Biomimetic Total Synthesis of Resorcylate Natural Products via a Decarboxylative, Allyl Migration and Aromatisation Sequence

A thesis submitted by

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In partial fulfilment of the requirements for the degree of

Doctor of Philosophy

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Declaration of Originality

I, Katie Elizabeth Anderson, certify that the research described in this manuscript was undertaken under the supervision of Professor Anthony G. M. Barrett, Imperial College London, and is my own unaided work unless otherwise stated within the manuscript.

Katie Elizabeth Anderson

8th July 2013, London
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Abstract

Angelico A (I), angelicoin B (II), cristatic acid (III) and grifolic acid (IV) (Figure A1) are members of the resorcylate family of natural products which contain a common 6-alkyl-2,4-dihydroxy benzoic acid core (β-resorcylate unit).

Figure A1

The total syntheses of angelicoin A (I) and angelicoin B (II) from 2,2,6-trimethyl-4H-1,3-dioxin-4-one V are reported using late stage aromatisation reactions via diketodioxinones as advanced intermediates. In the case of angelicoin A (I), biomimetic aromatisation was coupled with a highly regioselective palladium(0)-catalysed decarboxylative prenyl migration as the key step (Scheme A1).

Scheme A1

The palladium(0)-catalysed decarboxylative, prenylation and aromatisation sequence furnished both linear VII and branched adducts VI. Extensive optimisation of conditions to improve the ratio of linear to branched adducts involved the screening of palladium catalysts, ligands, solvents, reactions times, temperature and organic and inorganic bases.

The regioselectivity of this novel palladium(0)-catalysed decarboxylative prenyl migration was determined unambiguously through X-ray crystallographic studies. Furthermore, an intermolecular mechanism is proposed after thorough mechanistic studies.
including cross over and variable concentration experiments, base studies, and regioselectivity investigations.

Two synthetic approaches towards the total synthesis of cristatic acid methyl ester are reported. The first approach investigated a one-pot reaction to install the furan moiety \textbf{VIII} (Scheme A2), \textit{via} a Nef reaction, deprotection, decarboxylation and furan formation.

![Scheme A2](image)

The second approach attempted to perform a one-pot Pd(0)-decarboxylative allylation, TMSE deprotection and aromatisation to provide the core of cristatic acid \textbf{IX} (Scheme A3).

![Scheme A3](image)

Finally, studies towards the total synthesis of grifolic acid (\textbf{IV}) are reported utilising the palladium(0)-catalysed decarboxylative allyl migration and aromatisation sequence.

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Abbreviations

Δ  delta; change in; heat to reflux
δ  chemical shift
(−)  rotates a plane of light clockwise
(+)  rotates a plane of light anti-clockwise
° C  degrees Celsius
Å  Angström; bond lengths (X-ray Crystallography)
AAA  asymmetric allylic alkylation
Anal.  analytical
app.  apparent
aq.  aqueous
Ar  aromatic
ATP  adenosine triphosphate
B  base
BINAP  2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn  benzyl
Bpy  2,2’-bipyridine
br.  broad
Bt  benzotriazole
calc.  calculated
CAN  ceric ammonium nitrate
cat.  catalytic
CDI  1,1'-carbonyldiimidazole
CDK  cyclin-dependent kinase
Cl  chemical ionisation
cm⁻¹  reciprocal centimetre
COD  1,5-cyclooctadiene
conc.  concentration
COSY  correlation spectroscopy
Cp  cyclopentadienyl
d  doublet
d₆  deuterated
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIOP</td>
<td>2,3-(O)-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>DIPEA</td>
<td>(N,N)-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxylethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMI</td>
<td>1,3-dimethyl-2-imidazolidinone</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1(H))-pyrimidinone</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulphoxide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1(^{-})-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>DTBP</td>
<td>di-(\text{tert})-butyl peroxide</td>
</tr>
<tr>
<td>DUPHOS</td>
<td>1,2-bis((2R,5R)-2,5)-diisopropylphospholano)benzene</td>
</tr>
<tr>
<td>E</td>
<td>(\text{entgegen}) (on opposite sides)</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>et al.</td>
<td>\textit{et alii} (and others)</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectroscopy</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>GPR</td>
<td>G- protein coupled receptor</td>
</tr>
<tr>
<td>GSK3</td>
<td>glycogen synthase kinase 3</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HBTU</td>
<td>(O)-benzotriazole-(N,N,N',N')-tetramethyl-uronium-hexafluoro-phosphate</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HSP90</td>
<td>Heat Shock Protein 90</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum correlation</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner Wadsworth Emmons</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant (in NMR)</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropanolamine</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m</td>
<td>milli; multiplet (NMR spectroscopy); metre; medium (IR spectroscopy); meta</td>
</tr>
<tr>
<td>M</td>
<td>molarity; Mega</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MAP</td>
<td>mitogen-activated protein</td>
</tr>
<tr>
<td>M-CoA</td>
<td>malonyl coenzyme A</td>
</tr>
<tr>
<td>$m$-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Mes</td>
<td>mesitylene</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxy methyl ether</td>
</tr>
<tr>
<td>MOP</td>
<td>2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy; molecular sieves</td>
</tr>
<tr>
<td>MsCl</td>
<td>methanesulphonyl chloride</td>
</tr>
<tr>
<td>n</td>
<td>nano</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>tris(dibenzylideneacetone)dipalladium(0)</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>pH</td>
<td>measure of the activity of the (solvated) hydrogen ion</td>
</tr>
<tr>
<td>PHOX</td>
<td>phosphinothiazolines</td>
</tr>
<tr>
<td>pKa</td>
<td>acid dissociation constant at logarithmic scale</td>
</tr>
</tbody>
</table>
PMB  $p$-methoxybenzyl ether
ppm  parst per million
Pr  prenyl
py  pyridine
QUINAP  1-(2-diphenylphosphino-1-naphthyl)isoquinoline
$R$  *rectus* (clockwise rotation in descending order of priority)
RALs  resorcylic acid lactones
RBR  Ramburg Bäcklund Reaction
RCM  ring closing metathesis
$Re$  *Re* face (leading to ($R$) stereocentre)
Red-Al  sodium bis(2-methoxyethoxy)aluminium hydride
$R_f$  retention factor
Rochelle’s salt  potassium sodium tartrate
RSM  residual starting material
rt  room temperature
s  second; single (NMR spectroscopy); strong (IR spectroscopy)
$S$  *sinister* (anticlockwise rotation in descending order of priority)
SEM  2-(trimethylsilyl)ethoxymethyl ether
sh.  sharp
$Si$  *Si* face (leading to ($S$) stereocentre)
soln.  solution
t  triplet; time; *tert*
TBAF  tetra-*$n$-butylammonium fluoride
TBDPS  *tert*-butyldiphenylsilyl ether
TBS  *tert*-butyldimethylsilyl ether
TES  triethylsilyl ether
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl ether
TLC  thin layer chromatography
TMEDA  tetramethylethylenediamine
TMS  trimethylsilyl ether
TMSE  2-(trimethylsilyl)ethyl ether
TsOH  $p$-toluenesulfonic acid
UV  ultraviolet
$v_{\text{max}}$  strong and selected absorbances (in IR)
w  weak
wt. %  weight percentage
Z  \textit{Zusammen} (on the same side)
$\alpha$  alpha
$\beta$  beta
$\gamma$  gamma
1 Introduction

