C4 bond is extensively dissociated with only a small degree of bond formation between C1 and C6.\textsuperscript{60,61}

Scheme: 2.7

It is generally accepted that the rearrangement proceeds through a chair-like transition state (Scheme 2.7), whereby the oxyanionic bond sits in the pseudoequatorial orientation due to stereoelectronic effects. The equatorial oxyanionic bond is better aligned to channel surplus oxygen bound electrons to the allylic radical system through conjugation, thus destabilising the HOMO. This results in a better overlap of the HOMO and LUMO orbitals leading to a favourable transition state (Figure 2.2).
Studies are still unclear as to the true transition nature, but 1,4 diyl, aromatic or bis allyl systems have been accepted as reasonable transition states (Scheme 2.8).

Several well documented cases have been reported in which chairlike transition state has both pseudoequatorial and pseudoaxial orientations of the oxyanionic bond. Further examples have also shown that the pseudoaxial oxyanionic bond and boat like transition states are possible where the transition state is structurally enforced.\(^{62-64}\) It should be noted that the design of the molecule for rearrangements should be taken into account as steric of substituents can severely retard the rate of reaction or indeed stop it altogether.\(^{61}\)

Another example of the versatile nature of the AOC is its ability to translate chirality from reactant to product. The transfer of stereogenic centres is possible in high enantiomeric purity as shown in a paper by Lee, in which the first rearrangement of a flexible substrate with a single stereogenic centre (allylic alcohol 137) goes to the corresponding aldehyde on route to the synthesis of (+)-dihydromayurone (Scheme 2.9).\(^{65}\) The single stereogenic centre at the carbinol carbon was successfully transferred into the product with high enantiomeric purity (98:2). The efficiency of the chirality transfer was directly translated from the 98:2 equatorial/axial oxyanionic bond preference in the rearrangement and the strong preference for the equatorial status to the oxido substituent.

**Figure:** 2.2

Studies are still unclear as to the true transition nature, but 1,4 diyl, aromatic or bis allyl systems have been accepted as reasonable transition states (Scheme 2.8).
Further research on the AOC rearrangement by Paquette and co-workers found that pure (3R,5E)-1,5-heptadien-3-ol 138 and (3R,5Z)-1,5-heptadien-3-ol 140 undergo rearrangement with a modest 57-61% preference for equatorial oxygen.\textsuperscript{66,67} The data shows clearly that the E/Z pair of alcohols prefer to undergo the [3,3]-sigmatropic process through a chair transition state having the oxanyion orientated pseudo-equatorially as per 139 & 141. However, this preference is only slight signalling that the pseudoaxial alternatives are as accessible (Scheme 2.10).\textsuperscript{68,69}
Improved diastereoselection can be realised by placing an alkyl substituent on the tetrahedral carbon adjacent to that carrying the hydroxyl group. This is shown in the example of alcohols 142-144 (Scheme 2.11). In the first two examples the axial positioning of the oxido functionality induces 1,3-diaxial interactions that discourage operation of the pathways involving 145 and 146. When dienol 144 is used, the alkoxide and methyl groups are positioned axially and equatorially with little diaxial interactions. The 65:36 distribution of E/Z aldehydes shows the rearrangement to proceed more readily through transition state 147.\(^7\)

**Scheme: 2.11**

As exemplified in the literature, a stereoselective oxy-Cope rearrangement can be performed that favours only one chair like transition structure. This transition state would ensure efficient chirality transfer. To achieve this it is evident that a syn configuration is a prerequisite for an effective transfer of chirality such as substrate 142 (Scheme 2.11).
2.2.3 - Asymmetric Allylation

A requirement of the AOC in synthesising erogorgiaene was to have access to a syn alcohol in setting up the first desired stereocentre. To provide the necessary starting material for the AOC, our first key step an asymmetric allylation has to be developed. Recent advances in enantioselective formation of carbon–carbon bonds have focused on the allylmetal – aldehyde addition reaction (Scheme 2.12). The reaction has been employed in the synthesis of important structural subunits for many years. The reasons for the popularity of the method are its high degree of enantioselectivity and diastereoselectivity, the extreme diversity of reagent reactivity based on metal and the ability to access different stereodyads and latent functionality in the homoallylic alcohol product.

![Scheme 2.12]

In an allylation reaction, the ability of the metal to coordinate a chiral modifier held close to the reacting nucleophile and/or electrophile ensures high stereochemical information transfer. Excellent results have been obtained from the use of allylic titanium, allylic silanes and more recently allylic stannanes, chirally modified allylic borane and allylic trichlorosilane reagents. Addition of the latter reagent is catalysed by a Lewis base, typically DMF, DMSO and HMPA and their chiral analogues, which give excellent and predictable diastereoselectivity as well as enantioselectivity. Other substances such as formamides, urea derivatives, and catecholates can also act as Lewis bases through their basic oxygen.
2.2.3.1 - Reaction pathways

Three main types of allylation have been proposed in the early 1980’s by Denmark and Weber\textsuperscript{71,72} which take into account the postulated nature of the mechanism of addition of crotyl metal reagents to the carbonyl compound (Scheme 2.13). These reaction types can be divided into:

1 - Addition of allylic trichlorosilane catalyzed by chiral Lewis bases (also applies to B and Al reagents) (type I reagents: \textit{syn/anti} diastereoselectivity reflects the Z/E ratio of the alkene geometry).

2 - Addition of allylic organometallic reagents (Si, Sn) catalysed by chiral Lewis acids (type II reagents: predominantly \textit{syn} diastereoselective independent of starting allylic geometry).

3 - Addition of allylic organometallic reagents (Cr, Zn, In) generated in situ from the corresponding allylic halides catalyzed by chelating ligands (type III reagents: predominantly \textit{anti}-selective independent of starting allylic geometry).

\textbf{Scheme: 2.13}
Traditional methods for achieving catalytic enantioselective allylation relies on binding the electrophile (aldehyde) with a chiral Lewis acid which then activates it towards nucleophilic attack by the allylmetal reagent (type II). The advantages of the catalytic method, namely the use of small amounts of chiral controller and high enantioselectivities, are significantly offset by the lack of diastereoselectivity with substituted allylating reagents because of the non rigid nature of the transition structure (Scheme: 2.14). It has been shown that syn products are formed regardless of the double bond stereochemistry owing to steric in the open transition state.

Scheme: 2.14
Scheme: 2.15

In contrast type I reagents, such as allyltrihalosilanes are activated by coordination of a Lewis Base to the central electrophilic element (Scheme: 2.15) generating a hypercoordinate silicon species. A Lewis basic donor can enhance the activity of a Lewis acidic acceptor, this counter intuitive situation is clearly anticipated according to a set of empirical bond length and charge density variation rules formulated by Gutmann.\(^{73-75}\)

Gutmann recognized that formation of an acid-base adduct leads to an overall increase in the electron density in the acceptor fragment of the adduct, but the distribution of this electron density is not equal among the constituent atoms. Gutmann’s forth rule states upon coordination of a polyatomic donor to a polyatomic acceptor there will be a net increase in electron density on the donor atom and a net decrease of electron density on the acceptor atom. Thus upon coordination of a Lewis base, the central atom of a Lewis acid becomes more electrophilic with excess charge residing on the peripheral ligands. Taken to its logical limits, this transfer of electron density would result in an ionisation of one of the ligands from the Lewis acid. Once the ligand is ionised a full positive charge can be formally assigned to the central atom (Scheme 2.16).
The generation of the cationic species results in a significant increase in the Lewis acidity of the central atom, thus the Lewis base has activated the Lewis acid. The resulting complex with enhanced Lewis acidity is capable to coordinate the aldehyde. The reaction proceeds through a closed transition structure; it is here the chirality of the Lewis base can be expressed in the reaction gaining the high degree of enantio- and diastereoselectivity. The dissociation of the Lewis base from the product trichlorosilyl ether is required for catalyst turnover so it can re-enter the reaction cycle. This is made possible by the non covalent association between the chiral Lewis base and the chlorosilane substrate.

The ability of the Lewis base to effect the reaction selectivity has been explored in a variety of means, in 1994 Denmark first demonstrated the use of chiral phosphoramidate catalysts\textsuperscript{76} in allylation reactions because of silicon’s ability to expand its coordination number (up to six) to accommodate the Lewis base and aldehyde. Denmark showed that in the case of chiral phosphoramidate catalyst 149 (Figure 2.3) both oxygen atoms chelate to the highly acidic trichlorosilyl group, which causes ionization through the loss of one chloride ion. This ionisation process generates a cationic, octahedral silane (Figure 2.4) which undergoes reaction with the aldehyde via a closed chair-like type I mechanism.
Chiral mono phosphoramides can also catalyse a selective reaction but are less selective than the bis phosphoramides as they proceed via a pentacoordinate cationic silicon species. In later research, Kobayashi observed that DMF (as solvent) promoted the allylation of aldehydes (Scheme 2.17) and Iseki developed chiral DMF analogues derived from (S)-proline such as 150 for enantioselective additions.

Figure: 2.3

Figure: 2.4
In parallel chiral N-oxides have been developed as another class of highly selective catalysts, such as chiral mono pyridine N-oxides (151), (153) and bipyridine \(N,N\)-dioxides (152) acting as efficient catalysts in the allylation reaction.

In a recent publication by the Malkov group\(^{81}\) the mechanism of asymmetric allylation of aldehydes with allyltrichlorosilane, catalyzed by QUINOX 153 was investigated (Scheme 2.18).

The ability of QUINOX to catalyse the reaction with electron poor aldehydes was noticed in experiments on a variety of electron rich and electron poor benzaldehydes. QUINOX 153 exhibits a significant preference to electron poor aldehydes 96% ee with 4-CF\(_3\)C\(_6\)H\(_4\)CHO, whereas electron rich substrates reacted much slower with selectivities of 16% ee for 4-MeOC\(_6\)H\(_4\)CHO. The terpene derived METHOX 151 has also been shown to work well with a wide range of electron poor and electron rich benzaldehydes, exhibiting little dependence to the reaction rate and enantioselectivity on the nature of the Ar group. Results of 96% and 93% ee were obtained for 4-MeOC\(_6\)H\(_4\)CHO and 4-CF\(_3\)C\(_6\)H\(_4\)CHO respectively.
3.0 - Results and discussion

3.1 - Introduction

To develop a synthesis towards ergogorgiaene, it was necessary to explore the key synthetic steps needed to set up the three stereocentres featured in the natural product. In the first instance, cinnamaldehyde was picked as a simple model structure in order to develop the methodology. This in essence would allow us to synthesize an analogue of the natural product without the aromatic methyl group. From the review of literature exploring the versatilities of the oxy-Cope rearrangement it was clear that a syn alcohol 154a was required to gain the desired C-12 stereocentre with high chirality transfer. Theoretically, during the AOC of compound 154a, the syn relationship of the hydroxyl and methyl would lead to both groups taking pseudoequatorial positions which on completion of the rearrangement would give the C-12 hydrogen in the axial position and the C-8 methyl group in the equatorial position gaining the E alkene 155a (Scheme 3.1).

Scheme: 3.1
3.2 - Target synthesis

Scheme: 3.2

Compound 156 was the first synthetic target exploring the allylation, oxy-Cope and cationic cyclisation reactions (Scheme 3.2). Two commercially available compounds cinnamaldehyde 157a or α-methylcinnamaldehyde 157b were used as starting materials. Use of cinnamaldehyde would afford alcohol 154a (R = H), which in turn, through the oxy-Cope rearrangement, would set up the C-12 stereocentre. Cationic cyclisation and alkylation would set up the two final stereocentres. Use of α-methyl cinnamaldehyde would reduce the number of the synthetic pathway steps by introducing the C-13 methyl stereocentre prior to allylation and rearrangement. As will be explored, the two pathways have their own distinct advantages and disadvantages, these are discussed below.

3.3 - Methodology development

3.3.1 – Synthesis

Scheme: 3.3

The synthesis of model compound 156 starts with the allylation of simple cinnamaldehyde with cis-crotyl trichlorosilane made by a 1,4-addition of trichlorosilane to 1,3-butadiene (Scheme 3.3).82 After a high yielding allylation to form syn-alcohol 154a in 94% yield (syn-alcohol configuration is in accordance to literature data on 154a), the first stereocentre (C-12) was set up during the oxy-Cope rearrangement. The reaction proceeds as expected in a 71% yield. It was found that aldehyde 155a was formed as an 8:1 mixture of E/Z alkene isomers by analysis of literature ¹H NMR data of 155a.87 It is from the literature spectra the C-8 methyl group can be used to deduce a ratio of isomers (Scheme 3.4).
On analysis of the transition state it is clear that without any steric interactions of the oxyanion and methyl groups, the whole transition state can invert with the oxyanion and methyl groups taking an axial position just as easily (Scheme 3.1). Although a reasonable preference for this was seen (8:1 ratio), it is still detrimental to the overall diastereoselectivity over the course of the synthesis.

To improve the *E/Z* ratio, a series of reaction conditions were screened (Table 3.1). The results demonstrated that, contrary to expectations, an improvement in ratios was seen with an increase in temperature with the best results achieved at 50°C (entry 5). Change of base from KH to *t*-BuOK did nothing to improve yield/ratio and change of solvent from THF to diethyl ether stopped the reaction altogether. It was found that the optimal reaction conditions were with potassium hydride at 50 °C in THF.

**Table**: 3.1

<table>
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<th>Entry</th>
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<td>THF</td>
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<tr>
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<td>0</td>
<td>THF</td>
<td>6.6:1</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>KH</td>
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<tr>
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<td>THF</td>
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<td>80</td>
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<tr>
<td>6</td>
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</tr>
</tbody>
</table>
Using aldehyde 155a, several methods were explored to affect the cationic cyclisation and the set up of the C-9 stereocentre. Scheme 3.6 shows the first attempts towards the cyclisation; aldehyde 155a was protected as thioacetal and subjected to the cyclisation with an organic acid (CF₃SO₃H) which gave 158 as a 1:1 mixture of cis/trans isomers. By conduction nOe and TOCSY experiments on the two C-8 methyl groups it was possible to deduce the proton pattern along the carbon chain C-9 – C13 of the two isomers and which peaks correspond to the trans product (Figure 3.1). It is thought that the strong acid only gave a 1:1 mixture through a rapid cyclisation giving no favour to either isomer. Due to rapid degradation of the starting material/product, the acetal protection strategy was abandoned in favour of more stable derivatives.

Scheme: 3.6

Figure: 3.1
The second method (Scheme 3.7) explored the use of a weaker acid (MeSO₃H) to affect the cyclisation of methyl ester 159, it was hoped that a weaker acid would slow the reaction rate down and allow the desired product to be produced. Wittig chain extension of aldehyde 155a took place in a good yield (72%) and served to add the required chain length for future synthesis. The cationic cyclisation took place in a low yield of 35%, but set up the desired stereocentre in a >6:1 of trans/cis ratio due to the E/Z ratio of alkene formed in the AOC. These positive results of the cyclisation ratios show that weaker acids can be used to obtain the desired product.

Scheme: 3.7

The Wittig chain extension of aldehyde 155a provided a stable and easily isolated compound 159 that easily undergoes cationic cyclisation to form the desired product 160. At this stage it was attempted to perform a second cyclisation in order to gain the 5 membered ring 161. This second cyclisation would have led to the synthesis of another member of the natural product family ileabethoxazole. To date ileabethoxazole has only been isolated from natural sources and not synthesised in the laboratory. Even after heating and use of double the equivalents of acid, product 160 was the only stable product isolated.
A problem that has plagued the cyclisation is the poor yields obtained. A problem with slow reaction times and product decomposition has also led this reaction becoming a bottle neck of the synthesis. In all reactions monitored by TLC there is a clear indication of product formation. This does not always go to completion and can then lead to product decomposition seen by the appearance of base line tar on the TLC plate. Changing to a stronger acid does improve yields or reaction time, but does severely impede any reaction selectivity. Indeed when a stronger acid is used the reaction selectivity went in a 1:1 ratio as will be discussed later.

In an attempt to optimise the cyclisation reaction and improve the diastereomeric ratios, a series of experiments were devised exploring the conditions employed by Corey and Kerr research groups,\textsuperscript{30,54} such as the use of methanolic HCl and methanesulfonic acid with acetic acid, these failed to induce any cyclisation.

It was assumed that the optimum reagents were the ones we already used, thus in an attempt to improve the ratio of isomers the reaction temperature was investigated. The cyclisation was performed at -78, -40, -20, rt and 35°C. Reactions at low temperatures proceeded at a reduced rate or not at all, with no improvements in the diastereoselectivity. It was concluded that the original conditions at room temperature were the optimum for the reaction and were used.

The final stage of the model synthesis is the insertion of the C-13 methyl group. Attempts to insert the C-13 stereocentre first focused on alkylation of a methyl group on the newly formed methyl ester 160. It was envisaged that deprotonation at C-13 with LDA would form an extended enolate, which would then, on quenching with Mel form the desired product 162. However, only starting material was recovered (Scheme 3.8).

\begin{center}
Scheme: 3.8
\end{center}
The final method explored on this simple cinnamyl system was to introduce the C-13 stereocentre in ester 164 through a deprotonation/methylation sequence described by Kocienski in their synthesis of pseudopterosin. The required methyl ester 164 was synthesised in 53% over two steps by oxidation of aldehyde 155a (Scheme 3.9). Cationic cyclisation gave the desired trans conformation of the C-9 stereocentre in a 71% yield and >6:1 ratio of trans/cis. Deprotonation with LDA and methylation set up the final stereocentre (C-13) in 165. Although the $^1$H NMR of the major peak is concurrent with literature data of the hydrogenated compound, the aliphatic region is too messy to assign a ratio of isomers. Although promising as a route towards the synthesis of these natural products, the limitations of the AOC giving only an 8:1 E/Z ratio of isomers meant that the overall diastereoselectivity would be lowered. Kocienski showed that the methylation of a pure diastereomer of closely related pseudopterosin gave a >10:1 ratio of syn/anti products at the C-13 stereocentre. It is rationalised that the desired (R) stereochemistry is brought about from the alkylation taking place on the less hindered re-face of the enolate 166 in which the C-12(H) bond resides in the plane of the enolate in order to minimise allylic strain (Scheme 3.10).

Scheme: 3.9

Scheme: 3.10
As a result of the low diastereoselectivity obtained with simple cinnamaldehyde, it was decided to explore the use of α-methyl cinnamaldehyde as starting material 157b. The use of this compound incorporates the C-13 methyl in the molecule and will help lock the transition state during the AOC rearrangement. Aldehyde 155b was synthesised in two high yielding steps (80% and 77%) via allylation (syn-alcohol confirmed by correlation to literature data)\(^8^8\) and AOC with excellent stereocontrol giving the \(E\) isomer exclusively as shown by \(^1\)H NMR correlating to the major isomer of 155a (Scheme 3.11).

\[
\begin{align*}
\text{Scheme: 3.11} \\
\text{In this situation the methyl groups lock the transition state in the chair conformation stopping any inversion of the stereocentres (Scheme 3.12). An inversion of the transition state would gain the conformationally undesired state due to 1,3-diaxial interaction at the two methyl groups.}
\end{align*}
\]

Although control of the C-12 hydrogen in the axial position is achieved through this more locked transition state, it also poses a problem for the control of the C-13 stereocentre (α-methyl to aldehyde). As an outcome of using the oxy-Cope rearrangement the formation of the enolate effectively scrambles any stereogenic information at this position. No control was seen over the formation of the C-13 stereocentre which once protonated gave a 1:1
mixture of the diastereomers. A detailed account of the development of stereoselective oxy-Cope rearrangement and attempts to control the facial selectivity of the protonation will be further discussed in this chapter.

With a desire to keep the reaction sequence as short as practical, attention was turned to the deprotonation and reprotonation of the C-13 proton with the methyl group already incorporated in the molecule. Earlier attempts to control the stereochemistry of the methyl group already incorporated into the molecule had failed to yield any results by deprotonation and protonation with DBU (155b → 168). Methylation of the enolate with methyl iodide or bulkier dimethyl sulphate, only yielded a mixture of stereoisomers (167 → 155b) (Scheme 3.13).

Scheme: 3.13

A simple reaction of aldehyde 155b with LiHMDS and protonation with a slightly larger proton source (pentafluorophenol) than the conventionally used methanol yielded a promising 1:0.7 ratio of syn/anti isomers (Scheme 3.14). Indeed literature showed similar results with the protonation of lithium enolates with bulky phenol derivatives affording enriched products with high enantioselectivity.83 Even greater selectivity (2 : 1) was observed when a bulky proton source (2,6-di-t-butyl-4-methylphenol) was used instead of pentafluorophenol (selectivity of the protonation was determined through further synthesis to 175 and comparison to literature data of the C-13 methyl groups).14

Scheme: 3.14
With the results in hand, we refocused on selectively protonating the enolate 155b after the AOC rearrangement of α-methylcinnamyl derivative 154b. The results of the quenching the reaction with 2,6-diterbutyl-4-methylphenol showed a good selectivity of 3:1 (Scheme 3.15). This was compared again to pentafluorophenol (1 : 0.7) and t-BuOH (1 : 0.9) indicating that steric interactions play a noticeable role in the protonation of the enolate 169.

Scheme: 3.15

Aldehyde 170 was then subjected to the Wittig reaction with an 81% yield followed by the cationic cyclisation (Scheme 3.16).

Scheme: 3.16

Cyclisation of the 171 produced methyl ester 172 in a 1:3 ratio of syn:anti products. Comparing literature 1H NMR data of the hydrogenated product 175 unfortunately shows the desired diastereoisomer 172a was the minor product (Scheme 3.16). This shows that the undesired isomer is formed during the protonation of the enolate during the AOC. A positive message from these results is that cyclisation proceeded highly stereoselectively, no other significant isomers were formed to further complicate the picture.

Whilst trying to obtain an isomerically enriched C-13 stereocentre, the major product obtained after cyclisation was always the undesired isomer 172b. It was thus decided to quench the enolate of the AOC rearrangement with MeOH. This small proton source would yield the 1:1 ratio of isomers after cyclisation 155b, as the MeOH would not show any facial
selectivity during quenching of the enolate. The 1:1 ratio of diastereoisomers could then have a possibility of separation by chromatography/ preparative HPLC at a later stage. As such the synthesis was taken through a Wittig reaction to form methyl ester 173 in an 81% yield before subjecting to the cationic cyclisation at room temperature (Scheme 3.17). The cyclised product 174 had the correct trans stereochemistry however with a 1:1 mixture of C-13 isomers. Two more steps demonstrate a route to a formal synthesis of erogorgiaene (less methyl group in the aromatic ring) 176 through hydrogenation, followed by DIBAL reduction of the ester to gain the alcohol 176. Separation of diastereoisomers by TLC has been demonstrated and with the use of a preparative HPLC it could be possible to obtain diastereomERICALLY pure desired product. After this point, only oxidation and Wittig chain extension are required to produce the analogue of the natural product.

Scheme: 3.17
4.0 - Developments towards – Erogorgiaene

4.1 - Introduction

After developing and optimising the methodology for the key reaction steps, the synthesis of ergorgiaene was undertaken in two parts. The first makes use of the simple cinnamyl starting material with the prospect of inserting the C-13 methyl group at a later stage. The second synthesis starts with the α-methyl group already in place. Both reaction routes were to be explored to see their potential and best diastereoselectivity.

4.2 – Target synthesis

Synthesis of the target compound ergorgiaene 1 commenced from either 3-iodotoluene or m-tolualdehyde (Scheme 4.1), both cheap commercially available compounds. As explored in the method development, the two routes have their own advantages. It is envisaged that the aromatic methyl will have a para directing effect during the cationic cyclisation yielding the desired regioisomer.
4.3 - Synthesis

Early attempts to synthesise erogorgiaene were made starting from simple iodotoluene. Successful Heck coupling with acrolein diacetyl gave cinnamyl product 178 (93%) followed by allylation to give alcohol 179 in an 85% yield (Scheme 4.2). AOC rearrangement of the alcohol formed aldehyde 180 and was isolated in a 6:1 ratio of E/Z as previously seen from the method developments, this result demonstrates that substituents on the aromatic ring appear to play no role in the AOC rearrangement. The aldehyde was initially transformed to acid 181 and the cationic cyclisation attempted. Instead of the desired product, a double cyclisation took place to afford 182a and 182b as a 1:1 mixture. These products were isolated via preparative TLC and through detailed $^1$H NMR experiments using nOe and TOCSY the compound structures determined.

![Chemical structures](image)

**Scheme**: 4.2

In order to stop the double cyclisation taking place it was necessary to protect the carbonyl group. It was decided to protect the aldehyde prior to the cationic cyclisation. Protection was achieved using 1,2-ethanedithiol in a 71% yield. Cationic cyclisation of 183 (Scheme 4.3) gave a mixture of products. Isolation of these products was attempted using preparative TLC and reverse phase chromatography, but neither method could deliver a pure sample. However, by $^1$H NMR there is a distinctive difference of the C-8 methyl peaks that allowed us to use nOe and TOCSY experimentation to elucidate that the cyclisation produced the two regio isomers 184a and 184b. This result was disappointing and signalled a possible problem in controlling the regioselectivity of the cyclisation. This route was stopped due to this drawback.
In parallel, a synthetic route with the C-13 methyl group already incorporated into the starting material was investigated (Scheme 4.4). From simple m-tolualdehyde 185 the Wittig chain extension, DIBAL reduction and Swern oxidation gave the required cinnamyl aldehyde in high yields. Allylation of aldehyde 186 gave the required syn alcohol in 64% yield which was then subjected to the AOC rearrangement. The AOC rearrangement gave the E isomer exclusively as seen through the $^1$H NMR of the aldehyde proton showing only 1 peak, with a 1:1 ratio at the C-13 methyl stereocentre. This is again explained by the formation of the enolate during the AOC followed by non face-selective protonation.

