Towards the total synthesis of Diaporthichalasin

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

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Hugh Allen Hoather

School of Chemistry
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Abstract

(2E,4E,6E,8E)-2,4,6,8-Tetramethyldeca-2,4,6,8-tetraen-1-ol 267 was synthesised via three successive sequence of reactions comprising Horner-Wadsworth-Emmons olefination, followed by DIBAL-H reduction and then oxidation with activated manganese dioxide. When coupled with mono-methyl fumarate 273, the resulting tetraene methyl fumarate 272, comprising of a tri-substituted diene and doubly activated dienophile, cyclised in an intramolecular Diels Alder reaction to create adduct 274, with exclusive endo-stereochemistry. Four contiguous stereogenic centres were created in the reaction, one of which was a quaternary centre. This demonstrated the feasibility of the conjugated tetraene to successfully undergo Diels Alder reactions.

A condensation reaction of (R)1-benzoyl-5-benzylpyrrrolidin-2-one 303 with (5E,7E)-1-((1H-imidazol-1-yl)-5,7-dimethylnona-5,7-dien-1-one 324, followed by installation of the double bond of the dienophile, resulted (5S)-1-benzoyl-5-benzyl-3-((5E,7E)-5,7-dimethylocta-5,7-dienoyl)-1H-pyrrol-2(5H)-one 323. Adduct 323 cyclised in a Diels Alder reaction to give (3S,3aR,6aR,10aR)-2-benzyol-3-benzyl-4,5,6a-trimethyl-2,3,3a,4,6a,7,8,9-octahydrobenzo(d)isoindole-1,10-dione 322. This intramolecular Diels Alder reaction generated four stereogenic centres, of which, two are quaternary centres. The structure exhibited exo-stereo chemistry with respect to the pyrrolinone.

Acylation of (2E,4E,6E,8E)-2,4,6,8-Tetramethyldeca-2,4,6,8-tetraen-1-ol 267 gave (2E,4E,6E,8E)-2,4,6,8-Tetramethyldeca-2,4,6,8-tetraenyl-acetate 258, which was reacted with (E)-6-Bromo-1-tert-butyldimethylsilyl-2-hexene 280 to give (2E,8E,10E,12E)-8,10,12,14-Tetramethylhexadeca-2,8,12,14-pentaenal 23 after deprotection and oxidation. An Aldol reaction between (R)-tert-butyl 2-benzy1-5-oxopyrrrolidine-1-carboxylate 292 and (2E,8E,10E,12E)-8,10,12,14-Tetramethylhexadeca-2,8,12,14-pentaenal 23 produced (5R)-tert-butyl-5-benzy1-3-((2E,8E,10E,12E,14E)-1-hydroxy-8,10,12,14-tetramethylhexadeca-2,8,10,12,14-pentaen-1-yl)-2-oxopyrrrolidine-1-carboxylate 340. This brought the synthesis to within four steps of attempting the domino Diels Alder reactions to put in place the isoindolone core fused to the 13 membered tricyclic system of diaporthichalasin 1.
Declaration

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The Author

The author is a mature student who returned to University after taking early retirement from a career in local government and industry. He graduated from the Open University with a first class degree and later went on to obtain an MBA. For the last three and a half years he has undertaken research into the total synthesis of a natural product under the supervision of Professor E J Thomas at the University of Manchester.
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Finally, my deepest thanks go to my family and especially my wife Kathryn. Without their love and support this work would have been impossible. It is to them, and my son Stuart, who we tragically lost too early in his life, that I dedicate this work.
In loving memory of Stuart and for my family.....
### Terms and abbreviations

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<th>Description</th>
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<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2′-azobis(2-propionitrile)</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene</td>
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<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
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<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
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</tr>
<tr>
<td>cat.</td>
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<tr>
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<tr>
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<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>δ</td>
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</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DIAD</td>
<td>Di-isopropylazodicarboxylate</td>
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<tr>
<td>DIBAL-H</td>
<td>Di-isobutylaluminium hydride</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N′-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Di-isopropylethylamine (Hunig’s base)</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
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<td>Dess-Martin Periodinane</td>
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<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>d.r</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>E</td>
<td>Entgegen (trans)</td>
</tr>
<tr>
<td>EDCI</td>
<td>Ethyl(dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact ionization</td>
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<td>Electrospray</td>
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<tr>
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<td>Equivalents</td>
</tr>
<tr>
<td>FMO</td>
<td>Frontier Molecular Orbital</td>
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<td>FTIR</td>
<td>Fourier transform infrared</td>
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</tr>
<tr>
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<td>Hour/s</td>
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<tr>
<td>HMDS</td>
<td>Hexamethyldisilazide</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
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HWE
HWE
Horner-Wadsworth-Emmons

i
Iso

IMDA
Intramolecular Diels Alder

IR
Infrared

L
Litre

LDA
Lithium di-iso-propylamine

m
Multiplet

M
Molarity / general metal group

M+
Molecular ion

Me
Methyl

MHz
Megahertz

min
Minutes

mg
Milligrams

mmol
Millimoles

mol
Moles

MPt
Melting point

Ms
Methanesulfonyl

MS
Molecular sieves / Mass spectrometry

m/z
Mass to charge ratio

n
normal

NMO
N-Methylmorpholine-N-oxide

NMR
Nuclear magnetic resonance

nOe
Nuclear Overhauser effect

P
General protecting group

PCC
Pyridinium chlorochromate

PDC
Pyridinium dichromate

Petrol
40-60 Petroleum ether

Ph
Phenyl

ppm
Parts per million

PPTS
Pyridinium para-toluenesulfonic acid

Pr
Propyl

q
Quartet

R
General group

Rf
Retention factor

Rochelle’s salt
Potassium sodium tartrate

rt
Room temperature

s
Singlet

sat.
Saturated

SEM
2-(trimethylsilyl)ethoxymethoxy

s.m.
Starting material

t
Triplet

t
tertiary

TBAF
Tetra-n-butylammonium fluoride

TBDPS
tert-butyldiphenylsilyl

TBS
tert-butyldimethylsilyl

TES
Triethylsilyl

Tf
Trifluoromethanesulfonyl

TFA
Trifluoroacetic acid

THF
Tetrahydrofuran
THP  Tetrahydropyran-2-yl
TLC  Thin layer chromatography
TMS  Trimethylsilyl (tetramethylsilane)
TPAP  Tetra-\textit{n}-propylammonium perruthenate
Ts  4-Toluenesulfonyl
\textmu{}l  Microlitres
\textmu{}mol  Micromoles
UV  Ultraviolet
\nu{}  Wavenumber
X  General group
X_c  Chiral auxiliary
Y  General group
Z  Zusammen (\textit{cis})
Chapter 1
Introduction

1.1 Preface

This thesis relates to research carried out by the author over the past three years working towards the total synthesis of a natural product. Nature constantly produces fascinating and intriguingly complex organic molecules in the most elegant ways. Many have diverse biological functions and some are life-saving. Synthetic chemists strive to replicate what nature may have taken thousands of years to perfect, because science that leads to a better understanding and possible harnessing of cellular level activity has the potential to improve life. The target of this research is the natural compound diaporthichalasin.

Diaporthichalasin is a member of a large family of natural compounds called cytochalasans that have been the subject of much research because of their biological importance and structural complexity. Diaporthichalasin is no exception; not only is it a challenging synthetic target, but it shows potent inhibition of a cytochrome enzyme, which has a key role in the biosynthesis of lipids, steroids and other secondary metabolites.

The biosynthesis is believed to arise via a polyketide pathway and this synthesis primarily follows a biomimetic strategy involving the construction of a long, highly functionalised carbon chain designed to enable two intramolecular Diels Alder reactions to consecutively take place to form the isoindolone core and tricyclic system of rings with the correct stereochemistry in place. Deprotection and pyrrolidinone oxidation will complete the synthesis. This late stage Diels Alder approach is the acknowledged biosynthetic route. There are ten stereogenic centres in diaporthichalasin and four of them are quaternary centres. Establishing the Diels Alder conditions for forming the quaternary centres in diaporthichalasin is a key feature of this research.
Early work on the syntheses of less complex members of the cytochalasan family has successfully utilised the late stage Diels Alder approach. This research builds on this earlier work to encompass Diels Alder reactions on a linear conjugated tetraene and a highly functionalised pyrrolidinone, both of which are shown to form the desired quaternary centres.

Figure 1 shows the structure and stereochemistry of diaporthichalasin 1.

Figure 1  Diaporthichalasin 1

1.2  Background

Cytochalasans were independently discovered in 1966 in Switzerland by Rothweiler and Tamm\(^1\) and in the United Kingdom by Aldridge et al.\(^2\) They were found to be structurally complex organic compounds endowed with remarkable biological properties in that they are biologically active fungal metabolites that permeate cell membranes and cause cells to stop translocating.\(^3\) These critical biological functions have made cytochalasans important tools in cell research and hence attractive synthetic targets. Since their discovery, a large number of this class of natural compounds have been isolated from a variety of filamentous fungi.\(^4\)
1.3 **The Cytochalasans - structure and stereochemistry**

Three characteristic examples of the cytochalasan family are shown in Figure 2. The cytochalasans generally comprise an isoindolone unit fused to a highly functionalised 11-13 or 14-membered macrocyclic ring and differ according to whether they possess an isopropyl, an indoyl or a phenyl group at C10 arising from incorporation of leucine, tryptophan or phenylalanine respectively. The stereochemistry is consistent for all cytochalasans and this is particularly true of the absolute configuration of the isoindolone ring system. In general, the 6-membered ring of the isoindolone unit is in a twist-boat conformation and is cis-fused to its 5-membered counterpart. The isoindolone unit is trans-fused to the macrocyclic ring system within which the macrocyclic ring carbons are in chair conformations. The stereochemistry at C10 adopts variable compound specific conformations.

![Aspochalasin A, Chaetoglobosin C, Cytochalasin A](image)

**Figure 2** Three characteristic members of the cytochalasan family with systematic numbering

Diaporthichalasin 1 follows this general pattern but is notably different in that instead of a macrocyclic ring, it contains a tricyclic ring system. The central
isoindolone core is present but the compound differs in that the cyclopentanone ring is *cis*-fused to the isoindolone unit on one side and *cis*-fused to the cyclohexene ring on the other. The cyclohexene ring is *trans*-fused to the cyclohexane ring. To complete the structure, a para-phenol group is attached at C10 rather than a phenyl group and there is a hydroxyl group at C3. There are ten stereogenic centres, four of which are quaternary centres at C3, C8, C9 and C16 (Figure 1, page 16).

1.4 **Biological activity of cytochalasans**

The cytochalasans have been shown to have a wide range of biological activities. Their effects on cells include cytoplasmic cleavage during cell division, prevention of cell movement, platelet aggregation, breakdown of blood clots and phagocytosis.\(^9\)\(^-\)\(^1\)\(^1\) Two (L-696,474 and cytochalasin A) have been reported to act as HIV protease inhibitors,\(^1\)\(^2\) whilst cytochalasin A and cytochalasin B inhibit glucose transport across the plasma membrane.\(^1\)\(^3\) Another example is cytochalasin E, which prevents the growth of new blood vessels.\(^1\)\(^4\) It is interesting to note that the highly functionalised structure of the macrocyclic element of the cytochalasans appears to be central in the determination of their biological activities.\(^1\)\(^5\) As such they are compounds of considerable biological importance.

1.5 **The mechanism of the biological activity of cytochalasans**

The cellular activity of certain members of the cytochalasan family comes from their ability to permeate cell membranes and bind to the barbed, fast growing end of actin filaments, effectively inhibiting elongation at that end.\(^1\)\(^6\) Growth is therefore limited to the other end of the filament which, as a consequence, elongates more slowly until the filaments reach a steady state with monomers in solution. Binding to the barbed end in this way not only acts as a blocking mechanism to filament growth, but has also been shown to inhibit both the association and dissociation of subunits thereby altering actin’s ability to
polymerise. This inhibition has also been reported to induce cell cycle arrest or apoptosis. In addition to binding tightly to the ends of filaments, specific cytochalasans are thought to effect actin polymerisation by direct interaction with monomeric actin. As an example, studies have shown that cytochalasin D interacts with actin monomers and filaments in the presence of ADP and ATP. For clarification, actin monomers have mainly bound ATP and filaments have bound ADP. Goddette and Frieden, and others found that cytochalasin D increased the rate of spontaneous polymerisation of actin monomers; increased the rate of ATP hydrolysis of actin monomers; and induced dimerisation of ATP-actin monomers.

This ability to block an end of actin filaments, nucleate polymerisation and shorten filaments, as capping proteins in nature do, has led to cytochalasans being extensively used as models for actin-binding proteins to study the role of actin in biological processes.

### 1.6 Discovery and isolation

During a search for biologically active compounds in the forests of Bangkok in 2006, Pornpakakul and co-workers discovered diaporthichalasin from the endophytic fungus *Diaporthe Sp. Bkk3* found on *Croton sublyratus* leaves. It was isolated by growing mycelia from the fungus on malt extract agar. After 60 days the mycelia were filtered, extracted into hexane and methanol, concentrated, then, after flash chromatography on silica, recrystallisation gave diaporthichalasin 1.

A diastereoisomer of diaporthichalasin 1 was discovered earlier in 1995 by Horn *et al.* who reported the isolation of an antimicrobial compound from an endophytic *Phomopsis* sp. from surface sterilised twigs of *Salix gracilostyla* (variety melanostachys). This diastereoisomer was named phomopsichalasin 2. Colonies of the isolate were grown on malt agar from which a conidial suspension was prepared and seed cultures incubated. Fermentation was achieved on a medium of Nabisco Original Shredded Wheat and flash chromatography isolated phomopsichalasin in the form of an oil.
1.7 Biological aspects of diaporthichalasin and phomopsichalasin

Biological testing has shown that phomopsichalasin \( 2 \) possesses antibacterial activity against various bacteria including *Bacillus subtilis*, *Salmonella gallinarum*, *Staphylococcus auras* and *Candida tropicalis*,\(^{25}\) whereas diaporthichalasin \( 1 \) exhibits potent inhibition of the cytochrome P450 enzyme CYP3A4, with an IC\(_{50}\) value of 0.626 \( \mu \text{M} \).\(^{24}\) Cytochrome P450 enzymes are recognised as having a key role in the biosynthesis of lipids, steroids and other secondary metabolites and have been shown to be responsible for drug metabolism, carcinogenesis and degradation of xenobiotics.\(^{24}\) Most importantly, CYP3A4 is one of the most abundant enzymes in human liver microsomes, metabolising a high percentage of drugs bio-transformed by this family of enzymes.\(^{26}\)

1.8 Structure determination

![Figure 3](image)

**Figure 3** Diaporthichalasin \( 1 \) and Phomopsichalasin \( 2 \) with systematic numbering

The structure of phomopsichalasin \( 2 \) was assigned on the basis of an array of 1D and 2D NMR and mass spectral data analysis. This established the molecular formula to be \( \text{C}_{32}\text{H}_{41}\text{NO}_4 \) and determined that there were six methyl groups, two
double bonds, two carbonyl groups and a phenol ring. The stereochemistry was reported to be as set out in structure 2 of Figure 3. The cyclopentanone ring is \textit{trans}-fused to the isoindolone moiety at C8 and C9 and \textit{cis}-fused to the cyclohexene ring at C13-C22, which in turn is \textit{trans}-fused to the cyclohexane ring at C16-C21.

The structure of diaporthichalasin 1 on the other hand was determined using NMR and mass spectrometry techniques with confirmation by a single-crystal X-ray study. Pornpakakul and co-workers characterisation was consistent with the characterisation of phomopsichalasin by Horn \textit{et al.} but showed the cyclopentanone ring to be \textit{cis}-fused to the isoindolone moiety at C8 and C9.

Optical rotation and different biological activity distinguishes the two isomers. Diaporthichalasin 1 showed strong negative optical rotation, \([\alpha]_{D}^{20} -135 \) (c 0.14, MeOH) and has no anti-microbial activity in contrast with the weak negative rotation of phomopsichalasin 2, \([\alpha]_{D}^{25} -7.16\) (concentration not reported) and its biological activity against the three cell cultures described earlier.

However, in 2012 Thomas Hoye and co-workers undertook an in depth study of both compounds and on the basis of empirical and computational shift analysis reassigned the relative configuration of phomopsichalasin to that of diaporthichalasin. Their study showed both compounds to be identical with the structure of diaporthichalasin. The techniques that Hoye used were more refined than those available to Horn \textit{et al.} some 15 years earlier and so, on the evidence of Hoye \textit{et al.} the compound that was thought to have the structure of phomopsichalasin 2 has yet to be discovered.

1.9 \textit{Biosynthetic pathway of diaporthichalasin}

Building on the work of Vederas and Tamm, who suggested that the biosynthesis of the cytochalasans arose \textit{via} polyketide synthase and non-ribosomal peptide synthase pathways, and Stocking and Williams, who reviewed evidence of Diels Alder mechanisms in the biosynthesis of all of the
known classes of natural products,\textsuperscript{29} Pornpakakul \textit{et al.}\textsuperscript{24} proposed that the biosynthesis of diaporthichalasin involved the construction of long chain pyrrolineone 4 (Figure 4, page 23) with the phenol fragment derived from tyrosine. From this precursor the three fused rings can be created by two domino [4+2] \textit{intra}-molecular Diels Alder reactions. The dienophile of the perhydroisoindole can present in two orientations to the diene, resulting in either an \textit{exo} or \textit{endo} Diels Alder reaction with the perhydroisoindole. The terminal diene and the more reactive perhydroisoindole moiety of diaporthichalasin may occur \textit{via} an \textit{exo}-selective Diels Alder reaction. However, if the terminal diene and the perhydroisoindole moiety proceed \textit{via} an \textit{endo}-selective Diels Alder reaction this would lead to the as yet undiscovered diastereoisomer of diaporthichalasin. In either case the second Diels Alder reaction would follow immediately and form the top two rings. Oxidation at C3 gives the target compound diaporthichalasin 1.\textsuperscript{29,30} However, in principle either of the two IMDA reactions could occur \textit{en-route} from 4 to 1. Figure 4 illustrates the sequence that is thought to be the biosynthetic pathway including the \textit{endo}- and \textit{exo-} transition states.

It is possible that nature has a specific enzyme catalyst to mediate the \textit{intra}molecular Diels Alder reactions and dictate the conformational factors affecting the stereoselectivity of these reactions.
Figure 4  Postulated biosynthetic pathway to 1 and 2 showing the endo- and exo-transition states\textsuperscript{24}
Eight stereogenic centres are generated in this sequence of reactions including quaternary centres at C8, C9 and C16, which may affect the rate of the reaction.

Construction of the decalin system may be an important early step in the formation of the tricyclic rings of diaporthichalasin because it is quite possible that the first Diels Alder reaction puts the top two rings of the tricyclic system in place first by forming a bicyclic trans-fused [4.4.0]-decalin system, which includes a quaternary centre at the ring junction. As intermediate species, the bicyclic [4.4.0]-decenes 9 and 10 may be more thermodynamically favoured species than the intermediate isoindolone macrocycles 5 and 8. Analogous but less hindered Diels Alder reactions that form decalins are known. Diels Alder reactions of dodeca-2,8,10-trienoates and long chain 2,8,10-trienals have been reported under thermal conditions and at room temperature with imidazolidinone catalysts. Figure 5 shows this alternative pathway.

Figure 5  Formation of bicyclic [4.4.0]-decenes via endo-processes

Diels Alder reactions leading to the bicyclic [4.4.0]-decenes are both endo-processes that take place on different faces of the diene.

MacMillan et al. have successfully constructed similar decalin systems using organocatalysis via intramolecular Diels Alder cyclisations of trienal aldehydes in their synthesis of solanapyrone D. They described synthesising several
bicyclic systems with good enantioselectivities using first and second generation imidazolidinone catalysts. A pertinent feature of the work of MacMillan et al. to that of the synthesis of diaporthichalasin is that their synthesis generated cycloadducts that had a quaternary methyl group.

1.10 Evidence for one-pot Diels Alder cyclisations in the formation of macrocyclic rings

There is some evidence that the one-pot transformation using Diels Alder cyclisation might be fruitful in the biomimetic synthesis of diaporthichalasin 1. Thomas et al.,37 in their syntheses of several cytochalasans, have shown the viability of using an intramolecular Diels Alder reaction to assemble the isoindolone and the 11-membered macrocyclic rings simultaneously. In early studies of cytochalasans with a 13-membered macrocycle ring, using the one-pot approach, they showed that cyclisation produced an almost equal mixture of endo- and exo-products.38 Interestingly, the cyclisation of the aspochalasin precursor 11 (Figure 6), which has an additional 8´ methyl substituent gave mainly the exo-adduct 12 from the (8´E) isomer and the endo-adduct 13 from the (8´Z) isomer (ratio 3:2 respectively).39 The formation of the exo-adduct from the (8´E)-Diels Alder precursor is the precise stereoselectivity required to form the 13-membered ring and isoindolone unit occurring in the more complex diaporthichalasin 1, and hence shows the feasibility of a biomimetic one-pot approach to the synthesis of this natural product.
Despite this early work the efficient formation of macrocyclic rings is still a major problem in organic synthesis because of competing intermolecular processes.

### 1.11 Retrosynthetic analysis of diaporthichalasin

Retrosynthetic analysis lends support to the hypothesis for the biosynthetic route. Disconnection of diaporthichalasin 1 between C4-C5; C4-C9; C8-C9; C13-C22; and C16-C21 (Figure 7, page 27) leads to the open chain tetraene 14. Essentially the molecule has been “unzipped” to form the precursor to the 13-carbon macrolide structure and the isoindolone unit.
Open chain acid 14 will undergo reduction to its corresponding aldehyde 3 (Figure 4, page 23) which will cyclise in a Knoevenagel reaction to form the reduced isoindolone 15. Disconnection between C5 and C6 of isoindolone 15 gives pyrrolidinone 16 and the open chain aldehyde 18. Pyrrolidinone 16 can be synthesised from commercially available L-tyrosine. Alternatively, a disconnection between C4 and C5 of isoindolone 15 will give long chain aldehyde 17, which on further disconnection between C5 and C6 of aldehyde 17 will leave an N-acetyltyrosinol fragment, plus the open chain aldehyde 18. Disconnection of 18 at C2 and C3 will give 20, which can be obtained, after disconnection at C8 and C9, from addition of 21 with the vinyl lithium reagent derived from the iodide 19, prepared by a Negishi reaction on the corresponding alkyne, in the presence of Yb(OTf)₃. Oxidation of 20 to the corresponding ketone and conversion to the enol triflate will give the tetraene on treatment of the triflate with lithium dimethyl cuprate. Deprotection, oxidation and a silyl Wittig reaction will lead to aldehyde 18. Aldehyde 21 can be obtained from commercially available tiglic aldehyde 22 by phosphonate condensation and subsequent reduction (Figure 8, page 28).
Figure 8  Disconnection of pyrrolidinone 15
Chapter 2

Aims and objectives of this research

2.1 Aims

The aim of this research is to achieve the total synthesis of diaporthichalasin 1, and possibly one or more of its diastereoisomers with methods that, as closely as possible, follow the accepted biosynthetic pathway.

2.2 Objectives

The first objective is to synthesise the conjugated tetraene. However, the methyl group at C18 of diaporthichalasin 1 (Figure 7, page 27) may, with its stereochemistry and position in the plane of the five methyl substituents of tetraene 14, have been particularly time consuming to construct, so it was felt prudent, at this early stage, to simplify the structure. Our preliminary target molecule was therefore open chain aldehyde 23, which only differed from 18 in that there is no methyl group at C6 (Figure 9). This simplification may more easily allow appropriate conditions for cyclisation to be established for the open chain tetraene, which can then be further developed to facilitate the late stage Diels Alder cyclisation to form the central core of diaporthichalasin 1.

![Figure 9](image_url) Conjugated aldehyde 18 and preliminary target molecule, aldehyde 23
The second key objective is to investigate the capacity of the penta-substituted conjugated tetraene to undergo an *intra*-molecular Diels Alder cyclisation in which a quaternary centre is formed. Ideally, this would involve forming a bicyclic [4.4.0]-decalin system via a Diels Alder cyclisation of aldehyde 23. If successful, this cyclisation would have the key advantage of putting in place two of the six-membered rings of diaporthichalasin 1, with the correct stereochemistry (Figure 10). An added advantage would also be that the conjugated tetraene would be utilised early in the synthesis, thereby avoiding potential problems from this acid sensitive structure later in the synthesis.

![Synthetic route to bicyclic [4.4.0]-decalin 24](image)

**Figure 10** Synthetic route to bicyclic [4.4.0]-decalin 24

The further objective is to synthesis the isoindolone core of diaporthichalasin 1 and in the process form two quaternary centres (Figure 11, page 31). This can be approached either by a stepwise construction of a pyrrolidinone, the chemistry of which is known, or alternatively by synthesising a pyrrolinone via a Knoevenagel cyclisation of an imide. In either case, this will establish the viability of the pyrrolinone fragment of diaporthichalasin 1 undergoing a Diels Alder reaction with a trisubstituted diene, as is required in the natural system.
With this knowledge in hand, the research will then concentrate on the biomimetic route by synthesising long chain pyrrolinone 26, then subjecting it to two cascade Diels Alder cyclisation reactions to form, in one-pot, the isoindolone core and tricyclic rings of diaporthichalasin 1 (Figure 12).

If these objectives are achieved the research will have established a biomimetic route to an analogue of diaporthichalasin 1.
Chapter 3

Synthesis of the cytochalasans

3.1 Overview

There have been two different general approaches to the syntheses of cytochalasans. One follows the biomimetic route that first involves constructing a long functionalised open chain then subjecting it to a number of cascade reactions that substantially results in the target molecule being formed in a one-pot reaction. The other strategy forms the isoindolone unit first then constructs the precursor to the macrocycle in a stepwise fashion before final closure to form the macrocycle. Both strategies have resulted in the successful synthesis of cytochalasans but the late stage intramolecular Diels Alder cyclisation approach is a biomimetic route.

3.2 The late stage IMDA strategy in the total synthesis of cytochalasans

Both Thomas et al. and Stork et al. independently followed the biomimetic route and showed it was possible to construct the six membered ring of the isoindolone core and the large macrocyclic ring simultaneously in a late stage intramolecular Diels Alder cyclisation of a long chain dienophile.\textsuperscript{41-46} In a preliminary communication, reported in 1978 on a cytochalasan type system, Thomas et al. demonstrated the feasibility of simultaneously forming the macrocycle and reduced isoindolone moiety in a stereoselective intramolecular Diels Alder reaction. Diene anhydride 28 was refluxed in a dilute solution of toluene for 4 days.\textsuperscript{47} The major product, which is structurally related to cytochalasin B, was adduct 29 reported in a 27% yield, (Scheme 1, page 33). The intramolecular Diels Alder reaction of diene anhydride 28 was both regioselective and stereoselective in forming lactone 29 and proved to be useful in the later biomimetic syntheses of other cytochalasans.
Scheme 1  The model Diels Alder reaction reported by Thomas et al.

Reagents and conditions: a) toluene, reflux 90 h.

Further details of this biomimetic approach to cytochalasin synthesis followed in 1983\(^4\) and in addition to demonstrating the feasibility of forming the macrocycle of a cytochalasin via a late stage Diels Alder reaction, this method had the added advantage of avoiding the difficult macrolactonisation of a tertiary alcohol that was performed by Masamune et al.\(^4\)

While Stork and co-workers applied the technique to cytochalasin B, Thomas et al. used it successfully in the synthesis of proxiphomin,\(^4\) cytochalasins H,\(^3\) G,\(^5\) D,\(^4\) and in the synthesis of a geometric isomer of aspochalasin C\(^5\) (Figure 13). The early hypothesis that the biosyntheses of cytochalasans involve the macrocycle forming via Diels Alder reactions later received experimental support from gene cluster analysis.\(^5\)

![Chemical structures](image)

Cytochalasin H  Cytochalasin G  Aspochalasin C  Cytochalasin D

Figure 13  Cytochalasans synthesised by Thomas et al.
3.2.1 Total synthesis of Cytochalasin B (Stork et al.)

The first total synthesis of a cytochalasin was achieved in 1978 when Stork et al. reported the synthesis of cytochalasin B 34\(^\text{S3}\) (Figure 14). The approach taken by Stork et al. was to prepare the functionalised carbon chain then subject it to a regioselective [4+2] intermolecular Diels Alder cycloaddition to construct the reduced isoindolone moiety. To complete the synthesis they used a silver(I) assisted lactonisation protocol previously developed by Masamune et al. in 1977.\(^\text{S4}\)

![Figure 14 Cytochalasin B 34](image)

Stork et al. began the synthesis by converting the acetate of optically pure (+)-citronellol to acetate 35 then subjecting it to a Kolbe coupling with the acetate of the 1-ethyl ester of (+)-malic acid 36 to give the desired cross coupling product, diacetate 37 (Scheme 2, page 35). Reduction of diacetate 37 gave octanetriol 38, which established the secondary methyl and hydroxy groups with the correct stereochemistry. Further elaboration by acetonide formation then Collins oxidation gave the aldehyde 40.
Phosphonate 47 was formed in 6 steps using standard chemistry (Scheme 3, page 36). In detail, condensation of glycidaldehyde 41 with carbethoxymethylene triphenylphosphorane gave the unsaturated ester 42. Formic acid converted ester 42 to glycol 43 the primary alcohol of which was protected as the tert-butylidimethylsilyl ether 44. Condensation of ketone 44 with ethyldenetriphenylphosphorane resulted in the trans,trans-dienic ester 45 in a 5.7:1 ratio with its trans, cis isomer. Reduction of ester 45 gave alcohol 46, which was converted to phosphonate 47 by sequential treatment with butyl lithium followed by toluenesulfonyl chloride and finally sodium diethylphosphite. Phosphonate 47 was converted to its sodium salt before being reacted with aldehyde 40 to give triene 48.
**Scheme 3**  Stork et al. synthesis of triene 48

Reagents and conditions:  a) 30% excess carbethoxymethylene triphenylphosphorane in benzene, 1.5 hr. reflux, 87%.  b) formic acid, 30 min, 76%.  c) (i) TBSCl, (ii) CrO₃-2pyr, 78%.  d) ethylidenetriphenylphosphorane, THF, -78 °C, 45 min, 74%.  e) sodium bis(methoxyethoxy)aluminium hydride, toluene, 45 min, 89%.  f) (i) -30 °C, 3:1 ether:HMPA, butyl lithium, (ii) tolenesulfonyl chloride (1:1 equiv), 30 min, (iii) sodium diethylphosphite, (1.3 eq) in toluene, 12 hr. rt. 73%.  g) (i) sodium hydride, benzene, methanol (0.25 eq), 2 hr, 55 °C. (ii) aldehyde 40, 55 °C, 12 hr. 50%

Amino ester 49 was converted to hydroxypyrrolone ester 50, which upon O,N-diacetylation followed by hydrolysis-decarboxylation and reacetylation of the liberated hydroxyl group, gave the required dienophile 51 (Scheme 4).

**Scheme 4**  Stork et al. synthesis of dienophile 51

Reagents and conditions.  a) methoxalyl chloride, chloroform, pyridine, b) (i) acetic anhydride-pyridine, N-dimethylaminopyridine (cat.) 30 min., rt., (ii) Me₅SO : NaCl : water, (50 : 2.8 : 1), 135-140 °C 1.5 hr. N₂. (iii) Ac₂O.
Triene 48 and dienophile 51 were combined in a [4+2] cycloaddition to give a mixture of the desired regioisomer 52 and an undesired regioisomer in the ratio of 4:1, favouring 52 (Scheme 5).

![Chemical structure](image)

**Scheme 5**  Stork *et al.* synthesis of regioisomer 52

Reagents and conditions: a) (i) xylene, 170 °C, 4 days. (ii) 3:1:1 acetic acid-water-THF rt. 12 hr. (iii) acetone-\( p \)-TsOH, 1.5 hr. rt. 67%.

Conversion of 52 to the methylenecyclohexanol 56 was achieved in 4 steps by removing the silicon protecting group followed by epoxidation, bromination and finally \( \beta \)-elimination (Scheme 6, page 38). The terminal isopropylidene conversion to the 4-hydroxy trans-\( \alpha,\beta \)-unsaturated ester 57 was achieved by release of the 1,2-glycol, protection of the primary alcohol as the tert-butylidimethylsilyl ether and the two secondary hydroxyls as their tetrahydropyranyl ethers. Then deprotection of the primary alcohol followed by oxidation to the aldehyde and condensation with methyltriphenylphosphoranylidene acetate gave ester 57. Finally 4-hydroxy trans-\( \alpha,\beta \)-unsaturated ester 57 was converted to acid 59 in the presence of ethanolic sodium hydroxide.
Scheme 6  Stork et al. synthesis the hydroxyl unsaturated acid 59

Reagents and conditions: a) (tert-butyl hydroperoxide, Mo(CO)$_6$, 1.5 hr., reflux in benzene, 95%.
b) carbon tetrabromide. c) (i) triphenyl phosphine, 4 hr. rt. (ii) Zn dust/sodium iodide, acetone, 4 hr. reflux. d) (i) acetic acid-THF, 4 hr., rt. (ii) TBDMSCl 74%. (iii) Dihydropyranyl ether, 63%.
(iv) tetrabutylammonium fluoride. (v) Collins oxidation. (vi) methyltriphenylphosphoranylidyne acetate, 1.5 hr., reflux in benzene, 68%. (vii) acetic acid-THF, 12 hr., rt, 50%. e) 1 N ethanolic sodium hydroxide, 60 °C, 1 hr.

The synthesis was completed by the cyclisation of 59 using silver(I) assisted lactonisation developed by Masamune et al. to give cytochalasin B 34 (Scheme 7).

Scheme 7  Silver(I) assisted lactonisation developed by Masamune et al.
3.2.2 Macrolactonisation procedure of Masamune et al.

Masamune and co-workers developed a procedure for the macrolactonisation of tertiary alcohols with an activated thiol ester that enabled closure of the macrocycle of cytochalasans to take place without the use of mercury(II) salts.\(^{54}\) The non-discriminating reactivity of mercury(II) towards electron-rich centres is particularly problematic with cytochalasans, many of which have been found not to survive treatment with mercury(II).\(^{49}\) The method, involving activation of the thiol ester with silver(I) in the presence of an alcohol to form the lactone, overcame this problem.

![Mechanism of the closure of the macrocycle](image)

**Figure 15** Mechanism of the closure of the macrocycle

Masamune *et al.* demonstrated the utility of this new method with a series of reactions and in the process showed the transformation of cytochalasin B \(^{34}\) into cytochalasin A \(^{71}\), which involved breaking and reforming the macrocycle.

Starting with an isomeric mixture of cytochalasin B *cis*-tetrahydropyranyl ethers \(^{60}\), Masamune and co-workers subjected it to alkaline hydrolysis to give the *seco* acid \(^{61}\). Sequential treatment of acid \(^{61}\) with diethylphosphorochloridate and benzenethiolate formed benzenethiol ester \(^{62}\). Diacetate-thiol ester \(^{63}\) was delivered by acid treatment followed by acetylation of \(^{62}\). A mixture of \(^{63}\), Ag(I) and Na\(_2\)HPO\(_4\) gave the cyclised product \(^{64}\), which was then hydrolysed to give the monoacetate \(^{65}\). Protection of the liberated hydroxyl group with THP gave \(^{66}\), which on treatment with methanesulfonyl chloride followed by sodium cyanoborohydride caused reductive migration of the double bond to give \(^{67}\). *Seco* acid \(^{68}\) then resulted from alkaline hydrolysis of \(^{67}\). To achieve the benzenethiol ester of \(^{68}\) from which \(^{69}\) was obtained, the procedure for \(^{63}\) above was followed (treatment of \(^{68}\) with
diethylphosphorochloridate and benzenethiolate followed by acid treatment then acetylation to give 69). A Sharpless epoxidation on 69 by treatment with tert-butylhydroperoxide and vanadyl acetylacetonate provided the 6,7-epoxide 70, which subsequently transformed into 63 upon the application of acid followed by acetylation. When 63 is subjected to silver(I)-assisted lactonisation and mild alkaline hydrolysis, cytochalasin B 34 is produced. Oxidation of 34 with MnO₂ provides cytochalasin A 71, (Scheme 8).

Scheme 8 Masamune et al. lactonisation procedure

Reagents and conditions: (a) (i) 1 N ethanolic NaOH 60 °C 1 hr. (ii) diethyl phosphorochloridate then thallium benzenethiolate. (iii) acetic acid. (iv) acetic anhydride. (v) Na₂HPO₄, AgCF₃CO₂, benzene, reflux 2 hr. (vi) THP, (b) methanesulfonyl chloride then sodium cyanoborohydride. (c) NaOH, 60 °C 1 hr. (d) tert-butyl hydroperoxide, vanadyl acetylacetonate. (e) (i) 2 M HCl in 50% aq. acetone. (ii) acetic anhydride. (f) (i) Na₂HPO₄, AgCF₃CO₂, benzene, reflux 2 hr. (ii) NaOH, 60 °C 1 hr., (g) MnO₂.
3.2.3 **Total synthesis of Proxiphomin**

Proxiphomin 72 was believed to be a biosynthetic precursor of cytochalasin B 34 (synthesised by Stork *et al.* in 1978 and Myers *et al.* in 2004) and as Figure 16 shows, there are close structural similarities between them. In 1989 Thomas and Whitehead applied a biomimetic approach to the total synthesis of proxiphomin by using an intramolecular Diels Alder reaction to close the 13-membered ring.41

![Figure 16](image)

The structural similarities of proxiphomin 72 and cytochalasin B 34

The starting material chosen for the synthesis of proxiphomin 72 was (3R)-(+-)citronellol 73, prepared from (R)-(+-)-pulegone (Scheme 9, page 42). This facilitated the early introduction of the required chiral centre at C3. After protection of alcohol 73 with TBSCI, an ozonolysis followed by work-up with dimethyl sulphide gave aldehyde 75. Condensation with phosphonium ylide derived from 76 gave (Z)-alkene 77. Treatment of alkene 77 with TBAF generated alcohol 78 and subsequent hydrogenation gave (8R)-ethyl 10-hydroxy-8-methyldecanoate 79. Swern oxidation of alcohol 79 gave aldehyde 80, which was condensed with stabilised phosphonate 81 to give E,E,E-triene 82. Subsequent ester hydrolysis and treatment with 1,1′-carbonyldimidazole gave the imidazolyl hexadecatriene 84. Condensation with pyrrolidinone 85 resulted in 86 as a mixture of epimers at C3. Regioselective phenylselenation of 86 followed by oxidative elimination gave the unstable Diels Alder precursor 88. This was diluted and heated at 100 °C to produce a 52:48 ratio of the of the *exo:endo*-isomers 89 and 91 respectively. Debenzoylation of the Diels Alder
products gave compounds 90 and 92 and the less polar isomer 92 was converted into Proxiphomin 72 after phenylselenation to 93, then oxidative elimination (Scheme 9).

