Towards the total synthesis of chaetochalasin A

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Abstract

This thesis describes tin and non-tin mediated approaches towards the total synthesis of chaetochalasin A 1 through an intramolecular domino Diels-Alder approach, and subsequent synthesis of the Diels-Alder analogues exo NH 13E-272, endo NH 13E-273, exo NH 13Z-287 and endo NH 13Z-288 through an intramolecular Diels-Alder approach.

The initial tin mediated route involved the initial formation of alcohol 119, which exhibited a 2,4-syn methyl arrangement, put in place through the use of two chiral auxiliary mediated asymmetric alkylations. Subsequent functionalisation of alcohol 119 led to aldehyde 215, which incorporated a vinyl stannane functional group. The α,β-unsaturated aldehyde 215 was then reacted with β,γ-BT-sulphone 120 under trans selective Julia conditions to give predominantly the (1E,7E,9E,11E) isomer of vinyl stannane 117. However, subsequent Stille reactions to form the Z,E diene functional group, between vinyl stannane 117 and vinyl iodide 118 resulted in a product that exhibited extreme isomerisation of the triene functional group.

A subsequent non-tin mediated route involved the synthesis of aldehyde 229 from alcohol 119, which then underwent a trans selective Julia olefination with BT-sulphone 120 to give predominantly the (2E,8E,10E,12E) isomer of ester 228. Ester 228 was then converted into aldehyde 227, which then underwent a Z-selective olefination to put in place the 2Z,4E diene of methyl ester 226. Further functionalisation of methyl ester 226 using past methodology within the Thomas group led to pyrrolinone 110. Subsequent small scale attempts to convert pyrrolinone 110 into chaetochalasin A 1 through a domino Diels-Alder reaction proved ineffective.

Formation of the exo NH 13E-272, endo NH 13E-273, exo NH 13Z-287 and endo NH 13Z-288 Diels-Alder analogues involved the initial conversion of alcohol 119 into aldehyde 275, followed by trans selective Julia olefination with BT-sulphone 120 to give predominantly the (4E,10E,12E,14E) isomer of ester 274. Further functionalisation of ester 274 using past methodology within the Thomas group, led to pyrrolinone 243, which then underwent an intramolecular Diels-Alder reaction to give the 13E : 13Z isomers in a 1 : 1 ratio, with each isomer exhibiting an exo : endo geometry in a 5 : 4 ratio.
Declaration

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### Terms and abbreviations

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobis(2-propionitrile)</td>
</tr>
<tr>
<td>APCI</td>
<td>Atmospheric Pressure Chemical Ionisation</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>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>BT</td>
<td>Benzo[1,2-\text{a}:4,3-\text{b}]thiazolyl-2-yl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzyloxy</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionisation</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIAD</td>
<td>Di-\text{isopropyl}azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Di-\text{isobutyl}aluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Di-\text{isopropylethylamine} (Hunig’s base)</td>
</tr>
<tr>
<td>dm</td>
<td>decimetre</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>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin Periodinane</td>
</tr>
<tr>
<td>DMPA</td>
<td>Dimethylolpropionic acid</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-Bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact ionization</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectroscopy</td>
</tr>
<tr>
<td>g</td>
<td>Grams</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>3</td>
<td>Tertiary</td>
</tr>
<tr>
<td>TADA</td>
<td>Transannular Diels-Alder</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-(n)-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyle</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran-2-yl</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl (tetramethylsilane)</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetra-(n)-propylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>4-Toluenesulfonyle</td>
</tr>
<tr>
<td>(\mu)g</td>
<td>Micrograms</td>
</tr>
<tr>
<td>(\mu)mole</td>
<td>Micromoles</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>(\nu)</td>
<td>Wavenumber</td>
</tr>
<tr>
<td>VLC</td>
<td>Vacuum liquid chromatography</td>
</tr>
<tr>
<td>X_2</td>
<td>Chiral auxiliary</td>
</tr>
</tbody>
</table>
1.0 Introduction

1.1 Preface

This thesis relates to work carried out by the author towards the total synthesis of chaetochalasin A 1. Chapter 1 is intended as a review of the isolation, structure and biological/cytotoxic importance of chaetochalasin A 1, followed by discussion of the structurally related cytochalasans and their synthesis through intramolecular Diels-Alder and macrocyclization reactions, along with possible biosynthetic pathways. Chapters 2 and 3 detail synthetic approaches towards the synthesis of chaetochalasin A 1, whilst Chapter 4 refers to the synthesis of structurally similar analogues of chaetochalasin A 1.

1.2 Chaetochalasin A 1

1.2.1 Discovery and isolation

During an ecological investigation studying the effects on sclerotia of the fungus *Aspergillus flavus* following burial in soil, it was found that a number of the fungi *Chaetomium spp.* had colonised the sclerotia, indicating possible parasitic behaviour towards *Aspergillus flavus* through the use of antifungal agents. A further study of the *Aspergillus flavus* sclerotia resulted in a further fungus *Chaetomium brasiliense* (NRRL 22999) being discovered. An organic extract was taken from *Chaetomium brasiliense*, which was shown to exhibit both antiinsectan behaviour towards *Helicoverpa zea* and antifungal effects towards *Aspergillus flavus*.\(^1\) Fractionation of the substrate by silica gel VLC, followed by reversed phase HPLC led to the isolation of chaetochalasin A 1 and the known compounds 19-O-acetyl-chaetoglobosins A and D,\(^2\) and chaetoglobosins D\(^3\) and F\(_{ex}\).\(^4\)

1.2.2 Cytotoxic, antiinsectan and antifungal activity

The biological activity of chaetochalasin A 1 was further investigated, showing cytotoxicity with an average GI\(_{50}\) value of 8.1 μg/mL against the National Cancer Institute’s 60-cell line assay and antibacterial activity towards both *Staphylococcus*
aureus (ATCC 25923) and Bacillus subtilis (ATCC 6051). The antiinsectan and antifungal behaviour mentioned previously was not attributed to chaetochalasin A but instead to chaetoglobosins D and 19-O-acetyl-chaetoglobosins A and D which were shown to induce both effects.

1.2.3 Structure determination

Structural assignment of chaetochalasin A initially proceeded with HREIMS and $^{13}$C NMR data being used in order to determine the molecular formula of C$_{27}$H$_{39}$NO$_{2}$. NMR assignments were then elucidated through a combination of $^1$H NMR, COSY data and HMQC and HMBC results. The relative stereochemistry and structure were then confirmed by data obtained through X-ray crystallographic analysis (Figure 1.1).

![Figure 1.1: The absolute stereochemistry of chaetochalasin A](image)

1.2.4 Related natural products

Currently two compounds have been isolated from fungi which belong to the same class of natural product as chaetochalasin A. Phomopsichalasin 2 (Figure 1.2 on page 14) was isolated by Horn and co-workers in 1995 from the surface of sterilised twigs of Salix gracilostyla. Later in 2006, diaporthichalasin 3 was discovered by Pornakakul and co-workers from the endophytic fungi Diaporthe sp. Bkk3, which inhabits Croton sublyratus leaves. Diaporthichalasin 3 was shown to exhibit potent inhibition of the cytochrome P450 enzyme, CYP3A4, with an IC$_{50}$ value of 0.626 μM.
1.3 The cytochalasans

1.3.1 Cytochalasan diversity

Although chaetochalasin A 1 (Figure 1.1 on page 13), phomopsichalasin 2 and diaporthichalasin 3 have pentacyclic structures, they do appear to be structurally related to the cytochalasans. A structural similarity that is common to all these compounds is the connectivity of the six membered ring being in a cis-fused relationship to the five membered isoindolone ring.

The cytochalasans consist of a highly substituted hydrogenated isoindolone unit fused to a 10- to 14-membered macrocycle, which may be either a carbocycle, a cyclic carbonate or a lactone. Cytochalasans are divided into specific groups (Figure 1.3 on page 15) depending on the type of amino acid incorporated during biosynthesis, resulting in the isoindolone bearing either a benzyl group (cytochalasins, i.e. cytochalasin A 4), a 2-methylpropyl group (aspochalasins, i.e. aspochalasin A 5), a methyl group (alalachalasins, i.e. alalachalasin C 6), a p-methoxybenzyl group (pyrichalasins, i.e. scoparasin A 7) or a (indol-3-yl)methyl group (chaetoglobosins, i.e. chaetoglobosin O 8).
The first cytochalasan to be discovered was cytochalasin A 4 by Rothweiler and Tamm in 1966, isolated from the fungal *Phoma* strain S 298. Since then there have been a hundred different types of cytochalasans discovered, isolated from many different fungi; which include *Rosellinia, Ascochta* and *Phomopsis*, to name but a few. These cytochalasan producing fungi are not isolated to a particular geographical location and seem to pervade many different types of ecological niches.

### 1.3.2 Biological activity

The cytoskeleton of eukaryotic cells is made of microfilaments, which are themselves made from polymerised actin monomers. Cytochalasans are able to permeate the cell membrane and bind to the barbed end of the actin filaments, resulting ultimately in the inhibition of polymerisation. This effect is dose dependent with sub-toxic amounts resulting in nuclear division with no cytokinesis, which in turn produces multinucleated cells; or alternatively with toxic amounts leads to cell apoptosis.

Other effects on biological activity have also been observed which include inhibition of protein synthesis, prevention of growth of new blood vessels by cytochalasin E, inhibition of thyroid secretion and the release of growth hormones.

### 1.3.3 Cytotoxic activity

Due to the cytochalasans’ direct influence on essential cellular functions, they have also been shown to demonstrate highly cytotoxic effects. Chaetoglobosins A, B, D, J, Q and T show significant cytotoxicity towards P388 murine leukemia cell lines.
and chaetoglobosins A-G and J display cytotoxicity towards Hela cells, with IC₅₀ values being between 3-20 μg/mL. Several studies have also shown that there is a structure-activity relationship with regards to toxicity, with two main structural areas of the cytochalasans having particular importance. Firstly, the isoindolone nucleus provides the greatest effect on cytotoxic activity, with studies showing that changing the C(10) group (Figure 1.3 on page 15) from a phenyl/indolyl to an isopropyl moiety results in a decrease in efficacy. Secondly, the macrocyclic ring is also necessary to achieve bioactivity; different size rings however show neither an advantage nor disadvantage to the process.

1.3.4 Antimicrobial and antiparasitic activity

As well as the above properties, cytochalasans also exhibit antifungal and antibacterial effects. Research has shown that cytochalasin A 4 inhibits the growth of Escherichia coli and B. subtilis, whereas cytochalasin E has been shown to inhibit the growth of the reptile parasite Entamoeba invadens.

1.4 Intramolecular Diels-Alder approaches towards the Cytochalasans

1.4.1 Preliminary work directed towards the Cytochalasans

Initial research carried out to test the validity of using an intramolecular Diels-Alder approach towards the synthesis of cytochalasans was performed in 1978. Thus, after synthesising diene-anhydride 9, intramolecular reactions were carried out under high dilution (100 mg per 100ml) in refluxing toluene (Scheme 1.1 on page 17). This resulted in the complete consumption of starting material and isolation of the major endo 10 compound in a 27% yield, and 5% of a minor compound 11 identified as a regioisomer of 10.
The above results should be contrasted with later research undertaken in 1983. Here pyrrolinone 12 (Scheme 1.2) was heated at 100°C, which resulted in two Diels-Alder adducts (endo 13 : exo 14 = 85 : 15).

The first synthesis of a cytochalasan was achieved by Stork and co-workers in 1978, in which cytochalasin B 15, a naturally occurring [14]-cytochalasin, was made using an intermolecular Diels-Alder reaction.

Several years later Stork managed to synthesise cytochalasin B 15 through an intramolecular reaction (Scheme 1.3 on page 18). Here, the previously synthesised trienic acid 16 was reacted with hydroxypyrrolone 17 to give tetraene 18. Tetraene 18 was then heated at 180-190°C for 6 days, resulting in two Diels-Alder adducts (endo 19 : exo 20 = 4 : 1). The endo 19 adduct was then taken through a subsequent 8 steps which resulted in the synthesis of cytochalasin B 15.
Although there was no discussion made with regards to the endo/exo stereochemistry, it should be noted that the results closely follow the results in Scheme 1.2 on page 17.

1.4.3 Total synthesis of proxiphomin 21

The first total synthesis of the cytochalasan proxiphomin 21,\(^{25}\) a naturally occurring [13]-cytochalasin,\(^{26}\) was achieved in 1985. The synthetic scheme below (Scheme 1.4 on page 19) outlines some of the key later steps in the synthesis; which were then adopted as general methodology for further syntheses within the research group.

The initial key step in the synthesis involved reacting aldehyde 22 (synthesised in 6 steps) with the lithium salt of dienylphosphonate 23 (Scheme 1.4 on page 19), which proved to be highly trans selective in forming ester 24, in a \((10E,12E,14E):(10Z,12E,14E) = 95:5\) ratio. Ester 24 was then converted into acid 25, which was then reacted with 1,1’-carbonyldiimidazole to give imidazolide 26. Imidazolide 26 was then reacted with the anion of pyrrolidinone 27 to give oxopyrrolidinone 28 as a mixture of epimers.\(^{25}\)
This was then followed by regioselective phenylselenation to give selenide 29 as a mixture of epimers (Scheme 1.4), with subsequent oxidative-elimination to give the unstable pyrrolinone 30. The chloroform solution of pyrrolinone 30 was then diluted with toluene (100 mg per 100 ml) and heated at 100 °C, which resulted in two Diels-Alder adducts exo 31 and endo 32. Upon debenzylation the two compounds were separable by column chromatography, resulting in the exo NH 33 and the endo NH 34 adducts. The endo NH 34 adduct was then taken through a further two steps resulting in the synthesis of proxiphomin 21.25

In comparison with the earlier work (Scheme 1.3 on page 18) which showed high endo stereoselectivity, the stereoselectivity here proved disappointing with an endo 32 : exo 31 = 52 : 48 ratio. Both the endo 32 and exo 31 adducts were formed by the cycloaddition of the triene onto the less-hindered face of the pyrrolinone. At this stage there was no investigation into why the stereoselectivity of the Diels-Alder reaction was so unselective.

Scheme 1.4: Synthetic route to proxiphomin 21

Reagents and conditions: (i) n-BuLi, HMPT, THF, -78°C, 73%; (ii) NaOH, EtOH/H2O, 93%; (iii) 1,1-carbonyldiimidazole, THF, r.t., 90%; (iv) LHMDS, THF, -78°C, 61%; (v) LHMDS, PhSeCl, -78°C, 75%; (vi) m-CPBA, (30%) H2O2, CDCl3/PhCl, -50°C; (vii) toluene, 100 °C, 12 h, 50-55% from 29; (viii) KOH, benzene/MegOH, r.t., 75%; (ix) LDA, THF/hexane, PhSeCl, -78°C, 62%; (x) pyridine, (30%) H2O2, DCM/H2O, r.t., 65%.
1.4.4 Total synthesis of cytochalasin H 35

The successful synthesis of proxiphomin 21\textsuperscript{27} was then followed one year later by the total synthesis of cytochalasin H 35, a naturally occurring [11]-cytochalasin.\textsuperscript{28} The synthetic scheme detailed below (Scheme 1.5) briefly outlines some of the key later steps seen in the synthesis.

The previously synthesised aldehyde 36 (synthesised in 16 steps) was reacted with the lithium salt of dienylphosphonate 23 (Scheme 1.5), which resulted in the highly trans selective formation of methyl ester 37. Methyl ester 37 was then converted to the unstable pyrrolinone 38, with methodology used in the synthesis of proxiphomin 21 (Scheme 1.4 on page 19). The chloroform solution of pyrrolinone 38 was then diluted with toluene and heated at 80-100°C, which resulted in only the endo adduct 39. Debenzylation of the endo adduct 39 gave the endo NH 40 adduct which was subsequently taken through a further seven steps to give the natural product cytochalasin H 35.\textsuperscript{27}

Scheme 1.5: Synthetic route to cytochalasin H 35

The yield from the Diels-Alder reaction was a promising 35% with 2% of minor impurities that were not characterised. Again the endo adduct was formed by the cycloaddition of the triene onto the less-hindered face of the pyrrolinone. There was no

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Reagents and conditions: (i) n-BuLi, HMPT, THF, -78°C, 87%; (ii) NaOMe, MeOH/H\textsubscript{2}O, r.t., 98%; (ii) 1,1-carbonyldimidazole, THF, r.t., 95%; (iv) LiHMDS, 27, THF, -78°C, 87%; (v) LiHMDS, PhSeCl, THF, -78°C, 96%; (vi) m-CPBA, (30%) H\textsubscript{2}O\textsubscript{2}, CDCl\textsubscript{3}, -50°C; (vii) toluene, 80-100 °C, 5 h, 38% over 3 steps; (viii) NaOH, MeOH/H\textsubscript{2}O, r.t., 95%; (ix) LDA, TMSCI, THF, -78°C, 98%; (x) PhSeCl, THF, then TBAF, 0°C, 78%; (xi) pyridine, (30%) H\textsubscript{2}O\textsubscript{2}, DCM, r.t., 68%; (xii) NaBH\textsubscript{4}, EtOH, 0°C, 72%; (xiii) Ac\textsubscript{2}O, DMAP, pyridine, 89%; (xiv) m-CPBA, DCM, -20°C to 0°C, 71%; (xv) aluminium isopropoxide, xylene, 125°C, 87%; (xvi) (5%) HF, MeCN, 40%.
investigation at this stage as to why the Diels-Alder reaction was entirely endo selective, or how this related to the complete unselectivity seen in the synthesis of proxiphomin 21.27

Quickly following the total synthesis of cytochalasin H 35, a more efficient synthetic route was envisaged, which involved the functionalisation of the macrocycles C(18) at a later stage.29 Some of the key steps are briefly outlined in the synthetic scheme below (Scheme 1.6).

This involved taking the alternative aldehyde 41 (synthesised in 6 steps) and reacting it with the lithium salt of dienylphosphonate 23 (Scheme 1.6), which resulted in the highly trans selective formation of ester 42, in a (8E,10E,12E) : (8Z,10E,12E) = 95 : 5 ratio. Using the methodology detailed in the synthesis of proxiphomin 21 (Scheme 1.4 on page 19), ester 42 was converted into the unstable pyrrolinone 43 and subsequently heated at 80°C for 16 hours to give only the endo 13Z-44 (2%) and endo 13E-45 (56%) adducts.29

Scheme 1.6: Alternative synthetic route to cytochalasin H 35
Debenzylation of the endo 13Z-44 and endo 13E-45 adducts gave the endo NH 13Z-46 and endo NH 13E-47 adducts. The endo NH 13E-47 adduct was then subjected to hydrolysis to remove the ketal protecting group and subsequently reacted with methylmagnesium chloride to give hydroxyl ketone 48 as a single diastereoisomer (Scheme 1.6 on page 21). At this stage the formal synthesis was complete, as SEM-protection of the C(18) alcohol would give 40, which would then be followed by known chemistry seen in the original synthesis (Scheme 1.5 on page 20) to give cytochalasin H 35.29

1.4.5 Total synthesis of cytochalasin G 49

Following the synthesis of cytochalasin H 35, attention then turned towards the total synthesis of cytochalasin G 49,30 another naturally occurring [11]-cytochalasin with a tryptophan derived C(3) indolymethyl substituent.31 The synthetic scheme below (Scheme 1.7) shows the key Diels-Alder step of the synthesis.

Due to the structural similarities between cytochalasin H 35 and cytochalasin G 49, the initial synthetic route towards the pyrrolinone 50 was virtually the same. The Diels-Alder reaction with pyrrolinone 50 resulted in the formation of a single endo 51 (31%) adduct, with 2% of minor products that were not identified (Scheme 1.7). Subsequent acetal hydrolysis, epoxidation and N-debenzylation gave cytochalasin G 49. Again there was no investigation as to why the stereoselectivity of the Diels-Alder reaction was entirely endo selective.30

Scheme 1.7: Synthetic route to cytochalasin G 49

Reagents and conditions: (i) toluene, 86°C, 5.5 h, 33% over 2 steps; (ii) (5%) HCl, THF, r.t., 71%; (ii) m-CPBA, DCM, r.t., 39%; (iv) NaOH, MeOH/H2O, r.t., 62%.
1.4.6 Evidence towards the endo/exo stereoselectivity

The results arising from the synthesis of cytochalasin B 15, proxiphomin 21 cytochalasin H 35 and cytochalasin G 49, indicated that the size of the macrocycle ring formed during the Diels-Alder reaction may influence the endo/exo selectivity. In order to test this hypothesis, varyingly sized macrocycles were synthesised through an intramolecular Diels-Alder reaction.

The first study involved the synthesis of pyrrolinone 52, which was then diluted with toluene and refluxed at 100°C for 12 hours (Scheme 1.8). This gave rise to only the endo adduct 53 with an 11-membered macrocycle, which correlated with the results obtained in the Diels-Alder reactions of cytochalasin H 35 and cytochalasin G 49.\(^\text{32}\)

\[52\] \[53\]

Reagents and conditions: (i) toluene, 100°C, 12 h, 40% over 2 steps.

Scheme 1.8: Key Diels-Alder step in a model system resulting in an 11-membered macrocycle

A second study involved the synthesis of the pyrrolinone 54, which was then diluted with toluene and refluxed at 100°C, giving rise to a mixture of adducts with 13-membered macrocycles in an endo 55 : exo 56 = 1 : 1 ratio (Scheme 1.9).\(^\text{33}\) The results obtained here were consistent with the Diels-Alder reaction of proxiphomin 21.

\[54\] \[55\] \[56\]

Reagents and conditions: (i) toluene, reflux, 100°C, 50% over 2 steps.

Scheme 1.9: Key Diels-Alder step in a model system resulting in a 13-membered macrocycle
1.4.7 Total synthesis of an isomer of aspochalasin C 57

Having successfully synthesised two [11]-cytochalasins (cytochalasin H 35 and cytochalasin G 49), attention then turned towards the synthesis of aspochalasin C 57, another [11]-cytochalasin. Aspochalasin C 57 belongs to a small group of cytochalasins known as the alachalasins; these alachalasins differ in having a methyl substituent at the C(14) position and no methyl group at the C(16) position. The synthetic scheme detailed below (Scheme 1.10) briefly outlines some of the key later steps seen in the synthesis.

The previously synthesised ketone 58 (synthesised in 10 steps) was reacted with the lithium salt of dienylphosphonate 23, which resulted in the formation of ester 59 as a mixture of isomers in a \((8E,10E,12E) : (8Z,10E,12E) = 4 : 1\) ratio (Scheme 1.10).}

\[
\text{Scheme 1.10: Synthetic route to diol 66}
\]

Reagents and conditions: (i) KHMSDS, HMPA, THF, \(-78^\circ\text{C}\) to r.t., 92%; (ii) NaOH, EtOH+H\(_2\)O, r.t., 97%; (iii) 1,1-carbonyldimidazole, THF, r.t., 92%; (iv) LiHMDS, 61, THF, \(-78^\circ\text{C}\); (v) LiHMDS, PhSeCl, THF, \(-78^\circ\text{C}\), 80% over 2 steps; (vi) m-CPBA, (30%) H\(_2\)O\(_2\), CDCl\(_3\), \(-50^\circ\text{C}\); (vii) toluene, 90°C, 5 h, 34% over 2 steps; (viii) NaOH, MeOH\(_2\)H\(_2\)O, r.t., 75%; (ix) LOA, TMSOCl, THF, \(-78^\circ\text{C}\); (x) PhSeCl, THF, 0°C, 60% over 2 steps; (xi) (30%) H\(_2\)O\(_2\), pyridine/DCM, r.t., 58%; (xii) (2%) HCl, MeOH\(_2\)H\(_2\)O, r.t., 90%.
Using methodology developed in previous syntheses of cytochalasans, ester 59 was then converted into pyrrolinone 60, through the use of pyrrolidinone 61. Pyrrolinone 60 was then diluted with toluene and refluxed at 90°C, giving rise to a mixture of Diels-Alder adducts 62 (Scheme 1.10 on page 24). Upon N-debenzoylation, three compounds were formally identified in an (exo NH 13E-63) : (endo NH 13E-64) : (endo NH 13Z-65) = 2 : 1 : 3 ratio. Due to insufficient time and the lack of the endo NH 13E-64 adduct, which was needed to synthesise aspochalasin C 57, it was decided that the endo NH 13Z-65 adduct should be carried forward through the last four steps. This resulted in the formation of diol 66, which is an isomer of aspochalasin C 57.34

The results obtained were far from what was expected with the usual exclusive endo selectivity for [11]-cytochalasans. The (8E,10E,12E)-60 pyrrolinone upon cyclization gave poor stereoselectivity with an (exo NH 13E-63) : (endo NH 13E-64) = 2 : 1 mixture of adducts being seen following deprotection, whereas the formation of (8Z,10E,12E)-60 pyrrolinone was highly stereoselective, giving rise to the endo NH 13Z-65 adduct following deprotection. A possible explanation put forward was that the 8-Me of the pyrrolinone 60 somehow discourages cyclization endo to the pyrrolinone ring with respect to the (8E,10E,12E) isomer but not for the (8Z,10E,12E) isomer. The precise steric reasoning behind this however, was not investigated.

It should also be noted that the ratio of Diels-Alder adducts (exo NH 13E-63 and endo NH 13E-64) : (endo NH 13Z-65) = 1 : 1 does not reflect the ratio of the starting material pyrrolinone 60 (8E,10E,12E) : (8Z,10E,12E) = 4 : 1. Two possible explanations have been put forward to explain the increase in the amount of endo NH 13Z-65 adduct. Firstly, it may reflect a more efficient cyclization of (8Z,10E,12E)-60 pyrrolinone over (8E,10E,12E)-60 pyrrolinone. Secondly, under the reaction conditions the trienes maybe equilibrating before cyclization occurs. However, no evidence was forthcoming for either of the two possibilities.

1.4.8 Total synthesis of cytochalasin D 67

In 1999 a further naturally occurring [11]-cytochalasin, cytochalasin D 67, was synthesised through the Diels-Alder approach.36 The synthetic scheme shown below (Scheme 1.11) briefly outlines some of the key later steps seen in the synthesis.
The previously synthesised aldehyde 68 (synthesised in 4 steps) was reacted with the lithium salt of dienylphosphonate 23, which proved reasonably trans selective in forming ester 69, with an (8E,10E,12E) : (8Z,10E,12E) = 9 : 1 ratio (Scheme 1.11). Using methodology developed during previous syntheses of cytochalasans, ester 69 was then converted into pyrrolinone 70 and subsequently heated at 80°C for 8 h to give only endo 13Z-71 (4%) and endo 13E-72 (30%) adducts.

![Diagram](https://via.placeholder.com/150)

Scheme 1.11: Synthetic route to cytochalasin D 67

The endo 13E-72 adduct was then taken through a series of functional group interconversions (Scheme 1.11), which put in place the C(6) exo-methylene group, C(7) TBS-protected alcohol and the C(17)-(18) acetonide group, seen in selenide 73. The last 7 steps in the synthesis resulted in the conversion of selenide 73 into cytochalasin D 67.

The results of the Diels-Alder reaction seem to support the evidence discussed previously (Section 1.4.6 on page 23), which suggests that Diels-Alder reactions, resulting in the formation of [11]-cytochalasins, go with complete endo stereoselectivity.
1.5 Other approaches towards the cytochalasans

The total syntheses outlined below offer alternative approaches towards the cytochalasins. In general the syntheses can be broken down into two main areas: (i) formation of the isoindolone nucleus, followed by (ii) formation of the macrocycle through macrocyclization. However, the strategies used to incorporate the stereocentres within the polyketide vary enormously.

1.5.1 Total synthesis of (-)-aspochalasin 74

In 1989 Trost and co-workers synthesised the [11]-cytochalasin (-)-aspochalasin B 74, with one of the key steps being a palladium catalysed macrocyclization. The synthetic scheme shown below (Scheme 1.12) briefly outlines some of the key later steps seen in the synthesis.

Isoindolone 75 (Scheme 1.12) was synthesised through an endo selective intermolecular Diels-Alder reaction using conditions developed by Tamm and co-workers, which involved reacting the previously synthesised alcohol 76 and Cbz-protected isoleucine derivative 77 with BHT in xylene under reflux.

Scheme 1.12: Synthetic route to (-)-aspochalasin B 74
Isoindolone 75 was then subjected to conditions resulting in lactone ring opening and subsequent oxidation of the primary alcohol gave aldehyde 78, which was then converted into diester 79 through a number of steps (Scheme 1.12 on page 27). Diester 79 was then converted into enol ether 80, followed by macrocyclization under palladium catalysed conditions to give sulphone 81 as a single diastereoisomer. The Z stereochemistry of the enol-ether double bond contained in sulphone 81 arose due to the preferred formation of a syn-(π-allyl)palladium intermediate. Sulphone 81 was then converted into (-)-aspochalasin B 74 through a Rubottom oxidation and subsequent removal of the sulphone group.37

1.5.2 Total synthesis of zygosporin E 82

Research undertaken by Vedejs and co-workers in 1990 resulted in the synthesis of the [11]-cytochalasin zygosporin E 82,39 where one of the key steps is sulphur mediated macrocyclization. The scheme shown below (Scheme 1.13 on page 29) outlines the synthetic route towards zygosporin E 82.

Isoindolone 83 was synthesised through an endo selective intermolecular Diels-Alder reaction using the previously synthesised triene 84 and pyrrolidinone 85 (Scheme 1.13 on page 29), which then underwent nucleophilic chloride displacement using 86, to give sulphide 87. Sulphide 87 was then converted to a transitory thioaldehyde before being trapped by a hetero-Diels-Alder reaction with diene 88, to give TBS ether 89 in a 66% yield, following equilibration.39

TBS ether 89 was subsequently converted to allylic chloride 90 through a series of steps (Scheme 1.13 on page 29) before undergoing a sulphur mediated macrocyclization, resulting in the sulphur bridged carbocycle 91. Carbocycle 91 was then methylated at the C(16) and C(18), followed by cleavage of the C(16)-S bond and S-methylation to give allylic silane 92. Allylic silane 92 was then converted to zygosporin E 82 by a series of four steps.
Scheme 1.13: Synthetic route to zygosporin E 82

1.5.3 Total synthesis of cytochalasin B 15

In 2004 Myers and Haidle provided an alternative route to the synthesis of the 14-membered macrocycle cytochalasin B 15, where one of the key steps was an intramolecular Horner-Wadsworth-Emmons olefination, which resulted in the required macrocyclization. The scheme shown below (Scheme 1.14 on page 30) outlines the synthetic route towards cytochalasin B 15.

Coupling of diene 93 and exo-methylene lactone 94 resulted in triene 95, which then underwent an intramolecular Diels-Alder cyclization to give predominantly the endo Diels-Alder adduct 96 (Scheme 1.14 on page 30). This was then followed by a series of functional group interconversions, including enol trapping, epoxidation,
oxidation, lactone ring opening and final oxidation of the hydroxy lactam to give aldehyde 97.40

Scheme 1.14: Synthetic route to cytochalasin B 15

Aldehyde 97 was then reacted with sulphone 98 under Julia conditions to give trans-olefin 99, which was subsequently converted to aldehyde 100 through 5 steps (Scheme 1.14). Aldehyde 100 then underwent an intramolecular Horner-Wadsworth-Emmons macrocyclization, followed by Boc and TBS deprotection and subsequent mild Mg(II)-induced rearrangement of the epoxide to give cytochalasin B 15.40
1.6 Biosynthetic research into the cytochalasans

1.6.1 Biosynthetic research towards chaetoglobosins A 101 and C 102

Investigations into the chaetoglobosin producer *Penicillium expansum* resulted in the first cytochalasan biosynthesis gene cluster being discovered. A key part of the gene cluster is known as CheA, which is responsible for catalysing the stepwise production of a nonaketide 103 from an acetyl-CoA unit 104 using eight malonyl-CoA extenders 105, which are loaded onto an acyl carrier protein (ACP) with the help of the acyl transferase domain (AT) (Figure 1.4 on page 32). Following each elongation stage, the enzymes ketoreductase (KR), dehydratase (DH) and enoylreductase (ER) facilitate the β-keto processing steps. Having formed the nonaketide 103 an activated tryptophan then attacks the polyketide chain to give an amide 106.41

Upon the off-loading of amide 106, two subsequent mechanistic pathways have been suggested. The C-terminal domain could function as a reductase, resulting in the formation of amido aldehyde 107, which could then undergo a Knoevenagel condensation to give pyrrolinone 108 (Figure 1.4 on page 32). Alternatively, the C-terminal domain could function as a Dieckmann cyclase, which would give pyrrolinone 108 directly. Pyrrolinone 108 could then undergo a Diels-Alder [4 + 2] cycloaddition, possibly with the help of a Diels-Alderase (in which there is growing evidence of their use in natural product synthesis)42 to give *endo* Diels-Alder adduct 109. *Endo* adduct 109 would then be subjected to oxidative reactions catalysed by the CheD, CheE and CheG gene clusters to give chaetoglobosins A 101 and C 102.41
Figure 1.4: Biosynthetic route towards chaetoglobosin A 101 and C 102 using the cytochalasans synthase CheA

1.7 Aims and objectives of the project

1.7.1 Synthesis of chaetochalasin A 1 through a domino Diels-Alder reaction

The ultimate aim of this project is to synthesise chaetochalasin A 1 through a domino Diels-Alder reaction from pyrrolinone 110, followed by Boc deprotection (Scheme 1.15 on page 33). This represents a biomimetic approach towards chaetochalasin A 1, which takes into account an early hypothesis that the biosynthesis of cytochalasans involves macrocycle forming intramolecular Diels-Alder reactions, and has recently received support from evidence derived from gene cluster analysis (as discussed Section 1.6.1). Although the gene cluster analysis is directed towards the cytochalasans and not chaetochalasin A 1, due to the close structural similarities
between the two, it is easy to envisage how a precursor towards chaetochalasin A 1 could fit into the biosynthetic gene cluster machinery.

**Scheme 1.15: Preliminary retrosynthetic analysis towards chaetochalasin A 1**

With regard to the latter Diels-Alder reaction postulated, this will involve an inverse electron demand Diels-Alder reaction between the electron rich dienophile and the electron deficient diene of the *exo 111* adduct (Scheme 1.15). The *endo 112* adduct is another probable Diels-Alder product and would result in an isomer of chaetochalasin A 1 following deprotection.

Although not common, these reactions are favoured due to them being transannular processes. Thus, many research groups have used transannular Diels-Alder reactions (TADA) to synthesise very complex polycyclic structures.$^{44}$

Research undertaken by Deslongchamps discovered a predictability of TADA reactions and hence TADA products, which relied on looking at the geometry of the dienophile and diene double bonds (Figure 1.5 on page 34).$^{45}$ The *cis-cis* dienes are of no use because they only produce rearranged products, due to the fact that the dienes’ cisoid conformation is very high in energy. The *cis-trans* and *trans-cis* diene systems only produce one TADA product, and due to their lower energy they only produce small amounts of rearranged products. On the other hand, the *trans-trans* diene systems can lead to the formation of two adducts, due to the fact that the flat diene cisoid conformation can easily flip.
Table 1.5: Nomenclature used to describe the double bond stereochemistry of the macrocyclic trienes and their corresponding tricyclic TADA adduct.

Applying the information above to the retrosynthetic analysis, it can be seen that a TADA reaction of the exo 111 adduct, displaying a CTT [(cis)-(trans)-(trans)] geometry, could only give rise to a CAC (cis-anti-cis) exo Boc 113 adduct (Scheme 1.16 on page 35).
Scheme 1.16: TADA reaction leading to exo Boc 113 adduct

With respect to the TADA reaction (Scheme 1.16), molecular model studies have shown that the exo-transition structure is readily accessible from the exo 111 adduct and should deliver the required exo Boc 113 adduct stereoselectively. In the depicted transition state (Figure 1.6), the C(14)-C(19) unit has adopted a conformation akin to the chair conformation of this particular fragment seen in chaetochalasin A 1, where the two methyl groups located at C(16) and C(18) are in pseudo-equatorial positions. The flexible conformation of the 13-membered ring in the exo adduct 111 leading to the transition state requires minimal reorganisation to give the pentacyclic framework of chaetochalasin A 1 in the conformation shown by its X-ray crystal structure.\(^1\)

Figure 1.6: TADA exo transition structure of the TADA reaction

It should be noted that the trans-disposition of 19-H and 22-H in chaetochalasin A 1 requires the exo adduct 111 to exist either as the (19E,21Z) isomer or the (19Z,21E) isomer (Scheme 1.15 on page 33). Molecular modelling studies indicate however, that the (19E,21Z) isomer is the most likely biosynthetic precursor.

With respect to the first intramolecular Diels-Alder reaction from triene-pyrrolinone 110, this should result in the formation of a mixture of exo 111 and endo 112 (Scheme 1.15 on page 33) 13-membered macrocycle trienes (the transition states of
such a reaction are discussed in Section 3.3.3 on page 90). This proposition takes into account evidence presented previously (Section 1.4). Thus, formation of 11-membered macrocycles through Diels-Alder reactions gives rise to only endo Diels-Alder adducts, whereas 13-membered macrocycles seem to give a mixture of both endo and exo adducts (proxiphomin 21 gave an endo 32 : exo 31 = 52 : 48 ratio) (Section 1.4.3, pages 18 to 19).

However, this information has to be analysed with respect to the additional C(10)-Me group seen within pyrrolinone 110. As seen with the 11-membered macrocycle aspochalasin C 57 (Section 1.4.7, pages 24 to 25), the additional methyl group may have had the effect of shifting the selectivity from, what should have been completely endo selective to a mixture of compounds in an exo NH 13E-63 : endo NH 13E-64 = 2 : 1 ratio (only taking into account the E isomers). Thus, the proposed initial Diels-Alder represents a cross over between the two above scenarios. Here a triene-pyrrolinone 110 containing an extra methyl group at C(10) is being reacted under Diels-Alder conditions to give a 13-membered macrocycle, which may result in an increased preference for the exo adduct 111 over the endo adduct 112 (Scheme 1.15 on page 33).

A possible complication with respect to the initial Diels-Alder reaction is the possibility that the (10E,12E,14E)-110 isomer (Figure 1.7 on page 37) may equilibrate to the (10Z,12E,14E)-110 isomer before cyclization, which was one possible conclusion mentioned with aspochalasin C 57 (Section 1.4.7 on page 25). This would undoubtedly result in an increase in the number of Diels-Alder products formed, which may in turn cause complications in their separation through column chromatography.

1.7.2 Broad approach towards pyrrolinone 110

The penultimate synthetic target before the domino Diels-Alder reaction would be pyrrolinone 110 (Figure 1.7 on page 37). It has been envisaged that the triene segment could be formed with high (10E,12E,14E) stereoselectivity; in which the C(12)-C(13) double bond would be formed through an E selective Julia olefination.
Figure 1.7: Pyrrolinone 110 - penultimate synthetic target before the Diels-Alder reaction

With respect to the 2Z,4E functional group (Figure 1.7), it is believed that this could be formed by a Stille reaction which would result in the formation of the C(3)-C(4) single bond. Formation of the 6,8-syn methyl arrangement would be achieved through the use of two chiral auxiliary mediated asymmetric alkylations. Finally, incorporation of the pyrrolinone fragment would be achieved using previously optimised chemistry. All four synthetic strategies are discussed in more depth in the Results and Discussion (Section 2.0).
2.0 Results and Discussion 1

2.1 Tin mediated route towards Chaetochalasin A 1

2.1.1 Retrosynthetic analysis of pyrrolinone 110

Through the use of known chemistry,\textsuperscript{25} it was envisaged that pyrrolinone 110 could be synthesised by phenylselenenylation of oxopyrrolidinone 114 followed by oxidative-elimination (Scheme 2.1). Oxopyrrolidinone 114 would in turn be derived from ester 115, by initial saponification to form an acid and subsequent treatment with 1,1’-carbonyldiimidazole to form an imidazolide, which would then be used to acylate pyrrolidinone 116.

![Scheme 2.1: Retrosynthetic analysis of pyrrolinone 110](image)

Ester 115 could then be synthesised by the Stille coupling of vinyl stannane 117 and known vinyl iodide 118\textsuperscript{46} (Scheme 2.1). Vinyl stannane 117 would ultimately be derived from alcohol 119 and BT-sulphone 120. This would involve the initial functionalisation of alcohol 119 to incorporate the vinyl stannane group and subsequent TBS deprotection, oxidation and Julia olefination with BT-sulphone 120 to give vinyl stannane 117.
2.1.2 Retrosynthetic analysis of alcohol 119

It was envisaged that alcohol 119 could be synthesised by a chiral auxiliary mediated alkylation of iodide 121 and subsequent removal of the auxiliary (Scheme 2.2). Iodide 121 would then be derived from known allylic bromide 122 through the use of a chiral auxiliary mediated alkylation, followed by removal of the auxiliary.

![Scheme 2.2: Retrosynthetic analysis of alcohol 119](image)

2.1.3 Synthesis of amide 123 and model alkylation studies

The first major decision to be made was the selection of which chiral auxiliary to use, in order to stereoselectively form the dimethyl functionality seen in alcohol 119. It was decided that a Myers based pseudoephedrine amide should be used, as they prove to be inexpensive and undergo efficient and highly diastereoselective alkylation reactions. Previous research by Myers and co-workers has shown that the alkylation of amide 123 with various alkyl halides installs a new methyl group with (R) stereochemistry in a high de. Thus, when amide 123 was alkylated with bromide 124 (Scheme 2.3), this resulted in the synthesis of α-branched amide 125, with the newly installed methyl group displaying (R) stereochemistry with a 96% de.

![Scheme 2.3: Synthetic route to amide 125](image)

The mechanistic detail, underlying the formation of the major product α-branched amide 125, arises from the electrophilic attack on the Z-enolate of 123 from
the same face (1,4-syn) as the carbon bound methyl group of α-branched amide 125, when the enolate is displayed in its planar extended conformation (Figure 2.1).  

![Figure 2.1: Mechanism of chiral auxiliary mediated alkylation](image)

Therefore, commercially available (+)-pseudoephedrine 126 was reacted with methyl propionate (Scheme 2.4) under basic conditions to give the known amide 123.

![Scheme 2.4: Synthetic route to amide 123](image)

Reagents and conditions: (i) NaOMe, methyl propionate, THF, r.t., 85%.

Before work commenced towards the synthesis of vinyl bromide 122, it was considered appropriate to test the chiral auxiliary mediated alkylation on a model system. The starting point involved the reduction of commercially available (2E)-methylbut-2-enoic acid 127 using LiAlH₄ (Scheme 2.5) to give known allylic alcohol 128, which upon bromination using PBr₃ gave known allylic bromide 129. Allylic bromide 129 was then used to alkylate amide 123, to give α-branched amide 130 in a 70% yield.

![Scheme 2.5: Synthetic route to α-branched amide 130](image)

Reagents and conditions: (i) LiAlH₄, Et₂O, 0°C to r.t., 60%; (ii) PBr₃, Et₂O, 0°C to r.t., 77%; (iii) LDA, LiCl, THF, 123, -78°C to 0°C, 70%.
2.1.4 Synthesis of allylic bromide 122

Following the success in the model system, synthesis of allylic bromide 122 (which was first synthesised by Enders and co-workers using the route discussed below) could now start. The synthesis was initiated by taking commercially available 2Z butenediol 131 and TBS protecting both hydroxyl groups (Scheme 2.6) to give bis-TBS compound 132. Bis-TBS compound 132 was then oxidatively cleaved with ozone to give aldehyde 133, which subsequently underwent a Horner-Wadsworth-Emmons reaction to give the corresponding esters 134 and 135 in a $2E : 2Z = 94 : 6$ ratio, which were separable by column chromatography. Ester 134 was then reduced using DIBAL-H to give alcohol 136, which was then reacted with mesyl chloride to form a transitory mesylate. The subsequent addition of LiBr gave known allylic bromide 137.

![Scheme 2.6: Synthetic route to allylic bromide 137](image)

Reagents and conditions: (i) imidazole, TBSCI, DCM, r.t., 97%; (ii) (a) O$_3$, DCM, -78°C, (b) PPh$_3$, r.t., 85%; (ii) LiBr, n-BuLi, triethyl phosphoropropionate, MeCN, 0°C to r.t., 97%; (iv) DIBAL-H, DCM, -78°C to -20°C, 94%; (v) (a) MeCl, Et$_3$N, -78°C to -40°C to (b) LiBr, 0°C, 89%.

During the synthesis of alcohol 136, nOe experiments indicated interactions through space between the signal at 1.66 ppm (2-Me) and the signal at 4.00 ppm (1-H$_2$). Also, coupling through space was observed between the 2-Me signal and the signal at 4.24 ppm (4-H$_2$) (Figure 2.2 on page 42). In comparison, no interaction through space was seen between the signal at 5.56 ppm (3-H) and the 2-Me signal. Both set of results indicated the presence of an $E$ geometry in the C(2)-(3) double bond.
2.1.5 Synthesis of alcohol 140 using chiral auxiliary mediated alkylations

Amide 123 was then alkylated using allylic bromide 137 (Scheme 2.7) to give α-branched amide 138 in an 89% yield. H NMR analysis of α-branched amide 138 indicated the presence of rotamers, which is caused by rotational isomerism about the N-C(O) bond and can be visualised due to the slow interconversion between the isomers at rt. Due to the rotational isomerisation, determination of the de proved to be inconclusive and high temperature NMR was subsequently performed. However, complete merging of the two isomers was not visualised at 100°C, which was the maximum temperature the probe could attain and, therefore, it was decided that the stereoselectivity would be measured through the use of Mosher studies once the chiral auxiliary had been removed.

Scheme 2.7: Synthetic route to alcohol 140

The next step in the synthesis was the removal of the chiral auxiliary group from amide 138, with the aim of obtaining a primary alcohol group at C(1). The initial
method investigated involved using (3.0M) sodium hydroxide under reflux conditions (Scheme 2.7 on page 42), in order to obtain a carboxylic acid group at C(1) which could then be reduced to alcohol 140. However, the harsh conditions also resulted in the removal of the TBS group to give alcohol 139. A later approach, through the use of lithium ammonia borane complex (LAB), proved to be more fruitful. This resulted in the removal of the auxiliary, with no detrimental effect on the TBS group, to give alcohol 140.48

In order to ascertain how stereoselective the chiral auxiliary mediated alkylation had been, Mosher studies50 were performed on alcohol 140. Therefore, alcohol 140 was reacted (Scheme 2.8) with both enantiomers of MTPA-Cl to give Mosher derivatives 141 and 142. Inspection of both 1H NMR spectra indicated the presence of only one diastereoisomer and thus it was tentatively assumed that alcohol 140 had a high ee with respect to the R stereochemistry seen with the 2-Me.