1.1 Resorcylic Acid Lactones (RALs)

Resorcylic Acid Lactones (RALs) are polyketide natural products which contain a common β-resorcylate unit 1\[^1\] (Figure 1). RALs have been known for decades since the isolation of radicicol (2) in 1953,\[^2\] followed by zearalenone (3) in 1962.\[^3\][\[^4\][

![Figure 1: Resorcylic Acid Lactones (RALs)](image)

RALs can vary widely in their structure, for example radicicol (2),\[^2\] zearalenone (3)\[^3\][\[^4\]] and aigialomycin D (4)\[^5\] contain the β-resorcylate unit 1, fused to a macrocyclic ring.\[^1\] While cristatic acid (5),\[^6\][\[^7\]] angelicin A (6),\[^8\][\[^9\]] angelicin B (7),\[^8\][\[^9\]] amorfrutin A (8)\[^10\] and
mycophenolic acid (9)\textsuperscript{[11]} contain the $\beta$-resorcylate unit 1 attached to terpenoid-like moieties. The resorcylate family of natural products have served as synthetic testing grounds for novel and elegant methodologies from academic groups for over the past 50 years (see Section 1.4 below).\textsuperscript{[12]} Additionally, the pharmaceutical industry\textsuperscript{[13][14]} (see Section 1.3 below for more information regarding mycophenolic acid (9)) have shown a great interest in the resorcylate family of natural products due to their wide array of biological properties (Figure 1).\textsuperscript{[15][16][17]}

1.2 Biological Properties of RALs

The RAL family of natural products portray a high diversity of biological properties. Radicicol (2) isolated from 	extit{Humicola fuscoatrais}\textsuperscript{[2]} is a potent and selective inhibitor of Heat Shock Protein 90 (HSP90).\textsuperscript{[18]} HSP90 is upregulated in cancer cells and radicicol (2) is a competitive ligand for the ATP binding site.\textsuperscript{[17]} Some RALs such as radicicol (2) also inhibit MAP kinases (MAP kinases regulate a cell’s response to its environment).\textsuperscript{[16]}

Aigialomycin D (4), isolated in 2002 from mangrove fungus 	extit{Aigialus parvus} BCC 5311\textsuperscript{[5]} has moderate antimalarial activity (low μM) but is also cytotoxic at similar concentrations.\textsuperscript{[5][16]} Additionally, it shows moderate kinase inhibition (low μM) of CDK1, CDK5 and GSK3.\textsuperscript{[19][20]} Zearaleone (3) isolated from 	extit{Fusarium graminearum}\textsuperscript{[3][4]} has estrogen agonistic properties and the macrocycle is able to adopt a conformation which mimics one of a steroid.\textsuperscript{[14][16]}

Angelicoin A (6) and angelicoin B (7) were isolated from the roots of the herb 	extit{Pleurospermum angelicoides}, found in the Himalayan mountains, in 2006 by Baba et al.\textsuperscript{[9]} The roots are used locally in Chinese medicine to treat typhoid and dysentery.\textsuperscript{[8]} Amorfrutin A (8) was isolated in 1981 by Mitscher et al., from the ethanolic extracts of the shrub 	extit{Amorpha...
1. Introduction

*fruticosa* originating in North America, China and Korea. Amorfrutin A (8) exhibits narrow spectrum antimicrobial activity against Gram-positive and acid-fast microorganisms.

Cristatic acid (5) was isolated in 1981 by Steglich *et al.* from the mushroom *Albatrellus cristatus*. It has been shown to have antibiotic activity against gram-positive bacteria, haemolytic function and to have an inhibitory effect on the Ehrlich carcinoma.

1.3 Mycophenolic Acid (9)

Mycophenolic acid (9) (Figure 1) was originally discovered in 1893 by Bartolomeo Gosio and utilised as an antibiotic treatment against *Bacillus anthracis*. Subsequently, it has been shown to possess many valuable biological properties such as antiviral, antifungal, antibacterial, antitumour and antipsoriasis. It is famously regarded as an immunosuppressant in kidney, heart and liver transplants and is currently marketed under two brands CellCept™ (Mycophenolate Mofitil) by Roche and Myfortic™ (Mycophenolate Sodium) by Novartis.

CellCept™ and Myfortic™ work by inhibiting IMPDH (Inosine Monophosphate Dehydrogenase) in purine biosynthesis which is necessary for the growth of T and B cells. Suppressing these cells reduces the risk of organ rejection following a transplant. However, suppression also weakens the body’s ability to defend against infection. Myfortic™ and CellCept™ can also be used in the treatment of autoimmune diseases, such as systemic lupus erythematosus and pemphigus vulgaris. Mycophenolic acid (9) exemplifies how valuable some resorcylate natural products can be within the pharmaceutical industry.
1 Introduction

1.4 Total Syntheses of RALs

1.4.1 Danishefsky’s Approach to Cycloproparadicol (10)

Danishefsky et al. published the total synthesis of cycloproparadicol (10) in 2004, utilising a Diels-Alder reaction to put in place the resorcylate core 11. The Diels-Alder reaction took place between cyclic diene 12 and ynolide 13 (Scheme 2).

The synthesis of ynolide 13 is shown below in Scheme 1. Ring Closing Metathesis (RCM) was unsuccessful under standard conditions, presumably due to the presence of the acetylene (owing to its linear form thus preventing cyclisation). Danishefsky et al. employed dicobalt to act as a protecting group for the alkyne 14 enabling the correct geometry to facilitate cyclisation. Complexion of dicobalt afforded complex 15, RCM followed by decomplexation then furnished macrocycle 13 in 50% yield over 2 steps. The next step in the synthesis involved the Diels-Alder reaction between ynolide 13 and cyclic diene 12 (Scheme 2).

![Scheme 1: Synthetic Route to Ynolide 13](image)

Heating ynolide 13 and cyclic diene 12 facilitated a Diels-Alder reaction; this was followed by selective desilylation of the TMS groups by silica gel chromatography, providing
resorcylate 11 in an excellent 78% yield. The final steps in the total synthesis are illustrated below in Scheme 3.

Scheme 2: Diels-Alder Reaction of Ynolide 13 with Cyclic Diene 12

It was necessary to protect the two phenolic groups as acetates 16 in order to enable oxidation of the secondary alcohol to a ketone. Thus, following phenolic protection, silylether 16 was deprotected permitting oxidation of the secondary alcohol to a ketone. The acetates were then deprotected, chlorination followed furnishing cycloproparadicicol (10) in a 70% yield. This synthesis exhibits two excellent methodologies which enabled gram quantities of cycloproparadicicol (10) to be produced for biological testing.

Scheme 3: Final Steps in the Synthesis of Cycloproparadicicol (10)

The synthetic route exemplifies the excellent targets that RALs can be to academic groups. This is shown again in the total synthesis of aigialolmycin D (4) by Harvery et al. (Section 1.4.2).
1.4.2 Harvey’s Approach to Aigialomycin D (4)

Harvey et al. published the total synthesis of aigialomycin D (4) in 2008.\textsuperscript{[31]} Two of the key steps in the total synthesis, RCM and a Ramburg-Bäcklund reaction (RBR) are shown below in Scheme 4.