Scheme 9  Thomas et al. total synthesis of Proxiphomin 72

Reagents and conditions: a) TBSCl. b) O₃ then DMS. c) 76 -78 °C. d) TBAF; e) 10% Pd-C. f) Swern oxidation. g) 81, BuLi, -78 °C. h) NaOH, EtOH, H₂O. i) 1-1’-carbonyldiimidazole. j) LiHMDS, 85 -78 °C. k) LiHMDS, PhSeCl, THF, -78 °C. l) m-CPBA, CDCl₃, H₂O₂, -50 °C. m) toluene, 100 °C, 5 hr. n) KOH, benzene, MeOH. o) LDA, THF-hexane, -78 °C; benzeneselenenyl chloride/THF. p) pyridine, 30% H₂O₂, H₂O, DCM.
In comparison with the earlier simplified system that Thomas et al. explored, this intramolecular Diels Alder reaction gave disappointing exo-endo selectivity, although with excellent regio-control with none of the undesired regioisomer being isolated.\textsuperscript{48} With this work Thomas et al. demonstrated that simultaneous formation of the macrocycle and the reduced isoindolone was synthetically achievable. At this time Thomas et al. did not investigate the reasons for the stereoselectivity of this reaction.

### 3.2.4 Total synthesis of Cytochalasin H

In their total synthesis of cytochalasin H 30 in 1986, Thomas and Whitehead completed the first synthesis of a naturally occurring [11]-cytochalasin.\textsuperscript{43} In doing so they used a strategy of subjecting long chain 3-(1-oxotrieny1)pyrrol-2(5H)-one 119 to an intramolecular Diels Alder reaction to form the [11]-cytochalasin skeleton 121 (Scheme 10, page 45). The desired stereochemistry at C18 of cytochalasin H 30 was achieved by utilising stereoselective peracid epoxidation of the open chain allylic alcohol 99.

![Cytochalasin H 30](image)

**Figure 17** Cytochalasin H 30

Synthesis of long chain pyrrol-2-(5H)-one 119 commenced with the silyl protection of hydroxy ester 94, which produced silyl ether 95. DIBAL-H reduction of ester 95 provided alcohol 96, which was subsequently oxidised to aldehyde 97 followed by Wittig condensation to give \(\alpha,\beta\)-unsaturated ester 98. DIBAL-H reduction then provided allylic alcohol 99. Epoxidation of alkene 99...
led to the desired isomer 100, which after reduction gave diol 101. This sequence of reactions put in place the functionality and stereochemistry of the C15 – C19 fragment of cytochalasin H 30. Oxidation of diol 101 gave aldehyde 102. Condensation of aldehyde 102 with methoxycarbonylphosphorane resulted in α,β-unsaturated hydroxy ester 103 in 65% yield. Acid catalysed deprotection of ester 103 gave diol 105 in 85% yield. However, selective oxidation of diol 105 to aldehyde 106 followed by a Wittig reaction gave a poor 30% yield of diene 107. This was overcome by protection of the tertiary alcohol 102 to give bis-protected diol 104 in a yield of 89%. Deprotection of 104 gave alcohol 108 and hydrogenation of this unsaturated hydroxyl ester provided the saturated ester 109 in 96% yield. Oxidation gave aldehyde 110, which was coupled with methylenetriphenylphosphorane followed by hydroboration to give alcohol 111. Swern oxidation of alcohol 111 gave aldehyde 112, which was coupled with dienylphosphonate 113 to give the E,E,E-triene 114 in a reasonable yield of 87%. Hydrolysis of the ester gave acid 115, which on treatment with 1,1’-carbonyldiimidazole, gave imidazolyl triene 116. Coupling 116 with N-benzylopyrrolidinone 85 under basic conditions, produced lactam 117. Thereafter, phenylselenation gave 118. Oxidative elimination then converted 118 to the Diels Alder precursor pyrrol-2-(5H)-one 119. Cyclisation of pyrrol-2-(5H)-one 119 occurred after dilution with anhydrous toluene and heating at 100 °C for 5 hours to give a single Diels Alder 11-membered macrocycle 120. This result was consistent with the endo-selective formation of [11]-cytochalasins during earlier model intramolecular reactions and did contrast with the non-stereoselective formation of [13]-cytochalasins under these conditions.41 Deprotection of 120 gave the 1-debenzoylated Diels Alder adduct 121 (Scheme 10, page 45).
Scheme 10  Synthesis of Diels Alder adduct 121

Reagents and conditions:  a) (i) TBDMS-Cl.  (ii) DIBAL-H.  b) Swern oxidation.  (c) Ph₃P=C(Me)CO₂Et.  (d) DIBAL-H.  (e) m-CPBA.  (f) LiAlH₄.  (g) TosCl (Tos = p-MeC₆H₄SO₂).  (h) Ph₃P=CHCO₂Me.  (i) Dowex, SEM = CH₂OCH₂CH₂SiMe₃.  (j) DIBAL-H.  (k) methylenetriphenylphosphorane.  (l) Dowex.  (m) 10% Pd/C.  (n) Swern oxidation.  (o) CH₃PPh₃.  (p) Swern oxidation.  (q) dienylphosphonate 113.  (r) NaOH.  (s) 1,1’-carbonyldi-imidazole.  (t) benzoyl pyrrolidone 85, LiHMDSD, THF, -78 °C.  (u) LiHMDSD, PhSeCl, THF, -78 °C.  (v) m-CPBA, CHCl₃, H₂O₂, -50 °C.  (w) (i) toluene, 100 °C, 5 hr. (37%).  (ii) NaOH, MeOH.
Addition of LDA and TMS-Cl to 121 resulted in silyl enol ether 122 (Scheme 11). Addition of TBAF and benzeneseleneny chloride yielded phenylseleno-ketone 123. Selenoxide elimination followed by stereoselective reduction gave the \((E)\)-\(\alpha,\beta\)-unsaturated alcohol 124, which was acylated to give acetate 125. Treatment with \(m\)CPBA produced epoxides 127 and 126, but the regioselectivity at 127:126 (65:35) was disappointing. Treatment of the desired isomer 127 with aluminium isopropoxide at 125 °C gave the \(exo\)-cyclic allylic alcohol 128. All that remained was removal of the SEM group to give the desired cytochalasin H 30. This synthesis gave further support to the suitability of utilising \(intramolecular\) Diels Alder reactions in the formation of similar complex natural products.

**Scheme 11** Thomas et al. completion of the synthesis of cytochalasin H 30

Reagents and conditions: a) LDA, TMS-Cl b) (i) Benzeneseleneny chloride, TBAF, (ii) \(H_2O_2\), py. c)\(NaBH_4\). d) \(Ac_2O\), py. e) \(m\)-CPBA, DCM, -20 °C. f) Al-isoproproxyde, 125 °C. g) HF, MeCN.

Later that year Thomas et al. reported a shortened synthesis to the same target.\(^{51}\) It had been shown earlier that it was possible to carry out
stereoselective reactions on cyclic compounds with the conformational preferences of the rings controlling the stereochemistry.\textsuperscript{58, 59} This work led to Thomas et al. developing a strategy that took advantage of a stereoselective Grignard addition where the preferred conformation of the large 11-membered ring controlled the stereochemistry of addition to the ketone. An X-ray crystal structure of the analogous cytochalasin G showed that C18 was less hindered than C21 and so should react preferentially, with addition taking place from the $\text{Si}$ face because the $\text{Re}$ face is shielded by the ring (Scheme 12). Treatment of ketone 129 with MeMgCl in THF gave the tertiary alcohol 130 in a yield of 84%. This approach to the synthesis significantly reduced the number of steps to cytochalasin H 30.

\[ \text{129} \xrightarrow{a} \text{130} \]

**Scheme 12** Construction of the chiral centre at C18 of macrocycle 130

Reagents and conditions: a) MeMgCl, THF.

### 3.2.5 *Total synthesis of cytochalasin G.*

Extending their earlier work, Thomas et al. then went on to apply this *intramolecular* Diels Alder methodology to the total synthesis of cytochalasin G 31, which at that time was the first synthesis of a non-phenylalanine derived cytochalasan.\textsuperscript{60} Instead of a phenyl substituent at C10, this [11]-cytochalasin contains a tryptophan derived substituent (Figure 18, page 48).
Figure 18  Key intermediates (131 and 132) in the synthesis of cytochalasin G 31

Familiar chemistry was used to synthesise the long chain imidazolyl triene 131. However, for the other key intermediate, optically active 5-indolylmethylpyrrolidinone 132, a new approach was devised starting with N-benzyloxycarbonyltryptophan methyl ester 133 (Scheme 13). DIBAL-H was used to reduce ester 133 to aldehyde 134, which was then condensed with the lithium salt of triethyl phosphonoacetate 135 to give the unsaturated ester 136 in 50% yield. After hydrogenation and deprotection under acid conditions, the resulting amino ester 137 was cyclised to give pyrrolidinone 138 which then only required bis-benzoxylation to give the target pyrrolidinone 132.

Scheme 13  Thomas et al. synthesis of key intermediate 132

Reagents and conditions:  (a) (i) DIBAL-H, -40 °C. (ii) Li[EtO₂CCHPO(OEt)₂]. (b) 10% Pd-C, acetic acid, EtOH. (c) (i) NaOH, EtOH. (ii) Benzoyl chloride, DMAP, Et₃N, DCM.
Acylation of 132 by imidazolyl triene 131 gave lactam 139 as a mixture of epimers at C3, which after treatment with base and benzeneseleneny1 chloride provided 140. The unstable 3-(1-oxotrieny1)pyrrol-2(5H)-one 141 was then generated after oxidative elimination and then, upon heating in a dilute solution of toluene gave stereoselectively the desired endo-Diels Alder adduct 142. From here, three steps were required to convert the Diels Alder adduct 142 into cytochalasin G 31. Acetal hydrolysis gave diketone 143, treatment with mCPBA then provided epoxide 144 and finally the two N-benzo1 groups were removed to give cytochalasin G 31 (Scheme 14).

Scheme 14  Thomas et al. synthesis of Cytochalasin G 31

Reagents and conditions: (a) (i) 132-LiHMDS, THF/hexane -70 °C. (ii) LiHMDS, SePhCl. (b) 30% H2O2, CHCl3, -50 °C, mCPBA, CHCl3. (c) toluene, reflux. (d) HCl, THF. (e) mCPBA, CHCl3, DCM. (f) NaOH, MeOH.
3.2.6 Total synthesis of cytochalasin D

In 1999 Thomas and Merrifield continued to employ the strategy of using an intramolecular Diels Alder reaction to form the reduced isoindolone and large ring fragments simultaneously and in doing so achieved the total synthesis of cytochalasin D 33 (Figure 19). The key step in this synthesis was closing the 11-membered ring while simultaneously introducing the required stereochemistry at four of the stereogenic centres, C4, C5, C8 and C9. Later in the synthesis, they made use of the conformational preferences of the 11-membered ring to control the configuration of the chiral centres formed at C18 and C21.

Figure 19  Cytochalasin D 33

Homoallylic alcohol 147, obtained from a reaction between methacrolein 145 and (E)-but-2-enylidisopinocampheylborane 146 prepared from (+)-pinene, was heated with triethyl orthoacetate in the presence of a catalytic amount of propionic acid in a Johnson Claisen reaction which, when subjected to a Swern oxidation, formed aldehyde 148. Condensation of aldehyde 148 with dienylphosphonate 149 produced the E,E,E-triene 150 with 10% of its Z,E,E-isomer also formed. Hydrolysis of ester 150 gave acid 151 and treatment with carbonyldiimidazole provided the acyl imidazole 152 which was used to acylate the N-benzoylpyrrolidinone 85 to give the 3-acylpyrrolidinone 153. Phenylselenation of 153 followed by oxidative elimination produced the unstable 3-acylpyrrol-2(5H)-one 155, which was not isolated but instead the
crude mixture was diluted in toluene and heated to 80 °C to facilitate the Diels Alder cyclisation. This produced the endo-adduct 156 in 30% yield. N-debenzoylation of 156 gave the NH-lactam 157, where regioselective and stereoselective epoxidation produced 158 as the only product. In contrast to epoxidation, when 156 was subjected to dihydroxylation, the major product was the diol 159 in a yield of 53%. This reaction was predominantly selective for the 6,7-double bond. Small amounts of 160 (4%) and 161 (16%) were also obtained. Selective mono-protection of the secondary alcohol group of 159 gave silyl ether 162, which after dehydration gave exo-cyclic alkene 163. This completed the functionality of the 6-membered ring of the isoindolone unit (Scheme 15, page 52).
Scheme 15  Towards the synthesis of Cytochalasin D 33

Reagents and conditions: a) -78 °C, 3 hr. then H₂O₂. b) MeC(OEt)₃, propanoic acid, 140 – 170 °C (48% from 145). c) 9-BBN then H₂O₂ (77%). d) (COCl)₂, dimethyl sulfoxide (77%). e) n-BuLi, THF, hexamethylphosphoramide (85%). f) NaOH, EtOH. g) CO(imidazole)₂, THF. h) LiN(SiMe₃)₂, PhSeCl (100%). i) mCPBA, H₂O₂, -50 °C to 0 °C. k) toluene, 80 °C (25 – 30% from 154). l) (i) NaOH, aq. MeOH (95%). (ii) mCPBA, -25 °C (92%). m) osmium tetroxide, pyridine (159 53%, 160 4%, 161 16%). n) tert-butyldimethylsilyl triflate, 2,6-lutidine (89%). o) thionyl chloride, Et₂N (85%).
Dihydroxylation of triene 163 was regioselective in favour of the C17-C18 diol 164, which was protected as the corresponding acetonide 165 before phenylselenenylation at C20 to give 166. N-debenzylation gave the NH-lactam 167 which, on oxidative elimination, gave enone 168. Stereoselective reduction under Luche’s conditions gave alcohol 169, which was then converted to acetate 170. After exchanging the tert-butyldimethylsilyl protecting group for the more acid stable SEM group, acid catalysed hydrolysis of the acetonide gave C17- C18 diol 172. Swern oxidation produced ketone 173 and deprotection of the 7-hydroxy group then gave cytochalasin D 33 (Scheme 16, page 54). During this synthesis, 7 chiral centres were introduced either during or subsequent to the Diels Alder reaction.
Scheme 16  Completion of the synthesis of cytochalasin D 33

Reagents and conditions: a) osmium tetroxide, pyridine (75%). b) 2,2-dimethoxypropane, toluene, p-sulfonic acid (cat.) (99%). c) lithium diisopropylamide, benzeneselenenyl chloride, -35 °C (70%). d) NaOH, aq. MeOH (97%). e) H$_2$O$_2$, pyridine (65%). f) sodium borohydride, cerium(III) chloride (93%). g) acetic anhydride, Et$_3$N, DMAP (81%). h) TBAF, THF (72%). i) SEMCl, Hunig's base (74%). j) HCl, THF (64%). k) oxalyl chloride, DMSO, Et$_3$N (75%). l) HF, acetonitrile (69%).
3.2.7 Synthesis of Aspochalasin C

Aspochalasin C \(32\) is a member of a small group of natural products (aspochalasans) that are structurally similar to cytochalasans. They are derived biosynthetically from leucine and so have a prop-2-yl substituent at C10 and also differ from cytochalasins D, H and G in having a methyl substituent at C14 and no methyl substituent at C16.

The approach of Thomas et al. to this synthesis was to construct the long chain trienoyl imidazole \(174\), condense it with the salt of the \(L\)-leucine derived pyrrolidinone \(175\) and subject the resultant pyrrolin-2-one \(176\) to a Diels Alder cyclisation (Scheme 17, page 56). The unstable pyrrolin-2-one \(176\), present as a mixture of \(E:Z\) isomers at C8 of 2:1 respectively, was diluted in toluene and heated at 85 °C for several hours to yield a mixture of Diels Alder products in a combined yield of 30%. After debenzoylation of \(177, 179\) and \(181\) by treatment with NaOH in methanol, flash chromatography separated the corresponding secondary amides \(178, 180\) and \(182\), which were identified as \((13Z)\)-endo, \((13E)\)-endo and \((13E)\)-exo isomers in a 3:2:1 ratio respectively. Interestingly, this result of low endo-exo selectivity for formation of \([13]\)-membered cytochalasins contrasts with those found for cyclisation of \([11]\)-membered cytochalasins via intramolecular Diels Alder reactions where the endo-exo selectivity observed clearly favoured the desired endo-isomers.43, 44 Thomas et al. speculated, on steric grounds, that the additional methyl attached
to C8 of the trienylpyrrolinone may discourage endo cyclisation to the pyrrolinone ring for the (8′E)-isomer but not for the (8′Z)-isomer and that formation of the increased percentage of (Z) adducts may simply be a consequence of more efficient cyclisation of the (8′Z)-trienylpyrrolinone 176. Alternatively, triene equilibrium before cyclisation may be the prevailing influence, but investigations to establish this were inconclusive. Treatment of 178 with LDA and TMSCl gave the silyl enol ether 183, which reacted with benzeneselenenyl chloride to give selenide 184. Oxidative elimination and deprotection of the acetal group produced isoaspochalasin C 185, the (13,14)-Z-isomer of aspochalasin C 32 (Scheme 17).

Scheme 17 Synthesis of aspochalasin C 32
Reagents and conditions: a) THF, -78 °C, LiHMDS to give 175. b) 174 -78 °C, LiHMDS, THF-hexane, benzeneselenenyl chloride. c) H₂O₂/H₂O, CHCl₃, -50 °C, mCPBA. d) toluene 90 °C. e) NaOH, MeOH, f) -78 °C, lithium isopropylamide, TMSCl. g) benzeneselenenyl chloride, THF. h) H₂O₂/H₂O, pyridine, DCM. i) MeOH/HCl.
3.2.8 Towards the total synthesis of chaetochalasin A

The total synthesis of chaetochalasin A 187 is currently underway within the Thomas Group and is of particular interest because it has close resemblance to diaporthichalasin 1 in that it contains a similar tricyclic subunit. The initial intent was to complete a biomimetic synthesis via the long chain aldehyde 186, where the final cascade reactions would take place in a one-pot sequence, starting with a Knoevenagel cyclisation to put in place the pyrrolinone unit followed in situ by two sequential stereoselective domino Diels Alder reactions to form the pentacyclic product 187 (Scheme 18).

![Scheme 18 Late stage cascade reactions in the biosynthesis of chaetochalasin A 187](image)

However, as the work unfolded, achieving the two domino Diels Alder reactions remained elusive and so the strategy deviated from those of pure biomimetic objectives. Instead, the group concentrated on a synthetic route to put in place the conditions for a single Diels Alder reaction to construct the isoindolone unit attached to the macrocycle holding all of the required stereochemistry. Progress to date on the synthesis is shown in Scheme 19 (page 59).
After a series of early steps to produce allylic alcohol 188, bromination gave 189, which was subjected to a chiral auxiliary mediated alkylation. LDA was used to install the chiral auxiliary 190. The chiral auxiliary was subsequently removed using LDA followed by NH₃BH₃, leaving alcohol 191. Alcohol 191 was converted to the corresponding iodide, which was then subjected to another chiral auxiliary mediated alkylation with 190, as above, to give alcohol 192 with the correct stereochemistry in place. Oxidation to the aldehyde followed by a Takai reaction produced an olefin with E-configuration, which after treatment with Bu₃SnCl and butyl lithium gave the vinyl stannane 193. TBAF deprotection of the silicon group and subsequent Dess-Martin oxidation produced aldehyde 194. A Julia olefination using 195 followed to give triene 196 with the all E-geometry. A Stille coupling with the iodopropanoate 197 resulted in ester 198. Treatment of ester 198 with N,N′-carbonyldiimidazole gave 199, which facilitated addition of the lithium salt of lactam 200 to give the pyrrolinone 201. Dilution of pyrrolinone 201 in toluene and heating at 90 °C for 5 hours resulted in a Diels Alder reaction involving the terminal diene and the doubly activated 3-acylpyrrolinone to give predominantly the exo-isomer 203.

The next steps will attempt to insert a double bond between C21 and C22 to put in place the dienophile for the second Diels Alder reaction to take place. The second Diels Alder reaction involves an inverse electron demand reaction, which will create a quaternary centre at C14. This trans-annular process is well established⁶¹, ⁶² and should result in the formation of the target compound chaetochalasin A 187 (Scheme 19, page 59).
Scheme 19  Progress on the synthesis of chaetochalasin A 187

Reagents and conditions: a) PBr₃, DCM. b) (i) 190 LDA, (ii) LDA, NH₄BH₄, 63%. c) (i) Ph₃P, I₂, Imid, 83%, (ii) LDA, 84%, (iii) LDA, NH₄BH₄, 57%. d) (i) DMP, (ii) Takai reaction, (iii) Bu₃SnCl, BuLi. e) (i) TBAF, (ii) DMP. f) LiHMDS, THF, -78 °C. g) 197. h) NaOH, carbonyldimidazole. i) (i) LiHMDS, THF, -78 °C, (ii) LiHMDS, THF, -78 °C, PhSeCl, (iii) H₂O₂/H₂O, mCPBA, -50 °C. i) Toluene, reflux. k) (i) LiHMDS, THF, -78 °C, PhSeCl, (ii) H₂O₂/H₂O, mCPBA, -50 °C. l) Toluene, reflux.
3.3  Stepwise strategies in the total synthesis of cytochalasans

The groups of Vedejs et al., Trost et al. and Myers et al. preferred a stepwise strategy in the total synthesis of cytochalasans. In general, they formed the isoindolone unit first by using an intermolecular Diels Alder reaction then separately constructing the macrocycle using a stepwise procedure. Myers and co-workers synthesised the macrolide as a separate fragment with its stereochemistry in place before coupling to the preformed isoindolone unit. Vedejs and co-workers made use of sulphide bridge chemistry in their synthesis of zygosporin E and Trost et al. used palladium(0) as a catalyst in the synthesis of the macrocycle in (-)-aspochalasin B.

3.3.1  Myers’ et al. synthesis of cytochalasin B

In 2004 Myers et al. also reported the total synthesis of cytochalasin B. In developing their stepwise strategy, instead of following the “natural” Diels Alder disconnection (Figure 21, page 61), they targeted a different disconnection of the isoindolone ring, which required prior migration of the cyclohexane double bond. This approach was chosen to enable a convergent and enantioselective synthetic route to be developed that permitted late-stage introduction of different macrocyclic elements. In carrying out the synthesis, the group demonstrated that the macrocycle could be closed at a late stage using an intramolecular HWE olefination.
The Diels Alder substrate 206 was constructed from \( N,N \)-dibenzylphenylalanal 207, which was derived from \( L \)-phenylalanine in 3 steps. By using \( L \)-phenylalanine as a starting material they were able to establish all stereo relationships in the bicyclic core (Scheme 20, page 62). HWE condensation of 207 with diethyl-3-oxo-2-butylyphosphonate 208 gave the \( \text{trans}-\alpha,\beta \)-unsaturated ketone with a 99:1 \( \text{trans: cis} \) selectivity and 98% enantiomeric excess. Because of the highly basic conditions needed for this reaction, the kinetically robust \( N,N \)-dibenzyl protecting system of Reece et al.\(^ \text{65} \) was chosen to reduce the risk of epimerisation of the neighbouring chiral centre. The subsequent selective mono-\( N \)-debenzylation was achieved following the procedure of Hungerhoff et al.\(^ \text{66} \) after which protection of the alcohol functionality with \( \text{tert} \)-butyldimethylsilyl triflate in the presence of 2,6-lutidine, provided the silyl enol ether 209. Synthesis of tertiary amine 206 was achieved by an addition-elimination sequence that occurred after combining silyl ether 209 with \( \text{exo} \)-methylene lactone 210. Intramolecular Diels Alder cyclisation of 206 in xylene at 150 °C gave two diastereoisomers 205 and 211 in respective yields of 77% and 14%. Both Diels Alder products arose from attack on a single
face of the diene due to allylic 1,3-strain factors. From adduct 205, the tricyclic alkene 204 was reached in 4 steps. N-Boc-protection (in exchange of the N-benzyl protecting group), cleavage of the silyl enol ether, regioselective deprotonation of ketone 212 and addition of 2-[N,N-bis(trifluoromethylsulphonyl)amino]-5-chloropyridine provided the corresponding enol triflate, which on reaction with lithium dimethylcuprate afforded the tri-substituted alkene 204.

### Scheme 20  Synthesis of key tricyclic precursor 204

Reagents and conditions:  

a) Ba(OH)₂, THF, 23 °C 87%. b) 2,3-Dichloro-5,6-dicyanobenzoquinone, CH₃Cl₂-pH 7 buffer, 23 °C 86%. c) tert-Butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH₂Cl₂, -78 °C 99%. d) MeOH, 23 °C 98%. e) m-Xylene, 150 °C 77%. f) H₂, 10% Pd/C, BOC₂O, Et₃N, EtOH, 23 °C 96%. g) TBAF, AcOH, THF, 0 °C. h) KHMDS, THF, -78 °C, 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, 93% (two steps). i) (CH₃)₂CuLi, THF, -78 °C to 0 °C 95%.

Tricyclic alkene 204 was transformed to the precursor of the macrolactone by epoxidation, achieving a single diastereoisomer, followed by cleavage of the N-
Boc group and oxidation of the resulting amine to give imine 213 (Scheme 21). Deformylation of epoxy imine 213 produced the hydroxy lactam 214 in 96% yield. Prior epoxidation of the cyclohexene ring in 204 enhanced the deformylation reaction as did optimising conditions, to induce deformylation by subjecting 213 to 1,2-diaminoethane in tert-amyl alcohol at room temperature.

\[ \text{Scheme 21} \quad \text{Myers et al. synthesis of the hydroxy lactam 214} \]

Reagents and conditions: a) Dimethyldioxirane, acetone, 23 °C, 100%. b) TFA, DCM, 0 °C. c) [Bis(trifluoroacetoxy)iodo]benzene, 4 Å MS, DCM, 23 °C, 92% (two steps). d) Ethylenediamine, tert-amyl alcohol, 23 °C 96%.

Scheme 22, page 64 shows the route Myers and co-workers employed to synthesise the macrocycle precursor 221. The key step involved the reductive coupling of \( N\text{-}\text{tert}-\text{butyl} \text{dimethylsilyl tosylhydrazone} \) 219 and an alkyllithium reagent formed \textit{in situ} from iodide 217. Jacobsen hydrolytic resolution and asymmetric alkylation methodologies established the stereochemistry of the intermediates 217 and 219 respectively, prior to their reductive coupling.
Scheme 22  Myers et al. synthesis of the macrocycle precursor 221

Reagents and conditions:  a) (1S,2S)-1,2-cyclohexanediamino-N,N’-bis(3,5-di-tert-butylsalicylidene)cobalt(II), AcOH, H₂O (0.45 eq.), 0 °C→23 °C 41%. b) tert-butyldimethylsilyl trifluoromethanesulphonate, Et₃N, DCM, 0 °C to 23 °C. c) H₂ Pd/C, EtOAc, 23 °C 79% (two steps). d) PPh₃, I₂, imidazole, DCM, 23 °C 86%. e) Dess-Martin periodinane, DCM, 23 °C. f) TsNH₂, THF, -78 °C. g) tert-butyldimethylsilyl trifluoromethanesulphonate, Et₃N, DCM, -78 °C. h) 217, tert-BuLi, Et₂O, -78 °C, 219, THF, AcOH, CF₃CH₂OH, -78 °C to 23 °C 90% (two steps). i) H₂ Pd/C, EtOAc, 23 °C 87%.  j) 1-Phenyl-1-H-tetrazole-5-thiol, PPh₃, diisopropyl azodicarboxylate (DIAD), THF, 23 °C 87%. k) m-Chloroperbenzoic acid, NaHCO₃, DCM, 23 °C 84%.

Oxidation of alcohol 214 followed by Kocienski-Julia coupling between the anion of 221 and 222 gave the trans-olefin 223, which after protection of the lactam, then stereoselective oxidation of the resultant imide, gave the tertiary alcohol 224 (Scheme 23, page 65). Under Shelkov conditions, acylation of the sterically hindered and electron deficient alcohol 224, followed by selective mono-deprotection and oxidation of the liberated alcohol group, gave the substrate for HWE ring closure to form the macrolactone 226. Finally, N-Boc cleavage of the macrocyclic intermediate 226 and hydrolysis of the silyl ether, followed by epoxide/allylic alcohol rearrangement of 227 gave the desired target molecule cytochalasin B 34 (Scheme 23, page 65).
Scheme 23  Myers et al. final stages in the synthesis of cytochalasin B 34.

Reagents and conditions:  a) Dess-Martin periodinane, NaHCO₃, DCM, 23 °C. b) 221, KHMDS, THF, -78 °C, -100 °C to 40 °C 60% (two steps). c) Lithium bis(trimethylsilyl)amide, THF, -78 °C, BOC₂O, -78 °C to -40 °C 80%. d) KHMDS, THF, -78 °C, trans-2-(phenylsulfonyl)-3-phenyloxaziridine, -100 °C to -78 °C 85%. e) Diethylphosphonoacetic acid, 1,3-dicyclohexylcarbodiimide, DCM, 23 °C 81%. f) HF-pyridine, THF, -20 °C 69%. g) Dess-Martin periodinane, NaHCO₃, DCM, 23 °C. h) NaOCH₂CF₃, CF₃CH₂OH, DME, 23 °C 65% (two steps). i) Mg(OCH₃)₂, CH₂OH, 23 °C 95%. j) TBAF, THF, 23 °C 96%. k) MgSO₄, benzene, 70 °C 66%.

3.3.2 Trost's et al. total synthesis of (-)-aspochalasan B

Trost et al reported the total synthesis of (-)-aspochalasan B in 1989, achieving the natural product in only 19 steps. The group's synthetic strategy was based on an observation of a general oxidation pattern (Figure 22, page 66) in the
macrocyclic fragment of the cytochalasin family of compounds and it was on this basis that the group developed the concept of forming a “template structure” in the form of an isoindolone moiety that contained key functional groups and that was flexible enough to accommodate adding a variety of macrocyclic entities to it.

![Figure 22](image)

**Figure 22** General oxidation pattern in the macrocyclic fragment of the cytochalasin family

Trost and co-workers demonstrated the flexibility general structure 228 afforded in that protonation or hydroxylation would reveal the ketone with simultaneous introduction of a proton or a hydroxy group, whilst elimination or reduction of the sulfone group would provide unsaturated or saturated derivatives respectively. It was imagined that macrocycle 230 could be formed by means of a Pd(0)-catalysed macrocyclisation of substrate 229 via a 2-alkoxy(π-allyl)palladium complex using an enolonium equivalent to instigate cyclisation. Use of the carbonate precluded the need for an exogenous base and the sulfone group served to conformationally anchor the 11-membered ring and ultimately control the diastereoselectivity of the hydroxylation. Trost and co-workers were successful in developing a synthetic strategy that had a versatile substitution pattern with the potential to accommodate the formation of many other natural 11-membered macrocycles. Additionally this illustrated the effectiveness of using transition metal catalysis to create 11-membered rings.
Aldehyde 237 is a key part of the synthesis and with its construction, Trost et al. demonstrated excellent diastereoselectivity of the Diels-Alder reaction by producing adduct 235 with greater than 10:1 diastereoselectivity (Scheme 24).

Scheme 24   Trost et al. synthesis of tetrahydroisoindoline aldehyde 237

Reagents and conditions: (a) (i) DIBAL-H, PhCH₃, -78 °C. (ii) CH₃(CO₂CH₃)₂, TiCl₄, CCl₄, THF, 0 °C, then C₅N₅N, rt, 54%. (b) 234, xylene, BHT, 130 °C, 30-40%. (c) (i) KOH, H₂O, MeOH, benzene, rt. then NaHSO₄ (ii) CH₃N₂, ether, MeOH, 94%. (d) (COCl)₂, DMSO, CH₂Cl₂ Et₃N, -78 °C, 90-100%.
In constructing the macrocycle with \((E)\) olefin geometry, the group were forced to use the Raucher, Chi and Jones protocol after their first choice of a Claisen rearrangement failed to form the vinyl ether.\(^{69}\) Use of lithium dipropenylcuprate with aldehyde 237 provided adduct 238 to which the phenyl sulfonyl group was added in the presence of \(n\)-butyl lithium and HMPA to give 239. Condensation and rearrangement of 239 to 240 was achieved with ethyl \(\beta,\beta\)-diethoxyacrylate and a catalytic amount of pyridine \(p\)-toluenesulfonate (PPTS) in chloroform. Chemoselective reduction of ester 241 with DIBAL-H in the presence of \(n\)-butyl lithium to the corresponding alcohol followed by oxidation to aldehyde 242 and chemoselective addition of the 1-ethoxyvinyl group to the aldehyde, using the cuprate led to methyl carbonate 243 after treatment of the alcohol with methyl carbonchloridate. Cyclisation to the 11-membered carbocycle 244 was achieved with a palladium(0), which was designed to give the desired \(Z\)-stereochemistry of the enol ether double bond. Treating a methylene chloride solution of enol ether 244 with peracetic acid in an excess of potassium carbonate gave the corresponding epoxide, which readily solvolysed to the \(\alpha\)-hydroxy lactone 245 using PPTS, water and THF. Exposure of the \(\beta\)-ketosulfone to benzyltrimethylammonium fluoride gave the target compound (-)-aspochalasan B 231 (Scheme 25, page 69).
Scheme 25  Trost et al. synthesis of the macrocycle and \((-\)\)-aspochalasin 231

Reagents and conditions: (a) \([\text{CH}_2=\text{C} (\text{CH}_3) ]_2 \text{CuLi}, \text{THF}, \text{-78 °C.}\) (b) \(\text{n-BuLi}, \text{CH}_3\text{SO}_2\text{Ph}, \text{THF, HMPA, 0 °C.}\) (c) \((\text{C}_2\text{H}_5\text{O})_2\text{C} = \text{CHCON} \text{Et}, \text{PPTS, rt.}\) (d) (i) 1 N aqueous KOH, THF, rt. then HCl. (ii) \(\text{PhCH}_3,\) reflux. (iii) \(\text{CH}_2\text{N}_2, \text{Et}_2\text{O, rt.}\) (e) (i) \(\text{n-BuLi, DIBAL-H, THF, 0 °C.}\) (ii) \(\text{PCC, DCM, rt.}\) (f) (i) \([\text{CH}_2=\text{C} (\text{CH}_3) ]_2 \text{CuLi, THF, \text{-78 °C.}\) (ii) \(\text{ClCO}_2\text{CH}_3, \text{CaH}_2\text{N, 0 °C.}\) (g) \(10\% \text{(Ph}_3\text{P})_4\text{Pd, 10% dppp, THF, rt. reflux.}\) (h) (i) peracetic acid, \(\text{K}_2\text{CO}_3.\) (ii) \(\text{PPTS, H}_2\text{O, THF, rt.}\) (i) \(\text{benzyltrimethylammonium fluoride, THF, methylene chloride, rt.}\)

3.3.3  Vedejs et al. total synthesis of zygosporin E

In 1988 Vedejs et al. reported the total synthesis of zygosporin E 246 (Figure 24, page 70).\(^70\) This was the most complex carbocyclic cytochalasin that had thus far been synthesised. The group achieved the synthesis by using a route to ring expansion based upon the 2,3-sigmatropic rearrangement of sulfonium ylides that they developed earlier in 1984.\(^71\) A sulphur bridge was inserted
between C20 and C16 (Scheme 26) in order to govern the introduction of asymmetric centres at C16 and C18. The key stereocentre at C20, adjacent to sulphur, was later removed. This stereochemistry of the sulphur bridge remotely controlled the construction of the eight asymmetric centres in the medium sized ring.

Familiar chemistry produced allylic chloride 247, and upon heating with sodium iodide, potassium carbonate and acetonitrile, sulphur ylide ring expansion occurred and gave the desired macrocycle 248 (Scheme 26, page 71). After some abortive chemistry, methylation was achieved at C16 to give 249 in an excellent yield of 100%. Selective deacylation of 249 gave 250, which when subjected to N-silylation produced 251. Enolisation at C18 followed by selective methylation, desilylation and reacylation of the nitrogen, gave a single major product 252. Reductive desulfonylation of 252 and N-deacylation gave 1:2.6 ratio of 253:254, which occurred due to enolate protonation via the less hindered face to give 254. N-Deacylation and electrophilic selenylation of 253 gave the stable allylic selenide 255, which upon periodate oxidation, was selectively converted into the allylic alcohol 256 via the 2,3-sigmatropic shift of a selenoxide with bond formation at the more accessible alkene β-face. Finally, mCPBA oxidation and thermal sulfoxide elimination gave d,l-zygosporin E 246 in 52% yield. The same sequence of steps from 254 produced d,l-16-epi-zygosporin E 257.
Scheme 26  Vedejs et al. total synthesis of zygosporin E 246

Chapter 4

Results and discussion part 1

4.1 Synthesis of conjugated tetraenyl acetate 258

The initial stage of the project involved the synthesis of conjugated tetraene acetate 258, which was obtainable via a series of Horner-Wadsworth-Emmons reactions starting with commercially available tiglic aldehyde 22 (Figure 25). Baldwin et al.72 have previously prepared similar tetraenes and concluded that they are non-polar and suffer from 1,3-allylic strain resulting from steric compression of the 1,3-methyl substituents in the polyene backbone. The behaviour of heavily substituted tetraene species in relation to a successful Diels Alder cyclisation is not well understood and so early work in this research will concentrate on establishing the viability of this chemistry.