Scheme 2.8: Synthetic route to Mosher derivatives 141 and 142

Alcohol 140 was then converted into the primary iodide 143 (Scheme 2.9), under Appel conditions,51 which was then used to alkylate amide 123 to give α,γ-branched amide 144. Subsequent removal of the auxiliary using LAB gave alcohol 119 in an 84% yield.48 Inspection of the 1H NMR of alcohol 119 indicated 3% of an unknown compound.

Scheme 2.9: Synthetic route to alcohol 119
With respect to both chiral auxiliary alkylations, four possible compounds could be synthesised (Figure 2.3). The major-major alcohol 119 was the desired alcohol and represents both chiral auxiliary alkylations giving the required (S,R) stereochemistry with respect to both the 4-Me and 2-Me groups. The minor-major alcohol 145 represents unwanted (R) stereochemistry at 4-Me resulting from the first alkylation and the required (R) stereochemistry at 2-Me resulting from the second alkylation. The major-minor 146 alcohol represents the required (S) stereochemistry at 4-Me resulting from the first alkylation and unwanted (S) stereochemistry at 2-Me resulting from the second alkylation. The minor-minor 147 represents both chiral auxiliary alkylations giving the unwanted (R,S) stereochemistry with respect to both the 4-Me and 2-Me groups.

![Figure 2.3: Possible products resulting from both chiral auxiliary mediated alkylations](image)

With respect to the evidence collected from the Mosher studies on alcohol 140 (Scheme 2.8 on page 43), formation of the unwanted (R) stereochemistry at 4-Me was kept to a minimal amount. This leads to the assumption that any significant formation of the minor-minor alcohol 147 (Figure 2.3) can be discounted, due to the fact that a second chiral auxiliary mediated alkylation on material containing the unwanted stereochemistry would result in predominately the minor-major alcohol 145.

It can, therefore, be assumed that if the second chiral auxiliary mediated alkylation was as stereoselective as the first, then there should be equal amounts of the minor-major alcohol 145 and the major-minor alcohol 146 present. However, determining the ratio of these compounds would be impossible through the use of $^1$H NMR analysis, due to them being enantiomers of one and other.

It was, therefore, desirable to synthesise alcohol 146 with the aim of comparing the $^1$H NMR spectra data with that of alcohol 119. Synthesis began by taking the commercially available (-)-pseudoephedrine 148 (Scheme 2.10 on page 45) and converting it into the known amide 149. Primary iodide 143 was then used to alkylate
amide 149 to give α,γ-branched amide 150. Subsequent removal of the auxiliary using LAB gave alcohol 146.

Scheme 2.10: Synthetic route to alcohol 146

Comparison of the $^1$H NMR spectra of both alcohol 119 and alcohol 146 indicated that the 3% unidentified additional peaks, mentioned previously (page 43) with respect to alcohol 119, was in fact due to alcohol 146/145, thereby indicating a de of 94% for alcohol 119.

2.1.6 Synthesis of BT-sulphone 120 and preliminary Julia studies

Having successfully synthesised alcohol 119 with a high degree of diastereoselectivity, attention then turned to the functionalisation of the molecule. It was decided that formation of the triene moiety through a modified Julia olefination$^{53}$ (Scheme 2.1 on page 38) should be given precedence over formation of the vinyl stannane functional group. This was due to the fact that failure at this stage would result in a rethink to the overall synthetic strategy of incorporating the triene group.

In order to obtain a triene as predominately the (E,E,E) isomer, the Julia olefination would need to show high $E\ trans$ selectivity with respect to the middle double bond of the triene and would be reliant on the formation of a sulphone that also displayed high $trans$ geometry.

With respect to the mechanistic detail, the Julia reaction consists of several distinct stages that can be divided into two broad mechanisms, where the structure of the substrates used determines the mechanistic pathway followed.

Metallation of sulphone 151 (using a BT sulphone as an example) is then followed by addition to aldehyde 152 (Scheme 2.11 on page 46) to form the β-alkoxysulphones 153 and 154. The unstable β-alkoxysulphones 153 and 154 then undergo
a facile Smiles rearrangement which occurs \textit{via} the spirocyclic intermediates 155 and 156 respectively, which results in the transfer of the heterocycle from the sulphur atom to the oxygen giving sulphinate salts 157 and 158. Antiperiplanar elimination of sulphur dioxide and lithium benzothiazolone results in the respective \textit{E-159} and \textit{Z-160} isomers.\textsuperscript{54}

\textbf{Scheme 2.11: Proposed mechanism for the modified Julia olefination}

An alternative mechanism involves the formation of the zwitterions 161 and 162, with subsequent elimination to give isomers \textit{E-159} and \textit{Z-160} (Scheme 2.12).\textsuperscript{54}

\textbf{Scheme 2.12: Proposed zwitterionic mechanism for the modified Julia olefination}

Alkene formation through the Julia reaction can be broadly categorised into three distinct areas: (i) synthesis of non-conjugated 1,2-disubstituted alkenes, (ii) synthesis of conjugated 1,2-disubstituted alkenes and (iii) synthesis of trisubstituted alkenes. However, for the purpose of the triene under investigation, only (ii) is relevant and for that reason this area only will be discussed.
Synthesis of conjugated 1,2-disubstituted alkenes can be further broken down into three synthetic strategies (Figure 2.4), where the conjugated system is synthesised from (a) an α,β-unsaturated aldehyde and a saturated heteroarylsulfone, (b) a saturated aldehyde and a β,γ-unsaturated heteroarylsulfone and (c) an α,β-unsaturated aldehyde and a β,γ-unsaturated heteroarylsulfone.

![Figure 2.4: Retrosynthetic disconnections for conjugated 1,2-disubstituted alkenes](attachment:image)

Synthetic strategy (a) often produces predominately E-alkenes irrespective of the sulphone used. Studies have also shown that the base used can have dramatic effects on the E/Z selectivity; i.e. using LiHMDS gave an E : Z = 95 : 5 ratio, whereas using NaHMDS gave an E : Z = 78 : 22. Other studies have also shown that the temperature at which the quenching is done can again affect the E/Z selectivity; i.e. quenching at -78°C gave an E : Z = 80 : 20 ratio, whereas quenching at -20°C gave an E : Z = 91 : 9 ratio.

With synthetic strategy (b) the E/Z ratio depends on whether the saturated aldehyde is α-branched or not. When the saturated aldehyde is unbranched the ratio heavily swings to formation of the Z isomer, whereas with α-branched aldehydes the E isomer is preferentially seen.

Synthetic strategy (c) offers a cross-over between the two previously mentioned strategies, where in some cases the E-isomer is preferably formed and in others the Z isomer is the dominant form. Research by Kocienski and co-workers indicated that the base used can affect the E/Z ratio, i.e. using LiHMDS gave an E : Z = 29 : 71 ratio, using NaHMDS gave a E : Z = 43 : 57 ratio and using KHMD gave an E : Z = 18 : 82 ratio.
The type of mechanistic pathway used (Figures 2.11 and 2.12 on page 46) is dependent on many factors and each of the above synthetic strategies shall be explained in turn.

Synthetic strategy (b) when no α-branching is seen, mainly gives the Z isomer. This is due to the fact that the diastereomeric equilibration (Figure 2.11 on page 46) between the syn 153 and anti 154 β-alkoxysulfones occurs via a retro addition/addition process, and as the energy barrier for the anti isomer to undergo the Smiles rearrangement is higher than the syn isomer, the spirocyclic intermediates 156 is the preferred choice, giving rise to the Z-160 isomer. When α-branching occurs, mainly the E-159 isomer is seen, which has tentatively been explained in two ways (Figure 2.11 on page 46), (i) mainly the anti β-alkoxysulfone 154 is formed, which then undergoes the Smiles rearrangement or (ii) other mechanistic pathways towards E-alkenes are energetically available to the syn β-alkoxysulfone 153.61

Synthetic strategy (a) is believed to occur through the zwitterionic pathway (Figure 2.12 on page 46) which nullifies the addition/retro addition process upon rapid collapse of spirocyclic intermediates 155 and 156 to give sulfinate salts 157 and 158, followed by E1 elimination of lithium benzothiazolone to give zwitterions 161 and 162. The unsaturated residue at R^2 on the aldehyde provides stabilisation of the carbenium ion and the resulting steric repulsion between R^1 and R^2 preferentially favours the E-159 isomer.61

With synthetic strategy (c) however, the mechanistic detail is less clear cut and, to date, no identifiable trends have been discovered. It may be that the overall structure of both substrates dictates the mechanistic pathway taken and hence whether the Z-160 or E-159 isomer is preferentially formed, or there may be a completely different pathway open to this type of reaction.61

Taking into account the lack of research within synthetic strategy (c) for this project, there was a certain amount of doubt as to how selective the Julia reaction would be. Thankfully, Kocienski and co-workers (as seen on page 47) showed that use of different bases could alter this selectivity,55 but there were still unknowns with respect to how altering the solvent and sulphone would affect the selectivity.
It was, therefore, decided that both BT-sulphone 120 (Scheme 2.1 on page 38 / Figure 2.5) and the PT-sulphone 163 (Figure 2.5) should be synthesised, in order to test how different sulphones in combination with different types of base/solvent could influence this type of Julia reaction.

![Chemical structures of BT-120 and PT-163 sulphones](image)

**Figure 2.5:** Target sulphones for trial Julia reactions

The heteroaryl sulphones 164 (Figure 2.6) required for the modified Julia reaction are usually prepared by a two step S-alkylation/S-oxidation sequence from the appropriate heteroaryl thiol 165 and proceed via the corresponding heteroaryl thioether 166. The alkylation reaction can be carried out in two ways: (a) using a Williamson-type reaction, where a heteroaryl thiol 165 is condensed with an alkyl halide 167 under basic conditions, or (b) through a Mitsunobu reaction between a heteroaryl thiol 165 and an aliphatic alcohol 168.

![General synthetic route to heteroaryl sulphones](image)

**Figure 2.6:** General synthetic route to heteroaryl sulphones used for modified Julia reactions

Oxidation of thioethers 166 (Figure 2.6) can be achieved through the use of peracid reagents such as m-CPBA, or through the use of ammonium molybdate tetrahydrate, which generally results in highly chemoselective oxidation at the sulphur atom.

The syntheses of both the BT-120 and PT-163 sulphones was initiated by taking commercially available 2-mercaptobenzothiazole 169 (in the case of the BT-sulphone 120) (Scheme 2.13 on page 50) and 1-phenyl-1H-tetrazole-5-thiol 170 (in the case of the PT-sulphone 163) and reacting them with allylic alcohol 128 under Mitsunobu conditions, to give BT-sulphide 171 and PT-sulphide 172. This was then followed by
Mo(VI) catalysed oxidation of both sulphides to give BT-sulphone 120 and PT-sulphone 163 in respective yields of 77% and 63%.

Scheme 2.13: Synthetic routes to BT-sulphone 120 and PT-sulphone 163

Having synthesised BT-sulphone 120, nOe experiments indicated interaction through space between the signal at 5.45 ppm (3-H) and the signal at 4.15 ppm (1-H$_2$) (Figure 2.7). In comparison, no interaction through space was seen between the 3-H signal and the signal at 1.83 ppm (2-Me). Both set of results indicated the presence of an $E$ geometry in the C(2)-(3) double bond.

Figure 2.7: nOe studies performed on BT-sulphone 120. A solid line indicates a detected nOe and dashed line indicates an undetected nOe

Having successfully synthesised both BT-sulphone 120 and PT-sulphone 163, attention then turned towards the synthesis of an aldehyde that could be used for trial Julia reactions. It was considered that vinyl aldehyde 173 (Scheme 2.14 on page 51) could be synthesised from the previously synthesised alcohol 119 (Scheme 2.9 on page 43), through the process of TIPS protection, TBS deprotection and subsequent oxidation.
Scheme 2.14: Retrosynthetic analysis of vinyl aldehyde 173

The synthesis began by taking alcohol 119 (Scheme 2.15) and TIPS protecting it using TIPSOTf to give bis-protected compound 174 in a 92% yield. Previous attempts to protect using TIPSCI only resulted in a small amount of product over a 24 hour period. Bis-protected compound 174 was then TBS deprotected using PPTS to give allylic alcohol 175, which was then subsequently oxidised using DMP to give vinyl aldehyde 173 in a 92% yield.

Scheme 2.15: Synthetic routes to vinyl aldehyde 173

Vinyl aldehyde 173 was then reacted with either BT-sulphone 120 (Scheme 2.16) or PT-sulphone 163, under various conditions (Table 2.1 on page 52), to give trienes (6E,8E,10E)-176, (6E,8Z,10E)-177 and (6E,8E,10Z)-178 in varying ratios, which depended on the conditions used.

Scheme 2.16: Synthetic routes to triene 176

The initial conditions used to carry out the Julia reaction (Table 2.1 on page 52, referred to as “standard”) involved cooling BT-sulphone 120 or PT-sulphone 163 in solvent to -60°C or -78°C, before the addition of cooled (-78°C) base and subsequent
stirring at the aforementioned temperature for 30 minutes. A cooled (-78°C) solution of vinyl aldehyde 173 in solvent was then added and allowed to stir at -78°C for 1 hour and then at r.t. for 1 hour. Following workup and column chromatography this procedure resulted in yields between 43% and 66%.

Later studies using the Barbier method (Table 2.1) referred to as “Barbier”, involved cooling the sulphone and vinyl aldehyde 173 in solvent to -60°C or -78°C, before the addition of cooled base (-78°C) and subsequent stirring at the aforementioned temperature for 1 hour and then at r.t. for 1 hour, resulted in yields of 74% and 75%.

The difference in yields (Table 2.1) could be due to self-condensation of the BT-Sulphone 120 in the standard method, caused by the prolonged time the molecules spend together following deprotonation, which has been seen to be more apparent with structurally simple BT-sulphones. However, this does not explain the low yields encountered with PT sulphone 163. It should be noted that there was no significant change in the ratio of trienes 176, 177 and 178 formed using the two methods.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Sulphonea</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp. °Cb</th>
<th>Yield %</th>
<th>176 : 177 : 178c ratio%</th>
</tr>
</thead>
<tbody>
<tr>
<td>standard</td>
<td>BT</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-78</td>
<td>62</td>
<td>88 : 6 : 6</td>
</tr>
<tr>
<td>standard</td>
<td>BT</td>
<td>LiHMDS</td>
<td>DMF</td>
<td>-60</td>
<td>66</td>
<td>53 : 42 : 5</td>
</tr>
<tr>
<td>standard</td>
<td>BT</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-60</td>
<td>65</td>
<td>92 : 4 : 4</td>
</tr>
<tr>
<td>standard</td>
<td>PT</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-78</td>
<td>57</td>
<td>69 : 28 : 3</td>
</tr>
<tr>
<td>standard</td>
<td>PT</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78</td>
<td>43</td>
<td>19 : 77 : 4</td>
</tr>
<tr>
<td>Barbier</td>
<td>BT</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-78</td>
<td>74</td>
<td>91 : 5 : 4</td>
</tr>
<tr>
<td>Barbier</td>
<td>BT</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-60</td>
<td>72</td>
<td>87 : 7 : 6</td>
</tr>
</tbody>
</table>

(a) either BT-sulphone 120 or PT-sulphone 163 was used; (b) temperature at which the deprotonation occurred; (c) (6E,8E,10E)-176, (6E,8Z,10E)-177 and (6E,8E,10Z)-178.

Table 2.1: Trial studies used to optimise Julia conditions in forming triene 176

The most important results (Table 2.1) with respect to the ratio of trienes formed during the reaction is seen when the sulphone, base and solvent are varied, and are summarised into three major points: (a) Changing the sulphone from BT-sulphone 120 to PT sulphone 163, with all other conditions remaining constant, led to an increase
of the (6E,8Z,10E)-177 isomer from 6% to 28%. (b) Changing the base from LiHMDS to KHMDS, with all other conditions remaining constant, led to an increase of the (6E,8Z,10E)-177 isomer from 28% to 77%. (c) Changing the solvent from THF to DMF, with all things remaining constant except temperature, led to an increase of the (6E,8Z,10E)-177 isomer from 6% to 42%.

With the above results in mind, it was decided that the optimal conditions to perform future Julia reactions would be that used in row 6 (Table 2.1 on page 52, highlighted in bold). Analysis of the $^1$H NMR spectrum of the reaction indicated a (6E,8E,10E)-176 : (6E,8Z,10E)-177 : (6E,8E,10Z)-178 = 91 : 5 : 4 ratio of trienes. Major triene (6E,8E,10E)-176 was identified by a trans coupling constant value of 15.3 Hz between 8-H and 9-H and (6E,8Z,10E)-177 triene was in turn identified through a cis coupling constant value of 11.5 Hz between 8-H and 9-H. The geometry of the 6E and 10E double bonds of both isomers were implied from the starting materials (Scheme 2.16 on page 51) used in the Julia reaction. Identification of the (6E,8E,10Z)-178 triene was provided at a later date through the analysis of other research (Section 2.2.2, pages 70-73).

2.1.7 Synthesis of pyrrolidinone 116

Having successfully optimised the Julia conditions for the preferential formation of the (6E,8E,10E)-176 triene, which could be later applied to the formation of vinyl stannane 117 (Scheme 2.1 on page 38), attention then shifted towards the synthesis of pyrrolidinone 116 (Scheme 2.1 on page 38).

Research indicated that pyrrolidinone 116 (Scheme 2.17) could be derived from the known 5-mono-substituted Meldrum’s acid 179 using literature precedent, which in turn could be derived from known acid 180 using literature precedent.

![Scheme 2.17: Retrosynthetic analysis of pyrrolidinone 116](image-url)
Synthesis of pyrrolidinone 116 commenced by taking the commercially available L-valine 181 \(^\text{(Scheme 2.18)}\) and Boc protecting the amine group to give acid 180.\(^70\) Subsequent DCC-mediated coupling of acid 180 to Meldrum’s acid, followed by reduction using NaBH\(_4\), gave 5-mono-substituted Meldrum’s acid 179,\(^68\) which was then refluxed in toluene for 5 hours to give pyrrolidinone 116.\(^69\) It should be noted that although 5-mono-substituted Meldrum’s acid 179 and pyrrolidinone 116 have been previously synthesised by other research groups, no data was provided for either compound.

\[ \text{O} \text{H} \text{NH}_2 \xrightarrow{\text{(i)}} \text{O} \text{H} \text{N} \text{Boc} \xrightarrow{\text{(ii)}} \text{O} \text{O} \text{C} \text{O} \text{N} \text{Boc} \xrightarrow{\text{(iii)}} \text{F} \text{O} \text{C} \text{O} \text{N} \text{Boc} \]

Reagents and conditions: (i) Boc\(_2\)O, NaOH, THF/H\(_2\)O, 0°C to r.t., 97%; (ii) (a) Meldrum's acid, DMAP, DCC, DCM, -5°C, 24 h, (b) NaBH\(_4\), AcOH, DCM, -5°C, 24 h, 78%; (iii) toluene, reflux, 5h, 99%.

**Scheme 2.18: Synthetic routes to pyrrolidinone 116**

### 2.1.8 Synthesis of pyrrolinone 188

Following the successful synthesis of pyrrolidinone 116, focus then shifted towards the forthcoming Stille reaction of vinyl iodide 118 and vinyl stannane 117 (Scheme 2.1 on page 38).

Synthesis of vinyl iodide 118 was achieved following a literature precedent,\(^46\) which involved taking commercially available ethyl propynoate 182 \(^\text{(Scheme 2.19)}\) and refluxing it with LiI and AcOH in MeCN, resulting in vinyl iodide 118 with 100% Z geometry, in a 83% yield.

\[ \text{O} \text{O} \text{C} \text{O} \text{I} \xrightarrow{\text{(i)}} \text{I} \text{C} \text{O} \text{I} \]

Reagents and conditions: (i) LiI, AcOH, MeCN, reflux, 83%.

**Scheme 2.19: Synthetic routes to vinyl iodide 118**

Previous research indicated that there was precedent for a Stille reaction between vinyl iodide 118 and a vinyl stannane.\(^71\) Thus, upon reacting the TBDPS
protected vinyl stannane 183 (Scheme 2.20) with vinyl iodide 118 using (MeCN)₂PdCl₂ in DMF, ester 184 was synthesised with complete retention of the E and Z double bonds.

\[
\begin{align*}
\text{TBDPSO} & \quad \text{SnBu}_3 \\ 183 & \quad + \quad \text{I} & \quad \text{O} \\ & \quad \text{OE} \\ 118 & \quad \xrightarrow{\text{()}} \\ & \quad \text{TBDPSO} & \quad \text{SnBu}_3 \\ & \quad \text{O} & \quad \text{OE} \\ 184 &
\end{align*}
\]

Reagents and conditions: (i) (MeCN)₂PdCl₂, DMF, r.t., ≥ 99%.

**Scheme 2.20: Synthetic route to ester 184**

With this in consideration it was decided that a trial system should be set up to test the Stille reaction on a similar sized non-functionalised alkyl chain as vinyl stannane 117 (Scheme 2.1 on page 38). It was, therefore, envisaged that ester 185 (Scheme 2.21) would be synthesised through the Stille coupling of vinyl stannane 186 and vinyl iodide 118. Vinyl stannane 186 in turn would be derived from 1-tridecyne 187 through the use of radical promoted hydrostannylation.

\[
\begin{align*}
\text{O} & \quad \text{OE} \\ 185 & \quad \xrightarrow{\text{SnBu}_3} \\ 186 & \quad + \quad \text{I} & \quad \text{O} \\ & \quad \text{OE} \\ 118 & \quad \xrightarrow{\text{SnBu}_3} \\ & \quad \text{OE} \\ 187 &
\end{align*}
\]

**Scheme 2.21: Retrosynthetic analysis of ester 185**

With respect to the radical promoted hydrostannylation, literature precedent indicated that refluxing commercially available 1-pentyne 188 (Scheme 2.22) in benzene, in the presence of tributyl tin hydride and AIBN, resulted in the synthesis of vinyl stannane 189 in a 1E : 1Z = 4 : 1 ratio.

\[
\begin{align*}
\text{SnBu}_3 & \quad \xrightarrow{\text{()}} \\ 188 & \quad \xrightarrow{\text{SnBu}_3} \\ 189 & \quad 1E : 1Z = 4 : 1
\end{align*}
\]

Reagents and conditions: (i) Bu₃SnH, AIBN, benzene, reflux, 84%.

**Scheme 2.22: Synthetic route to vinyl stannane 189**

Thus, taking into account the above findings, commercially available 1-tridecyne 187 underwent radical promoted hydrostannylation (Scheme 2.23) to give a
vinyl stannane 186 in a $1E : 1Z = 10 : 1$ ratio. Although the $E/Z$ ratio was better than expected with respect to the literature precedent (Scheme 2.22 on page 55), separation of the two isomers via column chromatography was not possible. Stannane 186 was then reacted with vinyl iodide 118 under the previously mentioned Stille conditions (Scheme 2.20 on page 55) to give ester 185 in a $(2Z,4E) : (2Z,4Z) = 10 : 1$ ratio.

![Scheme 2.23: Synthetic route to ester 185](image)

Reagents and conditions: (i) $i$-BuSnH, AlBN, benzene, reflux, 82%; (ii) (MeCN)$_2$PdCl$_2$, 118, DMF, r.t., 80%.

**Scheme 2.23: Synthetic route to ester 185**

The geometry of the double bond in both vinyl stannane 186 and ester 185 was determined by $^1$H NMR analysis. The $1E$ vinyl stannane 186, had a coupling constant value of 18.9 Hz between 1-H and 2-H, indicating a trans double bond. The cis geometry seen in 1Z vinyl stannane 186 was indicated through a coupling constant value of 12.4 Hz. With respect to ester 185, the geometry of the major $2Z,4E$-185 isomer was determined by a coupling constant value of 14.0 Hz between 4-H and 5-H and 11.4 Hz between 2-H and 3-H. The geometry of minor $2Z,4Z$-185 isomer was in turn determined by a coupling constant value of 11.5 Hz between 4-H and 5-H and 11.5 Hz between 2-H and 3-H.

It was then decided that through the use of known chemistry (Scheme 1.4 on page 19),$^{25}$ pyrrolinone 188 could be synthesised from ester 185 (Scheme 2.24) in order to ascertain the compatibility of the $Z,E$ diene functional group with the given chemical conditions.

![Scheme 2.24: Retrosynthetic analysis of pyrrolinone 188](image)
Thus, ester 185 (Scheme 2.25 on page 57) was hydrolysed to give acid 189, with no change in the double bond ratios being indicated by $^1$H NMR. Acid 189 was then converted to imidazolidine 190, with apparent partial loss of the 2Z,4Z geometry and the appearance of a new and more stable 2E,4E geometry, presumably through an unexpected reversible conjugate addition process. The geometry of the major (2Z,4E)-190 imidazolidine isomer was determined by $^1$H NMR spectroscopy, where a coupling constant of 15.4 Hz was seen between 4-H and 5-H and 11.3 Hz between 2-H and 3-H. With respect to the minor (2E,4E)-190 imidazolidine isomer, a coupling constant of 14.8 Hz was seen between the 4-H and 5-H and 14.9 Hz between 2-H and 3-H.

**Scheme 2.25: Synthetic route to imidazolidine 190**

Formation of imidazolidine 190 (Scheme 2.25) over different periods of time (Table 2.2) indicated that the (2Z,4E) to (2E,4E) isomers reached an equilibrium somewhere between 2 and 16 hours. The optimum conditions discovered involved a reaction time of 45 minutes giving a (2Z,4E) : (2E,4E) = 5 : 1 ratio, with a slight drop in the percentage yield to 82%.

<table>
<thead>
<tr>
<th>Time</th>
<th>(2Z,4E) : (2E,4E) ratio</th>
<th>Overall Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 h</td>
<td>(2Z,4E) : (2E,4E) = 1 : 1</td>
<td>96</td>
</tr>
<tr>
<td>2 h</td>
<td>(2Z,4E) : (2E,4E) = 3 : 1</td>
<td>94</td>
</tr>
<tr>
<td>45 min</td>
<td>(2Z,4E) : (2E,4E) = 5 : 1</td>
<td>82</td>
</tr>
</tbody>
</table>

**Table 2.2: Results showing the increase of the unwanted (2E,4E) isomer through a time dependent reversible conjugate addition mechanism**

The newly synthesised imidazolidine 190 was then used to acylate pyrrolidinone 116 (Scheme 2.26 on page 58) under basic conditions to give oxopyrrolidine 191 with a (2Z,4E) : (2E,4E) = 5 : 1 ratio, with both isomers existing entirely in their enolic form.
Subsequent phenyl selenenylation gave selenide 192 as a 10 : 4 mixture of epimers at C(2’) for the (2Z,4E) isomer with apparent masking of the (2E,4E) isomer. This was then followed by oxidative elimination, using m-CPBA and H₂O₂ in CDCl₃/H₂O, to give pyrrolinone 188.²⁵

![Scheme 2.26: Synthetic route to pyrrolinone 188](image)

Pyrrolinone 188 was left in solution, as prior research has shown that this type of compound has a tendency to polymerise upon isolation. A small sample taken out for ¹H NMR analysis indicated the presence of at least the (2Z,4E) isomer, with the characteristic peaks at 5.10 ppm (5’-H) and 8.08 ppm (6’-H).²¹

2.1.9 Work towards ester 115

Having successfully carried out trials on both the Stille reaction (Scheme 2.23 on page 56) and subsequent reactions (Scheme 2.25 on page 57 and Scheme 2.26 on page 58), attention could now be focussed on the synthesis of vinyl stannane 117, which would be used in conjunction with vinyl iodide 118 under Stille conditions to form ester 115 (Scheme 2.1 on page 38). Due to the predicted instability of the triene moiety, it was decided that alcohol 119 (Scheme 2.1 on page 38) should initially have the vinyl stannane segment incorporated before the formation of the triene functional group.

It was therefore envisaged that vinyl stannane 193 (Scheme 2.27 on page 59) could be synthesised from alkyne 194 through radical promoted stannylation (seen previously Scheme 2.23 on page 56). Alkyne 194 would in turn be synthesised from alcohol 119 through a process of oxidation and Seyferth-Gilbert homologation.⁷³
Scheme 2.27: Retrosynthetic analysis of vinyl stannane 193

Research precedent has shown that homologation of highly sensitive α-alkyl aldehydes\textsuperscript{74} using the Ohira-Bestmann modification\textsuperscript{75} of the Seyferth-Gilbert homologation results in alkynes with no epimerisation at the α-centre. Thus, Marshall and co-workers\textsuperscript{74} in 2000 took aldehyde 195 (Scheme 2.28) and reacted it with diazophosphonate 196, which resulting in the formation of alkyne 197 with the stereochemistry of the α-centre still intact.

\[ \text{HCO} - \text{OMe} \quad + \quad \text{MeO-PO-N}_2 \quad \xrightarrow{(i)} \quad \text{MeO} - \text{OMe} \quad \xrightarrow{(i)} \quad \text{OMe} \quad \text{OMe} \]

Reagents and conditions: (i) KO\text{-}Bu, THF, -78°C to r.t., 92%

Scheme 2.28: Synthetic route to alkyne 197

With the above strategy and research in mind, the synthetic route towards vinyl stannane 193 commenced by taking alcohol 119 (Scheme 2.29) and oxidising it with DMP in the presence of pyridine to give aldehyde 198.\textsuperscript{76} Attempts to perform the oxidation without pyridine, or to column the aldehyde resulted in epimerisation of the sensitive chiral centre at C(2), which was apparent by \textsuperscript{1}H NMR spectroscopy through the appearance of an extra aldehyde proton peak in a 1 : 1 ratio.

\[ \text{OH} \quad \xrightarrow{(i)} \quad \text{H} \quad \xrightarrow{(ii)} \quad \text{OTBS} \]

Reagents and conditions: (i) DMP, pyridine, DCM, r.t., 97%; (ii) (a) K\text{2}CO\text{3}, 196, MeOH, r.t., 66% or (b) t\text{-}BuOK, 196, THF\text{MeOH}, -78°C to r.t., 36%.

Scheme 2.29: Synthetic route to alkyne 199

This was then followed by an attempt to convert aldehyde 198 (Scheme 2.29) into alkyne 194 using the Ohira-Bestmann modification of the Seyferth-Gilbert...
homologation. However, attempted homologation through the process of adding diazo-phosphonate 196 (2.5 eq) in MeOH to a r.t. solution of aldehyde 198 (1 eq) with subsequent addition of K$_2$CO$_3$ (2.5eq) and stirring at r.t., resulted in alkyne 199 as an unexpected 5 : 3 mixture of epimers at C(7) in a 66% yield, which was apparent by $^1$H NMR spectroscopy through the appearance of an extra alkyne 9-H peak at 2.00 ppm. A possible explanation for alkyne 199 appearing as a mixture of epimers, involved the concept of competing deprotonation between aldehyde 198 and diazo-phosphonate 196, which was temperature dependent.

It was decided therefore, to modify the conditions, so emphasis was placed on the temperature and timing at which the deprotonation took place. Thus, deprotonation of diazo-phosphonate 196 (2.5 eq) (Scheme 2.29 on page 59) was carried out at -78°C using t-BuOK (2.5 eq) in THF/MeOH, with subsequent stirring at -78°C for 30 minutes. This was then followed by the addition of a -78°C solution of aldehyde 198 (1 eq) in THF/MeOH, with stirring at -78°C for 20 minutes and then at r.t.. This resulted in alkyne 199 as a 5 : 1 mixture of epimers at C(7) in a disappointing 36% yield. Due to the epimerisation at C(7) and subsequent modifications which resulted in low yields, it was decided that an alternative route towards alkyne 194 should be investigated.

Subsequent work employing Corey-Fuchs conditions proved to be more reliable in the synthesis of alkyne 194. The first step of the procedure involved the conversion of aldehyde 198 (Scheme 2.30) into vinyl dibromide 200, which was then transformed into alkyne 194 using n-BuLi through the process of lithium halogen exchange and subsequent elimination, with no evidence for epimerisation in either step.

![Scheme 2.30: Synthetic route to alkyne 194](image)

Reagents and conditions: (i) Zn, PPh$_3$, CBr$_4$, DCM, 0°C to r.t., 74%; (ii) n-BuLi, THF, -78°C, 80%.

Initial attempts to convert alkyne 194 (Scheme 2.31 on page 61) into vinyl stannane 193, using radical promoted hydrostannylation, resulted in a disappointing $8E : 8Z = 5 : 3$ ratio, in comparison to previous research which gave a $1E : 1Z = 10 : 1$ ratio.
for vinyl stannane \textit{186 (Scheme 2.23 on page 56)}. The \textit{trans} geometry of the 8\textit{E} isomer was indicated through a coupling constant of 18.9 Hz between 8-H and 9-H and the \textit{cis} geometry in turn was indicated by a coupling constant of 12.3 Hz between the corresponding protons.

\begin{center}
\includegraphics[width=\textwidth]{scheme2.31.png}
\end{center}

\textbf{Scheme 2.31: Synthetic route to vinyl stannane \textit{193}}

With the disappointing outcome of radical promoted hydrostannylation, attention then turned towards the use of palladium based methods to install the vinyl stannane group. Research indicated that there was relevant precedent for the conversion of alkynes with an \(\alpha\)-alkyl group into \textit{E}-vinyl stannanes.\textsuperscript{80} Here, alkyne \textit{201 (Scheme 2.32)} was successfully converted into vinyl stannane \textit{202} through the use \(n\)-\textit{Bu}_3\textit{SnH}, \textit{Pd(PPh}_3)_2\textit{Cl}_2 in THF at r.t.

\begin{center}
\includegraphics[width=\textwidth]{scheme2.32.png}
\end{center}

\textbf{Scheme 2.32: Synthetic route to vinyl stannane \textit{202}}

Using the above conditions however, resulted in the conversion of alkyne \textit{194} into a mixture of isomers (\textit{Scheme 2.33} on page 62), which consisted of vinyl stannane \(8\textit{E}-193\) : and presumed regioisomer \textit{203} = in a 6 : 4 ratio, in a combined yield of 50\%. With respect to regioisomer \textit{203}, \textsuperscript{1}H NMR analysis indicated the presence of multiplets at 4.84 ppm and 5.46 ppm, which was compatible with literature precedent.\textsuperscript{81} This, however, was by no means conclusive and no further work was undertaken to identify the regioisomer.
Scheme 2.33: Synthetic route to vinyl stannane 193 and regioisomer 203

With the lack of success in converting alkyne 194 into vinyl stannane 193 using radical and Pd based methods, it was decided that an alternative route towards ester 115 should be investigated. It was proposed that ester 115 (Scheme 2.34) could be synthesised by a Stille reaction between known vinyl stannane 204 and vinyl iodide 205. Vinyl iodide 205 in turn could be made through Julia olefination using BT-sulphone 120 and aldehyde 206. Synthesis of aldehyde 206 from aldehyde 198 would be achieved through Takai olefination to install the vinyl iodide functional group, followed by TBS deprotection and oxidation. It should be noted that there are ample precedents concerning the reaction of aldehydes bearing an α-stereocentre under Takai conditions, without any adverse effect on the stereocentre.

Scheme 2.34: Retrosynthetic analysis of ester 115

Literature precedent is also available for the Stille coupling of vinyl stannane 204 with simple vinyl iodides. Thus, vinyl stannane 204 (Scheme 2.35 on page 63) and vinyl iodide 207 were reacted together using Pd(CH3CN)2Cl2 to give diene 208 in a 78% yield.
Scheme 2.35: Synthetic route to diene 208

The new synthetic route was initiated by taking the previously synthesised aldehyde 198 (Scheme 2.28 on page 59) and converting it to vinyl iodide 209 in an 8E : 8Z = 94 : 6 ratio with a 76% yield (Scheme 2.36), under Takai olefination conditions. Vinyl iodide 209 was then TBS deprotected using TBAF to give alcohol 210, which was subsequently oxidised using DMP to give aldehyde 206 with no change in the 8E/8Z ratio. The trans geometry of the 8E isomer was indicated by a coupling constant value of 18.9 Hz between 8-H and 9-H and the cis geometry in turn was indicated by a coupling constant value of 12.3 Hz between the corresponding protons.

Scheme 2.36: Synthetic route to aldehyde 206

Literature precedent of Julia olefination using an aldehyde that has a vinyl iodide functional group is not abundant. One example discovered involved the coupling of BT-sulphone 211 (Scheme 2.37) with aldehyde 212, with no effect on the vinyl iodide functional group contained within ester 213.

Scheme 2.37: Synthetic route to ester 213
Several attempts were then made to convert aldehyde 206 into vinyl iodide 205, using BT-sulphone 120 (Scheme 2.38), under previously mentioned conditions (Scheme 2.16 on page 51). However, $^1$H NMR analysis indicated a mixture of multiple products that could not be identified.

![Scheme 2.38: Attempted synthetic route to vinyl iodide 205](image)

Reagents and conditions: (i) LiHMDS, 120, THF, -78°C to r.t.

Although the vinyl iodide group proved to be incompatible with the Julia olefination conditions used, it was decided that vinyl iodide 209 (Scheme 2.36 on page 63) could be converted into vinyl stannane 193 (Scheme 2.33 on page 61), which would then be introduced into the synthetic route (Scheme 2.1 on page 38) to give vinyl stannane 117.

Thus, vinyl iodide 209 was converted into vinyl stannane 193 (Scheme 2.39 on page 65) by treatment with $t$-BuLi in the presence of Bu$_3$SnCl, with retention of the $8E : 8Z = 94 : 6$ isomer ratio. Subsequent TBS deprotection using TBAF gave alcohol 214, which was then oxidised using activated MnO$_2$ to give aldehyde 215. Aldehyde 215 was then reacted with BT-sulphone 120 under previously optimised Julia conditions (Scheme 2.16 on page 51) to give vinyl stannane 117 as a $(1E,7E,9E,11E) : (1E,7E,9Z,11E) : (1E,7E,9E,11Z) = 88 : 7 : 5$ mixture of isomers, which were inseparable by column chromatography.
Scheme 2.39: Synthetic route to vinyl stannane 117

The major \((1E,7E,9E,11E)\)-117 (Scheme 2.39) isomer was identified by a trans coupling constant value of 15.3 Hz between 9-H and 10-H and the \((1E,7E,9Z,11E)\)-117 isomer was in turn identified through a cis coupling constant value of 11.5 Hz between 9-H and 10-H. The geometry of the \(7E\) and \(11E\) double bonds of both isomers was implied from the starting materials used in the Julia reaction. Identification of the \((1E,7E,9E,11Z)\)-117 isomer was provided at a later date through the outcome of other research (Section 2.2.2, pages 70-73).

Several attempts were then made to convert vinyl stannane 117 into ester 115 (Scheme 2.40) under previously discussed Stille conditions (Scheme 2.20 on page 55), but \(^1\)H NMR analysis indicated a mixture of multiple isomers that could not be characterised.

Scheme 2.40: Attempted synthetic route to ester 115
Although the triene functional group proved to be incompatible with palladium based coupling procedures, it is worth mentioning work that was concurrently being investigated with respect to the preceding work on pages 58-64, with respect to performing a Stille reaction on vinyl stannane 117 with an alternative vinyl iodide. Thus, it was demonstrated that ester 115 (Scheme 2.41) could be synthesised by a Stille reaction between vinyl stannane 117 and vinyl iodide 216. The appeal of this route would be a more convergent approach to the ultimate synthesis of chaetochalasin A 1.

![Scheme 2.41: Retrosynthetic analysis of ester 115](image)

The nearest literature precedent to such a Stille reaction involved reacting vinyl stannane 217 (Scheme 2.42) with vinyl iodide 218, resulting in ester 219 with complete retention of the double bond geometries. Although vinyl iodide 218 is structurally dissimilar from the β-keto tertiary amide group required in vinyl iodide 216, it was decided that time should be invested in testing the effect of such a functional group on the coupling procedure involved in the Stille reaction.

![Scheme 2.42: Synthetic route to ester 219](image)

It was believed that vinyl iodide 216 (Scheme 2.43 on page 67) could be synthesised from alkynyl iodide 220 using diimide reduction through the use of potassium (Z)-diazene-1,2-dicarboxylate. Research indicated that alkynyl iodide 220 in turn could be synthesised from alkyne 221 using silver catalysed iodination. Alkyne 221 could then be made from commercially available 3-(trimethyl silyl)propynoic acid.
222 through the use of previously utilised chemistry (Scheme 1.4 on page 19), followed by TMS deprotection.

Scheme 2.43: Retrosynthetic analysis of vinyl iodide 216

The synthesis began by taking commercially available 3-(trimethylsilyl) propynoic acid 222 (Scheme 2.44) and converting into imidazolide 223, which was then used to acylate pyrrolidinone 116 to give oxopyrrolidine 224. Oxopyrrolidine 224 was then TBS deprotected using TBAF to give alkyne 221 in a 74% yield. This was then followed by an attempt to convert alkyne 221 into iodide 220 (Scheme 2.43) using silver catalysed iodination, which instead gave bis-iodide 225 in a 55% yield.

Scheme 2.44: Synthetic route to bis-iodide 225

A subsequent attempt to convert alkyne 221 (Scheme 2.45 on page 68) into vinyl iodide 216 using conditions mentioned previously (Scheme 2.19 on page 54), resulted in the formation of base line material which could not be identified.
At this stage, work towards vinyl iodide 216 was stopped due to the results obtained from the Stille reaction (Scheme 2.39 on page 65), which indicated the incompatibility of the triene functional group with such a reaction. It was, therefore, decided that an alternative route towards the formation of the \( E,Z \) diene functional group should be investigated.

### 2.2 Non-tin mediated route towards Chaetochalasin A 1

#### 2.2.1 Retrosynthetic analysis towards pyrrolinone 110

As seen in the tin mediated retrosynthetic analysis (Scheme 2.1 on page 38), the latter stages leading to pyrrolinone 110 following formation of an ester (in this case methyl ester 226) are identical. It was postulated that methyl ester 226 (Scheme 2.46 on page 69) would be synthesised through a \( Z \)-selective Still-Gennari condensation\(^\text{92}\) using aldehyde 227, which would be synthesised by DIBAL-H reduction and oxidation of ester 228. Ester 228 in turn would be derived from aldehyde 229 and BT-sulphone 120 through the process of Julia olefination. Aldehyde 229 would be synthesised from aldehyde 198 through a process of Wittig homologation,\(^\text{93}\) TBS deprotection and oxidation.
2.2.2 Synthesis of methyl ester 226

The synthesis began by performing Wittig homologation on the previously synthesised aldehyde 198 (Scheme 2.29 on page 59) using (carbethoxymethylene) triphenylphosphorane,\(^{93}\) which only produced the 2\(E\) ester 230 in a 73% yield (Scheme 2.47). The trans geometry of the double bond was identified by a coupling constant of 15.6 Hz between 2-H and 3-H. Ester 230 was then TBS deprotected using PPTS to give allylic alcohol 231 which was then subsequently oxidised using activated MnO\(_2\), yielding aldehyde 229.

\[\text{Reagents and conditions: (i) (carbethoxymethylene)/triphenylphosphorane, DCM, r.t., 73%; (ii) PPTS, DCM/EtOH, r.t., 90%; (iii) MnO}_2\,\text{DCM, r.t., 85%}.\]

Scheme 2.47: Synthetic route to aldehyde 229

Several examples of literature precedent were found describing the Julia olefination of an aldehyde that has a vinyl ester functional group. One of these involved the coupling of PT-sulphone 232 (Scheme 2.48 on page 70) with aldehyde 233, to give ester 234 in a 93% yield, with no detrimental effect on the vinyl methyl ester group.\(^{94}\)
Consequently aldehyde 229 (Scheme 2.49) was then reacted with BT-sulphone 120 under previously optimised Julia conditions (Scheme 2.16 on page 51) to give ester 228 as a $(2E,8E,10E,12E):(2E,8E,10Z,12E):(2E,8E,10E,12Z) = 87 : 6 : 7$ mixture of isomers, which were inseparable by column chromatography.

The major $(2E,8E,10E,12E)$-228 isomer (Scheme 2.49) was identified by a coupling constant value of 15.4 Hz between $10\text{-}H$ and $11\text{-}H$ and the $(2E,8E,10Z,12E)$-228 isomer was in turn identified through a cis coupling constant value of 11.6 Hz between $10\text{-}H$ and $11\text{-}H$. Assignment of the geometry of the $8E$ and $12E$ double bonds of both isomers, along with the geometries of the $(2E,8E,10E,12Z)$-228 isomer, was provided by a more in-depth analysis, which is discussed next.

To determine if the C(12)-C(13) or the C(8)-C(9) double bond of ester 228 was isomerising, the $^1$H NMR spectrum (CDCl$_3$) (Figure 6.1 on page 182) of the $(2E,8E,10E,12Z)$-228 isomer (Scheme 2.49) was analysed with respect to the corresponding spectra of the $(8E,10E,12E)$-59 and $(8Z,10E,12E)$-59 isomers (Scheme 1.10 on page 24), the results of which are displayed below (Figure 2.8 on page 71).
Figure 2.8: Comparison of 1H NMR spectroscopic data of the (2E,8E,10E,12Z)-228, (8E,10E,12E)-59 and (8Z,10E,12E)-59 isomers

One of the key results to come from the above analysis is the position of the 11-H signal. With the (8E,10E,12E)-59 and (8Z,10E,12E)-59 isomers, the 11-H is seen at 6.18 ppm and 6.15 ppm respectively, whereas the (2E,8E,10E,12Z)-228 isomer has a 11-H situated at 6.57 ppm.

Further analysis of the 1H NMR (CDCl₃) spectrum of the (2E,8E,10E,12Z)-228 isomer with the 1H NMR spectrum (CDCl₃) of an unknown isomer of 59, which was speculated to be the 12Z isomer, indicated a clear overlap of all signals (Figure 2.9). Of particular importance is the close proximity of the 11-H signal for both the (2E,8E,10E,12Z)-228 (6.57 ppm) and (8E,10E,12Z)-59 (6.73 ppm) isomers.