Esterification between alcohol 17 and carboxylic acid 18 was accomplished utilising Mitsunobu conditions and provided ester 19 in a 94% yield. Oxidation of the sulphur moiety afforded sulphone 20 and RCM furnished macrocycle 21 in an 86% yield. A RBR was then performed which enabled the formation of olefin 22. Finally, deprotection afforded aigialomycin D (4).\textsuperscript{[31]}

Scheme 4: Synthesis of Aigialomycin D (4)\textsuperscript{[31]}
1.5 Traditional Methods for the Formation of RALs

Sections 1.1 to 1.4 have discussed why RALs are excellent synthetic targets. However, most RAL syntheses begin with a preformed aromatic unit, such as resorcylic acid (23) or orseillinic acid (24) (Figure 2). The remainder of the RAL is then usually constructed onto this unit.

![Resorcylic Acid (23) and Orselinic Acid (24)](image)

**Figure 2: Resorcylic Acid (23) and Orselinic Acid (24)**

This is exemplified in the total synthesis of radicicol (2) by Danishefsky et al.\[^{[32]}\] which began with the units shown in Scheme 5. Unit 25, is derived from orseillinic acid (24) through protection of the two phenolic groups and a radical chlorination of the aromatic methyl.

![Scheme 5: Retrosynthetic Analysis of Radicicol (2)](image)

**Scheme 5: Retrosynthetic Analysis of Radicicol (2)\[^{[32]}\]**

Beginning a total synthesis with orseillinic (24) or resorcylic acid (23) is a good method, however, often requires the use of protecting groups which can prove difficult to remove at the end of the synthesis. This is evident in Danishefsky’s total synthesis of cycloproporadicol (Section 1.4.1) whereby the addition and removal of protecting groups added an extra two steps to the total synthesis.\[^{[29]}\] For these reasons, Barrett et al. have
employed a biomimetic approach for the synthesis of RALs inspired by the biosynthesis of polyketides.

1.6 The Biosynthesis of Polyketides

The biosynthesis hypothesis was first postulated in the early 20th century by Collie. Collie’s ideas were later revived and formulated by Birch in the 1960’s into the polyketide hypothesis, which is still accepted today. The biosynthesis of a polyketide chain involves a number of decarboxylative Claisen thioester condensation reactions involving malonyl coenzyme A. Further reactions and reductive chemistries furnish the RAL 26 (Scheme 6).

![Scheme 6: Biosynthesis of a Polyketide and Aromatisation to an RAL](image)

The biosynthetic pathway is catalysed by polyketide synthases which are large multidomain enzymes found in a variety of fungal strains.\cite{16}
1 Introduction

1.7 Cyclisation of Polyketides

Inspired by the biosynthesis of polyketides Barrett et al. studied the work of Harris & Harris[37] for a synthetic method to cyclise polyketides. Harris et al. demonstrated that simple polyketide metabolites could undergo cyclisations under different pHs in order to generate different aromatic heterocycles (Scheme 7).[37]

Harris et al. showed that triketoacid 27 can undergo an aldol reaction over a pH range of 4 to strongly basic. Intermediate 28 can be seen under basic conditions but aromatises quickly to form resorcyclic acid 29. Treatment of triketoacid 27 with HF under anhydrous conditions provided 4-pyrone 32 and under acetic anhydride, triketoacid 27 formed enol lactone 31 (Scheme 7).[37]

Barrett et al. were interested in the transformation of tiketoacid 27 into resorcylic acid 29. The reaction conditions were studied further and optimised, discovering that careful pH control was essential for efficient aromatisation.[38] However, it was apparent that triketoacids
were not especially stable under ambient conditions and thus would be difficult to utilise and carry through in a total synthesis. Barrett et al. therefore searched for a method to ‘protect’ the polyketide chain and were enthused by the work of Hyatt et al.\[39\]

1.8 Dioxinone in Total Synthesis

In 1984, Hyatt et al. demonstrated that under elevated temperatures dioxinone 33 performs a retro Diels-Alder reaction to generate a highly electrophilic ketene 34 which can then be trapped by a range of nucleophiles such as alcohols and amines to provide the corresponding $\beta$-keto esters or $\beta$-keto amides (Scheme 8).\[39\]

\[
\begin{align*}
\text{Scheme 8: Opening of Dioxinone 33}
\end{align*}
\]

Dioxinone 33 has been exploited in a number of total syntheses\[40\] demonstrating its practical use. For example Paquette et al. utilised dioxinone 33 in the total synthesis of (+)-ikarugamycin in 1989.\[41\] Addition of the phosphorous dioxinone 36 provided vinyl dioxinone 37. Upon heating, 37 underwent a retro Diels-Alder reaction forming a ketene enabling macrocyclisation to furnish macrocycle 38 (Scheme 9).\[41\]
1 Introduction

Scheme 9: Dioxinone 36 in the Total Synthesis of (+)-Ikarugamycin

In essence dioxinone 33 can be envisaged as a protected keto-ester which facilitates polyketide chains to be utilised and carried through in a total synthesis. Utilising the work of Birch et al., Harris et al. and Hyatt et al. the Barrett group were able to devise a biomimetic retrosynthesis for the construction of resorcylate natural products.

1.9 Retrosynthesis for the Construction of Resorcylate Natural Products

Barrett et al. established that the resorcylate core 39 could be available from aromatisation of triketo-ester 10 which could in turn be obtained from heating triketo-ketene 41 in the presence of an alcohol. Finally, triketo-ketene 41 could be afforded from diketo-dioxinone 42 by thermolysis (Scheme 10). Following studies within the Barrett group and reaction optimisation, two main routes for the synthesis of the resorcylate core were established (Section 1.10).
1 Introduction

![Image of chemical structures]

**Scheme 10: Retrosynthesis for the Construction of Resorcylate Natural Products**

1.10 Synthesis of the Resorcylate Core 39

The two routes for the synthesis of the resorcylate core 39 are shown in Scheme 11. Route A involves thermolysis of diketo-dioxinone 42 to generate ketene 41 which is then trapped with alcohol 43 to afford triketo-ester 40. Cyclisation under basic conditions furnishes ester 44, acidic mediated dehydration then affords the resorcylate core 39.\(^{[42][43]}\) Standard conditions utilised within the Barrett group for this transformation (Route A) begin by heating diketo-dioxinone 42 in toluene with the respective alcohol 43. Alternatively, this first step can take place in a sealed tube with the addition of 4 Å molecular sieves. Following consumption of diketo-dioxinone 42, the reaction mixture is concentrated by rotary evaporation and redissolved in an alcoholic solvent such as MeOH or i-PrOH. An inorganic base is then added to the solution such as CsOAc, Cs₂CO₃ or K₂CO₃ to facilitate the cyclisation. Finally, TFA, acetic acid or HCl is added into the reaction mixture to enable dehydration to take place, furnishing the resorcylate core 39.\(^{[42][43]}\)

Route B proceeds by treating diketo-dioxinone 42 with base in order to facilitate cyclisation, dehydration then occurs utilising an acidic work-up, generating an isopropylidene protected resorcylate 45 which can be further substituted to afford the resorcylate natural product.\(^{[43]}\) Standard conditions utilised in the Barrett group for Route B include stirring diketo-
dioxinone 42 in CH₂Cl₂ with Et₃N or alternatively in MeOH with Cs₂CO₃. An acidic workup then takes place in order to provide resorcylate 45.[43]

![Scheme 11: Two Synthetic Routes for the Formation of the Resorcylate Core](image)

The Barrett approach for the formation of the resorcylate core has been named the ‘Late-Stage Aromatisation Strategy.’