![Disconnection of conjugated tetraene 258](image)

Using literature procedures, tiglic aldehyde 22 was added to a mixture of (carbethoxyethylidene)triphenylphosphorane in benzene and refluxed for 48 hours to give ester 260 as colourless oil in a good yield of 80% (Scheme 27).72 In this first reaction two isomers were isolated in the ratio 95:5 \((E,E):(E,Z)\). The difference in the polarity of the \((E,E)\) and \((E,Z)\) isomers was sufficient to isolate both compounds separately using flash column chromatography.
Scheme 27  Synthetic step to ester 260

The structure of the dominant ester 260 was determined from $^1$H and $^{13}$C n.m.r., mass spectrometry and infrared spectroscopy and the (E,E) stereochemistry was deduced from nOe experiments.

The proton n.m.r. spectrum showed the three methyl peaks clustered together in the high field environment ($\delta$ 1.63–1.75), as expected. The two methine protons were deshielded to low field at $\delta$ 5.36 and $\delta$ 5.82. The protons on the methyl group at C6 give rise to a single proton doublet (d) at high field ($\delta$ 1.69 ppm), because they are adjacent to and coupled with the methine proton at C5. This chemical shift is appropriate for a vinylic methyl group and the multiplicity is appropriate for methyl protons coupling to one methine proton. The coupling constant of this doublet was $J = 7.1$ Hz. Its coupling partner, the methine proton at C5, gave rise to a single proton quartet (q) at $\delta$ 5.36. This chemical shift is appropriate for a vinylic proton and the multiplicity is appropriate for the proton coupling to the terminal methyl group. The coupling constant of $J = 7.1$ Hz corresponded exactly, which allowed these protons to be unambiguously assigned. This proton n.m.r. data was consistent with that of the literature for this compound.72

The number of peaks in the $^{13}$C spectra was in accord with the molecular formula and, using the integrals in the $^1$H n.m.r. spectra, the relative number of protons was also consistent with the molecular formula. These combined results corresponded with the accurate mass measurement and the infrared spectrum showed the characteristic carbonyl C=O stretching peak at 1701 cm$^{-1}$. 
The resonance at δ 7.05 ppm, corresponding to the 3-CH proton had a strong nOe response to the irradiation of the resonance at δ 5.36 ppm, which corresponds to 5-CH, indicating protons 3-CH and 5-CH are close in space to each other (Figure 26). There were no observed nOe correlations between the C6, C4 and C2 methyl groups at δ 1.69, 1.77 and 1.93 ppm respectively because the chemical shifts were too close to each other for the nOe resonances to be clearly distinguished.

Scheme 28    Synthetic step to alcohol 261

Ester 260 was reduced using two equivalents of DIBAL-H at 0 °C to give the allylic alcohol 261 in a high yield of 97% (Scheme 28). DIBAL-H was the reducing agent of choice because it has been used extensively for the chemoselective reduction of α,β-unsaturated esters to allylic alcohols. Spectroscopic analysis (1H n.m.r., 13C n.m.r. and mass spectrometry) was consistent with the structure of alcohol 261 and in accordance with the literature data. A broad peak in the infrared spectrum at 3303 cm⁻¹ was indicative of O-H stretching and the (E,E) stereochemistry was determined from nOe spectroscopy. Enhancements could be seen between the resonance of the
1-H$_2$ protons at $\delta$ 3.98 ppm and the resonance of the 3-H proton at $\delta$ 5.82 and also between the resonances at $\delta$ 5.36 ppm, corresponding to the 5-H proton and at $\delta$ 5.82 ppm relating to the 3-H proton (Figure 27). This observed nOe supported alcohol 261 to be the (E,E) isomer.

![Figure 27](image)

**Figure 27**  Observed nOe correlations for alcohol 261

Allylic alcohol 261 was used without further purification and oxidised to its corresponding aldehyde 262 by treatment with 15 equivalents of activated MnO$_2$ in chloroform at room temperature for 72 hours and gave a high yield of 95% (Scheme 29). A peak in the $^1$H n.m.r. spectra at $\delta$ 9.31 ppm indicated the presence of the aldehyde proton. All spectral data were consistent with the literature.$^{72}$

![Scheme 29](image)

**Scheme 29**  Synthetic step to aldehyde 262

Activated MnO$_2$ was selected as the oxidant because it is a chemoselective oxidant particularly suited to the oxidation of allylic alcohols with the added advantage of oxidising under mild conditions.$^{74}$
Aldehyde 262 was chain extended to the corresponding (E,E,E)-triene ester 263 via a further Horner-Wadsworth-Emmons olefination using (carbethoxyethylidiene)triphenylphosphorane in benzene under reflux. Spectroscopic data, including the observed nOe correlations, confirmed ester 263 to be the (E,E,E)-isomer (Figure 28). Enhancements in the nOe spectra could be seen between the resonances of proton 3-H, at δ 7.09 ppm, and proton 5-H, at δ 5.96 ppm, and between the resonances of proton 5-H and proton 7-H at δ 5.47 ppm.

In a similar fashion to the series of reactions above, DIBAL-H reduction at 0 °C of ester 263 gave allylic alcohol 264 in a good yield of 95%, and oxidation of allylic alcohol 264, using activated MnO₂, resulted in aldehyde 265 in a yield of 77% (Scheme 31). All spectroscopic data was consistent with that of the literature.\(^{72}\)
The next reaction was the difficult step of forming conjugated tetraene 266. Conjugated tetraenes are potentially sensitive to photo-isomerisation of the double bonds or destruction, when exposed to light.\textsuperscript{75} To avoid this complication, precautions were taken to ensure that, during the formation step and all subsequent reactions involving the tetraene, the reactions were carried out in the absence of light. In addition, the conjugated double bonds of tetraenes are sensitive to acid so to avoid risk of acid contamination during reactions or in the purification processes, all silica used in flash column chromatography was base washed with an aqueous solution of potassium hydrogen carbonate followed by flushing with distilled water until the washings were neutral. This was followed by drying in the oven for 3 days at 170 °C. Similarly, after cleaning, all glassware was rinsed with a dilute aqueous solution of potassium hydrogen carbonate before drying. Over a period of 12 months there was no evidence that tetraenes 266, 267 or 258, which were kept undiluted in the freezer, were unstable and this may be due to the precautions taken to protect them from light and from acid.
Conjugated tetraene 266 was formed from aldehyde 265 using two equivalents of the previously used stabilised phosphorane in benzene and refluxed for 60 hours.

The structure of conjugated tetraene 266 was determined from $^1$H n.m.r., $^{13}$C n.m.r., mass spectroscopy and infrared spectroscopy and the stereochemistry was deduced from nOe spectroscopy. The proton n.m.r. spectrum showed the six methyl peaks in the compound were clustered together in the high field environment ($\delta$ 1.16 – 2.26 ppm), as expected. The four methine protons were deshielded to the low field environment ($\delta$ 6.04 - $\delta$ 7.65 ppm) with the methylene CH$_2$ protons deshielded to a lesser extent at $\delta$ 4.23 ppm. The protons on the methyl group at C10 gave rise to a single proton doublet ($J$ 6.9 Hz) at high field ($\delta$ 1.69 ppm) and coupled with the methine proton at C9, which gave rise to a corresponding quartet ($J$ 6.9 Hz), which allowed these protons to be unambiguously assigned. The methylene CH$_2$ protons at $\delta$ 4.23 ppm gave rise to a quartet ($J$ 6.9 Hz), which showed characteristic coupling to the adjacent methyl group at $\delta$ 1.16 ppm displayed as a triplet ($J$ 6.8 Hz). The number of peaks in the $^{13}$C spectra was consistent with the molecular formula and, using the integrals in the $^1$H n.m.r. spectra, the relative number of protons was also consistent with the molecular formula. The combined results corresponded with the exact mass measurement and the infrared spectrum showed the characteristic peak of ester carbonyl C=O stretching at 1701 cm$^{-1}$.

The resonance at $\delta$ 6.21 ppm corresponding to the 5-CH proton had a strong nOe correlation to the resonances at $\delta$ 7.65 ppm, corresponding to the 3-CH proton and the resonance at $\delta$ 6.04 ppm, belonging to the 7-CH proton. Similarly, the 7-CH resonance at $\delta$ 6.04 ppm had a strong nOe correlation to the resonance at $\delta$ 5.58 ppm of the 9-CH proton indicating that the relative stereochemistry between 3-CH and 5-CH, 5-CH and 7-CH and 7-CH and 9-CH are all syn (Figure 29, page 79).
The overall yield of the desired all (E,E,E,E)-isomer for this seven step procedure which gave 2,4,6,8-tetraenoate 266 was 12%. DIBAL-H at 0 °C was used to reduce tetraene ester 266 to tetraene alcohol 267 in a yield of 86% before being acetylated to tetraene 258 by treatment with acetic anhydride in the presence of pyridine (Scheme 33).

Scheme 33  Synthetic steps to tetraene acetate 258

Spectroscopic data for alcohol 267 and acetate 258 were consistent with the data from tetraene ester 266, including the nOe enhancements as shown in Figure 30, which confirmed the (E,E,E,E)-stereochemistry of the tetraene.

Figure 30  Observed nOe correlations for conjugated tetraene 267
4.1.1 Summary of the synthesis of conjugated tetraenyl acetate 258

Commencing with tiglic aldehyde 22 two successive sequences of reactions involving Horner-Wadsworth-Emmons olefination, DIBAL-H reduction and activated manganese dioxide oxidation gave the conjugated triene aldehyde 265. A further Horner-Wadsworth-Emmons olefination obtained the previously unreported \((E,E,E,E)\)-tetraene 266 which, on reduction using DIBAL-H, gave the alcohol 267. Further elaboration gave tetraene 258. Each Horner-Wadsworth-Emmons olefination, using the stabilised ylide in the non-polar solvent benzene, produced a \(\beta\)-unsaturated ester in excellent yields of between 80% and 86%. Stabilised ylides are known to be predominantly \(E\) directing.76

A small amount of the \((Z)\) isomer was formed with each Horner-Wadsworth-Emmons reaction (5%) but the proportions marginally decreased during the subsequent reduction and oxidation steps. Some isomerisation of the \((Z)\)-double bonds may have taken place to the thermodynamically more stable \((E)\)-configuration, as was suggested by Bartelt and co-workers.77

4.2 Intramolecular Diels Alder reaction for the introduction of a quaternary centre

An understanding of the stereochemical behaviour of IMDA reactions with respect to the conjugated tetraene is pivotal to its successful application in the synthesis of diaporthichalasin 1. To this end compounds containing doubly activated dienophiles from tetraenol 267 were synthesised with both maleate ester 273 and mono-methyl fumarate 275 and the stereochemical outcomes were investigated when they were subjected to intramolecular Diels Alder reactions. The stereochemical complexity of these reactions stems from the four contiguous stereogenic centres that are created, including a quaternary centre. The concerted, suprafacial nature of the bond forming process allows the potential generation of twelve stereo-isomeric products that are interrelated in regioselectivity, endo/exo and \(\pi\)-facial senses. Successful IMDA reactions on simple, unhindered conjugated tetraenes have been reported78 but
the intramolecular cycloaddition of dienophiles to sterically hindered linear conjugated tetraenes remains largely unexplored.

### 4.2.1 Attempted preparation of maleate ester 270

The direct preparation of maleate di-ester 270 by esterification of tetraenol 267 with maleic anhydride, followed by room temperature treatment with TMS-diazomethane failed. Carboxylic acid 269 was formed in a good yield of 86% (Scheme 34). However, treatment with TMS-diazomethane did not result in the corresponding methyl ester 270. Methylation of the carboxylic acid using methyl iodide was also not successful and neither was methylation using methanol,79

![Scheme 34 Failed attempt to produce the (Z)-maleate ester 270](image)

An alternative approach to forming the maleate di-ester involved opening the ring of maleic anhydride 268. Sabith and Chimicia’s work on ring opening of cyclic anhydrides to form half esters using BF	extsubscript{3}.Et	extsubscript{2}O was a possibility but in our hands BF	extsubscript{3}.Et	extsubscript{2}O mediated ring opening of maleic anhydride failed to produce the desired half ester.80 However, Xiaolong et al.81 showed that maleic anhydride stirred in 10 equivalents of methanol at room temperature for 3 hours
proceeded to afford the mono-methyl maleic acid 271 as clear oil in 99% yield (Scheme 35).

Scheme 35  Ring opening of maleic anhydride 268

Mono-methyl maleic acid 271 was then combined with tetraenol 267 using EDCI and DMAP in DCM initially at 0 °C and thereafter at room temperature. The reaction proceeded slowly and produced a mixture of (E)- and (Z)-isomers that were separated by column chromatography but in poor yields of 15%, each with 50% of the starting material recovered (Scheme 36). In view of the fact that this aspect of the investigation did not directly form part of the natural product synthesis, no serious attempt was made to optimise this reaction.

Scheme 36  Outcome of the combination of half acid 271 with tetraenol 267
4.2.2 Synthesis of tetraene-methyl fumarate 272

There was a different outcome when tetraenol 267 was combined in similar fashion with mono-methyl fumaric acid 273 using EDCI and DMAP in DCM. The reaction produced fumarate di-ester 272 in 50% yield with a smaller amount of the (Z)-isomer (10%) and no starting material (Scheme 37).

![Scheme 37](image)

Scheme 37  Outcome of the combination of mono-methyl fumarate 273 with tetraenol 267

As a consequence of the different chemical environments, an interesting distinction between the (E)- and (Z)-isomers was evident in the $^1$H n.m.r. spectra. Peaks for the 2-H and 3-H protons of the (Z)-isomer were doublets at 5.84 and 5.90 ppm with $J = 11.9$ Hz whereas peaks for these same protons in the (E)-isomer were shifted to low field at 6.95 ppm where the peaks overlapped and appeared as a singlet that integrated for two protons.

4.2.3 Intramolecular Diels Alder reaction of tetraene methyl fumarate 272

With tetraene methyl fumarate 272 now synthesised, the next step was to carry out the Diels Alder reaction to check the stability of the tetraene under Diels Alder conditions. Thus, tetraene methyl fumarate 272 was diluted in toluene (at a concentration of 0.001 g of reagent to 1 mL of toluene) and heated under reflux at 110 °C. The tetraene survived and the reaction resulted in a single
Diels Alder product. An optimum yield of 61% was achieved after 52 hours (Scheme 38, page 84).

![Diels Alder reaction of tetraene 272 to form carboxylate 274](image)

**Scheme 38**  Diels Alder reaction of tetraene 272 to form carboxylate 274

Protons 2-CH, 1-CH and 3-CH occupied close chemical shifts between 2.78 ppm and 3.05 ppm. Within this range one of the peaks at 3.05 ppm was a doublet of doublets (slightly overlapping), which allowed it to be unambiguously attributed to the 2-CH proton. The other two peaks were doublets. The broad doublet at 2.99 ppm was indicative of allylic coupling and therefore was assigned as the 3-CH proton. The stereochemistry, established from nOe experiments, showed that the reaction proceeded exclusively with *endo*-selectivity forming the lactone fused *cis* to the cyclohexene. Enhancements in the nOe spectrum could be seen between the resonance at 2.78 ppm corresponding to the 1-CH proton and the resonance at 1.17 ppm which corresponds to the 6-CH$_3$ protons indicating the relative stereochemistry between 1-CH and 6-CH$_3$ to be *syn*. Similarly, the resonance of the 1-CH proton at 2.78 ppm had a strong nOe to the resonance at 2.99 ppm corresponding to the 3-CH proton showing them also to be *syn* and hence the reaction to have *endo*-selectivity with respect to the lactone. The integrity of the (E)-diene tail of 274 was also confirmed by nOe enhancements observed between 3′-CH and 5′-CH protons (Figure 31, page 85).
Four stereogenic centres at C1, C2, C3 and C6 were formed in the reaction, one of which was a quaternary centre at C6 and Figure 32 shows the progression to this spatial arrangement via the transition state.

Figure 31  Observed nOe correlations for 274

Figure 32  Diels Alder reaction of tetraene 272 showing the endo-transition state.
Concurrently, and in conjunction with this study, fumarate di-ester 275 was constructed in similar fashion to tetraene methyl fumarate 272 and used as a simpler system to observe the stereochemical outcome of the IMDA reaction. When fumarate ester 275 was subjected to reflux in toluene at 110 °C for 5 days, it cyclised in an IMDA reaction to stereoselectively give lactone 276 with endo-selectivity with respect to the lactone in a yield of 25% (Scheme 39). The stereochemistry of lactone 276 was confirmed definitively by X-ray crystallography (Figure 33, page 87).

**Scheme 39**  IMDA reaction of fumarate ester 275 resulting in lactone 276
Figure 33  The crystal structure of lactone 276 confirming *endo*-stereoselectivity with respect to the lactone.

Table 1  Comparison of N.M.R. data for compounds 274 and 276

<table>
<thead>
<tr>
<th>No.</th>
<th>1H δ (m, J Hz)</th>
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<th>nOe</th>
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<td></td>
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<td>276</td>
<td>274</td>
</tr>
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<td>2.98 (dd)</td>
<td>H-1, H-3</td>
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<tr>
<td>3</td>
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<td>2.63 (m)</td>
<td>H-2</td>
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<td>1.45 (s)</td>
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<tr>
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<td>4.70 (s)</td>
<td>H-1</td>
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<tr>
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<td>3.48 (d, 8.8)</td>
<td>H-1</td>
</tr>
<tr>
<td>7</td>
<td>4.00 (d, 8.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 34  Comparison of observed nOe for Diels Alder products 274 and 276.
By analogy with the crystal structure of lactone 276 and in conjunction with the observed $^1$H n.m.r., COSY and nOe spectra for both compounds, the stereochemistry of the Diels Alder adduct 274 was assigned as having endo selectivity with respect to the lactone.

Both these results were surprising because they contrasted with many other findings on IMDA reactions carried out on similar, albeit simpler systems.\textsuperscript{78, 83} For example, in the work carried out by Paddon-Row and co-workers on doubly activated $E$- and $Z$-substituents in 1,3,8-nonatrienes, they found that exo-selectivity was predominantly favoured with the exo/endo-selectivity strongly dependent on the $E$-$Z$ stereochemistry of the dienophile with the $Z$-dienophile exhibiting a less pronounced shift towards the exo product. They attributed this selectivity to twist asynchronicity in the transition state.\textsuperscript{84} At this stage it is worth reiterating that the terms endo and exo are used to describe the orientation of the dienophile chain connection with respect to the diene. An endo presentation of substituents of the dienophile chain to the diene affords the cis-fused bicycle whereas an exo orientation of the dienophile chain to the diene gives the trans-fused cycloadduct.

### 4.3 Synthesis of (E)-6-bromohex-2-en-1-ol 277

Retrosynthetic analysis shows that aldehyde 23 can be constructed from a coupling of acetate 258 with (E)-6-bromohex-2-en-1-ol 277.

![Figure 35](image-url) Retrosynthetic analysis of preliminary target molecule 23
Following synthesis of tetraenyl acetate 258, alcohol 277 can be prepared in two steps from commercially available products by cross metathesis of 5-bromo-1-pentene 278 with 1,4-butenediol 279 in the presence of the second-generation Hoveyda-Grubbs catalyst. The resulting alcohol will be protected as TBS ether.

Tetraenyl aldehyde 23 will be obtained by combining protected alcohol 280 and tetraenyl acetate 258 using a copper catalysed chain extension reaction with a Grignard reagent derived from protected alcohol 280, followed by deprotection and oxidation to the corresponding aldehyde.

To construct (E)-6-bromohex-2-en-1-ol 277 a mixture of cis-2-butene-1,4-diol 279 and 5-bromopent-1-ene 278 in the presence of Hoveyda-Grubbs second generation catalyst, were subjected to a cross metathesis reaction to give the desired alcohol 277. Despite the second generation Grubbs ruthenium carbene complex being even more stable and active than the original first generation versions, in our hands it only gave a moderate yield of 60%. This was partly due to the difficulties in purification but could also have been as a result of the general problems that are encountered with cross metathesis in that often with cross metathesis reactions tetrasubstituted olefins are formed.\textsuperscript{85} Mass spectrometry and n.m.r. (\textsuperscript{1}H, \textsuperscript{13}C, nOe and COSY) confirmed the product to be allylic alcohol 277. Peaks in the n.m.r spectrum at $\delta$ 5.36 ppm and $\delta$ 5.49 ppm, showed two doublets of triplets with $J$ values of 15.4 Hz and 6.8 Hz. A value of 15.4 Hz is consistent with a trans-alkene, thereby providing evidence of the (E)-isomer. Allylic alcohol 277 was protected as the corresponding TBS ether 280 (Scheme 40, page 90). This silyl-protecting group was chosen because it is particularly suited to protecting alcohols, is easy to attach and remove in high yields and would not interfere with subsequent chemistry.
Grubbs and co-workers have conducted extensive kinetic studies on $L_2X_2Ru=CHR$ complexes and proposed the following mechanism that is consistent with the observed trends. Figure 36 shows the mechanism that may apply to the reaction between cis-2-butene-1,4-diol 279 and 5-bromopent-1-ene 278.

**Figure 36** Grubbs cross metathesis mechanism

### 4.4 Copper catalysed chain extension to form aldehyde 23

The protected 6-bromohex-2-en-1-ol 280 was converted to the corresponding Grignard reagent then reacted with tetraenyl acetate 258 in the presence of copper catalyst Li$_2$CuCl$_4$ at -78 °C to form the protected open chain all ($E,E,E,E$)-isomer 281 in 82% yield. The structure was assigned on the basis of its spectroscopic data. Peaks in the n.m.r spectrum at 5.53 ppm and 5.59 ppm
showing two doublets of triplets with \( J \) values of 15.1 Hz and 6.6 Hz confirmed the \((E)\) isomer at C2–C3. The silyl-protecting group of \(281\) was removed with TBAF under basic conditions to give long chain alcohol \(282\), which was immediately oxidised to the corresponding aldehyde \(23\) in a yield of 85% (Scheme 41).

**Scheme 41** Copper catalysed coupling to give the long chain aldehyde \(23\)

Unlike previous oxidations of alcohols to aldehydes in this synthesis, \(\text{MnO}_2\) was not successful at oxidising alcohol \(282\) to aldehyde \(23\). Two of the few disadvantages of using \(\text{MnO}_2\) as an oxidant are the high loadings required and the very slow reaction times. In using \(\text{MnO}_2\) to convert allylic alcohol \(282\) to tetaene aldehyde \(23\) fifteen equivalents were used but the reaction had still not gone to completion after 6 days. A further 10 equivalents were added but after 2 more days the reaction had still not gone to completion and the yield was poor at 38% after work-up. The long reaction time on this sensitive tetraenol \(282\) was a concern and we believe was a significant factor in the limited success of \(\text{MnO}_2\) as the oxidant. An alternative method of oxidation was therefore sought.
Of all the potential methods of oxidation that are available under basic conditions, *tetrapropylammonium perruthenate* (TPAP) seemed well suited to tetaenol 282. In a review of the oxidations of a wide range of molecules using TPAP, Ley and co-workers pointed to the attractiveness of using this readily soluble, non-volatile air stable, room temperature oxidant for alcohols because it displays high selectivity, alongside excellent tolerance to other functional groups present. The TPAP reagent is rendered catalytic when used with *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant. Although the review did not assess the suitability of TPAP to oxidise allylic alcohols that are part of a tetaene, they did have success in oxidising primary alcohols that were part of carbon chains containing dienes. The double bonds remained intact during the TPAP oxidations and we hoped that the four double bonds of tetaenol 282 may similarly not be affected during the oxidation process.\(^{88}\)

The mechanism of the TPAP/NMO system of oxidation of alcohols is complex and the precise nature of the species involved in the catalytic cycle is unknown. The complication with ruthenium is that the transition metal can occupy a large range of oxidation states from -2 to +8. Complexes of Ru\(^{VIII}\), Ru\(^{VII}\), Ru\(^{VI}\), Ru\(^V\), and Ru\(^{IV}\) are all stoichiometrically capable of oxidising alcohols to aldehydes or ketones.\(^{85}\)

In direct comparison with other oxidants (Swern, PDC, DMSO.SO\(_3\), Jones, PCC and Dess-Martin) Ley *et al.* showed that TPAP compared favourably in terms of yield. It was also shown to be particularly effective when unstable substrates or products were used.\(^{88}\)

For these reasons, TPAP with NMO as co-oxidant, in a 9:1 mixture of dichloromethane:acetonitrile as the solvent mixture was used to oxidise tetaenol 282 to aldehyde 23 instead of MnO\(_2\). These reaction conditions gave consistently higher yields of \(\sim 85\%\), with the added advantage of the reaction being completed in 1 hour. During this reaction 4Å molecular sieves were used to remove both the water of crystallisation of NMO and any water formed during the reaction. The structure of aldehyde 23 was assigned on the basis of spectroscopic data. Peaks in the \(^1\)H n.m.r. spectrum at 5.85 ppm and 5.95 ppm,
showing a doublet of triplets for the C3 proton, with $J$ values of 15.8 Hz and 7.6 Hz and a doublet for the C2 proton, with a $J$ value of 15.8 Hz, confirmed the (E)-isomer at C2–C3.

4.5 **Investigations into Diels Alder cyclisation of conjugated tetraene 23**

At this point in the synthesis, aldehyde 23, the preliminary target molecule, could be utilised in two distinctly different ways. On the one hand it could be used to investigate the chemistry of the biomimetic route to the synthesis of diaporthichalasin 1. This would be achieved by further extending the molecule to form a long chain aldehyde analogous to that of compound 4 (Figure 4, page 23), (but with the methyl group at C11 missing), then subjecting it to a Knoevenagel cyclisation to form a pyrrolinone followed by two domino Diels Alder reactions to put in place the tricyclic rings.

On the other hand, if we look again at the natural product, it can be seen that structures 283 and 284 (Scheme 42, page 94) are key intermediates in the synthesis of diaporthichalasin 1. Structures 283 and 284 could both be put in place, with the correct stereochemistry, if long chain aldehyde 18 could be persuaded to undergo cyclisation via an intramolecular Diels Alder reaction.

In the formation of the tricyclic rings of diaporthichalasin 1, the dienophile of 18 at C2–C3 and the diene at C10–C13 must undergo an intramolecular Diels Alder reaction. This reaction can take place earlier or later in the synthesis, depending on the chosen synthetic route. In a stepwise construction of the macrocycle, the cyclisation would take place early in the synthesis. If the biomimetic strategy was followed, then the cyclisation will occur in the latter stages, as part of the cascade Diels Alder reactions.
Using a LUMO-lowering organocatalytic strategy, it may be possible to synthesise both isomers by means of an *endo*-selective or *exo*-selective Diels Alder reaction of conjugated tetraene 18. The desired stereochemistry could be put in place by use of an asymmetric catalyst. Activation of the α,β-unsaturated carbonyl of tetraene 18 via the reversible formation of iminium ions should lower the LUMO of the dienophile and hence promote an *intramolecular* Diels Alder reaction. An *endo*-selective Diels Alder reaction of 18 will form diastereoisomer 284 leading to diaporthichalasin 1. An *exo*-selective reaction would form diastereoisomer 283, which could be used in the synthesis of the diastereoisomer of diaporthichalasin 1.

Pursuing this synthetic strategy has a key advantage in that the tetraene would be utilised early in the total synthesis, thereby avoiding potential problems later due to the sensitivity of the conjugated tetraene. If successful, the reaction would put in place two of the six membered rings with the correct stereochemistry and the terminal diene would be positioned to form the second Diels Alder reaction needed to construct the isoindolone moiety. Furthermore, investigating this chemistry would provide new information on the tolerance of sterically hindered conjugated tetraenes to enantioselective decalin formation.

However, in addition to the difficulties there may be with steric barriers, this approach is not without considerable stereochemical difficulties as outlined in the discussion in Appendix 1 (page 214) on the issues concerning IMDA reactions of tetraene 23.

**Scheme 42** Retrosynthesis of 284
4.5.1 *Investigations into IMDA reactions using the asymmetric organic catalysts of MacMillan et al.*

In 2005, MacMillan *et al.* demonstrated the value of organocatalytic reactions in the synthesis of the marine metabolite solanapyrone D. The group developed a number of asymmetric catalysts including 2nd generation catalyst 286 and 1st generation catalyst 289 and, using them in conjunction with various co-catalysts (TFA, HCl or HClO₄), synthesised a number of bicyclic compounds with high enantioselectivity from open chain trienes (Scheme 43, page 95). This methodology may enable an *intra*molecular Diels Alder reaction to take place on conjugated tetraene 23 under investigation in this study.

**Scheme 43** Examples of asymmetric organocatalysts developed by MacMillan *et al.*

However, there are key differences between our desired decalin 284 and MacMillan's *et al.* decalins 287 and 290. Steric congestion due to the additional methyl groups in the Diels Alder precursor to decalin 284 may significantly influence the formation of the quaternary centre of decalin 284. MacMillan *et al.* have demonstrated that it is possible to form a quaternary centre in adduct 290, but this was achieved with only one methyl group in the chain.
Nevertheless, it was decided to adopt the methodology of MacMillan et al. to attempt Diels Alder reactions of tetraene 23, to investigate whether cyclisation is possible on a more complex system than those reported by MacMillan et al.

The mechanism of the reaction involves the catalyst forming an iminium species with the aldehyde of 23 (Scheme 44, page 96). This exerts an electron withdrawing effect on the dienophile thereby lowering its LUMO. The effect is to reduce the energy gap between the HOMO of the diene and the LUMO of the dienophile. The asymmetric shape of the catalyst is designed to direct the reaction to a particular enantiomeric excess.

![Scheme 44](image)

**Scheme 44**  Diels Alder mechanism using the catalyst of MacMillan et al.

### 4.5.1.1 Results of the IMDA reaction using MacMillan’s et al. asymmetric organocatalysts

Reactions to induce cyclisation of aldehyde 23 were undertaken, at room temperature, using seven of MacMillan and co-worker’s asymmetric organocatalysts. The principle objective at this stage was to determine whether using an organocatalyst would result in cyclisation and if so, with what degree of stereo control. Table 1 gives a summary of the outcome of this series of experiments.
Scheme 45  Proposed Diels Alder cyclisation of aldehyde 23

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>289 HCl</td>
<td>Decomposition</td>
</tr>
<tr>
<td>289 HCl, Et₃N</td>
<td>Multiple spots on TLC, Complex n.m.r. spectra, &lt;10% starting material recovered. No product.</td>
</tr>
<tr>
<td>289 CHCl₂COOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>286 TFA</td>
<td>Decomposition</td>
</tr>
<tr>
<td>286 HCl</td>
<td>Decomposition</td>
</tr>
<tr>
<td>286 HCl, Et₃N</td>
<td>Multiple spots on TLC, Complex n.m.r. spectra, &lt;10% starting material recovered. No product.</td>
</tr>
<tr>
<td>291</td>
<td>Multiple spots on TLC, Complex n.m.r. spectra, &lt;10% starting material recovered. No product.</td>
</tr>
</tbody>
</table>

Table 1  Results of using MacMillan's et al. organocatalysts on aldehyde 23

With four of the catalysts (Table 1), the experiments were carried out under mildly acidic conditions (pH 3), due to the nature of the co-catalyst. Unfortunately, the conjugated tetraene proved to be sensitive to acid-mediated decomposition and in all cases decomposition of the starting material occurred. TLC showed multiple spots that were not separable by column chromatography and ¹H n.m.r. spectra of the crude reaction mixtures were complex and indecipherable.

Catalyst 291 was utilised under neutral conditions. Three distinct spots were present by TLC, which were separated by flash chromatography. Mass spectrometry on each of the compounds isolated indicated the correct
molecular ion was present but the $^1$H n.m.r. spectra were complicated by many overlapping peaks that could not be clearly and unambiguously assigned.

Two catalysts were used under basic conditions. Both gave two clear spots by TLC that were separated by flash chromatography. The correct molecular ion was present in both of the compounds that were isolated but the $^1$H n.m.r. spectra were complex with broad overlapping peaks that could not be assigned with any certainty. The broadening of the peaks may have been caused by hindered rotation and in order to resolve the spectra, the $^1$H n.m.r. and COSY were run at high temperature. This did sharpen the peaks, indicating the presence of rotamers, but not sufficiently for the compounds present to be characterised.

Unfortunately, all reactions with long chain aldehyde 23 and MacMillan’s 1st and 2nd generation catalysts failed to produce the desired Diels Alder cyclisation product.

### 4.5.2 IMDA using a Lewis acid

To ascertain whether or not cyclisation would occur without any stereo control, it was considered that the IMDA reaction may be induced using a Lewis acid. This may not give any control over the stereoselectivity, but would establish whether the IMDA reaction with the tethered tetraene in question was achievable. A Lewis acid is a simple but effective electron withdrawing group that has been used extensively in Diels Alder reactions.\(^90\)

In particular, Shishido et al. demonstrated success with IMDA reactions in forming a quaternary centre in a high yield of 92% and an 8:1 inseparable mixture of diastereoisomers using an aluminium based Lewis acid on a triene.\(^91\) This seemed an attractive approach because the quaternary centre they formed was similar to that desired in the product of the cyclisation of aldehyde 23.

Dimethyl aluminium chloride was chosen as the Lewis acid and 1.5 equivalents was added to aldehyde 23 in DCM at -78 °C and stirred for 12 hours. Multiple spots were present on the TLC and three compounds were isolated by column
chromatography. Each showed complex overlapping signals in the $^1$H n.m.r. spectrum that could not be confidently assigned. A variation of this procedure involved introducing the Lewis acid at -78 °C, then warming up the mixture to room temperature and stirring for 8 hours.\textsuperscript{92} TLC showed two distinct spots and two compounds were isolated by column chromatography. The proton n.m.r. spectrum of the more polar compound exhibited peaks that were complex and broad. This may have been indicative of hindered rotation due to the close spatial proximity of two equatorial methyl groups. Re-running the $^1$H n.m.r. spectra at high temperature did not sharpen the peaks but the product could not be characterised.

Unfortunately, in our hands, using dimethyl aluminium chloride as the Lewis acid, the IMDA reaction was not successful.

### 4.5.3 IMDA at reflux under high dilution

Diels Alder reactions readily take place under thermal conditions and therefore, in a final attempt to carry out a Diels Alder reaction on aldehyde 23, it was refluxed at 120 °C under high dilution conditions in toluene (0.001 g in 1 mL) for 10 days. The Diels Alder cyclisation failed to occur and starting material was recovered.

### 4.5.4 Summary of investigations into IMDA reactions of aldehyde 23

All attempts to induce aldehyde 23 to undergo an IMDA reaction were unsuccessful (Scheme 46, page 100). The failure of aldehyde 23 to cyclise may indicate that the first Diels Alder reaction does not take the route of initially forming a bicyclic [4.4.0]-decalin, as speculated earlier. However, it may be that the dienophile was simply not sufficiently activated for the reaction to occur. We do know, from earlier work in this study, that the steric factors on the tri-substituted diene can be overcome with the right conditions, so formation of the decalin cannot be ruled out. In any event, further reactions to cyclise aldehyde
23 were not pursued and the research returned to the original biomimetic approach.

![Scheme 46](image)

**Scheme 46**  Result of IMDA reaction on aldehyde 23

### 4.6 *Synthesis of pyrrolidinone 292*

In order to complete the synthesis of the long chain precursor to the domino Diels Alder reactions, the next step involved constructing pyrrolidinone fragment 292 (Figure 37). This route was chosen at this stage because the chemistry was known.\footnote{40}

![Figure 37](image)

**Figure 37**    Pyrrolidinone 292

Once synthesised, pyrrolidinone 292 would be coupled to aldehyde 23 and the resultant structure modified to the corresponding pyrrolinone by the insertion of a double bond between C4 and C5 by oxidative elimination of phenyl
In this way, we intend to put in place the dienophile to initiate the cascade IMDA reactions.

To ensure the pyrrolidinone substrate will become an effective dienophile, it is essential to have an electron withdrawing group on the nitrogen. This is because pyrrolidinone 293 has been shown to undergo tautomerism to the corresponding enol 294, which consequently can lead to racemisation at C5 giving the undesired 295 (Figure 38).

![Figure 38](image)

**Figure 38** Potential enolisation and racemisation of an unprotected pyrrolinone

With a protecting group on nitrogen, the pyrrolinone has been shown to resist tautomerisation due to the resonance taking place between structures 296 and 297, where it can be seen that the nitrogen lone pairs are delocalised onto the exocyclic carbonyl group. Subsequent tautomerisation of 297 to enol 298 does not occur since this would result in enol 298 having a destabilised $4\pi$ electron system (Figure 39, page 102).
Figure 39  The stabilising effect of an electron withdrawing group on the pyrrolidinone 296

Pyrrolidinone 292 was prepared in its optically pure form using the literature method of Smreina et al.96 The nitrogen of commercially available L-phenylalanine 299 was protected with a Boc group to give 300 in a yield of 77%. The next step involved a two carbon homologation using Meldrum’s acid in the presence of DMAP and DCC. Sodium borohydride and acetic acid completed the reaction sequence to give 301 in a yield of 78%. Finally, cyclisation to pyrrolidinone 292 was achieved in toluene under reflux in a high yield of 96% (Scheme 47).