Scheme: 4.4

Wittig chain extension of the aldehyde was completed in very poor yield 28% (unoptimized) forming the methyl ester. This was then taken on to 190 through cationic cyclisation. The cyclisation took place with methane sulfonic acid but again gave an inseparable 1:1 mixture of the syn/anti and regio isomers 190a and 190b. This mixture of regio isomers presents a problem with the developed route as it would require separation to gain the required regioisomer and gave extremely poor yields. As such it was decided to investigate preventing the undesired regioisomer from forming.
4.4 - Ortho Blocking

In summary, in the development of the two routes towards the synthesis of erogorgiaene it was seen that there is no control over the regio selectivity during the cationic cyclisation. Therefore, it was decided to block the ortho cyclisation site with a group that can be removed at a later stage. Use of a halogen such as bromine, would block the ortho position such that the cyclisation of 191 would produce the desired product 192 (Scheme 4.5). The bromine could then be removed at a later stage by reduction with LiAlH4.84

Scheme: 4.5

The first synthetic route commenced with the respective α-methylcinnamyl aldehyde 194, which was synthesised in three high yielding steps from commercial 193 by Wittig alkenylation, DIBAL reduction and Swern oxidation. Allylation of the aldehyde produced the syn alcohol 195 in a 70% yield; this was then subjected to the AOC rearrangement producing a close to equimolar mixture of 2 diastereoisomers and 2 unidentified by-products believed to be the cis/trans isomers (Scheme 4.6). It is believed that this has resulted from the bromine ‘bulk’ during the AOC having an influence on the substituent position or indeed the transition state of the AOC.

It was decided to push on the synthesis to see if it is just the free rotating ability of the Ar-C12 chain that has been hindered by the bulky bromine group. Wittig chain extension followed by cationic cyclisation gave an inseparable mixture of isomers appearing to come from both syn/anti and cis/trans. Although disappointing it is noted that the reaction did cyclise although the stronger triflic acid was used due to the electron withdrawing effects of the bromine substituent. This inseparable mixture led to the route being abandoned.
As an alternative route which protected the ortho position, the synthesis beginning with a demethyl (C-13) cinnamyl compound was investigated (Scheme 4.7). Cinnamyl aldehyde was synthesised by Wittig alkenylation of 193 followed by DIBAL reduction and Swern oxidation. Allylation of aldehyde 199 proceeded smoothly to afford the syn alcohol in a 76% yield which underwent the AOC rearrangement to produce the desired aldehyde 201 in a >12:1 E/Z ratio of isomers.

This interesting increase in E/Z ratios show that the bromine may have an influence during the transition state improving the ratios as stated with the previous reactions. Conversion of the aldehyde to the methyl ester by 202 oxidation and esterification with TMSCHN₂ proceeded in a 71% yield over two steps; this was subjected to the cationic cyclisation with MeSO₃H. The treatment with a softer organic acid again failed to induce the cyclisation; this is thought to be due to the deactivating effects of the bromine on the aromatic ring. However, when treated with triflic acid, the cyclisation proceeded in a 57% yield and a 3:1 ratio of cis/trans isomers.

Although disappointing compared to the previously gained 6:1 ratios without the bromine substituent, the product was subjected to alkylation in order to see the ratios of diastereomers. In order to install the C-13 stereocentre, the α-proton was removed with LDA and alkylation with MeI afforded the product. Only trace amount of product was isolated and it was characterised as mixture of isomers, showing no preference for facial selectivity.
4.5 – Conclusions

During the method development towards erogorgiaene it has become clear that our key reaction steps of allylation, oxy-Cope can be successful in setting up the desired skeleton. This however, has been overshadowed by the lack of regio-control of the cationic cyclisation and stereo-control of the C-13 stereocentre.

It became clear that two pathways are available in developing the synthetic sequence. The first pathway, without a C-13 methyl group present at the onset of the synthesis, offers a chance to set up the C-13 stereocentre at a later stage of the synthetic sequence. This however, is at the expense of increased number of synthetic steps and low overall diastereoselectivity. The second pathway with a methyl group incorporated into the molecule allows for a shorter synthesis with the benefits of greater E/Z control during the AOC. This does come with the drawback of the 1:1 ratio of C-13 isomers. However, this mixture of isomer is more preferable with the possibility of separation at a later stage.
Greater problems have arisen from the cyclisation onto the aromatic ring, without any substituents at the ortho position the cyclisation results in formation of two regioisomers. Introduction of bromine to block this position was unsuccessful during this synthesis but has been achieved by current group members post thesis. Control of the AOC was achieved by increasing the equivalents of 18-crown-6 to KH to 1:1 ratio. It is rationalised that possible halogen interaction with 18-crown-6 could be influencing the reaction.

From this point, our attention shifted to a more complex target in the pseudopterosin family with substituents at the ortho position which will alleviate the issues of regioselectivity in the cationic cyclisation.
5.0 - Developments of demethyl-elisabethadione synthesis

![Chemical structures of pseudopterosin family members](image)

**Figure: 5.1**

On reflection of the developments thus far in our synthesis of erogorgiaene, we faced difficulties in designing any methods that would ensure efficient control of regio- and diastereoselectivity. Fortunately, the issue of regioselectivity becomes irrelevant when four other members of the pseudopterosin family of natural products are considered (Figure 5.1). Each of these natural products has highly functionalised aromatic rings, allowing us to set up a route that would direct the cationic cyclisation to only one position. Although the structures of these natural products look rather complex, as in the case of colombiasin A, they can all be accessed from one key intermediate. The key intermediate alcohol 121 (Scheme 5.1) can be reached using methodology already explored in our synthesis thus far and provides the formal synthesis for the four natural products. From here, the total synthesis of elisabethadione (so far the only example) has been reported by Davies.47
In the development of the synthesis a simplified, commercially available model aldehyde 205 without the methyl group in the aromatic ring was used.

The synthesis starts with the Wittig alkenylation of 205 and reduction of the ethyl ester to the allylic alcohol (Scheme 5.2). Initial attempts to use the Swern oxidation to obtain the aldehyde were unsuccessful with only trace amounts of product formed. It was decided to use MnO₂, which although worked slower than the Swern oxidation, can tolerate a wider range of substrates. This gave an excellent yield of 84%.

Efforts to afford allylation of aldehyde 206 failed to work using the conventional CH₂Cl₂ and DMF as a solvent/catalyst system (Entry 1, Table 5.1). Aldehyde 206 contains a highly electron rich aromatic system which is believed to reduce electrophilicity of the carbonyl, thus deactivating it. Eventually, syn homoallylic alcohol 207 was synthesised in high yield by a slight change of reaction conditions (Entry 2). Changing to a more polar solvent and using
Hünig's base to 'mop' up the generated HCl allowed the reaction to precede smoothly in 91% yields. Entry 3 shows attempts to use a chiral catalyst to induce enantioselectivity. Unfortunately, these attempts failed to give any product.

![Image of Hünig's base and MK-10]

**Table: 5.1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Lewis Base</th>
<th>Additives</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>206</td>
<td>CH₂Cl₂</td>
<td>DMF</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>206</td>
<td>MeCN</td>
<td>DMF</td>
<td>Hünigs Base</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>206</td>
<td>MeCN</td>
<td>MK-10</td>
<td>Hünigs Base</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

In parallel to the Lewis base catalysed allylation employing allyltrichlorosilane reagents, it was also attempted to carry out the allylation using allylboronates under conditions of Bronsted acid catalysis. The reaction was attempted using 206 and commercially available *cis*-crotyl pinacol boronate in toluene with a chiral Bronsted acid (R)-TRIP (Scheme 5.3).

![Image of reaction scheme]

**Scheme: 5.3**
Entries 1-2 of table 5.2 show initial attempts afford the Lewis acid allylation with cis-crotylboronate 208. Entry 1 shows as expected no reaction to take place without any acid present, which on addition of triflic acid a trace amount of alcohol was seen. The addition of (R)-TRIP was attempted in order to gain the asymmetric product, this only produced a trace amount of product which led us to believe that the electronic nature of the substrate may be hindering the allylation.

To analyse if electronics could be influencing the reaction the use of simple substrate α-methylcinnamaldehyde was used and provided some interesting results. This simple substrate was subjected to the allylation at -40 °C with (R)-TRIP as a catalyst. The reaction proceeded with a full conversion to furnish the product in 77% ee, determined by analysis of the racemic product to entry 4 with chiral HPLC. This interesting result showed that the electron rich substituents appear to have deactivated the aldehyde. Due to the problems with developing asymmetric variant, it was decided to continue with the racemic version using cis-crotylsilane. This is due in part the high costs of obtaining or producing the cis-crotylboronate and difficulty in obtaining high enough enantiomeric excess. Current work in the group is focussing on the asymmetric allylation.
Following the allylation of 206, the AOC rearrangement of alcohol 207 was attempted using THF as solvent, this led to an unexpected problem as the rearrangement did not proceed and indeed gave a decomposed product. Switching to DME as solvent gave the desired aldehyde in a 68% yield, with a very high E/Z selectivity but with an expected 1:1 ratio of C-13 isomers (Scheme 5.4). After Wittig chain extension of the aldehyde 208, cationic cyclisation of 209 afforded the *trans* product with an increased 3:1 ratio of the desired isomer at the C-13 stereocentre. Although a better result was observed in the cyclisation, it happened at the expense of the reduced yield (35% yield). Monitoring the reaction by TLC revealed that longer reaction times led to an increase in ‘base line’ decomposition products. It is thought that the product decomposes either during the cyclisation or after. This can also explain why a greater than 3:1 ratio is seen in the isolated product. Recent attempts to optimize the cationic cyclisation have yielded some interesting results. Cyclisations carried out using MeCN as a solvent rather than CH₂Cl₂ produced a much slower rate of reaction.
when methanesulfonic acid was used. The reaction took over 2 days and still showed no signs of going to completion. By contrast, triflic acid showed a greater rate of reaction but led to extensive decomposition. Returning to the less polar CH₂Cl₂ and CHCl₃ showed again a reasonable rate of reaction but without an ability to push to completion even after adding additional equivalents of acid. After working up the reaction it was found that an enriched product 210 was isolated. It is unclear during the reaction whether the starting material or the undesired product had decomposed leaving 210 in an enriched ratio. Hydrogenation with H₂ over Pd/C in the H-Cube followed by DIBAL reduction and oxidation with PCC yielded product 213, thus accomplishing a formal synthesis of elisabethadione analogue, as reported by Davies.⁴⁷

Scheme: 5.5

An alternative synthetic route was explored using anti alcohol 214 prepared by allylation of the model aldehyde 206 with E-croyltrichlorosilane in a 68% yield (Scheme 5.5). It was envisaged that the asymmetric allylation could be achieved using an efficient chiral catalyst METHOX. This catalyst is known to produce anti homoallylic alcohols in excellent enantioselectivities and tolerates electron rich substrates. Once the anti alcohol 214 was obtained it was hoped that the AOC would obtain the E alkene 215, setting up the C-12 stereocentre. Initial predictions following knowledge gained on the AOC of simple substrates led us to believe only the desired substrate would be generated (Scheme 5.6). However, upon AOC rearrangement of anti alcohol 214 the product obtained was a mixture of alkenes in a 1:3 E/Z ratio. This unexpected result suggests that a lower energy transition state, possibly a boat, can be realised. As the reaction produced a substantial quantity of the other enantiomer this route was abandoned.
Scheme: 5.6
5.1 - Total synthesis of Elisabethadione

Scheme: 5.7

Having developed a synthetic route towards the advanced analogue of the natural product, we now focused on the full total synthesis of the natural elisabethadione (Scheme 5.7). Our experimentation on model analogues of the natural product has allowed us to optimize the key reaction conditions of the allylation, anionic oxy-Cope rearrangement and cationic cyclisation. The method described will be that of a racemic product as at the time we were unable to develop an asymmetric allylation that would work well on the relevant substrates.
Scheme: 5.8

The synthesis of elisabethadione starts by producing the starting cinnamyl aldehyde 223 (Scheme 5.8). This was done by the alkylation of 1,2,4-trimethoxy benzene 217 at the C-2 position proceeding in an excellent yield of 99%. This was followed by selective halogenation at the C-6 position, proven by $^1$H NMR nOe experiments of the neighbouring methoxy peaks C-1 and C-4, with C-4 (OMe) coupling to the proton at C-5. Lithiation by bromine exchange followed by the addition of DMF provided after hydrolysis the required aldehyde in a 78% yield.

Scheme: 5.9
Attempts were made to shorten the synthesis of the starting aldehyde 223 using a protected 1,2,4-trimethoxybenzaldehyde, this would allow the alkylation at the C-2 position (Scheme 5.9). It was envisaged that after protecting the aldehyde as an acetal, the alkylation via n-BuLi and MeI followed by an acidic workup would achieve the desired aldehyde 220. Unfortunately attempts to gain the protected aldehyde did not produce the desired aldehyde and only returned starting material. Possibly the electron rich nature of the aromatic ring made it difficult for the protection to proceed.

To complete the synthesis of the starting material, aldehyde 220 was subjected to the Wittig chain extension to produce the methyl ester 221 in an excellent yield 91%. Simple DIBAL reduction to the alcohol 222 in a 60% yield followed by oxidation to the aldehyde by MnO₂ in a 77% yield afforded the cinnamyl aldehyde 223.

In another attempt to shorten the reaction sequence, the investigation explored the use of the originally developed Heck reaction of the halogenated aromatic 219. However, only very poor conversions 15% were obtained with mainly dehalogenated product returned. It was suggested that the oxidative insertion was followed by fast protonolysis to afford the dehalogenated product (Scheme 5.10). Ammonia salts were the likely source of protons in the reaction. Optimization of the reaction conditions employing different ligands, varying solvent and additives did not bring significant improvements (Table 5.3). By changing the base, a 15% conversion was observed (entry 6). Changing the palladium source did offer a higher conversion but was still stopping at 20% (entry 8). Due to these results it was decided to carry on with the original synthesis (Scheme 5.8) to afford aldehyde 223.
Table: 5.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Additive</th>
<th>Palladium</th>
<th>Ligands</th>
<th>Conversions %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>K₂CO₃/KCl</td>
<td>nBu₄NOAc</td>
<td>Pd(OAc)₂</td>
<td>-</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>K₂CO₃/KCl</td>
<td>nBu₄NOAc</td>
<td>Pd(OAc)₂</td>
<td>DPPF</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>-</td>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>K₂CO₃</td>
<td>-</td>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>CsCO₃</td>
<td>nBu₄NBr</td>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>Na₂CO₃</td>
<td>-</td>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>15%</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>-</td>
<td>Pd(OAc)₂</td>
<td>DPPF</td>
<td>10%</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>-</td>
<td>PdCl₂</td>
<td>PPh₃</td>
<td>20%</td>
</tr>
</tbody>
</table>

The next key step in the reaction sequence is the allylation of aldehyde 223 to the desired syn alcohol. In an attempt to push forward with an asymmetric synthesis the allylation under Lewis acid conditions with (R)-TRIP and cis-crotylboronate was revisited. Initial results were attempted with the addition of an acid alongside (R)-TRIP to help catalyse the
reaction. Entries 1-2 (Table 5.4) show that the use of TFA catalysed the reaction enabling the desired product to be produced in a 50% yield with a disappointing enantiomeric excess of 33%. Further work by group members after this project had finished have managed to optimise the reaction conditions and have obtained a full conversion with an excellent enantiomeric excess of 90% (Entries 3-4).

Table: 5.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R)-TRIP (%)</th>
<th>Additive (%)</th>
<th>Temp °C</th>
<th>Yield (%) (Conversion)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Acetic acid (2.5)</td>
<td>-40</td>
<td>Trace</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>TFA (2.5)</td>
<td>-30</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>TFA (1)</td>
<td>-30</td>
<td>(100)</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>BzOH (1)</td>
<td>-30</td>
<td>(100)</td>
<td>90</td>
</tr>
</tbody>
</table>

Scheme: 5.11
Due to initial attempts producing poor yields and ee, the synthesis of the syn alcohol was completed in a racemic form by the allylation of cinnamyl aldehyde 223 with cis-crotyltrichlorosilane in a good yield 61% using DMF as the Lewis base (Scheme 5.11). The AOC rearrangement of alcohol 224 gave the desired aldehyde 225 with an unexpected 2:1 ratio of the C-13 stereocentre; it might be possible that the bulk of the methoxy groups could induce some facial selectivity during the quenching of the enolate thus gaining the 2:1 ratio seen. Wittig chain extension of aldehyde 225 gained the methyl ester in a 76% yield which was then subjected to cationic cyclisation by our optimised conditions of CHCl₃ and methanesulfonic acid at 40°C. This gave the desired trans product 227 in a 2:1 ratio at the C-13 stereocentre and exclusive control of the C-9 stereocentre in a 66% yield.

Scheme: 5.12

Having now set up the three required stereocentres it first became necessary to complete the side chain of the natural product (Scheme 5.12). This was accomplished in high yielding steps by hydrogenation of the double bond with H₂ over Pd/C catalyst furnishing the saturated methyl ester 228 in a 90% yield, followed by DIBAL reduction to alcohol 229 in a 79% yield. It is at this point that it is possible to separate out the two diastereoisomers by column chromatography. A small sample was separated out to gain enriched ¹H NMR spectra of 229 for both diastereoisomers. The use of a preparative HPLC would allow the separation at this point as a distinctive change in Rf of the two isomers is noticeable by TLC, unfortunately without the use of this equipment it was decided to attempt the total
synthesis and attempt a separation at a later stage. Oxidation with PCC afforded the aldehyde 230 in a 78% yield. Wittig chain extension with 1-methylethyldiene(triphenyl)phosphorane gave 231 in an 80% yield completing the side chain required for the natural product.

**Scheme: 5.13**

The final stage of the synthesis is the oxidation of the aromatic ring to the dione as per elisabethadione (Scheme 5.13). Treatment of 231 with lithium ethanthiolate in DMF at 180°C gave the bis phenol 233 as a red solid in 68% yield. As this was the first solid of the synthesis it was attempted to produce crystals for x-ray analysis to ascertain the true configuration of the stereocentres and indeed the whole molecule. By growing crystals through the vapour diffusion method with the product in ether and hexane as the diffusing solvent, a crystal was grown and found to be a mixture of 80:20 ratio in favour of the undesired C-13 isomer (Figure 5.2). As expected the crystal is a racemate mixture in a cetrosymmetric space group. Atom C(14) is disordered with major:minor components = 79.8:20.2(4)% which indicate some molecules with different relative stereochemistry at C(13). The OH and OMe groups are involved in H-bonding, resulting in 2D layer structure with the layers in the b/c plane (Figure 5.3). Future attempts at the synthesis of this molecule will have to produce an enantiomerically and diastereomerically pure compound to compare with the natural product. It should be noted that this is the first time this compound has had its crystal structure examined and the 1H NMR and 13C are both in
agreement with the Davies group’s synthesis of this molecule. As already stated it could be possible to separate any isomers by preparative TLC or HPLC once alcohol 229 has been isolated. Further work published by Davies and Kerr on isolated elisabethadione raise doubts that the published NMR spectral data for (+)-elisabethadione may not be the correct assignment.

Figure: 5.2

Figure: 5.3
To complete the synthesis, oxidation of diol 233 to the red ortho-quinone 234 with cerium ammonium nitrate was achieved in a 68% yield. The final step used TsOH in benzene to afford the natural product as a racemic mixture in a 2:1 ratio of diastereomers at the C-13 bond in a 75% yield. The assigned structure of elisabethadione was confirmed by comparisons to the natural product and that synthesised previously by the Davies group (See appendix Figure 8.4 and 8.5 for Davies NMR spectra). 47 What is clear on comparison of spectroscopic data, is the major $^1$H NMR peaks match that synthesised by Davies (Figure 5.4). It is still unclear without x-ray crystallography data as to which isomer is the correct natural product. This said, published journal papers have questioned the original natural product spectroscopic data, they go on to propose that the major isomer (observed in our synthesis) is indeed the correct characterisation of elisabethadione.

![Figure 5.4](image-url)
5.2 - Conclusion

The full synthesis of elisabethadione has shown the methodology employed is now complete and will allow a total synthesis on this class of natural product with highly functionalised aromatic rings. Future work is being focused on investigating the asymmetric variant of the allylation step to afford an enantiomerically enriched homoallylic alcohol. Once completed, the aim of the group will be to accomplish the total asymmetric synthesis of various natural products in this family through the key intermediate (alcohol 229).\textsuperscript{98}
6.0 - Experimental

General Methods

All reactions were carried out under an inert atmosphere in flame dried glassware unless otherwise stated. Room temperature refers to ambient room temperature (20-22 °C); 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled heating mantles. Reactions were monitored by thin layer chromatography using aluminum backed silica gel 60 Å (F254) plates; visualized using UV \textsubscript{254/286} nm and PMA dip. Flash chromatography was carried out using 60 Å silica gel as the stationary phase.

Melting points were determined on a Stuart scientific melting point SMP3 machine and are uncorrected. The NMR spectra were recorded in CDCl\textsubscript{3}, \textsuperscript{1}H at 400 MHz and \textsuperscript{13}C at 100.6 MHz on a Bruker spectrospin 400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million with chloroform-\textit{d}\textsubscript{1} (δ 7.26, \textsuperscript{1}H; δ 77.0, \textsuperscript{13}C) as standard unless otherwise indicated. Coupling constants (\textit{J}) are measured in Hz and are unadjusted; therefore due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured \textit{J} value of some coupling constants. The IR spectra were recorded on a PerkinElmer spectrum 65 FT-IR spectrophotometer for a thin film between NaCl plates. The mass spectra (HRMS) were measured on a Thermo Scientific Exactive Orbitrap spectrometer.

Enantiomeric excess was determined by chiral GC analysis (using a Hewlett Packard HP 6890 series GC system with a Gamma DEX 120 column) or by chiral HPLC analysis (using a Gilson HPLC system with a CHIRALPAK IA-3 or IB-3 columns). The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures.

Unless otherwise stated, all diastereomeric were recorded as mixtures and the major/ minor isomer peaks were deduced from the NMR spectra. All compounds (Unless stated) were synthesised as a racemic mixture.
6.1 - Synthesis of silanes

(2)-But-2-enyltrichlorosilane \(^{82}\)

Condensed 1,3-butadiene (8.40 mL, 46.40 mmol) was added to a solution of trichlorosilane (10.00 mL, 49.40 mmol) and Pd(PPh\(_3\))\(_4\) (100 mg) in a pressure tube and heated to 110 °C overnight. The solution was distilled at 50 °C, 3 mbar to give the **title compound** as a colourless liquid (6.59 g, 75 %); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) \(H\) 5.72-5.77 (m, 1H), 5.43-5.46 (m, 1H), 2.27 (d, \(J = 8.0\) Hz, 2H, 4-H), 1.58 (d, \(J = 6.8\) Hz, 3H, 1-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) \(C\) 128.3, 118.5, 24.7 (CH\(_2\), 4-C), 13.0.