### 1.11 Application of the Late-Stage Aromatisation Strategy

The Barrett group have demonstrated the large applicability of the late-stage aromatisation strategy in the total synthesis of resorcylate natural products.[44] One recent example was in the total synthesis of cruentaren A (46) by Marianne Fouché (Scheme 12).[45]

The synthesis begins with heating diketo-dioxinone 47 to facilitate ketene formation and then trapping with the alcohol 48. Cyclisation under basic conditions and acid mediated dehydration afforded resorcylate 49. Methylation of phenol 49 was achieved in 82% yield and this allowed alkyne metathesis furnishing alkyne 50 in an excellent 75% yield. PMB
deprotection afforded an alcohol which underwent azide formation via a Mitsunobu reaction. Subsequent Staudinger reduction efficiently gave amine 51. Amide bond formation between amine 51 and carboxylic acid 52 was achieved using HBTU as the coupling reagent. Monocleavage of the methyl group followed by silyl ether deprotections afforded resorcylate 53. The final step in the total synthesis involved a Lindlar reduction of the alkyne to give cruentaren A (46).}[45]
Introduction

Scheme 12: Synthesis of Cruentaren A (46)
1.12 Discovery of the Decarboxylative Allyl Migration

Recently Barrett et al. reported the total synthesis of aigialomycin D (4). The approach featured a key Pd(0)-catalysed deallylation and decarboxylation of allyl ester 54, employing morpholine as a nucleophilic palladium $\pi$-allyl cation scavenger, to provide the ketene precursor. Subsequent ketene trapping, aromatisation, RCM and deprotection gave aigialomycin D (4) in a 15% overall yield (Scheme 13).

![Scheme 13: Final Steps in the Synthesis of Aigialomycin D (4)](image)

During these studies Barrett et al. observed that reaction of allyl ester 54 with Pd(PPh$_3$)$_4$ in the absence of morpholine resulted in a modified Carroll rearrangement affording diketo-dioxinone 55. Subsequent ketene trapping with alcohol 56 gave triketoester. Aldol cyclisation using caesium acetate followed by acid mediated aromatisation provided resorcylate 57 in 42% yield over 3 steps. The regiochemistry of arene 57 was confirmed by nOe analysis in the $^1$H NMR spectrum (Scheme 14).

---

Having discovered this unusual transformation it is now exploited due to the known allylated resorcylate natural products such as cristatic acid (5), amorfrutin A (8), mycophenolic acid (9) and angelicoin A (6) (Figure 3).
1.13 Decarboxylation and Allylation: The Carroll Rearrangement

The Carroll rearrangement was discovered in the 1940’s and proceeds via a [3,3]-sigmatropic rearrangement followed by decarboxylation to provide γ,β-unsaturated carbonyl compounds 58 from allylic esters of β-ketocarboxylic acids 59 (Scheme 15). The reaction requires high temperatures, strongly basic conditions and its success can depend on the electronic properties and size of the substrate.

![Scheme 15: The Carroll Rearrangement](image)

In the 1980’s Tsuji et al. and Tsuda et al. both independently discovered that the Carroll rearrangement could be catalysed by Pd (Scheme 16). This enabled the reaction to be carried out under neutral and mild conditions (typically at temperatures between 0 and 25 °C). Scheme 16 illustrates the mechanism for the Tsuji-Trost reaction. First, the π-allyl-palladium complex 60 is formed by oxidative addition, followed by decarboxylation. Subsequent intermolecular allylation gives the allylated ketone 59.

![Scheme 16: Tsuji-Trost Reaction](image)

Additionally, Tsuji demonstrated that allyl cyanoacetate 61, derivatives of dialkyl-malonates 62 and nitro ester 63 can undergo decarboxylation-allylation to give allyl α-allyl carboxylate 64, α-allyl nitrile 65 and α-alkynitro alkane 66 respectively (Scheme 17), presenting the versatility of this transformation.
More recently Trost et al. and Tunge et al. have demonstrated that this pathway can be advanced onto more complicated systems.\cite{55,56,57}

### 1.14 Asymmetric Tsuji-Trost Reaction

Until recently an asymmetric catalytic transformation for the Claisen rearrangement had not been developed, with the majority of attempts focusing on Lewis acid activation.\cite{58} In 2004, Tunge et al. reported high levels of asymmetric induction through the utilisation of nucleophilic catalysts and chiral ligands.\cite{59} The group investigated the use of Pd$_2$(dba)$_3$ and Trost’s ligand \textit{69},\cite{60} which provided high levels of enantioselectivity for cyclic and methyl-substituted allyl compounds (Table 1). (The enantioselectivity of this reaction will be discussed in Section 1.16).
1 Introduction

Table 1: Asymmetric Palladium-Catalysed Rearrangements of $R^1$COCH$_2$CO$_2$R$^{[61]}$

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Time/ h</th>
<th>ee$^a$</th>
<th>Yield/ %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td></td>
<td>15</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td></td>
<td>15</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td></td>
<td>24</td>
<td>94</td>
<td>75</td>
</tr>
</tbody>
</table>

$^a$ Measured at 25 °C.
$^b$ Isolated yield after column chromatography.

1.15 Regio- and Enantioselective Tsuji-Trost Reaction

In 2004, Trost et al. published studies on a regio- and enantioselective decarboxylative allylic alkylation of ketones through allyl enol carbonates. Table 2 below illustrates some of the optimisation studies for alkylation at the tertiary carbon.$^{[61]}$ The results demonstrated excellent regio- and enantioselectivity in the creation of quaternary stereogenic centres.
1 Introduction

Table 2: Selected Optimisation Studies[61]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>ee$^b$</th>
<th>Yield of R-67/ %$^c$</th>
<th>Yield of 68/ %$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>DME</td>
<td>66</td>
<td>81</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>DME</td>
<td>76</td>
<td>87</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Toluene</td>
<td>31</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>Toluene</td>
<td>61</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>Toluene</td>
<td>60</td>
<td>85</td>
<td>1</td>
</tr>
</tbody>
</table>

$^a$ All reactions were performed on a 0.3 mmol scale at 0.1 M.
$^b$ The ee values (in percent) were determined by chiral GC.
$^c$ The yields (in percent) were determined by quantitative GC analysis using decane as internal reference.

Scheme 18: Chiral Ligands used in Optimisation Studies[61]

Trost et al. indicated that metal catalysed allylic alkylations are slow and consequently lead to enolate equilibrium which in turn can result in a competition between polyalkylation, loss of regioselectivity and alkylation of the original enolate. Nonetheless, Trost et al. were able to control the enolate equilibrium and induce regioselectivity by maintaining neutral conditions and having a low concentration of the enolate at any given time.[61]
1.16 Counterion Effect in Asymmetric Allylic Alkylation

In 2002, Trost et al. published work on the counterion effect in a Pd-catalysed asymmetric allylic alkylation (AAA) (Table 3). Table 3 demonstrates the importance in the choice of base for the alkylation of an enolate in terms of enantioselectivity. This can be explained by the cartoons in Scheme 19 below (Scheme 19 can also be utilised to explain the asymmetric Tsuji-Trost reaction discussed in Section 1.14 as well as the decarboxylative AAA, due to the nucleophile being comparable).