Scheme 47  Synthesis of pyrrolidinone 292
One consideration we had at this point was whether to protect the nitrogen with a benzoyl protecting group rather than a Boc group. A benzoyl group has different electron withdrawing properties due to greater delocalisation of the electrons onto the benzene ring and as a consequence may prove better protection against enolisation (Figure 39 page 101). We decided therefore to have available two batches of pyrrolidinone, one protected with a Boc group and the other with a benzoyl group. Changing the protecting group was achieved using TFA to remove the Boc group followed by re-protection with benzoyl chloride in DCM and NaOH in water (Scheme 48, page 103). The overall yield for the two step process was 53% and the structures of both compounds were confirmed by spectroscopic analysis.

![Scheme 48](image)

**Scheme 48** Changing the protecting group on pyrrolidinone 292

### 4.7 Intramolecular Diels Alder reaction to form two quaternary centres

Forming quaternary centres is a key feature in the biosynthesis of diaporthichalasin 1. The conjugated tetraene substituent of diaporthichalasin 1 has been shown to cyclise in a Diels Alder reaction forming one quaternary centre (Scheme 38, page 84). Our investigations now turned to the pyrrolinone fragment of diaporthichalasin, because it plays a key role as the dienophile in the Diels Alder reaction to form the isoindolone unit of diaporthichalasin 1. In this Diels Alder reaction involving the pyrrolinone 292, four stereogenic centres are formed, including two quaternary centres. In order to investigate this chemistry we constructed a simplified system involving the pyrrolidinone
substituent tethered to a conjugated diene containing trisubstituted carbon atoms. This closely mirrors the tricyclic core the natural product and the expectation was that the reaction would lead to cyclisation to form the central core of diaporthichalasin 1 containing two of the quaternary centres found in the natural product. The target compound was therefore isoindolone 25. A retrosynthetic analysis is given in Scheme 49 (page 104). Constructing isoindolone 25 would provide valuable information on the key oxidative elimination step in forming the dienophile from the pyrrolidinone substituent and also on the chemical behaviour of the pyrrolinone as the dienophile.

**Scheme 49**  Retrosynthetic analysis of isoindolone 25

Initially it was thought to utilise an Ireland-Claisen [3,3]-sigmatropic rearrangement to construct diene 308 (Scheme 50, page 105). Commercially available 2-bromopropene 307 was cooled to -78 °C and t-butyl lithium added slowly followed by dropwise addition of tiglic aldehyde 22. This formed alcohol 308 in a high yield of 98%. Acylation of alcohol 308 in pyridine gave ester 309 in a yield of 84%. However, when ester 309 was reacted with TMSCl in the presence of LDA at -78 °C and allowed to warm to room temperature and stirred overnight, the expected Ireland-Claisen rearrangement product did not result. The nature of ester 309 allowed the [3,3]-sigmatropic shift to occur in two different directions and this in fact is what happened. Unfortunately an
inseparable mixture of 310 and 311 was produced in a 1:1 ratio, so this strategy was abandoned.

Scheme 50  Result of the Ireland-Claisen [3,3]-sigmatropic rearrangement

After this disappointment, our next approach was to acetylate allylic alcohol 261 with acetic anhydride, in preparation for a reaction with commercially available allyl magnesium bromide in the presence of a copper catalyst (Scheme 51, page 106). The intention was to form the short hydrocarbon chain 315 then dihydroxylate at the terminal alkene to give diol 316. A chemoselective oxidation to ethyl ester 306 would allow conversion to its corresponding carboxylic acid and then we intended to use previous chemistry to synthesise isoindolone 25.

However, during the early stages of the Grignard reaction, monitoring by TLC indicated that the allyl magnesium bromide had preferentially formed its dimer
This Wurtz-type coupling, catalysed by copper(I), is a known side reaction of Grignard reactions\textsuperscript{97} and so this way forward was not pursued.

\begin{center}
\textbf{Scheme 51}  Failed reaction to form hydrocarbon 315
\end{center}

Our next strategy, set out in Scheme 52 (page 107) involved bromination of allylic alcohol 261. We first utilised methanesulfonyl chloride and lithium bromide in the presence of triethylamine to make the conversion. When this failed to produce the brominated product, we followed the method of Kim \textit{et al.}\textsuperscript{98} and used PBr\textsubscript{3} in DCM at -78 °C. The resulting allylic bromide 317 was used in the next step without purification and added immediately to diethyl malonate which produced di-ester 318 in 25\% yield over the two steps. The allylic bromide was not very stable, which may have been the reason for the poor yield. Mono-decarboxylation of di-ester 318, using lithium chloride and DMSO/H\textsubscript{2}O resulted in ester 306 in a low yield of 49\% and the $^1$H n.m.r. spectrum indicated the product was contaminated with material that could not be identified. At this stage the synthetic route began to look untenable. There was a poor yield for the bromination step to form 317 and formation of the di-ester 318 and subsequent mono-decarboxylation to 306 did not result in a clean product or an acceptable yield. Nevertheless the synthetic route was continued and conversion to the carboxylic acid 319 was achieved using 8
equivalents of lithium hydroxide in water and acidification with tartaric acid. The crude carboxylic acid was then used without purification. A solution of 1,1'-carbonyldiimidazole was added to crude acid 319 to give acyl imidazole 305 followed by coupling to the lithium enolate of pyrrolidinone 303 gave 2-oxopyrrolidinone 320. De-protonation of 2-oxopyrrolidine 320 using LiHMDS at -78 °C followed by addition of phenylselenyl chloride furnished two diastereoisomers of the selenide pyrrolidinone 321. Oxidative elimination of the phenyl selenide from the pyrrolidinone was accomplished using m-CPBA in chloroform in conjunction with aqueous hydrogen peroxide to give the pyrrolinone 304. This highly reactive species was then immediately injected into a dilute solution (1 mL of solvent to 1 milligram of reagent) of degassed toluene and heated for 50 hours at 110 °C. The 1H n.m.r. spectrum showed a complex mixture of compounds which made it difficult to unambiguously determine if a Diels Alder reaction had taken place.
Scheme 52  Attempted synthesis of isoindolone 25

4.8  Alternative intramolecular Diels Alder reaction to form two quaternary centres

In view of the problems encountered in trying to synthesise the exact tricyclic core of the natural product 25, it was decided to change our approach and construct a six-membered analogue 322. A retrosynthetic analysis is shown in Scheme 53. This synthesis would still provide key information on the chemistry of forming two quaternary centres using the pyrrolinone as a dienophile and also provide valuable experimental data with respect to the total synthesis of the natural product.
The tricyclic isoindolone 322 can be obtained from a Diels Alder reaction of pyrrolinone 323, which is available as a product of acyl imidazole 324 and pyrrolidinone 303. Acyl imidazolide 324 can be constructed from diene acetate 312 as before.

This new route commenced by protecting the alcohol of commercially available 3-bromopropanol 325 with TBS chloride to give silyl ether 326 (Scheme 54, page 109). The Grignard reagent then was formed using conditions by Xia et al. 99 This involved seeding the magnesium turnings, in anhydrous THF with a catalytic amount of iodine to initiate the reaction and controlling the speed of the addition of silyl ether 325, also in THF, to maintain the temperature of the reaction mixture at 30-35 °C. After complete addition, the resulting mixture was stirred at 40 °C for 1 hour to afford a solution of bromide 327. This was not isolated, and the mixture was then immediately cooled to -78 °C and Li₂CuCl₄ added followed by the diene acetate 312. The coupling reaction reached completion in less than 3 hours to give TBS-protected alcohol 328 in a yield of 91% (Scheme 54). The structure of protected alcohol 328 was assigned on the basis of its spectroscopic data.
Scheme 54  Synthetic route to TBS-protected alcohol 328

The silyl-protecting group of 328 was removed with TBAF to give alcohol 329, again in a good yield of 90%, which was immediately oxidised to the corresponding aldehyde 330 using TPAP with NMO as a co-oxidant (Scheme 55).

Scheme 55  Synthetic route to aldehyde 330

Conversion of aldehyde 330 to carboxylic acid 331 was achieved under Pinnick conditions and used without purification in the next step when a solution of 1,1'-carbonyldiimidazole in THF was added to give acyl imidazole 324. This compound was contaminated so the acid was converted to the corresponding methyl ester 332 in order to purify it by flash column chromatography. Direct purification of the acid was problematic. Thus, a solution of TMS-diazomethane in 2.0 M hexanes was added to crude acid 331 in a mixture of toluene and methanol using the method of Presser et al. After 45 minutes the reaction was completed to give methyl ester 332 in a good yield of 75% after purification. Methyl ester 332 was then treated with 12 equivalents of lithium
hydroxide in water to afford carboxylic acid 331 in a yield of 82%. The proton n.m.r. spectrum showed the acid 331 to be free of contamination. A solution of 1,1'-carbonyldiimidazole in THF was added to acid 331 to give acyl imidazole 324 in a yield of 83% (Scheme 56).

![Scheme 56](image)

Scheme 56  Synthetic route to acyl imidazolide 324

The precursor to the Diels Alder reaction was brought a step closer when pyrrolidinone 303 was deprotonated with LiHMDS, then immediately reacted with acyl imidazole 324 to furnish 2-oxypyrrolidine 333 (Scheme 57, page 111). The double bond of the dienophile was then put in place over two steps by the addition of phenylselenyl chloride to give a mixture of two diastereoisomers of selenide 334. Oxidative elimination of the phenyl selenide from the pyrrolidinone followed using mCPBA and hydrogen peroxide to give the reactive pyrrolinone 323. The two phase mCPBA/H₂O₂ system prevented the decomposition of the diene. At -50 °C mCPBA oxidises the selenide to a selenoxide, with the aqueous hydrogen peroxide remaining frozen. As the temperature warms to 0 °C the selenoxide bond breaks to give the pyrrolin-2-one plus PhSeOH, which is rapidly oxidised to Se(IV) thereby preventing it from destroying the diene. A sample, taken out for 1H n.m.r. analysis, indicated the presence of pyrrolinone 323 through the characteristic peak for the 4-H proton of the pyrrolinone at 7.91 ppm.102 Upon isolation, the reactive pyrrolinone 323
was injected immediately into a dilute solution (1 mL of solvent to 1 mg of reagent) of degassed xylene and refluxed at 140 °C for 21 hours. Two diastereoisomers of 322 were isolated in a ratio of 3.7:1 and in a combined yield of 33%.

Scheme 57  Synthesis of isoindolone 322

4.8.1  Determination of the stereochemistry of Diels Alder adduct 322

Given the complex structure of isoindolone 322 it was important to determine the exact structure of the compounds isolated. High resolution mass spectrometry of the major diastereoisomer established the molecular formula to be $C_{29}H_{31}NO_3$. Infrared spectroscopy displayed C=O peaks at 1729, 1703 and 1678 cm$^{-1}$ and aromatic C=C stretching at 1447 cm$^{-1}$. The $^{13}$C n.m.r. spectrum displayed the correct 25 carbon peaks. By way of a summary, Table 2 sets out the full n.m.r. data ($^{13}$C, $^1$H, COSY, HMBC and nOe) for isoindolone 322.
In the $^1$H n.m.r. spectrum of isoindolone 322, the relative number of protons under each peak integrated for three methyl groups, four sets of methene protons, four methine protons and ten aromatic protons giving the correct total of thirty one protons. The chemical shifts for each of the peaks were also in the correct chemical environment for the structure of isoindolone 322.

The peak at $\delta$ 3.19 ppm integrated for one proton and was a doublet of doublets with $J$ values of 4.1 Hz and 8.2 Hz. This suggested that this CH proton was situated between two other methine protons. The COSY spectra showed spin-spin coupling between this proton and one proton at $\delta$ 4.36 ppm and one at $\delta$
On this evidence and the evidence from the HMBC, two bond couplings linking this proton with the 4-CH$_3$ and 3-CH', the peak at δ 3.19 ppm was attributed as the 3a-CH proton. The peak at δ 4.36 ppm was displayed as a doublet of doublet of doublets and integrated for 1 proton. This indicated that it may be coupled with a single proton and two diastereotopic protons. The coupling constants of $J$ 2.8 Hz and $J$ 7.6 Hz, matched the coupling constants of the two diastereotopic protons at 1'-CH$_2$ at δ 3.04 ppm $J$ 7.6 Hz and δ 3.13 ppm and $J$ 2.8 Hz. The third coupling constant of this proton of $J$ 7.9 Hz was close to that attributed to 3a-CH at $J$ 8.2 Hz. This indicated that the peak at δ 4.36 ppm integrating for one proton was likely to be the 3-CH proton. These relationships were supported by the COSY and HMBC data. Unfortunately the peak at δ 1.87 ppm, also integrating for one proton, (established as the 4-CH proton from COSY and HMBC, Table 2) overlapped with one of the diastereotopic protons of 7-CH$_2$ and was displayed as a multiple so offered no further evidence via coupling constants. The singlet at δ 1.01 ppm integrated for three protons and this, in conjunction with the evidence from COSY and HMBC spectra, allowed it to be assigned as the 6a-CH$_3$ protons.

Establishing the orientation of the protons at 3-CH, 3a-CH, 4-CH and 6a-CH$_3$ of 320 will help determine the exo/endo stereochemistry of the Diels Alder and analysis of 1D nOe studies provided this evidence. The Diels Alder reaction has the advantage of being stereospecific in that the stereochemistry in the dienophile is faithfully reproduced throughout the course of the reaction. However, the dienophile of the pyrrolinone can present in two orientations to the diene, resulting in either the exo or endo stereochemistry with respect to the pyrrolinone in the cyclised product (Figures 40 and 41, page 115). Examination of the nOe data showed the resonance at δ 4.36 ppm, corresponding to the 3-CH proton, had a strong nOe correlation to the resonance from the 4-CH proton at δ 1.87-1.97 ppm suggesting that the relative stereochemistry between 3-CH and 4-CH is syn (Figure 40). There are no nOe correlations between the 3a-CH proton and 3-CH proton or between the 3a-CH proton and 4-CH proton indicating the relative stereochemistry between the 3a-CH proton and the protons at 3-CH and 4-CH to be anti. In addition the resonance of the 3-CH
proton at $\delta$ 4.36 ppm showed an interaction through space to the signal at $\delta$ 1.01 ppm corresponding to the 6a-CH$_3$ protons indicating a *syn* relationship. This evidence points to the structure having the *exo*-product with respect to the pyrrolinone (Figure 40).

![Diagram of molecule](image)

**Figure 40** Observed nOe correlations for isoindolone 322 and the assigned *exo*-stereochemistry

The IMDA reaction generated four stereogenic centres at C3a, C4, C6a and C10a, two of which are quaternary centres at C6a and C10a. Figure 41 shows the transition state in forming this product.
Figure 41  Diels Alder reaction of pyrrolinone 323 showing exo-transition state

Figure 42  Diels Alder reaction of pyrrolinone 323 showing endo-transition state

Figure 42 (page 115) shows the endo stereochemistry of the Diels Alder reaction. Unfortunately, the spectroscopic data for the second compound,
isolated in a yield of 7%, did not allow its structure to be unambiguously assigned as that shown as compound 335 in Figure 42. High resolution mass spectrometry did establish the molecular formula to be C_{29}H_{31}NO_3, but the $^1$H n.m.r. spectrum was contaminated so it was not possible to establish the relative number of protons or the stereochemistry.
Chapter 5

Results and discussion part 2

5.1 Introduction

We have demonstrated that the penta-substituted conjugated tetraene fragment of the natural product will, in the presence of a doubly activated dienophile, cyclise in an IMDA reaction and form a quaternary centre (Scheme 38, page 82). We have also demonstrated that the pyrrolidinone fragment of the natural product will, in the presence of a tri-substituted diene, also cyclise in an IMDA and form two quaternary centres (Scheme 58, page 118). With this information to hand we were now in a position to make progress towards completing the biomimetic synthesis.

5.2 Attempted synthesis of acyl imidazole 336

Pyrrolinone 26 should be available via a condensation reaction between acyl imidazole 336 and pyrrolidinone 303. Oxidising aldehyde 23 to the corresponding carboxylic acid 337 then activating it as acyl imidazolide 336 would prepare it for coupling to pyrrolidinone 303 to form long chain pyrrolinone 26 (Scheme 57, page 118).
Therefore, aldehyde 23, in t-butyl alcohol, was treated with a mixture of sodium hydrogen phosphate with sodium chlorite in water and an excess of 2-methyl-2-butene under Pinnick conditions.\textsuperscript{100} To protect the four conjugated double bonds of 23 from acid decomposition during work-up, the normal procedure of acidifying the aqueous phase to pH 3 was avoided by quenching the reaction with a saturated brine solution followed by traditional extraction processes (Scheme 59).\textsuperscript{104}

**Scheme 58**  Retrosynthesis of pyrrolinone 26

**Scheme 59**  Attempted oxidation of aldehyde 23
The resulting crude product from the reaction was not chromatographed because the base-washed silica used to preserve the acid sensitive tetraene during purification, was likely to remove the proton of the carboxylic acid and generate the carboxylate ion. As a consequence, the $^1$H n.m.r. spectrum of crude acid 337 was extremely complex. To ascertain whether there was a fundamental problem with the Pinnick reaction, as the $^1$H n.m.r. spectra indicated, an attempt was made to convert crude acid 337 to the corresponding methyl ester 338 using trimethylsilyl diazomethane in methanol. This stable ester species could be purified by column chromatography. Subsequently, the aim was then to convert the purified methyl ester 338 back to carboxylic acid 337 by saponification using lithium hydroxide followed by converting the resulting acid to acyl imidazole 336 (Scheme 60).

\[
\text{Scheme 60} \quad \text{Proposals to produce clean acyl imidazolide 334}
\]

Treatment of crude acid 337 with TMSCHN$_2$ gave methyl ester 338 but in poor yield (2%). This may suggest very little carboxylic acid 337 was present after the Pinnick oxidation.

The reagents used and mechanism for the Pinnick reaction may provide an insight into why the reaction failed on our particular conjugated tetraene. The Pinnick mechanism allows the formation of hypochlorite and these can cause side reactions, specifically in this case because the hypochlorite ions react with alkenes. The reaction conditions potentially overcome this problem by including a scavenger, 2-methyl-2-butene, in the reaction to mop-up the
hypochlorite (Figure 43). However, if the conjugated tetraene is more reactive than 2-methyl-2-butene, then it will preferentially react with the hypochlorite.

\[
\begin{align*}
\text{ClO}_2^- & \quad + \quad \text{H}_3\text{PO}_4^- \\
\stackrel{\text{H}}{\text{O}} & \quad \text{H} \\
\text{R} & \quad \text{H} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

**Figure 43**  Mechanism of the Pinnick reaction

The hope at this stage was that if pyrrolinone 26 (Scheme 58, page 118) could be obtained in quantitative yield, utilising the crude products 337 and 336 would be inconsequential to our strategy. Therefore, with some crude acid 337 still at hand, it was optimistically decided to take it through to try to form the stable Diels Alder precursor. Carboxylic acid 337 was therefore activated as its acyl imidazolide by treatment with 1,1′-carbonyldiimidazole. This provided crude acyl imidazolide 336 but again, the structure was not able to be unambiguously confirmed by n.m.r. spectroscopy. In an attempt to chromatograph the crude compound, a mixture of 80 parts dichloromethane to 20 parts methanol to 2 parts ammonia was used as the solvent system. This successfully separated the two compounds using a gradient eluting mixture of 1:1 to 1:4 [80 parts DCM to 20 parts methanol to 2 parts ammonia]:diethyl ether. Unfortunately, neither of the two compounds isolated was the desired acyl imidazole 336.

In the event, this synthetic approach was demonstrated to be ineffective because the critical step of forming the carboxylic acid failed under Pinnick conditions. At this stage, using a different set of conditions to form the
carboxylic acid was an option under consideration but instead we decided to pursue a different approach.

5.3 Model study to determine the feasibility of Aldol coupling to produce pyrrolidinone 343

To assemble the requisite molecular framework for the next stage of the synthesis, a direct coupling of long chain aldehyde 23 with pyrrolidinone 292 should be possible via an aldol reaction. Oxidation of the resulting alcohol 340 to the β-keto carbonyl 339 would put us to within two steps of the final domino Diels Alder reactions (Scheme 61).

![Scheme 61](image)

**Scheme 61** Retrosynthetic analysis of pyrrolidinone 339

It was decided that this proposed synthetic route would be first tested on model substrates. Therefore the aldol reaction between pyrrolidinone 292 and trans-2-cis-6-nonadienal 341 was undertaken (Scheme 62, page 122). The chemistry involved the condensation of enolate 342, derived from pyrrolidinone 292, with aldehyde 341 to give β-hydroxy lactam 343. The product of this crossed aldol reaction could be oxidised to give the desired corresponding β-keto carbonyl 342.
Reaction of *trans*-2-*cis*-6-nonadienal 341 with two equivalents of lithium enolate 342, generated from pyrrolidinone 292 using lithium bis(trimethylsilyl)amide solution (1.0 M in THF) at -78 °C for 1 hour, gave alcohol 343 in a yield of 67% (Scheme 62). Two new stereogenic centres were created at positions 3 and 6 where mixtures of *syn* and *anti* diastereoisomers were present, resulting in complex n.m.r. spectra. However, these diastereoisomers were inconsequential to the synthesis because they would be removed over the next three steps. Oxidation of allylic secondary alcohol 343 to ketone 344 failed using TPAP/NMO in DCM/acetonitrile (10:1) and was only marginally successful using PDC in DCM giving ketone 344 in a poor yield of 21%. In an attempt to improve this yield, 0.4 equivalent of pyridinium trifluoroacetate was added as this was reported to push slow oxidations of this type to completion more quickly. Unfortunately this did not significantly improve the yield. Dess-Martin periodinane (DMP) proved more successful in producing β-ketone 344. Using 1.5 equivalents of DMP gave 56% yield. The
result was a mixture of diastereoisomers including the corresponding enol tautomer, which made the n.m.r. spectra complex to decipher.

De-protonation of 2-oxopyrrolidine 344, using LiHMDS at 0 °C followed by addition of phenylselenyl chloride and stirring at room temperature for two hours, furnished two diastereoisomers of pyrrolidinone 346 (Scheme 62, page 122). Oxidative elimination of pyrrolidinone 346 was accomplished using mCPBA in chloroform in conjunction with aqueous hydrogen peroxide to give pyrrolinone 347 in a good yield of 79%.

5.4 Attempted synthesis of pyrrole-1-carboxylate 348

Following the successful procedures of the model system, pyrrolidinone 292 was lithiated at -78 °C using LiHMDS to form enolate 342 and after 1 hour at this temperature, a pre-cooled solution of aldehyde 23 in THF was added. Within two hours the aldol reaction produced alcohol 340 in a good yield of 83% after work-up and column chromatography (Scheme 63). A mixture of four diastereoisomers was present in the complex n.m.r. spectrum. However, as with the model system, these diastereoisomers would be removed over the next three steps.

Scheme 63  Aldol reaction of aldehyde 23 and pyrrolidinone 292
However, the oxidation of allylic alcohol 340 to its corresponding β-keto carbonyl 348 proved to be problematic (Figure 44).

![Diagram of oxidation process]

Figure 44 Intended oxidation of allylic alcohol 340 to β-keto carbonyl 348

The first reagent used was Dess-Martin periodinane, since this was successfully used in the model system. Unfortunately, DMP failed to oxidise the secondary alcohol and the 1H n.m.r. spectrum of the crude mixture seemed to indicate that the tetraene had been destroyed. Acetic acid is formed during this reaction but it was felt that by using 12 equivalents of pyridine, that this would preserve the tetraene. This appeared not to be the case, with the starting material decomposing. A variation on the Dess-Martin oxidation was tried using o-iodoxybenzoic acid (IBX),\(^\text{107}\) which proceeds without the generation of acetic acid. The reaction was carried out in a 1:1 mixture of DMSO and THF due to solubility. After work-up the crude filtrate showed two main spots by TLC but flash chromatography did not isolate the β-keto carbonyl product. As with DMP, the oxidising reagent IBX also failed to give the desired oxidation with decomposition occurring.

TPAP, which has been successfully used on this system earlier in the synthesis, also failed to oxidise alcohol 340 to ketone 348. After 10 minutes, TLC analysis appeared to indicate that the formation of ketone 348 was underway but the reaction failed to go to completion. Increasing the concentration of TPAP from 5 mol% to 10 mol% made no difference nor did the addition of 10% acetonitrile
to the solvent mixture, which has been shown to drive sluggish reactions to completion. The compounds that were isolated could not be identified as the desired product.

Chromium reagents, (such as Jones reagent) are widely used for converting secondary alcohols to the corresponding ketones, but since the reagents are strongly acidic they are clearly not the best method of oxidation for a compound containing a tetraene. However, Corey et al. developed the related but neutral pyridinium dichromate that rapidly oxidise 1° and 2° alcohols to their corresponding aldehydes and ketones respectively. The mild conditions under which PDC reacts has been shown to be successful in the oxidation of complex or highly sensitive substrates, where selectivity and effectiveness are crucial.

So PDC was the next reagent tested. Using 8 equivalents of PDC over a 24 hour period failed to work on this system even after the use of a small amount of pyridinium trifluoroacetate (0.4 equivalents) which, as Corey et al. demonstrated, allows the minimum use of PDC and maintains a satisfactory reaction rate as the oxidation nears completion.

Use of pyridine-SO₃ complex to activate DMSO under Parikh-Doering conditions was another oxidising reagent tested on this system. This reaction is a variation of the Swern oxidation but is carried out under basic conditions in the presence of triethylamine. Unfortunately, this protocol was also unsuccessful at oxidising alcohol 340 to ketone 348. After 2 hours the TLC plate was streaked and a ¹H n.m.r. spectrum of the crude mixture after work-up indicated the mixture did not contain any of the required product.

Activated MnO₂ (30 equivalents) in chloroform, stirred at room temperature for 6 days, also did not produce the desired oxidation product.

In summary, all efforts to perform the oxidation of the allylic alcohol 340 to the corresponding β-keto carbonyl 348 were unsuccessful (Figure 45). The reasons behind these failures were not investigated in this study. However, it may be that the harsh conditions of oxidation were not compatible with the sensitive
tetraene moiety and the milder conditions were not able to oxidise the somewhat hindered 2° alcohol.

![Figure 45](image)

**Figure 45** Failed attempt at the oxidation of allylic alcohol 340 to the β-keto carbonyl 348

An alternative route to progress the synthesis was therefore investigated, which involved installing the β-keto carbonyl functionality earlier in the synthesis.

### 5.5 Direct conversion of allylic alcohol 282 to the corresponding methyl ester 338

In 2002, Taylor and co-workers reported that activated alcohols can be directly transformed into esters in a one pot procedure (Scheme 64) using activated manganese dioxide and sodium cyanide in methanol under reflux.\(^{112}\)

![Scheme 64](image)

**Scheme 64** One pot oxidation procedure of an alcohol to a methyl ester
Although this work was carried out on less complex and more robust compounds than tetraene 282, if the tetraene survived it would open up the possibility of by passing the formation of the acid by creating methyl ester 338 directly from allylic alcohol 282 (Scheme 65).

**Scheme 65** Direct conversion of allylic alcohol 282 to the corresponding methyl ester 338

To this end, allylic alcohol 282 in THF was refluxed overnight in a mixture of sodium cyanide, activated manganese dioxide and methanol. Methyl ester 338 was isolated, but unfortunately the yield was poor (20%). A small percentage of the corresponding aldehyde that is formed in the first step of the four sequence reaction was also isolated however the overwhelming problem may have been due to the oxidising agent MnO₂. Earlier in this study we demonstrated that MnO₂ was not an effective oxidant for this substrate. To overcome this limiting factor, alcohol 282 was converted to aldehyde 23 under Ley conditions using TPAP, as previously reported and aldehyde 23 was then subjected to refluxing MeOH in the presence of sodium cyanide and activated manganese. This improved the yield for the oxidation to 43% (Scheme 66).
Unfortunately, the $^1$H n.m.r. spectrum of methyl ester 338 contained some puzzling aspects with regard to the 8-CH$_3$, 10-CH$_3$, 12-CH$_3$, 9-H, 13-H and 15-H protons. The compound contained the correct number of protons and the various peaks were present in the correct chemical shift regions however, three peaks, corresponding to the protons at 9-CH, 12-CH$_3$ and 13-CH were unexplained doublets instead of the expected singlets. Furthermore, the proton at C15 also appeared as a pentet rather than the expected quartet, as it should, if coupling with the terminal methyl group. There were also multiples for 8-CH$_3$ and 10-CH$_3$ instead of the expected singlets. The (E)-isomer at C2–C3 was however confirmed by the $J$ value of 15.4 Hz.

Despite these concerns, we proceeded with this strategy, which now left the way open to convert methyl ester 338 to carboxylic acid 337 and from there form acyl imidazole 336. This would activate the carbonyl group to facilitate coupling to pyrrolidinone 292 to give the desired $\beta$-keto carbonyl 348 (Scheme 67).
5.6  **Transformation of methyl ester 338 to carboxylic acid 337**

Methyl ester 338 in THF was treated with 21 equivalents of sodium hydroxide in water and stirred at room temperature until the reaction was completed. After aqueous work-up and acidification to pH 4, TLC showed two close, inseparable spots. Because the final crude mixture was not purified, there were many overlapping peaks in the $^1$H n.m.r. spectrum of crude acid 337, which made it difficult to be confident that the functional group conversion had taken place. In addition, there were anomalies in the $^1$H n.m.r. spectra at 4-H$_2$ and 7-H$_2$. Yet again, it seemed evident that there was a fundamental problem in forming the carboxylic acid in the presence of the conjugated tetraene.

5.7  **Issues concerning the synthetic route**

Three key issues with this chemistry had arisen by this point in the synthesis.

First, the Pinnick oxidation of aldehyde 23 to carboxylic acid 337 (Scheme 59, page 118) was unsuccessful and so prevented our original strategy from being pursued.

Second, model work suggested that there was a viable alternative route to synthesising the long chain precursor to the Diels Alder reaction via an aldol reaction to couple aldehyde 23 with pyrrolidinone 292. However, when this methodology was applied to the natural system, although the Aldol reaction was successful, oxidation of allylic alcohol 340 to β-keto carbonyl 348 did not take place, despite screening numerous oxidising agents. Without the β-keto carbonyl functionality in place it would be impractical to continue with the Diels Alder reaction because the mixtures of diastereoisomers present could seriously complicate the outcome of the reactions. The alcohol would also need to be protected, adding further steps and also, the dienophile would not be doubly activated, so the Diels Alder reaction might not actually occur.

Finally, in an attempt to establish another route to carboxylic acid 337, methyl ester 338 could only be produced in a modest yield with unexplained anomalies in the $^1$H n.m.r. spectrum.
5.8 Revised synthesis to ascertain the feasibility of a single Diels Alder reaction

In view of these issues, our thoughts turned to simplifying the synthesis in order to overcome the problems that had arisen with the chemistry. To this end we set about constructing a compound, analogous to that of long chain aldehyde 23, but without the double bond at C2–C3 (Figure 46).

![Simplified long chain aldehyde 349](image)

We hoped this change would have a positive impact on the elusive oxidation of the alcohol to its corresponding β-keto carbonyl. If this oxidation was successful on this simplified compound, it would enable a single Diels Alder reaction to be undertaken leading to the formation of an isoidolone unit attached to a 14-membered macrocycle. Within the macrocycle it should then be possible to install the omitted double bond at C21–C22 using PhSeCl (Figure 47). If this step was successful, it would enable the second Diels Alder reaction to proceed and complete the synthesis of a diaporthichalasin analogue.

![Proposed single Diels Alder reaction to form macrocycle 351](image)
The six-carbon chain extension of tetraene acetate 258 was constructed by protecting the alcohol of commercially available 6-bromo-1-hexanol 352 as the silyl ether 353 in 95% yield (Scheme 68). The protected 6-bromo-1-hexanol 353 was converted to the corresponding Grignard reagent and reacted with tetraene acetate 258 in the presence of copper catalyst Li₂CuCl₄ at -78 °C to give the protected (E,E,E,E)-isomer 354. Work-up was complicated by emulsions requiring copious amounts of water and solvent for extraction but resulted in isolating silyl ether 354 in a pleasing 84% yield. The structure was assigned on the basis of its spectroscopic data, which was consistent with the analogous silyl ether 281 previously synthesised (Scheme 41, page 91).

The silicon protecting group was removed using TBAF under basic conditions to provide long chain alcohol 355 in 77% yield. Oxidation of alcohol 355 with TPAP/NMO gave aldehyde 349 in a yield of 59% (Scheme 68).

Scheme 68  Synthesis of aldehyde 349

5.9  Aldol coupling of pyrrolidinone 292 with aldehyde 349

Pyrrolidinone 292 was deprotonated at 0 °C to form the corresponding enolate 342 and then cooled to -78 °C after which aldehyde 349 was added. Within an hour the aldol reaction produced long chain hydroxy lactam 356 in a yield of
83% after work-up and column chromatography (Scheme 69). A mixture of four diastereoisomers was anticipated to be present but the $^1$H n.m.r. spectrum indicated there was only one prominent diastereoisomer.

Scheme 69  Aldol reaction between aldehyde 349 and pyrrolidinone 292

5.10  Attempted synthesis of β-keto carbonyl 354

The key step of oxidising the alcohol 356 to the corresponding β-keto carbonyl 357 was attempted next. It was at this stage earlier in the synthesis that all efforts to oxidise the allylic alcohol failed. Interestingly, the problem with oxidation of allylic alcohol 340 was mirrored with alcohol 356. Dess-Martin periodinane, buffered with 12 equivalents of pyridine, failed to achieve the desired oxidation as did PDC under basic conditions using DCM or DMF as the solvent (Figure 48, page 133). Given the previous issues with this step further attempts at this oxidation were not pursued.
Figure 48  Attempted oxidation of β-keto alcohol of 356 to β-keto carbonyl 357

5.11 Direct transformation of aldehyde 349 to carboxylic acid 358

With this new knowledge, we needed to explore alternative ways to directly form carboxylic acid 358 from aldehyde 349, other than via a Pinnick reaction, which we have shown to be too harsh for the conjugated tetraene (Figure 49). If this could be achieved, the β-keto carbonyl group would already be in place after coupling with pyrrolidinone 292.

Figure 49  Proposed functional group transformation of aldehyde 349 to carboxylic acid 358

The literature shows many examples of this type of transformation using strong oxidising agents such as KMnO₄,¹¹³ chromic acid ¹¹⁴ and silver oxide ¹¹⁵ but we required a procedure that was both mild and reacted under basic conditions.
PDC goes some way to meeting these conditions and potentially will tolerate the conjugated tetraene.\textsuperscript{105} For these reasons it was the oxidising agent of choice.

Thus, PDC was added to aldehyde 349 at room temperature and monitored by TLC. Both DCM and DMF were tried as the solvent. Each reaction attempted gave multiple products and the crude $^1$H n.m.r. was complex. However, the methine peaks between $\delta$ 5.5 ppm and $\delta$ 6.0 p.p.m. did indicate that the tetraene may have survived the reaction. The crude mixture was then treated with 1'1-carbonyldiimidazole in preparation for coupling with pyrrolidinone 292. The crude $^1$H n.m.r. of the product of this reaction was again complex but did show the presence of the imidazole fragment in the new species and so this was taken through crude and reacted with pyrrolidinone 292, after deprotonation in the presence of LiHMDS. Unfortunately, the $^1$H n.m.r. spectrum of the product indicated that the tetraene double bonds did not survive the reaction.

5.12 Synthesis of unsymmetric imide 362

From the evidence thus far, it was clear that the conjugated tetraene is not compatible with the formation of a carboxylic acid substituent. Furthermore, and of greater concern, is that the conjugated tetraene may not be compatible with the conditions of oxidative elimination of phenylselenide in the preparation of the pyrrolinone dienophile for the Diels Alder reaction. This problem could be avoided if it could be shown that the desired pyrrolinone unit could be synthesised using an intramolecular Knoevenagel condensation from an open-chain precursor, e.g. 359 from 360 (Scheme 70, page 135).
To test this hypothesis, the plan was to again synthesis isoindolone 322 via the retrosynthetic route in Scheme 71, but in this case via a Knoevenagel condensation as envisaged in Scheme 70. This would require the synthesis of unsymmetrical imide 362 from L-phenylalanine 299 (Scheme 72, page 136).

On treatment with lithium aluminium hydride in THF, commercially available L-phenylalanine 299 was reduced to phenylalaninol 363 in a yield of 77%. O-silylation of alcohol 363 gave silyl ether 364. Acylation of this amine using benzoyl chloride in pyridine gave amide 365 in a high yield of 95%. Further acylation of amide 365 using acetyl chloride and pyridine in DCM resulted in imide 362 in a modest yield of 58% (Scheme 71, page 137).

Scheme 70  Retrosynthetic analysis of pyrrolinone 359

Scheme 71  Alternative synthetic route to isoindolone 322
5.13 Attempted coupling of acyl imidazole 367 with imide 362

The precise reaction conditions for coupling imidazolide 324 with imide 362 were not known so a series of test reactions were first undertaken to establish the appropriate reaction conditions. To model the synthesis we prepared an analogue of acyl imidazole 324 from commercially available hexanoic acid 366. This was achieved by adding a solution of 1,1'-carbonyldiimidazole to acid 366 to give acyl imidazole 367 (Scheme 73).
imide 362 in anhydrous THF at -78 °C. After a period of time, to allow deprotonation to take place, acyl imidazolide 367 in THF at -78 °C was added to the mixture. The mixture was left to stir at this temperature for two hours before being allowed to warm to room temperature and stirred for one hour. We anticipated that using hindered base, LiHMDS at -78 °C would form the enolate imide 368 (Scheme 74). However, as Table 3 shows, it was unclear whether or not formation of the enolate 368 occurred, because coupling with the imidazolide did not take place.