(\(E\))-But-2-enyltrichlorosilane \(^{86}\)

To a solution Cu(I)Cl (1.0 g, 11.04 mmol) and Et\(_2\)O (10 mL) was added crotylchloride (1.08 mL, 11.00 mmol) and hünigs base (4.78 mL, 27.60 mmol). After addition the solution was cooled to 0 °C and trichlorosilane (1.67 mL, 16.50 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was extracted and filtered under N\(_2\) then used directly in the next step.
6.2 - Method development - Simple cinnamyl synthesis

\[ \pm (3R,4R,E)-4\text{-}methyl\text{-}1\text{-}phenylhexa\text{-}1,5\text{-}dien\text{-}3\text{-}ol (154a) \]

Crotyltrichlorosilane (0.94 g, 5.00 mmol) was added dropwise to a solution of cinnamaldehyde (0.50 mL, 3.90 mmol) in DMF (1.94 mL 25.00 mmol) and CH₂Cl₂ (2 mL) at 0 °C under N₂ for 6 hrs. The reaction was quenched with saturated NaHCO₃ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x50 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated in vacuo producing the title compound as a light yellow oil 154a (0.67 g, 94 %); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta_H \) 7.41 (d, \( J = 7.6 \) Hz, 2H, 3'-H), 7.35 (t, \( J = 7.6 \) Hz, 2H, 2'-H), 7.14-7.15 (m, 1H, 1'-H), 6.62 (d, \( J = 15.9 \) Hz, 1H, 1-H), 6.26 (dd, \( J = 15.9, 6.5 \) Hz, 1H, 2-H), 5.85-5.87 (m, 1H, 5-H), 5.18 (d, \( J = 6.8 \) Hz, 1H, 6-H), 5.16 (s, 1H, 6-H), 4.24 (t, \( J = 6.5 \) Hz, 1H, 3-H), 2.34-2.40 (m, 1H, 4-H), 1.11 (d, \( J = 6.8 \), 3H, 7-H); \(^13\)C NMR (100 MHz, CDCl₃): \( \delta_C \) 139.9, 136.7 (q), 131.2, 129.9, 128.5, 127.8, 126.5, 116.0, 75.8, 43.9, 14.8; IR (neat) 3391.6, 2970.7, 1667.4, 1494.5, 1449.5, 1070.8, 965.6, 749.0 cm\(^{-1}\); HRMS (El) calculated for C\(_{13}\)H\(_{16}\)ONa [M]\(^+\), \( m/z \): 211.1093, found \( m/z \): 211.1091.
± (R,E)-3-Phenylhept-5-enal (155a)<sup>87</sup>

KH 30 % suspension in mineral oil (7.69 g, 192.00 mmol) was washed with THF (3x10 mL). Dry THF (50 mL) was added to the KH. 154a (1.81 g, 9.62 mmol) followed by 18-crown-6 (1.26 g, 4.80 mmol) was added to the solution and heated for 3 hrs at 50 °C. The solution was cooled to -78 °C and quenched with methanol (10 mL). The mixture was poured into a solution of ether (100 mL) and saturated NH₄Cl (30 mL). The organic layer was separated and washed with brine (20 mL), dried (Na₂SO₃) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 1 % ethyl acetate/petroleum ether) gave the title compound 155a as a yellow oil with a 8:1 E/Z ratio (1.57 g, 71 %); <sup>1</sup>H NMR (400 MHz, CDCl₃): δ<sub>H</sub> 9.59 (t, J = 6.4 Hz, 1H, 1-H), 7.10-7.30 (m, 5H), 5.32-5.39 (m, 1H, 6-H), 5.17-5.25 (m, 1H, 5-H), 3.14-3.16 (m, 1H, 3-H), 2.61-2.68 (m, 2H, 2-H), 2.20-2.26 (m, 2H, 4-H), 1.53 (d, J = 7.6 Hz, 3H, 7-H); <sup>13</sup>C NMR (100 MHz, CDCl₃): δ<sub>C</sub> 202.0 (CHO, 1-C), 143.7 (q), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.4 (CH), 126.5 (CH), 49.2 (CH₂, 2-C), 40.2 (CH, 3-C), 39.9 (CH₂, 4-C), 17.9 (CH₃, 7-C); IR (neat) 3027.6, 2917.7, 2723.0, 2714.8, 1602.9, 1590.6, 1494.9, 1452.8, 969.0, 700.9 cm⁻¹; HRMS (EI) calculated for C₁₃H₁₆ONa [M]+, m/z: 211.1093, found m/z: 211.1090. 
± (R,E)-2-(2-phenylhex-4-enyl)-1,3-dithiolane (137)

1,2-Ethanedithiol (0.33 ml, 4.00 mmol) was added to a solution of 155a (0.38 g, 2.00 mmol) in anhydrous CH₂Cl₂ (10 ml) and FeCl₃-SiO₂ (1.00 g). The reaction was stirred under N₂ at room temperature for 15 minutes. The reaction was quenched with 2M aqueous NaOH (10 mL) and extracted with CH₂Cl₂ (2x50 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the title compound as a pale yellow oil 137 in an 8:1 E/Z ratio (370 mg, 71%); ¹H NMR (400 MHz, CDCl₃): δH 7.20-7.24 (m, 2H), 7.08-7.15 (m, 3H), 5.30-5.36 (m, 1H, 5'-H), 5.18-5.24 (m, 1H, 4-H), 4.06 (t, J = 6.8 Hz, 1H, 1'-H), 3.00-3.19 (m, 4H, 3'-H), 2.64-2.71 (m, 1H, 2-H), 2.20-2.24 (m, 2H, 3-H), 2.04 (dd, J = 7.2, 7.2 Hz, 2H, 1-H), 1.51 (d, J = 6.4 Hz, 3H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δC 143.6 (q), 128.7, 128.4, 127.8, 126.9, 126.4, 51.6, 46.2, 40.1, 38.3, 38.1, 17.9; IR (neat) 2921.1, 1493.9, 1436.8, 1275.4, 966.0, 700.8 cm⁻¹; HRMS (EI) calculated for C₁₅H₂₀OS₂Na [M⁺], m/z: 303.0848, found m/z: 303.0841.

± 2-(((1R)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-1,3-dithiolane (158)

To a solution of 137 (370 mg, 1.40 mmol) in CH₂Cl₂ (10 mL) was added CF₃SO₃H (0.3 ml, 3.40 mmol). The reaction was stirred at -78 °C and allowed to warm to room temperature overnight. The reaction mixture was poured into saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (2x50 mL). The organic layers were combined, washed with brine (20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on a C18 column (eluting with 10 % water/acetonitrile) gave the title compound as a tan oil as a 1:1 mixture of diastereoisomers 158 (Trace);
Major isomer:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H 7.03-7.11$ (m, 4H), 4.53 (dd, $J = 8.2$, 4.0Hz, 1H, 3'-H), 3.16-3.25 (m, 4H), 2.82-2.89 (m, 1H), 2.00-2.05 (m, 3H), 1.90-1.97 (m, 2H), 1.43-1.56 (m, 2H), 1.18 (d, $J = 6.8$ Hz, 3H, 5-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_C$ 128.6 (q), 127.7 (q), 127.5, 125.6, 125.5, 123.2, 51.8, 46.5, 40.5, 38.0, 36.5, 32.6, 32.1, 22.4, 19.1; IR (neat) 2921.1, 1493.9, 1436.8, 1275.4, 966.0, 700.8 cm$^{-1}$; HRMS (EI) calculated for C$_{15}$H$_{20}$OS$_2$Na [M]$^+$, $m/z$: 303.0842, found $m/z$: 303.0848.

Minor isomer:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H 1.23$ (d, $J = 6.8$ Hz, 3H, 5-H).

± (R,2E,7E)-Methyl 5-phenylnoona-2,7-dienoate (159)

Methyl(triphenylphosphoranylidene)acetate (2.80 g, 8.40 mmol) was added to a solution of aldehyde 155a (0.85 g, 4.20 mmol) and water (10 mL) and heated at 90 °C overnight. The reaction was cooled and poured onto saturated NaHCO$_3$ (20 mL) and extracted with CH$_2$Cl$_2$ (2x50 mL). The organic layers were dried (MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the title compound as a yellow oil 159 in a 8:1 E/Z ratio (780 mg, 72 %); $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 7.04-7.22 (m, 5H), 6.74 (dt, $J = 15.6$, 7.2 Hz, 1H, 7-H), 5.67 (d, $J = 15.6$ Hz, 1H, 8-H), 5.29-5.38 (m, 1H, 2-H), 5.15-5.23 (m, 1H, 3-H), 3.59 (s, 3H, OCH$_3$), 2.65-2.68 (m, 1H, 5-H), 2.44-2.49 (m, 1H, 6-H), 2.36-2.42 (m, 1H, 6-H), 2.23 (t, $J = 6.8$ Hz, 2H, 4-H), 1.51 (d, $J = 7.6$ Hz, 3H, 1-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_C$ 166.8 (q, 9-C), 147.6 (CH, 7-C), 143.9 (q), 128.5 (ArCH), 128.4 (ArCH), 127.5 (ArCH), 127.2 (ArCH), 126.3 (ArCH), 122.2 (CH, 8-C), 51.3 (OCH$_3$), 45.2 (CH, 5-C), 39.3 (CH$_2$, 4-C), 38.4 (CH$_2$, 6-C), 17.9 (CH$_3$, 1-C); IR (neat) 2916.8, 1724.6, 1657.1, 1436.0, 1272.3, 1208.9, 1158.7, 968.1, 700.5 cm$^{-1}$; HRMS (EI) calculated for C$_{16}$H$_{20}$O$_2$Na [M]$^+$, $m/z$: 267.1356, found $m/z$: 267.1352.
± (E)-Methyl 4-((1R,4S)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (160)

Methane sulfonic acid (1.0 mL, 15.30 mmol) was added to a solution of ester 159 (0.18 g, 0.70 mmol) in anhydrous CH₂Cl₂ (10 mL) at -78 °C under N₂. The reaction was stirred and allowed to warm to room temperature overnight. The solution was quenched with saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (2x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a yellow oil in a >6:1 ratio of diastereoisomers 160 (0.06 g, 35 %); ¹H NMR (400 MHz, CDCl₃): δ 7.04-7.10 (m, 4H), 6.89-6.97 (m, 1H, 2-H), 5.79 (d, J = 15.6 Hz, 1H, 3-H), 3.66 (s, 3H, OCH₃), 2.83-2.91 (m, 2H), 2.43-2.49 (m, 1H, 1-H), 2.37-2.42 (m, 1H, 1'-H), 1.87-1.90 (m, 2H), 1.41-1.52 (m, 2H), 1.16 (d, J = 5.2 Hz, 3H, 5'-H); ¹³C NMR (100 MHz, CDCl₃): δ C 166.9 (q, 4-C), 148.1 (CH, 2-C), 142.2 (q), 139.0 (q), 128.6 (ArCH), 128.4 (ArCH), 126.0 (ArCH), 125.7 (ArCH), 122.4 (CH, 3-C), 51.4 (OCH₃), 39.8, 37.2, 32.3, 27.0, 23.7, 23.3 (CH₂, 5'-C); IR (neat) 2927.6, 1724.6, 1655.8, 1435.5, 1270.3, 1173.9, 755.7 cm⁻¹; HRMS (EI) calculated for C₁₆H₂₀O₂Na [M]+, m/z: 267.1356, found m/z: 267.1350.

± (R,E)-3-Phenylhept-5-enoic acid (238)

A solution of NaClO₂ (0.59 g, 6.60 mmol) in water (50 mL) was added dropwise over a 1 hr period to a stirred solution of 155a (0.83 g, 4.40 mmol) in MeCN (50 mL), Na₂H₃PO₄·H₂O (0.34 g, 2.20 mmol) and H₂O₂ 27 % (0.90 mL, 5.30 mmol) at 0 °C. The reaction was stirred for 3.5 hrs before Na₂SO₄ (20 mL) was added to destroy any unreacted HOCl and H₂O₂. The reaction was poured onto a saturated solution of NaHCO₃ (10 mL), acidified with 5% HCl (10 mL) then extracted with CH₂Cl₂ (2x50 mL). The organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo. The resulting yellow solution was used directly in the next step without purification.
± (R,E)-Methyl 3-phenylhept-5-enoate (163)

A solution of trimethylsilyl diazomethane (2.14 mL, 4.20 mmol) was stirred in a mixture of toluene (80 mL) and MeOH (16 mL) under N\textsubscript{2}. Acid 238 (0.73 g, 3.57 mmol) in MeOH (4.0 mL) was added and stirred for 30 minutes. The solution was diluted with ether (50 mL) and acetic acid (20 mL). The organic layer was separated and washed with saturated Na\textsubscript{2}CO\textsubscript{3} (10 mL), dried (MgSO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 163 (410 mg, 53 %); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 7.17-7.22 (m, 2H), 7.09-7.13 (m, 3H), 5.32-5.38 (m, 1H, 6-H), 5.19-5.23 (m, 1H, 5-H), 3.49 (s, 3H, OCH\textsubscript{3}), 3.06-3.10 (m, 1H, 3-H), 2.58-2.63 (m, 1H, 2-H), 2.43-2.49 (m, 1H, 2-H), 2.19-2.25 (m, 2H, 4-H), 1.52 (d, J = 6.0 Hz, 3H, 7-H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 172.9 (q, 1-C), 144.0 (q), 128.3 (ArCH), 127.5 (ArCH), 127.5 (CH, 5-C), 127.3 (CH, 6-C), 126.4 (ArCH), 51.4 (OCH\textsubscript{3}), 42.1 (CH, 3-C), 40.2 (CH\textsubscript{2}, 2-C), 39.5 (CH\textsubscript{2}, 4-C), 17.9 (CH\textsubscript{3}, 7-C); IR (neat) 3447.7, 2917.6, 1739.3, 1436.5, 1159.8, 968.4, 700.3 cm\textsuperscript{-1}; HRMS (EI) calculated for C\textsubscript{14}H\textsubscript{18}O\textsubscript{2}Na [M]+, m/z: 241.1199, found m/z: 241.1193.
± Methyl 2-((1R,4S)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (164)

Methanesulfonic acid (0.39 mL, 5.70 mmol) was added to a solution of ester 163 (0.25 g, 1.10 mmol) in CH$_2$Cl$_2$ (10 mL) at rt and stirred overnight. The reaction was poured onto a saturated solution of NaHCO$_3$ (10 mL) and extracted with CH$_2$Cl$_2$ (2x50 mL). The organic layer was washed with brine (10 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 164 in a >6:1 ratio of diastereoisomers (170 mg, 71 %);

**Major isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 7.15-7.21 (m, 4H), 3.74 (s, 3H, OCH$_3$), 3.37-3.34 (m, 1H, 1'-H), 2.96-2.98 (m, 1H, 4'-H), 2.68-2.73 (m, 1H, 1-H), 2.54-2.60 (m, 1H, 1-H), 2.01-2.08 (m, 2H, 3'-H), 1.62-1.64 (m, 1H, 2'-H), 1.54-1.57 (m, 1H, 2'-H), 1.30 (d, J = 7.2 Hz, 3H, 5'-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$C 173.2 (q, 2-C), 142.1 (q), 138.7 (q), 128.7 (ArCH), 128.3 (ArCH), 126.2 (ArCH), 125.8 (ArCH), 51.6 (OCH$_3$), 41.9 (CH$_2$, 1-C), 34.8 (CH, 1'-C), 32.2 (CH, 4'-C), 26.8 (CH$_2$, 3'-C), 24.2 (CH$_2$, 2'-C), 23.4 (CH$_3$, 5'-C); IR (neat) 2933.0, 1738.6, 1436.0, 1285.9, 1157.1, 1021.3, 756.9 cm$^{-1}$; HRMS (El) calculated for C$_{14}$H$_{18}$O$_2$Na [M]+, m/z: 241.1199, found m/z: 241.1192.

**Minor isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 1.35 (d, J = 6.8 Hz, 3H, 5'-H).
± (R)-methyl 2-((1R,4S)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (165)

LDA (1.6M in hexanes 2.38 mL, 3.57 mmol) was added to a solution of ester 164 (260 mg, 1.10 mmol) in anhydrous THF (20 mL) at -45 °C. The solution was stirred for 1 hr before Mel (0.44 mL, 7.10 mmol) in THF (10 mL) was added dropwise. The reaction was stirred for a further 2 hrs before quenching with MeOH (10 mL) and water (10 mL). The organic layer was separated and washed with brine (10 mL), dried (MgSO4) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 165 (0.22 g, 81 %);

Major isomer:

**1H NMR** (400 MHz, CDCl3): δH 6.99-7.17 (m, 4H), 3.57 (s, 3H, OCH3), 3.22-3.27 (m, 1H, 1'-H), 2.91-2.98 (m, 1H, 2'-H), 2.77-2.84 (m, 1H, 4'-H), 1.84-1.92 (m, 1H, 3'-H), 1.72-1.79 (m, 1H, 2'-H), 1.58-1.66 (m, 1H, 2'-H), 1.30-1.38 (m, 1H, 3'-H), 1.20 (d, J = 7.2 Hz, 3H, 5'-H), 0.93 (d, J = 6.4 Hz, 3H, 3-H); **13C NMR** (100 MHz, CDCl3): δC 176.4 (q, 1-C), 142.9 (q), 137.6 (q), 129.7 (ArCH), 127.7 (ArCH), 126.0 (ArCH), 125.6 (ArCH), 51.5 (OCH3), 44.0 (CH, 2-C), 40.4 (CH, 1'-C), 32.6 (CH, 4'-C), 29.5 (CH2, 3'-C), 23.2 (CH3, 5'-C), 22.1 (CH2, 2'-C), 12.0 (CH3, 3-C); **IR** (neat) 2949.2, 1736.2, 1445.1, 1195.0, 1166.7, 757.8 cm⁻¹; **HRMS** (EI) calculated for C15H20O2Na [M]+, m/z: 255.1356, found m/z: 255.1346.

Minor isomer:

**1H NMR** (400 MHz, CDCl3): δH 3.59 (s, 3H, OCH3), 1.18 (d, J = 7.2 Hz, 3H, 5'-H), 1.05 (d, J = 7.2 Hz, 3H, 3-H).
6.3 - Method development – α-methyl cinnamyl synthesis

± (3S,4R,E)-2,4-Dimethyl-1-phenylhexa-1,5-dien-3-ol (154b)

Crotyltrichlorosilane (0.96 g, 5.00 mmol) was added dropwise to a solution of α-methylcinnamaldehyde (0.54 mL, 4.00 mmol) in DMF (2.5 mL) and (20 mL) and stirred for 6 hrs. The reaction was quenched with saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (2x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 154b (640 mg, 80 %); ¹H NMR (400 MHz, CDCl₃): δ 7.25 (t, J = 7.6 Hz, 2H, 2'-H), 7.19 (d, J = 7.6 Hz, 2H, 3'-H), 7.14 (t, J = 7.2 Hz, 1H, 1'-H), 6.42 (s, 1H, 1-H), 5.69-5.78 (ddd, J = 17.6, 10.4, 7.2 Hz, 1H, 5-H), 5.03 (d, J = 17.6, Hz, 1H, 6-H), 4.98 (d, J = 10.4 Hz, 1H, 6-H), 3.94 (d, J = 6.4 Hz, 1H, 3-H), 2.42-2.47 (m, 1H, 4-H), 1.79 (s, 3H, 8-H), 1.02 (d, J = 6.8 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δ_c 140.8 (CH, 5-C), 138.8 (q), 137.6 (q), 129.0 (ArCH), 128.1 (ArCH), 126.5 (CH, 1-C), 126.4 (ArCH), 114.6 (CH₂, 6-C), 80.8 (CH, 3-C), 41.3 (CH, 4-C), 14.5 (CH₃, 7-C), 14.1 (CH₃, 8-C); IR (neat) 3401.4, 2930.3, 1668.8, 1492.5, 1387.7, 1096.4, 917.0 cm⁻¹; HRMS (El) calculated for C₁₄H₂₀ONa [M]⁺, m/z: 225.1250, found m/z: 225.1252.
± (3R,E)-2-methyl-3-phenylhept-5-enal (170)

A 30 % suspension of KH in mineral oil (2.49 g, 62.00 mmol) was washed with THF (3x10 mL). Dry THF (25 mL) was added to the KH. Alcohol 154b (1.1 g, 5.50 mmol) and 18-crown-6 (0.58 g, 2.20 mmol) were successively added to the solution and it was heated overnight at 50 °C. The solution was cooled to ~78 °C and quenched with 2,6-ditertbutyl-4-methylphenol (15.0 g, 70.0 mmol). The solution was poured onto a saturated solution of NH₄Cl (30 mL) and ether (100 mL). The organic layer was separated and washed with brine (20 mL), dried over (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 1% ethyl acetate/petroleum ether) gave the title compound 170 as a 3:1 mixture of diastereoisomers (850 mg, 77 %);

Major isomer:

1H NMR (400 MHz, CDCl₃): δH 9.70 (d, J = 2.8 Hz, 1H, 1-H), 7.12-7.37 (m, 5H), 5.39-5.48 (m, 1H, 6-H), 5.20-5.28 (m, 1H, 5-H), 3.00-3.05 (m, 1H, 3-H), 2.61-2.69 (m, 1H, 2-H), 2.40 (m, 2H, 4-H), 1.58 (d, J = 7.2 Hz, 3H, 7-H), 0.89 (d, J = 6.9 Hz, 3H, 8-H); 13C NMR (CDCl₃) δ 204.7 (CH, 1-C), 126.6 (q), 128.3 (ArCH), 128.4 (ArCH), 127.5 (ArCH), 128.1, 50.9, 46.6, 37.1 (CH₂, 4-C), 17.8 (CH₃, 7-C), 11.5 (CH₃, 8-C); IR (neat) 2920.4, 1711.3, 1455.1, 1197.6 cm⁻¹; HRMS (El) calculated for C₁₄H₁₈ONa [M⁺], m/z: 225.1250, found m/z: 225.1248.

Minor isomer:

1H NMR (400 MHz, CDCl₃): δH 9.60 (d, J = 2.0 Hz, 1H, 1-H), 1.58 (d, J = 7.2 Hz, 3H, 7-H), 1.12 (d, J = 7.0 Hz, 3H, 8-H).
± (2E,4R,5R,7E)-Methyl 4-methyl-5-phenylisooctanoic d,7-dienoate (171)

Methyl(triphenylphosphoranylidene)acetate (5.11 g, 15.30 mmol) was added to a solution of aldehyde 170 (1.55 g, 7.60 mmol) in water (20 mL) and heated at 90 °C overnight. The reaction was cooled and poured onto saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (2x100 mL). The organic layers were dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a clear oil 171 in a 3:1 ratio of diastereoisomers (1.60 g, 81 %);

**Major isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): δᵦ 6.99-7.25 (m, 5H), 6.75 (dd, J = 16.0, 8.0 Hz, 1H, 3-H), 5.62 (d, J = 16.0 Hz, 1H, 2-H), 5.30-5.39 (m, 1H, 8-H), 5.12-5.23 (m, 1H, 7-H), 3.62 (s, 3H, OCH₃), 2.56-2.59 (m, 1H, 4-H), 2.41-2.48 (m, 1H, 6-H), 2.27-2.32 (m, 1H, 5-H), 2.10-2.20 (m, 1H, 6-H), 1.49 (d, J = 8.0 Hz, 3H, 9-H), 0.93 (d, J = 8.0 Hz, 3H, 10-H); \(^1\)C NMR (100 MHz, CDCl₃): δₓ 167.0 (q, 1-C), 152.2 (CH), 141.7 (q), 128.7 (CH), 128.0 (CH), 126.3 (CH, 3-C), 126.3 (CH), 120.5 (CH, 2-C), 51.0 (CH, 4-C), 51.0 (OCH₃), 40.6, 35.6 (CH₃, 6-C), 17.9 (CH₃, 9-C), 17.8 (CH, 5-C), 17.3 (CH₃, 10-C); IR (neat) 2962.6, 1723.7, 1654.3, 1435.3, 1271.1, 1196.0, 967.6, 701.4 cm⁻¹; HRMS (El) calculated for C₁₇H₂₂O₂Na [M⁺], m/z: 281.1512, found m/z: 281.1518.

**Minor isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): δᵦ 6.85 (dd, J = 16.0, 8.0 Hz, 1H, 3-H), 5.75 (d, J = 16.0 Hz, 1H, 2-H), 3.67 (s, 3H, OCH₃), 1.44 (d, J = 8.0 Hz, 3H, 9-H), 0.89 (d, J = 8.0 Hz, 3H, 10-H).
± \((R,E)\)-Methyl 4-\((1R,4S)\)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (172)

Methanesulfonic acid (0.74 mL, 11.50 mmol) was added dropwise to a solution of 171 (0.60 g, 2.30 mmol) in CH\(_2\)Cl\(_2\) (25 mL) at -90 °C then warmed to room temperature. The reaction mixture was poured onto a saturated solution of NaHCO\(_3\) (20 mL) and extracted with CH\(_2\)Cl\(_2\) (2x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the title compound as a clear oil 172 in a 3:1 mixture of diastereoisomers (0.54 g, 91%);

**Major isomer 172b:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ\(_H\) 7.13-7.24 (m, 4H), 6.85 (dd, J = 12.4, 4.8 Hz, 1H, 3'-H), 5.76 (d, J = 12.4 Hz, 1H, 2'-H), 3.71 (s, 3H, OCH\(_3\)), 3.01-3.08 (m, 1H, 4'-H), 2.83-2.92 (m, 1H, 1'-H), 1.92-1.99 (m, 1H, 4-H), 1.58-1.64 (m, 2H, 3'-H), 1.37-1.43 (m, 2H, 2'-H), 1.28 (d, J = 7.0 Hz, 3H, 5'-H), 0.91 (d, J = 6.5 Hz, 3H, 5-H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ\(_C\) 167.1 (q), 152.6 (CH, 3-C), 142.9 (q), 137.8 (q), 128.6 (ArCH), 127.7 (ArCH), 126.0 (ArCH), 125.3 (ArCH), 120.3 (CH, 2-C), 51.4 (OCH\(_3\)), 43.0 (CH, 4'-C), 41.0 (CH, 1'-C), 32.3 (CH, 4-C), 29.2 (CH\(_2\), 3'-C), 22.7 (CH\(_2\), 2'-C), 22.4 (CH\(_3\), 5'-C), 17.7 (CH\(_3\), 5-C); IR (neat) 2961.7, 1723.4, 1435.5, 1271.3, 1173.7, 967.9 cm\(^{-1}\); HRMS (EI) calculated for C\(_{17}\)H\(_{22}\)O\(_2\)Na [M]\(^+\), m/z: 281.1512, found m/z: 281.1510.