Table 3: Counterion Effect in Palladium-Catalysed AAA of 1-Methyl-2-Tetralone[^62]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Ligand</th>
<th>Yield of 72/ %</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>(S,S)-69</td>
<td>90%</td>
<td>-33%</td>
</tr>
<tr>
<td>2</td>
<td>Cs$_2$CO$_3$</td>
<td>(S,S)-69</td>
<td>91%</td>
<td>+45%</td>
</tr>
<tr>
<td>3</td>
<td>Cs$_2$CO$_3$</td>
<td>(S,S)-73</td>
<td>93%</td>
<td>+90%</td>
</tr>
</tbody>
</table>

Figure 4: Ligand 73[^62]

When non-coordinating Cs$_2$CO$_3$ is the base in the reaction and with (S,S)-73 as the ligand, the enolate substrate approaches the Si face under the ‘flap’ of the ligand to avoid unfavourable steric interactions that would occur at the Re face (giving the (+)-enantiomer, Entry 3, Table 3). However, with the co-ordination of LDA the enolate enters from the Re face to avoid
disfavoured interactions between the ligand and the $i$-propyl groups on LDA (giving the (−)-enantiomer, Entry 1, Table 3). Thus enantioselectivity can be explained in this manner depending on the substrate and ligand being used in the transformation.

![Scheme 19: Cartoon Models for the Alkylation of a Charge Separated Palladium Enolate](image)

### 1.17 Enantioselective Ligand Studies

In 2004, Stoltz et al. carried out studies towards the enantioselective decarboxylation allylation reaction (Table 4) paying particular attention to the ligands used in the transformation. These studies showed that in the allylation step the phosphinoxazoline (PHOX) ligands were very good at producing enantioselectivity (Entries 7-10, Table 4).
Table 4: Results from Stoltz’s Enantioselective Ligand Screening\textsuperscript{[65]}

![Chemical Reaction Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time/ h</th>
<th>Yield of S-67/ %</th>
<th>ee/ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-Trost ligand 69</td>
<td>5</td>
<td>92</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>(R)-BINAP 74</td>
<td>5</td>
<td>76</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-Me-DUPHOS 75</td>
<td>5</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-DIOP 76</td>
<td>2</td>
<td>59</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>(R)-MOP 77</td>
<td>3</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>(R)-QUINAP 78</td>
<td>2</td>
<td>97</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>(R)-Ph-PHOX 79</td>
<td>2</td>
<td>95</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>(S)-Bn-PHOX 80</td>
<td>5</td>
<td>94</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>(R)-I-Pr-PHOX 81</td>
<td>2</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>(S)-t-Bu-PHOX 82</td>
<td>2</td>
<td>96</td>
<td>88</td>
</tr>
</tbody>
</table>

Figure 5: Ligands from Table 4\textsuperscript{[65]}
1 Introduction

1.18 Mechanistic Studies

In 2004, Tunge et al.\textsuperscript{[59]} performed mechanistic studies to establish the order of decarboxylation and allylation. Through utilisation of a quaternary $\alpha$-carbon 83, $\alpha$-deprotonation would not be possible therefore the only plausible mechanism would involve decarboxylation followed by allylation (Scheme 20). Ketoester 83 underwent Pd-catalysed decarboxylation allylation at a similar rate to other substrates (see Table 1 above) proving that decarboxylation precedes allylation.\textsuperscript{[59]}

![Scheme 20: Substrate and Reaction Conditions Utilised for Tunge’s Mechanistic Study\textsuperscript{[59]}](image)

In 2009, Stoltz et al. conducted a mechanistic study into the asymmetry of the palladium catalysed enantioselective decarboxylative allylation reactions of ketone enolates. X-ray crystal structures were obtained for the intermediates in the catalytic cycle providing evidence for the enantioselective allylic alkylation mechanism (Scheme 21).\textsuperscript{[66]}

Substrate 84 undergoes coordination to ester 85 to give complex 86 followed by oxidative addition to give carboxylate 87, \textit{(the resting state of the catalytic cycle)}. The next step is decarboxylation \textit{(the turnover limiting step of the catalytic cycle)} affording enolate 88. Finally, rapid C-C bond formation gives reductive elimination to form (S)-67 and substrate 84 which can continue the catalytic cycle by complexation with another ester 85.\textsuperscript{[66]}
1.19 Decarboxylation, Allylation and Migration

In 2011, Tunge et al. published work on a migratory decarboxylative coupling of coumarins. Scheme 22 illustrates optimised conditions for allyl ester 89\(^\text{[67]}\).

Scheme 22: Migratory Decarboxylative Allylation\(^\text{[67]}\)

Allylation usually occurs regiospecifically at the site bearing the carboxylate. Therefore when Tunge et al. discovered allylation with migration, mechanistic studies were conducted. Interestingly, it was found that allylation occurred followed by decarboxylation, which...
explained why the migration was occurring. This mechanism was deduced because carboxylic acid 90 was isolated in the reaction mixture after 2 h. The acid 90 could then be decarboxylated successfully by treatment with Pd(0) (Scheme 23).[67]

\[
\text{3 mol\% [Pd}_2\text{(dba)}_3\text{]} \quad 6 \text{ mol\% Xantphos 129} \quad \xrightarrow{\text{toluene, 70 °C, 24 h}} \quad 3 \text{ mol\% [Pd}_2\text{(dba)}_3\text{]} \quad 6 \text{ mol\% Xantphos 129},
\]

Scheme 23: Isolation of Carboxylic Acid 90 and Subsequent Decarboxylation[67]

1.20 Total Synthesis of Spirotryprostatin B via Diastereoselective Prenylation

In 2007, Trost et al. synthesised Spirotryprostatin B (91) with a related migratory decarboxylation-allylation (Scheme 24).[68] Trost et al. were able to perform a diastereoselective decarboxylative prenylation utilising Pd(0) and a phosphinooxazoline (PHOX) ligand. This work demonstrates the usefulness of the Tsuji-Trost reaction and its use in natural product synthesis. The synthesis also demonstrated that PHOX ligands could be utilised for prenyl groups, previously this ligand type had been limited to allyl or 2-substituted allyl groups.[68]
1.21 Application of the Decarboxylative Allylation and Migration Sequence

The aim of this research was to apply the Pd(0)-decarboxylative allylation migration (see Section 1.10) and the late-stage aromatisation strategy (see Section 1.12) to the total synthesis of resorcy late natural products. Figure 6 illustrates five resorcy late natural products that will be discussed and studied further throughout this thesis.

![Synthesis of Spirotryprostatin B (91)](image)

**Scheme 24: Synthesis of Spirotryprostatin B (91)**

The isolation and biological properties of amorfrutin A (8),\(^{10}\) cristatic acid (5),\(^{6,7}\) angelicoin A (6)\(^{8,9}\) and angelicoin B (7)\(^{8,9}\) were discussed in Section 1.1 above. Grifolic acid (92) was isolated in 1981 by Steglich et al. from the mushroom *Albatrellus cristatus*.\(^{6,69}\) Grifolic acid...
1 Introduction

(92) has shown GPR120 agonistic activity. The GPR120 is a G-protein-coupled receptor found within the intestinal tract and thought to play an important role in insulin release.\textsuperscript{[70]}

1.22 General Retrosynthetic Strategy

Scheme 25 below illustrates a general retrosynthetic strategy for the construction of angelicoin A (6), amorfrutin A (8), grifolic acid (92) and cristatic acid (5) (Figure 6). It was envisaged that resorcylate 93 could be obtained from aromatisation of triketo-acid 94 ($R_1^1=H$). Trapping of ketene 95 with the respective alcohol could afford triketo-acid 94. Ketene 95 could be obtained by heating diketo-dioxinone 96 under elevated temperatures to facilitate a retro Diels-Alder reaction. Finally, diketo-dioxinone 96 could be obtained following a decarboxylative allyl migration beginning with diketo-ester-dioxinone 97.