![Scheme 74](image)

**Scheme 74**  
Synthetic route to imide 369

<table>
<thead>
<tr>
<th>Imide 362 + LiHMDS</th>
<th>Imidazolide 367</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>-90 °C 60 min.</td>
<td>-90 °C, 6 hr. rt. 1 hr.</td>
<td>30% starting material</td>
</tr>
<tr>
<td>-78 °C 30 min.</td>
<td>-78 °C, 6 hr. rt. 1 hr.</td>
<td>90% starting material</td>
</tr>
<tr>
<td>-78 °C 30 min.</td>
<td>-78 °C, 2 hr. rt. 1 hr.</td>
<td>73% starting material</td>
</tr>
<tr>
<td>-78 °C 45 min.</td>
<td>-78 °C, 2 hr. rt. 1 hr.</td>
<td>86% starting material</td>
</tr>
<tr>
<td>-78 °C 60 min.</td>
<td>-78 °C, 2 hr. rt. 1 hr.</td>
<td>99% elimination</td>
</tr>
</tbody>
</table>

**Table 3**  
Summary of lithiation experiments on imide 362

When LiHMDS and imide 362 were mixed together at -78 °C or -90 °C for less than 1 hour, the enolate 368 was not formed. Instead, a large proportion of starting material was recovered in each case. However, when LiHMDS was mixed with imide 362 at -78 °C for 1 hour, before adding the imidazolide to the
mixture at this temperature, the result was elimination of the acyl group to leave amide 365. During formation of the enolate, the amide preferentially becomes a good leaving group (Figure 50).

![Figure 50](image)

**Figure 50** Elimination of acyl group

5.14 *Synthesis of alternative imide with Boc protection*

Evans *et al.* have shown that lithiation readily takes place on 3-acetyl-4-isopropyl-oxazolidin-2-one 371 (Figure 51) in numerous Aldol reactions.

![Figure 51](image)

**Figure 51** Structural similarities between imides 362 and 371

The key difference between 371 and imide 362 is the five membered ring containing an additional oxygen atom. Imide 362 could be made to closely resemble the structure of 371 if the benzoyl protecting group of imide 362 was exchanged for a Boc protecting group (Figure 52, page 139). This would
provide different electron delocalisation properties which may prevent elimination of the acyl group taking place.

![Figure 52 Boc-protected imide 372](image)

To this end, silyl ether 364 was prepared as above. Boc anhydride in THF gave amide 373 in a high yield of 95%. However, further acylation of amide 373, using n-BuLi and acetyl chloride in THF, failed to result in imide 372 (Scheme 75). A large amount of starting material was recovered, which suggests that deprotonation of the amide was not taking place or alternatively, elimination of the acyl group was occurring on work-up.

![Scheme 75 Synthetic route to imide 373](image)
The problem was overcome by reversing the final two reactions. Amide 364, with pyridine, was treated with a slight excess of acetyl chloride to give acylated amide 374 in a yield of 85%. When amide 374 was reacted with Boc-anhydride in the presence of sodium hydroxide, in a one to one mixture of THF and water, the result was the desired imide 372 in a good yield of 78% (Scheme 76).

![Scheme 76](image)

**Scheme 76**  Successful synthesis of imide 372

5.15 *Attempted coupling of acyl imidazole 367 with imide 372*

LiHMDS was cooled to -78 °C then added to a solution of imide 372 in anhydrous THF at -78 °C. After a period of 30 minutes, to allow deprotonation to take place, a pre-cooled (-78 °C) solution of imidazolide 367 in THF was added dropwise and the mixture left to stir at -78 °C for four hours. After slowly warming to room temperature, the mixture was stirred for one hour at this temperature. Unfortunately, coupling with imidazolide 367 did not take place (Scheme 77, page 141). After column chromatography, the $^1$H n.m.r. spectrum was complex and indecipherable and mass spectrometry showed no indication of the desired product present.
This change of direction to synthesis isoindolone 322 via a Knoevenagel condensation proved to be far more problematic than anticipated. Imide 362 could not be made to couple with acyl imidazole 367. Lithiation experiments resulted in either recovery of starting material or elimination of the acyl group. In an attempt to rectify this problem by changing the protecting group from a benzoyl group to a Boc group, coupling of imide 372 with acyl imidazole 367 did not occur.

Scheme 77  Synthetic route to imide 373
Chapter 6

Conclusions and future work

6.1 Conclusions

Conjugated tetraen-1-ol 267 was synthesised via three successive sequence of reactions comprising Horner-Wadsworth-Emmons olefination, followed by DIBAL-H reduction and then oxidation with activated manganese dioxide. When coupled with mono-methyl fumarate 273, the resulting tetraene methyl fumarate 272, comprising of a tri-substituted diene and doubly activated dienophile, cyclised in an intramolecular Diels Alder reaction to create adduct 274, with exclusive endo-stereochemistry. Four contiguous stereogenic centres were created in the reaction, one of which was a quaternary centre. This demonstrated the feasibility of the conjugated tetaene to successfully undergo Diels Alder reactions (Figure 53).

![Diels Alder reaction of conjugated tetraene 272](image)

A LUMO-lowering organocatalytic strategy was unsuccessful in an attempt induce a Diels Alder cyclisation on the extended conjugated tetraene, aldehyde 23. Using a typical Lewis acid also did not result in a cyclisation of aldehyde 23 and nor did simply exposing the compound alone to reflux under high dilution conditions (Figure 54, page 143).
The pyrrolidinone fragment of the natural product did however undergo a successful Diels Alder cyclisation when tethered to a tri-substituted diene. Pyrrolidinone 303 was condensed with acyl imidazole 324 and, after further elaboration to install the double bond of the dienophile, the resulting pyrrolinone 323 cyclised in a Diels Alder reaction to give isoindolone 322. This intramolecular Diels Alder reaction generated four stereogenic centres, of which, two are quaternary centres. The structure exhibited exo-stereochemistry with respect to the pyrrolinone.

An Aldol reaction between pyrrolidinone 292 and aldehyde 23 produced pyrrolidinone 340 (Figure 52). With pyrrolidinone 340 synthesised, we were four steps away from attempting the domino Diels Alder reactions to put in
place the isoindolone core fused to the 13 membered tricyclic system of diaporthichalasin 1.

**Figure 52**  Aldol reaction to form oxopyrrolidinone 338

All experiments to oxidise allylic alcohol 340 to its corresponding β-keto carbonyl 348 were unsuccessful. In an effort to overcome this, an analogous compound of alcohol 340 was synthesised, without the C7-C8 double bond. Unfortunately, this different compound similarly did not oxidise to its corresponding β-keto carbonyl. It may be that the harsh conditions of oxidation were not compatible with the sensitive tetraene and the milder conditions were not able to oxidise the somewhat hindered secondary alcohol.

The attempted synthesis of isoindolone 322 via a Knoevenagel condensation proved to be far more problematic than anticipated. Imide 360 could not be made to couple with acyl imidazole 367. Either the acyl group eliminated or starting material was recovered. Attempts to rectify this problem by changing the protecting group from a benzoyl group to a Boc group also failed to result in coupling of imide 372 with acyl imidazole 367.
6.2 Future work

We have demonstrated that the \((E,E,E,E)\)-conjugated tetraene, containing a tri-substituted diene and a doubly activated dienophile will undergo a Diels Alder reaction and form a quaternary centre. We have demonstrated that the pyrrolidinone fragment of the natural product will also undergo a Diels Alder reaction and form two quaternary centres. We have also synthesised, to within four steps of undertaking the domino Diels Alder reactions, the long chain precursor of an analogue of diaporthichalasin 1, which is believed to be the biomimetic route to the total synthesis. Future work involves changing the synthetic route to avoid the oxidation issue encountered so far. This may be achieved as follows:

Scheme 75 Synthetic route to domino Diels Alder reactions
Tetraene acetate 258 can be extended by a four carbon chain by way of a reaction with silyl ether 377, in the presence of Li$_2$CuCl$_4$. Deprotection of silyl ether 378, using TBAF will give alcohol 379 and subsequent oxidation with TPAP/NMO will produce aldehyde 380. A Wittig olefination reaction on aldehyde 380 will then put in place the required ester 381. Saponification of this ester, using LiOH, should afford the carboxylic acid 337, which on treatment with 1,1′-carbonyldiimidazole will give acyl imidazole 336. A condensation reaction between acyl imidazole 336 and pyrrolidinone 303 will provide the long chain pyrrolidinone 382. The double bond of the dienophile can then be installed using phenylselenium chloride followed by oxidative elimination using $m$CPBA to give pyrrolinone 26. Reflux under high dilution conditions should result in compound 383, which is an analogue of diaporthichalasin 1. Following this route should provide the required carboxylic acid via saponification, which avoids the previous difficult step of forming the carboxylic acid by means of oxidation.
Chapter 7

Experimental

7.1 Experimental techniques and apparatus

All reactions involving air or water-sensitive reagents or chemicals were performed under an atmosphere of dry nitrogen, using flame-dried glassware. Temperatures quoted are those of the external bath in degrees Celsius (°C).

Optical rotations were measured using an Optical Activity AA-100 Polarimeter with a 0.25 dm cell. Sample concentrations are quoted in g/100 mL.

Infrared spectra were recorded either on an AT1-Mattson Genesis Series FTIR spectrometer or using a thin film (solution DCM) between sodium chloride plates on a Perkins Elmer RX1 FTIR spectrometer. Absorption maxima ($v_{\text{max}}$) are quoted in wavenumbers (cm$^{-1}$).

Proton magnetic resonance spectra ($^1$H NMR) and Carbon magnetic resonance spectra ($^{13}$C NMR) were recorded on an Avance Bruker (300 MHz) spectrometer, a Bruker XC (400 MHz) spectrometer or a Bruker XC 500 MHz spectrometer. Chemical shifts ($\delta_\text{H}$ and $\delta_\text{C}$) are quoted in ppm (to the nearest 0.01 ppm) downfield of tetramethylsilane and coupling constants ($J$) are reported in Hz (to the nearest 0.1 Hz). Data is reported as follows; chemical shift, integration, multiplicity, (singlet (s), doublet (d), quartet (t), quintet (qn), multiplet (m), broad (br), or as any combination of these), atom.

Low resolution mass spectrometry was recorded on a Micromass Platform II spectrometer for positive and negative ion electrospray (ES). Molecular ions are reported as mass/charge ($m/z$) ratios.

High resolution mass spectrometry was recorded on a Thermo Finnigan MAT95XP. Molecular ions are reported as mass/charge ($m/z$) ratios.

Thin layer chromatography was performed using aluminium plates pre-coated with Merck silica gel 60 F$_{254}$. Detection was by ultraviolet absorption
and/or treatment with either basic potassium permanganate, ethanolic phosphomolybdic acid or anisaldehyde solutions followed by heating. Retention factors ($R_f$) are quoted to the nearest 0.01 cm.

**Flash chromatography** was carried out using Merck silica gel 60 (particle size 40-60 μm). Silica was base washed with an aqueous solution of potassium hydrogen carbonate followed by flushing with distilled water until the washings were neutral followed by drying for 3 days at 170°C.

Light petroleum refers to the fraction of light petroleum ether that distils between 40 and 60 °C, at atmospheric pressure. Light petroleum was distilled from 4Å molecular sieves prior to use. Ether refers to diethyl ether. Tetrahydrofuran was stored and dried over sodium/benzophenone ketal and distilled under an atmosphere of nitrogen prior to use. Brine refers to a saturated aqueous solution of sodium chloride.

All other reagents and solvents were obtained from commercial suppliers and were used as obtained or purified using standard techniques where necessary.
7.2 Experimental procedures

Ethyl (2\(E\),4\(E\))-2,4-dimethylhexa-2,4-dienoate (260)

To a stirred solution of (1-ethoxycarbonylethylidene)triphenylphosphorane (24.9 g, 68.6 mmol) in benzene (131 mL) was added tiglic aldehyde 22 (5.20 g, 61.8 mmol) at room temperature. The mixture was refluxed for 48 hr. then allowed to cool to room temperature and concentrated under reduced pressure. Diethyl ether (120 mL) was added and the resulting triphenylphosphine oxide removed by filtration. The yellow filtrate was concentrated under reduced pressure. Flash chromatography (19:1, light petroleum:ether) gave ester 260 as a colourless oil (8.04 g, 77%).

\(R_f\) 0.69 (4:1, light petroleum:ether);
\(\nu_{\text{max}}/\text{cm}^{-1}\) 2979, 2928, 2858, 1701, 1624, 1444, 1365, 1247, 1114, 1035, 746;
\(\delta_H\) (400 MHz, CDCl\(_3\)) 1.23 (3 H, t, \(J\) 7.1, OCH\(_2\)CH\(_3\)), 1.69 (3 H, d, \(J\) 7.1, 6-H\(_3\)), 1.77 (3 H, s, 2-CH\(_3\)), 1.93 (3 H, s, 4-CH\(_3\)), 4.14 (2 H, q, \(J\) 7.1, OCH\(_2\)CH\(_3\)), 5.66 (1 H, q, \(J\) 7.1, 5-H), 7.05 (1 H, s, 3-H);
\(\delta_C\) (100 MHz, CDCl\(_3\)) 14.0, 14.1, 14.3, 16.0, 60.6, 124.9, 130.9, 133.1, 142.9, 169.3;
\(m/z\) (ES) 169 (M\(^+\) + 1, 60%), 191 (M\(^+\) + 23, 100).

The spectral data were consistent with those reported in the literature.\(^{116}\)
(2E,4E)-2,4-Dimethylhexa-2,4-dien-1-ol (261)$^{116}$

To ester 260 (6.28 g, 37.4 mmol) in dry diethyl ether (87 ml) was added DIBAL-H (78 mL of a 1 M solution in hexanes) under nitrogen at 0 °C. After 1 hr. MeOH (0.36 ml) was added cautiously. A saturated solution of Rochelle’s salt (100 mL) was added and the mixture left to stir until the organic and aqueous layers had completely separated (2 hrs). The organic layer was extracted, washed with brine (70 ml), dried (MgSO$_4$), filtered and concentrated under reduced pressure to give alcohol 261 (4.55 g, 97%) as a colourless oil, which was used without further purification.

R$_f$ 0.20 (4:1, light petroleum:ether);
υ$_{max}$/cm$^{-1}$ 3308, 2913, 2857, 1439, 1377, 1066, 1006, 873;
δ$_H$ (400 MHz, CDCl$_3$), 1.63 (3 H, d, J $7.1$, 6-CH$_3$), 1.68 (3 H, s, 2-CH$_3$), 1.75 (3 H, s, 4-CH$_3$), 3.98 (2 H, d, J $5.3$, 1-H$_2$), 4.22 (1 H, d, J $5.1$, OH), 5.36 (1 H, q, J $7.1$, 5-H), 5.82 (1 H, s, 3-H);
δ$_C$ (100 MHz, CDCl$_3$) 13.72, 15.39, 16.53, 69.68, 124.75, 129.64, 133.08, 133.90; m/z (ES) 125 (M$^+$ – 1, 10%).

The spectral data were consistent with those reported in the literature.$^{116}$

(2E,4E)-2,4-Dimethylhexa-2,4-dienal (262)$^{116}$
Alcohol **261** (4.50 g, 36.1 mmol) in DCM (380 mL) was added activated MnO₂ (44.7 g, 514 mmol) at room temperature. After 72 hrs, the mixture was filtered through celite and the filtrate concentrated under reduced pressure to give aldehyde **262** (4.27 g, 95%) as a yellow oil, which needed no further purification.

R<sub>f</sub> 0.5 (4:1, light petroleum:ether);

\[ \nu_{\text{max}}/\text{cm}^{-1} \]
2916, 2848, 2709, 1669, 1620, 1439, 1388, 1349, 1191, 1013, 899, 838, 692;

\[ \delta_{\text{H}} \] (400 MHz, CDCl₃) 1.75 (3 H, d, J 7.6, 6-H<sub>3</sub>), 1.89 (3 H, s, 4-CH₃), 1.91 (3 H, s, 2-CH₃), 5.93 (1 H, q, J 7.6, 5-H), 6.6 (1 H, s, 3-H), 9.31 (1 H, s, CHO);

\[ \delta_{\text{C}} \] (100 MHz, CDCl₃) 9.56, 13.42, 14.71, 133.05, 134.08, 135.88, 154.19, 195.18;

\[ m/z \] (ES) 125 (M⁺ + 1, 2%), 147 (M⁺ + 23, 100).

The spectral data were consistent with those reported in the literature.<sup>116</sup>

**Ethyl (2E,4E,6E)-2,4,6-trimethylocta-2,4,6-trienoate (263)**<sup>116</sup>

![Structure of Ethyl (2E,4E,6E)-2,4,6-trimethylocta-2,4,6-trienoate (263)](image-url)

To (1-Ethoxycarbonylethylidene)triphenylphosphorane (25.0 g, 70.6 mmol) in benzene (150 mL) was added aldehyde **262** (4.20 g, 33.9 mmol) at room temperature. The reaction flask was covered in tin foil to protect the reaction from light. The mixture was refluxed under nitrogen for 48 hrs then allowed to cool to room temperature and concentrated under reduced pressure. Diethyl ether (150 mL) was added and the triphenylphosphine oxide removed by filtration. The yellow filtrate was concentrated under reduced pressure. Flash chromatography (19:1, light petroleum:ether) gave ester **263** as a colourless oil (5.04 g, 72%).
Rf 0.70 (4:1, light petroleum:ether);

$\nu_{\text{max}}$/cm$^{-1}$; 2921, 2853, 1702, 1247, 1110, 1014, 747;

$\delta_H$ (400 MHz, C$_6$D$_6$), 1.64 (3 H, d, $J$ 6.8, 8-H$_3$), 1.74 (3 H, s, 6-CH$_3$), 1.80 (3 H, s, 4-CH$_3$), 1.95 (3 H, s, 2-CH$_3$), 3.86 (2 H, d, $J$ 4.8, CH$_2$OH), 5.52 (1 H, q, $J$ 7.0, 7-H), 5.97 (1 H, s, 3-H), 6.01 (1 H, s, 5-H);

$\delta_C$ (100 MHz, C$_6$D$_6$), 13.87, 15.49, 16.96, 19.05, 69.23, 124.59, 130.08, 132.09, 19.05, 69.23, 124.59, 130.08, 132.09.

To ester 263 (3.70 g, 17.8 mmol) in dry diethyl ether (57 mL) was added DIBAL-H (37 mL of 1M in hexanes) under nitrogen at 0 °C. After 1 hr. MeOH (0.5 mL) was cautiously added. A saturated solution of Rochelle’s salt (60 mL) was added and the mixture left to stir until the organic and aqueous layers had completely separated (2 hrs). The organic layer was separated, washed with brine (50 mL), dried (MgSO$_4$), filtered and concentrated under reduced pressure to give alcohol 264 (2.8 g, 95%) as a colourless oil, which was used without further purification.

Rf 0.2 (4:1, light petroleum:ether);

$\nu_{\text{max}}$/cm$^{-1}$; 3304, 2912, 2855, 1439, 1376, 1005, 894;

$\delta_H$ (400 MHz, C$_6$D$_6$), 1.01 (1 H, t, $J$ 4.8, CH$_2$OH), 1.64 (3 H, d, $J$ 6.8, 8-H$_3$), 1.74 (3 H, s, 6-CH$_3$), 1.80 (3 H, s, 4-CH$_3$), 1.95 (3 H, s, 2-CH$_3$), 3.86 (2 H, d, $J$ 4.8, CH$_2$OH), 5.52 (1 H, q, $J$ 7.0, 7-H), 5.97 (1 H, s, 3-H), 6.01 (1 H, s, 5-H);

$\delta_C$ (100 MHz, C$_6$D$_6$), 13.87, 15.49, 16.96, 19.05, 69.23, 124.59, 130.08, 132.09.
133.87, 134.25, 135.49;
m/z (ES) 165 (M⁺ - 1, 15%), 367 (M⁺ + 201, 100).
The spectral data were consistent with those reported in the literature.¹¹⁶

(2E,4E,6E)-2,4,6-Trimethylocta-2,4,6-trienal (265)¹¹⁶

To alcohol 264 (0.30 g, 1.8 mmol) in DCM (6.5 ml) was added activated MnO₂ (2.35 g, 27.1 mmol) at rt. The reaction flask was wrapped in tin foil to exclude light. After 72 hrs the mixture was filtered through celite and concentrated under reduced pressure to give aldehyde 265 (0.12 g, 77%) as yellow oil, which needed no further purification.

Rf 0.42 (4:1, light petroleum:ether);
ν_max/cm⁻¹: 3330, 2963, 2919, 2856, 1671, 1599, 1435, 1385, 1359, 1190, 1018, 964;
δ_H (400 MHz, C₆D₆), 1.64 (3 H, d, J 6.8, 8-H₃), 1.71 (3 H, s, 6-CH₃), 1.91 (3 H, s, 4-CH₃), 2.03 (3 H, s, 2-CH₃), 5.54 (1 H, q, J 6.8, 7-H), 6.10 (1 H, s, 5-H), 6.45 (1 H, s, 3-H), 9.48 (1 H, s, CHO);
δ_C (100 MHz, C₆D₆), 10.98, 13.94, 16.41, 17.81, 129.10, 131.95, 133.47, 136.43, 142.22, 154.83, 194.74;
m/z (ES) (Found: M⁺, 164.1211, C₁₁H₁₆O requires M, 164.1202);
m/z (EI) 164 (M⁺, 100%).
The spectral data were consistent with those reported in the literature.¹¹⁶
Ethyl (2E,4E,6E,8E)-2,4,6,8-tetramethyldeca-2,4,6,8-tetraenoate (266)

To (1-Ethoxycarbonyl ethylidene) triphenylphosphorane (22.8 g, 62.8 mmol) in benzene (130 mL) was added aldehyde 265 (4.95 g, 30.2 mmol) at room temperature. The reaction flask was covered in tin foil to exclude light. The mixture was refluxed under nitrogen for 48 hrs then allowed to cool to room temperature and concentrated under reduced pressure. Diethyl ether (100 mL) was added and the resulting triphenylphosphine oxide removed by filtration. The yellow filtrate was concentrated under reduced pressure. Flash chromatography (19:1, light petroleum:ether) gave the title compound 266 (5.56 g, 74%) as a colourless oil.

R_f 0.70 (4:1, light petroleum:ether);
ν_max/cm⁻¹; 2977, 2917, 2857, 1701, 1610, 1443, 1365, 1245, 1109, 1025, 747;
δH (400 MHz, C₆D₆), 1.16 (3 H, t, J 6.9, CH₂CH₃), 1.69 (3 H, d, J 6.9, 10-H₃), 1.78 (3 H, s, 8-CH₃), 1.95 (3 H, s, 6-CH₃), 2.01 (3 H, s, 4-CH₃), 2.26 (3 H, s, 2-CH₃), 4.23 (2 H, q, J 6.8, OCH₂CH₃), 5.58 (1 H, q, J 6.9, 9-H), 6.04 (1 H, s, 7-H), 6.21 (1 H, s, 5-H), 7.65 (1 H, s, 3-H);
δC (100 MHz, C₆D₆), 13.86, 14.41, 14.53, 16.73, 18.50, 18.91, 60.54, 125.81, 126.44, 131.79, 132.27, 133.75, 136.31, 140.45, 144.02, 168.62;
m/z (ES) (Found: M⁺ + Na, 271.1698, C₁₆H₂₄O₂Na, requires M, 271.1669);
m/z (ES) 271 (M⁺ + 23, 100%).

(2E,4E,6E,8E)-2,4,6,8-Tetramethyldeca-2,4,6,8-tetraen-1-ol (267)
To ester 266 (0.16 g, 0.66 mmol) in dry diethyl ether (1.5 ml) was added DIBAL-H (1.4 mL of a 1M solution in hexanes) under nitrogen at 0°C. After 1 hr. MeOH (0.2 mL) was cautiously added. A saturated solution of Rochelle’s salt was added (1.8 mL) and the mixture was left to stir until the aqueous and organic layers completely separated (2hrs). The organic layer was separated, washed with brine, dried (MgSO₄), filtered and concentrated to give the title compound 267 (0.116 g, 86%) as yellow oil, which was used without further purification.

Rf 0.80 (4:1, light petroleum:ether);

νmax/cm⁻¹, 3305, 2972, 2912, 2855, 1439, 1376, 1006, 900;

δH (400 MHz, C₆D₆), 1.19 (1 H, d, J 4.6, 10-H₃), 1.66 (3 H, s, 2-CH₃), 1.69 (3 H, s, 8-CH₃), 1.90 (3 H, s, 6-CH₃), 1.93 (3 H, s, 4-CH₃), 3.75 (2 H, d, J 4.8, 1-H₂), 5.55 (1 H, q, J 6.8, 9-H), 6.12 (3 H, s, 3-H, 5-H and 7-H);

δC (100 MHz, C₆D₆), 12.51, 14.17, 15.56, 17.87, 17.98, 67.83, 123.52, 128.69, 130.95, 131.52, 132.56, 133.15, 133.90, 134.30;

m/z (EI) (Found: M⁺ + Na, 229.1665, C₁₄H₂₂ONa, requires M, 229.1665);

m/z (EI) 229 (M⁺ + 23, 100%).

(2E,4E,6E,8E)-2,4,6,8-Tetramethyldeca-2,4,6,8-tetraenyl acetate (258)

To alcohol 267 (3.50 g, 17.2 mmol) in dry DCM (69 ml) was added pyridine (21 ml, 26 mmol) and acetic anhydride (8.5 ml, 86 mmol) under nitrogen at 0°C. After 3 hrs, water (60 mL) and KHCO₃ (6 mL) was added and the organic layer and aqueous layer separated. The aqueous layer was washed with DCM (3 x 50 mL) and the organic layers combined, dried (Na₂SO₄) and concentrated under reduced pressure. Flash chromatography (50:1, light petroleum:ether) gave the title compound 258 (3.5 g, 82%) as a clear oil.
Rf 0.54 (4:1, light petroleum:ether);
$\nu_{\text{max}}$/cm$^{-1}$, 3472, 2972, 2913, 2856, 1737, 1439, 1373, 1222, 1018, 901;
$\delta_H$ (400 MHz, C$_6$D$_6$), 1.55 (3 H, d, J 7.1, 10-H$_3$), 1.65 (6 H, s, 2-CH$_3$ and 4-CH$_3$),
1.71 (3 H, s, 6-CH$_3$), 1.84 (3 H, s, 8-CH$_3$), 1.84 (3 H, s, OCCH$_3$), 4.45 (2 H, s, 1-H$_2$),
5.43 (1 H, q, J 7.1, 9-H), 5.91 (2 H, s, 3-H and 5-H), 5.94 (1 H, s, 7-H);
$\delta_C$ (100 MHz, C$_6$D$_6$), 13.93, 15.91, 16.91, 18.97, 19.21, 20.54, 70.71, 125.11,
130.67, 132.13, 132.30, 133.85, 133.89, 134.88, 136.10, 169.97;
m/z (EI) (Found: M$^+$, 248.1772, C$_{16}$H$_{24}$O$_2$ requires M, 248.1771);
m/z (ES) 249 (M$^+$ + 1, 10%), 271 (M + 23, 70%).

(2E,4E,6E,8E)-2,4,6,8-tetramethyldec-2,4,6,8-tetraen-1-yl(Z)-3-
carboxyprop-3-enoate (269)

To tetraenol 267 (0.20 g, 0.97 mmol) in DCM (10 mL) at 0 °C was added
triethylamine (0.22 mL, 1.6 mmol), maleic anhydride 268 (0.14 g, 1.5 mmol)
and DMAP (0.02 g, 0.09 mmol). The resulting solution was warmed to rt. and
stirred for 15 minutes. The reaction mixture was diluted with DCM (10 mL) and
washed successively with hydrogen chloride (10%, 10 mL), water (10 mL) and
saturated aqueous NaCl (10 mL). The organic fraction was dried (Na$_2$SO$_4$),
filtered and concentrated under reduced pressure to give the title compound
269 (0.27 g, 86%) as brown oil, used without further purification.

Rf 0.32 (1:1 light petroleum:ether);
$\nu_{\text{max}}$/cm$^{-1}$, 2917, 2857, 2500, 1723, 1643, 1565, 1439, 1378, 1204, 1161, 1062,
1024, 989, 961, 904, 814;
$\delta_H$ (400 MHz, C$_6$D$_6$), 1.71 (3 H, d, J 6.9, 10-H$_3$), 1.82 (3 H, s, 2-CH$_3$), 1.88 (3 H, s, 4-
CH$_3$), 2.02 (3 H, s, 6-CH$_3$), 2.03 (3 H, s, 8-CH$_3$), 4.62 (2 H, s, 1-H$_2$), 5.61 (1 H, q, J
6.9, 9-H), 5.75 (1 H br d, J 10.8, 3′-H), 6.08 (3 H, s, 3-H and 5-H and 7-H), 6.27 (1 H br d, J 10.6, 2′-H);

δC (100 MHz, C6D6), 13.71, 16.23, 16.99, 18.79, 20.16, 58.54, 126.83, 128.94, 132.88, 133.63, 134.33, 135.14, 136.33, 136.98, 140.17, 142.64, 165.51, 166.43;
m/z (ES) (Found: M+ -1, 303.1607, C18H23O4 requires M, 303.1601);
m/z (ES) 303 (M+ - 1, 100%).

**Methyl[(2E,4E,6E,8E)-2,4,6,8-tetramethyldeca-2,4,6,8-tetraen-1-yl) maleate (270)**

\[
\text{O} \quad 2 \quad 3 \quad \text{CO}_2\text{Me}
\]

To tetraenol 267 (0.20 g, 0.97 mmol) in DCM (3.2 mL) at 0 °C were added EDCI (0.22 g, 1.2 mmol), maleic half acid 271 (0.15 g, 1.2 mmol) and DMAP (0.01 g, 0.09 mmol). The mixture was warmed to rt. and stirred for 4 hrs. The reaction mixture was diluted with saturated aqueous NaHCO3 (3 mL) and the organic fraction extracted with EtOAc (3 x 3 mL). The organic extracts were dried (Na2SO4), filtered and concentrated under reduced pressure. Flash chromatography (20:1→10:1, light petroleum:EtOAc) gave the title compound 270 (0.045 g, 15%) as a clear oil.

Rf 0.26 (5:1, light petroleum:EtOAc);

\(\nu_{\text{max}}/\text{cm}^{-1}\): 2916, 2858, 1727, 1645, 1437, 1394, 1289, 1208, 1156, 1001, 980, 904, 811;

δH (500 MHz, C6D6), 1.71 (3 H, d, J 6.9, 10-H3), 1.81 (3 H, s, 2-CH3), 1.89 (3 H, s, 4-CH3), 1.99 (3 H, s, 6-CH3), 2.01 (3 H, s, 8-CH3), 3.49 (3 H, s, OCH3), 4.70 (2 H, s, 1-H2), 5.59 (1 H, q, J 6.9, 9-H), 5.84 (1 H, d, J 11.9, 3′-H), 5.90 (1 H, d, J 11.9, 2′-H), 6.06 (2 H, s, 3-H and 5-H), 6.07 (1 H, s, 7-H);

δC (125 MHz, C6D6), 13.91, 15.85, 16.82, 18.77, 19.13, 51.51, 71.61, 125.10,
129.79, 132.08, 132.22, 132.27, 133.89, 134.59, 134.87, 136.23, 136.26, 164.85, 165.41;
m/z (ES) (Found: M⁺ + Na, 341.1727, C₁₉H₂₆O₄Na requires M, 341.1724);
m/z (ES) 341 (M⁺ + 23, 50%), 336 (M⁺ + 18, 90%)

(Z)-4-methoxy-4-oxobut-2-enoic acid (271)

![Structure of (Z)-4-methoxy-4-oxobut-2-enoic acid (271)](image)

Maleic anhydride 268 (0.75 g, 7.6 mmol) in MeOH (3.1 mL) was stirred at rt. for 3 hrs to give the half ester 271 (0.99 g, 99%) as clear oil, which was used without further purification.

Rf 0.22 (1:1 light petroleum:ether);
νmax/cm⁻¹, 3592, 3056, 2957, 2849, 2591, 1709, 1632, 1438, 1402, 1215, 1162, 997, 942, 855, 817, 634
δH (300 MHz, C₆D₆), 3.29 (3 H, s, CH₃), 5.65 (1 H, d, J 12.4, 3-H), 5.87 (1 H, d, J 12.3, 2-H), 11.33 (1 H, br s, OH);
δC (75 MHz, C₆D₆), 52.15, 129.15, 132.42, 166.73, 167.38;
m/z (ES) (Found: M⁺ - 1, 129.0198, C₅H₆O₄ requires M, 129.0193);
m/z (ES-) 129 (M⁺ - 1, 100%).

Methyl [(2E,4E,6E,8E)-2,4,6,8-tetramethyldeca-2,4,6,8-tetraen-1-yl] fumarate (272)

![Structure of Methyl [(2E,4E,6E,8E)-2,4,6,8-tetramethyldeca-2,4,6,8-tetraen-1-yl] fumarate (272)](image)
To tetraenol 267 (0.10 g, 0.49 mmol) in DCM (1.6 mL) at 0 °C were added EDCI (0.11 g, 0.58 mmol), mono-methyl fumarate 273 (0.075 g, 0.58 mmol) and DMAP (0.006 g, 0.05 mmol). The mixture was warmed to rt. and stirred for 10 minutes. The reaction mixture was diluted with saturated aqueous NaHCO₃ (3 mL) and the organic fraction extracted with EtOAc (3 x 3 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (20:1 to 10:1, light petroleum:EtOAc) gave the title compound 272 (0.075 g, 50%) as a green oil.

Rᶠ 0.74 (1:1 light petroleum:EtOAc);

νmax/cm⁻¹, 2916, 2858, 1721, 1436, 1374, 1293, 1257, 1150, 1007, 977, 904, 733;

δ_H (400 MHz, C₆D₆), 1.60 (3 H, d, J 6.8, 10-H₃), 1.71 (3 H, s, 2-CH₃), 1.72 (3 H, s, 4-CH₃), 1.89 (3 H, s, 6-CH₃), 1.91 (3 H, s, 8-CH₃), 3.24 (3 H, s, OCH₃), 4.51 (2 H, s, 1-H₂), 5.49 (1 H, q, J 6.8, 9-H), 5.95 (2 H, s, 3-H and 5-H), 5.97 (1 H, s, 7-H), 6.95 (2 H, s, 2’-H and 3’-H);

δ_C (125 MHz, C₆D₆), 13.84, 15.80, 16.83, 18.87, 19.18, 51.62, 71.58, 125.20, 129.83, 132.03, 132.11, 133.45, 133.79, 133.84, 134.55, 135.02, 136.35, 164.55, 164.95;

m/z (ES) (Found: M⁺ + Na, 341.1729, C₁₉H₂₆O₄Na requires M, 341.1724);

m/z (ES) 341 (M⁺ + Na, 15%), 189 (M⁺ - 129, 100).

Methyl (1RS, 2SR, 3RS, 6SR)-4,6-dimethyl-3-[(2E,4E)-4-methylhexa-2,4-dien-2-yl]-9-oxo-8-oxadicyclo[4,3,0] non-4-en-2-ylcarboxylate (274)
The tetraene methyl fumarate 272 (0.180 g, 0.565 mmol) in degassed toluene (180 mL) was heated under reflux (110 °C) for 50 hrs in a reaction flask covered with foil to exclude light. The mixture was cooled to rt. then concentrated under reduced pressure. Flash chromatography (15:1→4:1, light petroleum:ether) gave the title compound 274 (0.109 g, 61%) as a pale yellow oil; 

Rf 0.26 (1:1, light petroleum:EtOAc); 

νmax/cm⁻¹, 3554, 2957, 2858, 1775, 1739, 1380, 1288, 1259, 1198, 1164, 1091, 1026, 799;  

δH (400 MHz, CDCl₃), 1.17 (3 H, s, 6-CH₃), 1.58 (3 H, d, J 6.8, 6′-H₃), 1.59 (3 H, s, 1′-H₃), 1.60 (3 H, s, 4-CH₃), 1.64 (3 H, s, 4′-CH₃), 2.78 (1 H, d, J 7.3, 1-H), 2.99 (1 H, d, J 5.8, 3-H), 3.05 (1 H, dd, J 6.0, 7.1, 2-H), 3.63 (3 H, s, OCH₃), 3.93 (1 H, d, J 8.8, 7-H), 4.00 (1 H, d, J 8.8, 7-H'), 5.23 (1 H, q, J 6.8, 5′-H), 5.32 (1 H, s, 5-H), 5.51 (1 H, s, 3′-H);  

δC (100 MHz, CDCl₃), 12.59, 14.93, 15.29, 21.24, 25.94, 38.12, 41.29, 45.11, 48.97, 51.11, 77.11, 122.93, 125.73, 130.47, 131.75, 132.05, 134.27, 172.39, 176.20;  
m/z (ES) (Found: M⁺ + Na, 341.1720, C₁₉H₂₆O₄Na requires M, 341.1724); m/z (ES) 319 (M⁺ + 1, 100%).  

(E)-6-Bromohex-2-en-1-ol (277) 

![E-Bromohex-2-en-1-ol](image) 

To cis-but-2-en-1,4-diol 279 (5.0 g, 34 mmol) and 5-bromopent-1-ene 278 (9.0 g, 102 mmol) in anhydrous DCM (170 mL) at rt. was added Hoveyda-Grubbs 2nd Generation Catalyst (0.21 g, 0.34 mmol). The reaction mixture was stirred at rt. for 4 hours. The mixture was concentrated under reduced pressure. Flash chromatography (2:1, light petroleum:ether) gave alcohol 277 as a pale yellow oil (3.11 g, 61%).
The spectral data were consistent with those reported in the literature.\textsuperscript{117}

**\textit{(E)}-6-Bromo-1-\textit{tert}-butyldimethylsilyloxy-hex-2-ene (280)**

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

To alcohol 277 (0.84 g, 4.7 mmol) in DCM (20 mL) at 0 °C was added imidazole (0.96 g, 14 mmol). To this was added (\textit{tert}-butyl)dimethylsilane chloride (1.06 g, 7.08 mmol). The mixture allowed to warm to room temperature and stirred under nitrogen for 1½ hrs. Water (25 mL) and DCM (40 mL) was added and the organic layer separated. The aqueous layer was extracted with DCM (3 x 25 mL) and the organic layers combined. The organic fraction was washed with brine (30 mL), dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. Flash chromatography (20:1, light petroleum:ether) gave the \textit{title compound} 280 (1.09 g, 78%) as a clear oil.
δ_C (100 MHz, CDCl₃); -4.92, 18.54, 26.27, 30.66, 32.20, 32.98, 63.91, 128.1, 131.2;

m/z (EI) 292 (M⁺, 60%), 237 (M⁺ Br⁻ - 57, 28%), 235 (M⁺ Br⁻ - 57, 26%).