**Minor isomer 172a:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ\(_H\) 5.85 (d, J = 12.4 Hz, 1H, 2'-H), 3.77 (s, 3H, OCH\(_3\)), 1.30 (d, J = 7.5 Hz, 3H, 5'-H), 1.17 (d, J = 6.0 Hz, 3H, 5-H).
± (R)-Methyl 4-(((1R,4S)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanoate (175)

A solution of ester 174 (0.83 g, 3.20 mmol) was circulated for 3.5 hours through an H-Cube (set at 2.0 mL/min, Full hydrogen, rt) equipped with a cartridge containing catalyst Pd/C 10 %. The solution was concentrated in vacuo to afford the title compound as a colourless oil 175 in a 3:1 mixture of diastereoisomers (0.75 g, 90 %);

**Major isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 7.03-7.18 (m, 4H), 3.53 (s, 3H, OCH$_3$), 2.81-2.86 (m, 1H, 4'-H), 2.30-2.38 (m, 2H), 2.08-2.21 (m, 2H), 1.81-1.91 (m, 2H), 1.52-1.61 (m, 2H), 1.34-1.43 (m, 2H), 1.20 (d, $J = 8.0$ Hz, 3H, 5'-H), 0.92 (d, $J = 8.0$ Hz, 3H, 5-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ$_C$ 174.3 (q, 1-C), 143.1 (q), 139.2 (q), 127.7 (ArCH), 127.0 (ArCH), 125.5 (ArCH), 125.3 (ArCH), 51.4 (OCH$_3$), 43.7, 42.2, 36.6, 32.9, 32.7, 30.9, 27.0, 22.1 (CH$_3$, 5'-C), 17.9 (CH$_3$, 5-C); IR (neat) 2955.5, 1739.3, 1435.8, 1197.4, 748.1 cm$^{-1}$; HRMS (El) calculated for C$_{17}$H$_{24}$O$_2$Na [M]+, m/z: 283.1669, found m/z: 283.1666.

**Minor isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 3.62 (s, 3H, OCH$_3$), 2.92-2.98 (m, 1H, 4'-H), 1.21 (d, $J = 8.0$ Hz, 3H, 5'-H), 0.58 (d, $J = 8.0$ Hz, 3H, 5-H).
\( \pm (R)-4-((1R,4S)-4\text{-Methyl}-1,2,3,4\text{-tetrahydronaphthalen}-1\text{-yl})\text{pentan-1-ol (176)} \)

DIBAL (1M in hexanes, 14.4 mL, 14.40 mmol) was added to a solution of 175 (0.75 g, 2.80 mmol) in anhydrous CH\(_2\)Cl\(_2\) (25 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL) and 5M HCl (20 mL) and extracted with CH\(_2\)Cl\(_2\) (3x100 mL). The organic layer was washed with brine (50 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 176 in a 1:0.8 mixture of diastereoisomers (0.53 g, 81%);

**Major isomer:**

\( ^1\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta \text{H 7.04-7.20 (m, 4H), 3.61 (t, J = 6.8 Hz, 2H, 1-H), 3.41-3.47 (m, 2H), 2.72-2.74 (m, 1H, 4'-H), 1.82-2.10 (m, 1H, 4-H), 1.85-1.86 (m, 2H), 1.48-1.59 (m, 2H), 1.17-1.32 (m, 3H), 1.21 (d, J = 6.8 Hz, 3H, 5'-H), 0.94 (d, J = 6.8 Hz, 3H, 5-H); IR (neat) 3368.4, 2931.6, 1487.2, 1058.8 cm}^\text{1}; \text{HRMS (El) calculated for C}_{16}\text{H}_{24}\text{ONa [M]}^+, \text{m/z: 255.1724, found m/z: 255.1714.} \)

**Minor isomer:**

\( ^1\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta \text{H 2.81-2.87 (m, 1H, 4'-H), 1.21 (d, J = 6.8 Hz, 3H, 5'-H), 0.58 (d, J = 6.8 Hz, 3H, 5-H).} \)
6.4 - Erogorgiaene synthesis - Simple cinnamyl

\[\text{(E)-3-}m\text{-Tolylacrylaldehyde (178)}^{[89]}\]

Acrolein diethylacetal (1.82 mL, 12.00 mmol), \(^6\text{Bu}_4\text{NOAc}\) (2.4 g, 8.00 mmol), palladium acetate (0.026 g, 0.10 mmol), KCl (0.3 g, 4.00 mmol), \(K_2\text{CO}_3\) (0.82 g, 6.00 mmol) were added in succession to a stirred solution of 3-iodotoluene (0.5 mL, 4.00 mmol) in DMF (8 mL). The reaction was stirred at 90 °C overnight. The reaction was cooled to room temperature and HCl (10 mL) added, diluted with ethyl acetate (50 mL) and water (10 mL). The organic layer was washed with brine (10 mL), dried (\(\text{Na}_2\text{SO}_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as yellow oil 178 (0.54 g, 93 %);

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta_H 9.72\) (d, \(J = 7.6\) Hz, 1H, 1-H), 7.47 (d, \(J = 15.6\) Hz, 1H, 3-H), 7.39-7.40 (m, 2H), 7.34 (t, \(J = 7.6\) Hz, 1H, 7-H), 7.28 (d, \(J = 3.6\) Hz, 1H), 6.73 (dd, \(J = 16.0, 7.6\) Hz, 1H, 2-H), 2.42 (s, 3H, 5-H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta_C 193.9\) (CHO, 1-C), 153.1, 138.6 (q), 133.4 (q), 132.1, 129.0, 128.8, 128.1, 125.7, 21.3 (CH\(_3\), 5-C); \(\text{IR}\) (neat) 2816.1, 1677.3, 1125.4, 972.6 cm\(^{-1}\); \textbf{HRMS} (El) calculated for C\(_{10}\)H\(_{10}\)ONa [M]\(^{+}\), \(m/z\): 169.0624, found \(m/z\): 169.0623.
± (3R,4R,E)-4-Methyl-1-m-tolylhexa-1,5-dien-3-ol (179)

Crotyltrichlorosilane (2.03 g, 10.80 mmol) was added to a solution of 178 (1.06 g, 7.20 mmol) in anhydrous DMF (1.85 mL) and CH₂Cl₂ (10 mL) and stirred at room temperature for 24 hrs. The reaction was quenched with NaHCO₃ (10 mL) and diluted with CH₂Cl₂ (50 mL) and water (20 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2x50 mL). The organic layers were combined and washed with brine (20 mL), dried (Na₂SO₃) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as orange oil 179 (1.24 g, 85 %); ¹H NMR (400 MHz, CDCl₃): δH 6.85-7.00 (m, 4H), 6.48 (d, J = 16.0 Hz, 1H, 1-H), 6.14 (dd, J = 16.0, 6.4 Hz, 1H, 2-H), 5.72-5.81 (ddd, J = 16.8, 9.2, 8.4 Hz, 1H, 5-H), 5.08 (d, J = 8.4 Hz, 1H, 6-H), 5.05 (s, 1H, 6-H), 4.11-4.13 (m, 1H, 3-H), 2.38-2.43 (m, 1H, 4-H), 2.27 (s, 3H, 8-H), 0.99 (d, J = 17.6 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 139.9, 138.1 (q), 136.6 (q), 131.3, 129.6, 128.4, 127.1, 123.6, 116.0, 75.8, 43.9, 21.4, 14.8; IR (neat) 3381.4, 2967.6, 1604.2, 1453.2, 964.4 cm⁻¹; HRMS (El) calculated for C₁₄H₁₈ONa [M⁺]: m/z: 225.1248, found m/z: 225.1248.
± (R,E)-3-m-Tolyhept-5-enal (180)

A 30 % suspension of KH in mineral oil (1.42 g, 35.60 mmol) was washed with anhydrous THF (3x5 mL). Anhydrous THF (10 mL) was added to the KH along with molecular sieves 4Å. Alcohol 179 (0.38 g, 1.80 mmol) followed by 18-crown-6 (2.11 g, 6.00 mmol) was added to the solution and heated for 3 hrs at 50 °C. The solution was cooled to -78 °C and quenched with methanol (10 mL). The solution was poured into a solution of ether (100 mL) and NH₄Cl (50 mL). The organic layer was separated and washed with brine (20 mL), dried (Na₂SO₃) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as a light orange oil 180 in a 6:1 E/Z ratio (0.28 g, 74 %); ¹H NMR (400 MHz, CDCl₃): δₜ 9.58 (t, J = 2.0 Hz, 1H, 1-H), 7.09-7.13 (m, 1H), 6.89-6.95 (m, 3H), 5.34-5.40 (m, 1H, 6-H), 5.19-5.25 (m, 1H, 5-H), 3.09-3.13 (m, 1H, 3-H), 2.55-2.69 (m, 2H, 4-H), 2.25 (s, 3H, 8-H), 2.15-2.22 (m, 2H, 2-H), 1.53 (d, J = 10.8 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 202.2 (CHO, 1-C), 143.7 (q), 138.1 (q), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 127.4 (ArCH), 127.3 (CH, 6-C), 124.4 (CH, 5-C), 49.2, 40.2, 40.0, 21.5 (CH₃, 8-C), 17.9 (CH₃, 7-C); IR (neat) 2916.9, 1724.1, 1438.4, 1196.7, 968.5 cm⁻¹; HRMS (EI) calculated for C₁₄H₁₈ONa [M⁺], m/z: 225.1261, found m/z: 225.1252.
± (R,E)-3-m-Tolylhept-5-enoic acid (181)

Aldehyde 180 (0.11 g, 0.50 mmol) was added to a solution of t-butyl alcohol (10 mL) and 2-methyl-2-butene (0.26 mL, 2.40 mmol). A solution of sodium chlorite (0.04 g, 0.40 mmol) and dihydrogen orthophosphate (0.04 g, 0.30 mmol) in water (5 mL) was added over a 10 minute period to the reaction. The solution was then stirred overnight at room temperature. The solvent was removed under vacuo and the residue dissolved in water (50 mL), the solution was extracted with hexane (3x20 mL). The aqueous layer was acidified to pH2 with 5M HCl and extracted with ether (3x20 mL). The combined ether layers were washed with water, dried (MgSO₄) and concentrated in vacuo producing acid 181 as a light yellow oil (0.05 g, 50 %); ¹H NMR (400 MHz, CDCl₃): δH 7.06-7.10 (m, 1H), 6.88-6.93 (m, 3H), 5.32-5.38 (m, 1H, 6-H), 5.17-5.23 (m, 1H, 5-H), 2.99-3.03 (m, 1H, 3-H), 2.61 (dd, J = 16.0, 6.8 Hz, 1H, 4-H), 2.47 (dd, J = 16.0, 8.4 Hz, 1H, 4-H), 2.24 (s, 3H, 8-H), 2.15-2.22 (m, 2H, 2-H), 1.51 (d, J = 7.2 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 177.8 (q, 1-C), 142.5 (q), 136.9 (q), 127.3 (ArCH), 127.2 (CH, 5-C), 127.1 (ArCH), 126.6 (CH, 6-C), 126.2 (ArCH), 123.2 (ArCH), 40.6 (CH, 3-C), 39.0 (CH₂, 4-C), 38.6 (CH₂, 2-C), 20.3 (CH₃, 8-C), 16.8 (CH₃, 7-C); IR (neat) 3023.8, 2918.3, 1708.0, 1437.7, 1297.8 cm⁻¹; HRMS (El) calculated for C₁₄H₁₇O₂ [M⁺], m/z: 217.1234, found m/z: 217.1223.
5,6-dimethyl-2a,3,4,5-tetrahydroacenaphthylen-1(2H)-one + 5,8-Dimethyl-2a,3,4,5-tetrahydroacenaphthylen-1(2H)-one:

CF₃SO₃H (0.2 mL) was added to a solution of 181 (0.05 g, 0.20 mmol) in CH₂Cl₂ (35 mL) at -78 °C and allowed to warm to room temperature overnight. The reaction solution was poured onto saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (2x20 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by preparative TLC on glass backed silica gel plates (eluting with 10 % ethyl acetate/petroleum ether) gave the title compounds 182a (0.001 g) and 182b (0.001 g);

(182a):

¹H NMR (400 MHz, CDCl₃): δ_H 7.23 (d, J = 7.6 Hz, 1H, 8-H), 6.98 (d, J = 7.6, 1H, 7-H), 2.96-3.04 (m, 2H), 2.74-2.83 (m, 2H), 2.50 (s, 3H, 9-H), 2.19-2.26 (m, 1H), 2.09-2.15 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H, 10-H); HRMS (EI) calculated for C₁₄H₁₆ONa [M]+, m/z: 223.1098, found m/z: 223.1090.

(182b):

¹H NMR (400 MHz, CDCl₃): δ_H 7.38 (d, J = 7.6 Hz, 1H, 6-H), 7.09 (d, J = 7.6 Hz, 1H, 7-H), 3.00-3.08 (m, 2H), 2.85 (dd, J = 18.0, 6.8 Hz, 1H, 5-H), 2.33 (s, 3H, 9-H), 2.11-2.28 (m, 2H), 1.50-1.59 (m, 2H, 4-H), 1.24 (d, J = 6.8 Hz, 3H, 10-H); HRMS (EI) calculated for C₁₄H₁₆ONa [M]+, m/z: 223.1098, found m/z: 223.1090.
± (R,E)-2-(2-m-tolylhex-4-enyl)-1,3-dithiolane (183)

1,2-ethanedithiol (0.33 ml, 4.00 mmol) was added to a solution of 180 (0.60 g, 2.90 mmol) in anhydrous CH₂Cl₂ (10 ml) and FeCl₃•SiO₂ (1.0 g). The reaction was stirred under N₂ at room temperature for 15 minutes. The reaction was quenched with 2M NaOH (10 ml) and extracted with CH₂Cl₂ (3x20 ml) The organic layer was washed with brine (20 ml), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a pale yellow oil 183 (0.37 g, 71 %); ¹H NMR (400 MHz, CDCl₃): δH 7.11 (t, J = 7.6 Hz, 1H), 6.88-6.59 (m, 3H), 5.19-5.24 (m, 1H, 5-H), 5.30-5.37 (m, 1H, 4-H), 4.06 (t, J = 7.6 Hz, 1H, 1'-H), 3.00-3.32 (m, 4H, 3'-H), 2.59-2.65 (m, 1H, 2-H), 2.26 (s, 3H, 7-H), 2.16-2.18 (m, 2H, 3-H), 2.02 (t, J = 7.6 Hz, 2H, 1-H), 1.52 (d, J = 5.6 Hz, 3H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δC 143.6 (q), 137.9 (q), 128.8, 128.5, 128.3, 127.2, 126.8, 124.8, 51.6, 46.1, 45.4, 40.1, 38.3, 38.1, 21.5, 17.9; IR (neat) 2920.4, 1605.9, 1436.9, 966.2, 705.6 cm⁻¹; HRMS (EI) calculated for C₁₆H₂₂O₂Na [M⁺], m/z: 317.1004, found m/z: 317.1003.

2-((4,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-1,3-dithiolane & 2-((4,5-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-1,3-dithiolane (184)

CF₃SO₃H (0.3 mL) was added to a solution of 183 (0.55 g, 1.90 mmol) in CH₂Cl₂ (10 mL) and was stirred at -78 °C before being allowed to warm to room temperature overnight. The reaction solution was poured into aqueous NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x20 ml) The organic layers were combined and washed with brine (20 ml), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as an inseparable mixture of the two products, (0.41 g, 74 %);
6.5 - Erogorgiaene synthesis – α-methyl cinnamyl

(\textit{E})-Ethyl 2-methyl-3-\textit{m}-tolylacrylate (239)

(Carbethoxyethylidene)triphenylphosphorane (2.8 g, 8.00 mmol) was added to a solution of \textit{m}-tolualdehyde (0.46 g, 4.00 mmol) in water (10 mL). The reaction was stirred at 90 °C for 3 days. The reaction was cooled to room temperature and extracted with CH\(_2\)Cl\(_2\) (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 239 (0.80 g, 99 %); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)\(_\text{H} 7.60\) (s, 1H, 3-H), 7.21 (t, \(J = 7.6\) Hz, 1H, 7-H), 7.13-7.12 (m, 2H), 7.06 (d, \(J = 7.2\) Hz, 1H, 4-H), 4.19 (q, \(J = 7.2\) Hz, 2H, 10-H), 2.30 (s, 3H, 5-H), 2.04 (s, 3H, 9-H), 1.27 (t, \(J = 7.2\) Hz, 3H, 11-H); \(^1\)^3C NMR (100 MHz, CDCl\(_3\)): \(\delta\)\(_C 168.7\) (q, 1-C), 138.8 (CH, 3-C), 137.9 (q), 135.9 (q), 130.3 (ArCH), 129.0 (ArCH), 128.4 (q), 128.2 (ArCH), 126.6 (ArCH), 60.8 (CH\(_2\), 10-C), 21.4 (CH\(_3\), 5-C), 14.3 (CH\(_3\), 11-C), 14.0 (CH\(_3\), 9-C); IR (neat) 2980.8, 1706.1, 1263.6, 1229.0, 1111.2, 791.9 cm\(^{-1}\); HRMS (EI) calculated for C\(_{13}\)H\(_{16}\)O\(_2\)Na [\textit{M}]\(^+\), \(m/z\): 227.1043, found \(m/z\): 227.1041.
(E)-2-Methyl-3-m-tolylprop-2-en-1-ol (240)

DIBAL (1M solution in hexane, 24.0 mL, 23.70 mmol) was added to a solution of 239 (0.97 g, 4.70 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (25 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL), 5M HCl (10 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as a colourless oil 240 (0.63 g, 83 %); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta \text{H} 7.26 (t, J = 8.0 Hz, 1H, 7-H), 7.12-7.13 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H, 3-H), 4.21 (s, 2H, 1-H), 2.38 (s, 3H, 5-H), 1.93 (s, 3H, 9-H), 1.73 (s, OH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta \text{C} 137.6 (q), 137.4 (q), 129.6 (ArCH), 128.0 (CH, 7-C), 127.2 (ArCH), 125.9 (ArCH), 125.1 (CH, 3-C), 76.7 (q), 69.0 (CH\textsubscript{2}, 1-C), 21.4 (CH\textsubscript{3}, 5-C), 15.3 (CH\textsubscript{3}, 9-C); IR (neat) 3324.4, 2917.3, 1603.7, 1446.9, 1068.9, 1010.1, 699.1 cm\textsuperscript{-1}; HRMS (EI) calculated for C\textsubscript{11}H\textsubscript{14}ONa [M]$, m/z: 185.0937, found m/z: 185.0933.
Under an inert atmosphere of N\textsubscript{2} at -78 °C, DMSO (0.31 mL, 4.50 mmol) was added dropwise to a solution of oxalyl chloride (0.54 mL, 5.80 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (20 mL). After stirring for 30 minutes alcohol 240 (0.63 g, 3.80 mmol) was added dropwise and stirred for a further hour. Triethylamine (3.7 mL, 26.60 mmol) was added and the reaction stirred for a further 1 hr. The reaction was warmed to room temperature and quenched with water (10 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3x20 mL). The organic layer was washed with brine (20 mL), dried (MgSO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 186 (0.36 g, 60 %); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textit{\delta}_H 9.60 (s, 1H, 1-H), 7.36-7.37 (m, 3H), 7.22-7.28 (m, 2H), 2.43 (s, 3H, 5-H), 2.10 (s, 3H, 4-H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \textit{\delta}_C 195.6 (CHO, 1-C), 150.1 (CH, 7-C), 138.3 (q), 138.2 (q), 135.1 (q), 130.7 (ArCH), 130.4 (ArCH), 128.6 (ArCH), 127.1 (ArCH), 21.4 (CH\textsubscript{3}, 5-C), 10.9 (CH\textsubscript{3}, 4-C); IR (neat) 2922.8, 1683.3, 1625.9, 1190.9, 1023.0, 784.8, 700.1 cm\textsuperscript{-1}; HRMS (EI) calculated for C\textsubscript{11}H\textsubscript{13}O [M]+, \textit{m/z}: 161.0961, found \textit{m/z}: 161.0958.
± (35,4R,E)-2,4-Dimethyl-1-m-tolyhexa-1,5-dien-3-ol (187)

Crotyltrichlorosilane (1.07 g, 5.70 mmol) was added dropwise to a solution of crude aldehyde 186 (0.63 mL, 3.80 mmol) in DMF (2.5 mL) and (20 mL) and stirred for 6 hrs. The reaction was quenched with NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x20 mL). The organic layer was washed with brine (20 mL), saturated NaHCO₃ (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 187 (0.31 g, 64 %); ¹H NMR (400 MHz, CDCl₃): δH 7.13-7.18 (m, 1H, 12-H), 6.95-7.01 (m, 3H), 6.39 (s, 1H, 1-H), 5.69-5.78 (ddd, J = 17.2, 8.4, 7.2 Hz, 1H, 5-H), 5.03 (d, J = 17.2 Hz, 1H, 6-H), 4.98 (d, J = 10.4 Hz, 1H, 6-H), 3.93 (d, J = 6.4 Hz, 1H, 3-H), 2.41-2.46 (m, 1H, 4-H), 2.27 (s, 3H, 8-H), 1.77 (s, 3H, 10-H), 1.02 (d, J = 6.8 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 140.8 (CH, 5-C), 138.5 (q), 137.6 (q), 137.5 (q), 129.7 (ArCH), 127.9 (CH, 3-C), 127.1 (ArCH), 126.6 (ArCH), 126.0 (ArCH), 114.6 (CH₂, 6-C), 80.9 (CH, 1-C), 41.3 (CH, 4-C), 21.4 (CH₃, 8-C), 14.5 (CH₃, 7-C), 14.1 (CH₃, 10-C); IR (neat) 3400.6, 2961.7, 1603.0, 1447.6, 1009.1, 911.3, 782.2 cm⁻¹; HRMS (El) calculated for C₁₅H₂₀ONa [M]+, m/z: 239.1406, found m/z: 239.1400.
\( \pm (2R,3R,E)-2\text{-methyl-3-\text{m}-tolylhept-5-enal} \) (188)

A 30 % suspension of KH in mineral oil (1.12 g, 28.00 mmol) was washed with anhydrous THF (3x10 mL). Anhydrous THF (25 mL) was added to the KH. Alcohol 187 (0.31 g, 1.40 mmol) and 18-crown-6 (0.18 g, 0.70 mmol) were successively added to the solution and heated overnight at 50 °C. The solution was cooled to -78 °C and quenched with MeOH (10 mL). The solution was poured into a solution of ether (100 mL) and NH₄Cl (50 mL). The organic layer was separated and washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 1 % ethyl acetate/petroleum ether) gave the *title compound* as a colourless oil 188 in a 1:1 ratio of diastereoisomers (0.18 g, 60 %);

**Major isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): δH  9.50 (d, J = 2.4 Hz, 1H, 1-H), 6.83-7.16 (m, 4H), 5.12-5.24 (m, 1H, 6/5-H), 5.31-5.40 (m, 1H, 6/5-H), 2.86-2.92 (m, 1H, 3-H), 2.52-2.57 (m, 1H, 2-H), 2.28-2.35 (m, 2H, 4-H), 2.26 (s, 3H, 9-H), 1.51 (s, 3H, 7-H), 1.02 (d, J = 6.8 Hz, 3H, 8-H); IR (neat) 2917.6, 1722.5, 1606.6, 1451.6, 1162.7, 967.2, 705.0 cm\(^{-1}\); HRMS (EI) calculated for C₁₅H₂₀ONa [M]\(^+\), \(m/z\): 239.1406, found \(m/z\): 239.1402.

**Minor isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): δH  9.60 (d, J = 2.8 Hz, 1H, 1-H), 1.49 (s, 3H, 7-H), 0.79 (d, J = 6.8 Hz, 3H, 8-H).
± (2E,4S,5R,7E)-Methyl 4-methyl-5-m-tolylnona-2,7-dienoate (189)

Methyl(triphenylphosphoranylidene)acetate (0.52 g, 1.57 mmol) was added to a solution of water (10 mL) and aldehyde 188 (0.17 g, 0.70 mmol) and the reaction heated at 90 °C overnight. The reaction mixture was poured onto saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (2x50 mL). The organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the title compound as a clear oil 189 in a 1:1 mixture of diastereoisomers (0.06 g, 28%);

Isomer 1:

¹H NMR (400 MHz, CDCl₃): δH 6.73-7.15 (m, 4H), 6.73-6.87 (m, 1H, 3-H), 5.74 (d, J = 15.6 Hz, 1H, 2-H), 5.30-5.39 (m, 1H, 8-H), 5.13-5.24 (m, 1H, 7-H), 5.02-5.41 (m, 3H, 6/5-H), 3.62 (s, 3H, OCH₃), 2.40-2.48 (m, 1H, 4-H), 2.25 (s, 3H, 12-H), 1.49 (d, J = 5.2 Hz, 3H, 9-H), 0.75 (d, J = 6.8 Hz, 3H, 10-H); IR (neat) 2917.9, 1723.7, 1654.8, 1435.6, 1270.2, 1172.1, 967.5, 704.2 cm⁻¹; HRMS (EI) calculated for C₁₈H₂₄O₂Na [M]+, m/z: 295.1679, found m/z: 295.1662.