![Scheme 25: Retrosynthetic Strategy](image-url)
1 Introduction

1.23 Alternative Strategies for the Incorporation of an Allyl Moiety onto the Resorcylic Core

The retrosynthetic strategy (Scheme 25) would enable the formation of a substituted aromatic resorcylic to be completed in a four step one-pot synthesis under mild conditions. Standard conditions for the introduction of allylic moieties onto aromatic rings utilises high temperatures and strong bases. For example, in 1995, Anderson et al. published the total synthesis of mycophenolic acid (9). They utilised high temperatures to execute a [2,3]-sigmatropic rearrangement to add an allyl moiety on to the aromatic unit (Scheme 26).[71]

![Scheme 26: Addition of Allyl moiety in the synthesis of Mycophenol Acid (9)[71]](image)

In 2009, Yoshida et al. published the total synthesis of radulainin E.[72] Yoshida et al. utilised Fürstner’s procedure for the regioselective C-allylation. However, as Scheme 27 illustrates the procedure was not very reliable as two isomers 98 and 99 were obtained, nonetheless it was possible to transform 99 into 98 by heating in o-dichlorobenzene. The procedure for the incorporation of the allyl moiety also employed high temperatures and strong bases.[72]

![Scheme 27: C- Allylation in the Total Synthesis of Radulanin D][72]
1.24 Research Project Aims

The aim of this research project was to demonstrate a Pd(0)-catalysed regioselective decarboxylative, alkylation and aromatisation sequence utilising mild conditions for the synthesis of resorcylate natural products. The resorcylate natural products studied include angelicoin B (7), angelicoin A (6), cristatic acid (5), amorfrutin A (8) and grifolic acid (92) (Figure 6). Additionally, optimisation and mechanistic studies were conducted into the Pd(0)-catalysed regioselective decarboxylative-alkylation and aromatisation sequence and X-ray crystallography was utilised to verify unambiguously the novel regioselectivity.
2 The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)\textsuperscript{II}

2.1 Previous Studies for the Construction of Angelicoin B (7)

Angelicoin B (7)\textsuperscript{[8][9]} (Figure 7) was chosen as a synthetic target to demonstrate the biomimetic late-stage aromatisation strategy (see Section 1.10 of the Introduction).\textsuperscript{[42][43]}

\begin{center}
\includegraphics[width=0.25\textwidth]{fig7.png}
\end{center}

\textit{Figure 7: Angelicoin B (7)}

Previous studies, within the Barrett group, for the construction of angelicoin B (7) are illustrated below in Scheme 28.\textsuperscript{[73]} The first step in the synthesis utilised a similar method first described by Tararov et al. in 2006.\textsuperscript{[74]} Thermolysis of Meldrum’s acid and trapping of the resulting ketene with allyl alcohol provided carboxylic acid 100 in a 30\% yield. Acid 100 was then treated with oxalyl chloride and catalytic DMF in order to afford acid chloride 101. Simultaneously, dioxinone 33 was treated with LiHMDS for 2.5 h and then acid chloride 101 was added in order to facilitate a Claisen condensation and provide ketoester-dioxinone 102 in a 20\% yield. Addition of MgCl\textsubscript{2} and pyridine followed by acid chloride 103 furnished diketo-ester dioxinone 104. Treatment of diketoester-dioxinone 104 with Pd(PPh\textsubscript{3})\textsubscript{4} and morpholine followed by late stage aromatisation conditions\textsuperscript{[42][43]} provided resorcylate 105 in 39\% yield over 4 steps. Deprotection of the silyether 105 followed by acid mediated

lactonisation afforded lactone 106 which was then selectively methylated in order to provide angelicoin B (7) in an overall 5.5% yield and 9 linear steps from dioxinone.

Scheme 28: Synthetic Route for the Synthesis of Angelicoin B (7)

There were a number of key steps that needed attention in the synthesis (Scheme 28): yield optimisation was essential for the thermolysis of allyl alcohol with Meldrum’s acid; the Claisen condensation of acid chloride 101 onto dioxinone 33 and the decarboxylation, deallylation and aromatisation steps.

2.2 Yield Optimisation Studies

Thermolysis of allyl alcohol and Meldrum’s acid had previously been carried out at 80 °C for 8 h giving a yield of 30% (Scheme 28). It was thought that the low yield could be because the reaction had not gone to completion. Thus, it was decided to increase the temperature to 100 °C and heat for 18 h, pleasingly this increased the yield to 70% (Scheme 32).
The Claisen condensation reaction between dioxinone 33 and acid chloride 101 had formerly provided ketoester-dioxinone 102 in a 20% yield (Scheme 28). This low yield could have been due to two effects. Firstly, dioxinone 33 had been stirred in LiHMDS for 2.5 h prior to the addition of acid chloride 101, presumably, this was too long and decomposition of dioxinone 33 or THF was occurring. Accordingly, it was ensured that an excess of HMDS was added to THF prior to addition of n-BuLi and that dioxinone 33 was stirred for 1 h in LiHMDS preceding the addition of acid chloride 101 (Scheme 29).[75][76][77]

It was hypothesised that the second cause for the low yield of keto-ester-dioxinone 102 was due to the reaction temperature following the addition of acid chloride 101. The reaction had been allowed to warm from –78 °C to 0 °C over 2 h (following the addition of acid chloride 101). Generally, the addition of an enolate with an acid chloride should occur very quickly at –78 °C.[78] Hence the reaction was monitored at –78 °C and quenched when complete. Completion of the reaction took 2 h at –78 °C, providing keto-ester-dioxinone 102 in 65% yield (Scheme 29).

![Scheme 29: Formation of Ketoester-Dioxinone 102](image)

The next step was to optimise the Pd(0)-decarboxylative deallylation and aromatisation sequence. Formerly, the aromatisation had been carried out utilising standard aromatisation conditions providing methyl ester 105 in 39% yield over 4 steps (Scheme 28). However, it was predicted that isoproplyidene protected resorcylate 107 could be formed by stirring diketo-dioxinone 108 with morpholine for 18 h (Scheme 30). This is because it has been shown within the Barrett group that diketo-dioxinones can be aromatised, utilising bases such
as triethylamine, into the corresponding isopropylidene protected resorcylates (see Section 1.10 of the Introduction).

Therefore the Pd(0)-decarboxylative deallylation reaction was repeated with an excess of morpholine providing isopropylidene protected resorcylate 107 in a pleasing 80% yield (Scheme 30).

\[ \text{Pd(0)-Decarboxylative Deallylation and Aromatisation} \]

Deprotection of the silyl ether 107 was achieved by treatment with H$_2$SiF$_6$ and lactonisation was facilitated under acidic conditions affording lactone 106 in an 82% yield over 2 steps. Finally, it was necessary to validate the final yield for the selective methylation of phenol 106. Selective methylation was undertaken furnishing angelicoin B (7) in a 79% yield (Scheme 31).

\[ \text{Scheme 31: Final Steps in the Synthesis of Angelicoin B (7)} \]

The selective methylation was an interesting step because two phenol moieties were present on the aromatic ring 106. pKa values of phenols with EWGs in the ortho and para positions are normally comparable, but in this case the indicated proton (Figure 8) was energetically stabilised by Hydrogen bonding and thereby the pKa should have increased, making it less available for methylation. In addition, the para phenol had increased accessibility for methylation compared with the ortho phenol. Nevertheless, the reaction had to be monitored...
closely because, if left for too long, methylation occurred on both phenol functionalities (Figure 8).