Figure 2.9: Comparison of 1H NMR spectroscopic data of the (2E,8E,10E,12Z)-228 and (8E,10E,12Z)-59 isomers

Further evidence came from subsequent research, which identified precedent for the triene functional group, seen with respect to (2E,4E,6E)-235 tetraene and (2Z,4E,6E)-236 tetraene (Figure 2.10 on page 72). The analysis shows clear overlap
of all signals for the \((2E,8E,10E,12E)-228\) and \(\(2E,4E,6E\)-235\) tetraene, as well as the \((2E,8E,10E,12E)-228\) and \(\(2Z,4E,6E\)-236\) tetraene.

\[
\begin{align*}
(2E,8E,10E,12E)-228 & : \\
& \text{5.84 ppm, d, J 10.9} \\
& \text{6.18 ppm, d, J 15.2} \\
(2E,4E,6E)-235 & : \\
& \text{5.88 ppm, d, J 10.7} \\
& \text{6.17 ppm, d, J 15.3} \\
(2E,8E,10E,12Z)-228 & : \\
& \text{5.93 ppm, d, J 10.9} \\
& \text{6.57 ppm, d, J 15.3} \\
(2Z,4E,6E)-236 & : \\
& \text{5.97 ppm, d, J 10.0} \\
& \text{6.57 ppm, d, J 15.0} \\
\end{align*}
\]

**Figure 2.10:** Comparison of \(1H\) NMR spectroscopic data of the \((2E,8E,10E,12Z)-228\), \((2E,4E,6E)-235\) tetraene and \((2Z,4E,6E)-236\) tetraene

Subsequent NOe studies provided more evidence for the geometry of the \((2E,8E,10E,12E)-228\) and \((2E,8E,10E,12Z)-228\). With respect to the \((2E,8E,10E,12E)-228\) isomer (Figure 2.11), interactions through space were observed between the signal at 5.55 ppm (13-H) and the signals at 6.33 ppm (10-H) / 1.74 ppm (13-Me). No interaction through space was seen between the signal at 5.84 ppm (9-H) and 1.79 (8-Me). Also, no interaction through space was seen between the 13-H signal and the signal located at 1.79 ppm (12-Me).

\[
\begin{align*}
(2E,8E,10E,12E)-228 & : \\
& \text{5.84 ppm, d, J 10.9} \\
& \text{6.18 ppm, d, J 15.2} \\
(2E,8E,10E,12Z)-228 & : \\
& \text{5.93 ppm, d, J 10.9} \\
& \text{6.57 ppm, d, J 15.3} \\
\end{align*}
\]

**Figure 2.11:** NOe studies performed on the \((2E,8E,10E,12E)-228\) and \((2E,8E,10E,12Z)-228\) isomers. A solid line indicates a detected NOe and dashed line indicates an undetected NOe.
With respect to the \((2E,8E,10E,12Z)\)-228 isomer (Figure 2.11 on page 72), interactions through space was observed between the signal at 5.41 ppm (13-H) and the signals at 1.74 ppm (13-Me) / 1.79 ppm (12-Me). No interaction through space was seen between the signal at 5.93 ppm (9-H) and 1.79 (8-Me). Also, no interactions through space were seen between the 13-H signal and the signals located at 6.43 ppm (10-H) and 6.57 ppm (11-H).

### 2.2.3 Synthesis of pyrrolinone 110

With respect to the upcoming Z-selective Still-Gennari condensation outlined previously (Scheme 2.46 on page 69), research precedent indicated that the reaction conditions required were compatible with compounds bearing a sensitive \(\gamma\)-chiral centre, as seen in ester 228. Thus, when aldehyde 237 was reacted (Scheme 2.50) with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate in the presence of 18-crown-6, using KHMDS as base, methyl ester 238 was produced in a 70% yield with no detrimental effect on the \(\gamma\)-chiral centre.\(^{98}\)

![Scheme 2.50: Synthetic route to methyl ester 238](image)

Reagents and conditions: (i) KHMDS, 18-crown-6, THF, r.t., bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate, \(-78^\circ C, 70\%\).

The newly synthesised ester 228 (Scheme 2.49 on page 70) was then reduced with DIBAL-H to give allylic alcohol 239 (Scheme 2.51 on page 74), which was subsequently oxidised using activated MnO\(_2\) to give aldehyde 227. Aldehyde 227 was then subject to a Still-Gennari condensation,\(^{92}\) which led to methyl ester 226 in a 86% yield, with a \((2Z,4E,10E,12E,14E) : (2E,4E,10E,12E,14E) = 95 : 5\) ratio, separable by column chromatography. Formation of the \(2Z,4E\) geometry seen in the \((2Z,4E,10E,12E,14E)\)-226 isomer was indicated by a coupling constant value of 15.3 Hz between the 4-H and 5-H and 11.4 Hz between the 2-H and 3H.
Methyl ester 226 was then hydrolysed to give acid 240 (Scheme 2.52 on page 75), which was then converted into imidazolide 241. In order to minimise the reversible conjugate addition seen previously (Scheme 2.25 on page 57), the optimised reaction time of 45 min was used. No $^1$H NMR spectra or any other data was acquired at this stage due to the possible instability of the compound, and thus upon formation it was quickly used to acylate pyrrolidinone 116 to give oxopyrrolidinone 114 entirely in its enolic form in a 58% yield, with an isomer ratio of $(2Z,4E,10E,12E,14E) : (2Z,4E,10E,12Z,14E) = 73 : 5 : 22$. $^1$H NMR spectroscopic analysis indicated the presence of both the $(2Z,2E)$ and $(2E,4E)$ isomers in a ratio of 10 : 1, and were interpreted with respect to previous results that displayed reversible conjugate addition (Scheme 2.25 on page 57).
Scheme 2.52: Synthetic route to pyrrolinone 110

Subsequent phenyl selenenylation of oxopyrrolidine 114 (Scheme 2.52) resulted in the formation of selenide 242. Upon inspection of the crude $^1$H NMR spectrum of selenide 242, it was discovered that further isomerisation of the C(14)-C(15) double bond had occurred resulting in an increase of the 14Z isomer. The isomer ratio of selenide 242 was not determined due to the sample being crude. Further evidence for the formation of the compound was provided mass spectrometry on the crude compound, which showed a signal at 668 (M$^+$ + 1, 70%).

It was decided that due to the lack of material following purification and the possible sensitivity of the compound, selenide 242 should be carried straight through to the next reaction without any further data being acquired. Subsequent oxidative elimination (Scheme 2.52) using m-CPBA and H$_2$O$_2$ in CDCl$_3$/H$_2$O resulted in the conversion of selenide 242 into pyrrolinone 110. A sample taken out for $^1$H NMR spectroscopic analysis indicated the presence of the pyrrolinone 110 through the characteristic peaks at 5.08 ppm (5'-H) and 8.04 ppm (6'-H).21

During the synthesis of pyrrolinone 110 there was a gradual increase in the amount of the Z terminal double bond of the triene functional group, with some
reactions showing a greater propensity towards this process. The DIBAL-H reduction was one such reaction, which involved stirring ester 228 (Scheme 2.51 on page 74) at -78°C with subsequent warming to r.t. before the quench. In retrospect, it may have been more beneficial to attempt the quench at a lower temperature to minimise the isomerisation. Formation of the oxopyrrolidine 114 and selenide 242 (Scheme 2.52 on page 75) was also accompanied by a dramatic increase in isomerisation. Due to a lack of material at such a late stage of a long linear synthesis, no modifications of reaction conditions were investigated. From the results however, it could be reasoned that the triene is both sensitive to strongly basic and acidic conditions.

Following the conditions outlined previously (Scheme 1.10 on page 24) the remaining pyrrolinone 110 in CDCl₃ (Scheme 2.53) was then introduced into degassed toluene at 40°C. The mixture was then subsequently degassed at 40°C for 30 minutes, before being heated at reflux at 90°C for 6 hours; in an attempt to convert pyrrolinone 110 into exo Boc adduct 113 through a domino Diels-Alder reaction. ¹H NMR analysis of the crude product showed no identifiable products and further purification by column and subsequent ¹H NMR analysis of various fractions, again proved inconclusive.

**Scheme 2.53: Attempted synthetic route towards exo Boc adduct 113**

The lack of success in the Diels-Alder reaction raised several potential issues which could be broadly categorised into two main areas: (i) problems relating to the overall synthetic route leading up to selenide 242 (Scheme 2.52 on page 75), (ii) problems relating to the oxidative elimination and Diels-Alder reactions.

(i) The problems relating to the synthetic route can again be broken down into two main areas: (a) isomerisation of the terminal double bond of the triene functional group, (b) the reversible conjugate addition (Scheme 2.52 on page 75), resulting in an increase of the unwanted (2E,4E) diene of 241. Although both effects would not prove
disastrous towards the Diels-Alder reaction, they would in all probability lead to extra Diels-Alder adducts, which in turn could cause problems with isolation and characterisation.

(ii) The problems relating to the latter steps include both the oxidative elimination reaction and the performance of the Diels-Alder reaction on pyrrolinone 110, with respect to the use of a Boc protecting group, both of which are addressed in the following chapter (Section 3.1, pages 78 to 79).

It was, therefore, decided that a simpler pyrrolinone 243 (Figure 2.12), which lacked the Z component of the Z,E diene, should be synthesised. Such a change would simplify the synthetic sequence, resulting in a reduction in the number of steps the triene functional group would be subject to.

![Figure 2.12: Target for new synthetic route](image)

With success in this area, the expertise acquired in handling the triene functional group and performing the oxidative elimination and subsequent Diels-Alder reaction, would then be directed towards a further attempt at synthesising chaetochalasin A 1.
3.0 Results and Discussion 2

3.1 Resolution of potential problems

Before any work was undertaken on the synthesis of the pyrrolinone 243 (Figure 2.12 on page 77) through the new synthetic route, it seemed prudent to investigate potential problems associated with the oxidative elimination and Diels-Alder reactions on a simpler system. Before investigation of this new system began however, it was decided that the Boc group on pyrrolidinone 116 (Scheme 2.18 on page 54) should be replaced with a benzoyl group; the rationale of which is discussed next (Section 3.1.1, pages 78 to 79).

3.1.1 Research into N-protected pyrrolinones

Past research into the formation of pyrrolinones indicated that upon synthesising 3-acetylpyrrol-2(5H)-one 244, it quickly underwent irreversible tautomerisation to give predominately the enol form 245 (Figure 3.1).99

![Figure 3.1: Irreversible tautomerisation 3-acetylpyrrol-2(5H)-one 244](image)

Further research undertaken investigated the effect of protecting the nitrogen atom with an electron withdrawing benzoyl group.100 Thus, upon successful synthesis of pyrrolinone 246 (Figure 3.2 on page 79), ¹H NMR analysis indicated an absence of its corresponding enol tautomer. The rationale behind this is that the lone pair is delocalised into the benzoyl protecting group, resulting in the zwitterionic species 247. Subsequent tautomerisation of 247 to enol 248 does not occur, as this would lead to an unfavourable anti-aromatic 4π electron system.
The above results were backed up by subsequent research where several Bz-protected pyrrolinones were synthesised. One example involved the synthesis of pyrrolinone 249 (with no presence of the corresponding enol tautomer) (Scheme 3.1), which was then subsequently heated under reflux with the commercially available (2E,4E)-hexa-2,4-diene 250 in a Carius tube containing benzene. This resulted in the successful synthesis of the endo 251 and exo 252 Diels-Alder adducts, in a ratio of 4 : 1.

Scheme 3.1: Intermolecular Diels-Alder reaction to endo 251 and exo 252 adducts

With the above results in mind, a potential problem of using a Boc protecting group is that it is less electron withdrawing than a benzoyl group, which could result in a decrease in the constitution of zwitterionic resonance form 253 (Figure 3.3). This, in theory, would result in an increase in the proportion of enol tautomer 255 when exposed to Diels-Alder conditions. Even if the tautomerisation was not irreversible; it would certainly lead to epimerisation of the C(5’), which would result in extra unwanted Diels-Alder compounds. Due to this possible scenario, it was deemed prudent to replace the Boc group with a benzoyl protecting group.

Figure 3.3: Potential formation of enol tautomer 255
3.1.2 Synthesis of pyrrolidinone 256

The synthesis was initiated by the deprotection of the Boc-protected pyrrolidinone 116, using TFA (Scheme 3.2), to give deprotected pyrrolidinone 257. This was then subsequently benzyol protected using benzoyl chloride in pyridine to give pyrrolidinone 256, in an 84% yield.

Scheme 3.2: Synthetic route to pyrrolidinone 256

It was deemed advisable upon Boc-deprotection to ascertain how enantioselective the synthetic sequence had initially been towards pyrrolidinone 116 (Scheme 2.18 on page 54). Thus, the deprotected pyrrolidinone 257 (Scheme 3.3) was reduced to pyrrolidine 258 with lithium aluminium hydride, and subsequently reacted with both enantiomers of MTPA-Cl\textsuperscript{50} to give Mosher derivatives 259 and 260. \textsuperscript{1}H NMR analysis indicated the presence of only one diastereoisomer for each of the Mosher derivatives, and thus it was assumed that the deprotected pyrrolidinone 257 had an ee $\geq$ 96%.

Scheme 3.3: Synthetic route to Mosher derivatives 259 and 260
3.1.3 Synthesis of isoindolone 268

Having successfully synthesised pyrrolidinone 256 (Scheme 3.2 on page 80), attention was then turned towards the development of a simple intermolecular Diels-Alder reaction. Through the use of known chemistry, it was envisaged that pyrrolinone 261 (Scheme 3.4) could be synthesised by phenylselenenylation of oxopyrrolidinone 262 followed by oxidative-elimination. Oxopyrrolidinone 262 would in turn be derived from hexanoic acid 263, by initial formation of an imidazolide, which would then be used to acylate pyrrolidinone 256.

![Scheme 3.4: Retrosynthetic analysis of pyrrolinone 261](image)

The synthesis began by taking commercially available hexanoic acid 263 (Scheme 3.5 on page 82) and reacting it with 1,1'-carbonyldiimidazole to give imidazolide 264. This was then used to acylate pyrrolidinone 256 to give oxopyrrolidinone 262 in a 76% yield, as a mixture of epimers at C(3) : enol = 2 : 1 ratio, with the epimers existing in a 1 : 1 ratio. Evidence towards the formation of the enol compound was provided by the presence of the characteristic 4'-OH peak in the $^1$H NMR spectrum at 12.32 ppm. Subsequent phenylselenenylation of oxopyrrolidinone 262 gave selenide 265 as a 1.0 : 0.4 mixture of epimers at C(3) in a 77% yield. Selenide 265 then underwent a process of oxidative elimination using $m$-CPBA and H$_2$O$_2$ in CDCl$_3$/H$_2$O, to give pyrrolinone 261.
Scheme 3.5: Synthetic route to pyrrolinone 261

Pyrrolinone 261 (Scheme 3.6) was then introduced into degassed toluene and heated under reflux with commercially available (1E,3E)-1,4-diphenylbuta-1,3-diene 266 at 110°C for 96 hours to give only the Diels-Alder endo-267 adduct, which was subsequently deprotected using NaOH in MeOH/H2O to give isoindolone 268. The 1H NMR spectrum of isoindolone 268 is displayed in Figure 6.2 on page 183.

Scheme 3.6: Synthetic route to isoindolone 268

Discussed on page 83 are some of the key nOe studies taken from Figure 3.4 which indicate endo geometry for isoindolone 268.

<table>
<thead>
<tr>
<th>Response</th>
<th>Proton(s) irradiated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
</tr>
</tbody>
</table>

Figure 3.4: 1-D nOe studies on isoindolone 268
Irradiation of the signal at 2.70 ppm (4-H) proton (Figure 3.5) showed an interaction through space to the signal at 2.86 ppm (5-H) proton, indicating a cis relationship. Interaction through space was also seen between the 5-H and the signal at 4.28 ppm (8-H), which again indicated a cis relationship.

**Figure 3.5: nOe studies performed on isoindolone 268.** A solid line indicates a detected nOe and dashed line indicates an undetected nOe. Results depicted also take into account molecular modelling studies.

The above results indicate that the 5-Ph and the 8-Ph are in the favourable equatorial positions. If on the other hand they were placed in the more unfavourable axial positions, both the 5-H and 8-H would be too far away from one another to interact through space.

With regards to the experimental procedure, initial attempts to effect the oxidative-elimination of selenide 265 (Scheme 3.5 on page 82) resulted in a substantial amount of PhSe based compounds, apparent through the additional aromatic protons seen in the 1H NMR of the crude product. Although this proved to have no detrimental effect on the Diels-Alder reaction, it could be envisaged that if a significant amount of selenium was present in any Diels-Alder reaction involving the sensitive triene compounds being present, problems may arise. Two possibilities were put forward to explain the presence of the selenium: (a) problems associated with the oxidative-elimination process or (b) problems relating to the removal of the eliminated selenium species.

(a) The general conditions for the oxidative elimination involve reacting selenide 265 in CDCl3 at -48°C with H2O2 and m-CPBA, stirring at -48°C for 30-40 minutes and subsequent warming to 0°C. During the reaction the peracid is responsible for the oxidation of selenide 265 (Scheme 3.7 on page 84) to selenoxide 269, which is then eliminated upon warming, resulting in pyrrolinone 261. Therefore, if elimination was not complete, this would account for the selenium being present.
(b) The gradual warming to 0°C is also accompanied by the release of H₂O₂, which is trapped within the frozen water throughout the oxidation process. Upon release it oxidises the eliminated seleninic acid 270 (Scheme 3.7) to selenic acid 271, which is less electrophillic and therefore less likely to react with triene functional group. The selenic acid 271 produced is then removed using mild base, which deprotonates the acid, and is subsequently removed in the aqueous layer. Thus, if the deprotonation of selenic acid 271 is incomplete, this would provide an alternative reason for selenium residues being present.

Scheme 3.7: General oxidative-elimination process

With regards to the former problem, the conditions used to bring about the oxidative-elimination of selenide 265 (Scheme 3.7) involved stirring at -48°C for 45 minutes and then transferring to an ice bath with subsequent stirring for 15 minutes. It was reasoned that 15 minutes in an ice bath was insufficient time to allow the temperature to increase from -48°C to 0°C. This was backed up experimentally by careful monitoring of the internal temperature, which showed a temperature of -20°C after 15 minutes in the ice bath. Increasing the time in the ice bath was one option; however, this would lead to the possibility of an increase in the polymerisation of pyrrolinone 261. Therefore, upon completion of the stirring at -48°C the solution was allowed to stir out of the ice bath at r.t, until it reached the temperature of 0°C (10-15 minutes on average).

With respect to the incomplete deprotonation of selenic acid 271 produced (Scheme 3.7), it was decided that upon adding aqueous Na₂CO₃, vigorous stirring for 5 minutes should be employed to circumvent the potential problem.

The combined employment of the above strategies led to the formation of pyrrolinone 261 (Scheme 3.5 on page 82) without any PhSe derivatives being present and thus provided a proven method for future oxidative-elimination reactions.
3.2 Retrosynthetic analysis towards Diels-Alder adducts 272 and 273

3.2.1 Preliminary retrosynthetic analysis

It was believed that the *exo* NH 13E-272 (Scheme 3.8) and *endo* NH 13E-273 adducts could be derived from an intramolecular Diels-Alder reaction on pyrrolinone 243. Unlike the retrosynthetic analysis towards chaetochalasin A 1 (Scheme 1.15 on page 33), no domino Diels-Alder reaction would be possible here due to the absence of the Z component of the Z,E diene.

![Scheme 3.8: Preliminary retrosynthetic analysis towards the exo NH 13E-272 and endo NH 13E-273 Diels-Alder adducts](image)

3.2.2 Retrosynthetic analysis towards pyrrolinone 243

It was anticipated that pyrrolinone 243 (Scheme 3.9 on page 86) could be synthesised from ester 274 and pyrrolidinone 256, using previously discussed chemistry (Scheme 2.1 on page 38). Ester 274 would be derived from aldehyde 275 and BT-sulphone 120 through the process of Julia olefination. Formation of aldehyde 275 from allylic alcohol 276 would be achieved through a Johnson-Claisen rearrangement, TBS deprotection and subsequent oxidation. Allylic alcohol 276 would in turn be synthesised from the previously prepared (Scheme 2.29 on page 59) aldehyde 198 through the use of vinyl magnesium bromide.103
Scheme 3.9:  Retrosynthetic analysis towards pyrrolinone 243

3.3 Synthetic route towards Diels-Alder adducts 272, 273, 287 and 288

3.3.1 Synthesis of ester 274

The synthesis was initiated by taking aldehyde 198 (Scheme 3.10 on page 87) and reacting it with vinyl magnesium bromide to give allylic alcohol 276 as a diastereomeric mixture (2:1) at C(3).\textsuperscript{103} Allylic alcohol 276 was then subjected to a Johnson-Claisen rearrangement to give ester 277, entirely as the 2\textit{E} isomer, which was indicated by a coupling constant value of 15.3 Hz between 4-H and 5-H. Ester 277 was then TBS deprotected using PPTS in DCM/EtOH to give alcohol 278, which was oxidised using activated MnO\textsubscript{2} to give aldehyde 275. Aldehyde 275 was then reacted under previously optimised Julia conditions (Scheme 2.16 on page 51) with BT-sulphone 120 to give ester 274 in a 74\% yield with a (10\textit{E},12\textit{E},14\textit{E}) : (10\textit{E},12\text{Z},14\textit{E}) : (10\textit{E},12\textit{E},14\text{Z}) = 91 : 4 : 5 ratio, the components of which were inseparable by column chromatography.

The major (10\textit{E},12\textit{E},14\textit{E})-274 isomer (Scheme 3.10 on page 87) was identified by a coupling constant of 15.3 Hz between 12-H and 13-H and the (10\textit{E},12\text{Z},14\textit{E})-274 isomer was in turn identified through a \textit{cis} coupling constant of 11.6 between 12-H and 13-H. Identification of the (10\textit{E},12\textit{E},14\text{Z})-274 isomer was based on results from previous research (Section 2.2.2, pages 70-71).
Having successfully synthesised ester 274, it was then hydrolysed to give acid 279 (Scheme 3.11 on page 88), which was subsequently converted into imidazolide 280. Imidazolide 280 was then used to acylate pyrrolidinone 256 under basic conditions to give oxopyrrolidine 281 in a 79% yield, as a mixture of epimers at C(2'): enol = 2 : 1 ratio, with the epimers existing in a 1 : 1 ratio. Evidence supporting the identity of the enol compound was provided by the presence of the characteristic 4'-OH peak in the $^1$H NMR spectrum at 12.29 ppm. Subsequent phenyl selenenylation of oxopyrrolidine 281 gave selenide 282 in a 92% yield as a 1 to 0.4 mixture of epimers at C(2'). The isomer ratio of selenide 282 was $(10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 76 : 3 : 21$. 

Scheme 3.10: Synthetic route towards ester 274

3.3.2 Synthesis of pyrrolinone 243
Scheme 3.11: Synthetic route towards oxopyrrolidine 281

Through the use of base washed glassware and silica, the isomerisation of the terminal double bond of the triene functional group resulting in an increase in the (10E,12E,14Z) isomer was minimised leading to the formation of imidazolide 280 (Scheme 3.11). However, formation of both oxopyrrolidine 281 and selenide 282 proved to be problematic with regards to this issue. With respect to oxopyrrolidine 281, the isomerisation was reduced by changing the temperature of the solutions of both the base and imidazolide 280 from 0\(^\circ\)C to -78\(^\circ\)C, before addition.

The most extreme isomerisation though, was seen in the synthesis of selenide 282. Initial attempts to buffer the solution (using pyridine or Et\(_3\)N) of oxopyrrolidine 281 before the addition of PhSeCl, or attempts to buffer the PhSeCl solution before addition, led to recovery of starting material with no product visible. However, through a combination of reducing the equivalents of base and PhSeCl (which had been recrystallised to remove any HCl\(^{104}\) down to 1.1 equivalents instead of the respective 1.5 and 4.0 equivalents, combined with the alteration of the solution temperature of both the base and PhSeCl from 0\(^\circ\)C to -78\(^\circ\)C, led to a dramatic drop from (40-50\%) to 20\% of the unwanted (10E,12E,14Z)-282 isomer.
3.3.3 Synthesis of Diels-Alder adducts 272, 273, 287 and 288

Selenide 282 then underwent oxidative elimination using \textit{m}-CPBA and H$_2$O$_2$ in CDCl$_3$/H$_2$O$_2$, to give pyrrolinone 243 (Scheme 3.12). A sample taken out for $^1$H NMR spectroscopic analysis indicated the presence of pyrrolinone 243 through the characteristic peaks at 5.09 ppm (5'-H) and 8.06 ppm (6'-H).\textsuperscript{21} Pyrrolinone 243 was then directly introduced into 40°C degassed toluene, without being concentrated under reduced pressure beforehand. The mixture was then subsequently degassed at 40°C for 30 minutes, before being heated under reflux at 90°C for 10 hours.

The solvent was then removed under reduced pressure, and subsequent $^1$H NMR spectroscopic analysis indicated the presence of four compounds, with two of the compounds being in a 1 : 1 ratio. Purification was achieved through initial column chromatography (1: 15 Et$_2$O: pet. ether), followed by more time intensive column chromatography (1: 80 Et$_2$O: pet. ether) to give the top spot as an off white foam (11%), the lower spot as a clear liquid (12%) and mixed fractions of both components as an off white liquid (2%).

Scheme 3.12: Synthetic route to Diels-Alder adducts
The top spot consisted of two compounds in an exo 13E-283 and endo 13E-284 = 5 : 4 ratio (Scheme 3.12 on page 89), and the lower spot consisted of two compounds in an exo 13Z-285 and endo 13Z-286 = 5 : 4 ratio. Preliminary $^1$H NMR spectroscopic analysis performed after the initial column but before separation of the two spots also indicated that the 13E and 13Z isomers appeared in a 1 : 1 ratio.

All four Diels-Alder adducts were formed by the addition of the triene functional group onto the less hindered face of the pyrrolinone away from the isopropyl group at C(3) (Figure 3.6). With respect to the formation of the endo adducts 13E-284 and 13Z-286, the addition takes place with the triene endo to the pyrrolinone ring, whereas for the exo adducts 13E-283 and 13Z-285, the triene is exo to the pyrrolinone ring.

Figure 3.6: Endo/exo selectivity dictated by positioning of triene functional group

The mixture containing the exo 13Z-285 and endo 13Z-286 adducts was then debenzoylated to give the exo NH 13Z-287 (38%) and endo 13Z NH 288 (29%) adducts in a 5 : 4 ratio (Scheme 3.13 on page 91). Separation of the two compounds by column chromatography proved to be difficult and mixed fractions were recovered (9%).
Scheme 3.13: Synthetic route to the exo NH 13Z-287 and endo NH 13Z-288 adducts

The remaining mixture containing the exo 13E-283 and endo 13E-284 adducts was then debenzyolated, resulting in the formation of the exo NH 13E-272 (32%). The endo NH 13E-273 adduct was also isolated along with an unknown isomer (11%), in a 5: 2 ratio (Scheme 3.14). Column chromatography of the exo NH 13E-272 and endo NH 13E-273 adducts proved to be extremely difficult and mixed fractions (with none of the unknown isomer present) were also recovered (32%). The unknown isomer was not seen in the mixture consisting of the exo 13E-283 and endo 13E-284 adducts (Scheme 3.12 on page 89), presumably due to masking of the minor unknown compounds peaks.

Scheme 3.14: Synthetic route to the exo NH 13E-272 and endo NH 13E-273 adducts

3.3.4 Determination of stereochemistry of Diels-Alder adducts 272, 273, 287 and 288

A preliminary indication of the stereochemistry of the debenzyolated Diels-Alder adducts was made by comparing their $^1$H NMR spectra with those of the debenzyolated Diels-Alder adducts isolated and characterised in work towards the total synthesis of aspachalasin C 57 (Section 1.4.7, pages 24-25).
Evidence towards the exo/endo stereochemistry can be seen with respect to the chemical shift of the 13-H, and coupling values between the 7-H and 8-H (Figure 3.7). With respect to the 13-H chemical shift exo compounds appear around 4.71-4.84 ppm, whereas endo compounds appear around 5.62-6.32 ppm. With regards to the coupling constants between 7-H and 8-H, exo compounds exhibit coupling constants of ~6 Hz, which is consistent with the smaller C(7)-H to C(8)-H dihedral angle. In contrast the endo compounds exhibit coupling constants of around ~0-1 Hz due to the dihedral angle of C(7)-H to C(8)-H being around 90°.34

Evidence towards the 13E/Z selectivity was not as forthcoming through 1H NMR analysis; however, comparison of the 13-H chemical shifts of compounds from both studies does indicate an overlap of these signals (Figure 3.7). The 1H NMR spectra of the exo NH 13E-272 (Figure 6.1 on page 184), exo NH 13Z-287 (Figure 6.2 on page 186) and endo NH 13Z-288 (Figure 6.3 on page 188) isomers are displayed in the appendix (Section 6.0).

Further evidence towards the stereochemistry of the debenzoylated Diels-Alder adducts is provided through the analysis of 1D nOe studies. The results of the nOe studies performed upon the exo NH 13E-272 (Table 6.1 on page 185), exo NH 13Z-287 (Table 6.2 on page 187) and endo NH 13Z-288 (Table 6.3 on page 189) isomers are displayed in (Section 6.0) and discussed below.
The following are some of the key nOe studies (Table 6.1 on page 185) which indicate exo geometry in this Diels-Alder adduct. Irradiation of the signal at 2.64 ppm (3-H) showed an interaction through space to the signal at 1.94 ppm (5-H) (indicating a cis relationship) and no response to the signal at 1.18 ppm (11-Me) (Figure 3.8). Irradiation of the signal at 3.02 ppm (4-H) showed strong interactions with regard to both the 11-Me signal and the signal at 4.84 ppm (13-H). Further to this, irradiation of the 5-H signal indicated interaction through space to the signal at 1.67 ppm (12-Me), with no response being seen to the 4-H signal and the signal located at 3.77 ppm (8-H). Lastly, irradiation of the 11-Me signal resulted in a strong interaction being seen with 13-H signal, thus showing a cis relationship. Evidence towards the 13E geometry was seen upon the irradiation of H-13 signal with no interaction through space to the signal located at 1.80 ppm (14-Me).

Figure 3.8: nOe studies performed on exo NH 13E-272 Diels-Alder adduct. A solid line indicates a detected nOe and dashed line indicates an undetected nOe. Results depicted also take into account molecular modelling studies

The above results indicate that the 11-Me and the 8-(carbon chain) are in the unfavourable axial positions (Figure 3.8). If on the other hand they were placed in the more favourable equatorial positions, both the 5-H and 8-H now become close in space; however, the nOe studies show no interaction through space between these protons. Also, irradiation of the 8-H indicates interaction through space to one of the 22-H protons; molecular model studies show that if 8-H was located in an axial position such an interaction would be impossible.

With the above information in mind it is important to consider the possibility that the 10E,12E,14E isomer of pyrrolinone 243 (Scheme 3.12 on page 89) may have isomerised during the Diels-Alder reaction to give the (10E,12E,14Z) isomer (plus any
formed during the synthetic process leading to pyrrolinone 243, and undergone a Diels-Alder reaction. Two scenarios can be envisaged, either both the 8-(carbon chain) and the 5-H occupy axial positions or they occupy equatorial positions. In the former case this would result in 5-H and 4-H being cis to one another and very close in space; no such relationship is seen with the nOe results. In the latter case the 8-H and 11-Me would be close in space; again no such relationship is seen.

(b) The exo NH 13Z-287 Diels-Alder adduct

The following are some of the key nOe studies (Table 6.2 on page 187) which indicate exo geometry in this Diels-Alder adduct. Irradiation of the signal at 2.70 ppm (3-H) resulted in an interaction through space being seen to the signal at 1.96 ppm (5-H) (Figure 3.9). Irradiation of the signal at 2.86 ppm (4-H) brought about strong responses in the signals at 4.81 ppm (13-H) and the 0.96 ppm (11-Me), which indicated a cis relationship. Irradiation of the 5-H signal resulted in a strong response being seen with the signal at 1.70 ppm (12-Me). Irradiation of 12-Me signal was inconclusive with respect to the 5-H signal, due to the the fact that it overlaps with the signal at 1.69 ppm (14-Me), but molecular model studies show that the 5-H and 14-Me are sufficiently spatially removed from each other and thus coupling can be discounted. Also, irradiation of the 5-H signal resulted in no response being seen with 4-H signal and the signal at 3.76 ppm (8-H) (however, irradiation of 4-H with respect to the 8-H signal resulted in an inconclusive result due to nearby protons being irradiated as well). Lastly, irradiation of the 11-Me signal resulted in a strong response being seen with 13-H signal, thus indicating a cis relationship.

![Figure 3.9: nOe studies performed on exo NH 13Z-287 Diels-Alder adduct. A solid line indicates a detected nOe and dashed line indicates an undetected nOe. Results depicted also take into account molecular modelling studies](image-url)
Evidence towards the 13Z geometry was seen upon the irradiation of 13-H signal, which resulted in interactions through space to the signals of 14-Me and 12-Me (Figure 3.9 on page 94). This by itself is by no means conclusive, however molecular model studies show that the 13-H and 12-Me are too far away in space to interact and thus it could be inferred that irradiation of the 13-H signal could only result in a response being seen with the 14-Me signal.

With respect to the 11-Me and the 8-(carbon chain) occupying the unfavourable axial positions, results here matched those obtained with the exo 13-E-272 Diels-Alder adduct.

(c) The endo 13Z-288 Diels-Alder adduct

The following are some of the key nOe studies (Table 6.3 on page 189) which indicate endo geometry in this Diels-Alder adduct. Irradiation of the signal at 2.88 ppm (3-H) resulted in an interaction through space being seen to the signal at 1.15 ppm (11-Me) (Figure 3.10), but no response was seen to the signal at 2.56 ppm (5-H) (which is always seen with exo compounds) due to the cis relationship. Irradiation of signal at 2.29 ppm (4-H) proved to be inconclusive with respect to 5-H signal, due to the fact that 4-H and 22-H had overlapping signals and 5-H and 21-H’ appeared as a multiplet at the same chemical shift. Interaction through space would be expected between the 21-H’ and 22-H signals and thus no conclusion can be drawn with respect to the 4-H and 5-H signal coupling. Further to this, unlike the exo compounds, no interaction through space was seen between 4-H signal and the signal at 5.62 ppm (13-H). Also, upon irradiation of the 5-H signal a strong response was seen with the signal at 3.72 ppm (8-H), indicating a cis relationship.

Figure 3.10: nOe studies performed on endo NH 13Z-288 Diels-Alder adduct. A solid line indicates a detected nOe and dashed line indicates an undetected nOe. Results depicted also take into account molecular modelling studies
Evidence towards the 13Z geometry was seen upon irradiation of 13-H signal which resulted in an interaction through space to the signal at 1.66 ppm (14-Me) (Figure 3.10 on page 95). However, irradiation of 14-Me signal was inconclusive with respect to an interaction through space to 13-H, signal due to inability to irradiate the 14-Me without irradiating the signal at 1.74 ppm (12-Me) as well. However, molecular model studies show that the 13-H and 12-Me are too far away in space to interact, and thus it could be inferred that irradiation of 14-Me signal would result in a response being seen with the 13-H signal.

The above results indicate that the 11-Me and the 8-(carbon chain) are in the favourable equatorial positions (Figure 3.10 on page 95). If on the other hand they were placed in the more unfavourable axial positions, both the 5-H and the 8-H become too far away in space to interact; however, the nOe studies show an interaction through space between the two protons.

As seen with the exo compound, it is worth considering the possibility that the 10E,12E,14E isomer of pyrrolinone 243 (Scheme 3.12 on page 89) may have isomerised during the Diels-Alder reaction to the 10E,12E,14Z isomer plus any formed during the synthetic process leading to pyrrolinone 243, and undergone a Diels-Alder reaction. Again, two scenarios can be envisaged, either both the 8-H and the 5-Me occupy axial positions or they occupy equatorial positions. However, in both cases this would result in the 8-H and the 5-H being in a trans relationship and thus being sufficiently far apart to expect no interaction through space. As interaction through space is seen between 8-H and 5-H signals, this idea can be discounted.

(d) The endo NH 13E-273 Diels-Alder adduct

For the most part nOe studies on this compound proved to be inconclusive, due to the lack of material and the presence of an unknown isomer. However, irradiation of the signal at 3.35 ppm (8-H) did indicate an interaction through space to the signal at 2.65 ppm (5-H), indicating endo geometry.
**3.3.5 Analysis of Diels-Alder selectivity**

As previously mentioned (Section 1.4.7, pages 24-25), the work directed towards the synthesis of aspochalasin C 57 initially involved the formation of pyrrolinone 62 in an $8E : 8Z = 3 - 4 : 1$ ratio of isomers. Subsequent Diels-Alder reaction on pyrrolinone 62 resulted in three Diels-Alder adducts which upon debenzoylation gave the $exo$ NH 13E-63, $endo$ NH 13E-64 and $endo$ NH 13Z-65 adducts, in a respective ratio of $2 : 1 : 3$; which can alternatively be viewed as a $13E : 13Z = 1 : 1$ ratio (Scheme 3.15).  

![Scheme 3.15: Diels-Alder adducts obtained during studies directed towards the synthesis of aspochalasin C 57](image)

The distribution of Diels-Alder products was ascribed to the following: firstly, it may reflect a more efficient cyclization of the $8Z$ pyrrolinone 62 over the $8E$ pyrrolinone 62 or secondly, under the reaction conditions, the trienes may be equilibrating before cyclization occurs.  

However, in the current work, pyrrolinone 243 (Scheme 3.16 on page 98) was used as the precursor in the Diels-Alder reaction, and only consisted of the $10E$ isomer. This resulted in the formation of the $exo$ 13E-283, $endo$ 13E-284, $exo$ 13Z-285 and $endo$ 13Z-286 adducts, in a $13E : 13Z = 1 : 1$ ratio, with each isomer exhibiting an $exo : endo$ geometry in a $5 : 4$ ratio. Thus, taking into account both sets of results, it would seem that it is irrelevant to how isomerically pure you get the pyrrolinone at the double bond under question, because it will simply equilibrate under the Diels-Alder reaction conditions.
Another point of interest is the lack of any Diels-Alder products (in both the work directed towards aspochalasin C 57 and the current research) through the use of a pyrrolinone that exhibits an isomerised terminal bond. This seems to suggest that such an isomer either cannot undergo a Diels-Alder reaction or it undergoes such a reaction at a very slow rate. Both theories could be ascribed to steric reasons, possibly due to the terminal methyl pointing inwards.

3.3.6 Conclusion

(a) Tin mediated synthetic route towards chaetochalasin A 1

Formation of alcohol 199 (Scheme 3.17 on page 99) bearing the 2,4-syn arrangement of methyl groups with a de of 94%, was achieved through the use of chiral auxiliary mediated alkylations. Alcohol 199 was then functionalised to give aldehyde 215, which was then reacted under optimised Julia conditions with BT-sulphone 120 to create predominately the trans isomer of the C(9)-(10) double bond of vinyl stannane 117. Subsequent attempts to introduce the C(3)-(4) single bond of ester 115 through Stille coupling of vinyl stannane 117 and vinyl iodide 118 led to a mixture of isomers that could not be characterised.

**Scheme 3.16**: Diels-Alder adducts obtained from the studies directed towards the synthesis of chaetochalasin A 1
Scheme 3.17: Synthetic route towards ester 115

(b) Non-tin mediated synthetic route towards chaetochalasin A 1

Oxidation of alcohol 119 (Scheme 3.18 on page 100) and subsequent Wittig homologation resulted in the formation of the trans C(2)-C(3) double bond seen in aldehyde 229. Aldehyde 229 was then reacted under optimised Julia conditions with BT-sulphone 120 to create predominately the trans isomer of the C(10)-(11) double bond of ester 228. Subsequent DIBAL-H reduction, oxidation and Still-Gennari condensation on ester 228 led to methyl ester 226 with predominately the cis C(2)-(3) double bond. Ester 226 was then converted into pyrrolinone 110, which was then used in an attempt to synthesise exo Boc adduct 113 through a domino Diels-Alder reaction. However, no identifiable compounds were obtained from the reaction.
(c) Synthetic route to Diels-Alder adducts 272, 273, 274 and 288

Oxidation of alcohol 119 (Scheme 3.19 on page 101), followed by subsequent use of vinyl magnesium bromide and performance of a Johnson-Claisen rearrangement, resulted in the formation of the trans C(4)-C(5) double bond seen in aldehyde 275. Aldehyde 275 was then reacted under optimised Julia conditions with BT-sulphone 120 to create predominately the trans isomer of the C(12)-(13) double bond of ester 274. Ester 274 was then converted into pyrrolinone 243, which was then converted into adducts exo NH 13E-272, endo NH 13E-273, exo NH 13Z-274 and endo NH 13Z-288, through an intramolecular Diels-Alder reaction and subsequent benzoyl deprotection. The adducts obtained were seen in a 13E : 13Z = 1 : 1 ratio, with each isomer exhibiting an exo : endo geometry in a 5 : 4 ratio. Formation of the unwanted 13Z isomers could be ascribed to equilibration of the C(10)-(11) double bond of pyrrolinone 243 during the Diels-Alder reaction.
3.3.7 Future work

One possible route towards chaetochalasin A 1 would initially involve the synthesis of more of the exo NH 13E-272 Diels-Alder adduct, accompanied by possible optimisation of the Diels-Alder reaction to try and reduce the unwanted formation of the exo NH 13Z-287 and endo NH 13Z-288 adducts.

Exo NH 13E-272 could then be reacted with LDA and TMSCl to give the enol ether 289, which, upon reaction with PhSeCl, would give selenide 290. Oxidative elimination of the phenylselenyl group would hopefully give exo 291 triene with a C(23)-(24) cis double bond, which would then be subsequently heated to afford chaetochalasin A 1 through an intramolecular transannular Diels-Alder reaction (Scheme 3.20 on page 102). It should be noted that this synthetic chemistry has been previously investigated with successful results, but the oxidative elimination of the phenylselenyl group resulted in the formation of an isolated E double bond. The presence of the C(21)-(22) trans double bond in selenide 290 may however induce a certain amount of structural rigidity, where formation of the 23E double bond would be disfavoured due to steric interactions.
Scheme 3.20: Proposed synthetic route towards chaetochalasin A 1

An alternative strategy towards chaetochalasin A 1 would involve the large scale repetition of the previously discussed synthetic route (Section 2.2, pages 68 to 76) with the new found experience in handling the unstable triene functional group and performing the oxidative elimination/Diels-Alder reactions.

Reagents and conditions: (i) LDA, TMSCI, THF, -78°C, (ii) PhSeCl, THF, 0°C, (iii) (30%) H₂O₂ in H₂O, DCM/pyridine, r.t., (iv) toluene, 90°C.
4.0 Experimental

4.1 General information

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen. Temperatures quoted are for the external heating / cooling source.

Low resolution mass spectra were recorded on an Micromass Platform II spectrometer (with respect to ES, APCI and LCMS) and on a Agilent 5975C Triple Axis GCMS (with respect to GC/MS and EI/CI). High resolution mass spectra were recorded on a Thermo Finnigan MAT95XP. Molecular ions are reported as mass/charge (m/z) ratios.

Melting points were measured using a Sanjo Gallenkamp MPD350 heater and are uncorrected.

Optical rotations were measured using an Optical Activity Ltd. AA-100 polarimeter with a 0.25 dm cell. The sample concentration is quoted in and mg/cm$^3$.

Infrared spectra were recorded either on an AT1-Mattson Genesis Series FTIR spectrometer or using a thin film (solution DCM) between NaCl plates on a Perkin-Elmer RX1 FTIR spectrometer. Absorption maxima ($\nu_{\max}$) 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, Bruker XC (400MHz) spectrometer or a Bruker XC (500MHz) spectrometer. Chemical shifts ($\delta_H$ and $\delta_C$) 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 are reported as follows; chemical shift, integration, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or as any combination of these), atom.

Flash column chromatography was carried out using Merck silica gel 60 (particle size 40-60 μm). Neutralised silica was prepared by stirring the above silica in sat. aq. KHCO$_3$, before filtration and rinsing with deionised water until the washing were around pH 7, which was then followed by rigorous oven drying. The neutralised
silica was used for all compounds that contained a vinyl stannane group and which contained the triene functional group.

Thin layer chromatography (TLC) was performed using plastic plates pre-coated with Polygram® SIL G/UV_{254} silica gel from Machery-Nagel GmbH & Co. Retention factors (R_f) are quoted to the nearest 0.01. Detection of the compounds was achieved through the use of ultraviolet absorption or treatment with potassium permanganate, anisaldehyde or phosphomolybdic acid solutions, followed by heating.

The petroleum ether used (referred to as pet. ether) is the fraction that boils between 40°C-60°C at atmospheric pressure and was distilled prior to use. THF was dried over sodium/benzophenone and was distilled under a nitrogen atmosphere prior to use. DCM was dried over calcium hydride and was distilled under a nitrogen atmosphere prior to use. Benzene, toluene, diethyl ether, ethyl acetate and xylene were all bought in as anhydrous solutions and were only used as a solvent for given reactions.

The following solutions were bought from Sigma-Aldrich, LDA as a (1.75M in THF/heptane/ethylbenzene), n-BuLi (1.6M in hexanes), t-BuLi (1.7M in hexanes) and LiHMDS (1.0M in THF).

All other reagents and solvents were obtained from commercial suppliers and were used as obtained.
4.2 Experimental procedures

*N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylpropionamide 123*

To a solution of (+)-pseudoephedrine 126 (1.00 g, 6.06 mmol) in THF (7 ml) was added NaOMe (0.164 g, 3.03 mmol) with stirring at r.t. for 15 min. Methyl propionate (1.07 g, 12.1 mmol, 1.16 ml) was then added, which was then followed by stirring at r.t. for 1.5 h. To the reaction mixture was then added HCl (3.0M) (4 ml), with subsequent separation of the aqueous layer from the organic layer. The aqueous layer was then washed with DCM (12 ml x 4) and the combined organic layers were then washed with H2O (12 ml), dried (MgSO4) and concentrated under reduced pressure to afford the product as a white solid (1.30 g). Column chromatography (SiO2, 3 : 1 EtOAc : pet. ether) gave the title compound as a white solid in a 1 : 0.4 rotamer ratio (1.14 g, 85%).