Isomer 2:

¹H NMR (400 MHz, CDCl₃): δH 5.62 (d, J = 15.6 Hz, 1H, 2-H), 2.24 (s, 3H, 12-H), 1.44 (d, J = 8.0 Hz, 3H, 9-H), 0.92 (d, J = 6.8 Hz, 3H, 10-H).
(E)-Methyl 4-(4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (190)

Methanesulfonic acid (0.1 mL) was added to a solution of 189 (0.06 g, 0.20 mmol) in CH₂Cl₂ (10 mL) at -78 °C and warmed to room temperature. The reaction was poured onto a saturated solution of NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x10 mL). The organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo. ¹H NMR analysis of the product shows a complex mixture believed to be regio and stereo isomers (Shown above).
6.6 - Method development – synthesis with aromatic bromine (α-methyl):

(E)-Ethyl 3-(2-bromophenyl)-2-methylacrylate (241)

(Carbethoxyethylidene)triphenylphosphorane (2.80 g, 8.00 mmol) was added to a solution of 2-bromobenzaldehyde (0.49 g, 4.00 mmol) in water (10 mL). The reaction was stirred at 90 °C for 3 days. The reaction was cooled and poured onto a saturated solution of NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the title compound as a colourless oil 241 (1.00 g, 99%); ¹H NMR (400 MHz, CDCl₃): δH 7.72 (s, 1H, 3-H), 7.63 (d, J = 8.0 Hz, 1H), 7.29-7.36 (m, 1H), 7.20 (t, J = 8.4 Hz, 1H), 4.31 (q, J = 14.4, 7.2 Hz, 2H, 5-H), 1.99 (s, 3H, 4-H), 1.38 (t, J = 7.2 Hz, 3H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δC 168.0 (q, 1-C), 137.9 (ArCH), 136.3 (q), 132.7 (CH, 3-C), 130.5 (ArCH), 130.3 (q), 129.4 (ArCH), 127.0 (ArCH), 124.1 (q), 61.0 (CH₂, 5-C), 14.3 (CH₃, 6-C), 13.9 (CH₃, 4-C); IR (neat) 3411.3, 2981.7, 1705.6, 1466.2, 1250.6, 1109.3, 759.8 cm⁻¹; HRMS (EI) calculated for C₁₂H₁₄O₂Br, C₁₂H₁₄O₂Br [M]+, m/z: 269.0172, 271.0152, found m/z: 269.0168, 271.0145.
(E)-3-(2-Bromophenyl)-2-methylprop-2-en-1-ol (242)

DIBAL (1M in hexanes, 23.0 mL, 22.80 mmol) was added to a solution of 241 (1.23 g, 4.50 mmol) in anhydrous CH₂Cl₂ (25 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL) and 5M HCl (10 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 20 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 242 (0.99 g, 97 %); ¹H NMR (400 MHz, CDCl₃): δₜ 7.49 (d, J = 8.0 Hz, 1H), 7.17-7.20 (m, 2H), 6.99-7.04 (m, 1H), 6.46 (s, 1H, 3-H), 4.15 (s, 2H, 1-H), 1.77 (s, OH), 1.70 (s, 3H, 4-H); ¹³C NMR (100 MHz, CDCl₃): δC 139.2 (q), 137.6 (q), 132.5 (ArCH), 130.7 (ArCH), 128.1 (ArCH), 126.8 (ArCH), 124.4 (CH, 3-C), 124.2 (q), 68.2 (CH₂, 1-C), 15.0 (CH₃, 4-C); IR (neat) 3324.8, 2914.3, 1465.9, 1024.5, 749.2 cm⁻¹; HRMS (EI) calculated for C₁₀H₁₅NOBr, C₁₀H₁₅NOBr [M⁺], m/z: 244.0332, 246.0312, found m/z: 244.0327, 246.0304.
(E)-3-(2-Bromophenyl)-2-methylacrylaldehyde (194)\(^\text{92}\)

Under an inert atmosphere at \(-78 \, ^\circ\text{C}\), DMSO (2.81 mL, 39.60 mmol) was added dropwise to a solution of oxalyl chloride (19.8 mL, 39.60 mmol) in anhydrous CH\(_2\)Cl\(_2\) (50 mL). After stirring for 30 minutes alcohol 242 (4.51 g, 19.80 mmol) was added dropwise and stirred for a further hour. Triethylamine (13.0 mL, 99.00 mmol) was added and the reaction stirred for a further 1 hour. The reaction was warmed to room temperature and quenched with water (20 mL) and extracted with CH\(_2\)Cl\(_2\) (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO\(_4\)) and concentrated in \textit{vacuo}. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the \textit{title compound} as a colourless oil 194 (3.26 g, 73 %); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) H, 9.70 (s, 1H, 1-H), 7.69 (d, \(J = 8.0\) Hz, 1H), 7.40-7.48 (m, 3H), 7.27 (t, \(J = 7.6\) Hz, 1H), 1.96 (s, 3H, 4-H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) C 195.2 (CHO, 1-C), 148.0 (CH), 139.9 (q), 135.0 (q), 133.1 (CH), 130.4 (CH), 130.3 (CH), 127.2 (CH), 124.5 (q), 10.8 (CH\(_3\), 4-C); \textit{IR} (neat) 1684.0, 1434.8, 1185.4, 1013.7, 753.9 cm\(^{-1}\); \textit{HRMS} (EI) calculated for C\(_{10}\)H\(_{10}\)OBr [M]\(^+\), \(m/z\): 224.9910, found \(m/z\): 224.9904.
± (35,4R,E)-1-(2-bromophenyl)-2,4-dimethylhexa-1,5-dien-3-ol (195)

Crotyltrichlorosilane (4.0 g, 21.70 mmol) was added to a solution of aldehyde 194 (3.26 mL, 14.40 mmol) in DMF (5.0 mL) and (25 mL) under N₂ and stirred for 6 hrs. The reaction was quenched with saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried over (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 195 (2.81 g, 70 %); ¹H NMR (400 MHz, CDCl₃): δ, 7.50 (d, J = 8.0 Hz, 1H), 7.14-7.21 (m, 2H), 7.00-7.04 (m, 1H), 6.43 (s, 1H, 1-H), 5.75-5.84 (ddd, J = 17.6, 10.4, 5.2 Hz, 1H, 5-H), 4.99-5.08 (dd, J = 17.6, 5.2 Hz, 2H, 6-H), 4.01 (d, J = 6.0 Hz, 1H, 3-H), 2.43-2.48 (m, 1H, 4-H), 1.65 (s, 3H, 8-H), 1.06 (d, J = 6.8 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δ, 140.9 (CH, 5-C), 140.2 (q), 137.8 (q), 132.4 (ArCH), 130.7 (ArCH), 128.1 (ArCH), 126.8 (ArCH), 126.1 (CH, 1-C), 124.2 (q), 114.8 (CH₂, 6-C), 79.9 (CH, 3-C), 41.3 (CH, 4-C), 14.3 (CH₃, 7-C), 14.0 (CH₃, 8-C); IR (neat) 3429.3, 2975.1, 1465.8, 1024.4, 914.0, 750.8 cm⁻¹; HRMS (El) calculated for C₁₄H₁₇OBrNa, C₁₄H₁₉OBrNa [M⁺], m/z: 303.0355, 305.0335, found m/z: 303.0349, 305.0328.

± (3R,E)-3-(2-bromophenyl)-2-methylhept-5-enal (196)

A 30 % suspension of KH in mineral oil (8.0 g, 200 mmol) was washed with THF (3x10 mL). Dry THF (50 mL) was added to the KH. Alcohol 195 (2.81 g, 10.00 mmol) and 18-crown-6 (1.32 g, 5.0 mmol) were successively added to the solution and heated overnight at 50 °C. The solution was cooled to -78 °C and quenched with MeOH (10 mL). The solution was poured into a solution of ether (100 mL) and saturated NH₄Cl (50 mL). The organic layer was separated and washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as yellow oil 196 in a mixture of 2 isomers and by-products (1.53 g, 55 %);
Major isomer:

$^1H$ NMR (400 MHz, CDCl$_3$): $\delta$H 9.50 (d, $J = 2.0$ Hz, 1H, 1-H), 7.01-7.51 (m, 4H), 5.33-5.35 (m, 1H, 5-H), 5.13-5.17 (m, 1H, 6-H), 2.92-2.94 (m, 1H), 2.56-2.59 (m, 1H, 2-H), 2.29-2.36 (m, 1H), 1.46-1.50 (m, 2H, 4-H), 1.03 (d, $J = 7.2$ Hz, 3H, 7-H), 0.79 (d, $J = 7.2$ Hz, 3H, 8-H); IR (neat) 3429.7, 1723.4, 1452.3, 967.1, 701.7 cm$^{-1}$; HRMS (EI) calculated for C$_{14}$H$_{17}$OBrNa [M]+, m/z: 303.0355, found m/z: 303.0346.

Minor isomer:

$^1H$ NMR (400 MHz, CDCl$_3$): $\delta$H 9.58 (d, $J = 1.6$ Hz, 1H, 1-H), 1.01 (d, $J = 7.2$ Hz, 3H, 7-H), 0.84 (d, $J = 6.8$ Hz, 3H, 8-H).

$\pm$ (2E,7E)-Methyl 5-(2-bromophenyl)-4-methylnona-2,7-dienoate (197)

Methyl(triphenylphosphoranylidene)acetate (3.67 g, 11.00 mmol) was added to a solution of aldehyde 196 (1.53 g, 5.40 mmol) and water (25 mL) and heated at 90 °C overnight. The reaction was cooled and poured onto a saturated solution of NaHCO$_3$ (20 mL) and extracted with CH$_2$Cl$_2$ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4% ethyl acetate/petroleum ether) gave the title compound as a clear oil 197 (1.59 g, 87%).

Major isomer:

$^1H$ NMR (400 MHz, CDCl$_3$): $\delta$H 6.99-7.23 (m, 4H), 6.75 (dd, $J = 7.6$, 7.6 Hz, 1H, 3-H), 5.62 (d, $J = 15.2$ Hz, 1H, 2-H), 5.14-5.33 (m, 2H, 7/8-H), 3.62 (s, 3H, OCH$_3$), 2.56-2.59 (m, 2H), 2.26-2.31 (m, 1H), 1.41-1.51 (m, 3H, 9-H), 0.96 (d, $J = 6.8$ Hz, 3H, 10-H); IR (neat) 2963.1, 1723.8, 1435.5, 1271.3, 1172.8, 967.1, 701.7 cm$^{-1}$; HRMS (EI) calculated for C$_{17}$H$_{21}$O$_2$BrNa, C$_{17}$H$_{21}$O$_2$BrNa [M]+, m/z: 359.0617, 361.0597, found m/z: 359.0609, 361.0588.

Minor isomer:

$^1H$ NMR (400 MHz, CDCl$_3$): $\delta$H 6.85 (dd, $J = 12.4$, 12.0 Hz, 1H, 3-H), 5.75 (d, $J = 16.0$ Hz, 1H, 2-H), 3.63 (s, 3H, OCH$_3$), 0.93 (d, $J = 6.4$ Hz, 3H, 10-H).
± (E)-Methyl 4-((1R)-8-bromo-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (198)

Methanesulfonic acid (0.48 mL, 7.40 mmol) was added to a solution of ester 197 (0.50 g, 1.40 mmol) in CH₂Cl₂ (10 mL) at -78 °C and warmed to room temperature. The reaction was poured onto a saturated solution of NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (2x20 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound 198 as a clear oil (0.40 g, 80 %);

**Major isomer:**

\[^1H\text{NMR}\ (400 \text{ MHz, CDCl}_3): \delta_{\text{H}} 6.95-7.17 (m, 3H), 6.75 (dd, J = 6.8, 6.4 Hz, 1H, 3'-H), 5.74 (d, J = 15.6 Hz, 1H, 2'-H), 3.66 (s, 3H, OCH₃), 2.92-2.97 (m, 1H, 4'-H), 2.72-2.81 (m, 2H, 3''-H), 1.83-1.88 (m, 2H), 1.50-1.52 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H, 5'-H), 0.81 (d, J = 6.8 Hz, 3H, 5''-H); IR (neat) 2958.9, 1724.4, 1434.6, 1274.0, 1175.2, 986.4, 753.0 cm\(^{-1}\); HRMS (El) calculated for C₁₇H₂₁O₂BrNa, C₁₇H₂₁O₂⁸¹BrNa [M]+, m/z: 359.0617, 361.0597, found m/z: 359.0605, 361.0584.**

**Minor isomer:**

\[^1H\text{NMR}\ (400 \text{ MHz, CDCl}_3): \delta_{\text{H}} 3.59 (s, 3H, OCH₃), 1.19 (d, J = 6.8 Hz, 3H, 5'-H), 1.06 (d, J = 6.8 Hz, 3H, 5''-H).**
6.7 - Method development – synthesis with aromatic bromine (simple cinnamyl):

(E)-Methyl 3-(2-bromophenyl)acrylate (243)

2-Bromobenzaldehyde (1.17 mL, 10.00 mmol) was added to a solution of methyl(triphenylphosphoranylidene)acetate (6.6 g, 20.00 mmol) and water (25 mL) and heated at 90 °C overnight. After cooling, the reaction mixture was poured onto a saturated solution of NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (2x50 mL). The organic layer was washed with brine (200 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 243 in a 4:1 E/Z ratio (2.20 g, 92 %); *¹H NMR (400 MHz, CDCl₃): δH 7.98 (d, J = 16.0 Hz, 1H, 3-H), 7.51-7.55 (m, 2H), 7.13-7.25 (m, 2H), 6.31 (d, J = 16.0 Hz, 1H, 2-H), 3.75 (s, 3H, OCH₃); *¹³C NMR (100 MHz, CDCl₃): δC 166.8 (q), 143.1 (CH, 3-C), 134.4 (q), 133.4 (ArCH), 131.2 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 125.3 (q), 120.6 (CH, 2-C), 51.8 (OCH₃); IR (neat) 2949.6, 1721.8, 1635.2, 1436.0, 1318.2, 1174.9, 1026.7, 760.5 cm⁻¹; HRMS (EI) calculated for C₁₀H₉O₂BrNa, C₁₀H₉O₂¹¹⁷BrNa [M]+, m/z: 262.9678, 264.9658, found m/z: 262.9673, 264.9652.

(E)-3-(2-Bromophenyl)prop-2-en-1-ol (244)

DIBAL 1M in hexane (45.6 mL, 45.60 mmol) was added to a solution of 243 (2.2 g, 9.10 mmol) in anhydrous CH₂Cl₂ (50 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (20 mL) and 5M HCl (20 mL) then extracted with CH₂Cl₂ (3x100 mL). The organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 244 in a 4:1 E/Z ratio (1.57 g, 81 %); *¹H NMR (400 MHz, CDCl₃): δH 7.47 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 6.8 Hz, 1H), 7.03 (t, J = 6.4 Hz, 1H), 6.88 (d, J = 16.0 Hz, 1H, 3-H), 6.24 (dt, J = 16.0, 5.6 Hz, 1H, 2-H), 4.29 (dd, J = 1.6, 5.6 Hz, 2H, 1-H); *¹³C NMR (100 MHz, CDCl₃): δC 136.5 (q), 132.9 (ArCH), 131.6 (CH, 2-C), 129.7 (CH, 3-C), 128.9 (ArCH), 127.5 (ArCH), 127.1 (ArCH), 123.6 (q), 63.6 (CH₂, 1-C); IR (neat) 3390.9, 1650.6, 1465.9, 1020.7, 745.7 cm⁻¹.
(E)-3-(2-Bromophenyl)acrylaldehyde (199)$^{95}$

Under $N_2$ at -78 °C DMSO (1.04 mL, 14.70 mmol) was added dropwise to a solution of oxylchloride (7.35 mL, 14.70 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL). After 30 minutes a solution of 244 (1.57 g, 7.37 mmol) in CH$_2$Cl$_2$ (10 mL) was added and the reaction stirred for 1 hr. Et$_3$N (10.0 mL, 70 mmol) was added and the reaction stirred for a further 1 hr before warming to rt. The reaction as quenched with water (20 mL) and extracted with CH$_2$Cl$_2$ (2×100 mL). The organic layer was washed with brine (50 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the *title compound* as a yellow solid 199 (1.28 g, 82 %); \( ^1H \text{NMR} \) (400 MHz, CDCl$_3$): $\delta$H 9.74 (d, $J = 8.0$ Hz, 1H, 1-H), 7.63 (d, $J = 11.6$ Hz, 1H, 3-H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.27-7.31 (m, 2H), 7.19-7.25 (m, 1H), 6.19 (dd, $J = 11.2$, 8.0 Hz, 1H, 2-H); \( ^{13}C \text{NMR} \) (100 MHz, CDCl$_3$): $\delta$C 192.3 (CHO, 1-C), 147.8 (CH, 3-C), 134.3 (q), 133.1 (ArCH), 132.2 (ArCH), 131.1 (ArCH), 131.0 (CH, 2-C), 127.2 (ArCH), 123.6 (q); IR (neat) 3435.4, 1678.3, 1464.8, 1128.7 cm$^{-1}$; HRMS (EI) calculated for C$_9$H$_8$OBr, C$_9$H$_8$O$_8^{181}$Br [M]$^+$, $m/z$: 210.9764, 212.9744, found $m/z$: 210.9750, 212.9730.
± (3R,4R,E)-1-(2-bromophenyl)-4-methylhexa-1,5-dien-3-ol (200)

Crotyltrichlorosilane (2.27 g, 12.20 mmol) was added dropwise to a solution of aldehyde 199 (1.28 g, 6.00 mmol) in DMF (5.0 mL) and CH₂Cl₂ (50 mL) at 0 °C under N₂ for 24 hrs. The reaction was quenched with saturated NaHCO₃ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₃) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 200 (1.23 g, 76%); ¹H NMR (400 MHz, CDCl₃): δ H 7.57 (d, J = 8.0 Hz, 1H, 3'-H), 7.51 (d, J = 7.6 Hz, 1H, 6'-H), 7.28 (t, J = 7.6 Hz, 1H, 5'-H), 7.12 (t, J = 7.6 Hz, 1H, 4'-H), 6.93 (d, J = 16.0 Hz, 1H, 1'-H), 6.18 (dd, J = 16.0, 6.4 Hz, 1H, 2-H), 5.82-5.91 (ddd, J = 16.0, 8.4, 6.0 Hz, 1H, 5-H), 5.19 (d, J = 6.0 Hz, 1H, 6-H), 5.15 (s, 1H, 6-H), 5.28 (t, J = 6.4 Hz, 1H, 3-H), 2.49-2.54 (m, 1H, 4-H), 1.78 (s, OH), 1.12 (d, J = 7.2 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δ C 139.7 (CH, 5-C), 136.8 (q), 133.1 (CH, 3-C), 132.9 (CH, 3'-C), 130.0 (CH, 1-C), 128.8 (CH, 4'-C), 127.4 (CH, 5'-C), 127.2 (CH, 6'-C), 123.6 (q), 116.2 (CH₂, 6-C), 75.6 (CH, 3-C), 43.8 (CH, 4-C), 14.8 (CH₃, 7-C); IR (neat) 3391.6, 2969.6, 1466.6, 1023.7, 965.2 cm⁻¹; HRMS (El) calculated for C₁₃H₁₅OBrNa, C₁₃H₁₅O⁺BrNa [M⁺, m/z]: 289.0209, 291.0189, found m/z: 289.0191, 291.0170.
\( \pm (R,E)-3\text{-}(2\text{-bromophenyl})\text{hept}-5\text{-enal} \ (201) \)

KH 30 % suspension in mineral oil (5.94 g, 148 mmol) was washed with DME (3x10 mL). Dry DME (200 mL) was added to the KH. 200 (2.27 g, 8.50 mmol) followed by 18-crown-6 (1.12 g, 4.20 mmol) was added to the solution and heated for 3 hrs at 50 °C. The solution was cooled to -78 °C and quenched with methanol (10 mL). The mixture was poured into a solution of ether (100 mL) and saturated NH₄Cl (20 mL). The organic layer was separated and washed with brine (20 mL), dried (Na₂SO₃) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a yellow oil 201 in a 12:1 E/Z ratio (1.66 g, 73 %); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 9.69 (t, \( J = 2.4 \) Hz, 1H, 1-H), 7.58 (d, \( J = 8.0 \) Hz, 1H, 6'-H), 7.30 (t, \( J = 7.2 \) Hz, 1H, 4'-H), 7.19 (d, \( J = 8.0 \) Hz, 1H, 3'-H), 7.09 (t, \( J = 7.6 \) Hz, 1H, 5'-H), 5.43-5.52 (m, 1H, 6-H), 5.29-5.37 (m, 1H, 5-H), 3.81-3.90 (m, 1H, 3-H), 2.67-2.82 (m, 2H, 2-H), 2.38-2.45 (m, 1H, 4-H), 2.25-2.36 (m, 1H, 4-H), 1.64 (d, \( J = 6.0 \) Hz, 3H, 7-H); \(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta_c \) 201.5 (CHO 1-C), 142.3 (q), 133.1 (CH, 6'-C), 128.4 (CH, 6-C), 128.0 (CH, 5'-C), 127.9 (CH, 5-C), 127.6 (CH, 3'-C), 127.6 (CH, 4'-C), 124.7 (q), 48.8 (CH₂, 2-C), 38.5 (CH₂, 4-C), 38.4 (CH, 3-C), 17.9 (CH₃, 7-C); IR (neat) 3915.9, 1723.9, 1686.4, 1452.4, 967.9 cm⁻¹; HRMS (EI) calculated for C₁₃H₁₆OBr, C₁₃H₁₆O₈₁Br [M⁺], m/z: 267.0379, 269.0359, found m/z: 267.0374, 269.0355.
\( \pm (R,E)\)-3-(2-bromophenyl)hept-5-enoic acid (245)

A solution of NaClO\(_3\) (0.90 g, 10.00 mmol) in water (15 mL) was added dropwise to a mixture of 201 (1.66 g, 6.20 mmol) in acetonitrile (15 mL) and NaH\(_2\)PO\(_4\).H\(_2\)O (0.11 g, 12.40 mmol) at 0 °C. The reaction was stirred in a water bath overnight. The reaction was quenched with 5M HCl (10 mL) and extracted with ether (3x50 mL). The organic layer was washed with brine (10 mL), dried (MgSO\(_4\)) and concentrated in vacuo. The compound was used directly in the next step.

\[ \pm (R,E)\]-methyl 3-(2-bromophenyl)hept-5-enoate (202)

A solution of trimethylsilyldiazomethane (3.70 mL, 7.40 mmol) was stirred in a mixture of toluene (130 mL) and MeOH (27 mL) under N\(_2\). Acid 201 (1.75 g, 6.10 mmol) in MeOH (7 mL) was added dropwise and stirred for 30 minutes. The reaction was diluted with ether (50 mL) and acetic acid (10 mL). The organic layer was washed with saturated Na\(_2\)CO\(_3\) (20 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 202 in a 12:1 E/Z ratio (1.30 g, 71 %); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.56 (d, \( J = 8.0 \) Hz, 1H, 6'-H), 7.27 (t, \( J = 8.0 \) Hz, 1H, 4'-H), 7.18 (d, \( J = 8.0 \) Hz, 1H, 3'-H), 7.06 (t, \( J = 7.6 \) Hz, 1H, 5'-H), 5.42-5.43 (m, 1H, 6-H), 5.32-5.34 (m, 1H, 5-H), 3.72-3.78 (m, 1H, 3-H), 3.60 (s, 3H, OCH\(_3\)), 2.59-2.72 (m, 2H, 2-H), 2.35-2.37 (m, 1H, 4-H), 2.26-2.31 (m, 1H, 4-H), 1.62 (d, \( J = 6.0 \) Hz, 3H, 7-H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \)C 172.4 (q), 142.7 (q), 133.0 (CH, 6'-C), 127.9 (CH, 6-C), 127.8 (CH, 5-C), 127.7 (CH, 5'-C), 127.6 (CH, 3'-C), 127.4 (CH, 4'-C), 124.9 (q), 51.5 (CH\(_3\)), 40.2 (CH, 3-C), 38.8 (CH\(_2\), 2-C), 38.3 (CH\(_2\), 4-C), 17.9 (CH\(_3\), 7-C); IR (neat) 2950.6, 1738.8, 1436.3, 1162.2, 1022.3, 968.2, 754.6 cm\(^{-1}\); HRMS (El) calculated for C\(_{14}\)H\(_{17}\)O\(_2\)BrNa, C\(_{14}\)H\(_{17}\)O\(_2\)\(^{81}\)BrNa [M]', \( m/z \): 319.0304, 321.0284, found \( m/z \): 319.0301, 321.0280.
± Methyl 2-((1R,4S)-8-bromo-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (203)

Trifluoromethanesulfonic acid (0.44 mL, 5.00 mmol) was added to a solution of 202 (0.16 g, 0.50 mmol) in CH₂Cl₂ (10 mL) at -78 °C and warmed to room temperature overnight. The reaction was poured onto a saturated solution of NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x20 mL). The organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ethyl acetate/petroleum ether) gave the title compound as a clear oil 203 in a 3:1 ratio of diastereoisomers (0.08 g, 57%);

Major isomer:

¹H NMR (400 MHz, CDCl₃): δₜ 7.31 (d, J = 7.6 Hz, 1H, 7'-H), 7.02 (d, J = 7.6 Hz, 1H, 5'-H), 6.92 (t, J = 7.6 Hz, 1H, 6'-H), 3.65 (s, 3H, OCH₃), 3.52-3.56 (m, 1H, 1'-H), 2.90-2.92 (m, 1H, 4'-H), 2.69 (dd, J = 1.6 Hz, 1H, 1'-H), 2.34 (dd, J = 11.6 Hz, 1H, 1'-H), 1.90-1.64 (m, 1H, 2'-H), 1.63-1.67 (m, 1H, 2'-H), 1.45-1.46 (m, 2H, 3'-H), 1.15 (d, J = 7.2 Hz, 3H, 9'-H); ¹³C NMR (100 MHz, CDCl₃): δc 172.8 (q), 144.9 (q), 137.6 (q), 130.7 (CH, 7'-C), 128.8 (CH, 5'-C), 127.5 (CH, 6'-C), 125.2 (q), 51.6 (OCH₃), 38.1 (CH₂, 1'-C), 34.5 (CH, 1'-C), 32.3 (CH, 4'-C), 24.6 (CH₂, 3'-C), 24.5 (CH₃, 9'-C), 21.5 (CH₂, 2'-C); IR (neat) 2935.2, 1737.4, 1433.9, 1275.2, 1161.0 cm⁻¹; HRMS (El) calculated for C₁₄H₁₇O₂BrNa, C₁₄H₁₇O₂BrNa [M⁺]⁺, m/z: 319.0301, 321.0280, found m/z: 319.0304, 321.0284.