2.3 Total Synthesis of Angelicoin B (7)

Scheme 32 below illustrates the final synthetic route to angelicoin B (7), which was completed in an overall yield of 29% over 6 linear steps starting from dioxinone 33.
2.4 Retrosynthetic Analysis of Angelicoin A (6)

Having successfully completed the total synthesis of angelicoin B (7) utilising the late-stage aromatisation strategy, it was decided to conduct studies towards the total synthesis of angelicoin A (6) utilising the Pd(0)-decarboxylative allylation and aromatisation sequence. It was envisaged that angelicoin A (6) could be prepared from the aromatic precursor 109 through deprotection of the alcohol followed by lactonisation. Late stage aromatisation could be used to obtain the resorcylate 109. It was thought that a Pd(0)-decarboxylative prenylation could be facilitated to give diketone-dioxinone 110 starting from diketo-ester-dioxinone 111 (Scheme 33).

![Scheme 33: Retrosynthetic Analysis of Angelicoin A (6)](image)

2.5 Previous Studies Towards the Total Synthesis of Angelicoin A (6)

Studies towards the total synthesis of angelicoin A (6) had formerly been carried out within the Barrett group (Scheme 34).[^73^] Formation of diketo-prenylester-dioxinone 111 was carried out in a similar manner to the synthesis of diketo-allylester-dioxinone 104 described in section 2.2 above. Diketoester-dioxinone 111 was then treated with Pd(PPh₃)₄ in the absence of morpholine in order to facilitate a Pd(0)-decarboxylative prenylation. Standard aromatisation conditions[^43^] were then undertaken providing resorcylate 109 in a 12% yield.
over 4 steps. The final steps were attempted however, unfortunately lactonisation under acidic conditions led to the formation of tricycle 112 due to cyclisation between the phenol and the protonated prenyl moiety (Scheme 35).

Scheme 34: Previous Studies Towards the Synthesis of Angelicoin A (6)

Scheme 35: Cyclisation under Acidic Conditions

It was apparent that all the yields in the synthesis required optimisation, particularly the Pd(0)-decarboxylative prenylation. Furthermore, an alternative method was required for the lactonisation step. Accordingly, detailed studies towards the synthesis of angelicoin A (6) were conducted, focusing on each synthetic step.
2.6 Studies Towards the Synthesis of Keto-Dioxinone 113

2.6.1 Synthesis of Acid 114

The desired acid 114 was obtained utilising a similar method to that used by Tararov et al.\textsuperscript{[74]} Thermolysis of Meldrum’s acid and trapping of the resulting ketene with prenyl alcohol provided acid 114 in a 51% yield (Scheme 36 illustrates a proposed mechanism).

![Scheme 36: Proposed Mechanism for the Formation of Acid 114](image)

In order to improve the yield of the reaction it was decided to increase the temperature to 140 °C, the boiling point of prenyl alcohol. However, the yield decreased to 30% presumably due to decomposition of the starting materials. The next strategy was to reduce the temperature to 120 °C, use two equivalents of prenyl alcohol and improve the reaction workup. The usual workup commenced with the stirring of the reaction mixture in a saturated aqueous solution of NaHCO\textsubscript{3} for 10 min. This was increased to 5 h to ensure that all the acid 114 had formed the corresponding Na salt and would not be lost in workup. These three alterations increased the yield of acid 114 to an excellent 94%.

2.6.2 Synthesis of Ketoester-Dioxinone 113

The next step of the synthesis was the formation of the acid chloride 115, which was obtained utilising oxalyl chloride and catalytic DMF (Scheme 34). Ketoester-dioxinone 113 was formed by treating dioxinone 33 with LiHMDS followed by the addition of acid chloride 115.
The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)

(Scheme 34). It was predicted that the mechanism progressed via a ketene intermediate which was then attacked by the lithium enolate of dioxinone to provide diketo-dioxinone 113 (Scheme 37).

Scheme 37: Proposed Mechanism for the Formation of Ketoester-Dioxinone 113

The yield of this transformation was improved in the synthesis of angelicoin B (7) (see Section 2.2 above). These optimisation factors were applied to this reaction and the reaction yield increased to 45%. In order to improve the yield further, a concentration study was undertaken (Table 5).

Table 5: Concentration Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration/ M</th>
<th>Yield/ %\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.046</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>0.023</td>
<td>45</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yield after column chromatography.

The results illustrated that the reaction yield was higher at a low concentration (Entry 1, Table 5). It was hypothesised that at low concentration the number of collisions between the molecules would decrease leading to fewer side reactions. The effect of concentration slowed overall rates of reactions, which lead to a higher yield for the energetically favoured reaction.\textsuperscript{[81]} Interestingly, no addition onto C-2 of dioxinone 33 (Scheme 37) was observed.

To improve the yield further the benzotriazole leaving group was investigated. Formerly within the Barrett Group the benzotriazole leaving group has provided higher yields in this
transformation compared to the corresponding acid chloride.\textsuperscript{[82]} This is presumably because benzotriazole is a softer and more stable leaving group than the chloride (please see Section 2.7.2 below for a detailed explanation).\textsuperscript{[82][83]} The benzotriazole amide 116 can be isolated, stored and characterised prior to treatment with dioxinone 33, whereas the acid chloride 115 is formed \textit{in situ} (therefore it is hard to assess when the reaction has gone to completion and if the acid chloride that has been formed is decomposing).

Benzotriazole was pre-stirred with thionyl chloride for 1 h, acid 114 was then added and the mixture stirred for 24 h affording benzotriazole amide 116 in 81\% yield. Benzotriazole amide 116 was then added to the lithium enolate derived from dioxinone 33, furnishing ketoester-dioxinone 113 in an excellent 93\% yield (Scheme 38).

2.7 Studies Towards the Synthesis of Diketo-Prenylester-Dioxinone 111

2.7.1 Acid Chloride 117

Steps for the formation of acid 118 were achieved following a similar procedure by Tschaen \textit{et al.}\textsuperscript{[85]} Protection of alcohol 119 with TIPSOTf afforded silylether in 70\% yield. A number of conditions were then investigated for the hydrolysis; stirring in LiOH/THF gave no conversion to the acid 118, thus the hydroxide source was changed to NaOH and the ester
stirred for 18 h, giving only 30% conversion. However, stirring ester in NaOH/THF for 72 h gave full conversion to the acid 118. Conversion of the acid 118 to the acid chloride 117 was achieved using oxalyl chloride and catalytic DMF (Scheme 39).

Scheme 39: Steps in the Formation of Acid Chloride 117

2.7.2 Diketo-Prenylester-Dioxinone 111

The synthesis of diketo-prenylester-dioxinone 111 was based on a similar procedure reported previously in the Barrett group.\[^{82}\] Ketoester-dioxinone 113 was treated with MgCl\(_2\) and pyridine, with MgCl\(_2\) acting as a chelating agent enabling pyridine to deprotonate at the correct position (Scheme 40 shows the proposed mechanism).\[^{86,87}\] Subsequently, addition of acid chloride 117 furnished diketo-prenylester-dioxinone 111 in a modest 50% yield.