Rf = 0.14 (1 : 1, EtOAc : petrol); m.p 114.6-115.6°C; [α]D26 +103.9, (c 2.0, MeOH);
νmax/cm⁻¹ 3383(br), 3028, 2978, 2938, 1619, 1473, 1452, 1405, 1375, 1299, 1199, 1122, 1053, 1026, 921, 837 and 816; δH (400MHz, CDCl3) (1 : 0.4 rotamer ratio, asterisk denotes minor rotamer peaks) 0.89 (1.2H, d, J 6.8, 2-CH3*), 1.04 (7.2H, m, 2-CH3, 6-H5 and 6-H5*), 2.22 (2H, m, 5-H2), 2.31 (0.4H, dq, J 15.1, 7.4, 5-H5*), 2.44 (0.4H, dq, J 15.1, 7.4, 5-H5*), 2.72 (3H, s, N-CH3), 2.83 (1.2H, s, N-CH3*), 3.92 (0.4H, dq, J 8.5, 6.8, 2-H*), 4.39 (2H, m, 2-H and 1-OH), 4.49 (1.4H, m, 1-H and 1-H*), 7.20 (2H, m, Ar*) and 7.28 (5H, m, Ar); δC (75MHz, CDCl3) (asterisk denotes minor rotamer peaks) 9.1, 9.5*, 14.4, 15.2*, 26.7*, 26.8, 27.5, 32.6*, 58.2, 58.4*, 75.4*, 76.5, 126.4, 126.9*, 127.6, 128.2*, 128.3, 128.6*, 141.3*, 142.4, 174.9* and 176.1; m/z (ES+) 222 (M+ + 1, 100%) and 244 (M+ + 23, 53%).

*(2E*)-methylbut-2-en-1-ol 128*
To a solution of LiAlH₄ (1.56 g, 41.0 mmol) in Et₂O (10 ml) at 0°C was added (2E)-methylbut-2-enoic acid 127 (2.00 g, 20.0 mmol) in Et₂O (6 ml), with subsequent stirring at 0°C for 30 min and then at r.t. for 3 h. The reaction mixture was cooled to 0°C before the addition of H₂O (8 ml), 15% aq. NaOH (8 ml) and H₂O (25 ml). The precipitate was then filtered over celite® and washed with Et₂O (20 ml x 3). The aqueous layer was then separated from the organic layer and washed with Et₂O (10 ml x 3), with the combined organic layers being sequentially washed with HCl (1.0M) (15 ml), sat. aq. NaHCO₃ (15 ml) and brine (15 ml). The organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as a clear liquid (1.03 g, 60%).

Rᵣ = 0.29 (1 : 2, Et₂O : pet. ether); νmax/cm⁻¹ 3306(br), 2918, 2862, 1674, 1445, 1381, 1218, 1067, 1046, 1002, 955, 829 and 773; δH (300MHz, CDCl₃) 1.62 (3H, dq, J 6.7, 1.1, 4-H₃), 1.66 (3H, m, 2-CH₃), 1.75 (1H, s, 1-OH), 3.99 (2H, m, 1-H₂) and 5.48 (1H, qq, J 6.7, 1.3, 3-H); δC (75MHz, CDCl₃) 13.0, 13.3, 69.0, 121.0 and 135.5; m/z (ES+) 195 (2 x M⁺, +23, 100%).

(2E)-1-bromo-2-methylbut-2-ene 129

To a solution of allylic alcohol 128 (0.784 g, 9.12 mmol) in Et₂O (19 ml) at 0°C was added PBr₃ (1.24 g, 4.56 mmol, 0.43 ml) drop wise. The resulting solution was stirred at 0°C for 30 min, with subsequent stirring at r.t. for 3 h. To the reaction mixture was then added sat. aq. K₂CO₃ (18 ml). The aqueous layer was then separated from the organic layer and washed with Et₂O (18 ml x 3). The combined organic layers were then washed with brine (18 ml), dried (MgSO₄) and concentrated under reduced pressure in ice cold water to afford the title compound as a clear oil (1.05 g, 77%).

Rᵣ = 0.64 (100% pet. ether); νmax/cm⁻¹ 2919, 1664, 1438, 1381, 1230, 1201, 1144, 1020, 964, 875, 825 and 776; δH (300MHz, CDCl₃) 1.64 (3H, dq, J 6.8, 0.8, 4-H₃), 1.76 (3H, m, 2-CH₃), 3.99 (2H, m, 1-H₂) and 5.70 (1H, m, 3-H); δC (75MHz, CDCl₃) 13.9, 14.3, 41.8, 125.8 and 132.7; m/z (EI/CI) 150 (M⁺, Br81, 6%), 148 (M⁺, Br79, 6%), 69 (M⁺ - Br79, 73%) and 67 (M⁺ – Br81, 11%).
(5R,7E)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N,5,7-trimethylhex-7-enamide

To a solution of LiCl (0.343 g, 8.16 mmol) in THF (2 ml) was added LDA (1.75M in THF/heptane/ethylbenzene) (0.303 g, 2.83 mmol, 1.62 ml), which was then cooled to -78°C. A 0°C solution of amide 123 (0.300 g, 1.36 mmol) in THF (6 ml) was added dropwise with sequential stirring at -78°C (1 h), 0°C (15 min) and then at r.t. for 5 min. The mixture was then cooled back down to 0°C before the dropwise addition of allylic bromide 129 (0.405 g, 2.72 mmol) in THF (2 ml) with subsequent stirring 0°C for 1 h. To the reaction mixture was then added sat. aq. NH₄Cl (4 ml), followed by the further addition of sat. aq. NH₄Cl (16 ml). The aqueous layer was then separated from the organic layer and washed with EtOAc (8 ml x 4). The combined organic layers were then dried (MgSO₄), concentrated under reduced pressure to afford the product as a orange liquid (0.41 g). Column chromatography (SiO₂, 1 : 1 EtOAc : pet. ether) gave the title compound as a light yellow oil in a 1 : 0.3 rotamer ratio (0.275 g, 70%).

Rf = 0.45 (1 : 1, EtOAc : pet. ether); [α]D²⁹ +72.7, (c 2.9, CHCl₃); (Found M⁺ + Na, 312.1922. C₁₈H₂₇O₂NNa requires M⁺, 312.1945); v_max/cm⁻¹ 3369(br), 2973, 2930, 2361, 2341, 2105, 1451, 1408, 1373, 1300, 1199, 1108, 1082, 1050, 1027, 912, 837, 752, 733, 700, 668 and 613; δH (400MHz, CDCl₃) (asterisk denotes minor rotamer peaks) 1.00 (1.8H, m, 2-CH₃ and 5-CH₃*), 1.03 (3H, d, J 6.8, 2-CH₃), 1.08 (3H, d, J 6.8, 5-CH₃), 1.56 (6H, m, 7-CH₃ and 9-H₃), 1.59 (0.9H, s, 7-CH₃*), 1.64 (0.9H, s, 9-H₃*), 1.96 (1H, dd, J 13.6, 7.3, 6-H), 2.05 (0.3H, dd, J 13.6, 8.2, 6-H*), 2.16 (0.3H, br.s, 1-OH*), 2.25 (1H, dd, J 13.6, 6.8, 6-H*), 2.47 (0.3H, dd, J 13.6, 5.6, 6-H*), 2.77 (1H, m, 5-H), 2.84 (3H, s, N-CH₃), 2.89 (0.9H, s, NCH₃*), 3.00 (0.3H, m, 5-H*), 4.09 (0.3H, m, 2-H*), 4.43 (2H, m, 2-H and 1-OH), 4.57 (1.3H, m, 1-H and 1-H*), 5.21 (1H, m, 8-H), 5.30 (0.3H, m, 8-H*), 7.26 (1.5H, m, Ar*) and 7.35 (5H, m, Ar); δC (75MHz, CDCl₃) (asterisk denotes minor rotamer peaks that were visible) 13.3, 14.4, 15.5*, 15.8, 15.8*, 16.8, 17.3*, 26.9¹, 32.7, 33.7*, 34.8, 43.6, 58.1, 58.6*, 75.2*, 76.4, 120.7, 120.8*, 126.3, 126.9*, 127.5, 128.2, 128.6*, 132.8, 133.4*, 141.2*, 142.5, 177.7* and 178.9; m/z (ES+) 290 (M⁺ + 1, 72%) and 312 (M⁺ + 23, 100%).
(2Z)-1,4-Bis(tert-butyldimethylsilanyloxy)-but-2-ene $^{132}$

To a cooled solution ($0^\circ$C) of imidazole (13.9 g, 204 mmol) in DCM (50 ml) was slowly added 2Z butenediol $^{131}$ (6.00 g, 68.2 mmol, 5.60 ml) followed by TBSCl (21.1 g, 140 mmol), with stirring at r.t. for 2.5 h. To the reaction mixture was then added H$_2$O (100 ml) followed by extraction with Et$_2$O (3 x 100 ml). The combined organic layers were then washed with H$_2$O (4 x 100 ml) and brine (100 ml), dried (MgSO$_4$) and concentrated under reduced pressure to afford the title compound as a clear liquid (20.9 g, 97%).

$R_f = 0.78$ (1 : 6, EtOAc : pet. ether); $\nu_{\text{max}}$/cm$^{-1}$ 2955, 2930, 2886, 2857, 1472, 1463, 1390, 1362, 1253, 1078, 1006, 939, 833, 773 and 667; $\delta_H$ (400MHz, CDCl$_3$) 0.07 [12H, s, 2 x Si(CH$_3$)$_2$], 0.90 [18H, s, 2 x Si(CH$_3$)$_3$], 4.24, (4H, d, $J$ 4.0, 1-$H_2$ and 4-$H_2$) and 5.56 (2H, t, $J$ 4.0, 2-$H$ and 3-$H$); $\delta_C$ (100MHz, CDCl$_3$) -5.2, 18.3, 25.9, 59.6 and 130.2; $m/z$ (ES+) 339 (M$^+$ + 23, 100%).

(tert-Butyldimethylsilanyloxy)-acetaldehyde $^{133}$

A solution of bis-TBS compound $^{132}$ (20.2 g, 63.9 mmol) in DCM (100 ml) was purged with nitrogen followed by oxygen at -78°C until the solution turned a light blue. The excess ozone was flushed out with subsequent addition of PPh$_3$ (19.6 g, 74.7 mmol) at -78°C. The mixture was then allowed to warm to r.t., with additional stirring for 2 h. The solvent was then concentrated under reduced pressure to afford the product as a white solid (45.4 g). Column chromatography (SiO$_2$, 1 : 40 Et$_2$O : pet. ether) gave the title compound as a clear oil (18.89 g, 85%).

$R_f = $ Elongated band on TLC plate; $\nu_{\text{max}}$/cm$^{-1}$ 2954, 2930, 2887, 2858, 1739, 1472,1362, 1254, 1125, 1006, 939, 878, 834, 777, 685, 669 and 638; $\delta_H$ (400MHz, CDCl$_3$) 0.10 [6H, s, Si(CH$_3$)$_2$], 0.93 [9H, s, Si(CH$_3$)$_3$], 4.22 (2H, d, $J$ 0.8, CH$_2$) and 9.70 (1H, t, $J$ 0.8, CHO); $\delta_C$ (75MHz, CDCl$_3$) -5.4, 18.3, 25.8, 69.6 and 202.3; $m/z$ (EI/CI) 117 (M$^+$ - 57, 100%) and 89 ([M$^+$ - 115, 70%].
(2E)-ethyl-4(tert-butyldimethylsilanyloxy)-2-methyl-but-2-enoate 134 and (2Z)-ethyl-4(tert-butyldimethylsilanyloxy)-2-methyl-but-2-enoate 135

A solution of anhydrous LiBr (5.00 g, 57.5 mmol) in MeCN (115 ml) was stirred at r.t. for 15 min. Triethyl phosphopropionate (10.3 g, 43.1 mmol, 9.23 ml) was then added dropwise at r.t., with further stirring for 15 min. The solution was then cooled to 0°C before the addition of n-BuLi (1.6M in hexanes) (2.94 g, 46.0 mmol, 28.7 ml) and subsequent stirring at 0°C for 15 min. This was followed by the addition of aldehyde 133 (5.00 g, 28.7 mmol) in MeCN (35 ml) to the reaction mixture, with stirring at r.t. for 22 h. To the reaction mixture was then added aqueous HCl (1.0M) (40 ml) followed by washing with Et₂O (4 x 100 ml). The combined organics were washed with brine (100 ml), dried (MgSO₄) and concentrated under reduced pressure to afford the product as a yellow liquid (14.75 g). Column chromatography (SiO₂, 1 : 20 Et₂O : pet. ether) gave the title compound (2E isomer) as a clear liquid (6.82 g, 92%).

Rᶠ = 0.45 (10 : 1, pet. ether : Et₂O); νmax/cm⁻¹ 2956, 2930, 2857, 1714, 1656, 1464, 1382, 1365, 1326, 1240, 1132, 1108, 1059, 1006, 939, 834, 815, 775, 724, 678 and 653; δH (400MHz, CDCl₃) 0.09 [6H, s, Si(CH₃)₂], 0.91 [9H, s, Si(CH₃)₃], 1.30 (3H, t, J 7.1, OCH₂CH₃), 1.82 (3H, q, J 1.3, 2-CH₃), 4.20 (2H, q, J 7.1, OCH₂CH₃), 4.35 (2H, dq, J 5.7, 1.3, 4-H₂) and 6.78 (1H, tq, J 5.7, 1.3, 3-H); δC (75MHz, CDCl₃) -5.3, 12.6, 14.2, 18.3, 25.9, 60.5, 60.6, 127.3, 141.3 and 167.7; m/z (ES+) 276 (M⁺ + 17, 100%). The other title compound (2Z isomer) was seen as a clear liquid (0.37 g, 5%). Rᶠ = 0.50 (10: 1, pet. ether: Et₂O); (Found M⁺ + H, 259.1719. C₁₃H₂₇O₃Si requires M 259.1724); νmax/cm⁻¹ 2956, 2930, 2858, 2360, 1714, 1650, 1463, 1370, 1329, 1252, 1224, 1139, 1101, 1059, 1032, 1006, 939, 832, 775, 667 and 608; δH (400MHz, CDCl₃) 0.07 [6H, s, Si(CH₃)₂], 0.90 [9H, s, Si(CH₃)₃], 1.29 (3H, t, J 7.1, OCH₂CH₃), 1.90 (3H, q, J 1.8, 2-CH₃), 4.18 (2H, q, J 7.1, OCH₂CH₃), 4.60 (2H, dq, J 4.8, 1.9, 4-H₂) and 6.10 (1H, tq, J 4.8, 1.5 3-H); δC (75MHz, CDCl₃) -5.3, 14.2, 18.3, 19.7, 25.9, 60.3, 62.1, 125.7, 145.8 and 167.3; m/z (ES+) 259 (M⁺ + 1, 46%) and 281(M⁺ + 23, 100%).
(2E)-4-(tert-Butyldimethylsilyl oxy)-2-methylbut-2-en-1-ol 136\textsuperscript{47}

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\begin{align*}
&\text{OH} \\
&\text{OTBS}
\end{align*}
\]

A solution of ester 134 (11.6 g, 44.9 mmol) in DCM (120 ml) was cooled to -78°C before the addition of DIBAL-H (1.0M in DCM) (16.5 g, 116 mmol, 116 ml). The solution was then stirred at -78°C for 1 h with further warming to -20°C before the addition of MeOH (120 ml), followed by sat. aq. potassium sodium tartrate (360 ml). The reaction mixture was then diluted with Et\textsubscript{2}O (1000 ml) and allowed to warm to r.t. over 40 min. The aqueous layer was then separated from the organic layer and washed with Et\textsubscript{2}O (5 x 500 ml). The combined organic layers were then washed with brine (2x 500ml), dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to afford the product as a light yellow liquid (10.2 g). Column chromatography (SiO\textsubscript{2}, 1 : 3 Et\textsubscript{2}O : pet. ether) gave the title compound as a light yellow liquid (9.12 g, 94%).

R\textsubscript{f} = 0.36 (1 : 1, pet. ether : Et\textsubscript{2}O); ν\textsubscript{max}/cm\textsuperscript{-1} 3348(br), 2954, 2929, 2857, 2360, 2342, 1472, 1387, 1361, 1254, 1387, 1361, 1254, 1112, 1066, 1004, 939, 831, 813, 773 and 666; δ\textsubscript{H} (400MHz, CDCl\textsubscript{3}) 0.07 [6H, s, Si(CH\textsubscript{3})\textsubscript{2}], 0.90 [9H, s, Si(CH\textsubscript{3})\textsubscript{3}], 1.66 (3H, m, 2-CH\textsubscript{3}), 1.82 (1H, br.s, OH), 4.00 (2H, s, 1-H\textsubscript{2}), 4.24 (2H, m, 4-H\textsubscript{2}) and 5.56 (1H, tq, J 6.3, 1.4, 3-H); δ\textsubscript{C} (75MHz, CDCl\textsubscript{3}) -5.2, 13.7, 18.4, 26.0, 59.9, 68.2, 125.1 and 136.1; m/z (ES+) 239 (M\textsuperscript{+} + 23, 100%).

((2E)-4-Bromo-3-methylbut-2-enyloxy)-tert-butyldimethylsilane 137\textsuperscript{47}

\[
\begin{align*}
&\text{Br} \\
&\text{OTBS}
\end{align*}
\]

To a -78°C solution of alcohol 136 (1.00 g, 4.63 mmol) in DCM (18 ml) was added Et\textsubscript{3}N (0.654 g, 6.48 mmol, 0.90 ml) followed by MesCl (0.585 g, 5.09 mmol, 0.40 ml). The solution was stirred at -78°C for 45 min, with further stirring at -40°C for 45 min. Anhydrous LiBr (1.61 g, 18.5 mmol) was then added and reaction stirred at 0°C for 3 h. The reaction mixture was then poured into pentane (10 ml), washed with H\textsubscript{2}O (2 x 10 ml), followed by washing of the aqueous phase with Et\textsubscript{2}O (2 x 10 ml). The combined organic phases were then washed with brine (28 ml), dried (MgSO\textsubscript{4}) and concentrated
under reduced pressure to afford the product as a light yellow liquid (1.37 g). Column chromatography (SiO2, 1 : 20 Et2O : pentane) gave the title compound as a clear liquid (1.15 g, 89%).

Rf = 0.53 (20 : 1, pentane : Et2O); \(\nu_{\text{max}} / \text{cm}^{-1}\) 2953, 2929, 2856, 2358, 2340, 1579, 1538, 1471, 1463, 1435, 1385, 1361, 1256, 1217, 1197, 1098, 1061, 1006, 832, 812, 774, 666, 613 and 606; \(\delta_H\) (400MHz, CDCl3) 0.81 [6H, s, Si(CH3)2], 0.91 [9H, s, Si(C2H5)3], 1.78 (3H, m, 3-CH3), 3.96 (2H, d, J 0.5, 4-H2), 4.22 (2H, dq, J 6.1, 0.8, 1-H2) and 5.72 (1H, m, 2-H); \(\delta_C\) (75MHz, CDCl3) -5.2, 15.0, 18.3, 25.9, 40.6, 60.2, 130.7 and 132.7; \(m/z\) (EI/CI) 223 (M+ Br81 - 57, 77%), 221 (M+ Br79 - 57, 54%) and 199 (M+ - Br79, 17%).

**\((5R,7E)-6-(\text{tert-butyldimethylsilyl})\text{oxy})-N-(\text{1S,2S})-1-hydroxy-1-phenylpropan-2-yl)-N,2,4-trimethylhex-4-enamide 138**

To a solution of LiCl (1.95 g, 46.4 mmol) in THF (11 ml) was added LDA (1.8M in THF/heptane/ethylbenzene) (1.72 g, 16.1 mmol, 8.94 ml), which was then cooled to -78°C. An ice cooled solution of amide 123 (1.70 g, 7.74 mmol) in THF (20 ml) was added dropwise with sequential stirring at -78°C (1 hour), 0°C (15 min) and then at r.t. for 5 min. The mixture was then cooled back down to 0°C before the dropwise addition of allylic bromide 137 (3.24 g, 11.6 mmol) in THF (11 ml) with subsequent stirring 0°C for 40 min. To the reaction mixture was then added sat. aq. NH4Cl (72 ml), followed by the further addition of sat. aq. NH4Cl (288 ml). The aqueous layer was then separated from the organic layer and washed with EtOAc (144 ml x 6). The combined organic layers were then dried (MgSO4), concentrated under reduced pressure to afford the product as an orange liquid (4.65g). Column chromatography (SiO2, 1 : 2 EtOAc : pet. ether) gave the title compound as a light yellow oil in a 1 : 0.3 rotamer ratio (2.89g, 89%).

Rf = 0.17 (2 : 1, Et2O : petrol); \([\alpha]_D^{29} +37.0, (c 0.4, \text{CHCl3})\); (Found M+ + Na, 442.2750. C24H41O3NNaSi requires \(M\) 442.2748); \(\nu_{\text{max}} / \text{cm}^{-1}\) 3371(br), 2929, 2856, 2361, 1620, 1462, 1407, 1378, 1253, 1196, 1074, 1053, 1005, 939, 833, 774, 700, 667 and 614; \(\delta_H\) (400MHz, CDCl3) (1 : 0.3 rotamer ratio, asterisk denotes minor rotamer peaks) 0.04
[6H, s, Si(CH$_3$)$_2$], 0.06 [1.8H, s, Si(CH$_3$)$_2$], 0.88 [9H, s, SiC(CH$_3$)$_3$], 0.89 [2.7H, s, Si(CH$_3$)$_3$], 0.99 (0.9H, d, J 6.8, 2-CH$_3$), 1.07 (6.9H, m, 2-CH$_3$ and 5-CH$_3$ and 5-CH$_3$), 1.59 (3H, s, 7-CH$_3$), 1.68 (0.9H, s, 7-CH$_3$), 2.00 (1H, dd, J 14.1, 7.3, 6-H), 2.08 (0.3H, dd, J 13.6, 7.8, 6-H$^\ddagger$), 2.30 (1H, dd, J 14.1, 6.8, 6-H$^\ddagger$), 2.52 (0.3H, dd, J 13.6, 6.4, 6-H$^\ddagger$), 2.74 (0.3H, br.s, 1-OH$^\ddagger$), 2.81 (1H, m, 5-H), 2.89 (3H, s, N-CH$_3$), 2.90 (0.9H, s, N-CH$_3$), 3.06 (0.3H, m, 5-H$^\ddagger$), 4.08 (0.3H, m, 2-H$^\ddagger$), 4.17 (2.6H, m, 9-H$_2$ and 9-H$_2$), 4.34 (1H, br s, 1-OH), 4.45 (1H, m, 2-H), 4.54 (0.3H, m, 1-H$^\ddagger$), 4.61 (1H, m, 1-H), 5.30 (1H, tq, J 7.3, 1.0, 8-H), 5.42 (0.3H, m, 8-H$^\ddagger$), 7.27 (1.5H, m, Ar$^\ddagger$), 7.35 (5H, m, Ar); $\delta$C (100MHz, CDCl$_3$) (asterisk denotes minor rotamer peaks that were visible) – 5.3, - 5.2 $^\ddagger$, 14.3, 15.5$^\ddagger$, 16.5$^\ddagger$, 16.5, 16.8, 17.2$^\ddagger$, 18.2, 18.3$^\ddagger$, 25.8, 25.9, 27.0$^\ddagger$, 32.4$^\ddagger$, 33.6, 34.6, 43.1, 43.1$^\ddagger$, 58.0$^\ddagger$, 60.0, 75.1$^\ddagger$, 76.1, 126.2, 126.3, 126.7$^\ddagger$, 127.4, 128.0$^\ddagger$, 128.1, 128.5$^\ddagger$, 134.2, 135.0$^\ddagger$, 141.4$^\ddagger$, 142.4, 177.3$^\ddagger$ and 178.3; m/z (ES+) 442 (M$^+$ + 23, 100%).

(4E)-(2R)-6-Hydroxy-2,4-dimethylhex-4-enoic acid 139

A solution of α-branched amide 138 (0.200 g, 0.476 mmol) in tert-butanol (0.8 ml), MeOH (0.8 ml) and (3.22M) NaOH (0.100 g, 2.40 mmol, 0.75 ml) was refluxed for 48 h. The reaction mixture was then cooled down to r.t. and the solvents removed under reduced pressure before the addition of water (6 ml) and DCM (6 ml). The aqueous layer was then separated from the organic layer and washed with DCM (6 ml x 2), with subsequent acidification of the aqueous layer to pH 1 using H$_2$SO$_4$ (3.0M). The acidified aqueous layer was then washed with EtOAc (6 ml x 5). The combined organic layers were then dried (MgSO$_4$) and concentrated under reduced pressure gave the title compound as a clear liquid (0.05 g, 72%).

R$_f$ = 0.39 (3 : 1, EtOAc : petrol); [$\alpha$]$_D^{22}$ -7.7, (c 1.3, CHCl$_3$); (Found M$^+$ + Na, 181.0830. C$_8$H$_{14}$O$_3$Na requires $M$ 181.0835); $\nu_{max}$/cm$^{-1}$ 3291(br), 2974, 2936, 2600, 1703, 1460, 1384, 1230, 1181, 1122, 1097, 1075, 1045, 988, 910, 852, 816, 732 and 629; $\delta$H (400MHz, CDCl$_3$) 1.15 (3H, d, J 6.9, 2-CH$_3$), 1.67 (3H, s, 4-CH$_3$), 2.10 (1H, dd, J 13.8, 6.9, 3-H), 2.40 (1H, dd, J 13.8, 8.1, 3-H$^\ddagger$), 2.66 (1H, m, 2-H), 4.14 (2H, m, 6-H$^\ddagger$), 5.42
(1H, tq, J 8.1, 1.2, 5-H) and 7.12 (1H, br s, 6-OH); δ \text{c} (100MHz, CDCl\textsubscript{3}) 16.0, 16.7, 37.8, 43.5, 59.0, 125.6, 136.3 and 181.7; \text{m/z} (ES+) 181 (M\textsuperscript{+} + 23, 100%).

(4E)-(2R)-6-(tert-Butyldimethylsilyloxy)-2,4-dimethylhex-4-en-1-ol 140

To a cooled (0°C) solution of LDA (1.8M in THF/heptane/ethylbenzene) (1.02 g, 9.52 mmol, 5.29 ml) in THF (3 ml) was added NH\textsubscript{3}.BH\textsubscript{3} (90%) (0.328 g, 9.52 mmol), with stirring at 0°C for 15 min and then at r.t. for 15 min. The solution was then cooled to 0°C before the addition of α-branched amide 138 (1.00 g, 2.38 mmol) in THF (7 ml), with subsequent stirring at r.t. for 1.5 h. To the reaction mixture was then added HCl (1.0M) (50 ml) followed by separation of the aqueous layer from the organic layer and subsequent washing of the aqueous layer with EtOAc (50 ml x 4). The combined organic layers were then washed with sat. aq. NaHCO\textsubscript{3} (50 ml), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.75 g). Column chromatography (SiO\textsubscript{2}, 1 : 1 Et\textsubscript{2}O : pet. ether) gave the title compound as a clear liquid (0.49 g, 80%).

R\text{f} = 0.47 (1 : 1, Et\textsubscript{2}O : pet. ether); [α]\text{D}\textsubscript{30} \textsuperscript{30} +4.6, (c 1.1, CHCl\textsubscript{3}); (Found M\textsuperscript{+} + Na, 281.1907. C\textsubscript{14}H\textsubscript{30}O\textsubscript{2}SiNa requires M 281.1914); v\text{max}/cm\textsuperscript{-1} 3350(br), 2954, 2928, 2857, 2364, 1668, 1462, 1382, 1361, 1253, 1081, 1040, 1005, 938, 833, 813, 773 and 665; δ\text{H} (400MHz, CDCl\textsubscript{3}) 0.07 [6H, s, Si(CH\textsubscript{3})\textsubscript{2}], 0.89 (3H, d, J 6.3, 2-CH\textsubscript{3}), 0.90 [9H, s, Si(CH\textsubscript{3})\textsubscript{3}], 1.54 (1H, br.s, OH), 1.64 (3H, m, 4-CH\textsubscript{3}), 1.86 (2H, m, 3-H and 2-H), 2.12 (1H, m, 3-H'), 3.43 (1H, dd, J 10.6, 5.6, 1-H), 3.50 (1H, dd, J 10.6, 5.6, 1-H'), 4.19 (2H, m, 6-H\textsubscript{2}) and 5.35 (1H, tq, J 6.3 1.2, 5-H); δ\text{c} (100MHz, CDCl\textsubscript{3}) -5.1, 16.2, 16.6, 18.4, 26.0, 33.7, 44.1, 60.1, 68.4, 126.2 and 135.7; \text{m/z} (ES+) 281 (M\textsuperscript{+} + 23, 100%).
(2'S)-(2R,4E)-6-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-4-en-1-yl-3',3',3'-trifluoro-2-methoxy-2-phenylpropanoate 141

To a solution of alcohol 140 (0.015 g, 0.058 mmol) in DCM (2 ml) at r.t. was added Et₃N (0.012 g, 0.12 mmol, 0.017 ml), followed by (R)-(−)-MTPA-Cl (0.022 g, 0.087 mmol, 0.016 ml) and then DMAP (0.021 g, 0.17 mmol), with subsequent stirring at r.t. for 15 min. To the reaction mixture was then added DCM (10 ml) and sat. aq. NaHCO₃ (10 ml). The aqueous layer was then separated from the organic layer, the aqueous layer and washed with DCM (10 ml x 3). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the product as a yellow solid (0.054 g). Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compound as a clear liquid (0.020 g, 71%).

Rᵣ = 0.38 (10 : 1, pet. ether : Et₂O); [α]D⁰⁻3.3 (c 0.3, CHCl₃); (Found M⁺ + Na, 497.2293. C₂₄H₃₇O₄F₃NaSi requires M 497.2305); νmax/cm⁻¹ 2954, 2856, 2360, 2341, 1749, 1464, 1387, 1251, 1168, 1122, 1081, 1023, 835, 775, 719, 696 and 668; δH (400MHz, CDCl₃) 0.07 [6H, s, Si(CH₃)₂], 0.89 (3H, d, J 6.6, 2-CH₃), 0.91 [9H, s, Si(CH₃)₃], 1.58 (3H, m, 4-CH₃), 1.83 (1H, m, 3-H), 2.06 (2H, m, 2-H and 3-H'), 3.56 (3H, q, J 1.2, 2'-OCH₃), 4.14 (1H, dd, J 10.7, 5.4, 1-H), 4.17 (1H, dd, J 10.7, 5.8, 1'-H'), 4.18 (2H, m, 6-H₂), 5.29 (1H, tq, J 6.3, 1.2, 5-H), 7.42 (3H, m, Ar) and 7.53 (2H, m, Ar); δC (100MHz, CDCl₃) -5.1, 16.1, 16.6, 16.6, 18.4, 26.0, 30.4, 43.4, 55.4, 60.1, 70.8, 127.1, 127.2, 127.3, 128.4, 129.6, 132.3, 134.0 and 166.6; m/z (ES+) 497 (M⁺ + 23, 100%).

(2'R)-(2R,4E)-6-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-4-en-1-yl-3',3',3'-trifluoro-2-methoxy-2-phenylpropanoate 142
To a solution of alcohol 140 (0.021 g, 0.081 mmol) in DCM (2 ml) at r.t. was added Et₃N (0.016 g, 0.16 mmol, 0.022 ml), followed by (S)-(+-)MTPA-Cl (0.031 g, 0.12 mmol, 0.022 ml) with final addition of DMAP (0.030 g, 0.24 mmol), with subsequent stirring at r.t. for 15 min. To the reaction mixture was then added DCM (10 ml) and sat. aq. NaHCO₃ (10 ml). The aqueous layer was then separated from the organic layer and washed with DCM (10 ml x 3). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the product as a yellow solid (0.074 g). Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compound as a clear liquid (0.029 g, 74\%).

Rᶠ = 0.36 (10 : 1, pet. ether : Et₂O); [α]D⁴² +22.0, (c 1.4, CHCl₃); (Found M⁺ + Na, 497.2314. C₂₄H₃₇O₄F₃NaSi requires M⁺ 497.2305); νmax/cm⁻¹ 2955, 2927, 2856, 2360, 2341, 1749, 1464, 1387, 1252, 1169, 1122, 1081, 1023, 842, 813, 776, 719, 696 and 668; δH (400MHz, CDCl₃) 0.07 [6H, s, Si(CH₃)]₂, 0.89 (3H, d, J 6.6, 2-CH₃), 0.91 [9H, s, Si(CH₃)₃], 1.60 (3H, m, 4-CH₃), 1.85 (1H, m, 3-H), 2.06 (2H, m, 2-H and 3-H'), 3.56 (3H, q, J 10.7, 2'-OCH₃), 4.05 (1H, dd, J 10.7, 6.2, 1-H), 4.19 (2H, m, 6-H₂), 4.26 (1H, dd, J 10.7, 5.0, 1-H'), 5.31 (1H, tq, J 6.3, 1.2, 5-H), 7.42 (3H, m, Ar) and 7.53 (2H, m, Ar); δC (100MHz, CDCl₃) -5.1, 16.1, 16.6, 16.6, 18.4, 26.0, 30.4, 43.4, 55.4, 60.1, 70.8, 127.1, 127.2 127.3, 128.4, 129.6, 132.3, 134.0 and 166.6; m/z (ES+) 497 (M⁺ + 23, 100%).

(5R,2E)-tert-butyl((6-iodo-3,5-dimethylhex-2-en-1-yl)oxy)dimethylsilane 143

To a solution of alcohol 140 (0.322 g, 1.25 mmol) in DCM (13 ml) was added PPh₃ (0.508 g, 1.94 mmol) and imidazole (0.132 g, 1.94 mmol), with stirring for 10 min. I₂ (0.434 g, 1.71 mmol) was then added and the reaction mixture was allowed to stir for 1.5 h at r.t. To the reaction mixtures was then added sat. aq. Na₂S₂O₃ (14 ml), the aqueous layer was then separated from the organic layer and washed with DCM (40 ml x 4). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the product as a white solid (1.06 g). Column chromatography (SiO₂, 100% pet. ether to remove top spot then 99 : 1, pet. ether : Et₂O) gave the title compound as a clear liquid (0.38 g, 83\%).
Rf = 0.44 (20 : 1, hexane : Et2O); [α]D<sup>20</sup> -8.8, (c 1.6, CHCl3); (Found M<sup>+</sup> - C₄H₉, 311.0313. C₁₀H₂₀OISi requires M 311.0323); ν<sub>max</sub>/cm<sup>-1</sup> 2955, 2927, 2885, 2856, 1670, 1638, 1472, 1461, 1380, 1360, 1314, 1253, 1221, 1194, 1151, 1101, 1055, 1005, 938, 833, 813, 773 and 665; δ<sub>H</sub> (400MHz, CDCl₃) 0.91 [9H, s, Si(CH₃)₃], 0.97 (3H, d, <i>J</i> 6.6, 5-CH₃), 1.61 (3H, m, 3-CH₃), 1.68 (1H, m, 5-H), 1.88 (1H, dd, <i>J</i> 13.5, 7.2, 4-H), 2.10 (1H, dd, <i>J</i> 13.5, 7.2, 4-H'), 3.07 (1H, td, <i>J</i> 6.3, 1.2, 2-H); δ<sub>C</sub> (100MHz, CDCl₃) 5.1, 16.2, 17.2, 18.4, 20.6, 26.0, 32.7, 46.5, 60.1, 127.1, and 134.2; <i>m/z</i> (EI/CI) 311 (M<sup>+</sup> - 57, 4%).

(5R,7S,9E)-11-((tert-butyldimethylsilyl)oxy)-N-(1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N,5,7,9-tetramethyloct-9-enamide 144

To a solution of LiCl (1.15 g, 27.3 mmol) in THF (4 ml) was added LDA (1.8M in THF/heptane/ethylbenzene) (0.920 g, 8.60 mmol, 4.78 ml), which was then cooled to -78°C. A 0°C solution of amide 123 (1.00 g, 4.52 mmol) in THF (13 ml) was then added dropwise with sequential stirring at -78°C (1 h), 0°C (15 min) and then at r.t. for 10 min. To the mixture was then added iodide 143 (0.791 g, 2.15 mmol) in THF (8 ml) with subsequent stirring r.t. for 19 h. To the reaction mixture was then added sat. aq. NH₄Cl (40 ml), followed by the further addition of sat. aq. NH₄Cl (240 ml). The aqueous layer was then separated from the organic layer and washed with EtOAc (240 ml x 5). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the crude product as a light orange liquid (1.99 g). Column chromatography (SiO₂, 1 : 2 EtOAc : pet.ether) gave the title compound as a clear oil in a 1 : 0.2 rotamer ratio (0.85 g, 86%).

Rf = 0.24 (2 : 1, pet. ether : EtOAc); [α]D<sup>29</sup> +41.0, (c 1.6, CHCl₃); (Found M<sup>+</sup> + Na, 484.3230. C₂₇H₄₇O₃NNaSi requires M 484.3217); ν<sub>max</sub>/cm<sup>-1</sup> 3378 (br), 2955, 2927, 2856, 1620, 1462, 1408, 1378, 1360, 1300, 1253, 1197, 1083, 1051, 1005, 938, 843, 813, 774, 700 and 665; δ<sub>H</sub> (400MHz, CDCl₃) (1 : 0.2 rotamer ratio, asterisk denotes minor rotamer peaks) 0.06 [7.2H, m, Si(CH₃)₂ and Si(CH₃)<sub>3</sub>'], 0.71 (3H, d, <i>J</i> 6.6, 7-CH₃), 0.86 (0.6H, d, <i>J</i> 6.6, 7-CH₃'), 0.90 [10.8H, m, Si(CH₃)<sub>3</sub> and Si(CH₃)<sub>3</sub>'], 1.02
(2.4H, m, 6-H, 6-H', 5-CH₃* and 2-CH₃*), 1.04 (3H, d, J 6.8, 5-CH₃*), 1.14 (3H, d, J 6.8, 2-CH₃), 1.56 (1H, m, 7-H), 1.60 (3H, s, 9-CH₃), 1.60 (0.6H, m, 9-CH₃*), 1.67 (1.2H, m, 7-H* and 6-H*), 1.73 (1H, dd, J 13.0, 8.4, 8-H), 1.73 (0.2H, m, 8-H*), 1.88 (0.2H, m, 6-H*), 1.97 (1H, dd, J 13.0, 6.1, 8-H*), 2.06 (0.2H, dd, J 13.0, 5.5, 8-H*), 2.69 (1H, m, 5-H), 2.83 (3H, s, NCH₃), 2.88 (0.6H, s, NCH₃*), 3.01 (0.2H, m, 5-H*), 4.08 (0.2H, m, 2-H*), 4.19 (2.4H, m, 11-H₂ and 11-H₂*), 4.37 (1H, m, 2-H), 4.55 (0.2H, m, 1-H*), 4.61 (1H, t, J 7.1, 1-H), 5.27 (1H, tq, J 6.3, 1.1, 10-H), 5.30 (0.2H, m, 10-H*), 7.24 (1H, m, Ar*), 7.33 (5H, m, Ar); δC (100MHz, CDCl₃) (asterisk denotes minor rotamer peaks that were visible) -5.4*, -5.1, 14.3, 15.4*, 16.0, 16.0, 17.9, 18.3, 18.3, 18.7*, 19.4, 19.7*, 25.9, 26.9*, 28.1, 28.3*, 33.1*, 33.9, 41.1, 41.3*, 47.8, 57.9*, 60.2, 60.2*, 75.1*, 76.3, 125.9*, 126.1, 126.1, 126.9*, 127.4, 128.2, 128.3*, 135.4, 135.8*, 141.3*, 142.6, 177.5* and 178.8; m/z (ES+) 484 (M⁺ + 23, 100%).

(6E)-(2R,4S)-8-(tert-Butyl-dimethyl-silanyloxy)-2,4,6-trimethyl-oct-6-en-1-ol 119

To a cooled (0°C) solution of LDA (1.8M in THF/heptane/ethylbenzene) (4.73 g, 44.2 mmol, 24.5 ml) in THF (13 ml) was added NH₃·BH₃ (1.52 g, 44.2 mmol), with stirring at 0°C for 15 min and then at r.t. for 15 min. The solution was then cooled to 0°C before the addition of α,γ-branched amide 144 (5.10 g, 11.0 mmol) in THF (37 ml), with subsequent stirring at r.t. for 2 h. To the reaction mixture was then added HCl (1.0M) (10 ml) followed by separation of the aqueous layer from the organic layer and subsequent washing of the aqueous layer with EtOAc (10 ml x 4). The combined organic layers were then washed with sat. aq. NaHCO₃ (10 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude product as a light yellow liquid (4.68 g). Column chromatography (SiO₂, 1 : 10, EtOAc : pet. ether) gave the title compound as a clear liquid (2.79 g, 84%).

Rᵣ = 0.18 (1 : 3, Et₂O : pet. ether); [α]D⁰³² +7.5, (c 2.4, CHCl₃); (Found M⁺ + Na, 323.2365. C₁₇H₃₆O₂NaSi requires M 323.2377); ν₃max/cm⁻¹ 3348(br), 2953, 2927, 2856, 2360, 1668, 1462, 1379, 1361, 1253, 1092, 1042, 1005, 938, 833, 813, 773, 734 and 665; δH (400MHz, CDCl₃) 0.07 [6H, s, Si(CH₃)₂], 0.84 (3H, d, J 6.2, 4-CH₃), 0.90 [9H,
N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-N-methylpropionamide

To a solution of (-)-pseudoephedrine 148 (3.00 g, 18.2 mmol) in THF (21 ml) was added NaOMe (0.491 g, 9.09 mmol) with stirring at r.t. for 15 min. Methyl propionate (3.20 g, 36.4 mmol, 3.49 ml) was then added, with subsequent stirring at r.t. for 1.5 h. To the reaction mixture was then added HCl (3.0M) (12 ml) with subsequent separation of the aqueous layer from the organic layer. The organic layer was then washed with DCM (36 ml x 4) and the combined organic layers were then washed with H2O (36 ml), dried (MgSO4) and concentrated under reduced pressure to afford the product as a white solid (4.69g). Column chromatography (SiO2, 3 : 1 EtOAc : pet.) gave the title compound as a white solid in a 1 : 0.35 rotamer ratio (3.11 g, 77%).

Rf = 0.14 (1 : 1, EtOAc : pet. ether); m.p 114.9-115.2°C; [α]D28 -102.1, (c 0.95, MeOH); vmax/cm-1 3373(br), 2974, 2935, 2875, 1611, 1492, 1456, 1429, 1399, 1378, 1361, 1318, 1279, 1229, 1204, 1175, 1122, 1088, 1076, 1062, 1025, 979, 887, 856, 818, 761, 700, 645 and 629; δH (400MHz, CDCl3) (1 : 0.35 rotamer ratio, asterisk denotes minor rotamer peaks) 0.90 (1.05H, d, J 6.8, 2-CH3*), 1.06 (7.05H, m, 2-CH3, 6-H3 and 6-H3*), 2.24 (2H, m, 5-H2), 2.33 (0.35H, dq, J 15.1, 7.4, 5-H*), 2.46 (0.35H, dq, J 15.1, 7.4, 5-H*), 2.73 (3H, s, N-CH3), 2.85 (1.05H, s, N-CH3*), 3.93 (0.35H, dq, J 8.5, 6.8, 2-H*), 4.37 (1H, m, 2-H), 4.50 (1.35H, m, 1-H and 1-H*), 7.21 (1.75H, m, Ar*), 7.29 (5H, m, Ar); δC (100MHz, CDCl3) (asterisk denotes minor rotamer peaks that were visible) 9.1, 9.6*, 14.4, 15.2*, 26.7*, 26.8, 27.5, 32.6*, 58.2, 75.4*, 76.6, 126.4, 126.9*, 127.6, 128.3, 128.6*, 141.2*, 142.4, 174.9* and 176.1; m/z (ES+) 222 (M+ + 1, 100%).
To a solution of LiCl (0.421 g, 10.0 mmol) in THF (1 ml) was added LDA (1.8M in THF/heptane/ethylbenzene) (0.338 g, 3.16 mmol, 1.76 ml), which was then cooled to -78°C. A 0°C solution of amide 149 (0.367 g, 1.66 mmol) in THF (7 ml) was then added dropwise with sequential stirring at -78°C (1 h), 0°C (15 min) and then at r.t. for 10 min. To the mixture was then added iodide 143 (0.290 g, 0.790 mmol) in THF (2 ml) with subsequent stirring r.t. for 19 h. To the reaction mixture was then added sat. aq. NH₄Cl (16 ml), followed by the further addition of sat. aq. NH₄Cl (100 ml). The aqueous layer was then separated from the organic layer and washed with EtOAc (100 ml x 5). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the crude product as a dark orange oil (0.569 g). Column chromatography (SiO₂, 1 : 2 EtOAc : pet. ether) gave the title compound as a light orange oil in a 1 : 0.2 rotamer ratio (0.302 g, 83%).

Rᵣ = 0.29 (2 : 1, pet. ether : EtOAc); [α]_D²⁷ -49.9, (c 1.7, CHCl₃); (Found M⁺ + Na, 484.3234, C₂₅H₂₇O₃NNaSi requires M 484.3217); νₓₓₓ / cm⁻¹ 3380 (br), 2955, 2928, 2856, 1619, 1462, 1408, 1377, 1253, 1198, 1083, 1051, 1005, 834, 813, 774, 732, 700 and 665; δₓₓₓ (500MHz, CDCl₃) (asterisk denotes minor rotamer peaks) 0.00 [1.2H, s, Si(CH₃)₂⁺], 0.01 [6H, m, Si(CH₃)₂], 0.72 (3H, d, J 6.6, 7-CH₃), 0.78 (0.6H, d, J 6.6, 7-CH₃⁺), 0.83 [1.8H, s, Si(CH₃)₃⁺], 0.84 [9H, s, Si(CH₃)₃], 0.93 (0.6H, d, J 6.7, 2-CH₃⁺), 0.98 (3H, d, J 6.7, 5-CH₃), 0.99 (0.6H, m, 5-CH₃⁺), 1.05 (3H, d, J 6.7, 2-CH₃), 1.27 (2.4H, m, 6-H₂ and 6-H₂⁺), 1.48 (3H, s, 9-CH₃), 1.53 (1.8H, m, 9-CH₃⁺, 7-H and 7-H⁺), 1.70 (1H, dd, J 13.4, 8.6, 8-H), 1.72 (0.2H, m, 8-H⁺), 1.89 (1H, dd, J 13.4, 6.0, 8-H⁺), 2.05 (0.2H, dd, J 13.4, 5.6, 8-H⁺), 2.64 (1H, m, 5-H), 2.79 (3H, s, NCH₃), 2.83 (0.6H, s, NCH₃⁺), 2.90 (0.2H, m, 5-H⁺), 4.01 (0.2H, m, 2-H⁺), 4.12 (2H, d, J 6.4, 11-H₂⁺), 4.12 (0.4H, m, 11-H₂⁺), 4.40 (1H, m, 2-H), 4.50 (0.2H, d, J 8.8, 1-H⁺), 4.53 (1H, d, J 7.7, 1-H), 5.22 (1H, t, J 6.4, 10-H), 5.24 (0.2H, m, 10-H⁺), 7.19 (1H, m, Ar⁺) and 7.28 (5H, m, Ar); δₓₓ (125MHz, CDCl₃) (asterisk denotes minor rotamer peaks that were visible) -5.2, 14.4, 15.4⁺, 16.0, 16.1, 16.1⁺, 16.9, 17.5⁺, 18.3, 18.4, 19.3⁺, 19.3, 25.9, 28.2⁺, 28.3, 33.1⁺, 34.1, 40.8⁺, 40.9, 47.8, 58.0⁺, 60.1, 60.2⁺, 75.2⁺, 76.4, 125.9⁺,
126.3, 126.3, 126.8, 127.5, 128.2, 128.6, 135.2, 135.6, 141.3, 142.5, 177.9 and 179.2; m/z (ES+) 484 (M+ + 23, 100%).