1-tert-butyldimethylsilyloxy(2E,8E,10E,12E,14E)-8,10,12,14-tetramethylhexadeca-2,8,10,12,14-pentaen-1-yl (281)

Bromohexene 280 (1.20 g, 4.03 mmol) was dissolved in THF (4 mL) and slowly added to magnesium turnings in THF (1 mL) under nitrogen with warming to maintain reflux. Reflux was maintained for further 1.5 hrs then cooled to -78 °C. Lithium tetrachlorocuprate (0.8 mL of a 0.1M solution in THF) was added followed by tetraenyl acetate 258 (0.50 g, 2.0 mmol) in THF (2 mL). The solution was allowed to warm to rt. and was then stirred for 19 hours, after which was poured into water (20 mL). The mixture was concentrated under reduced pressure to remove excess THF, extracted with diethyl ether (3 x 50 mL), washed with brine (50 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (100:1, light petroleum:ether) gave the title compound 281 (0.66 g, 82%) as a colourless oil.

R_f 0.83 (20:1, light petroleum:ether);

ν_max/cm⁻¹; 2954, 2927, 2855, 1471, 1462, 1377, 1360, 1252, 1100, 1059, 1005, 968, 832, 813, 773, 667;
δ_H (400 MHz, C₆D₆) 0.09 [6 H, s, Si(CH₃)₂], 0.90 [9 H, s, Si(C(CH₃)₃)], 1.18-1.45 (4 H, m, 5-H₂ and 6-H₂), 1.46 (3 H, s, 8-CH₃), 1.52 (3 H, d, J 6.8, 16-H₃), 1.63 (3 H, s, 10-CH₃), 1.65-2.07 (4 H, m, 4-H₂ and 7-H₂), 1.83 (3 H, s, 12-CH₃), 1.91 (3 H, s, 14-CH₃), 4.02 (2 H, d, J 4.5, 1-H₂), 5.41 (1 H, q, J 6.8, 15-H), 5.53 (1 H, dt, J 15.1, 4.2, 2-H), 5.59 (1 H, dt, J 15.1, 6.6, 3-H), 5.77 (1 H, s, 9-H), 5.95 (2 H, s, 11-H and 13-H).
\[ \delta_C (100 \text{ MHz, CDCl}_3) -4.95, 13.80, 18.05, 18.54, 19.36, 19.49, 22.75, 26.15, \\
27.98, 29.31, 34.60, 64.13, 127.71, 128.03, 128.35, 130.12, 130.57, 130.87, \\
131.02, 134.17, 134.40, 144.02; \\
m/z (EI) \text{ (Found: } M^+ 402.3314, C_{26}H_{46}OSi \text{ requires } M, 402.3312); \\
m/z (AP^+) 403 (M^+ + 1, 76\%).
\]

\[(2E,8E,10E,12E,14E)-8,10,12,14-\text{Tetramethylhexadeca-2,8,10,12,14-pentaen-1-ol (282)}\]

To tetraene 281 (0.88 g, 2.2 mmol) in THF (22 mL) at 0 °C was added TBAF in THF (1.0 M, 6.6 mL, 6.6 mmol) and stirred at 0 °C for 1 hr. then rt. for 2 hrs. An aqueous phosphate buffer (pH 7.0, 20 mL) was added and the organic fraction extracted with diethyl ether (4 x 30 mL). The organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated under reduced pressure. Flash chromatography (10:1→4:1, light petroleum:ether) gave the title compound 281 (0.554 g, 88%) as a colourless oil.

R\textsubscript{f} 0.14 (4:1, light petroleum:ether);

\[\nu_{\text{max}}/\text{cm}^{-1} : 3311, 2927, 2855, 1439, 1375, 1088, 1004, 968, 899;\]

\[\delta_H (400 \text{ MHz, C}_6\text{D}_6) 1.24-1.46 (4 \text{ H, m, 5-H_2 and 6-H_2}), 1.46 (3 \text{ H, s, 8-CH}_3), 1.52 \\
(3 \text{ H, d, } J 6.9, 16-H_3), 1.63-1.86 (4 \text{ H, m, 4-H_2 and 7-H_2}), 1.73 (3 \text{ H, s, 10-CH}_3), \\
1.88 (3 \text{ H, s, 12-CH}_3), 1.92 (3 \text{ H, s, 14-CH}_3), 3.77 (2 \text{ H, d, } J 7.3, 1-H_2), 4.00 (1 \text{ H, brs, OH}), 5.43 (1 \text{ H, q, } J 6.9, 15-H), 5.42 (1 \text{ H, dt, } J 15.4, 7.3, 2-H), 5.43 (1 \text{ H, dt, } J \\
15.4, 7.3, 3-H), 5.78 (1 \text{ H, s, 9-H}), 5.94 (2 \text{ H, s, 11-H and 13-H}); \]

\[\delta_C (100 \text{ MHz, CDCl}_3) 13.90, 16.97, 18.08, 19.41, 19.55, 27.97, 29.25, 32.54, 41.01, \\
63.55, 124.73, 127.85, 128.04, 128.23, 130.19, 130.63, 133.46, 134.24, 134.48, \\
136.37;\]
\(m/z\) (EI) (Found: M\(^+\), 288.2447, C\(_{20}\)H\(_{32}\)O requires M, 288.2448);

\(m/z\) (EI) 288, (AP\(^+\)) 289 (M\(^+\) + 1, 100%).

**(2E,8E,10E,12E)-8,10,12,14-Tetramethylhexadeca-2,8,12,14-pentaenal (23)**

Solid TPAP (5 mol %, 0.006 g, 0.02 mmol) was slowly added to alcohol 282 (0.10 g, 0.35 mmol), NMO (0.06 g, 0.5 mmol) and 4Å powered molecular sieves (0.17 g) in DCM:CH\(_3\)CN (9:1) (1 mL) at rt under nitrogen. The reaction mixture was concentrated under reduced pressure then diluted with diethyl ether (5 mL), filtered through silica and eluted with EtOAc (3 x 5 mL) followed by DCM (2 x 5 mL). The filtrate was concentrated under reduced pressure and flash chromatography (20:1, light petroleum:ether) gave the *title compound 23* (0.0854 g, 86%) as a colourless oil;

R\(_f\) 0.41 (4:1, light petroleum:ether);

\(\nu_{\text{max}}/\text{cm}^{-1}\); 2929, 2856, 2722, 1690, 1637, 1440, 1376, 1158, 1122, 1010, 972, 899;

\(\delta_H\) (500 MHz, C\(_6\)D\(_6\)) 0.99 (2 H, tt, \(J\) 7.5, 8.0, 5-H\(_2\)), 1.12 (2 H, tt, \(J\) 7.6, 8.0, 6-H\(_2\)), 1.52 (3 H, d, \(J\) 6.7, 16-H\(_3\)), 1.63 (3 H, s, 8-CH\(_3\)), 1.70 (3 H, s, 10-CH\(_3\)), 1.82 (2 H, m, 7-H\(_2\)), 1.88 (3 H, s, 12-CH\(_3\)), 1.91 (2 H, m, 4-H\(_2\)), 1.92 (3 H, s, 14-CH\(_3\)), 5.42 (1 H, q, \(J\) 6.7, 15-H), 5.85 (1 H, d, \(J\) 15.8, 2-H), 5.87 (1 H, s, 9-H), 5.93 (1 H, dt, \(J\) 15.8, 7.6, 3-H), 5.95 (2 H, s, 11-H and 13-H), 9.23 (1 H, dd, \(J\) 7.6, 1-H);

\(\delta_C\) (125 MHz, CDCl\(_3\)) 13.89, 16.95, 18.01, 19.38, 19.52, 27.57, 27.71, 32.43, 40.69, 124.88, 127.84, 130.85, 132.40, 132.28, 133.33, 133.96, 134.67, 135.84, 156.89, 192.67;

\(m/z\) (ES) (Found: M\(^+\) + Na, 309.2185, C\(_{20}\)H\(_{30}\)ONa requires M, 309.2189);

\(m/z\) (ES) 287 (M\(^+\) + 1, 15%), 309 (M\(^+\) + 23, 100).
(S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid (300)\textsuperscript{96}

To L-phenylalanine 299 (1.0 g, 6.1 mmol) in THF/H\textsubscript{2}O (1:1, 18 mL) was added sodium hydroxide (0.53 g, 13 mmol). This was followed by the slow addition of Boc anhydride (1.58 g, 7.26 mmol) and the mixture was stirred at rt. for 4 hrs. After removing THF under reduced pressure the aqueous mixture was acidified with aqueous hydrogen chloride (1 M) to pH 4. The acidic aqueous solution was extracted with DCM (4 x 50 mL). The organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated under reduced pressure to give acid 300 (1.46 g, 91\%) as clear viscous oil;

R\textsubscript{f} 0.34 (1:1, light petroleum:ether);
[\alpha]\textsuperscript{27}D +29 (c = 0.5, EtOH);
\nu\textsubscript{max}/cm\textsuperscript{-1}, 3424, 3063, 3030, 2979, 2934, 1713, 1661, 1498, 1455, 1394, 1368, 1266, 1159, 1052, 849, 699, 655;
\delta\textsubscript{H} (400 MHz, acetone-\textit{d}) 1.37 [9 H, s, OC(CH\textsubscript{3})\textsubscript{3}], 3.01 (1 H, dd, J 8.8, 13.8, 3-H), 3.22 (1 H, dd, J 8.8, 13.8, 3-H\textsuperscript{1}), 4.40-4.47 (1 H, m, 2-H), 6.09 (1 H, m, NH), 7.29-7.34 (5 H, m, ArH);
\delta\textsubscript{C} (100 MHz, acetone-\textit{d}) 29.95, 38.15, 55.02, 79.23, 127.45, 129.13, 130.17, 138.57, 156.32, 173.59;
m/z (ES) (Found: M\textsuperscript{+} + Na, 288.1204, C\textsubscript{14}H\textsubscript{19}O\textsubscript{4}NNa requires M, 288.1206); m/z (ES) 288 (M\textsuperscript{+} + 23, 100%).
(R)-tert-butyl(1-(2′,2’-dimethyl-4’,6’-dioxo-1’,3′dioxan-5-yl)-3-phenylpropan-2-yl)carbamate(301)\(^{96}\)

To L-amino acid 300 (7.14 g, 26.9 mmol) in DCM (100 mL) was added Meldrum’s acid (4.27 g, 29.6 mmol) and DMAP (4.93 g, 40.4 mmol). The reaction mixture was cooled to -5 °C and a solution of DCC (6.11 g, 29.6 mmol) in DCM (50 mL) was added dropwise over 1 hr. The mixture was left stirring at -5 °C overnight. After warming to rt. the mixture was filtered and the filtrate sequentially washed with KHSO\(_4\) (5%, 4 x 50 mL), brine (50 mL), dried (MgSO\(_4\)) and filtered. The solution was cooled to -5 °C and AcOH (98%, 18 mL) was added followed by the gradual addition in small portions of NaBH\(_4\) (2.5 g, 67 mmol) over 1 hour while stirring then left stirring overnight at -5 °C. After warming to rt. the reaction mixture was sequentially washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was dried (MgSO\(_4\)), filtered, concentrated under reduced pressure and recrystallized with diethyl ether to give the title compound 301 (7.87 g, 78%) as a white solid;

R\(_f\) 0.71 (4:1, light petroleum:ether);

m.p. 127 °C – 127.5 °C; lit.\(^{96}\) 127 °C.

[\(\alpha\)]\(_{30D}\) +3.8 (c = 1.0, EtOH); lit.\(^{96}\) [\(\alpha\)]\(_D\) +3.8 (c = 2.0, EtOH);

\(\nu\)\(_{\text{max}}\)/cm\(^{-1}\), 3343, 2932, 2851, 1783, 1749, 1689, 1532, 1441, 1370, 1283, 1165, 986;

\(\delta\)\(_H\) (400 MHz, CDCl\(_3\)), 1.29 [9 H, s, OC(CH\(_3\))\(_3\)], 1.67 (3 H, s, 2′-CH\(_3\)CH\(_3\)), 1.72 (3 H, s, 2′-CH\(_3\)CH\(_3\)), 2.10 (1 H, m, 3′-CH), 2.20 (1 H, m, 3′-CH’), 2.79 (2 H, d, J 6.3, 4-CH\(_2\)), 3.85 (1 H, m, 3-H), 4.17 (1 H, m, 5-H), 4.41 (1 H, m, NH), 7.11-7.27 (5 H, m, ArH);

\(\delta\)\(_C\) (100 MHz, CDCl\(_3\)), 28.24, 28.57, 31.36, 41.84, 44.27, 49.90, 79.69, 105.02,
126.71, 128.69, 129.32, 137.06, 156.39, 165.58;
m/z (ES) (Found: M⁺ + Na, 400.1715, C₂₀H₂₇O₆NNa requires M, 400.1731);
m/z (ES) 400 (M⁺ + 23, 100%).

The spectral data were consistent with those reported in the literature.⁹⁶

(R)-tert-butyl 2-benzyl-5-oxopyrrolidine-1-carboxylate(292)⁹⁶

A solution of amine 301 (7.80 g, 20.7 mmol) in toluene (150 mL) was heated under reflux overnight. Upon cooling to rt. the mixture was concentrated under reduced pressure to give pyrrolidinone 292 (5.48 g, 96%) as brown oil, which was used without further purification;

Rf 0.42 (2:1, light petroleum:ether);
[α]²⁷D +46.5 (c = 0.5, EtOH); lit.⁹⁶ [α]₀ +48.5 (c = 1.5, EtOH);
νmax/cm⁻¹, 2968, 2929, 2855, 1780, 1748, 1708, 1351, 1305, 1255, 1148, 699;
δH (400 MHz, CDCl₃), 1.51 [9 H, s, OC(CH₃)₃], 1.73 (1 H, ddt, J 1.5, 6.3, 11.4, 3-CH), 1.88 (1 H, ddt, J 2.1, 10.3, 21.1, 3-CH'), 2.25 (2 H, dd, J 1.4, 10.3, 4-H₂), 2.66 (1 H, dd, J 9.1, 13.4, 1'-CH), 3.06 (1 H, dd, J 3.5, 13.1, 1'-CH'), 4.26-4.33 (1 H, dddd, J 1.5, 3.5, 7.6, 12.6, 2-CH), 7.08-7.27 (5 H, m, ArH);
δC (100 MHz, CDCl₃), 21.74, 28.05, 31.08, 39.49, 59.10, 83.15, 126.58, 128.68, 129.38, 137.09, 149.93, 174.45;
m/z (ES) (Found: M⁺ + Na, 298.1413, C₁₆H₂₁O₃N₂Na requires M, 298.1414);
m/z (ES) 298 (M⁺ + 23, 100%).

The spectral data were consistent with those reported in the literature.⁹⁶
(R)-5-benzylpyrrolidin-2-one (302)

To pyrrolidinone 292 (0.10 g, 0.36 mmol) in DCM (3 mL) was added TFA (0.06 mL 0.7 mmol) dropwise. The resultant mixture was stirred at rt. open to the atmosphere for 2 hours. The mixture was neutralised with NaHCO₃ (3 mL) and extracted with EtOAc (3 x 10 mL). The organic fractions were washed with water (10 mL), brine (10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound 302 (0.058 g, 93%), which was used without further purification.

Rf 0.34 (EtOAc);
[α]³⁰ D +65.3 (c = 0.5, EtOH);
νmax/cm⁻¹, 3212, 2926, 2280, 1687, 1453, 1259, 1085, 1030, 811, 742.699, 642;
δH (400 MHz, C₆D₆), 1.78 (2 H, dddd, J 1.5, 2.3, 6.8, 11.9, 4-H₂), 2.25 (2 H, dd, J 1.8, 7.3, 3-H₂), 2.65 (1 H, dd, J 8.2, 13.5, 1'-CH), 2.77 (1 H, dd, J 5.7, 13.5, 1'-CH'), 3.82 (1 H, tt, J 6.3, 13.3, 5-H), 6.81-7.06 (5 H, m, ArH), 7.93 (1 H br s, NH);
δC (100 MHz, C₆D₆), 29.02, 33.02, 41.31, 54.18, 125.32, 127.32, 128.21, 136.63, 176.78;
m/z (ES) (Found: M⁺ + 1, 176.1076, C₁₁H₁₄ON requires M, 176.1070);
m/z (ES) 373 (M⁺ + M⁺ + 23, 100%).
(R)-1-benzoyl-5-benzylpyrrolidin-2-one (303)\textsuperscript{118}

Pyrrolidinone 302 (0.41 g, 2.3 mmol) was dissolved with stirring in NaOH (0.28 g, 7.0 mmol) in water (40 mL). The resultant mixture was cooled to about 10–15 °C in an ice/water bath and benzoyl chloride was added dropwise while keeping the temperature between 10–15 °C. After the addition was complete the reaction mixture was stirred for 2.5 hrs at rt. An excess of aqueous hydrogen chloride (1M, 20 mL) was added. The mixture was filtered and the precipitate washed with ice cold diethyl ether to give pyrrolidinone 303 (0.52 g, 80%) as a yellow oil;

R\textsubscript{f} 0.26 (2:1, light petroleum:ether);
[\alpha]^{30}\textsubscript{D} +176 (c = 0.25, EtOH); lit.\textsuperscript{118} [\alpha]^{30}\textsubscript{D} +164 (c = 0.375, CHCl\textsubscript{3});

\nu\textsubscript{max}/\text{cm}^{-1}, 3061, 2946, 1741, 1663, 1304, 1232, 1190, 735, 696;

\delta\textsubscript{H} (500 MHz, C\textsubscript{6}D\textsubscript{6}), 1.86 (1 H, ddd, J 2.2, 4.3, 6.3, 8.3, 10.3, 4-H), 2.00 (1 H, dddd, J 4.3, 3.8, 8.8, 13.1, 4-H\textsuperscript{`}), 2.31 (2 H, ddd, J 1.0, 2.8, 6.0, 3-H\textsubscript{2}), 2.81 (1 H, dd, J 8.6, 13.4, 1\textsuperscript{`}-CH), 3.21 (1 H, dd, J 3.3, 13.1, 1\textsuperscript{`}-CH\textsuperscript{`}), 4.63 (1 H, dddd, J 0.8, 4.3, 7.8, 12.2, 5-H), 7.12 – 7.29 (8 H, m, ArH), 7.85 (2 H, m, ArH);

\delta\textsubscript{C} (125 MHz, C\textsubscript{6}D\textsubscript{6}), 22.11, 31.35, 38.98, 58.35, 126.96, 127.95, 128.33, 129.38, 129.64, 131.84, 135.86, 137.53, 170.72, 173.96;

m/z (ES) (Found: M\textsuperscript{+}, 280.1335, C\textsubscript{18}H\textsubscript{18}O\textsubscript{2}N requires M, 280.1333);

m/z (ES) 280 (M\textsuperscript{+} + 1, 100%).

The spectral data were consistent with those reported in the literature.\textsuperscript{118}
2-Bromopropene 307 (4.0 mL, 42 mmol) in THF (50 mL) was cooled to -78 °C and t-butyllithium (62 mL) was added dropwise. The resulting yellow solution was stirred for 15 minutes at -78 °C then tiglic aldehyde 22 (4.0 mL) was added dropwise. The mixture was stirred at -78 °C for a further 10 minutes then allowed to warm to rt. Water (50 mL) was added to the reaction mixture then diluted with diethyl ether (50 mL) and extracted with diethyl ether (3 x 30 mL). The organic layers were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (9:1, light petroleum:EtOAc) gave the title compound 308 (5.12 g, 98%) as a yellow oil.

Rf 0.59 (3:1, light petroleum:EtOAc);

νmax/cm⁻¹, 3367, 2974, 2919, 2862, 1652, 1446, 1380, 1096, 1052, 991, 872, 818, 622;

δH (300 MHz, CDCl₃), 1.60 (1 H, br s, OH), 1.54 (3 H, s, 2-CH₃), 1.62 (3 H, s, 4-CH₃), 1.66 (3 H, d, J 6.7, 6-H₃), 4.43 (1 H, s, 3-H), 4.94 (1 H, d, J 1.1, 1-H), 5.09 (1 H, br s, 1-H'), 5.60 (1 H, q, J 6.7, 5-H);

δC (75 MHz, CDCl₃), 10.98, 13.14, 18.89, 80.77, 110.50, 122.01, 135.86, 145.52;

m/z (ES) (Found: M⁺ + Na, 149.1074, C₈H₁₄ONa requires M⁺, 149.1078);

m/z (ES) 149 (M⁺ + 23, 5%), 207 (M⁺ + 81, 100%).
(E)-2,4-dimethylhexa-1,4-dien-3-yl acetate (309)

To alcohol 308 (5.12 g, 40.6 mmol) in DCM (120 mL) was added acetyl chloride (3.19 g, 40.6 mmol) and the mixture was cooled to 0 °C under nitrogen. Pyridine (5.14 g, 65.0 mmol) was added dropwise and a white precipitate formed. The mixture was stirred for 2 hrs at 0 °C then aqueous hydrogen chloride (1 M, 20 mL) was slowly added. The organic fraction was extracted with DCM (3 x 20 mL) and the organic extracts were washed with saturated aqueous NaHCO₃ (40 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (9:1, light petroleum:EtOAc) gave the title compound 309 (5.76 g, 84%) as a yellow oil;

Rₐ 0.69 (3:1 light petroleum:EtOAc);

νmax/cm⁻¹, 2923, 1721, 1637, 1535, 1420, 1363, 1253, 1170, 1026, 993, 903, 822;

δH (300 MHz, CDCl₃), 1.56 (3 H, s, 2-CH₃), 1.64 (3 H, s, 4-CH₃), 1.66 (3 H, d, J 5.2, 6-H₃), 2.11 (3 H, s, OCCH₃), 4.93 (1 H, d, J 1.3, 1-H), 4.97 (1 H, br s, 1-H'), 5.48 (1 H, s, 3-H), 5.61 (1 H, q, J 5.2, 5-H);

δC (75 MHz, CDCl₃), 11.67, 13.26, 19.12, 21.22, 81.47, 111.54, 123.73, 132.02, 141.91, 169.90;

m/z (ES) (Found: M⁺ + Na, 191.1152, C₁₀H₁₆ONa requires M, 191.1158);
m/z (ES) 191 (M⁺ + 23, 100%).
(2E,4E)-2,4-dimethylhexa-2,4-dien-1-yl acetate (307)

To alcohol 261 (3.0 g, 23 mmol) in dry DCM (95 mL) was added pyridine (30.6 mL, 356 mmol) and acetic anhydride (11.2 mL, 119 mmol) at 0 °C under nitrogen. The reaction was monitored by TLC. After completion (2 hrs.), a solution of water with potassium bicarbonate (10:1, H₂O:KHCO₃) (60 mL) was added and the mixture extracted with DCM (3 x 50 mL). The organic fractions were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (50:1, light petroleum:ether) gave the title compound 312 (3.78 g, 95%) as a yellow oil;

Rf 0.6 (4:1, light petroleum:ether);
νmax/cm⁻¹, 2978, 2932, 1734, 1443, 1151, 1032, 866;
δH (400 MHz, CDCl₃), 1.64 (3 H, d J 7.0, 6-H₃), 1.71 (3 H, s, 4-CH₃), 1.76 (3 H, s, 2-CH₃), 2.04 (3 H, s, OCCH₃), 4.44 (2 H, s, 1-H₂), 5.40 (1 H, q, J 6.8, 5-H), 5.86 (1 H, s, 3-H);
δC (100 MHz, CDCl₃), 13.67, 15.61, 16.33, 21.04, 21.00, 125.54, 128.90, 132.73, 132.89, 171.02;
m/z (ES) (Found: M⁺ + 1, 169.1148, C₁₀H₁₆O₂ requires M, 169.1150);
m/z (ES) 191 (M⁺ + 23, 100%).

(2E,4E)-1-bromo-2,4-dimethylhexa-2,4-diene (317)
To alcohol 261 (1.0 g, 7.9 mmol) in DCM (9.5 mL) under an inert nitrogen atmosphere at -10 °C was slowly added phosphorous tribromide (0.73 g, 2.7 mmol) in DCM (10 mL). After all the phosphorous tribromide was added the mixture was stirred for a further 20 mins then a saturated aqueous solution of ice-cold sodium bicarbonate (10 mL) was added. The organic layer was separated from the aqueous layer and the aqueous fraction extracted with ice-cold diethyl ether (2 x 10 mL). The organic fractions were washed with ice-cold brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure at 0 °C. The crude title compound 317 (1.27 g, 85%) was used immediately without further purification or characterisation.

**Diethyl 2-[(2E,4E)-2,4-dimethylhexa-2,4-diene-1-yl]malonate (318)**

Diethyl malonate (1.08 g, 6.74 mmol) was treated with NaH (0.30 g, 7.4 mmol) in dry THF (7.6 mL) at 0 °C for 30 minutes. (2E,4E)-1-Bromo-2,4-dimethylhexa-2,4-diene 317 (1.27 g, 6.74 mmol) was added to the mixture and stirred for 2 hrs at rt. After addition of saturated aqueous NH₄Cl (8 mL) the mixture was extracted with diethyl ether (2 x 10 mL) and the organic fraction was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (15:1→4:1 light petroleum:ether) gave the title compound 318 (0.371 g, 25%) as a colourless oil;

Rᵥ 0.50 (4:1 light petroleum:ether);

νᵢₘₐₓ/cm⁻¹, 2982, 2933, 2860, 1732, 1446, 1369, 1231, 1149, 1097, 1030, 906, 864, 731;

δ_H (500 MHz, CDCl₃), 1.19 (6 H, t, J 6.9, 7.3, OCH₂CH₃), 1.58 (3 H, d, J 6.9, 6-H₃), 1.60 (3 H, s, 2-CH₃), 1.69 (3 H, s, 4-CH₃), 2.54 (2 H, d, J 7.9, 1-H₂), 3.49 (1 H, t, J
7.9, OCCH), 4.11 (4 H, q, J 6.9, 7.3, OCH₂CH₃), 5.22 (1 H, q, J 6.6, 5-H), 5.61 (1 H, s, 3-H);
δC (125 MHz, CDCl₃), 13.62, 14.09, 16.51, 17.35, 39.52, 50.89, 61.33, 123.96, 130.38, 131.69, 133.09, 169.24;
m/z (ES) (Found: M⁺ + Na, 291.1558, C₁₅H₂₄O₄Na requires M, 291.1567);
m/z (ES) 291 (M⁺ + 23, 100%).

(4E,6E)-ethyl 4,6-dimethylocta-4,6-dienoate (306)

A mixture of malonate 318 (0.37 g, 1.4 mmol), LiCl (0.18 g, 4.1 mmol), H₂O (0.020 mL, 1.4 mmol) and DMSO (2.75 mL) was heated under reflux for 5 hours (150 °C). Saturated NH₄Cl (aq) (3 mL) was added and the mixture extracted with diethyl ether (3 x 3 mL). The organic fractions were dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. Flash chromatography (10:1, light petroleum:ether) gave the title compound 306 (0.132 g, 49%) as yellow oil;

Rf 0.30 (4:1, light petroleum:ether);

νmax/cm⁻¹, 2978, 2932, 1734, 1442, 1151, 1032, 866;
δH (500 MHz, CDCl₃), 1.18 (3 H, t, J 7.3, OCH₂CH₃), 1.59 (3 H, d, J 6.9, 8-H₃), 1.63 (3 H, s, 4-CH₃), 1.69 (3 H, s, 6-CH₃), 2.25-2.54 (4 H, m, 2-H₂ and 3-H₂), 4.06 (2 H, q, J 7.3, OCH₂CH₃), 5.20 (1 H, q, J 6.9, 7-H), 5.58 (1 H, s, 5-H);
δC (125 MHz, CDCl₃), 13.71, 14.27, 16.54, 17.53, 33.39, 35.66, 60.63, 121.48, 123.60, 129.55, 133.73, 173.48;
m/z (ES) (Found: M⁺ + Na, 219.1352, C₁₂H₂₀O₂Na requires M, 219.1356);
m/z (ES) 219 (M⁺ + 23, 100%), 197 (M⁺ + 1, 10).
Ester 306 (0.13 g, 0.65 mmol) in THF (3.2 mL) was treated dropwise with LiOH (0.060 g, 2.6 mmol) in H₂O (3.2 mL) at rt. under nitrogen. On completion the reaction was acidified to pH 5 using ice-cold aqueous hydrogen chloride (1 M) dropwise. The organic fraction was extracted with ice-cold EtOAc (3 x 5 mL), washed with ice-cold water (20 mL), ice-cold brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound 319 (0.0717 g, 60%) as a colourless oil;

Rₖ 0.57 (1:2, light petroleum:ether);

vₘₐₓ/cm⁻¹, 2973, 2915, 2859, 1708, 1442, 1297, 1212, 1048, 911, 734;

δ_H (400 MHz, CDCl₃), 1.59 (3 H, d, J 7.1, 8-H₃), 1.62 (3 H, s, 4-CH₃), 1.69 (3 H, s, 6-CH₃), 2.16-2.54 (4 H, m, 2-H₂ and 3-H₂), 4.72 (1 H, q, J 7.1, 7-H), 5.60 (1 H, s, 5-H), 11.44 (1 H, br s, COOH);

δ_C (100 MHz, CDCl₃), 12.60, 15.72, 16.68, 32.02, 34.18, 120.52, 122.67, 128.67, 132.57, 179.03;

m/z (ES) (Found: M⁺ - 1, 167.1080, C₁₀H₁₅O₂ requires M, 167.1077); m/z (ES) 167 (M⁺ - 1, 100%).

(4E,6E)-1-(1H-imidazol-1-yl)-4,6-dimethylocta-4,6-dien-1-one (305)
1 1'-Carbonyldiimidazole (0.090 g, 0.53 mmol) was added to a solution of acid 319 (0.070 g, 0.42 mmol) in THF (1.45 mL) and the mixture stirred at rt. for 2 hours. The solution was diluted with cold diethyl ether (5 mL), washed with cold water (5 mL), cold brine (5 mL) and the aqueous phases extracted with diethyl ether (3 x 5 mL). The organic fractions were dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was dissolved in benzene (10 mL), dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to give the title compound 305 (0.078 g, 86%) as yellow oil.

R$_f$ 0.12 (1:2, light petroleum:ether);

$\nu_{\text{max}}$/cm$^{-1}$, 3123, 2915, 2857, 1733, 1651, 1527, 1474, 1382, 1298, 1224, 1208, 1085, 955, 752, 649;

$\delta_H$ (500 MHz, CDCl$_3$), 1.62 (3 H, s, 4-CH$_3$), 1.59 (3 H, d, $J$ 6.9, 8-H$_3$), 1.73 (3 H, s, 6-CH$_3$), 2.43 (2 H, t, $J$ 7.9, 3-H$_2$), 2.91 (2 H, t, $J$ 7.9, 2-H$_2$), 5.25 (1 H, q, $J$ 6.9, 7-H), 5.62 (1 H, s, 5-H), 7.03 (1 H, s, 4'-H), 7.41 (1 H, s, 5'-H), 8.09 (1 H, s, 2'-H);

$\delta_C$ (125 MHz, CDCl$_3$), 12.69, 16.66, 22.70, 33.29, 33.73, 115.03, 123.19, 127.30, 129.60, 130.04, 130.91, 135.14, 168.15;

m/z (ES) (Found: M$^+$ + 1, 219.1423, C$_{13}$H$_{18}$N$_2$O requires M, 219.1418);

m/z (ES) 219 (M$^+$ + 1, 100%).

**(5R)-1-benzoyl-5-benzyl-3-[(4E,6E)-4,6-dimethylocta-4,6-dienoyl]pyrrolidin-2-one (320)**
LiHMDS in THF (1.0 M, 0.64 mL, 0.64 mmol) was cooled and added to pyrrolidin-2-one (0.18 g, 0.64 mmol) in THF (1.5 mL) at -78 °C. After 1 hr, a cooled solution of acyl imidazole (0.070 g, 0.32 mmol) in THF (0.32 mL) was added dropwise and stirring was continued at -78 °C for 2.5 hrs. Saturated aqueous NH₄Cl was added at -78 °C (1.5 mL) and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with diethyl ether (3 x 5 mL) and the organic fractions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (7:1, light petroleum:ether) gave the title compound (0.09 g, 66%) as a pinkish oil. There were a mixture of four compounds present comprising two diastereoisomers and the enol of both. Enol ratio 2.5:1; diastereoisomer ratio 2.5:1. All peaks in the ¹H n.m.r. spectrum overlapped apart from those corresponding to the enol hydrogen and the hydrogen at 5´-H.

Rf 0.53 (1:1, light petroleum:ether);
[α]²⁰ D -4.8 (c = 0.5, EtOH);
νmax/cm⁻¹, 3029, 2916, 2857, 2253, 1738, 1714, 1673, 1448, 1374, 1347, 1280, 1225, 1178, 907, 726, 702, 648;
δH (500 MHz, CDCl₃), 1.51 (3 H, d, J = 6.7, 8´-H₃), 1.59 (3 H, s, 6´-CH₃), 1.69 (3 H, s, 4´-CH₃), 1.89 (1 H, m, 5-CH), 2.28-2.34 (2 H, m, 4-H₂), 2.42 (1 H, m, 5-CH´), 2.63-2.81 (2 H, m, 3´-H₂), 3.16-3.34 (2 H, m, 2´-H₂), 4.46 (1 H, m, 5-H), 5.27 (1 H, q, J = 6.7, 7´-H), 5.58 (1 H, s, 5´-H), 5.60 (1 H, s, 5´-H), 5.63 (1 H, s, 5´-H), 7.13-7.42 (10 H, m, CH₂ArH and OCArH), 11.38 (0.4 H, s, 1´-OHenol), 11.40 (1 H, s, 1´-OHenol);
δC (125 MHz, CDCl₃), 11.46, 13.63, 13.64, 13.67, 14.48, 16.66, 16.68, 16.71, 17.81, 22.65, 23.86, 29.08, 33.88, 33.94, 39.25, 39.65, 41.59, 41.87, 54.91, 55.97, 56.75, 57.22, 123.53, 123.59, 123.80, 126.87, 126.89, 127.13, 127.82, 127.90, 128.09, 128.66, 128.73, 128.75, 129.15, 129.57, 129.65, 129.67, 129.76, 129.92, 129.97, 131.85, 132.20, 132.61, 133.08, 133.11, 133.29, 133.33, 134.45, 134.49, 136.37, 136.77, 136.86, 170.49, 170.59, 170.65, 170.83, 170.93, 172.66, 203.57;
m/z (ES) (Found: M⁺ + 1, 403.2397, C₂₈H₃₂O₃N requires M, 430.2377);
m/z (ES⁺) 822 (2M⁺ + 23, 100%), 452 (M⁺ + 23, 65).
(5S)-1-benzoyl-5-benzyl-3-[(4E,6E)-4,6-dimethylocta-4,6-dienoyl]-3-phenylselanylpyrrolidin-2-one (321)

A solution of LiHMDS in THF (1.0 M, 0.15 mL, 0.15 mmol) at -78 °C was added to pyrrolidinone 320 (0.057 g, 0.13 mmol) in THF (1.2 mL) at -78 °C. After 1 hr. at this temperature a cooled solution of PhSeCl (0.030 g, 0.15 mmol) in THF (0.6 mL) was added to the mixture and stirring continued at -78 °C for 2 hrs. Saturated aqueous NH₄Cl (2 mL) was added and the mixture allowed to warm to rt. Water was added (3 mL) and the organic fraction extracted with diethyl ether (3 x 5 mL). The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (20:1→15:1, light petroleum:ether) gave the title compound 321 (0.052 g, 67%) as a light green oil, (two diastereoisomers in a 1:1 ratio). All peaks in the ¹H n.m.r. spectrum overlapped apart from those corresponding to the hydrogen at 5´-H.

Rₖ 0.38 (4:1, light petroleum:ether);
[α]³⁰D -32.6 (c = 0.25, EtOH);
νmax/cm⁻¹, 3059, 3029, 2927, 2857, 2842, 1727, 1682, 1438, 1346, 1273, 1220, 1022, 800, 741, 691, 651;
δH (500 MHz, CDCl₃), 1.49 (3 H, d, J 6.8, 8´-H₃), 1.58 (3 H, s, 6´-CH₃), 1.67 (3 H, s, 4´-CH₃), 1.89 (1 H, m, 5-CH), 2.26 (2 H, t, J 6.8, 4-H₂), 2.40 (1 H, m, 5-CH´), 2.59-2.78 (2 H, m, 3´-H₂), 3.11-3.31 (2 H, m, 2´-H₂), 4.40 (1 H, m, 5-H), 5.21 (1 H, q, J 6.8, 7´-H), 5.60 (1 H, s, 5´-H), 5.61 (1 H, s, 5´-H), 7.04-7.59 (15 H, m, CH₂ArH and OCArH and SeArH);
δC (125 MHz, CDCl₃), 12.62, 13.91, 15.66, 16.72, 16.83, 21.60, 22.93, 30.13, 32.99, 34.14, 36.12, 36.22, 37.14, 37.62, 54.63, 54.99, 58.98, 120.44, 122.52,
123.61, 124.76, 125.86, 127.00, 128.19, 128.32, 128.38, 128.45, 128.63, 128.73, 128.75, 129.06, 129.34, 131.63, 131.81, 132.33, 132.36, 133.25, 134.47, 134.98, 136.06, 136.48, 136.52, 169.86, 169.97, 199.68, 200.19; m/z (ES) (Found: M+ + Na, 608.1677, C₃₄H₃₅O₃NNa requires M, 608.1675); m/z (ES) 608 (M+ + 23, 100%).