Minor isomer:

¹H NMR (400 MHz, CDCl₃): δₜ 3.64 (s, 3H, OCH₃), 1.24 (d, J = 7.2 Hz, 3H, 9'-H).
± Methyl 2-{(1R,4S)-8-bromo-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl}propanoate (204)

LDA 1.6 M in hexane (1.38 mL, 2.00 mmol) was added dropwise to a solution of 203 (0.08 g, 0.90 mmol) in anhydrous THF (5 mL) at -45 °C. The solution was stirred for 1 hr before MeI (0.18 mL, 3.00 mmol) in anhydrous THF (5 mL) was added dropwise. The reaction was stirred for a further 12 hrs before quenching with water (5 mL) and extracted with ether (3x20 mL). The organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 204 (Trace) Unable to interpret ¹H or ¹³C NMR, due to mixture of 2 isomers. C-13 ¹H NMR shows a 0.7:1 ratio of diastereoisomers; IR (neat) 2938.3, 1735.1, 1456.4, 1196.4, 754.3 cm⁻¹; HRMS (EI) calculated for C₁₅H₁₉O₂BrNa, C₁₅H₁₉O₂ BrNa [M⁺], m/z: 333.0461, 335.0440, found m/z: 333.0455, 335.0434.
6.8 - (±)-Demethylelisabethadione synthesis

Ethyl 2-methyl-3-(2,4,5-trimethoxyphenyl)propanoate (246)

To a solution of 2,4,5-trimethoxybenzaldehyde (1.96 g, 10.00 mmol) in water (25 mL) was added (Carbethoxyethylidene)triphenylphosphorane (7.24 g, 20.00 mmol) and the solution heated to 90 °C for 2 days. The reaction was cooled and poured onto a saturated solution of NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 246 (2.8 g, 99 %); ¹H NMR (400 MHz, CDCl₃): δH 7.74 (s, 1H), 6.82 (s, 1H), 6.46 (s, 1H), 4.19 (q, J = 7.2 Hz, 2H, 5-H), 3.85 (s, 3H, OCH₃), 3.77 (s, 6H, OCH₃), 2.01 (s, 3H, 4-H), 1.27 (t, J = 7.2 Hz, 3H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δC 168.8 (q), 152.7 (q), 150.2 (q), 142.4 (q), 134.1 (CH), 126.9 (q), 116.3 (q), 113.8 (CH), 96.8 (CH), 60.6 (CH, 5-C), 56.6 (OCH₃), 56.3 (OCH₃), 56.0 (OCH₃), 14.3 (CH₃, 4-C) 14.3 (CH₃, 6-C); IR (neat) 2937.3, 1700.8, 1514.8, 1465.3, 1250.6, 1214.9, 1109.4, 1032.9 cm⁻¹; HRMS (EI) calculated for C₁₅H₂₀O₅Na [M]⁺, m/z: 303.1203, found m/z: 303.1199.
2-Methyl-3-(2,4,5-trimethoxyphenyl)propan-1-ol (247)

DIBAL (1M solution in hexane, 33.7 mL, 33.70 mmol) was added to a solution of 246 (3.15 g, 11.20 mmol) in anhydrous CH₂Cl₂ (100 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL), 5M HCl (10 mL) and extracted with CH₂Cl₂ (2x100 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 247 (2.40 g, 92%); ¹H NMR (400 MHz, CDCl₃): δₙ 6.74 (s, 1H), 6.45 (s, 2H), 4.13 (s, 2H, 3-H), 3.83 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 1.79 (s, 3H, 4-H); ¹³C NMR (100 MHz, CDCl₃): δ C 151.6 (q), 148.6 (q), 142.4 (q), 136.8 (q), 120.5 (CH), 117.9 (q), 114.1 (CH), 97.2 (CH), 69.2 (CH₂, 3-C), 56.6 (OCH₃), 56.3 (OCH₃), 56.1 (OCH₃), 15.4 (CH₃, 4-C); IR (neat) 3486.9, 2935.4, 1510.5, 1464.5, 1205.5, 1034.4, 875.8 cm⁻¹; HRMS (EI) calculated for C₃₃H₂₆O₄Na [M⁺], m/z: 261.1097, found m/z: 261.1095.

2-Methyl-3-(2,4,5-trimethoxyphenyl)propanal (206)

To a solution of 247 (2.4 g, 10.00 mmol) in CH₂Cl₂ (20 mL) was added MnO₂ (2.6 g, 30.00 mmol) and the reaction stirred for 60 hours until completion by TLC. The solution was poured through a pad of celite and concentrated in vacuo producing 206 as a yellow solid (1.99 g, 84%). Mp = 96.8-98.2 °C; ¹H NMR (400 MHz, CDCl₃): δₙ 9.59 (s, 1H, 3-H), 7.60 (s, 1H), 7.12 (s, 1H), 6.57 (s, 1H), 3.97 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.89 (s, 3H, OCH₃), 2.08 (s, 3H, 4-H); ¹³C NMR (100 MHz, CDCl₃): δ C 195.7 (CHO, 3-C), 153.4 (q), 151.7 (q), 144.5 (CH), 142.7 (q), 135.9 (q), 115.7 (q), 113.4 (CH), 96.6 (CH), 56.6 (OCH₃), 56.4 (OCH₃), 56.0 (OCH₃), 11.1 (CH, 4-C); IR (neat) 2931.5, 1652.2, 1597.9, 1506.6, 1286.7, 1210.0, 1028.1 cm⁻¹; HRMS (EI) calculated for C₃₂H₂₇O₄Na [M⁺], m/z: 259.0941, found m/z: 259.094.
± (35,4R,E)-2,4-Dimethyl-1-(2,4,5-trimethoxyphenyl)hexa-1,5-dien-3-ol (207)

To a solution of 206 (0.47 g, 2.00 mmol) in anhydrous MeCN (10 mL), DMF (10 mL) and hunigs base 4 eq (1.39 mL, 8.00 mmol) under N2 was added crotyltrichlorosilane (0.94 g, 5.00 mmol) and the reaction stirred overnight. The reaction was quenched with saturated NaHCO3 (10 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was washed with brine (10 mL), dried (MgSO4) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 20 % ethyl acetate/petroleum ether) gave the title compound a light yellow oil 207 (0.53 g, 91 %); ¹H NMR (400 MHz, CDCl3): δH 6.70 (s, 1H, 6'-H), 6.45 (s, 1H, 1-H), 6.42 (s, 1H, 3'-H), 5.75 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H, 5-H), 5.02 (d, J = 17.2 Hz, 1H, 6-H), 4.99 (d, J = 10.4 Hz, 1H, 6-H), 3.95 (d, J = 6.8 Hz, 1H, 3-H), 3.82 (s, 3H, OCH3), 3.75 (s, 3H, OCH3), 3.72 (s, 3H, OCH3), 2.38-2.46 (m, 1H, 4-H), 1.72 (s, 3H, 8-H), 1.04 (d, J = 6.8 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl3): δC 151.8 (q), 148.6 (q), 142.4 (q), 141.1 (CH), 138.0 (q), 121.7 (CH), 118.2 (q), 114.3 (CH, 5-C), 114.3 (CH2, 6-C), 97.6 (CH, 3'-C), 81.0 (CH, 3-C), 56.7 (OCH3), 56.5 (OCH3), 56.1 (OCH3), 41.5 (CH, 4-C), 14.9 (CH3, 7-C), 14.0 (CH3, 8-C); IR (neat) 3502.9, 2933.7, 1608.1, 1510.6, 1464.5, 1219.9, 1035.5 cm⁻¹; HRMS (EI) calculated for C17H24O4Na [M⁺, m/z: 315.1567, found m/z: 315.1560.
±(2R,3R,E)-2-methyl-3-(2,4,5-trimethoxyphenyl)hept-5-enal (208)

A 30% suspension of KH in mineral oil (5.8 g, 145 mmol) was washed with anhydrous DME (3x10 mL). Anhydrous DME (150 mL) was added to the KH. Alcohol 207 (2.12 g, 7.20 mmol) and 18-crown-6 (0.95 g, 3.60 mmol) were successively added to the solution and heated overnight at 50 °C. The solution was cooled to -78 °C and quenched with MeOH (10 mL). The solution was poured into a solution of ether (100 mL) and NH₄Cl (50 mL). The organic layer was separated and washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound producing as yellow oil 208 (1.43 g, 68 %);

Major isomer:

1H NMR (400 MHz, CDCl₃): δ_H 9.50 (d, J = 2.0 Hz, 1H, 1'-H), 6.54 (s, 1H, 3'/6'-H), 6.42 (s, 1H, 3'/6'-H), 5.31-5.35 (m, 1H, 6-H), 5.12-5.24 (m, 1H, 5-H), 3.81 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.30-3.42 (m, 1H, 3-H), 2.55-2.61 (m, 1H, 2-H), 2.28-2.31 (m, 2H, 4-H), 1.51 (d, J = 4.0 Hz, 3H, 7-H), 0.76 (d, J = 7.2 Hz, 8-H); 13C NMR (100 MHz, CDCl₃): δ_C 205.1 (CH, 1'-C), 151.4 (q), 148.1 (q), 142.8 (q), 128.9 (q), 128.5 (CH, 5-C), 127.2 (CH, 6-C), 113.2 (ArCH 6'-C), 97.5 (ArCH, 3'-C), 56.8 (OCH₃), 56.2 (OCH₃), 56.0 (OCH₃), 50.5 (CH, 2-C), 38.4 (CH, 3-C), 36.0 (CH, 4-C), 17.9 (CH₃, 7-C), 10.9 (CH₃, 8-C); IR (neat) 2934.7, 1720.6, 1511.2, 1454.1, 1205.3, 1035.4 cm⁻¹; HRMS (EL) calculated for C₁₇H₂₄O₄Na [M⁺], m/z: 315.1578, found m/z: 315.1770.

Minor isomer:

1H NMR (400 MHz, CDCl₃): δ_H 9.59 (d, J = 2.8 Hz, 1H, 1'-H), 6.58 (s, 1H, 3'/6'-H), 6.43 (s, 1H, 3'/6'-H), 3.81 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 1.49 (d, J = 8.0 Hz, 3H, 7-H), 0.98 (d, J = 6.8 Hz, 3H, 8-H).
± \((2E,4S,5R,7E)\)-methyl 4-methyl-5-(2,4,5-trimethoxyphenyl)nona-2,7-dienoate (209)

Methyl(triphenylphosphoranylidene)acetate (3.22 g, 9.60 mmol) was added to a solution of 208 (1.41 g, 4.80 mmol) in water (50 mL) and the reaction heated to 95 °C over the weekend. The reaction was cooled to rt and poured onto saturated NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as a colorless oil 209 (1.58 g, 95%);

**Major isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): δₖ 6.87 (dd, J = 9.2, 8.8 Hz, 1H, 3'-H), 6.52 (s, 1H, 3'/6'-H), 6.43 (s, 1H, 3'/6'-H), 5.72 (d, J = 15.6 Hz, 1H, 2-H), 5.18-5.28 (m, 1H, 8-H), 5.05-5.16 (m, 1H, 7-H), 3.81 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 3.66 (s, 3H, OCH₃), 2.92-2.98 (m, 1H, 5-H), 2.42-2.51 (m, 1H, 4-H), 2.09-2.28 (m, 2H, 6-H), 1.45 (d, J = 6.4 Hz, 3H, 9-H), 0.78 (d, J = 6.8 Hz, 3H, 10-H); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 167.1 (q, 1-C), 152.1 (CH, 3-C), 151.9 (q), 147.6 (q), 142.6 (q), 129.3 (CH, 7-C), 126.2 (CH, 8-C), 122.0 (q), 119.8 (CH, 2-C), 112.9 (ArCH, 3'/6'-C), 97.6 (ArCH, 3'/6'-C), 56.6 (OCH₃), 56.5 (OCH₃), 56.0 (OCH₃), 51.3 (OCH₃), 41.6 (CH, 5-C), 40.3 (CH, 4-C), 34.7 (CH₂, 6-C), 17.9 (CH₃, 9-C), 16.7 (CH₃, 10-C); IR (neat) 2930.1, 1721.1, 1510.2, 1205.0, 1036.4 cm⁻¹; HRMS (EI) calculated for C₂₀H₂₈O₃Na [M⁺], m/z: 371.1829, found m/z: 371.1822.

**Minor isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): δₖ 6.82 (dd, J = 8.8, 8.0 Hz, 1H, 3'-H), 6.48 (s, 1H, 3'/6'-H), 6.42 (s, 1H, 3'/6'-H), 5.60 (d, J = 14.0 Hz, 1H, 2-H), 5.28-5.37 (m, 1H, 8-H), 5.13-5.20 (m, 1H, 7-H), 3.81 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃), 3.62 (s, 3H, OCH₃), 3.09-3.15 (m, 1H, 5-H), 2.52-2.61 (m, 1H, 4-H), 2.18-2.29 (m, 2H, 6-H), 1.49 (d, J = 8.0 Hz, 3H, 9-H), 0.92 (d, J = 7.2 Hz, 3H, 10-H).
(S,E)-Methyl 4-((1R,4S)-5,6,8-trimethoxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (210)

Trifluoromethanesulfonic acid (0.66 mL, 7.50 mmol) was added to a solution of 209 (0.52 g, 1.50 mmol) in CHCl₃ (20 mL) at 40 °C. The reaction was stirred for 7 hrs before being quenched with saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x20 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound 210 as a yellow oil in a 3:1 ratio of diastereoisomers (0.18 g, 35 %). For analytical purposes, an aliquot of enriched product was separated by column chromatography on silica gel gaining the desired isomer; ¹H NMR (400 MHz, CDCl₃): δH 6.83 (dd, J = 16.0, 7.2 Hz, 1H, 3'-H), 6.30 (s, 1H, 7'-H), 5.50 (d, J = 16.0 Hz, 1H, 2-H), 3.80 (s, 3H, OCH₃), 3.71 (s, 6H, OCH₃), 3.62 (s, 3H, OCH₃), 3.06-3.08 (m, 1H, 4'-H), 2.99-3.00 (m, 1H, 1'-H), 2.72-2.74 (m, 1H, 4-H), 1.65–1.75 (m, 4H), 1.05 (d, J = 6.8 Hz, 3H, 9'-H), 1.00 (d, = 6.8 Hz, 3H, 5'-H); ¹³C NMR (100 MHz, CDCl₃): δC 167.3 (q), 154.9 (CH, 3-C), 153.4 (q), 150.8 (q), 140.4 (q), 137.5 (q), 118.8 (q), 118.3 (CH, 2-C), 94.4 (CH, 7'-C), 60.9 (OCH₃), 55.8 (OCH₃), 55.3 (OCH₃), 51.3 (OCH₃), 40.2 (CH, 4-C), 36.4 (CH, 1'-C), 27.1 (CH, 4'-C), 25.8, 22.7 (CH₃, 9'-C), 18.7 (CH₃, 2'/3'-C), 17.3 (CH₃, 5-C); IR (neat) 2935.8, 1721.5, 1464.2, 1328.1, 1204.5, 1053.4 cm⁻¹; HRMS (El) calculated for C₂₀H₂₈O₅Na [M]⁺, m/z: 371.1840, found m/z: 371.1454.
± (S)-Methyl 4-((1R,4S)-5,6,8-trimethoxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanoate (211)

A solution of compound 210 (0.44 g, 1.20 mmol) in MeOH was circulated for 2 hrs through an H-Cube (set at 2.0 mL/min, Full hydrogen, rt) equipped with a cartridge containing catalyst Pd/C 10%. The reaction solution was concentrated in vacuo to give the title compound as a colourless oil 211 in a 3:1 ratio of diastereoisomers (0.36 g, 82%);

**Major isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 6.27 (s, 1H, 7'-H), 3.79 (s, 3H, OCH$_3$), 3.72 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 3.56 (s, 3H, OCH$_3$), 3.05-3.09 (m, 1H, 4'-H), 2.80-2.81 (m, 1H, 1'-H), 2.24-2.29 (m, 1H, 3-H), 2.10-2.14 (m, 1H, 3-H), 1.83-1.85 (m, 1H, 3'-H), 1.63-1.71 (m, 4H), 1.35-1.49 (m, 2H), 1.08 (d, $J = 6.8$ Hz, 3H, 9'-H), 0.67 (d, $J = 6.8$ Hz, 3H, 5-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$C 174.7 (q), 153.6 (q), 138.5 (q), 137.3 (q), 120.0 (q), 94.2 (CH, 7'-C), 60.8 (OCH$_3$), 55.8 (OCH$_3$), 55.1 (OCH$_3$), 51.4 (OCH$_3$), 37.2, 35.7 (CH, 1'-C), 32.8 (CH$_2$, 3-C), 30.7, 27.3 (CH, 4'-C), 25.9, 22.8 (CH$_3$, 9'-C), 20.4, 17.7 (CH$_3$, 5-C); IR (neat) 2933.5, 1737.2, 1597.8, 1463.9, 1327.9, 1203.7, 1053.6 cm$^{-1}$; HRMS (EI) calculated for C$_{20}$H$_{30}$O$_5$Na [M]$^+$, $m/z$: 373.1985, found $m/z$: 373.1981.

**Minor isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 6.28 (s, 1H, 7'-H), 1.06 (d, $J = 6.4$ Hz, 3H, 9'-H), 0.71 (d, $J = 6.8$ Hz, 3H, 5-H).
± (S)-4-((1R,4S)-5,6,8-Trimethoxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentan-1-ol (212)

DIBAL (1M in hexanes, 7.6 mL, 7.60 mmol) was added to a solution of 211 (1.12 g, 3.80 mmol) in anhydrous CH₂Cl₂ (100 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL), 5M HCl (10 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Producing title compound 212 as a light yellow oil in a 3:1 ratio of diastereoisomers. Product used directly in the next step;

**Major isomer:**

$^1$H NMR (400 MHz, CDCl₃) δH 6.27 (s, 1H, 7'-H), 3.78 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.68 (s, 3H, OCH₃), 3.47-3.50 (m, 2H, 1'-H), 3.05-3.09 (m, 1H, 4'-H), 2.79-2.82 (m, 1H, 1'-H), 1.82-1.88 (m, 1H, 3'-H), 1.65-1.73 (m, 3H), 1.53-1.58 (m, 1H, 3-H), 1.27-1.41 (m, 2H), 1.13-1.17 (m, 2H, 2-H), 1.08 (d, J = 6.8 Hz, 3H, 9'-H), 0.70 (d, J = 7.2 Hz, 3H, 5-H); $^{13}$C NMR (100 MHz, CDCl₃): δC 153.6 (q), 150.3 (q), 140.5 (q), 137.4 (q), 120.5 (q), 94.3 (CH, 7'-C), 63.4 (CH₂, 1-C), 60.9 (OCH₃), 55.8 (OCH₃), 55.2 (OCH₃), 37.2, 36.0 (CH, 1'-C), 31.4 (CH₂, 3-C), 31.3 (CH₂, 2-C), 27.3 (CH, 4'-C), 26.0 (CH₂, 3'-C), 22.8 (CH₃, 9'-C), 20.3, 18.2 (CH₃, 5-C); IR (neat) 3400.7, 2934.1, 1598.1, 1464.5, 1328.1, 1203.8, 1053.5 cm⁻¹; HRMS (EI) calculated for C₁₉H₃₀O₄Na [M]^+ m/z: 345.2036, found m/z: 345.2021.

**Minor isomer:**

$^1$H NMR (400 MHz, CDCl₃) δH 6.28 (s, 1H, 7'-H), 1.06 (d, J = 6.4 Hz, 3H, 9'-H), 0.70 (d, J = 6.8 Hz, 3H, 5-H).
± (4S)-4-((1R)-5,6,8-trimethoxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanal (213)

To a solution of 212 (0.32 g, 0.90 mmol) in anhydrous CH₂Cl₂ (20 mL) was added pyridinium chlorochromate (0.32 g, 1.50 mmol) at 0 °C. The solution was stirred for 1.5 hrs at rt before being diluted with ether (50 mL) and filtered through a pad of celite and concentrated. Purification by column chromatography on silica gel (eluting with 4% ethyl acetate/petroleum ether) gave the title compound 213 as a colorless oil in a 3:1 mixture of diastereoisomers (0.04 g, 13%);

Major isomer:

¹H NMR (400 MHz, CDCl₃): δₙ 9.58 (t, J = 1.6 Hz, 1H, 1'-H), 6.27 (s, 1H, 7'-H), 3.78 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.68 (s, 3H, OCH₃), 3.05-3.13 (m, 1H, 4'-H), 2.78-2.86 (m, 1H, 1'-H), 2.30-2.46 (m, 1H, 2'-H), 2.16-2.24 (m, 1H, 2'-H), 1.78-1.88 (m, 4H), 1.61-1.75 (m, 2H), 1.38-1.47 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H, 9'-H), 0.69 (d, J = 6.8 Hz, 3H, 5-H); ¹³C NMR (100 MHz, CDCl₃): δₙ 203.5 (CHO, 1'-C), 153.6 (q), 150.4 (q), 140.5 (q), 137.3 (q), 119.9 (q), 94.3 (CH, 7'-C), 60.8 (OCH₃), 55.8 (OCH₃), 55.2 (OCH₃), 42.6 (CH₂, 2'-C), 37.1 (CH₂, 2'-C), 35.7 (CH, 1'-C), 27.7 (CH, 4'-C), 27.3 (CH₂, 3'-C), 26.0 (CH₂, 3'-C), 22.7 (CH₃, 9'-C), 20.2 (CH, 4'-C), 17.9 (CH₃, 5-C); IR (neat) 2933.8, 1723.8, 1598.1, 1482.6, 1328.3, 1235.9, 1203.8, 1086.9, 1053.5 cm⁻¹; HRMS (El) calculated for C₁₉H₂₈O₄Na [M⁺, m/z] 343.1880, found m/z: 343.1877.