(2S,4S,6E)-8-((tert-butyldimethylsilyl)oxy)-2,4,6-trimethyloct-6-en-1-ol 146

To a cooled (0°C) solution of LDA (1.8M in THF/heptane/ethylbenzene) (0.158 g, 1.48 mmol, 0.82 ml) in THF (0.5 ml) was added NH₃·BH₃ (90%) (0.051 g, 1.5 mmol), with stirring at 0°C for 15 min and then at r.t. for 15 min. The solution was then cooled to 0°C before the addition of α,γ-branched amide 150 (0.170 g, 0.370 mmol) in THF (1.5 ml), with subsequent stirring at r.t. for 2 h. To the reaction mixture was then added HCl (1.0M) (8 ml) followed by separation of the aqueous layer from the organic layer and subsequent washing of the aqueous layer with EtOAc (8 ml x 4). The combined organic layers were then washed with sat. aq. NaHCO₃ (8 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude product as a clear liquid (0.151 g). Column chromatography (SiO₂, 1 : 10, EtOAc : pet. ether) gave the title compound as a clear liquid (0.082 g, 75%).

Rᵣ = 0.36 (1 : 5, EtOAc : pet. ether); [α]D²⁴ -12.0, (c 1.0, CHCl₃); (Found M⁺ + Na, 323.2381. C₁₇H₃₆O₂NaSi requires M 323.2377); ν_max/cm⁻¹ 3342(br), 2955, 2927, 2857, 1462, 1380, 1361, 1253, 1094, 1042, 1005, 939, 909, 833, 813, 774, 733 and 665; δ_H (400MHz, CDCl₃) 0.07 [6H, s, Si(CH₃)₂], 0.82 (3H, d, J 6.5, 4-CH₃), 0.88 (3H, d, J 6.7, 2-CH₃), 0.90 [9H, s, Si(CH₃)₃], 1.08 (2H, m, 3-H₂), 1.48 (1H, br s, 1-OH), 1.59 (3H, m, 6-CH₃), 1.72 (2H, m, 2-H and 4-H), 1.85 (1H, dd, J 13.3, 7.6, 5-H), 1.95 (1H, dd, J 13.3, 6.9, 5-H’), 3.39 (1H, dd, J 10.5, 6.6, 1-H), 3.47 (1H, dd, J 10.5, 5.9, 1-H’), 4.20 (2H, m, 8-H₂) and 5.29 (1H, tq, J 6.3, 1.3, 7-H); δ_C (100MHz, CDCl₃) -5.1, 16.1, 16.2, 18.4, 19.3, 26.0, 27.7, 33.2, 40.2, 48.4, 60.2, 69.0, 126.1 and 135.6; m/z (ES+) 323 (M⁺ + 23, 100%).
(2E)-2-((2-methylbut-2-en-1-yl)thio)benzo[d]thiazole 171

To a solution of allylic alcohol 128 (0.208 g, 2.42 mmol) in THF (8 ml) was added 2-mercaptobenzothiazole 169 (0.606 g, 3.63 mmol) followed by PPh₃ (0.951 g, 3.63 mmol). The reaction mixture was cooled down to 0°C before the addition of DIAD (0.733 g, 3.63 mmol, 0.71 ml), with sequential stirring at 0°C for 10 min and at r.t. for 3 h. The reaction mixture was then concentrated under reduced pressure to afford the crude product as a light brown liquid (3.52 g). Column chromatography (SiO₂, 1 : 30, Et₂O : pet. ether) gave the title compound as a light yellow liquid (0.442 g, 78%).

Rᶠ = 0.37 (20 : 1, petrol : ether); (Found M⁺ + Na, 258.0383. C₁₂H₁₃NS₂ requires M 258.0382); vₓmax/cm⁻¹ 3059, 2978, 2913, 2856, 2289, 1939, 1901, 1822, 1782, 1667, 1558, 1455, 1425, 1380, 1308, 1274, 1237, 1205, 1158, 1125, 1076, 1018, 990, 933, 879, 850, 828, 780, 725, 704 and 666; δₓH (400MHz, CDCl₃) 1.64 (3H, dq, J 6.8, 1.0, 4-H₃), 1.79 (3H, m, 2-CH₃), 4.01 (2H, m, 1-H₂), 5.66 (1H, qq, J 6.8, 1.3, 3-H), 7.30 (1H, ddd, J 8.6, 7.3, 1.3, 6'-H), 7.42 (1H, ddd, J 8.6, 7.3, 1.3, 5'-H), 7.76 (1H, dd, J 8.6, 1.3, 7'-H) and 7.89 (1H, dd, J 8.6, 1.3, 4'-H); δₓC (100MHz, CDCl₃) 13.7, 15.0, 43.0, 120.9, 121.5, 124.1, 124.9, 125.9, 130.0, 135.2, 153.1 and 167.2; m/z (ES+) 258 (M⁺ + 23, 100%).

(2E)-2-((2-methylbut-2-en-1-yl)sulfonyl)benzo[d]thiazole 120

To a cooled solution (0°C) of BT-sulphide 171 (6.60 g, 28.1 mmol) in EtOH (200 ml) was added ammonium molybdate tetrahydrate (16.3 g, 13.2 mmol) in H₂O₂ (28% in H₂O) (318.4 g, 2809 mmol, 287.0 ml), with consecutive stirring at 0°C for 15 min and at r.t. for 30 min. Reaction mixture then diluted with EtOAc (2000 ml), followed by cooling to 0°C and addition of sat. aq. Na₂S₂O₃ (400 ml) and H₂O (1000 ml). The aqueous layer was then separated and washed with EtOAc (4 x 1000 ml). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the crude product as a viscous purple liquid (59.28 g). Column chromatography
(SiO$_2$, 100% Et$_2$O followed by a further column in 1 : 10, Et$_2$O : pet. ether) gave the title compound as a white solid (5.74 g, 77%).

R$_f$ = 0.11 (5 : 1, pet. ether : Et$_2$O); m.p 90.1-91.4°C; (Found M$^+$ + Na, 290.0271. C$_{12}$H$_{13}$O$_2$N$_2$S$_2$ requires 290.0280); anal. calcd for C$_{12}$H$_{13}$O$_2$N$_2$S$_2$: C 53.91, H 4.90, N 5.24, S 23.99, found: C 53.72, H 4.97, N 5.21, S 23.53; $\nu_{\text{max}}$/cm$^{-1}$ 2927, 2855, 1667, 1553, 1466, 1403, 1311, 1235, 1197, 1143, 1084, 1022, 850, 771, 732, 692 and 641; $\delta$H (400MHz, CDCl$_3$) 1.55 (3H, dq, $J$ 6.8, 1.0, 4-H$_3$), 1.83 (3H, m, 2-CH$_3$), 4.15 (2H, s, 1-H$_2$), 5.45 (1H, qq, $J$ 6.8, 0.8, 3-H), 7.59 (1H, ddd, $J$ 8.6, 7.3, 1.3, 6'-H), 7.64 (1H, ddd, $J$ 8.6, 7.3, 1.3, 5'-H), 8.01 (1H, dd, $J$ 8.6, 1.3, 7'-H) and 8.23 (1H, dd, $J$ 8.6, 1.3, 4'-H); $\delta$C (100MHz, CDCl$_3$) 14.1, 16.6, 64.4, 122.2, 122.5, 125.4, 127.5, 127.9, 132.1, 136.9, 152.6 and 165.8; m/z (ES+) 557 (M$_2^+$ + 23, 100%), 290 (M$^+$ + 23, 56%).

(2E)-2-((2-methylbut-2-en-1-yl)thio)-phenyl-tetrazole 172

![Structure of (2E)-2-((2-methylbut-2-en-1-yl)thio)-phenyl-tetrazole 172](image)

To a solution of allylic alcohol 128 (0.100 g, 1.16 mmol) in THF (2 ml) was added 1-phenyl-1H-tetrazole-5-thiol 170 (0.310 g, 1.74 mmol) followed by PPh$_3$ (0.456 g, 1.74 mmol). The reaction mixture was cooled down to 0°C before the addition of DIAD (0.351 g, 1.74 mmol, 0.34 ml), with sequential stirring at 0°C for 10 min and at r.t. for 3 h. The reaction mixture was then concentrated under reduced pressure to afford the crude product as a yellow liquid (1.60 g). Column chromatography (SiO$_2$, 1 : 2, Et$_2$O : pet. ether) gave the title compound as a light yellow liquid (0.226 g, 79%).

R$_f$ = 0.58 (1 : 1, Et$_2$O : pet. ether); (Found M$^+$ + H, 247.1022. C$_{12}$H$_{15}$N$_4$S requires M 247.1012); $\nu_{\text{max}}$/cm$^{-1}$ 2982, 2932, 2855, 1667, 1597, 1500, 1443, 1410, 1383, 1320, 1277, 1242, 1206, 1100, 1076, 1015, 981, 923, 827, 761, 695 and 685; $\delta$H (400MHz, CDCl$_3$) 1.56 (3H, dq, $J$ 6.8, 1.0, 4-H$_3$), 1.67 (3H, m, 2-CH$_3$), 4.00 (2H, m, 1-H$_2$), 5.61 (1H, qq, $J$ 6.8, 1.0, 3-H) and 7.53 (5H, m, Ar); $\delta$C (100MHz, CDCl$_3$) 13.6, 14.8, 42.7, 123.7, 125.7, 129.1, 129.6, 129.9, 133.6 and 154.1; m/z (ES+) 247 (M$^+$ + 1, 100%).
(2E)-2-((2-methylbut-2-en-1-yl)sulfonyl)-phenyl-tetrazole 163

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\text{Ph}
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To a cooled solution (0°C) of PT-sulphide 172 (0.656 g, 2.67 mmol) in EtOH (20 ml) was added ammonium molybdate tetrahydrate (1.55 g, 1.25 mmol) in H₂O (30% in H₂O) (30.3 g, 267 mmol, 27.3 ml), with consecutive stirring at 0°C for 15 min and at r.t. for 1 h. Reaction mixture then diluted with EtOAc (200 ml), followed by cooling to 0°C and addition of sat. aq. Na₂S₂O₃ (60 ml) and H₂O (100 ml). The aqueous layer was then separated and washed with EtOAc (100 ml x 4). The combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the crude product as a viscous purple liquid (72.0 g). Column chromatography (SiO₂, 100% Et₂O followed by a further column in 1 : 10, Et₂O : pet. ether) gave the title compound as a light yellow liquid (0.467 g, 63%).

\[ R_f = 0.34 \] (2 : 1, pet. ether : Et₂O); (Found M⁺ + Na, 301.0726. C₁₂H₁₄O₂N₄NaS requires 301.0730); \( \nu_{max}/\text{cm}^{-1} \) 2986, 2918, 1665, 1595, 1497, 1461, 1422, 1401, 1337, 1297, 1255, 1229, 1203, 1139, 1105, 1076, 1046, 1015, 982, 918, 877, 840, 788, 761, 734, 687 and 638; \( \delta_{H} \) (400MHz, CDCl₃) 1.65 (3H, d, \( J 6.8 \), 4-\( \text{H}3 \)), 1.77 (3H, t, \( J 1.2 \), 2-\( \text{CH}3 \)), 4.34 (2H, s, 1-\( \text{H}2 \)), 5.65 (1H, q, \( J 6.8 \), 3-\( \text{H} \)) and 7.60 (5H, m, Ar); \( \delta_{C} \) (100MHz, CDCl₃) 14.2, 16.7, 65.5, 121.0, 125.2, 129.5, 131.3, 133.0, 133.6 and 153.4; \( m/z \) (ES+) 579 (M⁺₂ + 23, 100%), 301 (M⁺ + 23, 53%).

(2R,4S,6E)-2,4,6-trimethyl-1-((triisopropylsilyl)oxy)oct-6-en-8-((tert-butyldimethylsilyl)oxy) 174

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\begin{array}{c}
\text{OTIPS} \\
\text{OTBS}
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To a cooled (-78°C) solution of alcohol 119 (0.493 g, 1.64 mmol) in DCM (10 ml) was added Et₃N (0.248 g, 2.46 mmol, 0.34 ml) and then TIPSOTf (0.603 g, 1.97 mmol, 0.53 ml), with stirring at -78°C for 20 min and then r.t. for 30 min. To the reaction mixture was then added sat. aq. NH₄Cl (40 ml), with subsequent separation of the aqueous layer from the organic layer. The aqueous layer was then washed with Et₂O (40 ml x 4) and
the combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a clear liquid (0.820 g). Column chromatography (SiO₂, 100% pet. ether) gave the title compound as a clear liquid (0.689 g, 92%).

R₇ = 0.52 (1 : 50, Et₂O : pet. ether); [α]₀⁺³⁴ +2.4, (c 0.5, CHCl₃); (Found M⁺, 456.3802. C₂₅H₅₆O₂Si₂ requires M 456.3813); νmax/cm⁻¹ 2928, 2866, 1667, 1463, 1382, 1254, 1096, 1064, 1007, 939, 919, 882, 835, 774, 680 and 659; δH (500MHz, CDCl₃) 0.08 [6H, s, Si(CH₃)₂], 0.82 (3H, d, J 6.1, 4-CH₃), 0.90 (1H, m, 3-H), 0.91 [9H, s, Si(CH₃)₃], 0.92 (3H, m, 2-CH₃), 1.08 [21H, m, Si(CH(CH₃)₃)₂ and Si(CH(CH₂)₃)₂], 1.35 (1H, m, 3-H'), 1.59 (3H, s, 6-CH₃), 1.71 (3H, m, 5-H, 4-H and 2-H), 2.05 (1H, m, 5-H'), 3.44 (1H, dd, J 9.5, 6.5, 1-H), 3.54 (1H, dd, J 9.5, 5.1, 1-H'), 4.20 (2H, d, J 6.3, 8-H₂) and 5.29 (1H, t, J 6.3, 7-H); δC (125MHz, CDCl₃) -5.1, 12.0, 16.1, 17.8, 18.1, 18.4, 20.1, 26.0, 28.2, 33.4, 41.2, 47.6, 60.3, 68.4, 125.9 and 135.9; m/z (EI/Cl) 456 (M⁺, 2%).

(5S,7R,2E)-3,5,7-trimethyl-8-((triisopropylsilyl)oxy)oct-2-en-1-ol 175

To a solution of bis-protected compound 174 (0.689 g, 1.51 mmol) in DCM (6 ml)/MeOH (6 ml) at r.t. was added PPTS (0.038 g, 0.15 mmol), with subsequent stirring at r.t. for 4 h. To the reaction mixture was then added sat. aq. NaHCO₃ (50 ml), which was then washed with Et₂O (100 ml x 4). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.470 g). Column chromatography (SiO₂, 1 : 5 Et₂O : pet. ether) gave the title compound as a clear liquid (0.443 g, 86%).

R₇ = 0.15 (1 : 3, Et₂O : pet. ether); [α]₀⁺³⁴ +2.7, (c 0.6, CHCl₃); (Found M⁺ + Na, 365.2847 C₂₀H₄₂O₂NaSi requires M 365.2847); νmax/cm⁻¹ 3313(br), 2944, 2866, 1667, 1462, 1382, 1246, 1098, 1063, 995, 919, 882, 786, 680 and 658; δH (400MHz, CDCl₃) 0.83 (3H, d, J 6.2, 5-CH₃), 0.90 (1H, m, 6-H), 0.92 (3H, d, J 6.7, 7-CH₃), 1.08 [21H, m, Si(CH(CH₃)₂)₂ and Si(CH(CH₂)₃)₂], 1.21 (1H, br s, 1-OH), 1.37 (1H, m, 6-H'), 1.64 (3H, s, 3-CH₃), 1.72 (3H, m, 7-H, 5-H and 4-H), 2.07 (1H, m, 4-H'), 3.45 (1H, dd, J 9.6, 6.3, 8-H), 3.53 (1H, dd, J 9.6, 5.3, 8-H'), 4.16 (2H, d, J 6.8, 1-H₂) and 5.40 (1H, t, J 6.8,
2-H); δc (100MHz, CDCl₃) 12.0, 16.1, 17.7, 18.0, 20.1, 28.1, 33.4, 41.1, 47.6, 59.4, 68.4, 124.8 and 138.9; m/z (ES+) 365 (M⁺ + 23, 100%).

(5S,7R,2E)-3,5,7-trimethyl-8-((triisopropylsilyl)oxy)oct-2-enal 173

To a r.t. solution of alcohol 175 (0.202 g, 0.589 mmol) in DCM (5 ml) was added DMP (0.499 g, 1.18 mmol), which was then stirred at r.t. for 1 h. To the reaction mixture was then added Et₂O (30 ml) with the further addition of sat. aq. NaHCO₃: Na₂S₂O₃ (30 ml). The aqueous layer was then separated from the organic layer, washed with Et₂O (10 ml x 4) and the combined organic layers were subsequently washed with brine (30 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as an off white liquid (0.224 g). Column chromatography (SiO₂, 1 : 10, Et₂O : pet. ether) gave the title compound as a clear liquid (0.185 g, 92%).

Rf = 0.53 (1 : 3, Et₂O : pet. ether); [α]D²⁶ +11.6, (c 0.9, C₆H₆); (Found M⁺ + Na, 363.2698. C₂₀H₄₀O₂NaSi requires M 363.2690); νmax/cm⁻¹ 2943, 2866, 1675, 1631, 1610, 1462, 1382, 1247, 1196, 1100, 1067, 1013, 996, 919, 882, 785, 680 and 659; δH (400MHz, CDCl₃) 0.87 (3H, d, J 6.2, 3-CH₃), 0.92 (3H, d, J 6.7, 7-CH₃), 0.98 (1H, m, 6-H), 1.07 {21H, m, Si [CH(CH₃)₃] and Si [CH(CH₃)₂]₃}, 1.42 (1H, m, 6-H'), 1.72 (1H, m, 7-H), 1.89 (2H, m, 5-H, 4-H), 2.15 (3H, d, J 1.1, 3-CH₃), 2.27 (1H, m, 4-H'), 3.49 (1H, dd, J 9.6, 5.8, 8-H'), 3.52 (1H, dd, J 9.6, 5.5, 8-H'), 5.87 (1H, d, J 8.2, 2-H) and 9.99 (1H, d, J 8.2, 1-H); 12.0, 17.4, 17.7, 18.0, 20.1, 28.7, 33.3, 41.1, 48.6, 68.2, 128.8, 163.4 and 191.2; m/z (ES+) 363 (M⁺ + 23, 100%).
triisopropyl((2\(R\),4\(S\),6\(E\),8\(E\),10\(E\))-2,4,6,10-tetramethyldodeca-6,9,10-trien-1-yl)oxy)silane 176

To a -78°C solution of vinyl aldehyde 173 (0.040 g, 0.12 mmol) and BT-sulphone 120 (0.047 g, 0.18 mmol) in THF (2 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.029 g, 0.18 mmol, 0.18 ml), with sequential stirring at -78°C for 1 h and at r.t. for 2 h. To the reaction mixture was added NaOH (1.0M) (5 ml) and then Et\(_2\)O (8 ml). The aqueous layer was then separated from the organic layer and washed with Et\(_2\)O (8 ml x 4). The combined organic layers were then washed with brine (5 ml), dried (\(\text{Na}_2\text{SO}_4\)) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.071 g). Column chromatography (SiO\(_2\), 100% pet. ether) gave the title compound as a light yellow liquid in a (\(6\ E\),8\(E\),10\(E\)) : (\(6\ E\),8\(Z\),10\(E\)) : (\(6\ E\),8\(E\),10\(Z\)) = 91 : 5 : 4 ratio (0.034 g, 74%).

\(R_f = 0.24\) (100% pet. ether); \([\alpha]^\theta_{D}\) +7.5 (c 0.8, C\(_6\)H\(_6\)); (Found M\(^+\), 392.3478 C\(_{25}\)H\(_{48}\)OSi requires M 392.3469); \(\nu_{\text{max}} / \text{cm}^{-1}\) 2943, 2921, 2865, 1643, 1462, 1381, 1248, 1097, 1068, 1013, 996, 958, 882, 791, 680 and 659; \(\delta_H\) (400MHz, C\(_6\)D\(_6\)) [\((6\ E,8\ E,10\ E)\) isomer] 0.92 (3H, d, \(J = 6.1\), 4-\(CH_3\)), 0.99 (1H, m, 3-\(H\)), 1.01 (3H, d, \(J = 6.6\), 2-\(CH_3\)), 1.13 {21H, m, Si \([\text{CH(CH}_3]_2\)} and Si \([\text{CH(H(CH}_3]_2\), 1.50 (1H, m, 3-\(H'\)), 1.60 (3H, d, \(J = 7.1\), 11-\(CH_3\)), 1.75 (6H, m, 10-\(CH_3\) and 6-\(CH_3\)), 1.82 (3H, m, 5-\(H\), 4-\(H\) and 2-\(H\)), 2.18 (1H, dd, \(J = 17.2\), 9.3, 5-\(H'\)), 3.48 (1H, dd, \(J = 9.4\), 6.2, 1-\(H\)), 3.57 (1H, dd, \(J = 9.4\), 5.1, 1-\(H'\)), 5.54 (1H, q, \(J = 7.1\), 11-\(H\)), 6.07 (1H, d, \(J = 10.8\), 7-\(H\)), 6.35 (1H, d, \(J = 15.3\), 9-\(H\)) and 6.54 (1H, dd, \(J = 15.3\), 10.8, 8-\(H\)), [visible peaks for \((6\ E,8\ Z,10\ E)\) isomer] 5.68 (1H, q, \(J = 6.9\), 11-\(H\)), 5.93 (1H, d, \(J = 11.5\), 7-\(H\)) and 6.26 (1H, t, \(J = 11.5\), 8-\(H\)), [visible peaks for \((6\ E,8\ E,10\ Z)\) isomer] 5.36 (1H, q, \(J = 7.3\), 11-\(H\)), 6.12 (1H, d, \(J = 11.5\), 7-\(H\)), 6.64 (1H, dd, \(J = 15.1\), 11.5, 8-\(H\)) and 6.75 (1H, d, \(J = 15.1\), 9-\(H\)); \(\delta_C\) (100MHz, C\(_6\)D\(_6\)) [(\(6\ E,8\ E,10\ E)\) isomer only] 12.6, 12.7, 14.4, 17.2, 18.5, 18.7, 20.9, 29.4, 34.3, 41.9, 48.9, 69.1, 123.3, 126.6, 128.2, 135.8, 136.6 and 136.8; \(m/z\) (AP+) 393 (M\(^+\) + 1, 100%).
(2S)-((tert-butoxycarbonyl)amino)-3-methylbutanoic acid 180

To a solution of L-valine 181 (4.68 g, 40.0 mmol) in THF/H₂O (1:1) (100 ml) at 0°C was added NaOH (3.52 g, 88.0 mmol). This was then followed by the slow addition of Boc₂O (10.5 g, 48.0 mmol) to the reaction mixture with subsequent stirring at 0°C for 0.5 h and at r.t. for 10 h. The solvent was then concentrated under reduced pressure and the aqueous layer washed with DCM (2 x 100 ml). The aqueous layer was then acidified with HCl (1.0M) to pH 4 and then washed with DCM (4 x 200 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as clear viscous liquid in a 1 : 0.55 rotamer ratio (8.43 g, 97%).

Rf = 0.51 (1 : 1, Et₂O: pet. ether); [α]D²⁵ -8.2 (c 1.0, AcOH); v̇max / cm⁻¹ 3332, 2969, 2937, 1712, 1660, 1505, 1394, 1368, 1306, 1254, 1157, 1092, 1045, 1016, 915, 861, 778, 733 and 647; δH (400MHz, CDCl₃) (1 : 0.55 rotamer ratio, asterisk denotes minor rotamer peaks) 0.92 [3H, d, J 7.1, 3-CH(CH₃)₃], 0.96 [1.65H, d, J 7.1, 3-CH(CH₃)₃], 0.99 [3H, d, J 6.8, 3-CH(CH₃)₅], 1.00 [1.65H, m, 3-CH(CH₃)₅], 1.44 [9H, s, C(CH₃)₃], 1.44 [4.95H, s, C(CH₃)₅], 2.19 [1.55H, m, 3-CH(CH₃)₂ and 3-CH(CH₃)₂], 4.02 (0.55H, m, 2-H'), 4.26 (1H, dd, J 9.1, 4.5, 2-H'), 5.10 (1H, d, J 9.1, NH), 6.44 (0.55H, d, J 7.6, NH'), 11.8 (1H, br. s, OH), 11.8 (0.55H, br.s, OH'); δC (100MHz, CDCl₃) (asterisk denotes minor rotamer peaks) 17.4, 17.5*, 19.0, 19.1*, 28.1*, 28.3, 30.8*, 31.0, 58.3, 60.0*, 80.0, 81.6*, 155.8, 157.1*, 176.9* and 177.2; m/z (ES+) 240 (M⁺ + 23, 100%).

(2R)-tert-butyl(3-(2',2'-dimethyl-4',6'-dioxo-1',3'-dioxan-5'-yl)-2-methylbutan-1-yl)carbamate 179

To a solution of acid 180 (6.00 g, 28.0 mmol) in DCM (100 ml) was added Meldrum’s acid (4.39 g, 30.5 mmol) and DMAP (5.12 g, 42.0 mmol), with subsequent cooling to -5°C. A solution of DCC (6.34 g, 30.8 mmol) in DCM (50 ml) was then added slowly
over 0.5 h, with further stirring at -5°C for 24 h. The reaction mixture was then warmed
to r.t., with subsequent filtration. The solution was then sequentially washed with 5%
aq. KHSO$_4$ (4 x 50 ml) and brine (50 ml), dried (MgSO$_4$) and concentrated under
reduced pressure until 100 ml of solvent remained. The solution was then cooled to
5°C before the addition of 98% AcOH (17 ml) which was then followed by the gradual
addition of NaBH$_4$ (2.65 g, 70.0 mmol) over 1h and subsequent stirring at -5°C for 15 h.
The reaction mixture was then sequentially washed with H$_2$O (3 x 50 ml) and brine (2 x
30 ml). The organic layer was then dried (MgSO$_4$), concentrated under reduced
pressure and recrystallised using Et$_2$O to afford the title compound as a white solid
(6.90 g, 76%).

R$_f$ = 0.18 (1 : 1, Et$_2$O: pet.ether); m.p 120-121°C; $[\alpha]_D^{28}$ -16.0 (c 0.3, C$_6$H$_6$); (Found M$^+$ - H, 328.1772. C$_{16}$H$_{26}$NO$_6$ requires 328.1765); $v_{\text{max}}$ / cm$^{-1}$ 3303, 2962, 2929, 1791,
1751, 1674, 1626, 1535, 1434, 1388, 1364, 1347, 1313, 1290, 1270, 1254, 1227, 1208
and 1186; $\delta_H$ (400MHz, CDCl$_3$) 0.94 [3H, d, $J$ 7.1, CH(C$_3$H$_3$)], 0.96 [3H, d, $J$ 6.9,
CH(CH$_3$’)], 1.40 [9H, s, C(CH$_3$)$_3$], 1.74 (3H, s, 2’-CH$_3$), 1.79 (3H, s, 2’-CH$_3$’), 1.80
[1H, m, CH(CH$_3$)$_2$], 2.10 (1H, ddd, $J$ 14.2, 11.7, 2.8, 3-H), 2.24 (1H, ddd, $J$ 14.2, 6.8,
2.3, 3-H’), 3.73 (1H, m, 2-H), 3.94 (1H, dd, $J$ 6.8, 2.8, 5’-H) and 4.48 (1H, d, $J$ 9.7, 1-
NH); $\delta_C$ (100MHz, CDCl$_3$) 17.8, 19.0, 25.8, 28.2, 28.5, 29.1, 32.6, 44.4, 54.3, 79.4,
104.9, 156.8, 165.6 and 166.0; m/z (ES-) 328 (M$^+$ - 1, 100%).

(2R)-tert-butyl 2-isopropyl-5-oxopyrrolidine-1-carboxylate 116

A solution of 5-mono-substituted Meldrum’s acid 179 (1.65 g, 5.02 mmol) in toluene
(30 mL) was refluxed for 5 h. Upon cooling, the organic layer was concentrated under
reduced pressure to afford the product as a clear liquid (1.18 g). Column chromatography (SiO$_2$, 1 : 1 Et$_2$O : pet. ether) gave the title compound as a white solid
(1.14 g, 99%).

R$_f$ = 0.25 (1 : 1, Et$_2$O : pet. ether); m.p 30-31°C, $[\alpha]_D^{29}$ +77.5 (c 0.5, C$_6$H$_6$); (Found M$^+$
+ Na, 250.1408. C$_{12}$H$_{21}$O$_3$NNa requires 250.1414); anal. calcd for C$_{12}$H$_{21}$O$_3$N: C 63.41,
H 9.31, N 6.16, found: C 63.56, H 9.72, N 6.13; $v_{\text{max}}$ / cm$^{-1}$ 2964, 1783, 1745, 1712,
1473, 1391, 1367, 1299, 1255, 1231, 1205, 1150, 1100, 1023, 956, 916, 863, 847, 822, 794, 781 and 663; δH (400MHz, CDCl3) 0.86 [3H, d, J 6.9, CH(CH3)], 0.94 [3H, d, J 7.1, CH(CH3′)], 1.53 [9H, s, C(CH3)3], 1.83 (1H, m, 3-H), 2.00 (1H, m, 3-H′), 2.23 [1H, m, CH(CH3)2], 2.43 (1H, ddd, J 18.1, 10.3, 3.3, 4-H), 2.53 (1H, ddd, J 18.1, 10.5, 9.6, 4-H′) and 4.08 (1H, ddd, J 9.1, 4.3, 2.3, 2-H); δC (100MHz, CDCl3) 15.7, 17.9, 19.0, 27.9, 30.5, 32.2, 62.4, 82.6, 150.1 and 174.9; m/z (ES+) 250 (M+ + 23, 100%).

(2Z)-ethyl 3-iodoacrylate 118

To a solution of LiI (1.50 g, 11.2 mmol) in MeCN (10 ml) was added ethyl propynoate 182 (1.00 g, 10.2 mmol, 1.03 ml) and AcOH (0.672 g, 11.2 mmol, 0.64 ml). The reaction mixture was then refluxed at 76°C for 14 h and then allowed to warm up to r.t. before the addition of H2O (30 ml). The aqueous layer was then separated from the organic layer and then washed with Et2O (50 ml x 3). The combined organic layers were then dried (MgSO4) and concentrated under reduced pressure to afford the product as a yellow liquid (2.15 g). Column chromatography (SiO2, 1 : 10 EtOAc : pet. ether) gave the title compound as a clear liquid (1.91 g, 83%).

Rf = 0.46 (1 : 10, EtOAc : pet. ether); νmax / cm−1 3064, 2981, 2900, 1721, 1598, 1445, 1390, 1366, 1276, 1192, 1159, 1095, 1024, 942, 872, 804, 761, 731 and 639; δH (400MHz, CDCl3) 1.32 (3H, t, J 7.1, CH3), 4.25 (2H, q, J 7.1, CH2), 6.89 (1H, d, J 8.8, 2-H) and 7.44 (1H, d, J 8.8, 3-H); δC (100MHz, CDCl3) 14.1, 60.7, 94.7, 129.8 and 164.5; m/z (ES+) 249 (M+ + 23, 100%).

(1E)-tributyl(tridec-1-en-1-yl)stannane 186
To a solution of 1-tridecyne 187 (0.500 g, 2.78 mmol) in benzene (6 ml) was added Bu₃SnH (0.809 g, 2.78 mmol, 0.75 ml) and AIBN (0.010 g, 0.056 mmol), which was then refluxed at 84°C for 4 h. The reaction mixture was then diluted with Et₂O (60 ml) and sequentially washed with sat. aq. NH₄Cl (20 ml) and brine (20 ml). The organic layer was then dried (MgSO₄) and concentrated under reduced pressure to afford the product as a clear liquid (1.43 g). Column chromatography (SiO₂, 100% hexane + 1% Et₃N) gave the title compound as a clear liquid in a 1E : 1Z = 10 : 1 ratio (1.03 g, 79%).

Rf = 0.89 (100% pet. ether); v_max / cm⁻¹ 2956, 2922, 2853, 2361, 1599, 1464, 1377, 1341, 1292, 1182, 1072, 988, 961, 874, 721, 691 and 666; δ_H (400MHz, CDCl₃) (1E isomer) 0.91 [18H, m, Sn(CH₂CH₂CH₂CH₃)₃, Sn(CH₂CH₂H₂CH₃)₃ and CH₃], 1.35 [24H, m, Sn(CH₂CH₂CH₂CH₃)₃ and 9 x CH₂], 1.53 [6H, m, Sn(CH₂CH₂CH₂CH₃)₃], 2.15 (2H, q, J 5.8, 3-H2), 5.83 (1H, d, J 18.9, 1-H) and 5.97 (1H, dt, J 18.9, 5.8, 2-H), (visible peaks for 1Z isomer) 2.03 (2H, q, J 7.0, 3-H2) and 6.54 (1H, dt, J 12.4, 7.0, 2-H); δ_C (100MHz, CDCl₃) (1E isomer only) 9.4, 10.2, 13.7, 14.1, 22.7, 27.3, 28.9, 29.1, 29.2, 29.4, 29.5, 29.7, 29.7, 31.9, 37.9, 126.9 and 149.9; (FTMS) 415 [M⁺ (¹²⁰Sn) - 57, 100%], 413 [M⁺ (¹¹⁸Sn) - 57, 60%], 411 [M⁺ (¹¹⁶Sn) - 57, 31%).

(2Z,4E)-ethyl hexadeca-2,4-dienoate 185

To a solution of vinyl stannane 186 (1.99 g, 4.23 mmol) in DMF (12 ml) was added vinyl iodide 118 (0.798 g, 3.53 mmol) in DMF (12 ml), followed by PdCl₂(MeCN)₂ (0.018 g, 0.071 mmol) with subsequent stirring at r.t. for 24 h. To the solution was then added (10%) aq. ammonia (24 ml), and then washed with Et₂O (3 x 360 ml). The combined organic layers were then sequentially washed with H₂O (120 ml) and brine (120 ml), dried (MgSO₄) and concentrated under reduced pressure to afford the product as a black liquid (2.25 g). Column chromatography (SiO₂, 1 : 100 Et₂O : pet. ether) gave the title compound as a dark orange liquid in a (2Z,4E) : (2Z,4Z) = 10 : 1 ratio (0.79 g, 80%).
RF = 0.54 (1:10, Et2O:pet. ether); (Found M⁺ + Na, 303.2285. C₁₈H₂₃O₂Na requires M 303.2295); v_max / cm⁻¹ 2923, 2853, 2360, 1715, 1637, 1601, 1465, 1421, 1388, 1367, 1301, 1274, 1177, 1096, 1062, 1031, 999, 962, 932, 819, 764, 722 and 615; δ_H (400MHz, CDCl₃) [(2Z,4E) isomer] 0.88 (3H, t, J 7.1, CH₃), 1.28 (19H, m, OCH₂CH₃ and 8 x CH₂), 1.43 (2H, m, 7-H₂), 2.20 (2H, q, J 7.1, 6-H₂), 4.18 (2H, q, J 7.1, OCH₂CH₃), 5.56 (1H, d, J 11.4, 2-H), 6.07 (1H, dt, J 14.0, 7.1, 5-H), 6.55 (1H, t, J 11.4, 3-H) and 7.37 (1H, dq, J 14.0, 11.4, 1.2, 4-H), [visible peaks for (2Z,4Z) isomer] 2.26 (1H, q, J 7.2, 6-H₂), 5.67 (1H, d, J 11.5, 2-H), 5.91 (1H, m, 5-H), 6.93 (1H, dt, J 11.5, 1.0, 3-H) and 7.28 (1H, m, 4-H); δ_C (100MHz, CDCl₃) [(2Z,4E) isomer only] 14.1, 14.3, 22.7, 28.8, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 33.0, 59.8, 115.4, 126.8, 145.4, 145.8 and 166.6; m/z (ES⁺) 303 (M⁺ + 23, 100%).

(2Z,4E)-hexadeca-2,4-dienoic acid 189

To a solution of ester 185 (0.789 g, 2.82 mmol) in EtOH (16 ml) at r.t. was added NaOH (2.37 g, 59.2 mmol) in H₂O (2.5 ml) with subsequent stirring at r.t. for 3 h. Reaction then acidified to pH 2 using HCl (1.0M) and then washed with Et₂O (120 ml x 4). The combined organics were then washed with H₂O (120 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as a cream solid in a (2Z,4E) : (2Z,4Z) = 10 : 1 ratio (0.70 g, 99%).

RF = 0.33 (1:3, Et₂O:pet. ether); m.p 53-54°C; (Found M⁺ - H, 251.2017. C₁₆H₂₇O₂ requires M 251.2016); v_max / cm⁻¹ 3044, 2953, 2913, 2848, 2754, 2586, 1789, 1693, 1674, 1635, 1602, 1473, 1465, 1444, 1379, 1315, 1300, 1292, 1248, 1234, 1226, 1145, 1124, 1085, 1076, 1048, 1011, 1002, 963, 870, 853, 824, 773, 748, 723, 700, 661, 645 and 617; δ_H (400MHz, CDCl₃) [(2Z,4E) isomer] 0.89 (3H, t, J 7.2, CH₃), 1.29 (16H, m, 8 x CH₂), 1.44 (2H, m, 7-H₂), 2.22 (2H, q, J 7.1, 6-H₂), 5.59 (1H, d, J 11.4, 2-H), 6.14 (1H, dt, J 14.1, 7.1, 5-H), 6.67 (1H, t, J 11.4, 3-H), 7.35 (1H, ddq, J 14.1, 11.4, 1.0, 4-H) and 12.14 (1H, br.s, COOH), [visible peaks for (2Z,4Z) isomer] 2.28 (1H, q, J 7.1, 6-H₂), 5.70 (1H, d, J 11.5, 2-H), 5.98 (1H, m, 5-H), 7.06 (1H, dt, J 11.5, 1.0, 3-H) and 7.28 (1H, m, 4-H); δ_C (100MHz, CDCl₃) [(2Z,4E) isomer only] 14.1, 22.7, 28.8, 29.3,
29.4, 29.5, 29.6, 29.6, 29.6, 31.9, 33.1, 114.7, 127.0, 147.3, 147.8 and 172.5; \textit{m/z} (ES-) 251 (M$^+$ - 1, 100%).

\((2Z,4E)-1-(1H\text{-imidazol-1-yl})\text{hexadeca-2,4-dien-1-one 190}\)

To a solution of acid \textbf{189} (0.700 g, 2.78 mmol) in THF (14 ml) at r.t. was added 1,1’-carbonyldiimidazole (0.572 g, 3.53 mmol), with subsequent stirring at r.t. for 45 min. The reaction mixture was then diluted with Et$_2$O (100 ml) and sequentially washed with H$_2$O (20 ml) and brine (20 ml), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the \textit{title compound} as a cream solid in a \((2Z,4E) : (2E,4E) = 5 : 1\) ratio (0.803 g, 82%).

R$_t$ = 0.20 (6 : 1, Et$_2$O : pet.ether); m.p 45-46°C; (Found M$^+$ + H, 303.2424. C$_{19}$H$_{31}$ON$_2$ requires M 303.2431); \textit{v}\textsubscript{max} / cm$^{-1}$ 3129, 3107, 2955, 2916, 2871, 2850, 2358, 1758, 1706, 1628, 1588, 1525, 1471, 1445, 1381, 1358, 1313, 1278, 1244, 1095, 1077, 1045, 1005, 981, 961, 922, 901, 872, 849, 830, 810, 796, 764, 717, 700, 662, 645 and 605; \(\delta\text{H}\) (400MHz, CDCl$_3$) [(2Z,4E) isomer] 0.88 (3H, t, \(J 6.8\), CH$_3$), 1.28 (16H, m, 8 x CH$_2$), 1.47 (2H, m, 7-H$_2$), 2.27 (2H, q, 7.1, 6-H$_2$) 6.18 (1H, d, \(J 11.3\), 2-H), 6.33 (1H, dt, \(J 15.4, 7.1, 5-H\)), 6.89 (1H, t, \(J 11.3, 3-H\)), 7.11 (1H, m, 3’-H), 7.44 (1H, ddq, \(J 15.4, 11.2, 1.3, 4-H\)), 7.53 (1H, t, \(J 1.5, 5’-H\)) and 8.20 (1H, s, 6’-H), [visible peaks for (2E,4E) isomer] 6.44 (1H, d, \(J 14.9, 2-H\)), 6.96 (1H, m, 5-H) and 7.66 (1H, dd, \(J 14.8, 9.9, 4-H\)); \(\delta\text{C}\) (100MHz, CDCl$_3$) [(2Z,4E) isomer only] 14.1, 22.6, 28.5, 29.2, 29.3, 29.4, 29.5, 29.5, 29.6, 31.8, 33.2, 111.9, 116.2, 127.1, 130.7, 136.1, 150.6, 150.9 and 161.3; \textit{m/z} (ES+) 325 (M$^+$ + 23, 100%).
(5'R,1E)-tert-butyl-2'-(2Z,4E)-1-hydroxyhexadeca-2,4-dien-1-ylidene)-5'-isopropyl-3'-oxopyrrolidine-4'-carboxylate 191

To a -78°C solution of pyrrolidinone 116 (0.730 g, 3.22 mmol) in THF (6 ml) was added a 0°C solution of LiHMDS (1.0M in THF) (0.538 g, 3.22 mmol, 3.22 ml), with subsequent stirring at -78°C for 1 h. This was then followed by the addition of a 0°C solution of imidazolide 190 (0.486 g, 1.61 mmol) in THF (2 ml), with further stirring at -78°C for 3 h. To the reaction mixture was then added sat. aq. NH₄Cl (3 ml), which was then allowed to warm to r.t. before the addition of sat. aq. NH₄Cl (30 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 100 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light orange liquid (1.50 g). Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compound as a light orange liquid in a (2Z,4E) : (2E,4E) = 5 : 1 ratio (0.480 g, 65%).

Rᶠ = 0.13 (1 : 10, Et₂O : pet. ether); [α]D²⁸ +50.2 (c 0.6, CHCl₃); (Found M⁺ + Na, 484.3412. C₂₈H₄₇O₄NNa requires 484.3397); νmax / cm⁻¹ 2959, 2923, 2853, 1757, 1715, 1667, 1625, 1572, 1465, 1382, 1367, 1294, 1252, 1224, 1148, 1097, 1046, 1032, 993, 974, 954, 892, 853, 801, 742, 721, 692 and 653; δH (500MHz, CDCl₃) [(2Z,4E) isomer] 0.76 [3H, d, J 6.9, CH(CH₃)], 0.87 (3H, t, J 7.1, CH₃), 0.91 [3H, d, J 6.9, CH(CH₃)], 1.26 (16H, m, 8 x CH₂), 1.41 (2H, m, 7-CH₂), 1.54 [9H, s, C(CH₃)₃], 2.18 (2H, q, J, 7.1, 6-CH₂), 2.27 [1H, m, CH(CH₃)₂], 2.41 (1H, dd, J 15.8, 2.4, 6'-H), 2.63 (1H, dd, J 15.8, 9.7, 6'-H'), 4.09 (1H, m, 5'-H), 5.49 (1H, d, J 11.7, 2-H), 5.96 (1H, dt, J 14.2, 7.1, 5-H), 6.35 (1H, t, J 11.7, 3-H), 7.25 (1H, dd, J 14.2, 11.7, 4-H) and 12.07 (1H, d, J 1.7, 1-OH), [visible peaks for (2E,4E) isomer] 5.86 (1H, d, J 15.1, 2-H), 6.18 (1H, m, 5-H), 6.52 (1H, m, 3-H), 7.40 (1H, m, 4-H) and 11.7 (1H, d, J 1.6, 1-OH); δC (125MHz, CDCl₃) [(2Z,4E) isomer only] 14.1, 14.5, 18.5, 21.3, 22.6, 28.2, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 30.4, 31.9, 33.1, 60.0, 82.6, 102.0, 116.4, 128.5, 139.3, 144.1, 150.3, 163.7 and 173.3; m/z (ES+) 484 (M⁺ + 23, 100%).
(5'R)-tert-butyl-2'-(2Z,4E)-hexadeca-2,4-dienoyl)-5'-isopropyl-3'-oxo-2'-
(phenylselanyl)pyrrolidine-4'-carboxylate 192

To a -78°C solution of oxopyrrolidine 191 (0.020 g, 0.043 mmol) in THF (0.4 ml), was
added a -78°C solution of LiHMDS (1.0M in THF) (0.011 g, 0.065 mmol, 0.065 ml),
with subsequent stirring at -78°C for 1 h. This was then followed by the addition of a
solution of PhSeCl (0.033 g, 0.17 mmol) in THF (0.1 ml) with subsequent stirring at
-78°C for 2.5 h. To the reaction mixture was then added sat. aq. NH₄Cl (2 ml), which
was then allowed to warm to r.t. before the addition of sat. aq. NH₄Cl (2 ml). The
aqueous layer was then separated from the organic layer and subsequently washed with
Et₂O (4 x 15 ml). The combined organic layers were then dried (Na₂SO₄) and
concentrated under reduced pressure to afford the product as a light yellow liquid (0.051 g).
Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compound
as a light yellow liquid as a mix. of epimers at C(2') with the epimers having an a : b = 1 : 0.4 ratio (0.015 g, 56%).