(3-bromopropoxy)(tert-butyl)dimethylsilane (326)

To 3-bromopropanol 325 (5.0 g, 36 mmol) in DCM (200 ml) at 0 °C was added imidazole (7.34 g, 108 mmol). To this was added (tert-butyl)dimethylsilane chloride (8.1 g, 54 mmol). The mixture allowed to warm to room temperature and stirred under nitrogen for 1.5 hrs. Water (200 ml) and DCM (200 ml) was added and the organic layer separated. The aqueous layer was extracted with DCM (3 x 50 mL) and the organic layers washed with brine (200 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (20:1, light petroleum:ether) gave (3-bromopropoxy)(tert-butyl)dimethylsilane 326 (8.9 g, 98%) as a clear oil.

Rf 0.61 (4:1, light petroleum:ether);
νmax/cm⁻¹, 2953, 2929, 2856, 1471, 1361, 1254, 1099, 1061, 951, 832, 774, 663; δH (400 MHz, CDCl₃), 0.00 [6 H, s, Si(CH₃)₂], 0.83 [9 H, s, SiC(CH₃)₃], 1.97 (2 H, tt, J 5.8, 6.6, 2-H₂), 3.45 (2 H, t, J 6.6, 3-H₂), 3.67 (2 H, t, J 5.8, 1-H₂);
δC (125 MHz, CDCl₃), -5.35, 18.31, 25.88, 30.67, 35.56, 60.46; m/z (ES) 335 (M+ + 83, 95 %).
To a mixture of magnesium turnings (0.44 g, 18 mmol) and iodine (catalytic amount) in anhydrous THF (10 mL) was slowly added (3-bromopropoxy)(tert-butyl)dimethylsilane 326 (3.52 g, 13.9 mmol) in THF (15 mL) at room temperature. After the reaction was initiated, the speed of the addition of (3-bromopropoxy)(tert-butyl)dimethylsilane was controlled to maintain the temperature of the reaction mixture at 30-35 °C. After the addition was complete the resulting mixture was stirred at 40 °C for 1 hr. to afford a solution of 3-(tert-butyl-dimethyl-silanyloxy)-propylmagnesium bromide. The mixture was then cooled to -78 °C and CuLi2Cl4 (2.78 mL, 0.278 mmol) was added followed by diene acetate 312 (1.17 g, 6.95 mmol) in THF (7 mL). The mixture was warmed to rt. and stirred for 2 hrs, then poured into water (10 mL) and concentrated under reduced pressure to remove most of the THF. The aqueous fraction was extracted with diethyl ether (3 x 30 mL) and the organic extracts were dried (Na2SO4), filtered and concentrated under reduced pressure. Flash chromatography (50:1, light petroleum:ether) gave the title compound 328 (1.78 g, 91%) as a pale yellow oil; 

RI 0.71(20:1, light petroleum:ether);

νmax/cm⁻¹, 2929, 2857, 1471, 1462, 1443, 1386, 1360, 1253, 1097, 1005, 967, 833, 772, 660;

δH (400 MHz, CDCl₃), 0.00 [6 H, s, Si(CH₃)₂], 0.84 [9 H, s, Si(CH₃)₃], 1.38 – 1.49 (4 H, m, 2-H₂ and 3-H₂), 1.62 (3 H, d, J 6.8, 9-H₃), 1.66 (3 H, s, 5-CH₃), 1.69 (3 H, s, 7-CH₃), 1.98 (2 H, t, J 7.0, 4-H₂), 3.56 (2 H, t, J 6.3, 1-H₂), 5.26 (1 H, q, J 6.8, 8-H), 5.58 (1 H, s, 6-H);

δC (100 MHz, CDCl₃), -5.31, 13.63, 16.77, 17.62, 18.39, 24.21, 25.99, 32.43, 40.38, 63.25, 122.97, 128.86, 133.70, 135.23;
m/z (EI) (Found: M⁺ - C₄H₉, 225.1667, C₁₃H₂₅Si requires M, 225.1669); m/z (GC/MS) 283 (M⁺ + 1, 100%).

\((5E,7E)-5,7\text{-dimethyl}n\text{ona}-5,7\text{-dien}-1\text{-ol} (329)\)

To a cold solution (0 °C) of silyl ether 328 (1.63 g, 5.77 mmol) in anhydrous THF (16 mL) was added TBAF (1.0 M in THF), (17.3 mL, 17.3 mmol) and stirred at 0 °C for 1 hr. then at rt. for 2 hrs. Water (20 mL) was added to the reaction mixture and extracted with diethyl ether (3 x 20 mL). The organic fractions were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (4:1, light petroleum:ether) gave the title compound 329 (0.87 g, 90%) as a colourless oil;

Rᶠ 0.53 (1:2, light petroleum:ether);

\(ν_{\text{max}}/\text{cm}^{-1}\), 3307, 3033, 2932, 2858, 2736, 1496, 1458, 1426, 1408, 1378, 1322, 1137, 1114, 1062, 988, 952, 870, 835, 773, 613;

\(δ_H\) (400 MHz, CDCl₃), 1.23 (1 H, br, s, OH), 1.36-1.49 (4 H, m, 2-H₂ and 3-H₂), 1.57 (3 H, d, J 6.8, 9-H₃), 1.61 (3 H, s, 5-CH₃), 1.64 (3 H, s, 7-CH₃), 1.95 (2 H, t, J 6.8, 4-H₂), 3.55 (2 H, t, J 6.3, 1-H₂), 5.22 (1 H, q, J 6.8, 8-H), 5.54 (1 H, s, 6-H);

\(δ_C\) (100 MHz, CDCl₃), 13.63, 16.76, 17.64, 24.13, 32.36, 40.32, 62.98, 123.10, 129.06, 133.63, 134.92;

m/z (ES) (Found: M⁺ + Na, 191.1408, C₁₁H₂₀ONa requires M, 191.1407);

m/z (ES) 242 (M⁺ + 74, 100%), 191 (M⁺ + 23, 18).
Solid TPAP (0.091 g, 0.26 mmol) was added slowly to a stirred mixture of alcohol 329 (0.87 g, 5.2 mmol), NMO (0.91 g, 0.26 mmol) and 4 Å molecular sieves (3.8 g) in DCM:MeCN (10:1), (15 mL), at rt. under nitrogen. On completion the reaction mixture was concentrated under reduced pressure, diluted with DCM (15 mL), filtered through silica and eluted with EtOAc (3 x 20 mL) and DCM (2 x 20 mL). The filtrate was concentrated under reduced pressure and flash chromatography (30:1→20:1, light petroleum:ether) gave the title compound 330 (0.53 g, 62%); 

Rf 0.49 (4:1, light petroleum:ether); 

νmax/cm⁻¹, 2972, 2914, 2859, 1724, 1442, 1375, 1297, 1212, 1048, 911, 734; 

δH (500 MHz, CDCl₃), 1.57 (3 H, d, J 6.9, 9-H₃), 1.61 (3 H, s, 7-CH₃), 1.64 (3 H, s, 5-CH₃), 1.68 (2 H, tt, J 7.3, 7.6, 3-H₂), 1.96 (2 H, t, J 7.2, 4-H₂), 2.32 (2 H, t, J 7.2, 2-H₂), 5.22 (1 H, q, J 6.9, 8-H), 5.53 (1 H, s, 6-H), 9.68 (1 H, s, CHO); 

δC (125 MHz, CDCl₃), 13.71, 16.73, 17.48, 20.31, 39.76, 43.16, 123.41, 130.02, 133.42, 133.79, 202.71; 

m/z (EI) [Found: M⁺, 166.1349, C₁₁H₁₈O requires M⁺, 166.1352]; 

m/z (GC/MS) 166 (M⁺, 100%).

(5E,7E)-5,7-dimethylnona-5,7-dienoic acid (331)

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Method 1

Aldehyde 330 (0.050 g, 0.30 mmol) was dissolved in t-butanol (6.3 mL), and 2-methyl-2-butene (3.0 mL). A solution of sodium chlorite (0.25 g, 2.78 mmol) and sodium dihydrogenphosphate (0.29 g, 2.1 mmol) in water (2.5 mL) was added dropwise. The mixture was stirred at rt. for 1 hr. Brine (10 mL) was added and the organic fraction extracted with EtOAc (3 x 10 mL). The aqueous layer was acidified with aqueous hydrogen chloride (1.0 M) to pH 4 then re-extracted with EtOAc (2 x 10 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (1:1, 40-60 Petroleum ether:EtOAc) gave the title compound 331 (0.053 g, 96%) as a colourless oil.

Method 2

To a solution of methyl ester 332 (0.05 g, 0.16 mmol) in THF (1.0 mL) at rt. under nitrogen was added LiOH (0.045 g, 1.9 mmol) in H₂O (1.0 mL) and the mixture stirred at rt. for 26 hours. The reaction mixture was acidified to pH 5 by adding aqueous hydrogen chloride (1.0 M) dropwise and the organic fraction extracted with EtOAc (3 x 5 mL), washed with water (5 mL), brine (5 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound 331 as a yellow oil, (0.043 g, 92%).

Rf 0.73 (1:2, light petroleum:ether);
νmax/cm⁻¹, 2975, 2934, 1703, 1649, 1441, 1377, 1251, 1172, 1149, 1071, 938, 878, 855, 782, 702;
δH (400 MHz, CDCl₃), 1.56 (3 H, d, J 6.8, 9-H₃), 1.60 (3 H, s, 5-CH₃), 1.64 (3 H, s, 7-CH₃), 1.68 (2 H, tt, J 6.8, 7.5, 3-H₂), 1.97 (2 H, t, J 7.6, 4-H₂), 2.24 (2 H, t, J 7.6, 2-H₂), 5.22 (1 H, q, J 6.8, 8-H), 5.54 (1 H, s, 6-H), 10.60 (1 H, br s, COOH);
δC (100 MHz, CDCl₃), 13.61, 16.69, 17.48, 22.87, 33.31, 39.77, 123.35, 129.89, 133.48, 133.74, 179.61;
m/z (ES) (Found: M⁺, 182.1304, C₁₁H₁₈O₂ requires M⁺, 182.1307);
m/z (GCMS) 181.9 (M⁺, 100%).
(5E,7E)-methyl 5,7-dimethylnona-5,7-dienoate (332)

To a stirred solution of carboxylic acid 331 (0.30 g, 1.6 mmol) in a (3:2) mixture of toluene:MeOH (17 mL) was added dropwise, TMSCHN₂ in hexanes (2.0 M) until the yellow colour persisted (0.8 mL, 2.4 mmol). The mixture was stirred for 45 minutes at rt. then concentrated under reduced pressure. Flash chromatography (4:1, light petroleum:ether) gave the title compound 332 (0.246 g, 75%) as colourless oil;

Rᶠ 0.62 (4:1, light petroleum:ether);

νmax/cm⁻¹, 2949, 2859, 1737, 1651, 1435, 1373, 1307, 1248, 1196, 1168, 1149, 1068, 1009, 915, 877, 847, 732, 621;

δH (400 MHz, CDCl₃), 1.46 (3 H, d, J 6.8, 9-H₃), 1.50 (3 H, s, 7-CH₃), 1.53 (3 H, s, 5-CH₃), 1.56 (2 H, tt, J 7.3, 7.6, 3-H₂), 1.84 (2 H, t, J 7.6, 4-H₂), 2.08 (2 H, t, J 7.6, 2-H₂), 3.46 (3 H, s, OCH₃), 5.11 (1 H, q, J 6.8, 8-H), 5.42 (1 H, s, 6-H);

δC (100 MHz, CDCl₃), 13.60, 16.70, 17.50, 23.16, 33.45, 39.90, 51.45, 123.28, 129.73, 133.52, 133.92, 174.21;

m/z (ES) (Found: M⁺ + Na, 219.1362, C₁₂H₂₀O₂Na requires M, 219.1356);

m/z (ES) 219 (M⁺ + 23, 30%), 413 (M⁺ + 217, 100),

(5E,7E)-1-(1H-imidazol-1-yl)-5,7-dimethylnona-5,7-dien-1-one (324)

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1,1'-Carbonyldiimidazole (0.20 g, 1.2 mmol) was added to carboxylic acid 331 (0.20 g, 1.1 mmol) in THF (3.8 mL) at rt. and stirred under nitrogen for 4 hours. On completion the solution was concentrated under reduced pressure to remove the THF. The residue was dissolved in diethyl ether (5 mL) then washed consecutively with saturated NH₄Cl (aq) (5 mL), NaHCO₃ (aq) (5 mL) and brine (5 mL). The organic layer was separated, then dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound 324 (0.199 g, 83%) as colourless oil.

Rf 0.24 (1:5, light petroleum:ether);
νmax/cm⁻¹, 2916, 2852, 1737, 1644, 1526, 1474, 1385, 1270, 1235, 1090, 1060, 958, 911, 732, 649;
δH (500 MHz, C₆D₆), 1.61 (3 H, d, J 6.9, 9-H₃), 1.68 (3 H, s, 7-CH₃), 1.67 (3 H, s, 5-CH₃), 1.89 (2 H, tt, J 7.1, 7.3, 3-H₂), 2.08 (2 H, t, J 7.3, 4-H₂), 2.76 (2 H, t, J 7.3, 2-H₂), 5.25 (1 H, q, J 6.9, 8-H), 5.57 (1 H, s, 6-H), 6.99 (1 H, s, 4'-H), 7.11 (1 H, s, 2'-H), 7.75 (1 H, s, 5'-H);
δC (125 MHz, C₆D6), 13.71, 16.82, 17.53, 22.18, 33.81, 39.66, 116.05, 123.77, 130.48, 130.83, 133.17, 136.19, 145.83, 169.02;
m/z (ES) (Found: M⁺ + 1, 233.1647, C₁₄H₂₁N₂O requires M, 233.1649);
m/z (ES) 233 (M⁺ + 1, 100%), 255 (M⁺ + 23, 100).

\((5R)-1\text{-Benzyloxy}-5\text{-benzyl}-3\text{-[\((5E,7E)\text{-dimethyl}n\text{ona}5,7\text{-dienoyl}]pyrrolidin-2\text{-one}}\) (333)

Imidazolide 324 was azeotroped in benzene prior to the reaction.
LiHMDS in THF (1.0 M, 0.43 mL, 0.43 mmol) was cooled and added to pyrrolidinone 303 (0.12 g, 0.43 mmol) in THF (1 mL) at -78 °C. After 1 hr. a cooled solution of imidazolide 324 (0.055 g, 0.24 mmol) in THF (0.22 mL) was added dropwise and stirring at -78 °C continued for 2 hrs. The mixture was allowed to warm to rt. and stirring continued for 1 hour. Saturated aqueous NH₄Cl was added (2 mL) and the organic fraction was extracted with EtO₂ (3 x 2 mL). The organic fraction was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (7:1, light petroleum:ether) gave the title compound 333 (0.102 g, 95%) as a pinkish oil. There were a mixture of four compounds present comprising two diastereoisomers (ratio 1:1) and the enol. All peaks in the ¹H n.m.r. spectrum overlapped.

Rf 0.24, (4:1, light petroleum:ether);
[α]²⁸D +13.3 (c = 0.5, EtOH);
νmax/cm⁻¹, 3049, 2930, 2852, 2857, 2279, 1739, 1715, 1681, 1638, 1449, 1373, 1346, 1284, 1228, 1090, 1026, 812, 703, 658;
δH (400 MHz, CDCl₃), 1.25 – 1.47 (2 H, m, 3'-H₂), 1.51 (3 H, d, J 6.8, 9'-H₃), 1.59 (3 H, s, 5'-CH₃), 1.63 (3 H, s, 7'-CH₃), 1.77 – 1.89 (2 H, m, 4'-H₂), 1.94 – 2.13 (2 H, m, 2'-H₂), 2.27 (1 H, m, 4-H), 2.51 (1 H, m, 4'-H'), 2.69 (1 H, m, 5-CH), 2.90 – 3.04 (1 H, m, 5'-H'), 3.29 (1 H, dd, J 3.2, 13.0, 3-H), 4.45 – 4.54 (1 H, m, 5-H), 5.30 (1 H, q, J 7.0, 8'-H), 5.63 (1 H, s, 6'-H), 6.93 – 7.06 (5 H, m, OCArH), 7.17 – 7.70 and 7.55 – 7.70 (5 H, m, CH₂ArH), 12.12 (1 H, s, 1'-OHenol);
δC (100 MHz, CDCl₃), 11.40, 13.63, 13.64, 13.67, 14.50, 16.68, 16.69, 16.72, 17.83, 22.67, 23.83, 29.18, 32.58, 32.67, 33.87, 33.96, 35.24, 35.78, 39.28, 39.66, 41.60, 41.88, 54.91, 55.95, 56.76, 57.21, 123.54, 123.61, 123.82, 126.87, 126.90, 127.16, 127.81, 127.93, 128.12, 128.67, 128.73, 128.76, 129.18, 129.59, 129.65, 129.69, 129.77, 129.92, 129.96, 131.88, 132.22, 132.63, 133.11, 133.16, 133.31, 133.37, 134.48, 134.51, 136.39, 136.78, 136.89, 170.51, 170.58, 170.68, 170.87, 170.90, 172.68, 201.56;
m/z (ES) (Found: M⁺ + Na, 466.2364, C₂₉H₃₃NO₃Na requires M, 466.2353);
m/z (ES) 466 (M⁺ + 23, 100%).
A solution of LiHMDS in 1.0 M THF (0.24 mL, 0.24 mmol) at -78 °C was added to a stirred solution of pyrrolidinone 333 (0.098 g, 0.22 mmol) in THF (1.9 mL) at -78 °C. After 1 hr. at this temperature a cooled solution of phenylselenium chloride (0.047 g, 0.24 mmol) in THF (0.94 mL) was added to the mixture and stirred at -78 °C for 2 hrs. Saturated aqueous NH₄Cl (2 mL) was added and the mixture was allowed to warm to rt. Water was added (3 mL) and the organic fraction extracted with diethyl ether (3 x 5 mL). The organic fractions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (15:1, light petroleum:ether) gave the title compound 334 (0.106 g, 80%) as clear oil.

R₇ 0.34 (4:1, light petroleum:ether);
[α]²⁸D +29.6, (c = 1.0, EtOH);

νₓₜₐₓ/cm⁻¹, 3024, 3059, 2929, 2852, 2270, 1727, 1682, 1600, 1438, 1346, 1273, 1218, 1177, 1213, 1021, 1000, 812, 795, 741, 690, 655;

δₜ (400 MHz, C₆D₆), 1.54 (3 H, d, J 6.8, 9°-H₃), 1.70 (3 H, s, 5°-CH₃), 1.63 (3 H, s, 7°-CH₃), 1.87 (2 H, tt, J 6.6, 7.3, 3°-H₂), 2.58 (2 H, t, J 6.8, 4°-H₂), 2.74 (2 H, dd, J 3.0, 6.3, 4°-H₂), 2.81 (1 H, dd, J 2.8, 10.6, 5-CH), 3.24 (1 H, dd, J 2.8, 6.8, 5-CH°), 3.10-3.17 (2 H, m, 2°-H₂), 4.54 (1 H, ddd, J 3.0, 7.3, 13.0, 5-H), 5.36 (1 H, q, J 6.8, 8°-H), 5.74 (0.1 H, s, 6°-H), 6.77-7.70 (15 H, m, CH₂ArH, and OCArH and SeArH);

δc (100 MHz, C₆D₆), 13.72, 16.93, 17.73, 23.40, 31.75, 38.27, 38.37, 40.14, 55.92, 60.61, 123.32, 127.03, 127.79, 127.92, 128.80, 129.91, 130.00, 130.06, 130.13, 132.44, 133.89, 134.44, 135.17, 136.65, 137.08, 137.68, 171.00, 171.09, 201.69;
m/z (ES) (Found: M+ + Na, 622.1942, C35H37NO3SeNa requires M, 622.1947); m/z (ES) 622 (M+ + 23, 100%).

(3S,3aR,6aR,10aR)-2-benzoyl-3-benzyl-4,5,6a-trimethyl-2,3,3a,4,6a,7,8,9-octahydrobenzo(d)isoindole-1,10-dione (322)

Selenide 323 (0.040 g, 0.072 mmol) in CDCl₃ (3.5 mL) was cooled to -50 °C. Hydrogen peroxide (0.086 mL, 0.76 mmol) in water (0.4 mL) was cooled to 0 °C then added to the mixture and stirred at -50 °C for 1 minute. mCPBA (0.019 g, 0.086 mmol) in CDCl₃ (2.2 mL), cooled to 0 °C, was added to the mixture and stirred for 15 minutes at -50 °C. The reaction mixture was removed from the -50 °C bath and allowed to warm to 0 °C then vigorously stirred for 5 minutes. Ice-cold saturated aqueous NaHCO₃ (8 mL) was added and stirred vigorously for 5 minutes. The aqueous and organic layers were separated and the organic fraction was sequentially washed with ice-cold saturated NaHCO₃ (aq) (8 mL), ice-cold water (8 mL) and ice-cold brine (8mL). The organic fraction was dried (Na₂SO₄), filtered then injected into warm, dry xylene (50 mL) that had been degassed with nitrogen for several hrs. The mixture was refluxed at 140 °C for 21 hrs then concentrated under reduced pressure. Flash chromatography (100:1→50:1→30:1, light petroleum:ether) gave the title compound 322 (0.0083 g, 26%).

Rᶠ 0.29 (4:1, light petroleum:ether);
[α]²⁴D +86 (c = 0.4, EtOH);
νmax/cm⁻¹, 2955, 2938, 2862, 1729, 1703, 1678, 1447, 1278, 1212, 1176, 909, 806, 730, 698, 667;
δ_H (500 MHz, CDCl_3), 1.01 (3 H, s, 6α-CH_3), 1.04 (3 H, d, J 7.2, 4-CH_3), 1.36 (1 H, m, 7-H), 1.57 (3 H, s, 5-CH_3), 1.61-1.66 (1 H, m, 9-H), 1.69-1.76 (1 H, m, 9H'), 1.87-1.97 (2 H, m, 4-H and 7H'), 2.39 (1 H, dddd, 1.3, 4.7, 9.8, 14.5, 8-H), 2.66 (1 H, dddd, J 3.2, 6.3, 11.3, 14.5, 8-H'), 3.04 (1 H, dd, J 7.6, 13.8, 1'H), 3.13 (1 H, dd, J 2.8, 13.8, 1'H'), 3.19 (1 H, dd, J 4.1, 8.2, 3a-H), 3.19 (1 H, dd, J 2.8, 7.6, 7.9, 3-H), 5.05 (1 H, s, 6-H), 7.17-7.21 (5 H, m, CH_2ArH), 7.31 (2 H, t, J 7.6, OCArH), 7.43-7.47 (3 H, m, OCArH);

δ_C (125 MHz, CDCl_3), 20.36, 21.50, 21.77, 25.14, 35.06, 37.13, 37.18, 39.23, 41.77, 41.95, 63.00, 65.88, 126.98, 127.97, 128.54, 129.16, 129.58, 130.07, 132.54, 134.49, 137.69, 137.76, 171.37, 172.42, 208.04;

m/z (ES) (Found: M⁺ + Na, 464.2187, C_{29}H_{31}NO_3Na requires M, 464.2197), [ES] (Found: M⁺ + 1, 442.2372, C_{29}H_{32}NO_3 requires M, 442.2377);

m/z (ES) 464 (M⁺ + 23, 100%).

(2E,8E,10E,12E,14E)-Methyl 8,10,12,14-tetramethylhexadeca-2,8,10,12,14-pentaenoate (338)

To a mixture of aldehyde 23 (0.27 g, 0.94 mmol), NaCN (0.046 g, 0.94 mmol) and activated MnO₂ (1.68 g, 18.7 mmol) stirring in THF (10 mL) at rt. was added MeOH (0.50 mL, 9.3 mmol). The reaction was heated to reflux (75 °C) and left overnight. The mixture was cooled to rt., filtered through celite, eluted with DCM (20mL) and the solvent removed under reduced pressure. The mixture was washed with water (2 x 30 mL) and the aqueous phase extracted with DCM (3 x 30 mL). The organic layers were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (30:1, light petroleum:ether) gave the title compound 338 (0.127 g, 43%) as a yellow oil.
There are anomalies in the \(^1\)H n.m.r. spectra at 8-CH\(_3\), 10-CH\(_3\), 12-CH\(_3\), 9-H, 13-H and 15-H.

R\(_f\) 0.55, (4:1 Petroleum ether:Diethyl ether);

\(\nu\)\(_{\text{max}}\)/cm\(^{-1}\): 2931, 2855, 1724, 1657, 1435, 1268, 1175, 1032, 978, 899;

\(\delta\)\(_{\text{H}}\) (500 MHz, C\(_6\)D\(_6\)): 1.09-1.17 (2 H, m, 5-H\(_2\)), 1.18-1.26 (2 H, m, 6-H\(_2\)), 1.59 (3 H, d, J 6.6, 16-H\(_3\)), 1.71 (3 H, s, 14-CH\(_3\)), 1.74 (3 H, dd, J 1.3, 3.2, 12-CH\(_3\)), 1.77-1.83 (3 H, m, 10-CH\(_3\)), 1.86-1.91 (3 H, m, 8-CH\(_3\)), 1.92-1.99 (4 H, m, 4-H\(_2\) and 7-CH\(_2\)), 3.41 (3 H, s, OCH\(_3\)), 5.48 (1 H, quintet, J 6.6, 15-H), 5.78 (1 H d, J 7.3, 9-H), 5.84 (1 H dt, J 2.8, 15.8, 2-H), 5.92 (1 H, s, 11-H), 6.00 (1 H, d, J 9.5, 13-H), 7.01 (1 H, dt, J 2.8, 15.8, 3-H);

\(\delta\)\(_{\text{C}}\) (125 MHz, C\(_6\)D\(_6\)): 13.84, 16.95, 17.91, 19.29, 19.50, 27.87, 32.18, 40.68, 50.92, 121.52, 124.27, 124.75, 130.64, 132.46, 133.47, 133.96, 134.27, 135.73, 136.02, 149.27, 166.58;

m/z (ES) (Found: \(M^+1\), 317.2464, C\(_{21}\)H\(_{33}\)O\(_2\) requires \(M\), 317.2476);

m/z (ES) 315 (\(M^+\cdot 1\), 20%), 313 (\(M^+\cdot 3\), 100).

\((2E,8E,10E,12E,14E)-1-(1H-imidazol-1-yl)-8,10,12,14-tetramethylhexadeca-2,8,10,12,14-pentaenoic acid (337)\)

To a solution of methyl ester 338 (0.10 g, 0.32 mmol) in THF (1.6 mL) at rt. under nitrogen was added LiOH (0.090 g, 3.8 mmol) in H\(_2\)O (1.6 mL) and the mixture stirred at rt. for 26 hours. The reaction mixture was acidified to pH 5 by adding 1M HCl dropwise and the organic fraction extracted with EtOAc (3 x 10 mL), washed with water (10 mL), brine (10 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated under reduced pressure to give the title compound 337 as a yellow oil, (0.092 g, 96%).

There were anomalies in the \(^1\)H n.m.r. spectra at 4-H\(_2\) and 7-H\(_2\).
Rf 0.42, (1:1, light petroleum:ether);

ν\text{max}/\text{cm}^{-1}, 2930, 2860, 1699, 1650, 1438, 1378, 1284, 1094, 898, 686;

δ\text{H} (500 MHz, C\text{6}D\text{6}), 1.00-1.07 (2 H, m, 5-H\text{2}), 1.08-1.14 (2 H, m, 6-H\text{2}), 1.53 (3 H, d, J 6.8, 16-H\text{3}), 1.64 (3 H, s, 8-CH\text{3}), 1.70 (2 H, s, 4-H\text{2}), 1.73 (2 H, s, 7-H\text{2}), 1.86 (3 H, s, 14-CH\text{3}), 1.89 (3 H, s, 12-CH\text{3}), 1.92 (3 H, s, 10-CH\text{3}), 5.43 (1 H, q, J 6.8, 15-H), 5.71 (1 H, d, J 14.1, 2-H), 5.88 (1 H, s, 9-H), 5.96 (1 H, s, 11-H), 5.96 (1 H, s, 13-H), 6.95 (1 H dt, J 6.8, 15.4, 3-H), 10.19 (1 H, br s, OH);

δ\text{C} (125 MHz, C\text{6}D\text{6}), 12.50, 15.59, 16.62, 17.90, 18.12, 26.24, 26.38, 30.84, 39.32, 120.09, 123.37, 128.33, 131.06, 131.96, 132.11, 132.57, 134.29, 148.00, 150.93, 171.44;

m/z (ES) (Found: M\text{+} - 1, 301.2179, C\text{20}H\text{29}O\text{2} requires M, 301.2173);

m/z (ES) 301 (M\text{+} - 1, 90%), 325 (M\text{+}+23, 100).

(5R)-1-\text{tert}-\text{Butyloxycarbonyl}-5-benzyl-3-[(2E,6Z)-1-hydroxynona-2,6-dien-1-yl]-2-oxopyrrolidine (343)

Pyrrolidinone 292 (0.50 g, 1.8 mmol) in THF (6 mL) was added dropwise to a solution of THF (15.3 mL) and LiHMDS (1.0 M in THF, 3.8 mL, 3.8 mmol) at 0 °C then stirred for 5 minutes. The reaction mixture was cooled to -78 °C and aldehyde 341 (0.25 g, 1.8 mmol) in THF (4 mL) was added dropwise. The resultant mixture was stirred at -78 °C for 1 hr. Saturated NH\text{4}Cl in MeOH (20 mL) was added at -78 °C and the mixture allowed to warm to rt. then diluted with EtO\text{2} (100 mL) and DCM (50 mL). The mixture was washed with water (2 x 50 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with saturated aqueous NH\text{4}Cl (2 x 100 mL), dried (Na\text{2}SO\text{4}), filtered and
concentrated under reduced pressure. Flash chromatography (2:1→1:1, light petroleum:ether) gave the title compound 343 (0.50 g, 67%) as a yellow oil. Three diastereoisomers in a 1:1:1 ratio. All peaks in the ¹H n.m.r. spectrum overlapped.

Rf 0.32, (1:1, light petroleum:ether); 
[α]²⁷° +33.9, (c = 1.0, EtOH); 
νmax/cm⁻¹, 3233, 2971, 2930, 2388, 2279, 1781, 1751, 1715, 1329, 1150, 812;
δH (500 MHz, C₆D₆), 0.97 (3 H, t, J 7.3, 9'-H₃), 1.60 [9 H, s, OC(CH₃)₃], 2.04 (2 H, q, J 7.3, 8'-H₂), 2.07-2.15 (4 H, m, 4'-H₂ and 5'-H₂), 2.39-2.43 (3 H, m, 3-H and 4-H₂), 2.45 (1 H, dd, J 8.2, 13.5, 5-CH), 3.10 (1 H, dd, J 8.2, 13.5, 5-CH'), 4.13 (1 H, dd, J 7.6, 7.9, 1'-H), 4.23 (1 H, m, 5-H), 5.41 (1 H, dt, J 6.9, 15.8, 3'-H), 5.43 (1 H, dd, J 6.9, 15.8, 2'-H), 5.64 (1 H, m, 7'-H), 5.78 (1 H, m, 6'-H), 7.10-7.22 (5 H, m, ArH);
δC (125 MHz, C₆D₆), 14.38, 14.49, 20.88, 21.12, 21.37, 22.10, 25.27, 27.01, 27.11, 28.05, 28.07, 28.14, 30.46, 31.19, 32.62, 32.65, 39.17, 39.26, 39.71, 46.82, 48.06, 57.18, 57.26, 57.29, 58.69, 70.04, 74.02, 74.18, 82.11, 82.38, 82.77, 82.83, 106.00, 126.86, 126.89, 127.00, 127.37, 127.91, 128.15, 128.27, 128.53, 128.58, 128.66, 128.79, 128.84, 129.72, 129.88, 129.81, 130.19, 130.78, 131.48, 132.15, 132.54, 132.54, 137.77, 137.89, 137.93, 150.49, 150.62, 151.03, 172.20, 173.76, 175.68;
m/z (ES) (Found: M⁺, 436.2455, C₂₅H₃₅O₄Na requires M, 436.2459);
m/z (ES) 436 (M⁺ + 23, 100%).

(5R)-1-tert-Butyloxycarbonyl-5-benzyl-3-[(2E,6Z)-nona-2,6-dienoyl]-2-oxopyrrolidine (344)
To a solution of alcohol 343 (0.050 g, 0.12 mmol) in DCM (3.6 mL) at 0 °C was added DMP (0.056 g, 0.13 mmol) and the reaction stirred for 15 minutes at 0 °C. The mixture was then warmed to rt. and stirred for 2.5 hrs. The resultant mixture was filtered through a short pad of silica gel using diethyl ether as an eluent. The eluent was concentrated under reduced pressure. Flash chromatography (3:1, light petroleum:ether) gave the title compound 344 (0.028 g, 56%) as a yellow oil; Single diastereoisomer with enol.

Rf 0.59 (1:1, light petroleum:ether);
[α]23D +38.6, (c = 0.9, CHCl3);
νmax/cm⁻¹, 2863, 2930, 2864, 1776, 1713, 1681, 1649, 1368, 1298, 1256, 1236, 1016, 780, 701;
δH (400 MHz, C₆D₆), 0.74 (3 H t, J 7.6 9¨-H3), 1.38 [9 H, s, OC(CH₃)₃], 1.77 (2 H, dt, J 6.0, 7.6, 4¨-H2), 1.83-1.86 (2 H, m, 5¨-H2), 1.87 (2 H, q, J 7.6, 8¨-H2), 1.92 (1 H, m, 3-H), 1.96 (2 H, dd, J 2.8, 8.6, 4-H2), 2.09 (1 H, dd, J 9.8, 13.1, 5-CH), 3.13 (1 H, dd, J 3.3, 13.1, 5-CH¨), 4.06 (1 H, ddt, J 3.0, 8.8, 12.6, 5-H), 5.07 (1 H, dt, J 10.5, 7.6, 7¨-H), 5.21 (1 H, dt, J 10.5, 7.3, 6¨-H), 5.45 (1 H, dt, J 15.4, 7.6, 3¨-H), 6.59 (1 H, d, J 15.4, 2¨-H), 6.85-6.98 (5 H, m, ArH) 12.56 (1 H, s, 1¨-OHenol);
δC (100 MHz, C₆D₆), 13.04, 19.50, 23.52, 25.14, 26.77, 31.79, 39.29, 55.67, 80.97, 98.91, 121.02, 125.49, 126.88, 127.43, 128.29, 131.35, 136.31, 139.51, 160.97, 172.1, 188.97;
m/z (ES) (Found: M+, 411.2414, C₂₅H₃₃O₄N requires M, 411.2410);
m/z (ES) 412 (M+ +1, 100%).

(5S)-1-tert-Butyloxycarbonyl-5-benzyl-3-[(2E,6Z)-nona-2,6-dienoyl]-2-oxo-3-phenylselanylpyrrolidine (346)
A solution of LiHMDS in THF (1.0 M, 0.30 mL, 0.30 mmol) at -78 °C was added to pyrrolidinone 344 (0.082 g, 0.20 mmol) in THF (1 mL) at -78 °C under nitrogen. After 1 hr. at this temperature a cooled solution of PhSeCl (0.15 g, 0.79 mmol) in THF (0.6 mL) was added to the mixture then stirred at -78 °C for 2 hrs. Saturated ammonium chloride (2 mL) was added and the mixture allowed to warm to rt. Water was added (3 mL) and the organic fraction extracted with diethyl ether (3 x 5 mL). The organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (10:1→4:1, light petroleum:ether) gave the title compound 346 (0.062 g, 55%) as a yellow oil. Two diastereoisomers in a 1:1 ratio. All peaks in the ¹H n.m.r. spectrum overlapped.

Rf 0.27 (4:1, light petroleum:ether);
[α]₂⁸D +83.4, (c = 0.55, CHCl₃);
νmax/cm⁻¹, 3060, 2933, 2967, 1777, 1723, 1678, 1621, 1350, 1294, 1254, 1237, 1145, 999, 733, 690;
δH (400 MHz, CHCl₃), 0.90 (3 H t, J 7.5 9´-H₃), 1.53 [9 H, s, OC(CH₃)₃], 1.90-1.93 (2 H, m, 8´-H₂), 2.13-2.16 (2 H, m, 5´-H₂), 2.19-2.22 (2 H, m, 4-H₂), 2.29-2.32 (2 H, m, 4´-H₂), 2.35 (1 H, dd, J 2.5, 14.1, 5-CH), 3.03 (1 H, dd, J 3.1, 12.9, 5-CH'), 4.09 (1 H, ddt, J 3.0, 8.6, 10.8, 5-H), 5.28 (1 H, dt, J 10.9, 7.1, 6´-H), 5.36 (1 H, dt, J 10.9, 7.1, 7´-H), 7.01-7.04 (1 H, m, 2´-H), 7.05-7.49 (10 H, m, Ar-H ); 7.53-7.56 (1 H, m, 3´-H);
δC (100 MHz, CHCl₃), 10.95, 13.24, 13.27, 19.58, 24.77, 24.84, 26.68, 27.06, 27.87, 29.46, 31.71, 38.42, 38.89, 52.07, 55.26, 56.69, 57.88, 59.56, 82.79, 82.85, 124.98, 125.13, 125.69, 125.77, 126.32, 126.83, 127.57, 127.64, 128.21, 128.27, 128.32, 128.49, 128.86, 128.96, 129.03, 130.48, 131.80, 131.87, 133.53, 135.53, 135.77, 135.84, 135.98, 147.42, 147.90, 148.53, 148.64, 169.15, 187.96; m/z (ES) (Found: M⁺ + acetonitrile + NH₄, 627.1882, C₃₃H₄₀O₄SeN₂H₄ requires M, 627.1887); m/z (ES) 627 (M⁺ + 60, 100%), 568 (M⁺ + 1, 25).
(5R)-1-tert-Butyloxycarbonyl-5-benzyl-3-[(2E,8E,10E,12E,14E)-1-hydroxy-8,10,12,14-tetramethylhexadeca-2,8,10,12,14-pentaen-1-yl]-2-oxopyrrolidine (340)

Pyrrolidinone 292 (0.12 g, 0.42 mmol) in THF (1.4 mL) was added dropwise to a solution of THF (2.9 mL) and LiHMDS (1.0 M in THF), (0.73 mL, 0.73 mmol) at 0 °C and stirred at this temperature for 5 minutes. The reaction mixture was cooled to -78 °C then aldehyde 23 (0.10 g, 0.35 mmol) was added dropwise and the mixture stirred at -78 °C for 1 hr. Saturated NH₄Cl in MeOH (6 mL) was added at -78 °C and the mixture allowed to warm to rt. then diluted with EtO₂ (15 mL) and DCM (10 mL). The mixture was washed with water (20 mL) and extracted with diethyl ether (3 x 20 mL). The organic fraction was washed with saturated aqueous NH₄Cl (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (2:1→1:1, light petroleum:ether) gave the title compound 340 (0.163 g, 83%) as a yellow oil.