Minor isomer:

¹H NMR (400 MHz, CDCl₃): δₙ 9.68 (t, J = 2.0 Hz, 1H, 1'-H), 1.06 (d, J = 6.8 Hz, 3H, 9'-H), 0.73 (d, J = 7.2 Hz, 3H, 5-H).
6.9 - Method development - Anti product synthesis

± (35,45,E)-2,4-dimethyl-1-(2,4,5-trimethoxyphenyl)hexa-1,5-dien-3-ol (214)

To a solution of 206 (0.28 g, 1.10 mmol) in MeCN (10 mL), DMF (10 mL) and hünigs base (0.82 mL, 4.70 mmol) under N₂ was added fresh (E)-But-2-enyltrichlorosilane (1.0 g, 5.00 mmol). The reaction was stirred and monitored by TLC until completion. The reaction was quenched with saturated NaHCO₃ (10 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 20 % ethyl acetate/petroleum ether) gave the title compound 214 as a yellow oil (0.23 g, 68 %); ¹H NMR (400 MHz, CDCl₃): δH 6.75 (s, 1H, 6'-H), 6.45 (s, 1H, 1-H), 6.41 (s, 1H, 3'-H), 5.71-5.80 (m, 1H, 5-H), 5.09-5.16 (m, 2H, 6-H), 3.83 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 2.31-2.40 (m, 1H, 4-H), 1.74 (s, 3H, 8-H), 0.92 (d, J = 7.2 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 151.7 (q), 148.6 (q), 142.4 (q), 141.2 (CH, 5-C), 137.0 (q), 123.2 (CH, 3'-C), 118.1 (q), 116.5 (CH₂, 6-C), 114.1 (CH, 1-C), 97.6 (CH, 3'-C), 81.5 (CH, 3-C), 56.7 (OCH₃), 56.5 (OCH₃), 56.1 (OCH₃), 42.4 (CH, 4-C), 16.9 (CH₃, 7-C), 12.8 (CH₃, 8-C); IR (neat) 3502.4, 2959.0, 1510.6, 1454.9, 1204.7, 1034.6 cm⁻¹; HRMS (EI) calculated for C₁₇H₂₄O₄Na [M]+, m/z: 315.1567, found m/z: 315.1566.
± (E)-2-Methyl-3-(2,4,5-trimethoxyphenyl)hept-5-enal (215)

A 30% suspension of KH in mineral oil (0.64 g, 15.60 mmol) was washed with anhydrous DME (3x10 mL). Anhydrous DME (100 mL) was added to the KH. Alcohol 214 (0.23 g, 0.70 mmol) and 18-crown-6 (0.1 g, 0.30 mmol) were successively added to the solution and heated overnight at 50 °C. The solution was cooled to -78 °C and quenched with MeOH (10 mL). The solution was poured into a solution of ether (50 mL) and NH₄Cl (25 mL). The organic layer was separated and washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as a yellow oil 215 in a 1:3 E/Z ratio (0.11 g, 48 %);

Major isomer:

1H NMR (400 MHz, CDCl₃): δH 9.50 (d, J = 2.0 Hz, 1H, 1-H), 6.54 (s, 1H, 3'/6'-H), 6.41 (s, 1H, 3'/6'-H), 5.33-5.36 (m, 1H, 6-H), 5.17-5.19 (m, 1H, 5-H), 3.81 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.34-3.41 (m, 1H, 3-H), 2.57-2.61 (m, 1H, 2-H), 2.28-2.36 (m, 2H, 4-H), 1.48 (d, J = 6.0 Hz, 3H, 7-H), 0.76 (d, J = 7.0 Hz, 8-H); 13C NMR (100 MHz, CDCl₃): δC 205.1 (CH, 1'-C), 151.8 (q), 148.1 (q), 142.8 (q), 128.9 (q), 128.5 (CH, 5-C), 127.2 (CH, 6-C), 113.1 (ArCH 6'-C), 97.5 (ArCH, 3'-C), 56.8 (OCH₃), 56.2 (OCH₃), 56.0 (OCH₃), 50.8 (CH, 2-C), 38.5 (CH, 3-C), 36.0 (CH, 4-C), 17.9 (CH₃, 7-C), 10.9 (CH₃, 8-C); IR (neat) 2935.2, 1720.7, 1511.7, 1206.1, 1036.0 cm⁻¹; HRMS (El) calculated for C₁₇H₂₄O₄Na [M]+, m/z: 315.1567, found m/z: 315.1566.

Minor isomer:

1H NMR (400 MHz, CDCl₃): δH 9.59 (d, J = 2.8 Hz, 1H, 1-H), 6.58 (s, 1H, 3'/6'-H), 6.42 (s, 1H, 3'/6'-H), 1.49 (d, J = 8.0 Hz, 3H, 7-H), 0.98 (d, J = 6.8 Hz, 3H, 8-H).
± (2E,7E)-methyl 4-methyl-5-(2,4,5-trimethoxyphenyl)nona-2,7-dienoate (216)

Methyl(triphenylphosphoranylidene) acetate (0.25 g, 0.75 mmol) was added to a solution of 215 (0.11 g, 0.30 mmol) in water (50 mL) and the reaction heated to 95 °C over the weekend. The reaction was cooled to rt and poured onto saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (2x50 mL). The organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound 216 as a colorless oil (0.07 g, 58 %);

Major isomer:

¹H NMR (400 MHz, CDCl₃): δₜₙ 6.82 (dd, J = 8.0, 6.4 Hz, 1H, 3-H), 6.52 (s, 1H, 3′/6′-H), 6.43 (s, 1H, 3′/6′-H), 5.75 (d, J = 15.2 Hz, 1H, 2-H), 5.20-5.30 (m, 2H, 8/7-H), 3.81 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 2.91-3.02 (m, 1H, 5-H), 2.45-2.62 (m, 1H, 4-H), 2.21-2.26 (m, 2H, 6-H), 1.50 (d, J = 6.0 Hz, 3H, 9-H), 0.77 (d, J = 7.0 Hz, 3H, 10-H); ¹³C NMR (100 MHz, CDCl₃): δc 167.2 (q, 1-C), 154.4 (CH, 3-C), 152.1 (q), 147.6 (q), 142.8 (q), 129.2 (CH, 7-C), 126.2 (CH, 8-C), 122.3 (q), 119.9 (CH, 2-C), 112.8 (ArCH, 3′/6′-C), 97.7 (ArCH, 3′/6′-C), 56.7 (OCH₃), 56.6 (OCH₃), 56.0 (OCH₃), 51.4 (OCH₃), 41.6 (CH, 5-C), 40.3 (CH, 4-C), 35.8 (CH₂, 6-C), 16.7 (CH₃, 9-C), 16.7 (CH₃, 10-C); HRMS (El) calculated for C₂₀H₂₈O₅Na [M]+, m/z: 371.1829, found m/z: 371.1824.

Minor isomer:

¹H NMR (400 MHz, CDCl₃): δₜₙ 6.87 (dd, J = 9.2, 7.2 Hz, 1H, 3-H), 6.48 (s, 1H, 3′/6′-H), 6.42 (s, 1H, 3′/6′-H), 5.60 (d, J = 15.6 Hz, 1H, 2-H), 3.81 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃), 3.62 (s, 3H, OCH₃), 1.48 (d, J = 5.2 Hz, 3H, 9-H), 0.91 (d, J = 6.8 Hz, 3H, 10-H).
6.10 - (±)-Elisabethadione synthesis

![Elisabethadione structure]

2,4-Dimethoxy-3-methylbenzaldehyde (248)

To a solution of anhydrous DMF (10 mL) at 0 °C was added POCl₃ (5.6 mL, 60 mmol) dropwise. The Vilsmeier complex was stirred at 0 °C for 30 minutes. The complex was added to a solution of 1,3-dimethoxy-2-methylbenzene (7.8 g, 50 mmol) in DMF (10 mL) at 110 °C. The reaction was stirred for 2 hours at which point another fresh portion of Vilsmeier complex was added. The reaction was stirred for a further 2 hours before being cooled and poured onto ice water and extracted with ethyl acetate (3x100 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound as a yellow solid 248 (4.75 g, 52 %); ¹H NMR (400 MHz, CDCl₃): δH 10.15 (s, 1H, 7-H), 7.67 (d, J = 8.8 Hz, 1H, 5-H), 6.67 (d, J = 8.8 Hz, 1H, 6-H), 3.83 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 2.09 (s, 3H, 8-H); ¹³C NMR (100 MHz, CDCl₃): δc 189.2 (CHO, 7-C), 164.0 (q), 162.6 (q), 127.9 (CH, 5-C), 122.8 (q), 120.1 (q), 106.5 (CH, 6-C), 63.1 (OCH₃), 55.9 (OCH₃), 8.5 (CH₃, 8-C); IR (neat) 2924.4, 1681.6, 1592.6, 1462.5, 1276.8, 1108.0, 807.0 cm⁻¹; HRMS (EI) calculated for C₁₀H₁₃O₃ [M⁺], m/z: 181.0944, found m/z: 181.0854.
2,4-Dimethoxy-3-methylphenol (249)\textsuperscript{56}

A solution of 248 (4.75 g, 26.30 mmol) and MCPBA 70 % (8.4 g, 39.40 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) was stirred at reflux for 24 hours. The reaction was cooled and concentrated in \textit{vacuo} before being dissolved in ethyl acetate (50 mL) and neutralized with NaHCO\textsubscript{3}. The organic layer was washed with brine (20 mL) and dried (MgSO\textsubscript{4}). The residue was dissolved in MeOH (15 mL) before a solution of saturated KOH (40 mL) was added and stirred at rt for 1 hour. The reaction was neutralized with 5 % HCl and extracted with ethyl acetate (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO\textsubscript{4}) and concentrated in \textit{vacuo}. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the \textit{title compound} as a yellow oil 249 (3.51 g, 80 %); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 6.68 (d, J = 8.8 Hz, 1H, 1-H), 6.46 (d, J = 8.8 Hz, 1H, 6-H), 3.70 (s, 6H, OCH\textsubscript{3}), 2.10 (s, 3H, OCH\textsubscript{3}), 1.18 (s, OH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 151.8 (q), 145.9 (q), 142.8 (q), 119.9 (q), 111.6 (CH, 1-C), 106.7 (CH, 6-C), 60.8 (OCH\textsubscript{3}), 56.0 (OCH\textsubscript{3}), 9.3 (CH\textsubscript{3}, 7-C); IR (neat) 3419.0, 2926.0, 1488.9, 1261.7, 1103.9, 731.3 cm\textsuperscript{-1}; HRMS (EI) calculated for C\textsubscript{10}H\textsubscript{14}O\textsubscript{3}Na [M]\textsuperscript{+}, m/z: 169.0884, found m/z: 169.0854.

1,2,4-Trimethoxy-3-methylbenzene (218)\textsuperscript{57}

NaH (1.49 g, 41.60 mmol) was added to a solution of 249 (3.51 g, 20.80 mmol) in anhydrous THF (100 mL) and DMF (10 mL). The solution was stirred at 0 °C for 1 hr before MeI (3.88 mL, 62.40 mmol) was added dropwise. The solution was allowed to warm to room temperature overnight before being quenched with HCl (5 mL) and extracted with ether (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO\textsubscript{4}) and concentrated in \textit{vacuo}. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the \textit{title compound} 218 as a purple oil (3.08 g, 81 %); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 6.72 (d, J = 8.8 Hz, 1H, 1-H), 6.56 (d, J = 8.8 Hz, 1H, 6-H), 3.84 (s, 3H, OCH\textsubscript{3}), 3.82 (s, 3H, OCH\textsubscript{3}), 3.80 (s, 3H, OCH\textsubscript{3}), 2.18 (s, 3H, 7-H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 147.2 (q), 142.9 (q), 141.9 (q), 115.9 (q), 104.0 (CH, 1-C), 99.9 (CH, 6-C), 55.1 (OCH\textsubscript{3}), 50.9 (OCH\textsubscript{3}), 50.6 (OCH\textsubscript{3}), 3.6 (CH\textsubscript{3}, 7-C); IR (neat) 2938.9, 1489.0, 1257.4, 1115.2, 717.6 cm\textsuperscript{-1}; HRMS (EI) calculated for C\textsubscript{10}H\textsubscript{14}O\textsubscript{3}Na [M]\textsuperscript{+}, m/z: 205.0835, found m/z: 205.0833.
1,2,4-Trimethoxy-3-methylbenzene alternative synthesis

*n*-BuLi 2.4M solution in hexane (74.0 mL, 177.60 mmol) was added to a solution of 1,2,4-trimethoxybenzene (22.2 mL, 148.0 mmol) in anhydrous THF (100 mL) at 0 °C. The reaction was stirred at rt for 1 hr before being cooled to -78 °C and Mel (12.4 mL, 200.0 mmol) was added and the reaction stirred for a further 1 hr. The reaction was quenched with saturated NH₄Cl (20 mL) and extracted with ether (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound as a purple oil (26.6 g, 99 %).

1-Bromo-2,4,5-trimethoxy-3-methylbenzene (219)⁹⁷

To a solution of 218 (3.08 g, 16.90 mmol) in acetonitrile (40 mL) was added *N*-bromosuccinimide (3.89 g, 21.90 mmol) and the reaction stirred at room temperature for 1 hr before being concentrated in vacuo. The solution was diluted with water (25 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound as a yellow oil 219 (4.43 g, 99 %); ¹H NMR (400 MHz, CDCl₃): δ 6.85 (s, 1H, 6-H), 3.75 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 3.68 (s, 3H, OCH₃), 2.17 (s, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 149.8 (q), 149.4 (q), 147.3 (q), 127.1 (q), 113.5 (CH, 6-C), 110.7 (q), 60.4 (OCH₃), 60.2 (OCH₃), 56.1 (OCH₃), 10.1 (CH₃, 7-C); IR (neat) 2936.8, 1481.3, 1237.6, 1089.2, 1007.9, 778.1 cm⁻¹; HRMS (EI) calculated for C₁₀H₁₃O₃BrNa, C₁₀H₁₃O₃⁺BrNa [M⁺], m/z: 282.9940, 285.9920, found m/z: 282.9936, 284.9916.
2,4,5-Trimethoxy-3-methylbenzaldehyde (220)

n-BuLi 1.6 M in hexane (80.0 mL, 194.0 mmol) was added to a solution of 219 (33.7 g, 129.1 mmol) in anhydrous THF (200 mL) at -78 °C. The mixture was stirred at -78 °C for 30 minutes before DMF (20.0 mL, 258.0 mmol) was added. The reaction was stirred for a further 10 minutes before being warmed to 0 °C for 1 hour. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound 220 a yellow solid (21.2 g, 78 %); H NMR (400 MHz, CDCl₃): δH 10.18 (s, 1H, 8-H), 7.13 (s, 1H, 6-H), 3.79 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 2.13 (s, 3H, 7-H); C NMR (100 MHz, CDCl₃): δC 189.2 (CHO, 8-C), 157.5 (q), 154.0 (q), 149.8 (q), 126.1 (q), 124.6 (q), 107.1 (CH, 6-C), 63.6 (OCH₃), 60.4 (OCH₃), 55.9 (OCH₃), 9.1 (CH₃, 7-C); IR (neat) 2940.2, 1682.3, 1481.9, 1389.8, 1087.8 cm⁻¹; HRMS (EI) calculated for C₁₁H₁₄O₄Na [M]⁺, m/z: 233.0784, found m/z: 233.0784.
(E)-Methyl 2-methyl-3-(2,4,5-trimethoxy-3-methylphenyl)acrylate (221)

(Carbethoxyethylidene)triphenylphosphorane (14.9 g, 41.20 mmol) was added to a solution of 220 (5.78 g, 27.50 mmol) in water (25 mL) and the solution heated to 90 °C for 2 days. The reaction was cooled and poured onto saturated NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3x100 mL). The organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 221 (7.35 g, 91 %); ¹H NMR (400 MHz, CDCl₃): δₙₙ 7.72 (s, 1H, 1-H), 6.64 (s, 1H, 6’-H), 4.20 (q, J = 7.2 Hz, 2H, 4-H), 3.77 (s, 6H, OCH₃), 3.58 (s, 3H, OCH₃), 2.17 (s, 3H, 7-H), 1.98 (s, 3H, 6-H), 1.29 (t, J = 7.2 Hz, 3H, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ₁₆₃ 168.6 (q), 151.7 (q), 148.7 (q), 134.8 (CH), 128.5 (q), 125.7 (q), 124.3 (q), 110.8 (CH, 6'-C), 61.3 (OCH₃), 60.7 (CH₂, 4-C), 60.3 (OCH₃), 56.0 (OCH₃), 14.3 (CH₂, 6-C), 14.3 (CH₃, 5-C), 9.4 (CH₃, 7-C); IR (neat) 2935.4, 1706.7, 1484.8, 1251.6, 1089.5, 754.4 cm⁻¹; HRMS (EI) calculated for C₁₆H₂₂O₅Na [M]+, m/z: 317.1356, found m/z: 317.1359.

(E)-2-Methyl-3-(2,4,5-trimethoxy-3-methylphenyl)prop-2-en-1-ol (222)

DIBAL 1M in hexane (21.0 mL, 21.00 mmol) was added to a solution of 221 (1.24 g, 4.20 mmol) in anhydrous CH₂Cl₂ (100 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL), 5M HCl (10 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil 222 (0.64 g, 60 %); ¹H NMR (400 MHz, CDCl₃): δₙₙ 6.58 (s, 1H, 6’-H), 6.50 (s, 1H, 1-H), 4.14 (s, 2H, 3-H), 3.75 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.55 (s, 3H, OCH₃), 2.14 (s, 3H, 5-H), 1.80 (s, 3H, 4-H); ¹³C NMR (100 MHz, CDCl₃): δ₁₆₃ 150.7 (q), 148.6 (q), 146.9 (q), 137.7 (q), 125.8 (q), 125.3 (q), 121.1 (CH, 1-C), 111.1 (CH, 6’-C), 69.0 (CH₂, 3-C), 60.6 (OCH₃), 60.3 (OCH₃), 56.0 (OCH₃), 15.4 (CH₃, 4-C), 9.4 (CH₃, 5-C); IR (neat) 3400.8, 2935.3, 1484.9, 1227.9, 1087.2, 1010.5, 853.4 cm⁻¹; HRMS (EI) calculated for C₁₄H₂₀O₄Na [M]+, m/z: 275.1250, found m/z: 275.1254.
(E)-2-Methyl-3-(2,4,5-trimethoxy-3-methylphenyl)acrylaldehyde (223)

MnO₂ (1.30 g, 13.00 mmol) was added to a solution of 222 (0.95 g, 3.70 mmol) in CH₂Cl₂ (100 mL) and stirred at rt for 24 hrs. The reaction was filtered through a pad of celite and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a white solid 223 (0.72 g, 77 %); Mp = 77.9-85.2 °C; ¹H NMR (400 MHz, CDCl₃): δH 9.55 (s, 1H, 3-H), 7.46 (s, 1H, 1-H), 6.85 (s, 1H, 6'-H), 3.79 (s, 6H, OCH₃), 3.62 (s, 3H, OCH₃), 2.17 (s, 3H, 5-H), 2.00 (s, 3H, 4-H); ¹³C NMR (100 MHz, CDCl₃): δC 195.6 (CHO, 3-C), 152.3 (q), 149.7 (q), 148.9 (q), 145.1 (CH, 1-C), 137.8 (q), 126.0 (q), 123.5 (q), 110.6 (CH, 6'-C), 61.7 (OCH₃), 60.4 (OCH₃), 56.0 (OCH₃), 11.1 (CH₃, 4-C), 9.4 (CH₃, 9-C); IR (neat) 2934.9, 1662.0, 1614.7, 1455.6, 1235.4, 1084.5, 999.0, 835.8 cm⁻¹; HRMS (El) calculated for C₁₄H₁₈O₄Na [M]+, m/z: 273.1093, found m/z: 273.1097.
(±) (35,4R,E)-2,4-dimethyl-1-(2,4,5-trimethoxy-3-methylphenyl)hexa-1,5-dien-3-ol (224)

Crotlytrichlorosilane (5.96 g, 31.70 mmol) was added to a stirred solution of 223 (5.29 g, 21.60 mmol) in anhydrous MeCN (50 mL), DMF (50 mL) and Hunigs base (14.7 mL, 84.60 mmol) and the reaction stirred for 24 hrs. The reaction was quenched with saturated NaHCO₃ (10 mL) and extracted with ethyl acetate (3x50 mL). The organic layer was separated and washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 20 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 224 (3.59 g, 55 %); ¹H NMR (400 MHz, CDCl₃): δH 6.54 (s, 1H, 6'-H), 6.45 (s, 1H, 1-H), 5.69-5.78 (ddd, J = 17.6, 10.4, 7.6 Hz, 1H, 5-H), 5.02 (dd, J = 17.6 Hz, 2H, 6-H), 4.94 (dd, J = 10.4 Hz, 2H, 6-H), 3.95 (d, J = 7.2 Hz, 1H, 3-H), 3.75 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 3.53 (s, 3H, OCH₃), 2.42-2.47 (m, 1H, 4-H), 2.13 (s, 3H, 9-H), 1.73 (s, 3H, 8-H), 1.05 (d, J = 6.4 Hz, 3H, 7-H); ¹³C NMR (100 MHz, CDCl₃): δC 150.7 (q), 148.5 (q), 146.8 (q), 140.9 (CH, 5-C), 139.1 (q), 125.9 (q), 125.3 (q), 122.5 (CH, 1-C), 114.4 (CH₂, 6-C), 111.2 (CH, 6'-C), 81.0 (CH, 3-C), 60.7 (OCH₃), 60.1 (OCH₃), 56.0 (OCH₃), 41.5 (CH, 4-C), 15.0 (CH₃, 9-C), 13.9 (CH₃, 8-C), 9.3 (CH₃, 7-C); IR (neat) 3447.4, 2959.5, 1484.9, 1228.2, 1088.8, 1011.8 cm⁻¹; HRMS (EI) calculated for C₁₈H₂₆O₄Na [M⁺]⁺, m/z: 329.1715, found m/z: 329.1723.

(R)-TRIP catalyzed allylation:

Pinicol ester (0.06 mL, 0.33 mmol) was added to a solution of 223 (0.05 g, 0.22 mmol), (R)-TRIP (0.008 g, 0.011 mmol), TFA (0.0003 mL, 0.005 mmol) in anhydrous toluene (3 mL) at -30 °C and the reaction stirred for 8 hours. The reaction was quenched with saturated NaHCO₃ (10 mL) and extracted with ethyl acetate (3x50 mL). The organic layer was separated and washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 20 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 224 (0.03 g, 50 %); Chiral HPLC (CHIRALPAK IB-3), Hexane:PrOH 95:5 at 1mL/min⁻¹ (tminor = 9.86 min, tmajor = 10.36 min) showed 32% ee.
± (2R,3R,E)-2-methyl-3-(2,4,5-trimethoxy-3-methylphenyl)hept-5-enal (225)

A 30% suspension of KH in mineral oil (7.5 g, 187.70 mmol) was washed with anhydrous DME (3x10 mL). Anhydrous DME (150 mL) was added to the KH. Alcohol 224 (3.59 g, 11.70 mmol) and 18-crown-6 (1.47 g, 5.58 mmol) were successively added to the solution and heated for 6 hrs at 40 °C. The solution was cooled to -78 °C and quenched with MeOH (10 mL). The solution was poured into a saturated solution of NH4Cl (25 mL) and ether (50 mL). The organic layer was separated and washed with brine (25 mL), dried over (MgSO4) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as yellow oil 225 (2.19 g, 61%);

Major isomer:

¹H NMR (400 MHz, CDCl3): δH 9.50 (d, J = 2.4 Hz, 1H, 1-H), 6.45 (s, 1H, 6'-H), 5.34-5.38 (m, 1H, 6-H), 5.16-5.20 (m, 1H, 5-H), 3.75 (s, 3H, OCH3), 3.62 (s, 3H, OCH3), 3.59 (s, 3H, OCH3), 3.33-3.38 (m, 1H, 3-H), 2.50-2.54 (m, 1H, 2-H), 2.27-2.30 (m, 2H, 4-H), 2.15 (s, 3H, 9-H), 1.51 (d, J = 6.0 Hz, 3H, 7-H), 1.02 (d, J = 7.2 Hz, 8-H); ¹³C NMR (100 MHz, CDCl3): δC 204.9 (CH, 1-C), 150.4 (q), 149.1 (q), 146.4 (q), 129.9 (q), 127.6 (CH, 5-C), 126.6 (CH, 6-C), 125.3 (q), 109.0 (ArCH 6'-C), 60.9 (OCH3), 60.2 (OCH3), 55.8 (OCH3), 50.8 (CH, 2-C), 38.8 (CH, 3-C), 34.3 (CH, 4-C), 17.8 (CH3, 7-C), 9.8 (CH3, 8-C), 9.3 (CH3, 9-C); IR (neat) 2937.2, 1722.0, 1487.5, 1238.6, 1087.9, 1013.6 cm⁻¹; HRMS (EI) calculated for C18H26O4Na [M⁺], m/z: 329.1723, found m/z: 329.1715.

Minor isomer:

¹H NMR (400 MHz, CDCl3): δH 9.59 (d, J = 3.6 Hz, 1H, 1-H), 6.41 (s, 1H, 6'-H), 3.77 (s, 3H, OCH3), 3.62 (s, 3H, OCH3), 3.55 (s, 3H, OCH3), 2.13 (s, 3H, 9-H), 1.49 (d, J = 5.2 Hz, 3H, 7-H), 0.79 (d, J = 6.8 Hz, 3H, 8-H).
± (2E,45,5R,7E)-methyl 4-methyl-5-(2,4,5-trimethoxy-3-methylphenyl)nona-2,7-dienoate (226)

Methyl(triphenylphosphoranylidene)acetate (4.78 g, 14.30 mmol) was added to a solution of 225 (2.19 g, 7.10 mmol) in water (50 mL) and the reaction heated to 95 °C over the weekend. The reaction was cooled to rt and poured onto a saturated solution of NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4% ethyl acetate/petroleum ether) gave the title compound as a 226 (2.36 g, 91%);

**Major isomer:**

¹H NMR (400 MHz, CDCl₃): δₙ 6.85 (dd, J = 8.0, 7.6 Hz, 1H, 3-H), 6.35 (s, 1H, 6'-H), 5.64 (d, J = 16.4 Hz, 1H, 2-H), 5.22-5.39 (m, 1H, 8-H), 5.07-5.20 (m, 1H, 7-H), 3.72 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 3.62 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 3.07-3.12 (m, 1H, 5-H), 2.53-2.60 (m, 1H, 4-H), 2.21-2.33 (m, 2H, 6-H), 2.13 (s, 3H, 11-H), 1.50 (d, J = 6.0 Hz, 3H, 9-H), 0.92 (d, J = 6.8 Hz, 3H, 10-H); ¹³C NMR (100 MHz, CDCl₃): δₙ 167.1 (q, 1-C), 152.9 (CH, 3-C), 151.1 (q), 148.7 (q), 146.1 (q), 129.7 (q), 129.1 (CH, 7-C), 126.8 (CH, 8-C), 124.9 (q), 120.1 (CH, 2-C), 109.2 (ArCH, 6'-C), 60.9 (OCH₃), 60.2 (OCH₃), 56.0 (OCH₃), 51.4 (OCH₃), 42.5 (CH, 5-C), 40.6 (CH, 4-C), 35.4 (CH₂, 6-C), 17.8 (CH₃, 9-C), 16.6 (CH₃, 10-C), 9.8 (CH₃, 11-C); IR (neat) 2935.8, 1722.6, 1487.4, 1236.1, 1087.2 cm⁻¹; HRMS (EI) calculated for C₂₁H₃₀O₅Na [M⁺], m/z: 385.1985, found m/z: 385.1980.