Rf = 0.19 (1 : 10, Et₂O : pet. ether); [α]D²⁰ +82.6 (c 0.8, CHCl₃); (Found M⁺ + Na,
640.2857. C₃₄H₅₁O₄NSeNa requires 640.2876); νmax / cm⁻¹ 2957, 2922, 2851, 1777,
1723, 1670, 1624, 1575, 1465, 1437, 1391, 1366, 1288, 1255, 1147, 1106, 1065, 1020,
998, 963, 849, 793, 739, 690 and 671; δH (300MHz, CDCl₃) 0.69 [4.2H, d, J 7.0,
CH(CH₃)a and CH(CH₃)b], 0.82 [4.2H, d, J 7.0, CH(CH₃)a and CH(CH₃)b], 0.89 (4.2H,
t, J 6.9, CH₃a and CH₃b), 1.29 (22.4H, m, 8 x CH₂a and 8 x CH₂b), 1.45 (2.8H, m, 7-
CH₂a and 7-CH₂b), 1.54 (12.6H, s, C(CH₃)₃a and C(CH₃)₃b), 1.80 (0.4H, dd, J 13.9, 7.6,
6'-Hb), 1.96 (1H, dd, J 14.9, 8.1, 6'-Ha), 2.27 [4.2H, m, CH(CH₃)₂a, CH(CH₃)₂b, 6-CH₂a
and 6-CH₂b], 2.53 (1H, dd, J 14.9, 6.3, 6'-H'a), 2.73 (0.4H, dd, J 13.9, 7.7, 6'-H'b),
3.90 (1.4H, m, 5'-Ha and 5'-Hb), 6.15 (1.4H, m, 5'-H'a and 5'-H'b), 6.60 (1.4H, t, J 11.3, 3-Ha
and 3-Hb), 6.92 (0.4H, d, J 11.3, 2-Hb), 6.94 (1H, d, J 11.3, 2-Ha) and 7.42 (8.4H, m, 4-
H'a, 4-Hb, SeAr²a and SeAr²b); δC (100MHz, CDCl₃) (only major epimer a shown) 14.1,
15.2, 18.4, 22.7, 27.9, 28.0, 28.7, 28.8, 29.3, 29.3, 29.5, 29.6, 29.6, 31.9, 33.2,
59.1, 83.5, 119.9, 127.7, 128.0, 129.2, 129.3, 130.2, 131.5, 137.6, 145.6, 148.3, 170.1 and 190.5; \textit{m/z} (ES+) 640 (M$^+$ + 23, 100%).

\textbf{(S)-\textit{tert}-butyl-2'-(2Z,4E)-hexadeca-2,4-dienoyl-5'-isopropyl-3'-oxo-6'H-pyrrole-3'-carboxylate 188}

To a -50°C solution of selenide 192 (0.034 g, 0.055 mmol) in CDCl$_3$ (4 ml) was added a 0°C solution of H$_2$O$_2$ (30%) (0.066 g, 0.58 mmol) in H$_2$O (0.5 ml) and then a 0°C solution of \textit{m}-CPBA (77%) (0.014 g, 0.061 mmol) in CDCl$_3$ (2 ml), with further stirring at -50°C for 30 min. The reaction mixture was then removed from the -50°C bath and was placed in a 0°C bath for 15 min with vigorous stirring. This was then followed by the addition of 0°C CDCl$_3$ (3 ml) and sequential washing with 0°C sat. aq. Na$_2$CO$_3$ (2 ml x 2) and 0°C H$_2$O (2 ml). The organic layer was then dried (Na$_2$SO$_4$) and, due to the reactivity of the product, the solution was not concentrated under reduced pressure.

\textbf{(2R,4S,6E)-8-((\textit{tert}-butyldimethylsilyl)oxy)-2,4,6-trimethyloct-6-enal 198}

To a solution of DMP (2.93 g, 6.92 mmol) in DCM (15 ml) at r.t. was added pyridine (3.28 g, 41.5 mmol, 3.35 ml) which was then stirred at r.t. for 15 min. This was then followed by the addition of alcohol 119 (1.04 g, 3.46 mmol) in DCM (15 ml), with stirring at r.t. for 2 h. To the reaction mixture was then added Et$_2$O (100 ml) with the further addition of sat. aq. NaHCO$_3$: Na$_2$S$_2$O$_3$ (100 ml). The aqueous layer was then separated from the organic layer, washed with Et$_2$O (100 ml x 4) and the combined organic layers were subsequently washed with brine (100 ml), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the \textit{title compound} as a light yellow liquid (1.00 g, 97%).
Rf = 0.38 (1 : 10, Et2O : pet. ether); \([\alpha]D^{28} -7.6, (c 0.8, C_6H_6); (Found M^+ + Na, 321.2217. C_{17}H_{34}O_2Si requires M 321.2220); \nu_{max}/\text{cm}^{-1} 2955, 2928, 2855, 2706, 1727, 1461, 1380, 1360, 1252, 1198, 1087, 1057, 1005, 938, 833, 813, 773, 742 and 665; \delta_H (500MHz, CDCl_3) 0.07 [6H, s, Si(CH_3)_2], 0.86 (3H, d, J 6.4, 4-CH_3), 0.91 [9H, s, Si(CH_3)_3], 1.09 (3H, d, J 6.9, 2-CH_3), 1.11 (1H, m, 3-H), 1.58 (3H, s, 6-CH_3), 1.70 (2H, m, 4-H and 3-H'), 1.80 (1H, dd, J 13.2, 7.9, 5-H), 2.00 (1H, dd, J 13.2, 6.0, 5-H'), 2.46 (1H, m, 2-H), 4.20 (2H, d, J 6.3, 8-H_2), 5.30 (1H, tq, J 6.3, 1.2, 7-H) and 9.57 (1H, d, J 2.6, 1-H); \delta_C (125MHz, CDCl_3) -5.1, 14.3, 16.1, 18.4, 19.7, 26.0, 28.3, 38.0, 44.1, 47.5, 60.2, 126.6, 135.1 and 205.3; m/z (ES+) 321 (M^+ + 23, 100%).

**dimethyl (1-diazo-2-oxopropyl)phosphonate 196**

![Structure](image)

A solution of dimethyl (2-oxo-propyl phosphonate) (1.00 g, 6.02 mmol) in toluene (25ml) and THF (5 ml) was cooled to 0°C with stirring for 30 min. To the reaction mixture was then slowly added NaH (60% in oil) (0.265 g, 6.62 mmol), with further stirring at 0°C for 1 h. Then 4-Acetamidobenzene sulfonyl azide (1.59 g, 6.62 mmol) was added slowly and reaction allowed to warm to r.t. with subsequent stirring at r.t. for 20 h. The mixture was then filtered through celite, washed with EtOAc (100 ml x 3) and the combined organic layers were then concentrated under reduced pressure to afford the product as a light yellow liquid (1.37 g). Column chromatography (SiO_2, 1: 1 EtOAc : pet. ether) gave the title compound as a light yellow liquid (1.04 g, 90%).

Rf = 0.28 (100% EtOAc); \nu_{max}/\text{cm}^{-1} 3493, 2959, 2859, 2120, 1655, 1593, 1537, 1450, 1364, 1258, 1179, 1161, 1014, 970, 927, 835, 803, 782, 731, 647 and 612; \delta_H (400MHz, CDCl_3) 2.27 (3H, s, CH_3), 3.84 (3H, s, OCH_3) and 3.86 (3H, s, OCH_3); \delta_C (100MHz, CDCl_3) 26.6, 53.1, 53.2, 189.3 and 189.4; m/z (ES+) 215 (M^+ + 23, 100%).
**tert-butyl(((5S,7R,8E)-9,9-dibromo-3,5,7-trimethylnona-2,8-dien-1-yl)oxy)dimethylsilane 200**

![Chemical Structure](image)

To a solution of PPh$_3$ (0.823 g, 3.12 mmol) in DCM (10 ml) was added Zn (0.204 g, 3.14 mmol), which was then cooled to 0°C before the addition of CBr$_4$ (1.04 g, 3.14 mmol). The reaction mixture was then stirred at 0°C for 15 min and then at r.t. for 20 min before the addition of aldehyde **198** (0.470 g, 1.57 mmol) in DCM (5 ml) and subsequent stirring at r.t. for 18 h. To the reaction was then added pentane (100 ml) with vigorous stirring for 1 h, which was then filtered through celite and washed with pentane (100 ml x 4). The combined organic layers were then dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.687 g). Column chromatography (SiO$_2$, 100% pet. ether) gave the **title compound** as a clear liquid (0.529 g, 74%).

R$_f$ = 0.41 (1 : 40, Et$_2$O : pet. ether); [α]$_D^{23}$ = -1.7 (c 0.7, C$_6$H$_6$); (Found M$^+$ - C$_{14}$H$_{29}$OBr$_2$Si requires 395.0036); $\nu_{max}$ / cm$^{-1}$ 2956, 2928, 2856, 2359, 1667, 1614, 1462, 1380, 1361, 1253, 1191, 1085, 1056, 1006, 968, 939, 833, 813, 773 and 665; $\delta_H$ (400MHz, CDCl$_3$) 0.08 [6H, s, Si(CH$_3$)$_2$], 0.87 (3H, d, J 6.4, 5-CH$_3$), 0.91 [9H, s, Si(CH$_3$)$_3$], 0.99 (3H, d, J 6.7, 7-CH$_3$), 1.05 (1H, ddd, J 13.6, 9.5, 4.7, 6-H') 1.35 (1H, ddd, J 13.6, 10.2, 4.2, 6-H'), 1.57 (1H, m, 5-H), 1.59 (3H, s, 3-CH$_3$), 1.83 (1H, dd, J 13.3, 7.6, 4-H), 1.93 (1H, ddd, J 13.3, 7.1, 4-H'), 2.59 (1H, m, 7-H), 4.21 (2H, d, J 6.3, 1-H$_2$), 5.29 (1H, tq, J 6.3, 1.2, 2-H) and 6.10 (1H, d, J 9.6, 8-H); $\delta_C$ (100MHz, CDCl$_3$) -5.0, 16.1, 18.4, 19.8, 19.9, 26.0, 28.6, 36.2, 43.3, 48.0, 60.2, 87.2, 126.3, 135.3 and 144.4; m/z (EI/CI) 399 (M$^+$ Br$^{81}$, Br$^{81}$ - 57, 26%), 397 (M$^+$ Br$^{81}$, Br$^{79}$ - 57, 49%) and 395 (M$^+$ Br$^{79}$, Br$^{79}$ - 57, 26%).

**tert-butyl(dimethyl)(((5S,7R,2E)-3,5,7-trimethylnon-2-en-8-yn-1-yl)oxy)silane 194**

![Chemical Structure](image)
To a solution of vinyl dibromide 200 (1.12 g, 2.47 mmol) in THF (14 ml) was added n-BuLi (1.6M in hexanes) (0.474 g, 7.41 mmol, 4.63 ml), with stirring at -78°C for 1.5 h. To the reaction mixture was then added sat. aq. NaHCO₃ (24 ml) with subsequent warming to r.t. The aqueous layer was then separated from the organic layer, washed with Et₂O (200 ml x 4) and the combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.41 g). Column chromatography (SiO₂, 100% pet. ether) gave the title compound as a clear liquid (0.582 g, 80%).

Rₐ = 0.53 (1 : 20, Et₂O : pet. ether); [α]₂⁵D -10.8, (c 1.3, CHCl₃); (Found M⁺ - CH₃, 279.2126. C₁₇H₃₁OSi requires 279.2139); νₙmax / cm⁻¹ 3312, 2955, 2927, 2856, 1668, 1471, 1461, 1379, 1360, 1325, 1252, 1199, 1117, 1084, 1054, 1005, 938, 833, 812, 773, 663 and 627; δH (400MHz, CDCl₃) 0.08 [6H, s, Si(CH₃)₂], 0.85 (3H, d, J 6.3, 5-CH₃), 0.91 [9H, s, Si(CH₃)₃], 1.04 (1H, ddd, J 13.3, 9.4, 4.7, 6-H), 1.18 (3H, d, J 6.8, 5-CH₃), 1.47 (1H, ddd, J 13.3, 11.0, 3.1, 6-H'), 1.61 (3H, s, 3-CH₃), 1.91 (3H, m, 5-H, 4-H and 4-H'), 2.02 (1H, d, J 2.4, 9-H), 2.53 (1H, m, 7-H), 4.21 (2H, d, J 6.3, 1-H₂) and 5.30 (1H, tq, J 6.3, 1.2, 2-H); δC (100MHz, CDCl₃) -5.1, 16.1, 18.4, 19.1, 21.7, 23.6, 26.0, 28.6, 43.6, 48.1, 60.2, 68.2, 88.8, 126.2 and 135.5; m/z (EI/CI) 294 (M⁺ 1%) and 279 (M⁺ - 15, 3%).

**tert-butyldimethyl[(2E,5S,7R,8E)-9-iodo-3,5,7-trimethylnona-2,8-dien-1-yl]oxy)dimethylsilane 209**

A solution of dried CrCl₂ (0.800 g, 6.50 mmol) in THF (4 ml) was stirred at rt for 15 min, and then cooled down to 0°C. A pre-cooled (0°C) solution of aldehyde 198 (0.195 g, 0.652 mmol) and CHI₃ (0.512 g, 1.30 mmol) in THF (6 ml) was then added, with further stirring at 0°C for 3 h. To the reaction mixture was then added Et₂O (100 ml), followed by filtration through celite and subsequent washing with Et₂O (50 ml x 4). The combined organic layers were then washed with sat. aq. Na₂S₂O₃ : brine (50 ml), dried (MgSO₄) and concentrated under reduced pressure to afford the product as a green
liquid (0.299 g). Column chromatography (SiO\(_2\), 100% pet. ether) gave the title compound as a light yellow liquid in a 8\(E\) : 8\(Z\) = 94 : 6 ratio (0.208 g, 76%).

\(R_f = 0.74\) (1 : 9, Et\(_2\)O : pet. ether); \([\alpha]_D^{29}\) -14.8, (c 0.7, CHCl\(_3\)); (Found M\(^+\) + Na, 445.1378 C\(_{18}\)H\(_{35}\)ONaSi requires M 445.1395); \(v_{\text{max}}/\text{cm}^{-1}\) 2954, 2926, 2854, 1668, 1600, 1459, 1380, 1360, 1459, 1380, 1360, 1252, 1199, 1174, 1085, 1055, 1006, 944, 833, 811, 773 and 665; \(\delta_H\) (400MHz, CDCl\(_3\)) (8\(E\) isomer) 0.08 [6H, s, Si(C\(_2\)H\(_3\))\(_2\)], 0.81 (3H, d, J 6.6, 5-CH\(_3\)), 0.91 [9H, s, Si(CH\(_3\))\(_3\)], 0.97 (1H, m, 6-H), 0.99 (3H, d, J 6.7, 7-CH\(_3\)), 1.29 (1H, ddd, J 13.7, 9.8, 4.3, 6-H'), 1.58 (3H, s, 3-CH\(_3\)), 1.61 (1H, m, 5-H), 1.80 (1H, dd, J 13.3, 7.6, 4-H), 1.92 (1H, dd, J 13.3, 6.9, 4-H'), 2.30 (1H, m, 7-H), 4.20 (2H, d, J 6.3, 1-H\(_2\)), 5.28 (1H, tq, J 6.3, 1.2, 2-H), 5.96 (1H, dd, J 14.4, 0.8, 9-H) and 6.32 (1H, dd, J 14.4, 8.6, 8-H), (visible peaks for 8\(Z\) isomer) 5.86 (1H, dd, J 9.1, 7.3, 8-H) and 6.12 (1H, dd, J 7.3, 1.0, 9-H); \(\delta_C\) (100MHz, CDCl\(_3\)) (8\(E\) isomer only) -5.0, 16.1, 18.4, 19.4, 20.7, 26.0, 28.1, 38.6, 43.3, 48.0, 60.2, 73.2, 126.3, 135.4 and 152.0; \(m/z\) (ES+) 321 (M\(^+\) + 23, 100%).

(2\(E\),5\(S\),7\(R\),8\(E\))-9-iodo-3,5,7-trimethylnona-2,8-dien-1-ol 210

To a cooled solution (0°C) of vinyl iodide 209 (0.123 g, 0.266 mmol) in THF (2 ml) was added TBAF (1.0M in THF) (0.208 g, 0.798 mmol, 0.80 ml), with sequential stirring at 0°C for 30 min and then at r.t. for 1 h. To the reaction mixture was then added sat. aq. NaHCO\(_3\) (4 ml), which was then washed with DCM (10 ml x 4). The combined organic layers were then dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.111 g). Column chromatography (SiO\(_2\), 1 : 2 Et\(_2\)O : pet. ether) gave the title compound as a clear liquid in a 8\(E\) : 8\(Z\) = 94 : 6 ratio (0.068 g, 83%).

\(R_f = 0.37\) (1 : 1, Et\(_2\)O : pet. ether); \([\alpha]_D^{28}\) -30.4, (c 0.5, CHCl\(_3\)); (Found M\(^+\) + NH\(_4\), 326.0975 C\(_{12}\)H\(_{23}\)ONI requires M 326.0975); \(v_{\text{max}}/\text{cm}^{-1}\) 3307(br), 2956, 2912, 2868, 2840, 2242, 1710, 1666, 1603, 1455, 1377, 1352, 1326, 1280, 1241, 1202, 1174, 1112, 1070, 992, 947, 907, 812, 766, 731, 669 and 646; \(\delta_H\) (400MHz, CDCl\(_3\)) (8\(E\) isomer) 0.81 (3H, d, J 6.6, 5-CH\(_3\)), 0.99 (3H, d, J 6.6, 7-CH\(_3\)), 1.00 (1H, m, 6-H), 1.28 (2H, m,
To a solution of DMP (0.144 g, 0.340 mmol) in DCM (1 ml) at r.t. was added pyridine (0.161 g, 2.04 mmol, 0.16 ml) which was then stirred at r.t. for 15 min. This was then followed by the addition of alcohol 210 (0.051 g, 0.17 mmol) in DCM (1 ml), with stirring at r.t. for 1 h. To the reaction mixture was then added Et₂O (10 ml) with the further addition of sat. aq. NaHCO₃ : Na₂S₂O₃ (10 ml). The aqueous layer was then separated from the organic layer, washed with Et₂O (10 ml x 4) and the combined organic layers were subsequently washed with brine (10 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a clear liquid (0.044 g). Column chromatography (SiO₂, 1 : 10, Et₂O : pet. ether) gave the title compound as a clear liquid in a 8E : 8Z = 94 : 6 ratio (0.040 g, 78%).

Rf = 0.69 (1 : 1, Et₂O : pet. ether); [α]D²⁹ -18.4, (c 0.5, DCM); (Found M⁺ + Na, 329.0366. C₁₂H₁₉OINa requires M 329.0373); νmax/cm⁻¹ 2957, 2923, 2869, 2840, 2360, 1668, 1629, 1604, 1455, 1404, 1380, 1323, 1280, 1243, 1195, 1120, 1083, 1038, 948, 888, 863, 808, 766, 703, 669 and 618; δH (400MHz, CDCl₃) (8E isomer) 0.85 (3H, d, J 6.6, 5-CH₃), 1.00 (3H, d, J 6.7, 7-CH₃), 1.06 (1H, ddd, J 13.7, 9.4, 4.8, 6-H), 1.27 (1H, ddd, J 13.7, 9.9, 4.5, 6-H), 1.74 (1H, m, 5-H), 2.10 (1H, dd, J 13.3, 8.0, 4-H), 2.13 (3H, d, J 1.3, 3-CH₃), 2.16 (1H, dd, J 13.3, 6.7, 4-H'), 2.30 (1H, m, 7-H), 5.84 (1H, dq, J 8.0, 1.0, 2-H), 6.00 (1H, dd, J 14.4, 0.8, 9-H), 6.31 (1H, dd, J 14.4, 9.1, 8-H) and 9.99 (1H, d, J 8.0, 1-H), (visible peaks for 8Z isomer) 6.16 (1H, d, J 7.3, 9-H); δC (100MHz, CDCl₃) (8E isomer only) 17.3, 19.2, 20.6, 28.5, 38.6, 43.3, 48.9, 73.7, 128.9, 151.4, 162.5 and 191.1; m/z (ES+) 329 (M⁺ + 23, 100%).
(2E,5S,7R,8E)-3,5,7-trimethyl-9-(tributylstannyl)nona-2,8-dien-1-ol 214

To a r.t. solution of vinyl iodide 209 (0.700 g, 1.66 mmol) in THF (16 ml) was added Bu₃SnCl (1.082 g, 3.32 mmol, 0.90 ml). The reaction was then cooled to -78°C before the addition of t-BuLi (1.7M in THF) (0.319 g, 4.98 mmol, 2.93 ml) and subsequent stirring at -78°C for 2 h. To the reaction mixture was then added sat. NH₄Cl in MeOH (60 ml), which was then allowed to warm to r.t. Solution was then washed with Et₂O (4 x 140 ml) and the combined organic layers were then washed with brine (80 ml), dried (MgSO₄) and concentrated under reduced pressure to afford the product as a clear liquid (3.45 g). Column chromatography (SiO₂, 100% pet. ether +1% Et₃N) gave vinyl stannane 193 as a clear liquid in an 8E : 8Z = 94 : 6 ratio (0.817 g, 84%).

To a 0°C cooled solution of vinyl stannane 193 (0.356 g, 0.608 mmol) in THF (4 ml) was added TBAF (1.0M in THF) (0.476 g, 1.82 mmol, 1.82 ml), with sequential stirring at 0°C for 40 min and then at r.t. for 1 h. To the reaction mixture was then added sat. aq. NaHCO₃ (8 ml), which was then washed with DCM (30 ml x 4). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to give the product as a clear liquid (0.332 g). Column chromatography (SiO₂, 1 : 10, Et₂O : pet. ether +1% Et₃N) gave the title compound as a clear liquid in an 8E : 8Z = 94 : 6 ratio (0.235 g, 82%).

Rᵣ = 0.63 (1 : 1, Et₂O : pet. ether); [α]₀D²⁵ = -22.0, (c 0.4, EtOH); (Found M⁺ + Na, 495.2726 C₂₄H₄₈ONa¹²⁰Sn requires M 495.2709); νmax/cm⁻¹ 3307(br), 2954, 2919, 2869, 2845, 2360, 2340, 1596, 1456, 1419, 1375, 1339, 1321, 1289, 1244, 1180, 1070, 988, 960, 873, 860, 771 and 667; δH (500MHz, C₆D₆) (8E isomer) 0.86 (3H, d, J 6.3, C₂H₃), 0.89 (1H, br s, 1-OH), 0.95 [9H, t, J 7.5, Sn(CH₂CH₂CH₂CH₃)₃], 0.99 [6H, m, Sn(CH₂CH₂CH₂CH₂CH₃)₃], 1.04 (1H, m, 6-H), 1.04 (3H, d, J 6.6, 7-CH₃), 1.38 [7H, m, 6-H', and Sn(CH₂CH₂CH₂CH₃)₃], 1.54 (3H, s, 3-CH₃), 1.62 [6H, m, Sn(CH₂CH₂CH₂CH₃)₃], 1.76 (2H, m, 5-H and 4-H), 1.96 (1H, dd, J 12.8, 6.3, 4-H'), 2.33 (1H, m, 7-H), 4.01 (2H, d, J 6.6, 1-H'), 5.40 (1H, t, J 6.6, 2-H), 5.90 [1H, ddd, J 33.1 (Sn-H), 18.9, 7.6, 8-H] and 6.07 [1H, dd, J 39.7 (Sn-H), 18.9, 9-H], (visible peaks for 8Z isomer) 2.05 (1H, dd, J 12.8, 5.9, 4-H), 2.20 (1H, m, 7-H) and 6.36 (1H, dd, J 12.3, 9.4, 8-H); δC (125MHz, C₆D₆) (8E isomer only) 10.2, 14.3, 16.4, 19.9, 22.2, 28.0,
To a rt solution of alcohol 214 (0.398 g, 0.845 mmol) in DCM (30 ml) was added activated MnO₂ (2.21 g, 25.4 mmol), with subsequent stirring at rt. for 1 h. The reaction mixture was then filtered through celite, washed with Et₂O (30 ml x 4) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.379 g). Column chromatography (SiO₂, 1 : 40 Et₂O : pet. ether + 1% Et₃N) gave the title compound as a clear liquid in a 8E : 8Z = 94 : 6 ratio (0.325 g, 82%).

Rf = 0.68 (1 : 2, Et₂O : pet. ether); [α]D²⁸ +7.2, (c 0.5, C₆H₆); (Found M⁺ + Na, 493.2450 C₂₄H₄₆ONa¹²⁰Sn requires M 493.2463); v_max/cm⁻¹ 2952, 2920, 2868, 2844, 1675, 1629, 1596, 1454, 1376, 1291, 1194, 1116, 1080, 990, 959, 863, 809, 770, 745, 689, 656 and 618; δH (500MHz, C₆D₆) (8E isomer) 0.69 (3H, d, J 6.2, 5-CH₃), 0.94 [19H, m, Sn(CH₂CH₂CH₂CH₃)₃, Sn(CH₂CH₂CH₂CH₃)₃, 7-CH₃ and 6-H], 1.15 (1H, ddd, J 13.6, 10.1, 3.8, 6-H'), 1.36 [6H, m, Sn(CH₂CH₂CH₂CH₃)₃], 1.58 [8H, m, Sn(CH₂CH₂CH₂CH₃)₃], 5-H and 4-H], 1.66 (3H, s, 3-CH₃), 1.80 (1H, m, 4-H'), 2.19 (1H, m, 7-H), 5.76 [1H, ddd, J 32.2 (Sn-H), 18.9, 7.7, 8-H], 5.81 (1H, m, 2-H), 5.99 [1H, dd, J 39.3 (Sn-H), 18.8, 9-H] and 9.88 (1H, d, J 7.8, 1-H), (visible peaks for 8Z isomer) 2.08 (1H, m, 7-H), 6.24 (1H, dd, J 12.3, 9.3, 8-H) and 9.93 (1H, d, J 7.9, 1-H); δC (125MHz, C₆D₆) (8E isomer only) 10.1, 14.4, 17.2, 19.6, 22.0, 28.0, 29.1, 30.0, 40.5, 44.3, 49.3, 126.4, 129.6, 155.6, 160.8 and 189.8; (ES+) 471 [M⁺ (¹²⁰Sn) + 1, 100%] and 469 [M⁺ (¹¹⁸Sn) + 1, 65%].
To a -78°C solution of aldehyde 215 (0.230 g, 0.490 mmol) and BT-sulphone 120 (0.196 g, 0.735 mmol) in THF (10 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.123 g, 0.735 mmol, 0.74 ml), with sequential stirring at -78°C for 1 h and at r.t. for 2 h. To the reaction mixture was added NaOH (1.0M) (20 ml) and then Et₂O (40 ml). The aqueous layer was then separated from the organic layer and washed with Et₂O (40 ml x 4). The combined organic layers were then washed with brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.309 g). Column chromatography (SiO₂, 100% pet. ether + 1% Et₃N) gave the title compound as a clear liquid in a (1E,7E,9E,11E) : (1E,7E,9Z,11E) : (1E,7E,9E,11Z) = 88 : 7 : 5 ratio (0.192 g, 75%).

Rf = 0.54 (100% pet. ether); [α]D° -9.0 (c 0.4, EtOH); (Found M⁺ - C₄H₉, 465.2544 C₂₃H₄₅¹²⁰Sn requires M⁺ 465.2538; νmax / cm⁻¹ 2952, 2918, 2868, 1595, 1454, 1375, 1323, 1180, 1070, 990, 956, 872, 794, 689 and 654; δH (500MHz, C₆D₆) [(1E,7E,9E,11E) isomer] 0.90 (3H, d, J 6.6, 5-CH₃), 0.97 [19H, m, Sn(CH₂CH₂CH₂CH₃)₃, Sn(CH₂CH₂CH₂CH₃)₃, 3-CH₃ and 4-H], 1.38 [7H, m, Sn(CH₂CH₂CH₂CH₃)₃ and 4-H'], 1.61 [9H, m, Sn(CH₂CH₂CH₂CH₃)₃ and 12-CH₃], 1.73 (3H, s, 11-CH₃), 1.77 (3H, s, 7-CH₃), 1.81 (1H, m, 5-H), 1.93 (1H, dd, J 13.2, 7.8, 6-H), 2.06 (1H, dd, J 13.2, 6.7, 6-H'), 2.33 (1H, m, 3-H), 5.52 (1H, q, J 6.9, 12-H), 5.85 [1H, ddd, J 32.9 (Sn-H), 18.9, 7.6, 2-H], 6.04 (1H, m, 8-H), 6.05 [1H, dd, J 39.5 (Sn-H), 18.9, 1-H], 6.32 (1H, d, J 15.3, 10-H) and 6.50 (1H, dd, J 15.3, 10.8, 9-H), [visible peaks for (1E,7E,9Z,11E) isomer] 5.64 (1H, q, J 7.1, 12-H) and 6.22 (1H, t, J 11.5, 10-H), [visible peaks for (1E,7E,9E,11Z) isomer] 5.34 (1H, q, J 7.3, 12-H), 6.08 (1H, d, J 11.3, 8-H), 6.60 (1H, dd, J 15.3, 11.3, 9-H) and 6.71 (1H, d, J 15.3, 10-H) δC (125MHz, C₆D₆) [(1E,7E,9E,11E) isomer only] 10.2, 12.6, 14.4, 14.4, 17.2, 20.1, 22.2, 28.1, 29.5, 30.0, 40.7, 44.6, 49.6, 123.2, 125.8, 126.5, 128.3, 135.8, 136.6, 136.7 and 156.2; m/z (EI/Cl) 465 [M⁺ (¹²⁰Sn) - 57, 100%), 463 [M⁺ (¹¹⁸Sn) - 57, 75%) and 461 [M⁺ (¹¹⁶Sn) - 57, 41%).
\((5R)\text{-}\text{tert-butyl 5-isopropyl-2-oxo-3-(3-(trimethylsilyl)propionoyl)pyrrolidine-1-carboxylate 224}\)"n

To a solution of 3-(trimethylsilyl)propynoic acid 222 (0.100 g, 0.704 mmol) in THF (2 ml) at r.t. was added 1,1'-carbonyldiimidazole (0.145 g, 0.894 mmol), with subsequent stirring at r.t. for 1 h. The reaction mixture was then diluted with Et₂O (15 ml) and sequentially washed with H₂O (5 ml) and brine (5 ml), then dried (Na₂SO₄) and concentrated under reduced pressure to afford the protected imidazole species 223 as a yellow solid (0.113 g, 84%).

To a solution of lactam 116 (0.708 g, 3.12 mmol) in THF (3 ml) at -78°C was added a pre-cooled -78°C solution of LiHMDS (1.0M in THF) (0.521 g, 3.12 mmol, 3.12 ml), with subsequent stirring at -78°C for 1 h. A pre-cooled -78°C solution of the protected imidazolide 223 (0.300 g, 1.56 mmol) in THF (3 ml) was then added to the -78°C solution with subsequent stirring at -78°C for 1.5 h. To the reaction mixture was then added sat. aq. NH₄Cl (3 ml), which was then allowed to warm to r.t. before the addition of sat. aq. NH₄Cl (30 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 60 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a dark orange liquid (0.999 g). Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compound as a white solid (0.341 g, 62%).

Rᵣ = 0.20 (1 : 10, Et₂O : pet. ether); m.p 89.3-90.3°C; [α]D⁺ 45.3 (c 0.9, CHCl₃); (Found M⁺ + Na, 374.1741. C₁₈H₂₉O₄NNaSi requires 374.1758); anal. calcd for C₁₈H₂₉O₄N₁Si: C 61.50, H 8.32, N 3.98, found C 61.53, H 8.44, N 3.83; νmax / cm⁻¹ 2961, 1717, 1670, 1625, 1468, 1385, 1367, 1356, 1332, 1320, 1315, 1367, 1356, 1332, 1320, 1288, 1257, 1249, 1221, 1140, 1096, 995, 970, 960, 936, 919, 893, 839, 789, 757, 699, 660 and 626; δH (500MHz, CDCl₃) 0.26 [9H, s, Si(CH₃)₃], 0.79 [3H, d, J 6.9, CH(CH₃)], 0.94 [3H, d, J 7.0, CH(CH₃)], 1.55 [9H, s, C(CH₃)₃], 2.30 [1H, m, CH(CH₃)], 2.43 (1H, dd, J 16.8, 2.1, 4-H), 2.67 (1H, dd, J 16.8, 9.6, 4-H'), 4.13 (1H, m, 5-H) and 11.2 (1H, s, OH); δC (125MHz, CDCl₃) -0.5, 14.4, 18.5, 22.0, 28.0, 30.2, 60.5, 83.2, 96.7, 105.0, 109.9, 146.7, 150.1 and 171.9; m/z (ES+) 374 (M⁺ + 23, 100%).
To a solution of oxopyrrolidine 224 (0.129 g, 0.366 mmol) in THF (9 ml) / MeOH (0.3 ml) at -78°C was added TBAF (1.0M in THF) (0.147 g, 0.549 mmol, 0.55 ml), with subsequent stirring at -78°C for 30 min. The reaction mixture was then poured into HCl (1.0M) (15 ml) and ice cooled H₂O (15.0 g). The solution was washed with Et₂O (4 x 30 ml) and the combined organic layers were then dried (MgSO₄) and concentrated under reduced pressure to afford the product as an orange liquid (0.120 g). Column chromatography (SiO₂, 1 : 1 Et₂O : pet. ether) gave the title compound as a light orange liquid (0.075 g, 74%).

Rf = 0.33 (1 : 1, Et₂O : pet. ether); [α]D³¹ +35.4 (c 0.7, CHCl₃); (Found M⁺ + Na, 302.1364. C₁₅H₂₁O₄NNa requires 302.1363); v_{max} / cm⁻¹ 3240, 2963, 2253, 2107, 1752, 1720, 1680, 1629, 1468, 1381, 1367, 1288, 1253, 1212, 1145, 1097, 1052, 996, 970, 909, 848, 788, 727 and 645; δH (500MHz, CDCl₃) 0.77 (3H, d, J 6.9, CH(C₃H₃)); 0.93 [3H, d, J 7.0, CH(CH₃)]; 1.54 [9H, s, C(CH₃)₃]; 2.28 [1H, m, CH(CH₃)₂]; 2.47 (1H, dd, J 16.8, 2.2, 4-H); 2.68 (1H, dd, J 16.8, 9.6, 4-H); 3.47 (1H, s, CCH); 4.14 (1H, m, 5-H) and 11.2 (1H, s, OH); δC (125MHz, CDCl₃) 14.4, 18.5, 21.9, 28.0, 30.3, 60.5, 76.5, 83.3, 85.4, 110.8, 146.0, 150.0 and 171.8; m/z (ES⁺) 581 (2M⁺ + 23, 100%).

(5R)-tert-butyl 3-iodo-3-(3-iodopropioloyl)-5-isopropyl-2-oxopyrrolidine-1-carboxylate 225

To a solution of alkyne 221 (0.026 g, 0.093 mmol) in DMF (3 ml) at r.t. was added NIS (0.026 g, 0.12 mmol) followed by AgNO₃ (0.003 mg, 0.019 mmol), with subsequent stirring at r.t. for 2 h. To the reaction mixture was then added sat. aq. NH₄Cl (3 ml), which was then washed with Et₂O (9 ml x 4). The combined organic layers were sequentially washed with H₂O (6 ml) and brine (6 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.056 g). Column
chromatography (SiO$_2$, 1 : 2 Et$_2$O : pet. ether) gave the title compound as a light yellow liquid (0.027 g, 55%).

R$_f$ = 0.27 (1 : 1, Et$_2$O : pet. ether); [α]$_D^{30}$ +60.0, (c 0.4, CHCl$_3$); (Found M$^+$ + H, 531.9461. C$_{15}$H$_{30}$O$_4$Ni$_2$ requires M 531.9476); $\nu_{\text{max}}$ / cm$^{-1}$ 2963, 2930, 2874, 1715, 1609, 1368, 1326, 1297, 1277, 1254, 1165, 1143, 1096, 1041, 1029, 1000, 978, 908, 878, 847, 808, 789, 766, 726, 671 and 645; $\delta_H$ (500MHz, CDCl$_3$) 0.81 [3H, d, $J_{6.9}$, CH(CH$_3$)$_3$], 0.92 [3H, d, $J_{7.0}$, CH(CH$_3$)$_3$]), 1.56 [9H, s, C(CH$_3$)$_3$], 2.34 [1H, m, CH(CH$_3$)$_2$], 2.67 (1H, dd, $J_{15.9}$, 3.9, 4-H), 2.88 (1H, dd, $J_{15.9}$, 10.6, 4-H') and 4.32 (1H, dt, $J_{10.6}$, 3.9, 5-H); $\delta_C$ (125MHz, CDCl$_3$) 14.5, 17.7, 22.7, 28.2, 30.2, 64.0, 83.6, 102.8, 110.7, 121.3, 149.8, 160.8 and 170.0; m/z (ES+) 554 (M$^+$ + 23, 100%).

(2E,4R,6S,8E)-ethyl-10-((tert-butyldimethylsilyl)oxy)-4,6,8-trimethyldeca-2,8-dienoate 230

To a r.t. solution of aldehyde 198 (1.45 g, 4.85 mmol) in DCM (60 ml) was added (carbethoxymethylene)triphenylphosphorane (3.38 g, 9.70 mmol), with subsequent stirring at r.t. for 14 h. The reaction mixture was then concentrated under reduced pressure to afford the product as a light orange liquid (5.47 g). Column chromatography (SiO$_2$, 1 : 20, Et$_2$O : pet. ether) gave the title compound as a clear liquid (1.30 g, 73%).

R$_f$ = 0.58 (1 : 5, Et$_2$O : pet. ether); [α]$_D^{28}$ -8.5, (c 0.8, C$_6$H$_6$); (Found M$^+$ + Na, 391.2625. C$_{21}$H$_{40}$O$_3$NaSi requires M 391.2639); $\nu_{\text{max}}$/cm$^{-1}$ 2957, 2928, 2857, 1721, 1652, 1462, 1380, 1368, 1341, 1302, 1254, 1202, 1176, 1141, 1085, 1050, 1006, 986, 939, 833, 813, 774, 726 and 665; $\delta_H$ (400MHz, C$_6$D$_6$) 0.08 [6H, s, Si(CH$_3$)$_2$], 0.70 (3H, d, $J_{6.5}$, 6-CH$_3$), 0.80 (3H, d, $J_{6.7}$, CH$_2$CH$_3$), 0.84 (1H, ddd, $J_{13.7}$, 9.3, 5.1, 5-H), 0.98 (9H, s, Si(CH$_3$)$_3$), 1.00 (3H, t, $J_{7.2}$, CH$_2$CH$_3$), 1.20 (1H, ddd, $J_{13.7}$, 9.6, 4.6, 5-H'), 1.41 (3H, s, 8-CH$_3$), 1.49 (1H, m, 6-H), 1.65 (1H, dd, $J_{13.2}$, 7.7, 7-H), 1.79 (1H, dd, 13.2, 6.8, 7-H'), 2.15 (1H, m, 4-H), 4.03 (2H, q, $J_{7.2}$, CH$_2$CH$_3$), 4.18 (2H, d, $J_{6.3}$, 10-H$_2$), 5.40 (1H, tq, $J_{6.3}$, 1.2, 9-H), 5.84 (1H, dd, $J_{15.6}$, 1.0, 2-H) and 6.91 (1H, dd, $J_{15.6}$, 8.6, 3-
$H$); $\delta_c$ (100MHz, $\text{C}_6\text{D}_6$) -4.5, 14.7, 16.4, 18.9, 19.9, 20.9, 26.5, 28.8, 34.8, 43.8, 48.5, 60.3, 60.6, 120.9, 127.5, 135.6, 154.4 and 166.5; $m/z$ (ES+) 391 (M$^+$ + 23, 100%).

(2E,4R,6S,8E)-ethyl 10-hydroxy-4,6,8-trimethyldeca-2,8-dienoate 231

To a solution of ester 230 (1.23 g, 3.33 mmol) in DCM (12 ml)/EtOH (12 ml) at r.t. was added PPTS (0.083 g, 0.33 mmol), with subsequent stirring at r.t. for 20 h. To the reaction mixture was then added sat. aq. NaHCO$_3$ (50 ml), which was then washed with Et$_2$O (100 ml x 4). The combined organic layers were then dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the product as a clear liquid (1.008 g). Column chromatography (SiO$_2$, 1 : 5 Et$_2$O : pet. ether to remove top spots and then 1 : 1 Et$_2$O : pet. ether) gave the title compound as a clear liquid (0.760 g, 90%).

$R_f$ = 0.26 (1 : 1, Et$_2$O: pet. ether); $[\alpha]_D^{28}$ -14.7, (c 0.3, $\text{C}_6\text{H}_6$); (Found M$^+$ + Na, 277.1784 C$_{13}$H$_{26}$O$_3$Na requires $M$ 277.1775); $\nu_{\text{max}}$/cm$^{-1}$ 3419(br), 2960, 2915, 2872, 2361, 1717, 1651, 1457, 1369, 1341, 1302, 1274, 1236, 1203, 1176, 1143, 1096, 1037, 986, 863, 775 and 726; $\delta_H$ (400MHz, $\text{C}_6\text{D}_6$) 0.72 (3H, d, $J$ 6.6, 6-CH$_3$), 0.80 (3H, d, $J$ 6.7, 4-CH$_3$), 0.86 (1H, ddd, $J$ 13.6, 9.3, 5.2, 5-H$'$), 1.00 (3H, t, $J$ 7.1, CH$_2$CH$_3$), 1.22 (1H, ddd, $J$ 13.6, 9.6, 4.6, 5-H$''$) 1.44 (3H, s, 8-CH$_3$), 1.50 (1H, m, 6-H), 1.67 (1H, dd, $J$ 13.4, 7.9, 7-H), 1.82 (1H, dd, $J$ 13.4, 6.7, 7-H$''$), 2.16 (1H, m, 4-H), 2.80 (1H, br s, 10-CH$_3$), 4.02 (2H, q, $J$ 7.1, CH$_2$CH$_3$), 4.12 (2H, d, $J$ 6.6, 10-H$_2$), 5.41 (1H, m, 9-H), 5.39 (1H, d, $J$ 15.5, 1.0, 2-H) and 6.91 (1H, dd, $J$ 15.6, 8.6, 3-H); $\delta_c$ (100MHz, $\text{C}_6\text{D}_6$) 14.7, 16.4, 19.9, 20.8, 28.8, 34.9, 43.8, 48.5, 59.5, 60.5, 120.8, 127.3, 136.6, 154.8 and 166.9; $m/z$ (ES+) 277 (M$^+$ + 23, 100%).
(2E,4R,6S,8E)-ethyl 4,6,8-trimethyl-10-oxodeca-2,8-dienoate 229

To a r.t. solution of alcohol 231 (0.749 g, 2.95 mmol) in DCM (60 ml) was added activated MnO₂ (7.70 g, 88.5 mmol), with subsequent stirring at r.t. for 2 h. The reaction mixture was then filtered through celite, washed with Et₂O (80 ml x 4) and concentrated under reduced pressure to afford the product as a yellow liquid (0.657 g). Column chromatography (SiO₂, 1 : 4 Et₂O : pet. ether) gave the title compound as a clear liquid (0.632 g, 85%).

Rt = 0.42 (1 : 1, Et₂O : pet. ether); [α]D²² +2.3, (c 0.7, C₆H₆); (Found M⁺ + Na, 275.1620 C₁₅H₂₄O₃Na requires M 275.1618); vₘₐₓ/cm⁻¹ 2961, 2927, 2872, 2361, 1715, 1670, 1631, 1458, 1382, 1368, 1341, 1303, 1274, 1236, 1197, 1177, 1142, 1095, 1037, 987, 931, 863, 809, 727 and 621; δH (400MHz, C₆D₆) 0.55 (3H, d, J 6.6, 6-C₃H₃), 0.75 (3H, d, J 6.7, 4-C₃H₃), 0.77 (1H, ddd, J 14.0, 9.2, 5.2, 5-H'), 1.00 (1H, ddd, J 14.0, 9.2, 5.2, 5-H'), 1.02 (3H, t, J 7.1, CH₂CH₃), 1.39 (1H, m, 6-H), 1.50 (1H, dd, J 13.2, 8.3, 7-H), 1.55 (3H, d, J 1.3, 8-CH₃), 1.70 (1H, dd, J 13.2, 6.2, 7-H'), 2.07 (1H, m, 4-H), 4.04 (2H, q, J 7.1, CH₂CH₃), 5.73 (1H, dq, J 7.8, 1.1, 9-H), 5.79 (1H, dd, J 15.6, 1.0, 2-H), 6.81 (1H, dd, J 15.6, 8.6, 3-H) and 9.84 (1H, d, J 7.8, 10-H); 14.7, 17.0, 19.4, 20.7, 28.9, 34.6, 43.7, 48.9, 60.5, 121.1, 129.6, 154.0, 161.0, 166.5 and 190.2; m/z (ES+) 275 (M⁺ + 23, 100%).

(2E,4R,6S,8E,10E,12E)-ethyl-4,6,8,12-tetramethyltetradeca-2,8,10,12-tetraenoate 228

To a -78°C solution of aldehyde 229 (0.245 g, 0.972 mmol) and BT-sulphone 120 (0.389 g, 1.46 mmol) in THF (10 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.243 g, 1.46 mmol, 1.46 ml), with sequential stirring at -78°C for 1 h and at r.t.
for 2 h. To the reaction mixture was added sat. aq. NaHCO$_3$ (20 ml) and then Et$_2$O (40 ml). The aqueous layer was then separated from the organic layer and washed with Et$_2$O (40 ml x 4). The combined organic layers were then washed with brine (20 ml), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.465 g). Column chromatography (SiO$_2$, 1 : 100 Et$_2$O : pet. ether) gave the title compound as a light yellow liquid in a (2E,8E,10E,12E) : (2E,8E,10Z,12E) : (2E,8E,10E,12Z) = 87 : 6 : 7 ratio (0.215 g, 73%).