Rf 0.35, (1:1, light petroleum:ether);

[α]²⁴_D +35.2, (c = 1.0, CHCl₃);

ν_max/cm⁻¹, 3478, 2929, 2856, 1779, 1715, 1368, 1302, 1254, 1148, 1020, 972, 739, 699;

δ_H (400 MHz, C₆D₆), 1.12-1.24 (2 H, m, 6´-H₂), 1.24-1.28 (2 H, m, 5´-H₂), 1.37 [9 H, s, OC(CH₃)₃], 1.48 (3 H, d, J 6.8, 16´-H₃), 1.60 (3 H, s, 8´-CH₃), 1.67-1.71 (6 H, m, 4-H₂, 4´-H₂ and 7´-H₂), 1.72-1.79 (1 H, m, 3-H), 1.81 (3 H, s, 10´-CH₃), 1.84 (3 H, s, 12´-CH₃), 1.87 (3 H, s, 14´-CH₃), 2.23 (1 H, dd, J 9.8, 13.1, 5-CH₂), 2.86 (1 H, dd, J 3.3, 13.1, 5-CH´), 3.90 (1 H, dd, J 7.3, 7.8, 1´-H), 4.27 (1 H, m, 5-H), 5.28 (1 H,
dd, $J 6.7, 15.4, 2'$-H), 5.38 (1 H, q, $J 6.8, 15'$-H), 5.54 (1 H, dt, $J 15.4, 6.8, 3'$-H), 5.72 (1 H, s, 9'-H), 5.82 (1 H, s, 11'-H), 5.90 (1 H, s, 13'-H), 6.85-6.98 (5 H, m, ArH);

$\delta $C (100 MHz, C$_6$D$_6$), 13.85, 13.89, 13.91, 15.62, 16.96, 17.00, 17.98, 18.06, 19.33, 19.40, 19.54, 21.38, 25.34, 27.85, 28.06, 28.09, 28.15, 29.11, 29.16, 31.19, 32.42, 39.21, 39.28, 40.87, 40.92, 46.87, 57.24, 58.67, 74.23, 77.73, 82.09, 82.77, 124.23, 124.73, 126.86, 127.02, 127.79, 127.91, 128.03, 128.15, 128.27, 128.79, 128.86, 128.93, 129.62, 129.72, 129.95, 130.59, 132.50, 133.13, 133.45, 133.99, 134.23, 134.46, 136.06, 136.35, 137.73, 137.91, 150.52, 151.08, 172.06, 175.67;

$m/z$ (ES) (Found: M$^+$ + Na, 584.3735, C$_{36}$H$_{51}$NO$_4$Na requires M, 584.3711); $m/z$ (ES) 560 (M$^+$ - 1, 10%), 584 (M$^+$ + 23, 50).

**((6-bromohexyl)oxy)(tert-butyl)dimethylsilane (353)**

![Chemical Structure](image_url)

To a stirred solution of 6-bromohexan-1-ol 352 (5.0 g, 27 mmol) in DCM (150 mL) at 0 °C was added imidazole (5.6 g, 83 mmol). To this was added (tert-butyl)dimethylsilane chloride (6.24 g, 41.4 mmol) and the mixture was allowed to warm to rt. then stirred for 1 hr. Water (120 mL) and DCM (120 mL) were added and the organic layer separated. The aqueous layer was extracted with DCM (3 x 50 mL) and the organic layers washed with brine (120 mL), dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. Flash chromatography (20:1, light petroleum:ether) gave the **title compound 353** (7.76 g, 95%) as a pale green oil.

R$_f$ 0.75 (4:1, light petroleum:ether);

$\nu_{\text{max}}$/cm$^{-1}$, 2930, 2856, 1462, 1387, 1360, 1252, 1098, 1006, 937, 833, 773, 660; $\delta $H (400 MHz, C$_6$D$_6$), 0.00 [6 H, s, Si(CH$_3$)$_2$], 0.93 [9 H, s, SiC(CH$_3$)$_3$], 1.05-1.12 (4 H, m, 3-H$_2$ and 4-H$_2$), 1.31 (2 H, tt, $J 6.6, 13.1, 2$-H$_2$), 1.41 (2 H, tt, $J 6.6, 13.4, 5$-
H$_2$), 2.88 (2 H, t, J 6.8, 6-H$_2$), 3.40 (2 H, t, J 6.3, 1-H$_2$);
$\delta$C (100 MHz, C$_6$D$_6$); -5.11, 18.51, 25.29, 26.16, 28.10, 32.84, 32.94, 33.61, 63.05;
m/z (ES) (Found: M$^+$ + 1, 295.1012, C$_{12}$H$_{27}$BrOSi requires M, 295.1016);
m/z (ES) 295 (M$^+$ + 1, 78%).

**tert-Butyldimethyl(((8E,10E,12E,14E)-8,10,12,14-tetramethylhexadeca-8,10,12,14-tetraen-1-yl)oxy)silane (354)**

![Chemical Structure](image)

[(6-Bromohexyl)oxy][(tert-butyldimethyl)silane 353 (7.70 g, 26.1 mmol) was dissolved in anhydrous THF (26 mL) and slowly added to magnesium turnings (1.27 g, 52.1 mmol) in THF (9 mL) under nitrogen and heated under reflux for 2 hrs. The mixture was cooled to -78 °C and CuLi$_2$Cl$_4$ (5.2 mL) was added followed by tetraene acetate 258 (3.24 g, 13.0 mmol) in THF (13 mL). The mixture was warmed to rt. and stirred overnight under nitrogen. The mixture was concentrated under reduced pressure and poured into water (30 mL), which produced a thick suspension. The organic fraction was extracted with diethyl ether by repeatedly diluting 2 mL of the suspension in water (200 mL) and extracting each of these fractions with diethyl ether (200 mL). The organic extracts were washed with water (200 mL), brine (200 mL), dried (Na$_2$SO$_4$), filtered and the organic fractions concentrated under reduced pressure. Flash chromatography (100:1, light petroleum:ether) gave the **title compound 354** (4.40 g, 84%) as a yellow oil.

R$_f$ 0.81 (10:1, light petroleum:ether);
$v_{\text{max}}$/cm$^{-1}$, 2928, 2856, 1463, 1386, 1254, 1098, 1006, 883, 773, 661;
$\delta$H (500 MHz, C$_6$D$_6$), 0.00 [6 H, s, Si(CH$_3$)$_2$], 0.91 [9 H, s, SiC(CH$_3$)$_3$], 1.27 – 1.33 (4 H, m, 4-H$_2$ and 5-H$_2$), 1.35 – 1.41 (2 H, m, 6-H$_2$), 1.42 – 1.50 (4 H, m, 2-H$_2$ and 3-H$_2$), 1.53 (3 H, d, J 6.9, 16-H$_3$), 1.64 (3 H, s, 8-CH$_3$), 1.76 (3 H, s, 14-CH$_3$), 1.88 (3 H, t, J 6.8, 6-H$_2$), 3.40 (2 H, t, J 6.3, 1-H$_2$); $\delta$C (100 MHz, C$_6$D$_6$); -5.11, 18.51, 25.29, 26.16, 28.10, 32.84, 32.94, 33.61, 63.05; m/z (ES) (Found: M$^+$ + 1, 295.1012, C$_{12}$H$_{27}$BrOSi requires M, 295.1016); m/z (ES) 295 (M$^+$ + 1, 78%).
H, s, 12-CH₃), 1.92 (3 H, s, 10-CH₃), 1.98 (2 H, t, J 7.6, 7-H₂), 3.49 (2 H, t, J 6.3, 1-H₂), 5.42 (1 H, q, J 6.9, 15-H), 5.79 (1 H, s, 9-H), 5.94 (2 H, s, 11-H and 13-H);
δC (125 MHz, C₆D₆), -4.90, 13.86, 16.94, 18.09, 18.52, 21.63, 23.04, 25.92, 28.49, 29.73, 29.76, 29.88, 33.23, 41.14, 63.30, 124.61, 130.48, 132.52, 133.49, 134.01, 134.14, 134.37, 136.53;
m/z (EI) (Found: M⁺, 404.3461, C₂₆H₄₈O₅Si requires M⁺, 404.3469);
m/z (EI) 404 (M⁺, 100%).

(8E,10E,12E,14E)-8,10,12,14-tetramethylhexadeca-8,10,12,14-tetraen-1-ol (355)

To a solution of tetraene 354 (4.40 g, 10.9 mmol) in anhydrous THF (108 mL) was added TBAF in THF (1.0 M, 32.6 mL) and stirred at 0 °C for 1 hr. Then at rt. for 2 hours. An aqueous phosphate buffer (pH 7, 100 mL) was added to the reaction mixture and the organic fraction extracted with diethyl ether (4 x 50 mL). The organic extracts were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (10:1→4:1, light petroleum:ether) gave the title compound 355 (2.42 g, 77%) as a yellow/green oil.

Rf 0.19 (10:1, light petroleum:ether);
νmax/cm⁻¹: 3326, 2927, 2854, 2360, 1708, 1438, 1376, 1251, 1025, 875, 834, 773, 668;
δH (400 MHz, C₆D₆), 0.87 (1 H, s, OH), 1.20 (6 H, br s, 4-H₂, 5-H₂ and 6-H₂), 1.32 – 1.42 (4 H, m, 2-H₂ and 3-H₂), 1.56 (3 H, d, J 6.8, 16-H₃), 1.67 (3 H, s, 8-CH₃), 1.80 (3 H, s, 14-CH₃), 1.92 (3 H, s, 12-CH₃), 1.96 (3 H, s, 10-CH₃), 2.01 (2 H, t, J 7.8, 7-H₂), 3.34 (2 H, t, J 7.0, 1-H₂), 5.46 (1 H, q, J 6.8, 15-H), 5.84 (1 H, s, 9-H), 5.98 (1 H, s, 11-H), 5.98 (1 H, s, 13-H);
Solid TPAP (0.0060 g, 0.017 mmol) was added to a stirred mixture of alcohol 355 (0.10 g, 0.34 mmol), NMO (0.060 g, 0.52) and 4Å molecular sieves (0.20 g) in DCM:CH₃CN (9:1) (1 mL) at rt. under nitrogen. The mixture was concentrated under reduced pressure, diluted with DCM (2 mL), filtered through silica and eluted with EtOAc (3 x 3 mL) and DCM (2 x 3 mL). The filtrate was concentrated under reduced pressure. Flash chromatography (80:1, light petroleum:ether) gave the title compound 349 (0.059 g, 59%) as a pale green liquid.

Rf 0.52 (4:1, light petroleum:ether);
ν_max/cm⁻¹, 2927, 2855, 2714, 1725, 1642, 1441, 1377, 1173, 1094, 1023, 901, 726, 691;
δ_H (400 MHz, C₆D₆), 0.93 – 1.07 (4 H, m, 5-H₂ and 6-H₂), 1.17 – 1.31 (4 H, m, 3-H₂ and 4-H₂), 1.52 (3 H, d, J 7.0, 16-H₃), 1.64 (3 H, s, 8-CH₃), 1.74 (3 H, s, 10-CH₃), 1.76 (3 H, s, 12-CH₃), 1.89 (3 H, s, 14-CH₃), 1.93-1.98 (4 H, m, 7-H₂ and 2-H₂), 5.42 (1 H, q, J 7.0, 15-H), 5.79 (1 H, s, 9-H), 5.95 (2 H, s, 11-H and 13-H), 9.24 (1 H, s, CHO);
δ_C (100 MHz, C₆D₆), 12.50, 15.56, 16.69, 18.01, 18.16, 20.80, 26.82, 27.90, 27.93, 39.65, 42.40, 123.35, 129.18, 131.08, 132.05, 132.59, 132.86, 133.09, 134.99, 199.32;
m/z (ES) (Found: M+ - 1, 287.2450, C20H32O requires M, 287.2454);
im/z (ES) 287 (M+ - 1, 100%), 289 (M+ + 1, 30).

\((5R)-1\text{-}\text{tert-butyloxycarbonyl}-5\text{-}\text{benzyl}-3\text{-}[(8E,10E,12E,14E)-6\text{-}\text{hydroxy}-8,10,12,14\text{-}\text{tetramethylhexadeca}-8,10,12,14\text{-}\text{tetraen}-1\text{-}\text{yl}]-2\text{-}\text{oxopyrrolidine} \) (356)

To LiHMDS in THF (1.0 M, 1.59 mL, 1.59 mmol) and THF (6.4 mL) at 0 °C, pyrrolidinone 292 (0.25 g, 0.91 mmol) in THF (3.0 mL) was added dropwise and stirred at 0 °C for a further 5 minutes. The reaction was cooled to -78 °C then aldehyde 349 (0.22 g, 0.76 mmol) in THF (2.2 mL) was added dropwise and the mixture stirred at -78 °C for 1 hr. Saturated NH₄Cl in MeOH (10 mL) was added and the reaction mixture diluted with diethyl ether (20 mL) and DCM (15 mL). The mixture was washed with water (30 mL) and extracted with diethyl ether (3 x 30 mL). The organic layer was washed with saturated aqueous NH₄Cl (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (2:1→1:1, light petroleum:ether) gave the title compound 356 (0.183 g, 83%) as a green oil.

Rf 0.19 (1:1, light petroleum:ether);
\([\alpha]^{30}_D +1.7 \ (c = 0.25, \text{EtOH})\);
\(\nu_{\text{max}}/\text{cm}^{-1} \), 3529, 2975, 2929, 2855, 1779, 1748, 1713, 1366, 1350, 1302, 1256, 1148, 849, 778, 701;
\(\delta_H \) (500 MHz, C₆D₆), 0.73 – 0.79 (2 H, m, 4-H₂), 1.11 – 1.27 (8 H, m, 3′-H₂ and 4′-H₂ and 5′-H₂ and 6′-H₂), 1.42 [9 H, s, OC(CH₃)₃], 1.41 (3 H, d, J 6.6, 16′-H₃), 1.64 (3 H, s, 10′-CH₃), 1.66 – 1.72 (2 H, m, 2′-H₂), 1.76 (3 H, s, 8′-CH₃), 1.88 (3 H, s,
(S)-2-amino-3-phenylpropan-1-ol (363)

Lithium aluminium hydride (2.30 g, 60.1 mmol) was suspended in THF (100 mL) at rt. L-Phenylalanine 299 (5.0 g, 30 mmol) was added slowly in small portions. The reaction mixture was heated at reflux overnight then cooled to rt. Saturated K₂CO₃ (aq) was added slowly. The mixture was filtered and the solvent evaporated under reduced pressure to give the title compound 363 (3.32 g, 77%), as a white solid.

m.p. 88.2 °C;
Rᶠ 0.03 (1:2, light petroleum:EtOAc);
[α]²⁸D -19.3 (c = 1.0, EtOH);
ν max/cm⁻¹, 3354, 3296, 3022, 2917, 2873, 2818, 1575, 1492, 1452, 1337, 1121, 1088, 1063, 961, 833, 752, 696;
δ H (500 MHz, CDCl₃), 2.05 (2 H, br s, NH₂), 2.44 (1 H, dd, J 8.8, 13.6, 3-H), 2.72 (1 H, dd, J 5.0, 13.6, 3-H’), 3.04 (1 H, dddd, J 3.8, 5.0, 8.8, 13.6, 2-H), 3.31 (1 H, dd, J
7.3, 10.7, 1-H), 3.56 (1 H, dd, J 4.1, 10.7, 1-H'), 7.10 – 7.25 (5 H, m, ArH); 
δC (125 MHz, CDCl3), 40.90, 54.30, 66.20, 126.43, 128.70, 129.26, 138.70; 
m/z (ES) (Found: M+ + 1, 152.1068, C9H14NO requires M, 152.1070); 
m/z (ES) 192 (M+ + 41, 100%), 152 (M+ + 1, 5).

(5)-1-tert-butyldimethylsilyloxy-3-phenylprop-2-ylamine (364)

To alcohol 363 (3.0 g, 19 mmol) in DCM (80 mL) at 0 °C was added imidazole (4.05 g, 59.6 mmol). To this was added TBSCl (4.50 g, 29.8 mmol) and the mixture allowed to warm to rt. then stirred for 2 hrs. Water (100 mL) and DCM (100 mL) were added and the organic fraction separated. The aqueous layer was extracted with DCM (3 x 50 mL). The organic fraction was washed with brine (100 mL), dried (Na2SO4), filtered and concentrated under reduced pressure. Flash chromatography (2:3, light petroleum:EtOAc) gave the title compound 364 (2.98 g, 58%) as clear oil.

Rf 0.23 (1:2, light petroleum:EtOAc);
[α]26D -2.7 (c = 1.0, EtOH);
νmax/cm⁻¹, 2960, 2931, 2852, 1601, 1569, 1496, 1474, 1358, 1250, 1092, 906, 835, 776, 729, 699;
δH (400 MHz, CDCl3), 0.00 [6 H, s, Si(CH3)2], 0.85 [9 H, s, Si(CH3)3], 1.51 (2 H, br s, NH2), 2.46 (1 H, dd, J 8.3, 13.4, 3-H), 2.73 (1 H, dd, J 5.3, 13.4, 3-H'), 3.03 (1 H, m, 2-H), 3.38 (1 H, dd, J 6.6, 9.8, 1-H), 3.52 (1 H, dd, J 4.3, 9.8, 1-H'), 7.12-7.27 (5 H, m, ArH);
δC (100 MHz, CDCl3), -5.35, 18.30, 25.93, 40.41, 54.37, 67.44, 126.23, 128.45, 129.28, 139.19;
m/z (ES) (Found: M⁺ + Na, 288.1756, C₁₅H₂₇NOSiNa requires M, 288.1755);
m/z (ES) 266 (M⁺ + 1, 100%).

(S)-(1-tert-butyldimethylsilyloxy-3-phenylpropan-2-yl) benzamide (365)

To amine 364 (2.10 g, 7.92 mmol) in pyridine (20 mL) at rt. was added benzoyl chloride (1.0 mL, 8.7 mmol) and the mixture stirred overnight. The precipitate was filtered through a silica plug then washed with EtOAc (10 mL) and DCM (10 mL). The mixture was concentrated under reduced pressure and the residue dissolved in EtOAc (2 x 20 mL), washed with saturated aqueous NaHCO₃ (20 mL) and extracted with EtOAc (2 x 20 mL). The organic fraction was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (8:1, light petroleum:EtOAc) gave the title compound 365 (2.75 g, 95%) as a white solid.

m.p. 58.2 °C
R_f 0.62 (1:1, light petroleum:ether);
[α]²⁶D -51.8 (c = 1.0, EtOH);
ν_max/cm⁻¹, 3297, 2952, 2926, 2854, 2360, 2339, 1633, 1597, 1537, 1485, 1470, 1251, 1084, 905, 833, 775, 728, 699;
δ_H (500 MHz, CDCl₃), 0.00 (3 H, s, SiCH₃), 0.02 (3 H, s, SiCH₃), 0.89 [9 H, s, Si(CH₃)₃], 2.89 (1 H, dd, J 8.5, 13.3, 3-H), 2.96 (1 H, dd, J 6.0, 13.5, 3-H'), 3.57 (2 H, d, J 3.5, 1-H₂), 4.34 (1 H, dddd, J 3.5, 6.3, 8.3, 13.7, 2-H), 6.42 (1 H, d, J 8.2, NH), 7.14-7.46 (8 H, m, CH₂ArH and OCArH), 7.65-7.69 (2 H, m, OCArH);
δ_C (125 MHz, CDCl₃), -5.37, -3.56, 18.27, 25.91, 37.09, 51.95, 62.45, 126.48, 126.77, 128.49, 128.62, 129.50, 131.42, 134.75, 138.11, 166.68;
m/z (ES) (Found: M$^+$ + 1, 370.2198, C$_{22}$H$_{32}$NO$_2$Si requires M, 370.2197); m/z (ES) 370 (M$^+$ + 1, 100%).

*N*-acetyl-*N*-[(S)-1-tert-butyldimethylsilyloxy-3-phenylpropan-2-yl]benzamide (362)

![Chemical Structure](image)

Amide 365 (0.22 g, 0.59 mmol), acetyl chloride (0.14 mL, 1.8 mmol) and pyridine (0.15 mL, 1.8) in DCM (6 mL) was stirred for 6 days at rt. The white precipitate (pyridine hydrochloride) was separated by filtration. The mixture was concentrated under reduced pressure and the residue treated with saturated aqueous NaHCO$_3$ (5 mL). The aqueous solution was extracted with DCM (5 x 5 mL) and the organic extracts washed with water (20 mL), brine (20 mL), dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. Flash chromatography (10:1, light petroleum:ether) gave *the title compound* 362 (0.13 g, 58%) as clear oil.

R$_f$ 0.88 (1:1, light petroleum:ether);

[α]$^{24D}$ -17.2 (c = 1.35, EtOH);

ν$_{max}$/cm$^{-1}$, 2950, 2927, 2852, 1697, 1659, 1471, 1360, 1309, 1232, 1106, 1005, 835, 776, 698,

δ$_H$ (500 MHz, CDCl$_3$), -0.02 (3 H, s, SiCH$_3$), 0.00 (3 H, s, SiCH$_3$), 0.83 [9 H, s, SiC(CH$_3$)$_3$], 1.81 (3 H, s, COCH$_3$), 2.96 (1 H, dd, J 5.7, 13.8, 3-H), 3.18 (1 H, dd, J 10.4, 13.6, 3-H$'$), 3.78 (1 H, dd, J 5.7, 10.9, 1-H), 4.16 (1 H, t, J 9.8, 2-H), 4.73 (1 H, br s, 1-H$'$), 7.10-7.28 (9 H, m, C$_2$H$_2$ArH and OCArH), 7.39-7.44 (1 H, m, OCArH);

δ$_C$ (125 MHz, CDCl$_3$), -5.47, 18.26, 25.87, 27.14, 35.05, 63.51, 126.55, 128.38, 128.49, 128.83, 129.40, 132.11, 136.51, 138.21, 174.48, 174.75;
To hexanoic acid (3.0 g, 26 mmol) in THF (300 mL) was added carbonyl di-imidazole (4.6 g, 28 mmol). The resultant mixture was stirred at rt for 4 hours. The mixture was concentrated under reduced pressure and the residue dissolved in diethyl ether (200 mL), then washed sequentially with saturated aqueous NH₄Cl (100 mL), saturated aqueous NaHCO₃ (100 mL) and brine (100 mL). The organic fraction was dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound 367 (4.1 g, 95%) as a colourless oil.

\[ \text{R}_f \ 0.16 \ (3:1, \ \text{light petroleum:ether}); \]

\[ \nu_{\text{max}}/\text{cm}^{-1}, 3158, 3133, 3108, 2956, 2930, 2868, 1735, 1524, 1470, 1390, 1321, 1221, 1099, 961, 759, 652; \]

\[ \delta_H \ (500 \text{ MHz, CDCl}_3), \ 0.91 \ (3 \text{ H, t, } J 7.3, 6\text{-H}_3), \ 1.37 \ (4 \text{ H, m, 4\text{-H}_2 \text{ and 5\text{-H}_2}), \ 1.79-1.83 \ (2 \text{ H, m, 3\text{-H}_2}), \ 2.85 \ (2 \text{ H, t } J 7.6, 2\text{-H}_2), \ 7.08 \ (1 \text{ H, dd, } J 0.9, 1.6, 5\text{'-H}), \ 7.47 \ (1 \text{ H, dd, } J 1.3, 1.6, 4\text{'-H}), \ 8.16 \ (1 \text{ H, br s, 2\text{'-H}}); \]

\[ \delta_C \ (125 \text{ MHz, CDCl}_3), 14.04, 22.54, 23.86, 31.22, 35.38, 116.19, 130.92, 136.21, 169.63; \]

\( m/z \) (ES) (Found: M⁺ + Na, 434.2129, C₂₄H₃₃NO₃Na, requires M, 434.2122); \( m/z \) (ES) 412 (M⁺ + 1, 100%).
**N-tert-butyloxycarbonyl-[(S)-1-tert-butyldimethylsilyloxy]-3-phenylpropan-2-yl (373)**

![Chemical Structure](https://example.com/structure.png)

To amine 364 (0.25 g, 0.94 mmol) in a 1:1 mixture of THF:H₂O (3 mL) was added NaOH (0.080 g, 2.1 mmol) at 0 °C. This was followed by the slow addition of Boc anhydride (0.25 g, 1.1 mmol) and the mixture stirred at rt. overnight. The mixture was concentrated under reduced pressure and the aqueous fraction acidified to pH 4 with aqueous hydrogen chloride (1.0 M). The aqueous solution was extracted with DCM (3 x 5 mL) and the organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (5:1, light petroleum:ether) gave the title compound 373 (0.241 g, 70%), as pale yellow oil.

R<sub>f</sub> 0.78 (5:1, light petroleum:ether);

[α]<sup>22</sup> <sub>D</sub> -27.3 (c =0.55, EtOH);

ν<sub>max</sub>/cm<sup>-1</sup>, 3353, 2958, 2928, 2855, 1678, 1527, 1454, 1358, 1291, 1248, 1170, 1118, 832, 697;

δ<sub>H</sub> (500 MHz, CDCl₃), 0.05 [6 H, s, Si(CH₃)₂], 0.93 [9 H, s, SiC(CH₃)₃], 1.42 [9 H, s, OC(CH₃)₃], 2.84 (2 H, d, J 7.6, 1-H₂), 3.51 (2 H, d, J 4.1, 3-H₂), 3.84 (1 H, m, 2-H), 4.77 (1 H, br d, J 8.2, NH), 7.20-7.31 (5 H, m, Ar-H);

δ<sub>C</sub> (125 MHz, CDCl₃), -5.42, 18.29, 25.92, 28.41, 37.34, 53.03, 62.86, 79.17, 126.26, 128.35, 129.47, 138.40, 155.38;

m/z (ES) (Found: M⁺ + Na, 388.2286, C₂₀H₃₅NO₃NaSi, requires M, 388.2278);
m/z (ES) 366 (M⁺ + 1, 100%).
N-[(S)-1-tert-butyldimethylsilyloxy]-3-phenylpropan-2-yl acetamide (374)

Amine 364 (1.61 g, 6.07 mmol) in DCM (10 mL) and triethylamine (1.60 mL, 15.8 mmol) were cooled to 0 °C. Acetyl chloride (0.52 mL, 6.7 mmol) was added dropwise and the mixture stirred for 2 hrs at 0 °C. Water was poured into the mixture and the organic fraction separated. The aqueous fraction was extracted with EtOAc (3 x 10 mL) and the organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (1:1, light petroleum:EtOAc) gave the title compound 374 (1.59 g, 85%) as colourless oil.

Rf 0.23 (1:1, light petroleum:ether);
[α]₂₈D -12.3 (c =1.0, CDCl₃);
νmax/cm⁻¹, 2954, 2929, 2857, 1694, 1360, 1260, 1228, 1180, 1107, 1070, 835, 776, 667;
δH (500 MHz, CDCl₃), -0.03 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃), 0.87 [9 H, s, SiC(CH₃)₃], 2.17 (3 H, s, OCCH₃), 2.91 (1 H, dd, J 5.4, 13.0, 3-H), 3.27 (1 H, dd, J 10.1, 13.8, 3-H'), 3.38 (1 H, dd, J 4.7, 10.1, 1-H), 4.11 (1 H, m, 2-H), 4.42 (1 H, dd, J 8.8, 10.1, 1-H'), 5.66 (1 H, d, J 8.3, NH), 7.12-7.31 (5 H, m, ArH);
δC (125 MHz, CDCl₃), -5.56, 18.09, 25.78, 34.68, 63.54, 63.90, 77.24, 126.73, 128.70, 129.02, 138.54, 174.97;
m/z (ES) (Found: M⁺ + Na, 330.1194, C₁₇H₂₉NO₂NaSi, requires M, 330.1198);
m/z (ES) 330 (M⁺ + 23, 100%).
To amide 374 (0.30 g, 1.0 mmol) in THF/H₂O (1:1), (10mL) was added sodium hydroxide (0.090 g, 2.8 mmol) at 0 °C. This was followed by the slow addition of Boc-anhydride (0.27 g, 1.2 mmol). The mixture was stirred at 0 °C for 30 minutes then stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the aqueous fraction washed with DCM (2 x 5 mL). The aqueous fraction was acidified to pH4 with aqueous hydrogen chloride (1.0 M) then extracted with DCM (2 x 10 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography (10:1, light petroleum:ether) gave the title compound 372 (0.33 g, 78%) as colourless oil.

Rf 0.58 (2:1, light petroleum:ether);
[α]²⁸D -17.0 (c =0.5, EtOH);

$ν_{\text{max}}$/cm⁻¹, 2955, 2930, 2858, 1808, 1772, 1695, 1369, 1260, 1229, 1181, 1113, 1065, 836, 775, 667;

$δ$H (500 MHz, CDCl₃), -0.03 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃), 0.83 [9 H, s, SiC(CH₃)₃], 1.50 [9 H, s, OC(CH₃)₃], 2.14 (3 H, s, OCCH₃), 2.87 (1 H, dd, J 5.0, 13.6, 3-H), 3.23 (1 H, dd, J 10.1, 13.6, 3-H'), 3.76 (1 H, dd, J 4.7, 10.1, 1-H), 4.07 (1 H, dddd, J 4.7, 9.8, 10.1, 13.8, 2-H), 4.18 (1 H, dd, J 8.8, 9.8, 1-H'), 7.07-7.28 (5 H, m, ArH);

$δ$C (125 MHz, CDCl₃), -5.59, 18.13, 25.71, 27.12, 27.49, 34.62, 63.57, 63.91, 85.20, 126.70, 128.65, 129.41, 139.14, 146.71, 175.01;

$m/z$ (ES) 407 (M⁺ 20%).
Chapter 8

References


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79. E. Fischer and A. Speier, Chemische Berichte, 1895, 28, 3252-3258.
90. Du Haifeng and Ding Kuiling, *2010, 1*, Handbook of Cyclization Reactions, 1-57
Appendix 1

Stereochemical issues relating to the IMDA reaction of tetraene 23

*Intramolecular* Diels Alder reactions are known to be governed by steric considerations\textsuperscript{103, 119} rather than the *endo*-rule, as is the case for *intermolecular* reactions, because in an *intra*molecular reaction the molecule folds up in the sterically most favoured way. For our sterically hindered tetraene 23 an IMDA reaction is fundamental to achieving the total synthesis of diaporthichalasin whether by the biomimetic route or indeed by the stepwise construction of the isoindolone unit and the 13-membered tricyclic ring system.

The *intra*molecular Diels Alder reaction is a [4+2] cycloaddition reaction where bonding overlap on two reacting centres results in two carbon-carbon σ-bonds and one π-bond being formed from three carbon-carbon π-bonds in what is generally a kinetic and irreversible reaction that proceeds under thermal conditions (Figure 49).

The reaction can be explained by FMO theory.\textsuperscript{120} The HOMO of the diene and the LUMO of the dienophile are close in energy with the diene normally being electron rich, often with the assistance of an electron donating group, (EDG) and the dienophile electron deficient. Electron deficiency is accomplished by addition of an electron withdrawing substituent (EWG), such as a carbonyl or nitrile. This has the effect of lowering the energy of the dienophile, which in effect activates the dienophile (Figure 54, page 216).

![Figure 53 Schematic Diels Alder reaction](image-url)
The interacting orbitals are shown on the right of Figure 53 (page 215) with the light and dark shades reflecting the two different signs. The size of the orbital depicts the size of the orbital coefficient, which is a measure of the electron population around the atom. The two atoms which have the largest coefficient of the frontier molecular orbital will advance more readily to transition-state bonding.

![Energy Diagram]

**Figure 54** FMO relationship between the dienophile and the diene.

The reaction occurs when the HOMO of the nucleophilic diene overlaps with the LUMO of the electrophilic dienophile to form two new σ-bonds. The two electrons of the HOMO of the diene slot into the empty LUMO of the dienophile forming a new σ-bond, (Figure 54).

The Diels Alder reaction is stereospecific. If there is stereochemistry in the dienophile then it is faithfully reproduced in the product.\textsuperscript{103} The Diels Alder reaction is *concerted* and *suprafacial* with respect to diene and dienophile and therefore the stereochemistries of both the diene and the dienophile are retained in the adduct as depicted in Figure 51.
One disadvantage of the Diels Alder reaction is the number of compounds that it can produce. Regioselectivity, diastereoselectivity and enantioselectivity can all impact on the final product.

**Regioselectivity in the Diels Alder reaction**

One problem of regioselectivity occurs because the dienophile can attack the diene in one of two orientations leading to regioisomers. For example, Figure 56 (page 214) shows that in an *inter* molecular Diels Alder reaction, $R^1$ can be adjacent to $R^3$ or $R^4$ leading to two different regioisomers.

**Figure 55** Examples of preservation of stereochemistry in Diels Alder reactions.
With an *intra*molecular Diels Alder reaction, this type of regioselectivity can be less of a problem because the diene and the dienophile are linked together by a carbon chain and this tether connecting the two reactive centres may constrain the orientation of the attack of the dienophile.

However, regioselectivity is still a major concern at this stage in the synthesis because the long chain aldehyde 23 contains three dienes (C8-C11, C10-C13, C12-C15) and the dienophile (C2-C3) can attack at any of these three reactive centres. In principle, three regioisomeric products are theoretically possible from an *intra*molecular Diels Alder reaction of aldehyde 23 through dienophile addition across C15 – C12, C13 – C10 or C11 – C8 (Figure 57, page 219).
In work carried out by Turner et al. in 2004 on double Diels Alder reactions of linear conjugated tetraenes involving intramolecular - intramolecular and intramolecular - intermolecular sequences it was established that linear conjugated tetraenes exhibit complete terminal regioselectivity in reactions with dienophiles. Computational studies in this work revealed this to be as a consequence of increased π-conjugation effects. The consequences of this may rule out the formation of regioisomer B above. However, the linear conjugated tetraenes used in the Turner studies were not influenced by steric effects, which are present in aldehyde 23 due to the five methyl groups situated along the backbone of the tetraene and this may have a bearing on the outcome of the Diels Alder reaction.

**Diastereoselectivity in the Diels Alder reaction**

Diastereoselectivity is also an issue with the IMDA reaction. The dienophile can undergo reaction via two different orientations with respect to the plane of the diene, referred to as endo or exo selectivity. Scheme 76 (page 220) shows that
two geometric isomers can be formed from an intramolecular reaction of compound 23 at any one of the three dienes present.

Scheme 76  Diels Alder reaction showing endo-exo-selectivity.
The enantiomers that can also be formed will be discussed later.

Normally in a Diels Alder reaction the *endo*-compound is preferentially formed because there is maximum overlap of the $\pi$-orbitals of the diene and the dienophile.

![Diagram of endo-exo transition states](image)

**Figure 58**  *Endo-exo* transition states.

Figure 58, depicting the FMO approach, shows that with the *endo*-transition state there is an additional favourable orbital overlap between the $\pi$-orbital in the diene and the $\pi^*$-orbital of the carbonyl. This results in a stabilisation of the *endo*-transition state, which preferably leads to the *endo*-product. This is known as the secondary orbital effect as it does not involve any of the reactive centres directly.\(^{119}\) According to the “*endo*-rule” the prominent diastereoisomer in a Diels Alder reaction should always be the *endo*-product but there are many reactions that do not obey the *endo*-rule. It is thought that reactions that do not follow the *endo*-rule are due to asynchronous bond formation.\(^{78}\) Although both new bonds in a Diels Alder reaction are initiated simultaneously in a concerted way they are often formed at significantly different rates due to asymmetric stretch asynchronicity or twist asynchronicity taking place in the transition state. Steric effects may enhance these stretch/twist asynchronicities. So, in an IMDA reaction of conjugated tetraene 23 the *endo*-rule is of limited use in predicting the stereochemical outcome.
*Enantioselectivity in Diels Alder reaction*

The final selectivity issue in the IMDA reaction is that of enantioselectivity. The dienophile can approach the diene from either face resulting in two enantiomeric forms of the desired product (Figure 59).

![Figure 59](image)

**Figure 59** Enantiomers of the *endo-exo* diastereoisomers

In summary, an *intra*-molecular Diels Alder reaction on the linear conjugated tetraene 23 may produce 3 regioisomers and for each of these regioisomers there can also be 2 diastereoisomers and 2 enantiomers making a total of 12 possible compounds. It is probable that a complex interplay of structural and electronic factors will determine cyclisation stereochemistries of conjugated tetraene 23. The exact nature of these factors has yet to be fully established; therefore the outcome of the cyclisation reactions could not be predicted.