**Minor isomer:**

¹H NMR (400 MHz, CDCl₃): δₙ 6.89 (dd, J = 9.2, 8.0 Hz, 1H, 3-H), 6.40 (s, 1H, 6'-H), 5.77 (d, J = 16.4 Hz, 1H, 2-H), 3.74 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.67 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 2.89-2.95 (m, 1H, 5-H), 2.14 (s, 3H, 11-H), 1.44 (d, J = 5.6 Hz, 3H, 9-H), 0.78 (d, J = 7.2 Hz, 3H, 10-H).
\( \pm (S,E)\)-methyl 4-((1R,4S)-5,6,8-trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (227)

Methanesulphonic acid (1.26 mL, 19.50 mmol) was added to a solution of 226 (2.36 g, 6.50 mmol) in CHCl₃ (20 mL) and the reaction stirred at 40 °C for 7 hrs. The reaction was quenched with saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3x50 mL). The organic layer was washed with brine (20 mL), dried MgSO₄ and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 4 % ethyl acetate/petroleum ether) gave the title compound as a light yellow oil in a 2:1 mixture of diastereoisomers 227 (1.70 g, 72%);

**Major isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \_H \) 6.85 (dd, \( J = 16.0, 7.2 \) Hz, 1H, 3-H), 5.55 (d, \( J = 16.0 \) Hz, 1H, 2-H), 3.84 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.67 (s, 3H, OCH₃), 3.67 (s, 3H, OCH₃), 3.08-3.15 (m, 1H, 4'-H), 2.96-2.99 (m, 1H, 2'-H), 2.81-2.89 (m, 1H, 4-H), 2.18 (s, 3H, 9'-H), 1.73-1.81 (m, 3H, 3'/1'-H), 1.38-1.42 (m, 1H, 3'-H), 1.25 (d, \( J = 7.2 \) Hz, 3H, 10'-H), 1.10 (d, \( J = 7.2 \) Hz, 3H, 5-H); \(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta \_C \) 167.3 (q), 154.4 (CH, 3-C), 152.8 (q), 150.0 (q), 147.2 (q), 134.6 (q), 126.8 (q), 122.5 (q), 118.5 (CH, 2-C), 60.5 (OCH₃), 60.3 (OCH₃), 59.9 (OCH₃), 51.2 (OCH₃) 41.1 (CH, 4-C), 37.6 (CH₂, 2'-C), 26.8 (CH, 4'-C), 25.8 (CH₂, 3'-C), 23.1 (CH₃, 10'-C), 18.8 (CH, 1'-C), 17.6 (CH₂, 5-C), 9.4 (CH₃, 9'-C); IR (neat) 2933.4, 1723.8, 1460.7, 1403.5, 1074.7 cm⁻¹; HRMS (EI) calculated for C₂₁H₃₀O₅Na [M⁺], m/z: 385.1985, found m/z: 385.1978.

**Minor isomer:**

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \_H \) 7.08 (dd, \( J = 15.6, 6.8 \) Hz, 1H, 3-H), 5.64 (d, \( J = 15.2 \) Hz, 1H, 2-H), 3.85 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 3.65 (s, 3H, OCH₃), 3.13-3.20 (m, 1H, 4'-H), 3.01-3.04 (m, 1H, 2'-H), 2.90-2.98 (m, 1H, 4-H), 2.14 (s, 3H, 9'-H), 1.70-1.93 (m, 3H, 3'/1'-H), 1.46-1.51 (m, 1H, 3'-H), 1.13 (d, \( J = 7.2 \) Hz, 3H, 10'-H), 0.93 (d, \( J = 7.2 \) Hz, 3H, 5-H).
± (S)-Methyl 4-((1R,4S)-5,6,8-trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanoate (228)\textsuperscript{38}

A solution of compound 227 (0.91 g, 2.50 mmol) in MeOH was circulated for 3 hrs through an H-Cube (set at 2.0 mL/min, Full hydrogen, rt) equipped with a cartridge containing catalyst Pd/C 10%. The reaction solution was concentrated in vacuo to give product 228 as colourless oil (0.82 g, 90%); Unable to interpret \textsuperscript{1}H & \textsuperscript{13}C NMR spectrum due to a mixture of diastereoisomers; IR (neat) 2933.4, 1738.0, 1457.9, 1403.5, 1069.0 cm\textsuperscript{-1}; HRMS (EI) calculated for C\textsubscript{21}H\textsubscript{32}O\textsubscript{5}Na [M]\textsuperscript{+}, m/z: 387.2142, found m/z: 387.2133.

± (S)-4-((1R,4S)-5,6,8-Trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentan-1-ol (229)\textsuperscript{47}

DIBAL 1M in hexanes (4.50 mL, 4.50 mmol) was added to a solution of 228 (0.82 g, 2.20 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (100 mL) and 4Å molecular sieves at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (5 mL), 5M HCl (5 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3x20 mL). The organic layer was washed with brine (20 mL), dried (MgSO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 229 in a 2:1 mixture of diastereoisomers (0.59 g, 79 %); For analytical purposes, an aliquot was separated of each isomer by preparative TLC (eluting with 10 % ethyl acetate/petroleum ether).
Major isomer:

$^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 3.78 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 3.57 (s, 3H, OCH$_3$), 3.53-3.62 (m, 2H, 1'-H), 3.05-3.12 (m, 1H, 4'-H), 2.76-2.80 (m, 1H, 1'-H), 2.10 (s, 3H, 9'-H), 1.85-1.96 (m, 2H, 3'/4'-H), 1.69-1.74 (m, 2H, 2'-H), 1.52-1.63 (m, 1H, 3-H), 1.35-1.41 (m, 1H, 3'-H), 1.24-1.31 (m, 1H, 3-H), 1.14-1.18 (m, 2H, 2-H), 1.07 (d, $J = 6.8$ Hz, 3H, 10'-H), 0.68 (d, $J = 6.8$ Hz, 3H, 5-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ$_C$ 153.0 (q), 149.5 (q), 147.2 (q), 134.5 (q), 128.4 (q), 122.1 (q), 63.3 (CH$_2$, 1-C), 60.5 (OCH$_3$), 60.1 (OCH$_3$), 59.9 (OCH$_3$), 37.9 (CH$_2$, 4-C), 37.2 (CH, 1'-C), 31.3 (CH$_2$, 3-C), 31.1 (CH$_2$, 2-C), 27.2 (CH, 4'-C), 26.4 (CH$_2$, 3'-C), 23.1 (CH$_3$, 10'-C), 20.2 (CH$_2$, 2'-C), 18.5 (CH$_3$, 5-C), 9.5 (CH$_3$, 9'-C).

Minor isomer:

$^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 3.77 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 3.57 (s, 3H, OCH$_3$), 3.44-3.50 (m, 2H, 1'-H), 3.02-3.09 (m, 1H, 4'-H), 2.71-2.74 (m, 1H, 1'-H), 2.10 (s, 3H, 9'-H), 1.77-1.88 (m, 2H, 3'/4'-H), 1.69-1.74 (m, 2H, 2'-H), 1.50-1.60 (m, 1H, 3-H), 1.38-1.40 (m, 1H, 3'-H), 1.26-1.34 (m, 2H, 2-H), 1.14-1.18 (m, 1H, 3-H), 1.08 (d, $J = 9.2$ Hz, 3H, 10'-H), 0.73 (d, $J = 6.4$ Hz, 3H, 5-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ$_C$ 152.8 (q), 147.1 (q), 134.8 (q), 128.6 (q), 122.2 (q), 76.7, 63.4 (CH$_2$, 1-C), 60.5 (OCH$_3$), 60.2 (OCH$_3$), 59.9 (OCH$_3$), 37.4 (CH, 4-C), 35.4 (CH, 1'-C), 31.2 (CH$_2$, 2-C), 30.6, 27.0, 26.4, 23.2 (CH$_3$, 10'-C), 18.6 (CH$_2$, 2'-C), 18.1 (CH$_3$, 5-C), 9.4 (CH$_3$, 9'-C); IR (neat) 3370.9, 2930.5, 1457.9, 1403.5, 1069.0 cm$^{-1}$; HRMS (El) calculated for C$_{20}$H$_{32}$O$_4$Na [M$^+$], m/z: 359.2193, found m/z: 359.2189.
± (S)-4,7-(1R,4S)-5,6,8-Trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanal (230) \(^\text{17}\)

To a solution of alcohol 229 (0.59 g, 1.70 mmol) in anhydrous CH\(_2\)Cl\(_2\) (20 mL) was added pyridinium chlorochromate (0.57 g, 2.60 mmol) in one portion at 0 °C. The reaction mixture was stirred at rt for 2 hrs then diluted with ether (100 mL). The crude reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as a pale yellow oil 230 in a 2:1 mixture of diastereoisomers (0.45 g, 78 %);

Major isomer:

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta_H\) 9.67 (t, \(J = 2.0\) Hz, 1H, 1'-H), 3.78 (s, 3H, OCH\(_3\)), 3.73 (s, 3H, OCH\(_3\)), 3.56 (s, 3H, OCH\(_3\)), 3.06-3.12 (m, 1H, 4'-H), 2.73-2.77 (m, 1H, 1'-H), 2.24-2.43 (m, 2H, 2-H), 2.09 (s, 3H, 9'-H), 1.79-1.94 (m, 2H, 4/3'-H), 1.51-1.62 (m, 2H, 3-H), 1.39 (d, \(J = 7.2\) Hz, 3H, 10'-H), 0.71 (d, \(J = 7.2\) Hz, 3H, 5-H);

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta_C\) 203.4 (CHO, 1-C), 152.8 (q), 149.7 (q), 134.7 (q), 127.9 (q), 122.3 (q), 60.5 (OCH\(_3\)), 60.1 (OCH\(_3\)), 59.9 (OCH\(_3\)), 42.4 (CH\(_2\), 2-C), 37.5 (CH, 4-C), 35.6 (CH, 1'-C), 27.4 (CH\(_2\), 3-C), 27.0 (CH, 4'-C), 26.4 (CH\(_2\), 3'-C), 23.2 (CH\(_3\), 10'-C), 18.8 (CH\(_2\), 2'-C), 18.1 (CH\(_3\), 5-C), 9.4 (CH\(_3\), 9'-C); \(\text{IR}\) (neat) 2932.9, 1725.1, 1459.3, 1403.8, 1073.3 cm\(^{-1}\); \(\text{HRMS}\) (El) calculated for C\(_{21}\)H\(_{34}\)O\(_5\)Na [M]\\(^+\), \text{m/z}: 389.2303, found \text{m/z}: 389.2288.

Minor isomer:

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta_H\) 9.70 (t, \(J = 2.0\) Hz, 1H, 1'-H), 1.08 (d, \(J = 6.8\) Hz, 3H, 10'-H), 0.71 (d, \(J = 6.8\) Hz, 3H, 5-H).
n-BuLi 2M solution in hexane (2.00 mL, 4.00 mmol) was added dropwise to a solution of isopropyltriphenyolphosphonium iodide (1.85 g, 4.30 mmol) in anhydrous THF (15 mL) at 0 °C under N₂. The mixture was stirred for 1 hr before aldehyde 230 (0.45 g, 1.30 mmol) in THF (15 mL) was added. The solution was allowed to stir at the same temperature for 30 minutes before warming to room temperature and refluxing for a further 2 hrs. After cooling, the reaction mixture was quenched with saturated NH₄Cl (10 mL) and extracted with ether (3x50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate/petroleum ether) gave the title compound as a colourless oil 231 in a 2:1 mixture of diastereoisomers (0.38 g, 80 %);

**Major isomer:**

1H NMR (400 MHz, CDCl₃): δ_H 5.06 (t, J = 6.4 Hz, 1H, 5'-H), 3.77 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.57 (s, 3H, OCH₃), 3.02-3.11 (m, 1H, 4'-H), 2.79-2.82 (m, 1H, 1'-H), 2.10 (s, 3H, 9'-H), 1.83-2.00 (m, 4H, 2/3/3'-H), 1.61-1.73 (m, 2H, 2'-H), 1.61 (s, 3H, 7'-H), 1.52 (s, 3H, 7'-H), 1.36-1.40 (m, 1H, 3'-H), 1.18-1.31 (m, 2H, 4'-H), 1.07 (d, J = 7.6 Hz, 3H, 10'-H), 0.65 (d, J = 6.8 Hz, 3H, 1'-H); 13C NMR (100 MHz, CDCl₃): δ_c 153.0 (q), 149.5 (q), 147.0 (q), 134.9 (q), 130.9 (q), 128.7 (q), 125.2 (CH, 5'-C), 122.2 (q), 60.5 (OCH₃), 60.1 (OCH₃), 59.9 (OCH₃), 37.5, 35.7 (CH₂, 4'-C), 35.6 (CH, 1'-C), 27.0 (CH), 4'-C, 26.6 (CH₃, 7'-C), 26.4, 25.7, 23.1 (CH₃, 10'-C), 18.5 (CH₂, 2'-C), 18.2 (CH₃, 1'-C), 17.6 (CH₃, 7'-C), 9.4 (CH₃, 9'-C); IR (neat) 2930.5, 2867.6, 1460.7, 1406.4, 1074.7 cm⁻¹; HRMS (EI) calculated for C₂₃H₂₄O₂Na [M]⁺, m/z: 383.2557, found m/z: 383.2549.

**Minor isomer:**

4.93 (t, J = 6.4 Hz, 1H, 5'-H), 3.72 (s, 3H, OCH₃), 3.56 (s, 3H, OCH₃), 2.69-2.72 (m, 1H, 1'-H), 1.57 (s, 3H, 7'-H), 1.47 (s, 3H, 7'-H), 1.08 (d, J = 6.8 Hz, 3H, 10'-H), 0.71 (d, J = 6.8 Hz, 3H, 1'-H).
± (SR,8S)-4-Methoxy-3,8-dimethyl-5-((S)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydrodronaphthalene-1,2-diol (233)\(^\text{17}\)

To a solution of ethanethiol (2.96 mL, 40.00 mmol) in anhydrous hexane (15 mL) at 0 °C under N\(_2\) was added n-BuLi 2M in hexane (5.00 mL, 10.00 mmol) and the reaction stirred at rt for 30 minutes. The mixture was concentrated in vacuo to give a white powder. The white powder and 231 (0.38 g, 1.00 mmol) was dissolved in anhydrous DMF (15 mL) and the reaction refluxed (180 °C) for 3 hrs. After cooling the reaction was acidified with 5 % HCl and extracted with ether (3x20 mL). The organic layer was washed with brine (10 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as an orange solid 233 in a 2:1 mixture of diastereoisomers (0.23 g, 68 %);

**Major isomer:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)H 5.15 (t, \(J = 6.4\) Hz, 1H, 5-H), 4.96 (s, OH), 4.82 (s, OH), 3.65 (s, 3H, OCH\(_3\)), 3.04-3.11 (m, 1H, 8'-H), 2.89 (t, \(J = 5.2\) Hz, 1H, 5'-H), 2.20 (s, 3H, 10'-H), 1.96-2.07 (m, 4H, 2/3/7'-H), 1.77-1.84 (m, 2H, 6'-H), 1.71 (s, 3H, 7-H), 1.62 (s, 3H, 7-H), 1.48-1.53 (m, 1H, 7'-H), 1.26-1.39 (m, 2H, 4-H), 1.20 (d, \(J = 6.8\) Hz, 3H, 9'-H), 0.76 (d, \(J = 7.2\) Hz, 3H, 1-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)C 150.6 (q), 140.1 (q), 136.9 (q), 130.8 (q), 127.3 (q), 125.3 (CH, 5-C), 124.6 (q), 114.9 (q), 60.5 (OCH\(_3\)), 37.6, 35.7 (CH\(_2\), 4-C), 35.4 (CH, 5'-C), 26.7 (CH, 8'-C), 26.4, 26.4, 25.7 (CH\(_3\), 7-C), 21.6 (CH\(_3\), 9'-C), 18.7 (CH\(_2\), 6'-C), 18.2 (CH\(_3\), 1-C), 17.7 (CH\(_3\), 7-C), 9.2 (CH\(_3\), 10'-C); IR (neat) 3425.2, 2927.6, 1641.8, 1450.0, 1376.2, 1295.5, 1285.2, 1094.3 cm\(^{-1}\); HRMS (EI) calculated for C\(_{21}\)H\(_{30}\)O\(_3\)Na [M\(^+\), m/z: 353.2092, found m/z: 353.2076.

**Minor isomer:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)H 3.63 (s, 3H, OCH\(_3\)), 1.67 (s, 3H, 7-H), 1.58 (s, 3H, 7-H), 1.21 (d, \(J = 6.8\) Hz, 3H, 9'-H), 0.80 (d, \(J = 7.1\) Hz, 3H, 1-H).
± (5R,8S)-4-Methoxy-3,8-dimethyl-5-((S)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,2-dione (234)

A solution of cerium ammonium nitrate (0.98 g, 1.80 mmol) in water (5 mL) was added to a solution of diol 233 (0.20 g, 0.60 mmol) in MeCN (15 mL) at 0 °C. The reaction was stirred for 20 minutes before water (10 mL) was added. The mixture was extracted with ether (3x20 mL) and the combined organic layers washed with brine (20 mL), dried (MgSO4) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 10% ethyl acetate/petroleum ether) gave the title compound as an orange/red oil 234 in a 2:1 mixture of diastereoisomers (0.13 g, 68%);

**Major isomer:**

**1H NMR** (400 MHz, CDCl3): δH 5.04 (t, J = 6.4 Hz, 1H, 5'-H), 3.84 (s, 3H, OCH3), 2.56-2.59 (m, 1H, 8'-H), 1.93-1.98 (m, 2H, 4'H), 1.90 (s, 3H, 10'-H), 1.76-1.67 (m, 4H), 1.64 (s, 3H, 7-H), 1.54 (s, 3H, 7-H), 1.24-1.35 (m, 3H), 1.01 (d, J = 7.2 Hz, 3H, 9'-H), 0.78 (d, J = 7.2 Hz, 3H, 1-H);

**13C NMR** (100 MHz, CDCl3): δC 181.2 (q), 179.4 (q), 167.7 (q), 150.5 (q), 140.3 (q), 131.6 (q), 124.4 (CH, 5-C), 119.7 (q), 61.2 (OCH3), 37.2 (CH, 5'-C), 36.4, 35.7, 26.3 (CH, 8'-C), 26.2 (CH2, 4-C), 25.8, 25.7 (CH3, 7-C), 21.3 (CH3, 9'-C), 18.5, 17.7 (CH3, 7-C), 17.5 (CH3, 1-C), 9.8 (CH3, 10'-C);

**IR** (neat) 2963.1, 1656.8, 1454.1, 1575.3, 1377.4, 1235.7 cm⁻¹; **HRMS** (EI) calculated for C21H30O3Na [M+] m/z: 353.1714, found m/z: 353.2087.

**Major isomer:**

**1H NMR** (400 MHz, CDCl3): δH 5.03 (t, J = 7.2 Hz, 1H, 5'-H), 1.68 (s, 3H, 7-H), 1.58 (s, 3H, 7-H), 0.99 (d, J = 7.6 Hz, 3H, 1-H).
± Elizabethadione (3)\textsuperscript{17}

4-Methylbenzenesulphonic acid (0.14 g, 0.70 mmol) was added to a solution of 234 (0.13 g, 0.40 mmol) in anhydrous benzene (7.0 mL) at rt. The reaction was stirred for 2 hrs before being diluted with ether (20 mL). The organic layer was washed with brine (20 mL), dried (MgSO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 1 % ethyl acetate/hexane) gave the title compound as an yellow solid 3 as a 2:1 mixture of diastereoisomers (0.09 g, 75 %);

**Major isomer:**

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 6.97 (s, OH), 5.12 (t, J = 6.4 Hz, 1H, 5'-H), 2.93-3.00 (m, 1H, 8'-H), 2.89-2.92 (m, 1H, 5'-H), 1.98-2.10 (m, 2H, 4-H), 1.95 (s, 3H, 10'-H), 1.76-1.90 (m, 2H), 1.71 (s, 3H, 7-H), 1.63-1.66 (m, 2H), 1.62 (s, 3H, 7-H), 1.45-1.51 (m, 1H), 1.19-1.37 (m, 2H, 3-H), 1.12 (d, J = 7.2 Hz, 3H, 9'-H), 0.83 (d, J = 6.8 Hz, 3H, 1-H); \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 187.9 (q), 182.9 (q), 150.6 (q), 148.2 (q), 143.1 (q), 131.3 (q), 124.5 (CH, 5-C), 116.8 (q), 36.9, 36.0 (CH\textsubscript{3}, 3-C), 35.1 (CH, 5'-C), 26.3, 26.1 (CH, 8'-C), 26.0, 25.7 (CH\textsubscript{3}, 7-C), 20.8 (CH\textsubscript{3}, 9'-C), 18.1, 17.7 (CH\textsubscript{3}, 7-C), 17.6 (CH\textsubscript{3}, 1-C), 8.2 (CH\textsubscript{3}, 10'-C); IR (neat) 3391.5, 2933.4, 1638.4, 1336.2, 1234.6, 1155.1 cm\textsuperscript{-1}; \textbf{HRMS} (El) calculated for C\textsubscript{20}H\textsubscript{28}O\textsubscript{3} [M]+, m/z: 316.1986.

**Minor isomer:**

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 5.03 (t, J = 6.0 Hz, 1H, 5-H), 1.68 (s, 3H, 7-H), 1.58 (s, 3H, 7-H), 0.87 (d, J = 6.8 Hz, 3H, 1-H).
7.0 - References


98. Further work has been carried out post viva which has completed the asymmetric synthesis of both (+)-Erogorgiaene and (+)-Elisabethadione. Refer to C. Incerti-Pradillos thesis for experimental work towards the asymmetric versions.
8.0 - Appendix

Crystal data for compound 233

Figure: 8.1

Figure: 8.2
**Figure**: 8.3

<table>
<thead>
<tr>
<th>Chemical Formula</th>
<th>$F(000) = 728$</th>
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<tbody>
<tr>
<td>$M_r = 332.46$</td>
<td>$D_{x} = 1.162$ Mg m$^{-3}$</td>
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<td>Monoclinic, $P2_1/c$</td>
<td>Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å</td>
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<tr>
<td>$a = 18.179$ (3) Å</td>
<td>Cell parameters from 4631 reflections</td>
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<tr>
<td>$b = 7.3992$ (10) Å</td>
<td>$\theta = 2.3$–$30.2$°</td>
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<tr>
<td>$c = 14.334$ (2) Å</td>
<td>$\mu = 0.08$ mm$^{-1}$</td>
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<tr>
<td>$\beta = 99.856$ (2)$^\circ$</td>
<td>$T = 150$ K</td>
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<tr>
<td>$V = 1899.6$ (5) Å$^3$</td>
<td>Plate, colourless</td>
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<td>$Z = 4$</td>
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**Data collection**

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<th>Instrument</th>
<th>5734 independent reflections</th>
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<td>Radiation source</td>
<td>4047 reflections with $I &gt; 2\sigma(I)$</td>
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<tr>
<td>Graphite</td>
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<tr>
<td>$\omega$ rotation with narrow frames scans</td>
<td>$\theta_{max} = 30.6$°, $\theta_{min} = 2.3$°</td>
</tr>
<tr>
<td>Absorption correction: multi-scan</td>
<td>$h = -25\rightarrow25$</td>
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<tr>
<td><em>SADABS</em> v2009/1, Sheldrick, G.M., (2009)</td>
<td>$k = -10\rightarrow10$</td>
</tr>
<tr>
<td>$T_{min} = 0.938$, $T_{max} = 0.997$</td>
<td>$l = -20\rightarrow20$</td>
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<td>21151 measured reflections</td>
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Refinement

Refinement on $F^2$

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.049$

$wR(F^2) = 0.143$

$S = 1.05$

5734 reflections

340 parameters

19 restraints

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0738P)^2 + 0.271P]$

where $P = (F_o^2 + 2F_c^2)/3$

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

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<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{iso}$/$U_{eq}$</th>
<th>Occ. (&lt;1)</th>
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Symmetry codes: (i) -x, -y+1, -z+1; (ii) x, -y+3/2, z+1/2.

Computing details

Data collection: Bruker APEX 2; cell refinement: Bruker SAINT; data reduction: Bruker SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL2012 (Sheldrick, 2012); molecular graphics: Bruker SHELXTL; software used to prepare material for publication: Bruker SHELXTL.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.
NMR data for (±)-elisabethadione (3)
Davies NMR data for (+)-elisabethadione (synthetic)\textsuperscript{17}