R$_f$ = 0.45 (1: 8 Et$_2$O : pet. ether); [α]$_D^{24}$ +36.7 (c 0.6, C$_6$H$_6$); (Found M$^+$ + Na, 327.2289 C$_{20}$H$_{32}$O$_2$Na requires M + Na, 327.2295); $\nu$ max / cm$^{-1}$ 2958, 2916, 2870, 2361, 1719, 1651, 1456, 1368, 1339, 1272, 1235, 1202, 1176, 1140, 1096, 1037, 986, 959, 861, 797, 725 and 620; $\delta$H (400MHz, C$_6$D$_6$) [(2E,8E,10E,12E) isomer] 0.73 (3H, d, $J$ 6.6, 6-H), 0.78 (3H, d, $J$ 6.8, 4-H), 0.87 (1H, ddd, $J$ 13.6, 9.3, 5.0, 5-H), 1.00 (3H, t, J 7.1, CH$_2$CH$_3$), 1.23 (1H, ddd, J 13.6, 9.7, 4.7, 5-H'), 1.60 (7H, m, 13-CH$_3$, 8-CH$_3$ and 6-H), 1.72 (3H, s, 12-CH$_3$), 1.76 (1H, dd, J 13.4, 7.8, 7-H), 1.91 (1H, dd, J 13.4, 6.8, 7-H'), 4.04 (2H, q, J 7.1, CH$_2$CH$_3$), 5.52 (1H, q, J 7.0, 13-H), 5.86 (1H, dd, J 15.6, 0.8, 2-H), 5.97 (1H, d, J 10.8, 9-H), 6.31 (1H, d, J 15.4, 11-H), 6.46 (1H, dd, J 15.4, 10.8, 10-H) and 6.93 (1H, ddd, J 15.6, 8.6, 3-H), [visible peaks for (2E,8E,10Z,12E) isomer] 5.63 (1H, q, J 7.2, 13-H) and 6.17 (1H, t, J 11.6, 10-H), [visible peaks for (2E,8E,10E,12Z) isomer] 5.34 (1H, q, J 7.3, 13-H), 6.01 (1H, d, J 10.9, 9-H), 6.56 (1H, dd, J 15.2, 10.9, 10-H) and 6.71 (1H, d, J 15.2, 11-H); $\delta$C (100MHz, C$_6$D$_6$) [(2E,8E,10E,12E) isomer only] 12.5, 14.4, 14.7, 16.9, 19.9, 20.9, 29.2, 34.8, 43.9, 49.1, 60.4, 120.9, 123.1, 126.7, 128.3, 135.8, 136.4, 136.7, 154.4 and 166.6; $m$/$z$ (ES+) 327 (M$^+$ + 23, 100%).

(2E,4R,6S,8E,10E,12E)-4,6,8,12-tetramethyltetra dec-2,8,10,12-tetraen-1-ol 239

To a -78°C solution of ester 228 (0.400 g, 1.32 mmol) in THF (12 ml) was added DIBAL-H (1.0M in hexanes) (0.562 g, 3.96 mmol, 3.96 ml) dropwise, with further stirring at -78°C for 1 h. The reaction mixture was then allowed to warm to r.t. before the addition of sat. aq. NH$_4$Cl (16 ml). This was then followed by the addition of DCM
(48 ml) and sat. aq. Rochelle’s salt (32 ml), with subsequent stirring at r.t. for 1.5 h. The aqueous layer was then separated from the organic layer and washed with DCM (80 ml x 4). The combined organic layers were then washed with brine (100 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.423 g). Column chromatography (SiO₂, 1 : 6 Et₂O : pet. ether) gave the title compound as a clear liquid in a (2E,8E,10E,12E) : (2E,8E,10Z,12E) : (2E,8E,10E,12Z) = 82 : 6 : 12 ratio (0.293 g, 85%).

\[ \text{Rf} = 0.55 \ (1 : 1 \text{Et}_2\text{O : pet. ether); } [\alpha]_D^{28} +29.3 \ (c \ 0.3, \text{C}_6\text{H}_6); \] (Found M⁺ + Na, 285.2195 C₁₈H₃₀ONa requires M⁺ 285.2189); \( \nu_{\text{max}} \ / \text{cm}^{-1} \) 3315 (br), 2954, 2914, 2867, 2360, 1642, 1456, 1378, 1269, 1083, 1005, 959, 796 and 620; \( \delta_H \) (400MHz, C₆D₆) [(2E,8E,10E,12E) isomer] 0.86 (3H, d, J 6.6, 6-C₃H₃), 0.94 (3H, d, J 6.7, 4-C₃H₃), 0.98 (1H, ddd, J 13.6, 9.2, 5.0, 5-H'), 1.22 (1H, br s, 1-OH), 1.29 (1H, ddd, J 13.6, 9.7, 4.6, 5-H'), 1.60 (3H, d, J 7.1, 13-CH₃), 1.70 (3H, s, 8-CH₃), 1.72 (1H, m, 6H), 1.73 (3H, s, 12-CH₃), 1.87 (1H, dd, J 13.4, 7.8, 7-H), 2.04 (1H, dd, J 13.4, 6.8, 7-H'), 2.19 (1H, m, 4-H), 3.89 (2H, d, J 5.3, 1-H₂), 5.37 (1H, ddt, J 15.5, 8.1, 1.0, 3-H), 5.50 (1H, dt, J 15.5, 5.6, 2-H), 5.52 (1H, m, 13-H), 6.05 (1H, d, J 10.8, 9-H), 6.34 (1H, d, J 15.4, 11-H) and 6.52 (1H, dd, J 15.4, 10.8, 10-H), [visible peaks for (2E,8E,10Z,12E) isomer] 5.67 (1H, q, J 7.1, 13-H), 5.91 (1H, d, J 11.7, 9-H) and 6.23 (1H, t, J 11.7, 10-H), [visible peaks for (2E,8E,10E,12Z) isomer] 6.09 (1H, d, J 11.1, 9-H), 6.61 (1H, dd, J 15.4, 11.1, 10-H) and 6.74 (1H, d, J 15.4, 11-H); \( \delta_C \) (100MHz, C₆D₆) [(2E,8E,10E,12E) isomer only] 12.6, 14.4, 17.1, 20.1, 22.2, 29.3, 34.8, 44.9, 49.3, 63.8, 123.2, 126.7, 128.2, 129.0, 135.8, 136.6, 136.7 and 137.9; \( m/z \) (ES+) 285 (M⁺ + 23, 100%).

\( (2E,4R,6S,8E,10E,12E)-4,6,8,12\text{-tetramethyltetradeca-2,8,10,12-tetraenal 227} \)

To a r.t. solution of allylic alcohol 239 (0.266 g, 1.02 mmol) in DCM (20 ml) was added activated MnO₂ (2.65 g, 30.5 mmol), with subsequent stirring at r.t. for 4 h. The reaction mixture was then filtered through celite, washed with Et₂O (20 ml x 4) and concentrated under reduced pressure to afford the product as a yellow liquid (0.223 g). Column chromatography (SiO₂, 1 : 15 Et₂O : pet. ether) gave the title compound as a
clear liquid in a \((2E,8E,10E,12E) : (2E,8E,10Z,12E) : (2E,8E,10E,12Z) = 80 : 6 : 14\) ratio (0.222 g, 84%).

\[ \text{Rf} = 0.46 \ (1 : 4, \ 	ext{Et}_2\text{O} : \text{pet. ether}); \ [\alpha]_D^{28} +92.0, \ (c 0.2, \text{C}_6\text{H}_6); \ (\text{Found M}^+ + \text{H}, 261.2212 \ \text{C}_{13}\text{H}_{29}\text{O} \text{requires} \ M 261.2213); \ \nu_{\max} / \text{cm}^{-1} 2960, 2915, 1690, 1634, 1456, 1378, 1149, 1096, 1032, 977, 959, 795 \text{ and } 621; \ \delta_{\text{H}} (400\text{MHz, C}_6\text{D}_6) \ [(2E,8E,10E,12E) \text{ isomer}] 0.70 (3H, d, \ J 6.6, 6-CH_3), 0.71 (3H, d, J 6.7, 4-CH_3), 0.83 (1H, ddd, J 13.6, 9.3, 5.3, 5-H), 1.14 (1H, ddd, J 13.6, 9.6, 4.8, 5-H'), 1.43 (1H, m, 6-H), 1.61 (6H, m, 13-CH_3 and 8-CH_3), 1.74 (3H, s, 12-CH_3), 1.79 (1H, dd, J 13.4, 5.8, 7-H), 1.90 (1H, dd, J 13.4, 6.9, 7-H'), 5.54 (1H, q, J 7.1, 13-H), 5.93 (1H, dd, J 15.6, 6.8, 3-H), 6.00 (1H, m, 9-H), 6.01 (1H, dd, J 15.6, 7.3, 2-H), 6.36 (1H, d, J 15.4, 11-H), 6.52 (1H, dd, J 15.4, 10.8, 10-H) and 9.36 (1H, d, J 7.3, 1-H), [visible peaks for \((2E,8E,10Z,12E)\) isomer] 5.66 (1H, m, 13-H) and 6.22 (1H, t, J 11.7, 10-H), [visible peaks for \((2E,8E,10E,12Z)\) isomer] 5.36 (1H, q, J 7.3, 13-H), 6.61 (1H, dd, J 15.3, 10.9, 10-H) and 6.76 (1H, d, J 15.3, 11-H); \ \delta_{\text{C}} (100\text{MHz, C}_6\text{D}_6) \ [(2E,8E,10E,12E) \text{ isomer only}] 12.6, 14.4, 17.0, 20.0, 20.5, 29.2, 35.0, 43.6, 49.0, 123.0, 127.0, 128.5, 132.4, 135.7, 136.1, 136.9, 162.5 and 193.1; m/z (ES+) 283 (M^+ + 23, 100%) and 261 (M^+ + 1, 44%).

\((2Z,4E,6R,8S,10E,12E,14E)\)-methyl-6,8,10,14-tetramethylhexadeca-2,4,10,12,14-pentaenoate 226

To a r.t. solution of K\(_2\)CO\(_3\) (0.255 g, 1.85 mmol) in toluene (8 ml) was added 18-crown-6 (0.976 g, 3.70 mmol), with subsequent stirring at r.t. for 1 h. The solution was then cooled down to -20°C before the addition of a pre-cooled (-20°C) solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.098 g, 0.31 mmol) and aldehyde 227 (0.080 g, 0.31 mmol) in THF (8 ml), with further stirring at 0°C for 3 h. To the reaction mixture was then added sat. aq. NH\(_4\)Cl (20 ml), which was then washed with Et\(_2\)O (40 ml x 4). The combined organic layers were then washed with brine (40 ml), dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.129 g). Column chromatography (SiO\(_2\), 1 : 60 Et\(_2\)O :
pet. ether) gave the title compound as a light yellow liquid in a (2Z,4E,10E,12E,14E) : (2Z,4E,10E,12Z,14E) : (2Z,4E,10E,12E,14Z) = 79 : 6 : 15 ratio (0.083 g, 86%).

Rf = 0.51 (1 : 9, Et₂O : pet. ether); [α]D27 +144.0, (c 0.3, C₆H₅); (Found M⁺ + Na, 339.2289 C₂₁H₃₂O₂Na requires M 339.2295); νmax/cm⁻¹ 2952, 2913, 2866, 1716, 1637, 1600, 1437, 1412, 1377, 1330, 1195, 1170, 1000, 958, 894, 816, 743 and 619; δH (400MHz, C₆D₆) [(2Z,4E,10E,12E,14E) isomer] 0.81 (3H, d, J 6.5, 8-CH₃), 0.87 (3H, d, J 6.6, 6-CH₃), 0.94 (1H, ddd, J 13.5, 9.3, 5.0, 7-H'), 1.28 (1H, ddd, J 13.5, 9.6, 4.6, 7-H'), 1.60 (3H, d, J 7.0, 15-CH₃), 1.66 (4H, m, 10-CH₃ and 8-H'), 1.74 (3H, t, J 0.9, 14-CH₃), 1.81 (1H, dd, J 13.3, 7.5, 9-H), 1.97 (1H, dd, J 13.3, 6.9, 9'-H'), 2.27 (1H, m, 6-H), 3.38 (3H, s, OCH₃), 5.53 (1H, q, J 7.0, 15-H), 5.62 (1H, dd, J 15.3, 8.5, 5-H), 5.63 (1H, d, J 11.4, 2-H), 6.02 (1H, d, J 10.8, 11-H), 6.31 (1H, t, J 11.4, 3-H), 6.34 (1H, d, J 15.2, 13-H), 6.52 (1H, dd, J 15.2, 10.8, 12-H) and 7.83 (1H, dd, J 15.3, 11.4, 4-H), [visible peaks for (2Z,4E,10E,12Z,14E) isomer] 5.92 (1H, d, J 11.5, 11-H) and 6.24 (1H, t, J 11.5, 12-H), [visible peaks for (2Z,4E,10E,12E,14Z) isomer] 5.36 (1H, q, J 7.2, 15-H), 6.07 (1H, d, J 10.9, 11-H), 6.62 (1H, dd, J 15.3, 10.9, 12-H) and 6.74 (1H, d, J 15.3, 13-H); δC (100MHz, C₆D₆) [(2Z,4E,10E,12E,14E) isomer only] 12.5, 14.4, 17.0, 20.0, 21.6, 29.4, 35.6, 44.5, 49.2, 51.0, 116.3, 123.2, 126.5, 126.7, 128.3, 135.8, 136.6, 136.7, 146.1, 151.3 and 166.9; m/z (ES+) 339 (M⁺ + 23, 100%).

(2Z,4E,6R,8S,10E,12E,14E)-6,8,10,14-tetramethylhexadeca-2,4,10,12,14-pentaenoic acid 240

![Diagram](image)

To a solution of methyl ester 226 (0.071 g, 0.23 mmol) in EtOH (3 ml) at r.t. was added NaOH (0.037 g, 0.92 mmol) in H₂O (1.5 ml) with subsequent stirring at r.t. for 18 h. The reaction mixture was then acidified to pH 5 by adding it to a 0°C solution of tartaric acid (0.338 g, 2.25 mmol) in H₂O (15 ml), with vigorous stirring for 2 min and subsequent washing with 0°C Et₂O (25 ml x 4). The combined organic layers were then sequentially washed with 0°C H₂O (25 ml x 2) and 0°C brine (25 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as a light yellow liquid in a (2Z,4E,10E,12E,14E) : (2Z,4E,10E,12Z,14E) : (2Z,4E,10E,12E,14Z) = 77 : 6 : 17 ratio (0.062 g, 92%).
\[ R_f = 0.53 \text{ (1 : 1 Et}_2\text{O : pet. ether)}; [\alpha]_D^{24} +169.3 \text{ (c 0.3, C}_6\text{H}_6); \text{(Found M}^+ - \text{ H, 301.2173 C}_{20}\text{H}_{29}\text{O}_2 \text{ requires M 301.2173);} \]

\[ v_{\max} \text{ cm}^{-1} 2960, 2913, 2868, 1687, 1632, 1597, 1440, 1378, 1286, 1253, 1232, 1180, 1087, 1004, 959, 862, 795, 748 \text{ and 698; } \delta_H (400MHz, C_6D_6) \]

\[ (2Z,4E,10E,12E,14E) \text{ isomer] 0.78 (3H, d, } J 6.5, 8-\text{CH}_3, 0.84 (3H, d, } J 6.7, 6-\text{CH}_3); 0.91 (1H, ddd, } J 13.6, 9.5, 5.1, 7-H'); 1.25 (1H, ddd, } J 13.6, 9.6, 4.5, 7-H'), 1.60 (3H, d, } J 7.1, 15-\text{CH}_3); 1.66 (4H, m, 10-\text{CH}_3 \text{ and 8-H}); 1.75 (3H, t, } J 0.9, 14-\text{CH}_3); 1.81 (1H, dd, } J 13.3, 7.5, 9-H'); 1.96 (1H, dd, } J 13.3, 7.0, 9-H'); 2.20 (1H, m, 6-H); 5.55 (1H, d, } J 11.4, 2-H); 5.56 (1H, m, 15-\text{CH}_3); 5.58 (1H, dd, } J 15.3, 8.6, 5-H); 6.03 (1H, d, } J 10.7, 11-\text{H}); 6.26 (1H, t, } J 11.4, 3-H); 6.36 (1H, d, } J 15.2, 13-H); 6.54 (1H, dd, } J 15.2, 10.7, 12-\text{H}); 7.60 (1H, dd, } J 15.3, 11.4, 4-H) \text{ and 11.67 (1H, br s, OH);} \]

\[ \delta_C (100MHz, C_6D_6) \]

\[ 12.6, 14.4, 17.0, 20.0, 21.5, 29.4, 35.6, 44.4, 49.2, 115.7, 123.2, 126.5, 126.7, 128.3, 135.8, 136.6, 136.7, 148.4, 152.7 \text{ and 172.9; } m/z (ES-) 301 (M}^+ - 1, 100\%). \]

\[(5'\text{R,1E})-\text{tert-butyl-2'-(}(2Z,4E,6R,8S,10E,12E,14E)-1-hydroxy-6,8,10,14\text{ tetramethylhexadeca-2,4,10,12-pentaen-1-ylidene)-5'-isopropyl-3'\text{-oxopyrrolidine-4'-carboxylate 114}\]

To a solution of acid 240 (0.082 g, 0.27 mmol) in THF (1 ml) at r.t. was added 1,1'-carbonyldiimidazole (0.055 g, 0.34 mmol), with subsequent stirring at r.t. for 45 min. The reaction mixture was then diluted with Et\_2O (30 ml) and sequentially washed with H\_2O (5 ml) and brine (5 ml), then dried (Na\_2SO\_4) and concentrated under reduced pressure to afford the title compound as a light yellow liquid (0.081 g, 85%).

To a -78°C solution of pyrrolidinone 116 (0.103 g, 0.454 mmol) in THF (3 ml) was added a 0°C solution of LiHMDS (1.0M in THF) (0.076 g, 0.45 mmol, 0.45 ml), with
subsequent stirring at -78°C for 1 h. This was then followed by the addition of a 0°C solution of imidazolide 241 (0.080 g, 0.23 mmol) in THF (1 ml), with further stirring at -78°C for 2 h. To the reaction mixture was then added sat. aq. NH₄Cl (2 ml), which was then allowed to warm to r.t. before the addition of sat. aq. NH₄Cl (10 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 20 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.172 g). Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compounds as a light yellow liquid in a (10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 73 : 5 : 22 ratio, all three isomers are in a (2Z,4E) : (2E,4E) = 10 : 1 ratio (0.067 g, 58%).

Rₛ = 0.58 (1 : 5, Et₂O : pet. ether); [α]D²⁸ +121.4 (c 0.8, C₆H₆); (Found M⁺ + H, 512.3751. C₃₂H₅₀O₄N requires 512.3735); νmax / cm⁻¹ 2962, 2921, 2360, 1715, 1622, 1455, 1368, 1290, 1255, 1148, 1049, 996, 969, 850 and 800; δH (500MHz, C₆D₆) [(2Z,4E,10E,12E,14E) isomer] 0.58 [3H, d, J 6.8, CH(CH₃)], 0.65 [3H, d, J 6.9, CH(CH₃’)], 0.84 (3H, d, J 6.5, 8-CH₃), 0.93 (3H, d, J 6.7, 6-CH₃), 0.99 (1H, ddd, J 13.4, 9.4, 4.8, 7-H), 1.34 (1H, ddd, J 13.4, 9.8, 4.4, 7-H’), 1.49 (9H, s, C(CH₃)₃), 1.61 (3H, d, J 6.9, 15-CH₃), 1.68 (5H, m, 10-CH₃, 8-H and 9-H), 1.75 (3H, s, 14-CH₃), 1.85 (1H, ddd, J 13.4, 7.8, 9-H’), 2.01 (2H, m, 6’-H and 6’-H’), 2.35 [2H, m, 6-H and CH(CH₃)₃], 3.93 (1H, m, 5’-H), 5.31 (1H, d, J 11.5, 2-H), 5.53 (1H, q, J 6.9, 15-H), 5.66 (1H, dd, J 15.1, 8.5, 5-H), 6.04 (1H, d, J 10.9, 11-H), 6.29 (1H, t, J 11.5, 3-H), 6.35 (1H, d, J 15.3, 13-H), 6.53 (1H, dd, J 15.3, 10.9, 12-H) 7.66 (1H, dd, J 15.1, 11.5, 4-H) and 12.97 (1H, s, 1-OH), [visible peaks for (2E,4E,10E,12E,14E) isomer] 3.78 (0.1H, m, 5’-H), 7.29 (1H, dd, J 15.3, 11.1, 4-H) and 12.65 (1H, s, 1-OH), [visible peaks for (2Z,4E,10E,12Z,14E) isomer] 5.92 (1H, d, J 11.4, 11-H), [visible peaks for (2Z,4E,10E,12E,14Z) isomer] 3.99 (1H, m, 5’-H), 6.09 (1H, d, J 11.3, 11-H), 6.63 (1H, dd, J 15.3, 11.3, 12-H) and 6.75 (1H, d, J 15.3, 13-H); δC (100MHz, C₆D₆) [(2Z,4E,10E,12E,14E) isomer only] 12.6, 13.6, 14.4, 14.7, 17.1, 18.7, 20.1, 21.1, 21.5, 21.9, 28.3, 28.5, 29.5, 30.5, 35.7, 44.7, 49.3, 60.2, .5, 103.5, 117.8, 123.2, 126.7, 35.8, 136.6, 139.4, 149.2, 151.6, 164.1 and 173.4; m/z (ES+) 510 (M⁺ - 1, 100%).
(5'S)-tert-butyl-5'-isopropyl-3'-oxo-2'-(2Z,4E,6R,8S,10E,12E,14E)-6,8,10,14-tetramethyl hexadeca-2,4,10,12,14-pentaenoyl)-6'H-pyrrole-3'-carboxylate 110

To a -78°C solution of oxopyrrolidine 114 (0.063 g, 0.12 mmol) in THF (1.5 ml) was added a 0°C solution of LiHMDS (1.0M in THF) (0.030 g, 0.18 mmol, 0.18 ml), with subsequent stirring at -78°C for 30 min. This was then followed by the addition of a solution of 0°C PhSeCl (0.092 g, 0.48 mmol) in THF (0.5 ml), with further stirring at -78°C for 4 h. To the reaction mixture was then added sat. aq. NH₄Cl (2 ml), which was then allowed to warm to rt before the addition of sat. aq. NH₄Cl (10 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 20 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.131 g). Column chromatography (SiO₂, 1 : 20 Et₂O : pet. ether) gave the title compound as a light yellow liquid (0.049 g, 60%).

To a -50°C solution of selenide 242 (0.046 g, 0.069 mmol) in CDCl₃ (4 ml) was added a 0°C solution of H₂O₂ (30%) (0.082 g, 0.73 mmol) in H₂O (0.5 ml) and then a 0°C solution of m-CPBA (77%) (0.017 g, 0.076 mmol) in CDCl₃ (2 ml), with further stirring at -50°C for 40 min. The reaction mixture was then removed from the -50°C bath and was placed in a 0°C bath for 15 min with vigorous stirring. This was then followed by the addition of 0°C CDCl₃ (3 ml) and sequential washing with 0°C sat. aq. Na₂CO₃ (2 ml x 2) and 0°C H₂O (2 ml). The organic layer was then dried (Na₂SO₄) and, due to the reactivity of the product, the solution was not concentrated under reduced pressure but was instead introduced into the next reaction.
**(5R)-isopropylpyrrolidin-2-one 257**

To a r.t. solution of pyrrolidinone 116 (0.122 g, 0.537 mmol) in DCM (4 ml) was added TFA (0.122 g, 1.07 mmol, 0.08 ml), with subsequent stirring at r.t. for 1 h. To the reaction mixture was then added sat. aq. NaHCO₃ (20 ml), the aqueous layer was then separated from the organic layer and washed with DCM (20 ml x 4). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light orange liquid (0.832 g). Column chromatography (SiO₂, 100% Et₂O to remove the top spots and then 1 : 10 MeOH: Et₂O) gave the title compound as a white solid (0.568 g, 94%).

Rᵣ = 0.46 (1 : 10, MeOH : Et₂O); m.p 57.0-60.0 °C; [α]D²⁸ +12.0 (c 0.4, C₆H₆); (Found M+ - C₃H₇, 84.0441. C₄H₆ON requires 84.0444); v_max/cm⁻¹ 3198, 3092, 2960, 2934, 2892, 2875, 1682, 1658, 1470, 1451, 1392, 1371, 1346, 1315, 1291, 1269, 1214, 1168, 1140, 1076, 1033, 995, 975, 956, 922, 885, 766, 681 and 626; δH (400MHz, CDCl₃) 0.89 [3H, d, J 6.8, CH(CH₃)], 0.94 [3H, d, J 6.7, CH(CH₃’)], 1.62 [1H, m, CH(CH₃)₂], 1.74 (1H, m, 4-H), 2.15 (1H, m, 4-’H), 2.31 (2H, m, 3-H and 3-’H), 3.37 (1H, q, J 7.0, 5-H) and 7.13 (1H, br s, 1-NH); δC (100MHz, CDCl₃) 18.0, 18.7, 24.5, 30.6, 33.4, 60.8 and 179.1; m/z (EI/Cl) 127 (M+, 1%) and 84 (M+ - 43, 100%).

**(5R)-1-benzoyl-5-isopropylpyrrolidin-2-one 256**

To a r.t. solution of pyrrolidinone 257 (8.11 g, 63.9 mmol) in pyridine (160 ml) was added benzoyl chloride (18.0 g, 128 mmmol, 14.9 ml), with subsequent stirring at r.t. for 4 h. To the reaction mixture was then added Et₂O (400 ml), which was then concentrated under reduced pressure (using benzene to azotrope off most of the pyridine) to afford the product as a dark yellow solid (23.39 g). Column
chromatography (SiO$_2$, 1 : 10 Et$_2$O : pet. ether to remove the top spots and then 1 : 1 Et$_2$O : pet.ether) gave the title compound as a white solid (12.39 g, 84%).

R$_f$ = 0.45 (2 : 1, Et$_2$O : pet.ether); m.p 136.0-138.0 °C; $[\alpha]_D^{26} +229.7$ (c 0.7, C$_6$H$_6$); (Found M$^+ +$ H, 232.1330. C$_{14}$H$_{18}$O$_2$N requires 232.1333); $\nu_{\text{max}}$/cm$^{-1}$ 2933, 2961, 2889, 2873, 1745, 1661, 1600, 1581, 1489, 1465, 1448, 1414, 1388, 1371, 1353, 1320, 1289, 1278, 1234, 1219, 1179, 1166, 1152, 1135, 1097, 1077, 973, 937, 883, 868, 836, 800, 744, 704, 667 and 622; $\delta_H$ (400MHz, C$_6$D$_6$) 0.63 [3H, d, J 6.8, CH(CH$_3$)$_2$], 0.70 [3H, d, J 6.7, CH(CH$_3$)$_2$], 1.22 (2H, m, 4- $H$ and 4-$H'$), 1.86 (1H, m, 3- $H$), 2.07 (1H, m, 3-$H'$), 2.34 [1H, m, CH(CH$_3$)$_2$], 4.28 (1H, m, 5-$H$), 7.19 (3H, m, Ar) and 7.84 (2H, d, J 7.4, Ar); $\delta_C$ (125MHz, C$_6$D$_6$) 15.8, 18.1, 18.9, 29.3, 32.4, 61.8, 128.9, 130.2, 132.4, 136.2171.3 and 175.1; $m/z$ (ES+) 254 (M$^+$ + 23, 35%) and 232 (M$^+$ + 1, 100%)

(2$R$)-2-isopropylpyrrolidine 258

To a r.t. solution of pyrrolidinone 257 (0.153 g, 1.21 mmol) in THF (5 ml) was added LiAlH$_4$ (0.092 g, 2.4 mmol) in THF (3 ml), which was subsequently refluxed at 66°C for 14 h. The reaction mixture was then allowed to warm to r.t. before being cooled to 0°C and followed by the slow addition of H$_2$O (20 ml). The solution was then filtered through celite and washed with Et$_2$O (20 ml x 3). The aqueous layer was then separated from the organic layer and washed with Et$_2$O (20 ml x 4). The combined organic layers were then dried (Na$_2$SO$_4$) and concentrated under reduced pressure (at 0°C) to afford the title compound as a clear liquid (0.095 g, 70%).

(2'S)-3',3',3'-trifluoro-1-((R)-2-isopropylpyrrolidin-1-yl)-2'-methoxy-2'-phenylpropan-1'-one 259

To a r.t. solution of pyrrolidinone 258 (0.012 g, 0.11 mmol) in DCM (0.5 ml) was added (R)-(−)-MTPA-Cl (0.054 g, 0.21 mmol) in DCM (0.5 ml), followed by the addition of
pyridine (0.033 g, 0.42 mmol, 0.03 ml) and subsequent stirring at r.t. for 16 h. To the reaction mixture was then added H₂O (5 ml), followed by washing with Et₂O (10 ml x 4). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.078 g). Column chromatography (SiO₂, 1 : 7 Et₂O : pet. ether) gave the title compound as a white solid (0.026 g, 75%).

R_f = 0.39 (1 : 2, Et₂O : pet. ether); m.p 151.2-152.9 °C; [α]D²⁴ +81.3 (c 0.3, C₆H₆); (Found M⁺ + H, 330.1669. C₁₇H₂₃O₂NF₃ requires 330.1676); v_max/cm⁻¹ 2969, 2880, 1651, 1468, 1455, 1422, 1391, 1307, 1267, 1174, 1166, 1156, 1106, 1080, 1057, 1022, 991, 946, 925, 897, 868, 790, 768, 729, 706, 692 and 662; δ_H(500MHz, CDCl₃) 0.68 [3H, d, J 6.9, CH(C₃H₃)], 0.90 [3H, d, J 7.0, CH(CH₃)], 1.65 (3H, m, 4-H, 4-H' and 3-H'), 1.76 (1H, m, 3-H'), 2.22 (1H, m, 5-H), 2.70 [1H, m, CH(CH₃)₂], 3.63 (1H, ddd, J 11.3, 7.1, 4.3, 5-H'), 3.66 (3H, q, J 1.7, OCH₃), 4.16 (1H, m, 2-H), 7.38 (3H, m, Ar) and 7.56 (2H, m, Ar); δ_C (125MHz, CDCl₃) 16.1, 19.5, 23.4, 25.2, 28.3, 46.7, 55.4, 63.5, 122.7, 125.0, 128.0, 129.0, 134.2 and 164.1; m/z (ES+) 352 (M⁺ + 23, 94%) and 330 (M⁺ + 1, 100%).

(2'R)-3',3',3'-trifluoro-1-((R)-2-isopropylpyrrolidin-1-yl)-2'-methoxy-2'-phenylpropan-1'-one 260

To a r.t. solution of pyrrolidinone 258 (0.010 g, 0.088 mmol) in DCM (0.5 ml) was added (S)-(+)MTPACl (0.045 g, 0.18 mmol) in DCM (0.5 ml), followed by the addition of pyridine (0.028 g, 0.35 mmol, 0.03 ml) and subsequent stirring at r.t. for 16 h. To the reaction mixture was then added H₂O (5 ml), followed by washing with Et₂O (10 ml x 4). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light orange liquid (0.064 g). Column chromatography (SiO₂, 1 : 7 Et₂O : pet. ether) gave the title compound as a white solid (0.020 g, 70%).

R_f = 0.47 (1 : 2, Et₂O : pet. ether); m.p 76.4-77.8 °C; [α]D²⁴ +160.0 (c 0.5, C₆H₆); (Found M⁺ + H, 330.1677. C₁₇H₂₃O₂NF₃ requires 330.1676); v_max/cm⁻¹ 2970, 2857,
1832, 1644, 1493, 1451, 1422, 1390, 1265, 1230, 1180, 1148, 1108, 1079, 1057, 1022, 992, 961, 945, 924, 896, 863, 786, 767, 741, 706, 691 and 651; δH (500MHz, CDCl3) 0.84 [3H, d, J 6.9, CH(CH3)], 0.94 [3H, d, J 7.0, CH(CH3’)], 1.19 (1H, m, 4-H), 1.60 (2H, m, 4-H’ and 3-H), 1.71 (1H, m, 3-H’), 2.54 [1H, m, CH(CH3)2], 3.05 (1H, ddd, J 11.6, 9.3, 6.2, 5-H), 3.14 (1H, ddd, J 11.6, 7.6, 3.4, 5-H’), 3.73 (3H, q, J 1.8, OCH3), 4.21 (1H, m, 2-H), 7.38 (3H, m, Ar) and 7.54 (2H, m, Ar); δC (125MHz, CDCl3) 16.4, 19.6, 23.7, 24.7, 29.0, 47.5, 55.2, 63.9, 124.9, 126.8, 128.2, 128.7, 129.2, 133.7 and 164.8; m/z (ES+) 352 (M+ + 23, 82%) and 330 (M+ + 1, 100%).

1-(1H-imidazol-1-yl)hexan-1-one 264

To a r.t. solution of hexanoic acid 263 (0.300 g, 2.59 mmol) in THF (12 ml) was added 1,1’-carbonyldiimidazole (0.839 g, 5.18 mmol), with subsequent stirring at r.t. for 20 h. The reaction mixture was the diluted with Et2O (100 ml) and sequentially washed with H2O (20 ml x 2) and brine (20 ml), dried (Na2SO4) and concentrated under reduced pressure to afford the title compound as a clear liquid (0.402g, 94%).

Rf = 0.16 (3 : 1, Et2O : pet.ether); (Found M+ + H, 167.1187. C9H15N2O1 requires M 167.1179); νmax / cm⁻¹ 3132, 2960, 2931, 2864, 2364, 1736, 1525, 1471, 1390, 1322, 1252, 1222, 1101, 1084, 1061, 1029, 964, 903, 832, 759, 727, 650 and 618; δH (400MHz, CDCl3) 0.87 (3H, t, J 7.1, 6-H3), 1.33 (4H, m, 5-H2 and 4-H2), 1.75 (2H, m, 3-H2), 2.81 (2H, t, J 7.4, 2-H2), 7.03 (1H, m, 3’-H), 7.42 (1H, t, J 1.5, 5’-H) and 8.11 (1H, s, 6’-H); δC (100MHz, CDCl3) 13.7, 22.2, 23.6, 30.9, 35.0, 115.8, 130.8, 136.0 and 169.4; m/z (ES+) 196 (M+ + 23, 80%) and 167 (M+ + 1, 100%).
(5R)-1-benzoyl-3-hexaonyl-5-isopropylpyrrolidin-2-one XX and (R,Z)-1-benzoyl-3-(4'-hydroxyhexylidene)-5-isopropylpyrrolidin-2-one 262

To a solution of pyrrolidinone 256 (1.39 g, 6.02 mmol) in THF (20 ml) at -78°C was added a pre-cooled -78°C solution of LiHMDS (1.0M in THF) (1.01 g, 6.02 mmol, 6.02 ml), with subsequent stirring at -78°C for 1 h. A pre-cooled -78°C solution of imidazolide 264 (0.500 g, 3.01 mmol) in THF (10 ml) was then added to the -78°C solution with subsequent stirring at -78°C for 5 h. To the reaction mixture was then added sat. aq. NH₄Cl (30 ml), which was then allowed to warm to rt before the addition of sat. aq. NH₄Cl (60 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 200 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow solid (1.77 g). Column chromatography (SiO₂, 1: 10 Et₂O : pet. ether) gave the title compound as a clear liquid as a mix. of epimers at C(3) : enol = 2 : 1 ratio, with the epimers having an a : b = 1 : 1 ratio (0.750 g, 76%).

Rᵣ = 0.39 (1 : 2, Et₂O : pet. ether); [α]ᵣ° +141.3 (c 0.6, C₆H₆); (Found M₊ + H, 330.2064, C₂₀H₂₈NO₃ requires 330.2062); v max / cm⁻¹ 2960, 2932, 2873, 1737, 1714, 1672, 1631, 1602, 1583, 1466, 1450, 1366, 1278, 1234, 1178, 1127, 1073, 1028, 1002, 971, 914, 884, 829, 803, 731, 694 and 657; δH (400MHz, C₆D₆) 0.79 [18H, m, CH(C₆H₃)a+b, CH(C₆H₃)b and CH(C₆H₃)enol], 0.91 (9H, m, 9'-H₃a+b and 9'-H₃b), 1.26 (12H, m, 8'-H₂a+b, 8'-H₂b, 7'-H₂a+b and 7'-H₂b), 1.60 (9H, m, 6'-H₂a+b, 6'-H₂b, 4'-H₂a+b and 4'-H₂b), 2.04 (2H, m, 5'-H₂a+b and 5'-H₂b), 2.35 [7H, m, CH(CH₃)₂a+b, CH(CH₃)₂b and 5'-H₂a+b and 5'-H₂b], 2.52 (2H, m, 4'-H₂a+b), 2.60 (1H, m, 4'-H₂b), 2.91 (2H, m, 5'-H₂a+b and 5'-H₂b), 3.18 (1H, t, J₉ 9.6, 3-H₆b), 3.47 (1H, dd, J₉ 9.3, 7.6, 3-H₆b), 4.23 (1H, m, 5'-H₂a+b), 4.51 (2H, m, 5'-H₂b), 7.20 (9H, m, Ara+b/eno), 7.79 (6H, m, Ara+b/eno) and 12.32 (1H, br s, 4'-OH/eno); δC (100MHz, C₆D₆) (epimers a/b and enol peaks were indistinguishable) 14.5, 14.5, 14.5, 15.0, 15.9, 18.7, 19.0, 19.6, 20.5, 21.0, 23.1, 23.2, 23.6, 26.1, 27.8, 29.3, 29.8, 31.8, 31.9, 32.0, 33.4, 43.2, 43.7, 55.3, 56.2, 60.0, 60.0, 60.7, 100.1, 128.2, 128.5, 128.6, 129.9, 130.0, 131.0, 132.2, 132.5, 133.0, 135.3, 135.7, 136.3, 170.8, 170.9, 171.4, 171.4, 171.9, 172.7, 173.7, 203.6 and 203.9; m/z (ES+) 352 (M₊ + 23, 100%) and 330 (M₊ + 1, 60%).
(5R)-1-benzoyl-3-hexanoyl-5-isopropyl-3-(phenylselanyl)pyrrolidin-2-one 265

To a -78°C solution of oxopyrrolidine 262 (0.303 g, 0.773 mmol) in THF (10 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.387 g, 2.32 mmol, 2.32 ml), with subsequent stirring at -78°C for 1h. This was then followed by the addition of a solution of PhSeCl (0.445 g, 2.32 mmol) in THF (5 ml), with further stirring at -78°C for 2 h. To the reaction mixture was then added sat. aq. NH₄Cl (20 ml), which was then allowed to warm to r.t. before the addition of sat. aq. NH₄Cl (30 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 100 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.902 g). Column chromatography (SiO₂, 1 : 100 Et₂O : pet. ether) gave the title compound as a light yellow liquid as a mix. of epimers at C(3) with the epimers having an a : b = 1 : 0.4 ratio (0.288 g, 77%).

R_f = 0.58 (1 : 2, Et₂O : pet. ether); [α]D²⁸ +210.0 (c 1.0, C₆H₆); (Found M+ + H, 486.1545. C₂₆H₃₂NO₃Se requires 486.1542); νmax / cm⁻¹ 3059, 2959, 2930, 2872, 1724, 1683, 1601, 1582, 1465, 1449, 1393, 1392, 1363, 1312, 1272, 1236, 1213, 1177, 1159, 1132, 1106, 1067, 1022, 1001, 982, 930, 887, 835, 802, 740, 691, 673 and 654; δH (400MHz, C₆D₆) (asterisk denotes epimer b) 0.56 [8.4H, m, CH(CH₃)a+b, CH(CH₃)‘a+b], 0.77 (1.2H, m, 9'-H₁b), 0.83 (3H, m, 9'-H₃a), 1.11 (1.6H, m, 8'-H₂b and 7'-H₂b), 1.23 (4H, m, 8'-H₂a and 7'-H₂a), 1.56 (0.8H, m, 6'-H₂b), 1.75 (2H, m, 6'-H₃a), 1.85 (1H, dd, J 15.0, 7.2, 4'-H₄), 2.00 (0.4H, dd, J 13.6, 9.3, 4'-H₄), 2.49 [2.4H, m, 4'-H₄ and CH(CH₃)₂a+b], 2.74 (0.4H, m, 5'-H₃b), 2.90 (0.4H, dd, J 13.6, 7.3, 4'-H₄b), 3.01 (1H, dd, J 17.4, 8.1, 6.4, 5'-H₅), 3.11 (0.4H, m, 5'-H₅b), 3.33 (1H, ddd, J 17.4, 8.3, 6.8, 5'-H₅a), 4.30 (0.4H, m, 5'-H₅b), 4.40 (1H, m, 5'-H₅b), 6.95 (4.2H, m, SeAra+b), 7.10 (4.2H, m, Ar₃b), 7.47 (2.8H, m, SeAr₃b) and 7.77 (2.8H, m, Ar₃b); δC (100MHz, C₆D₆) (asterisk denotes epimer b) 14.1*, 14.2, 14.7*, 15.0, 18.2, 18.2*, 22.8*, 22.9, 24.7, 24.8*, 26.9, 27.0, 27.2*, 28.0*, 31.4*, 31.7, 38.4*, 39.0, 58.5, 60.3*, 60.6, 61.8*, 126.8*, 128.2, 129.2*, 129.3*, 129.5, 129.5, 130.0*, 130.1, 130.3, 130.4*, 132.7, 132.9*, 134.6*, 135.0, 137.7*, 137.8, 171.1*, 171.1, 171.4, 171.5*, 200.6* and 202.1; m/z (ES+) 508 (M⁺ + 23, 100%) and 486 (M⁺ + 1, 90%).
(S)-1-benzoyl-3-hexanoyl-5-isopropyl-4H-pyrrol-2(5H)-one 261

To a -48°C solution of selenide 265 (0.342 g, 0.707 mmol) in CHCl₃ (16 ml) was added a 0°C solution of H₂O₂ (30%) (0.841 g, 7.42 mmol) in H₂O (2 ml) and then a 0°C solution of m-CPBA (77%) (0.318 g, 1.41 mmol) in CHCl₃ (8 ml), with further stirring at -48°C for 45 min. The reaction mixture was then removed from the -48°C bath and allowed to warm up to 0°C over the period of 10 min. This was then followed by the addition of 0°C CHCl₃ (30 ml) and sequential washing with 0°C sat. aq. Na₂CO₃ (25 ml x 2) and 0°C H₂O (25 ml). The organic layer was then dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as an orange gum (0.220 g, 95%).

(3S,4R,5R,8R,9S)-2-benzoyl-9-hexanoyl-3-isopropyl-5,8-diphenyl-2,3,4,5,8,9-hexahydro-1H-isoindol-1-one 267

To a solution of pyrrolinone 261 (0.220 g, 0.673 mmol) in toluene (5 ml) was added trans,trans-1,4-Diphenyl-1,3-butadiene 266 (1.39 g, 6.73 mmol), with subsequent degassing with nitrogen for 15 min. The reaction mixture was then refluxed at 120°C for 96 h and then concentrated under reduced pressure to afford the product as a white solid (1.60 g). Column chromatography (SiO₂, 1: 100 Et₂O: pet. ether to remove top spot and then 1: 10 Et₂O: pet. ether) gave the title compound as a viscous white liquid (0.153 g, 43%).

Rₚ = 0.46 (1 : 5, Et₂O : pet. ether); [α]₀²⁸ -16.0, (c 0.2, C₆H₆); (Found M⁺ + Na, 556.2832. C₃₆H₃₉NO₃Na requires M 556.2823); νₘₐₓ / cm⁻¹ 3062, 3030, 2961, 2931, 2872, 1732, 1710, 1689, 1683, 1602, 1584, 1494, 1454, 1392, 1372, 1347, 1305, 1272, 1205, 1179, 1127, 1097, 1078, 1030, 1004, 924, 873, 825, 806, 747, 696 and 659; δH
(400MHz, C$_6$D$_6$) 0.45 [3H, d, $J$ 6.6, CH$(CH_3)$], 0.66 [3H, d, $J$ 6.8, CH$(CH_3')$], 0.77 (3H, t, $J$ 7.3, 15’-H$_3$), 0.95 (3H, m, 12’-H and 14’-H$_2$), 1.10 (2H, m, 13’-H$_2$), 1.29 (1H, m, 12’-H’), 1.60 [1H, m, CH$(CH_3)_2$], 2.33 (2H, m, 11’-H$_2$), 2.80 (1H, dq, $J$ 10.6, 2.6, 5-H), 3.13 (1H, d, $J$ 10.6, 4-H), 4.13 (1H, q, $J$ 2.8, 8-H), 4.50 (1H, d, $J$ 10.3, 3-H), 5.78 (1H, dt, $J$ 9.8, 2.8, 7-H), 5.85 (1H, dt, $J$ 9.8, 2.6, 6-H), 7.00 (1H, m, Ar), 7.09 (3H, m, Bz-Ar), 7.18 (5H, m, Ar), 7.31 (2H, m, Ar) and 8.01 (2H, m, Bz-Ar); $\delta$C (100MHz, C$_6$D$_6$) 14.5, 19.4, 20.6, 23.1, 23.5, 31.7, 33.3, 42.8, 44.8, 45.0, 46.0, 65.2, 69.6, 127.7, 127.7, 128.8, 128.8, 129.4, 129.7, 130.3, 131.3, 131.8, 133.0, 133.1, 135.8, 141.1, 144.1, 172.0, 176.0 and 206.3; $m$/z (ES$^+$) 1089 (2 x M$^+$, +23, 47%) and 556 (M$^+$ + 23, 10%).

(3S,4R,5R,8R,9S)-9-hexanoyl-3-isopropyl-5,8-diphenyl-2,3,4,5,8,9-hexahydro-1H-isoindol-1-one 268

To a r.t. solution of endo-267 Diels-Alder adduct (0.017 g, 0.032 mmol) in MeOH (1 ml) was added a solution of NaOH (0.026 g, 0.64 mmol) in MeOH (1 ml) / H$_2$O (0.04 ml), with stirring at r.t. for 6 h. To the reaction mixture was then added H$_2$O (4 ml), which was then followed by washing with Et$_2$O (10ml x 3). The combined organic layers were then washed with brine (4 ml), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the product as a light yellow solid (0.010 g). Column chromatography (SiO$_2$, 1 : 5 Et$_2$O : pet. ether to remove top spots and then 100% Et$_2$O) gave the title compound as a clear liquid (0.008 g, 60%).

$R_f$ = 0.23 (1 : 1, Et$_2$O : pet. ether); [$\alpha$]$_D^{28}$ -12.0, (c 0.3, C$_6$H$_6$); (Found M$^+$ + H, 430.2747. C$_{29}$H$_{36}$NO$_2$ requires $M$ 430.2741); $\nu_{max}$ / cm$^{-1}$ 3199, 3029, 2958, 2929, 2871, 1691, 1602, 1493, 1454, 1388, 1266, 1132, 1077, 1030, 812, 754, 739, 698 and 634; $\delta$H (400MHz, C$_6$D$_6$) 0.36 [3H, d, $J$ 6.6, CH$(CH_3)$], 0.57 [3H, d, $J$ 6.7, CH$(CH_3')$], 0.73 (3H, t, $J$ 7.3, 15’-H$_3$), 0.92 (3H, m, 12’-H and 14’-H$_2$), 1.05 (2H, m, 13’-H$_2$), 1.24 [1H, m, CH$(CH_3)_2$], 1.40 [1H, m, 12’-H’], 2.39 (2H, m, 11’-H$_2$), 2.70 (1H, br d, $J$ 9.6, 4-H), 163
2.86 (1H, d, J 10.1, 5-H), 3.23 (1H, d, J 10.1, 3-H), 4.28 (1H, br s, 8-H), 5.90 (2H, m, 6-H and 7-H), 7.07 (8H, m, Ar), 7.25 (1H, d, J 5.0, NH) and 7.55 (2H, m, Ar); δc (100MHz, C6D6) 14.4, 19.3, 19.8, 23.1, 23.7, 31.7, 32.7, 42.3, 44.8, 46.1, 47.8, 65.1, 65.9, 127.5, 127.5, 129.0, 129.2, 129.5, 132.0, 132.2, 132.8, 141.8, 144.9, 177.5 and 207.7; m/z (ES+) 876 (2 x M+, +18, 70%), 447 (M+ + 18, 100%) and 430 (M+ + 1, 82%).

(4R,6S,8E)-10-((tert-butyldimethylsilyl)oxy)-4,6,8-trimethyldeca-1,8-dien-3-ol 276

To a -78°C solution of aldehyde 198 (7.40 g, 24.8 mmol) in THF (120 ml) was added vinyl magnesium bromide (1.0M in THF) (5.19 g, 39.6 mmol, 39.6 ml) dropwise, with subsequent stirring at r.t. for 50 min. To the reaction mixture was then added sat. aq. NH4Cl (300 ml) with stirring at r.t. for 5 min. The aqueous layer was then separated from the organic layer and washed with Et2O (400 ml x 4). The combined organic layers were then dried (Na2SO4) and concentrated under reduced pressure to afford the product as a light yellow oil (10.95 g). Column chromatography (SiO2, 1: 10 Et2O:pet.) gave the title compound as a clear liquid as a mix. of diastereoisomers at C(3) with the diastereoisomers having an a:b = 1 : 0.5 ratio (5.99 g, 74%).

Rf = top spot 0.28 (1 : 5, Et2O : pet. ether) and bottom spot 0.25 (1 : 5, Et2O : pet. ether); [α]D32 +16.0, (c 0.3, C6H6); (Found M+ + Na, 349.2527. C19H38O2NaSi requires M349.2534; νmax/cm⁻¹ 3396(br), 2954, 2927, 2856, 2361, 1667, 1641, 1461, 1379, 1361, 1252, 1199, 1088, 1054, 1004, 920, 833, 813, 773 and 665; δH (400MHz, C6D6) 0.12 [6H, s, Si(CH3)2a], 0.12 [3H, m, Si(CH3)2b], 0.84 (3H, d, J 5.8, 6-CH3a), 0.85 (1.5H, m, 6-CH3b), 0.88 (1.5H, d, J 6.8, 4-CH3b), 0.88 (3H, d, J 6.8, 4-CH3a), 0.94 (1.5H, m, 5-Ha and 5-Hb), 1.01 [9H, s, Si(CH3)3a], 1.01 [4.5H, m, Si(CH3)3b], 1.06 (0.5H, br s, 1-OHb), 1.09 (1H, br s, 1-OHf), 1.40 (0.5H, m, 5-H'ab), 1.46 (1H, m, 5-H'aa), 1.50 (1.5H, s, 8-CH3b), 1.52 (3H, s, 8-CH3a), 1.63 (4.5H, m, 7-Hf, 7-Hb, 6-Hf, 6-Hb, 4-Hf and 4-Hb), 2.02 (1.5H, m, 7-H'a and 7-H'ab), 3.77 (0.5H, t, J 5.2, 3-Hf), 3.83 (1H, s, 3-Ha), 4.23 (2H, d, J 6.4, 10-H2a), 4.23 (1H, m, 10-H2b), 5.03 (1H, dt, J 10.6, 1.6, 1-H'a), 5.03 (0.5H, m, 1-H'Hb), 5.13 (0.5H, dt, J 17.2, 1.6, 1-H'b), 5.16 (1H, dt, J 17.2, 1.6, 1-H'a), 5.50 (1H, q, J 6.1, 9-Hf), 5.50 (0.5H, m, 9-Hf), 5.73 (1H, ddd, J 17.2, 10.6, 5.5, 2-Hf) and 5.74
(0.5H, ddd, J 17.2, 10.4, 6.2, 2-H\(^6\)); δ\(C\) (100MHz, C\(_6\)D\(_6\)) (asterisk denotes minor b diastereoisomer peaks) -4.5\(^*\), -4.5, 15.3, 16.1\(^*\), 16.6\(^*\), 16.6, 18.9\(^*\), 18.9, 21.0, 21.1\(^*\), 26.5\(^*\), 26.6, 28.7, 28.8\(^*\), 36.5, 36.7\(^*\), 40.9\(^*\), 41.1, 47.7\(^*\), 47.9, 60.7\(^*\), 60.7, 76.1, 77.2\(^*\), 114.8, 115.6\(^*\), 127.0, 127.1\(^*\), 136.1\(^*\), 136.3, 140.0\(^*\) and 141.2; \(m/z\) (ES+) 349 (M\(^+\) + 23, 100%).

\((4E,6R,8S,10E)-ethyl\) 12-((\(tert\)-butyldimethylsilyl))-6,8, 10-trimethyldeca-4, 10-dienoate 277

![Chemical Structure]

To a solution of vinyl alcohol 276 (4.64 g, 14.2 mmol) and triethylorthoacetate (6.90 g, 42.6 mmol, 7.80 ml) in xylene (46 ml) was added propionic acid (0.05 ml), with subsequent refluxing at 145°C for 6 h. The solution was then concentrated under reduced pressure (using benzene to azeotrope the xylene and triethylorthoacetate) to afford the product as a clear liquid (6.35 g). Column chromatography (SiO\(_2\), 1 : 40, Et\(_2\)O : pet. ether) gave the \textit{title compound} as a clear liquid (5.11 g, 91%).

\(R_f = 0.28\) (1 : 10, Et\(_2\)O : pet. ether); [\(\alpha\)]\(D\)\(^{30}\) -2.7, (c 0.6, C\(_6\)H\(_6\)); (Found M\(^+\) + Na, 419.2957. C\(_{23}\)H\(_{44}\)O\(_3\)NaSi requires M 419.2952); \(v_{\text{max}}/\text{cm}^{-1}\) 2954, 2928, 2857, 2360, 1737, 1666, 1462, 1374, 1252, 1163, 1086, 1054, 1006, 971, 939, 834, 813, 774 and 665; δ\(H\) (400MHz, C\(_6\)D\(_6\)) 0.0 (6H, s, Si\((CH_3)_2\)), 0.81 (3H, d, J 6.5, 8-CH\(_3\)), 0.91 (1H, m, 7-H), 0.92 (3H, d, J 6.7, 6-CH\(_3\)), 0.98 (3H, t, J 7.1, CH\(_2\)CH\(_3\)), 0.99 (9H, s, Si\((CH_3)_3\)), 1.23 (1H, ddd, J 13.6, 10.1, 4.3, 7-H\'), 1.51 (3H, s, 10-CH\(_3\)), 1.63 (1H, m, 8-H), 1.76 (1H, dd, J 13.2, 7.8, 9-H), 1.91 (1H, dd, J 13.2, 6.8, 9-H\'), 2.12 (1H, m, 6-H), 2.18 (2H, m, 2-H\(_2\)), 2.26 (2H, m, 3-H\(_2\)), 3.95 (2H, q, J 7.1, CH\(_2\)CH\(_3\)), 4.21 (2H, d, J 6.3, 12-H\(_2\)), 5.19 (1H, ddt, J 15.3, 8.2, 1.0, 5-H), 5.32 (1H, dt, J 15.3, 6.3, 4-H) and 5.46 (1H, tq, J 6.3, 1.1, 11-H); δ\(C\) (100MHz, C\(_6\)D\(_6\)) -4.5, 14.7, 16.5, 18.9, 19.9, 22.5, 26.6, 28.6, 28.7, 34.9, 35.2, 44.9, 48.8, 60.3, 60.7, 127.2, 127.6, 136.0, 137.9 and 172.6; \(m/z\) (ES+) 420 (M\(^+\) + 1, 10%).
(4E,6R,8S,10E)-ethyl 12-hydroxy-6,8,10-trimethylldodeca-4,10-dienoate 278

To a solution of ester 277 (5.11 g, 12.9 mmol) in DCM (50 ml)/EtOH (50 ml) at r.t. was added PPTS (0.323 g, 1.29 mmol), with subsequent stirring at r.t. for 24 h. To the reaction mixture was then added sat. aq. NaHCO₃ (250 ml), which was then washed with Et₂O (500 ml x 4). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (13.95 g). Column chromatography (SiO₂, 1 : 3 Et₂O : pet. ether) gave the title compound as a clear liquid (3.45 g, 95%).

Rf = 0.32 (1 : 1, Et₂O : pet. ether); [α]D₃₀⁻8.0, (c 0.5, C₆H₆); (Found M⁺ + Na, 305.2075 C₁₇H₃₀O₃Na requires M 305.2088); νmax/cm⁻¹ 3358(br), 2956, 2913, 2868, 2359, 1735, 1668, 1445, 1373, 1345, 1296, 1255, 1163, 1096, 1067, 1008, 971, 856 and 777; δH (400MHz, C₆D₆) 0.82 (3H, d, J 6.5, 8-C₃H₃), 0.94 (1H, m, 7-H), 0.94 (3H, d, J 6.6, 6-C₃H₃), 0.97 (3H, t, J 7.1, CH₂CH₃), 1.08 (1H, br s, OH), 1.24 (1H, ddd, J 13.5, 9.9, 4.3, 7-H'), 1.49 (3H, s, 10-CH₃), 1.64 (1H, m, 8-H), 1.76 (1H, dd, J 13.3, 7.8, 9-H), 1.92 (1H, dd, J 13.3, 6.6, 9-H'), 2.14 (1H, m, 6-H), 2.20 (2H, m, 2-H₂), 2.28 (2H, m, 3-H₂), 3.96 (2H, q, J 7.1, CH₂CH₃), 4.04 (2H, d, J 6.7, 12-H₂), 5.21 (1H, ddt, J 15.3, 8.2, 1.0, 5-H), 5.34 (1H, dt, J 15.3, 6.3, 4-H) and 5.42 (1H, dq, J 6.7, 1.2, 11-H); δC (100MHz, C₆D₆) 14.7, 16.5, 19.9, 22.4, 28.6, 28.8, 34.9, 35.2, 44.9, 48.8, 59.7, 60.5, 126.9, 127.5, 137.2, 137.9 and 172.9; m/z (ES+) 305 (M⁺ + 23, 100%).

(4E,6R,8S,10E)-ethyl 6,8,10-trimethyl-12-oxododeca-4,10-dienoate 275

To a r.t. solution of alcohol 278 (0.459 g, 1.63 mmol) in DCM (50 ml) was added activated MnO₂ (4.25 g, 48.8 mmol), with subsequent stirring at r.t. for 1 h. The reaction mixture was then filtered through celite, washed with Et₂O (40 ml x 4) and
concentrated under reduced pressure to afford the product as a light yellow liquid (0.552 g). Column chromatography (SiO₂, 1 : 5 Et₂O : pet. ether) gave the title compound as a light yellow liquid (0.387 g, 85%).

Rf = 0.56 (1 : 1, Et₂O : pet. ether); [α]D³² +3.0, (c 0.4, C₆H₆); (Found M⁺ + Na, 303.1937 C₁₇H₂₈O₃Na requires M 303.1931); νmax/cm⁻¹ 2956, 2925, 2868, 1732, 1671, 1629, 1445, 1374, 1345, 1296, 1248, 1195, 1162, 1124, 1094, 1038, 972, 889, 859 and 808; δH (400MHz, C₆D₆) 0.64 (3H, d, J 6.3, 8-C₂H₃), 0.80 (1H, ddd, J 13.5, 8.9, 4.7, 7-H), 0.87 (3H, d, J 6.7, 6-CH₃), 0.98 (3H, t, J 7.1, CH₂CH₃), 1.01 (1H, ddd, J 13.5, 9.9, 4.2, 7-H'), 1.54 (2H, m, 8-H and 9-H), 1.59 (3H, d, J 1.2, 10-CH₃), 1.74 (1H, m, 9-H'), 2.01 (1H, m, 6-H), 2.19 (2H, m, 2-H₂), 2.26 (2H, m, 3-H₂), 3.96 (2H, q, J 7.1, CH₂CH₃), 5.11 (1H, ddt, J 15.4, 8.3, 1.2, 5-H), 5.29 (1H, dt, J 15.4, 6.1, 4-H), 5.83 (1H, dq, J 7.8, 1.2, 11-H) and 9.90 (1H, d, J 7.8, 12-H); δC (100MHz, C₆D₆) 14.7, 17.1, 19.5, 22.3, 28.5, 28.8, 34.8, 35.0, 44.6, 49.2, 60.4, 127.9, 130.0, 137.4, 161.2, 172.7 and 190.1; m/z (ES+) 303 (M⁺ + 23, 100%).

(4E,6R,8S,10E,12E,14E)-ethyl-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoate 274

To a -78°C solution of aldehyde 275 (0.456 g, 1.63 mmol) and BT-sulphone 120 (0.653 g, 2.44 mmol) in THF (50 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.408 g, 2.44 mmol, 2.44 ml), with sequential stirring at -78°C for 1 h and at r.t. for 1 h. To the reaction mixture was added sat. aq. NaHCO₃ (50 ml) and then Et₂O (100 ml). The aqueous layer was then separated from the organic layer and washed with Et₂O (100 ml x 4). The combined organic layers were then washed with brine (100 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.974 g). Column chromatography (SiO₂, 1 : 40 Et₂O : pet. ether) gave the title compound as a clear liquid in a (10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 91 : 4 : 5 ratio (0.401 g, 74%).
$R_t = 0.43$ (1 : 10 Et$_2$O : pet. ether); $[\alpha]_D^{28} +29.0$ (c 0.4, C$_6$H$_6$); (Found M$^+$ + Na, 355.2613 C$_{22}$H$_{36}$O$_2$Na requires $M$ 355.2608); $\nu_{\text{max}}$ / cm$^{-1}$ 2954, 2913, 2868, 1736, 1642, 1444, 1373, 1344, 1296, 1246, 1161, 1096, 1034, 958, 855, 795 and 619; $\delta_H$ (400MHz, C$_6$D$_6$) [(10E,12E,14E) isomer] 0.86 (3H, d, 6-H, 8-CH$_3$), 0.93 (3H, d, 6-CH$_3$), 0.96 (1H, m, 7-H), 0.97 (3H, t, J 7.2, CH$_2$CH$_3$), 1.27 (1H, ddd, J 13.5, 9.9, 4.3, 7-H'), 1.60 (3H, d, J 7.1, 15-CH$_3$), 1.73 (7H, m, 14-CH$_3$, 10-CH$_3$ and 8-H), 1.89 (1H, dd, J 13.3, 7.9, 9-H), 2.04 (1H, dd, J 13.3, 6.8, 9-H'), 2.14 (1H, m, 6-H), 2.20 (2H, m, 2-H$_2$), 2.28 (2H, m, 3-H$_2$), 3.96 (2H, q, J 7.2, CH$_2$CH$_3$), 5.19 (1H, ddd, J 15.3, 8.2, 5-H), 5.34 (1H, dt, J 15.3, 6.2, 4-H), 5.53 (1H, q, J 7.1, 15-H), 6.05 (1H, d, J 10.8, 11-H), 6.34 (1H, d, J 15.3, 13-H) and 6.53 (1H, dd, J 15.3, 10.8, 12-H), [visible peaks for (10E,12Z,14E) isomer] 5.67 (1H, q, J 7.1, 15-H), 5.91 (1H, d, J 11.6, 11-H) and 6.24 (1H, t, J 11.6, 12-H), [visible peaks for (10E,12E,14Z) isomer] 6.10 (1H, d, J 10.8, 11-H), 6.62 (1H, dd, J 15.3, 10.8, 12-H) and 6.75 (1H, d, J 15.3, 13-H); $\delta_C$ (100MHz, C$_6$D$_6$) [(10E,12E,14E) isomer only] 12.6, 14.4, 14.7, 17.1, 20.0, 22.5, 28.6, 29.2, 34.9, 35.2, 45.0, 49.4, 60.4, 123.2, 126.6, 127.6, 128.3, 135.8, 136.6, 136.8, 137.9 and 172.7; $m/z$ (ES+) 355 (M$^+$ + 23, 100%).

$\text{(4E,6R,8S,10E,12E,14E)-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoic acid}$

To a solution of ester 274 (0.365 g, 1.10 mmol) in EtOH (10 ml) at r.t. was added NaOH (0.180 g, 4.51 mmol) in H$_2$O (5 ml) with subsequent stirring at r.t. for 18 h. The reaction mixture was then acidified to pH 5 by adding it to a 0°C solution of tartaric acid (1.65 g, 11.0 mmol) in H$_2$O (60 ml), with vigorous stirring for 2 min and subsequent washing with Et$_2$O (100 ml x 4). The combined organic layers were then sequentially washed with 0°C H$_2$O (100 ml) and 0°C brine (100 ml), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the title compound as a light yellow liquid in a (10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 89 : 4 : 7 ratio (0.330 g, 99%).
R<sub>t</sub> = 0.37 (1 : 2 Et<sub>2</sub>O : pet. ether); [α]<sub>D</sub><sup>28</sup> +21.3 (c 0.6, C<sub>6</sub>H<sub>6</sub>); (Found M<sup>+</sup> - H, 303.2319 C<sub>20</sub>H<sub>33</sub>O<sub>2</sub> requires M 303.2329); ν<sub>max</sub> / cm<sup>-1</sup> 3036, 2953, 2912, 2868, 2831, 1706, 1642, 1439, 1410, 1376, 1295, 1267, 1209, 1023, 958, 789, 676 and 619; δ<sub>H</sub> (400MHz, C<sub>6</sub>D<sub>6</sub>) [(10E,12E,14E) isomer] 0.87 (3H, d, J 6.6, 8-CH<sub>3</sub>), 0.93 (3H, d, J 6.7, 6-CH<sub>3</sub>), 0.96 (1H, ddd, J 13.5, 9.5, 4.8, 7-H), 1.27 (1H, ddd, J 13.5, 9.9, 4.4, 7-H'), 1.60 (3H, d, J 7.1, 15-CH<sub>3</sub>), 1.70 (1H, m, 8-H), 1.74 (6H, m, 14-CH<sub>3</sub> and 10-CH<sub>3</sub>), 1.91 (1H, dd, J 13.4 7.9, 9-H), 2.05 (1H, dd, J 13.4, 6.9, 9-H'), 2.16 (5H, m, 6-H, 3-H<sub>2</sub> and 2-H<sub>2</sub>), 5.16 (1H, ddd, J 15.4, 8.1, 5-H), 5.26 (1H, dt, J 15.4, 6.0, 4-H), 5.54 (1H, q, J 7.1, 15-H), 6.06 (1H, d, J 10.8, 11-H), 6.36 (1H, d, J 15.3, 13-H), (1H, dd, J 15.3, 10.8, 12-H) and 12.1 (1H, br s, 1-OH), [visible peaks for (10E,12Z,14E) isomer] 5.68 (1H, q, J 7.1, 15-H), 5.92 (1H, d, J 11.6, 11-H) and 6.26 (1H, t, J 11.6, 12-H), [visible peaks for (10E,12E,14Z) isomer] 5.36 (1H, q, J 7.3, 15-H), 6.11 (1H, d, J 10.8, 11-H), 6.64 (1H, dd, J 15.3, 10.8, 12-H) and 6.76 (1H, d, J 15.3, 13-H); δ<sub>c</sub> (100MHz, C<sub>6</sub>D<sub>6</sub>) [(10E,12E,14E) isomer only] 12.6, 14.4, 17.1, 20.0, 22.4, 28.2, 29.2, 34.7, 35.2, 44.9, 49.4, 123.3, 126.7, 127.0, 128.2, 135.8, 136.6, 136.8, 138.2 and 180.6; m/z (ES-) 355 (M<sup>+</sup> + 35, 100%).

(4E,6R,8S,10E,12E,14E)-1-(1H-imidazol-1-yl)-8,10,14-tetramethylhexadeca-4,10,12,14-tetraen-1-one 280

To a r.t. solution of acid 279 (0.503 g, 1.66 mmol) in THF (20 ml) was added 1,1’-carbonyldiimidazole (0.536 g, 3.31 mmol), with subsequent stirring at r.t. for 18 h. The reaction mixture was the diluted with 0°C Et<sub>2</sub>O (150 ml) and sequentially washed with 0°C H<sub>2</sub>O (50 ml x 2) and 0°C brine (50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to afford the title compound as a light yellow liquid in a (10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 88 : 4 : 8 ratio (0.366 g, 95%).

R<sub>t</sub> = 0.18 (3 : 1, Et<sub>2</sub>O : pet.ether); [α]<sub>D</sub><sup>28</sup> +23.3, (c 0.6, C<sub>6</sub>H<sub>6</sub>); (Found M<sup>+</sup> + H, 355.2757. C<sub>23</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub> requires M 355.2744); ν<sub>max</sub> / cm<sup>-1</sup> 3125, 3038, 2953, 2913, 2866, 1737, 1640, 1526, 1473, 1380, 1296, 1270, 1221, 1110, 1085, 1062, 1022, 958, 895, 797, 751, 663, 648 and 618; δ<sub>H</sub> (400MHz, C<sub>6</sub>D<sub>6</sub>) [(10E,12E,14E) isomer] 0.87 (3H, d, J 6.6, 8-
(5′R)-4′-benzoyl-5′-isopropyl-2′-((4E,6R,8S,10E,12E,14E)-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoyl)pyrrolidin-3′-one 281 and (R,E)-benzoyl-2′-((4E,6R,8S,10E,12E,14E)-1-hydroxy-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraen-1-ylidene)-5′-isopropylpyrrolidin-3′-one 281

To a -78°C solution of pyrrolidinone 256 (0.691 g, 2.99 mmol) in THF (20 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.500 g, 2.99 mmol, 2.99 ml), with subsequent stirring at -78°C for 1 h. This was then followed by the addition of a -78°C solution of imidazolide 280 (0.531 g, 1.50 mmol) in THF (5 ml), with further stirring at -78°C for 6 h. To the reaction mixture was then added sat. aq. NH₄Cl (20 ml), which was then allowed to warm to rt before the addition of sat. aq. NH₄Cl (40 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 120 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (1.27 g). Column chromatography (SiO₂, 1 : 7 Et₂O : pet. ether) gave the title compounds as
a light orange liquid in a \((10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 84 : 4 : 12\) ratio, with the \((10E,12E,14E)\) isomer being displayed as a mix of epimers at \(C(2')\): enol = 2 : 1 ratio, with the epimers having an \(a : b = 1 : 1\) ratio and the \((10E,12Z,14E)\) and \((10E,12E,14Z)\) isomers being displayed as a mix of epimers at \(C(2')\), with the epimers having an \(a : b = 1 : 1\) ratio, no evidence for enol peaks were seen with these two isomers (0.609 g, 79%).

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R_f = 0.46 \quad (1 : 2, \text{Et}_2\text{O} : \text{pet. ether}) \quad [\alpha]_D^{28} +130.0 \quad (c \ 0.6, \text{C}_8\text{H}_6); \quad \text{(Found M}^+ + \text{H, 518.3629. C}_{34}\text{H}_{48}\text{NO}_3 \text{requires 518.3629)\; \nu_{max} / \text{cm}^{-1} 2959, 2915, 2871, 2360, 1737, 1716, 1673, 1633, 1602, 1449, 1378, 1279, 1236, 1177, 1134, 1117, 1077, 1028, 960, 888, 799, 738, 710, 693, 657 and 635;} \delta_H \quad (400\text{MHz, C}_6\text{D}_6) \quad [(10E,12E,14E) \text{ isomer}] 0.60 \quad [3H, d, J 6.8, \text{CH(CH}_3{\text{enol}}], 0.69 \quad [15H, m, \text{CH(CH}_3{\text{enol}}, \text{CH(CH}_3{\text{a+b and CH(CH}_3{\text{a+b}}}], 0.85 \quad (9H, m, \text{8-CH}_3{\text{enol and 8-CH}_3{\text{a+b}, 0.94 \quad (9H, m, \text{6-CH}_3{\text{enol and 6-CH}_3{\text{a+b}, 0.98 \quad (3H, m, 7-H^\text{enol and 7-H^\text{a+b}, 1.27 \quad (3H, m, 7-H^\text{enol and 7-H^\text{a+b}, 1.39 \quad (2H, m, 6'-H^\text{a+b}, 1.60 \quad (9H, d, \quad J 7.0, 15-CH}_3{\text{enol and 15-CH}_3{\text{a+b}, 1.71 \quad (21H, m, 14-CH}_3{\text{enol}, \quad 14-CH}_3{\text{a+b, 10-CH}_3{\text{enol}, \quad 10-CH}_3{\text{a+b, 8-H^\text{enol and 8-H^\text{a+b}, 1.89 \quad (3H, m, 3-H^\text{enol and 3-H^\text{a+b}, 2.06 \quad (6H, m, 9-H^\text{enol, 9-H^\text{a+b, 3-H^\text{enol and 3-H^\text{a+b, 2.16 \quad (3H, m, 6-H^\text{enol and 6-H^\text{a+b, 2.28 \quad (9H, m, 9-H^\text{enol, 9-H^\text{a+b, 2-H}_2^\text{enol and 2-H}_2^\text{a+b}, 2.36 \quad [3H, m, \quad \text{CH(CH}_3{\text{enol and CH(CH}_3{\text{a+b}, 2.48 \quad (3H, m, 6'-H^\text{enol and 6'-H^\text{a+b, 2.89 \quad (1H, t, J 9.6, 2'-H^\text{a}, 2.94 \quad (1H, m, 6'-H^\text{enol, 3.24 \quad (1H, dd, J 9.6, 7.7, 2'-H^\text{a}, 4.10 \quad (1H, m, 5'-H^\text{a}, 4.42 \quad (2H, m, 5'-H^\text{a} and 5'-H^\text{enol, 5.21 \quad (3H, m, 5-H^\text{enol and 5-H^\text{a+b, 5.32 \quad (3H, m, 4-H^\text{enol and 4-H^\text{a+b, 5.52 \quad (3H, q, J 7.0, 15-H^\text{enol and 15-H^\text{a+b, 6.04 \quad (3H, d, J 10.7, 11-H^\text{enol and 11-H^\text{a+b}, 6.33 \quad (3H, d, J 15.1, 13-H^\text{enol and 13-H^\text{a+b, 6.51 \quad (3H, m, 12-H^\text{enol and 12-H^\text{a+b, 7.09 \quad (9H, m, Ar), 7.65 \quad (2H, m, Ar), 7.76 \quad (4H, m, Ar) and 12.29 \quad (1H, s, 1-OH^\text{enol}, [\text{visible peaks for (10E,12Z,14E) isomer}] 5.65 \quad (2H, q, J 7.0, 15-H^\text{a+b}, 5.90 \quad (2H, d, J 11.8, 11-H^\text{a+b}, 6.22 \quad (1H, t, J 11.6, 12-H^a) and 6.23 \quad (1H, t, J 11.6, 12-H^b), \quad [\text{visible peaks for (10E,12E,14Z) isomer}] 6.09 \quad (2H, d, J 10.8, 11-H^\text{a+b}, 6.59 \quad (1H, dd, J 15.4, 10.8, 12-H^b), 6.63 \quad (1H, dd, J 15.4, 10.8, 12-H^b) and 6.72 \quad (2H, d, J 15.4, 13-H^\text{a+b,}\quad \delta_C \quad (100\text{MHz, C}_6\text{D}_6) \quad [(10E,12E,14E) \text{ isomer only, with enol and epimer a+b peaks that were visible}] 12.6, 12.6, 14.4, 15.0, 15.1, 15.9, 17.1, 17.1, 18.7, 18.7, 19.0, 19.4, 19.4, 20.0, 20.1, 20.2, 20.3, 21.1, 21.1, 22.4, 27.0, 27.8, 29.1, 29.2, 29.3, 29.8, 33.8, 35.2, 35.2, 35.3, 43.2, 43.7, 44.9, 45.0, 49.4, 49.4, 55.3, 56.3, 60.0, 60.0, 60.5, 100.3, 123.2, 123.2, 123.3, 126.6, 126.6, 126.7, 127.4, 127.6, 128.2, 128.6, 129.9, 130.1, 130.6, 132.2, 132.4, 133.0, 135.3, 135.7, 135.8, 135.8, 136.3, 136.5, 136.5, 136.7, 136.7, 137.0, 137.8, 138.2, 170.8, 170.8, 171.1, 171.4, 171.6, 171.7, 202.7 and 203.1; m/z (ES+) 518 (M}^+ + 1, 100%).

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(5'R)-benzoyl-5'-isopropyl-2'-(phenylselanyl)-2'-(4E,6R,8S,10E,12E,14E)-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoyl)pyrrolidin-3'-one 282

To a -78°C solution of oxopyrrolidine 281 (0.573 g, 1.11 mmol) in THF (18 ml) was added a -78°C solution of LiHMDS (1.0M in THF) (0.203 g, 1.22 mmol, 1.22 ml), with subsequent stirring at -78°C for 30 min. This was then followed by the addition of a solution of PhSeCl (0.234 g, 1.22 mmol) in THF (6 ml), with further stirring at -78°C for 2.5 h. To the reaction mixture was then added sat. aq. NaHCO₃ (50 ml), which was then allowed to warm to r.t. before the addition of sat. aq. NaHCO₃ (50 ml). The aqueous layer was then separated from the organic layer and subsequently washed with Et₂O (4 x 200 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a light yellow liquid (0.962 g). Column chromatography (SiO₂, 1 : 10 Et₂O : pet. ether) gave the title compound as a clear liquid in a (10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 76 : 3 : 21 ratio, with all isomers being displayed as a mix. of epimers at C(2') with the epimers having an a : b = 1 : 0.4 ratio (0.687 g, 92%).

Rₜ = 0.37 (1 : 4, Et₂O : pet. ether); [α]D²⁸ +192.7 (c 0.6, C₆H₆); (Found M⁺ + Na, 696.2939. C₄₀H₇₁NO₃SeNa requires 696.2927); ν max / cm⁻¹ 2959, 2912, 2360 1725, 1686, 1600, 1438, 1362, 1273, 1235, 1177, 1130, 1105, 1022, 1000, 960, 890, 798, 740, 691 and 652; δH (400MHz, C₆D₆) [(10E,12E,14E) isomer] 0.54 [3H, d, J 6.9, CH(CH₃)²], 0.55 [1.2H, d, J 6.8, CH(CH₃)³], 0.57 [1.2H, d, J 7.0, CH(CH₃)⁴], 0.58 [3H, d, J 6.8, CH(CH₃)⁵], 0.85 (1.2H, d, J 6.6, 8-CH₃), 0.87 (3H, d, J 6.5, 8-CH₃), 0.92 (1.2H, d, J 6.6, 6-CH₃), 0.95 (3H, d, J 6.6, 6-CH₃), 0.99 (1.4H, m, 7-Hₗ and 7-Hₗ), 1.26 (0.4H, m, 7-Hₗ), 1.29 (1.2H, m, 7-CH₃), 1.60 (4.2H, d, J 6.9, 15-CH₃ and 15-CH₃), 1.72 (9.8H, m, 14-CH₃, 14-CH₃, 10-CH₃, 10-CH₃, 8-CH₃ and 8-CH₃), 1.86 (2.4H, m, 9-Hₗ, 9-Hₗ and 6'-Hₗ), 1.99 (0.4H, dd, J 13.9, 8.9, 6'-Hₗ), 2.05 (1.4H, m, 9-Hₗ and 9-Hₗ), 2.18 (1.4H, m, 6-Hₗ and 6-Hₗ), 2.31 (0.8H, m, 3-H₂), 2.50 (4.4H, m, 6'-Hₗ, CH(CH₃)₃, CH(CH₃)₃ and 3-H₂), 2.85 (0.4H, m, 2-Hₗ), 2.88 (0.4H,
concentrated under reduced pressure but was instead introduced into the next reaction. Dried (Na\textsubscript{2}SO\textsubscript{4}) bath and allowed to warm up to 0°C stirring at 0°C. 171.6, 171.7 (1H, dd, J 11.0, 11-H\textsuperscript{a} and 11-H\textsuperscript{b}), 136.5, 137.0, 137.1 (1H, d, J 11.9, 12-H\textsuperscript{a}, 12.6, 13.6, 14.2, 14.4, 15.1, 15.3, 16.7, 17.1, 18.5, 18.6, 20.1, 20.2, 21.1, 22.3, 27.1, 27.1, 27.3, 27.6, 28.3, 28.3, 29.2, 29.2, 35.1, 35.2, 39.1, 39.6, 45.0, 45.1, 49.4, 49.4, 58.8, 60.6, 60.9, 61.9, 123.3, 123.4, 126.5, 126.6, 127.1, 127.9, 129.4, 129.5, 129.8, 129.9, 130.4, 130.5, 130.7, 130.7, 133.0, 133.3, 135.0, 135.3, 135.8, 135.9, 136.5, 136.5, 137.0, 137.1, 137.8, 137.8, 138.0, 138.0, 138.0, 138.1, 138.2, 171.4, 171.5, 171.6, 171.7, 200.4 and 201.7; m/z (ES+) 691 (M\textsuperscript{+} + 18, 100%).

(S)-4’-benzoyl-5’-isopropyl-2’-((4E,6R,8S,10E,12E,14E)6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoyl)-6’H-pyrrol-3’(5’H)-one 243

To a -48°C solution of selenide 282 (0.402 g, 0.597 mmol) in CHCl\textsubscript{3} (40 ml) was added a 0°C solution of H\textsubscript{2}O\textsubscript{2} (30%) (0.710 g, 6.27 mmol) in H\textsubscript{2}O (5 ml) and then a 0°C solution of m-CPBA (77%) (0.161 g, 0.716 mmol) in CDCl\textsubscript{3} (18 ml), with further stirring at -48°C for 50 min. The reaction mixture was then removed from the -48°C bath and allowed to warm up to 0°C over the period of 10 min with vigorous stirring. This was then followed by the addition of 0°C CDCl\textsubscript{3} (30 ml) and sequential washing with 0°C sat. aq. Na\textsubscript{2}CO\textsubscript{3} (20 ml x 2) and 0°C H\textsubscript{2}O (20 ml). The organic layer was then dried (Na\textsubscript{2}SO\textsubscript{4}) and, due to the reactivity of the product, the solution was not concentrated under reduced pressure but was instead introduced into the next reaction.
The solution of pyrrolinone 243 in CDCl$_3$ (90 ml) was introduced into toluene (400 ml) which had been degassed for 1h at 40°C. This was then followed by further degassing of the solution for 30 min at 40°C, which was then subsequently refluxed at 90°C for 10 h. The reaction mixture was then concentrated under reduced pressure to afford the product as a light yellow liquid (0.311 g). Column chromatography (SiO$_2$, 1 : 15 Et$_2$O : pet. ether followed by 1 : 80 Et$_2$O : pet. ether) gave the title compounds as a clear liquid in a (exo 13E : endo 13E = 5 : 4) ratio, which were inseparable by column chromatography (0.034 g, 11%). The other title compounds were seen as a clear liquid in a (exo 13Z : endo 13Z = 5 : 4) ratio, which were inseparable by column chromatography (0.038 g, 12%). Mixed fractions of the title compounds exo 13E, endo 13E, exo 13Z and endo 13Z were seen as an off white liquid (0.005 g, 2%).
To a r.t. solution of Diels-Alder exo NH 13Z-285 and endo NH 13Z-286 adducts (0.026 g, 0.050 mmol) in MeOH (1.4 ml) was added a solution of NaOH (0.033 g, 0.82 mmol) in MeOH (1.4 ml)/H₂O (0.05 ml), with subsequent stirring at r.t. for 3 h. To the reaction mixture was then added H₂O (10 ml) followed by washing with Et₂O (15 ml x 4). The combined organic layers were then washed with brine (10 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford the product as a clear liquid (0.020 g). Column chromatography (SiO₂, 1 : 4 Et₂O : pet. ether) gave the title compound exo 13Z as a clear liquid (0.008 g, 38%).

Rf = 0.28 (2 : 1, Et₂O : pet. ether); (Found M⁺ + H, 412.3219. C₂₇H₄₂NO₂ requires 412.3211); νmax/cm⁻¹ 3211, 2957, 2866, 2360, 1693, 1455, 1386, 1284, 1260, 1117, 972, 910, 800, 732, 667 and 648; δH (500MHz, CDCl₃) 0.83 [3H, d, J 6.6, 10-CH(C₃H₃)], 0.94 (3H, d, J 6.9, 16-CH₃), 0.96 (3H, d, J 6.9, 18-CH₃), 0.99 [3H, d, J 6.6, 10-CH(CH₃)₂], 1.02 (1H, ddd, J 13.4, 8.4, 2.4, 17-H), 1.21 (3H, d, J 7.3, 11-CH₃), 1.31 (1H, m, 17-H'), 1.41 [2H, m, 16-H and 10-CH(CH₃)₂], 1.66 (1H, m, 15-H), 1.69 (3H, s, 14-CH₃), 1.70 (3H, s, 12-CH₃), 1.85 (2H, m, 18-H and 15-H'), 1.96 (2H, m, 21-H and 5-H), 2.45 (1H, m, 21-H'), 2.58 (1H, ddd, J 19.5, 5.7, 2.2, 22-H), 2.70 (1H, d, J 8.9, 3-H), 2.85 (1H, ddd, J 19.5, 12.2, 2.4, 22-H'), 2.86 (1H, dd, J 4.1, 1.8, 4-H), 3.76 (1H, dd, J 9.5, 6.2, 8-H), 4.81 (1H, d, J 9.5, 13-H), 5.37 (2H, m, 20-H and 7-H), 5.52 (1H, dd, J 15.8, 7.4, 19-H) and 5.94 (1H, br s, 2-NH); δC (125MHz, CDCl₃) 16.7, 19.1, 19.4, 20.7, 22.2, 22.4, 23.8, 24.5, 30.5, 32.5, 34.8, 38.8, 39.6, 40.8, 44.5, 46.9, 48.9, 63.8, 68.6, 122.4, 122.7, 126.5, 136.2, 137.5, 137.8, 175.8 and 206.3; m/z (ES+) 434 (M⁺ + 23, 100%).

The other title compound endo 13Z was seen as a clear liquid (0.006 g, 29%).
$R_f = 0.53$ (2 : 1, Et$_2$O : pet. ether); (Found M$^+$ + H, 412.3213. C$_{27}$H$_{32}$NO$_2$ requires 412.3211); $v_{max}/\text{cm}^{-1}$ 3201, 2960, 2916, 2364, 1688, 1457, 1384, 1338, 1306, 1223, 1144, 1098, 970, 909 and 733; $\delta_H$ (500MHz, CDCl$_3$) 0.94 [14H, m, 18-CH$_3$, 17-$H$, 16-CH$_3$, 10-CH(CH$_3$) and 10-CH(CH$_3$')], 1.15 (3H, d, J 7.2, 11-CH$_3$), 1.29 (1H, m, 17-$H'$), 1.62 [1H, m, 10-CH(CH$_3$)$_2$], 1.66 (3H, d, J 1.3, 14-CH$_3$), 1.74 (5H, m, 18-$H$, 15-$H$ and 12-CH$_3$), 1.90 (1H, m, 15-$H'$), 2.10 (1H, m, 21-$H$), 2.27 (1H, ddd, J 16.1, 6.0, 2.5, 22-$H$), 2.29 (1H, m, 4-$H$), 2.56 (2H, m, 21-$H'$ and 5-$H$), 2.88 (1H, t, J 4.4, 3-$H$), 3.04 (1H, ddd, J 16.1, 12.1, 2.4, 22-$H'$), 3.72 (1H, d, J 10.4, 8-$H$), 5.32 (1H, dt, J 15.8, 6.1, 20-$H$), 5.43 (1H, br s, 7-$H$), 5.49 (1H, dd, J 15.8, 6.2, 19-$H$), 5.62 (1H, d, J 10.4, 13-$H$) and 6.02 (1H, s, 2-NH); $\delta_C$ (125MHz, CDCl$_3$) 14.5, 16.7, 16.9, 20.1, 20.7, 22.3, 23.5, 26.4, 30.9, 33.5, 34.4, 34.6, 38.4, 39.1, 45.4, 49.1, 51.4, 59.8, 67.1, 123.5, 125.4, 127.7, 135.9, 136.9, 138.1, 176.1 and 209.3; $m/z$ (ES$^+$) 434 (M$^+$ + 23, 100%) and 412 (M$^+$ + 1, 47%).

Mixed fractions of the title compounds exo 13Z and endo 13Z were seen as an off white liquid (0.002 g, 9%).

(3S,4R,5R,6E,8R,10S,13E,16S,18R,19E)-3-isopropyl-5,6,8,14,16,18-pentamethylcyclotrideca[15,3,0]isoindole-1,23dione 272 and

(3S,4R,5S,6E,8S,10S,13E,16S,18R,19E)-3-isopropyl-5,6,8,14,16,18-pentamethylcyclotrideca[15,3,0]isoindole-1,23 dione 273

To a r.t. solution of Diels-Alder exo NH 13E-283 and endo NH13E-284 adducts (0.024 g, 0.047 mmol) in MeOH (1.4 ml) was added a solution of NaOH (0.038 g, 0.94 mmol) in MeOH (1.4 ml)/H$_2$O (0.05 ml), with subsequent stirring at r.t. for 3 h. To the reaction mixture was then added H$_2$O (10 ml) followed by washing with Et$_2$O (15 ml x 4). The combined organic layers were then washed with brine (10 ml), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the product as a clear liquid (0.018 g). Column chromatography (SiO$_2$, 1 : 4 Et$_2$O : pet. ether) gave the title compound exo 13E as a clear liquid (0.006 g, 32%).

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\[ R_f = 0.33 \ (2 : 1, \text{Et}_2\text{O} : \text{pet. ether}); \ (\text{Found M}^+ + \text{H}, 412.3222. \ C_{27}H_{42}NO_2 \text{ requires 412.3211}); \ v_{\max}/\text{cm}^{-1} \ 3205, 2957, 2914, 2869, 2360, 2341, 2247, 1691, 1455, 1376, 1287, 1260, 1153, 1101, 1047, 1000, 968, 907, 811, 728 \text{ and 646}; \ \delta_H (500\text{MHz, CDCl}_3) \ 0.83 \ [3\text{H}, d, J 6.6, 10-\text{CH(CH}_3)] , \ 0.86 \ (3\text{H}, d, J 6.4, 16-\text{CH}_3) , \ 0.92 \ (3\text{H}, d, J 6.9, 18-\text{CH}_3) , \ 0.95 \ (1\text{H}, m, 17-H) , \ 1.00 \ [3\text{H}, d, J 6.6, 10-\text{CH(CH}_3')] , \ 1.18 \ (3\text{H}, d, J 7.3, 11-\text{CH}_3) , \ 1.31 \ [3\text{H}, m, 17'-H', 16-H \text{ and 10-CH(CH}_3) _2] , \ 1.39 \ (1\text{H}, m, 15-H) , \ 1.67 \ (3\text{H}, s, 12-\text{CH}_3) , \ 1.80 \ (3\text{H}, d, J 1.3, 14-\text{CH}_3) , \ 1.94 \ (4\text{H}, m, 21-H, 18-H, 15-H' \text{ and 5-H}) , \ 2.37 \ (1\text{H}, m, 21'-H') , \ 2.57 \ (1\text{H}, ddd, J 19.6, 5.0, 2.2, 22-H'), \ 2.64 \ (1\text{H}, d, J 9.5, 3-H) , \ 2.89 \ (1\text{H}, ddd, J 19.6, 12.5, 2.6, 22-H') , \ 3.02 \ (1\text{H}, dd, J 3.0, 1.4, 4-H) , \ 3.77 \ (1\text{H}, dd, J 9.4, 6.4, 8-H) , \ 4.84 \ (1\text{H}, dt, J 9.4, 1.3, 13-H) , \ 5.37 \ (2\text{H}, m, 20-H \text{ and 19-H}) , \ 5.45 \ (1\text{H}, d, J 6.4, 7-H) \text{ and } 5.93 \ (1\text{H}, s, 2-NH); \ \delta_C (125\text{MHz, CDCl}_3) 19.4, 19.5, 20.6, 21.8, 22.3, 22.6, 24.3, 30.3, 32.2, 34.0, 35.0, 37.2, 40.0, 41.5, 43.2, 44.0, 46.1, 63.7, 70.1, 121.4, 125.0, 127.5, 136.5, 137.0, 137.5, 175.7 \text{ and 206.0}; \ m/z (\text{ES+}) 434 (\text{M}^+ + 23, 72\% ) \text{ and } 412 (\text{M}^+ + 1, 100\%).

The other title compound endo 13E + unknown isomer = 5 : 2 ratio, was seen as a clear liquid (0.002 g, 11\%).

Mixed fractions of the title compounds exo 13Z and endo 13Z were seen as an off white liquid (0.006 g, 32\%).
5.0 References

8. Dictionary of Natural Products on DVD, version 18:1, CRC Press; Hampden Data Services Ltd.


Figure 6.1: \(^1\)H NMR of ester 228
Figure 6.2: $^1H$ NMR of isoindolone 268
Figure 6.3: $^1$H-NMR of the exo NH 13E-272 Diels-Alder adduct
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Table 6.1: 1-D nOe studies on exo NH 13E-272 Diels-Alder adduct
Figure 6.4: $^1$H-NMR of the exo NH 13Z-287 Diels-Alder adduct
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**Table 6.2:** 1-D nOe studies on exo 13Z-287 Diels-Alder adduct
Figure 6.5: $^1$H-NMR of the endo NH 13Z-288 Diels-Alder adduct
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**Table 6.3: 1-D nOe studies on endo NH 13Z-288 Diels-Alder adduct**