Scheme 40: Mechanism in the Formation of Diketo-Prenylester-Dioxinone 111\[^{86}\]
A number of side products, including O-acylation were observed during this reaction by $^1$H NMR spectroscopy. Therefore, it was decided to investigate each step of the reaction in order to further improve the yield. Formation of the acid chloride \(117\) was monitored by IR spectroscopy to determine the optimal reaction time, which was found to be 1 h at 0 °C. The next strategy was to lower the acylation reaction temperature; accordingly the reaction was carried out at −78 °C giving a 43% yield of prenyl ester \(111\).

Changing the leaving group in the Claisen condensation had dramatically increased the yield of ketoester-dioxinone \(113\) (Scheme 38). Consequently, three different leaving groups were studied in relation to this reaction; Weinreb amide \(120\), benzotriazole amide \(121\) and anhydride \(122\). These were chosen due to their differing levels of reactivity. The leaving groups provided soft electrophiles compared to hard acid chloride \(117\) and therefore decreased the possibility of O-acylation (Scheme 41).

\[
\text{Scheme 41: Diagram showing the Attack of C onto Soft Electrophiles and O onto Hard Electrophiles}
\]

The synthesis of electrophiles \(120\)-\(122\) is shown in Scheme 42. Weinreb amide \(120\) was synthesised by acid chloride formation of acid \(118\) followed by treatment with the Weinreb amide hydrochloride salt. Benzotriazole amide \(121\) was obtained utilising the same procedure described earlier in Section 2.7.1 (Scheme 38). Finally, anhydride \(122\) was formed in situ through treatment with \(\text{Et}_3\text{N}\) and pivaloyl chloride.
With compounds 120-122 in hand, the addition reaction was investigated. The Weinreb amide 120 and benzotriazole 121 leaving groups returned starting material and the pivilate leaving group 122 gave decomposition of the starting materials. Finally, the reaction was repeated with the acid chloride 177 using two equivalents of MgCl₂ (to ensure MgCl₂ chelation and so prevent O-acylation) which gave diketo-prenylester-dioxinone 111 in an excellent 81% yield (Scheme 43).

Scheme 43: Synthesis of Diketo-Ester-Dioxinone 111
2 The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)

2.8 Pd(0)-Decarboxylative-Prenylation and Late Stage Aromatisation

The next step to be investigated was the Pd(0)-decarboxylative prenylation and aromatisation sequence. Previous attempts within the Barrett group had been conducted affording resorcylate 109 in a 12% yield (Scheme 34).[73] Therefore, it was decided to conduct methodical optimisation studies into this transformation with the aim of screening different bases, ligands, catalysts, solvents, temperatures and reaction times.

Scheme 44: Decarboxylative Prenylation and Aromatisation

The first reaction that was carried out was to treat diketo-prenylester-dioxinone 111 with Pd(PPh₃)₄ (Scheme 45). The aim of this experiment was to observe the intermediates formed prior to performing the late-stage aromatisation conditions. Two products were obtained from this reaction, the branched product 123 in a 5% yield and the linear product 110 which aromatised within the reaction mixture to afford resorcylate 124 in an 18% yield. These results were extremely interesting and demonstrated a number of important points regarding this sequence.
Formerly, it was thought that only one isomer, the linear product 110, was observed in this transformation (Scheme 44). But, these results demonstrated that a branched isomer 123 was also present (Scheme 45). The Tsuji-Trost Pd(0)-decarboxylative allylation typically affords the linear product over the branched product, due to the nucleophile attacking the least hindered end of the π-Pd(0)-allyl intermediate.[89] Therefore the ratio of linear 110 to branched 123 product from the reaction (Scheme 45) was in accordance with a typical Tsuji-Trost Pd(0)-decarboxylative allylation.

Interestingly, the linear product 110 aromatised within the reaction mixture without the requirement of an additional base or the late-stage aromatisation conditions. This result demonstrated that it was energetically more favourable for linear-diketo-dioxinone 110 to aromatise. Presumably, during the course of the Pd(0)-decarboxylative prenylation the presence of an enolate 126 and/or carboxylate 125 (Figure 9) would be available to act as a base and facilitate the aromatisation. Deprotonation of diketo-dioxinone 110 to form enolate 127 would facilitate cyclisation and subsequent dehydration would furnish resorcylate 124 (Scheme 46 below shows a proposed mechanism).
Finally, branched product 123 did not aromatise within the reaction mixture presumably due to steric blocking cyclisation from occurring (Figure 10).

Due to the low yield of resorcylate 124 and diketo-dioxinone 123 (Scheme 45) it was apparent that either the starting material 111, the linear isomer 110 (prior to aromatisation) and the branched isomer 123 were decomposing during the reaction. When morpholine was used in the reaction (see Section 2.2) the yield of resorcylate 107 increased to 80% because morpholine was facilitating both deallylation and aromatisation. This reaction demonstrated that when a base was present the aromatisation of diketo-dioxinone 108 increased. Utilising
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this information it was decided to study the effect of a base in the Pd(0)-decarboxylative prenylation and aromatisation sequence.

2.9 Studies Towards the Use of Tertiary Amine Bases

Morpholine, a secondary amine, traps the \( \pi \)-allyl Pd complex enabling deallylation to occur.\cite{46,82} Accordingly, tertiary amines were explored because it was assumed they would facilitate aromatisation but not cause deallylation.\cite{43}

Unfortunately, overall the yield of resorcylate 124 and diketo-dioxinone 123 did not increase following this study (Table 6). However, interestingly the ratio of 123:124 did alter depending on the base and the reaction time. The first tertiary amine to be investigated was 4-methylmorpholine (Table 6, Entry 1). The yield decreased for both 123 and 124 and the ratio of 123:124 changed to 1:1. This result indicated that the base was affecting the linear to branched ratio but not noticeably affecting the aromatisation step. Tunge et al.\cite{90} have shown that changing the base in a decarboxylative allylation can dramatically affect the linear to branched ratio of the products obtained. Presumably, this is because the base can alter the terminus of attack on the \( \pi \)-allyl Pd complex. (The use of a base in this transformation will be discussed further in the mechanistic studies Section 3.5).

The next base to be screened was 4-ethylmorpholine (Table 6, Entry 2), the yield of 123 and 124 increased to 20\% but the ratio of 123:124 remained the same. It was thought that 4-ethylmorpholine was affecting the reaction in a similar manner to 4-methylmorpholine.

Guanidine (Table 6, Entry 3) provided 17\% of RSM and decomposition of the remaining diketo-prenylester-dioxinone 111. Consequently, 4-ethylmorpholine was screened again with a longer reaction time (Table 6, Entry 4); however, after 2 h the same result was observed as after 30 min (Table 6, Entry 2). A shorter reaction time of 10 min (Table 6, Entry 5) was
attempted, which provided the same result as for 30 min (Table 6, Entry 2) and 2 h (Table 6, Entry 4). It was apparent that the reaction was complete after 10 min and that the tertiary amine base was not increasing the yield of either resorcylate 124 or diketo-dioxinone 123.

Table 6: Results from the Tertiary Amine Base Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Tertiary Amine&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>123:124</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 min</td>
<td>4-Methylmorpholine</td>
<td><strong>123</strong> 5%, <strong>124</strong> 5%</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>30 min</td>
<td>4-Ethylmorpholine</td>
<td><strong>123</strong> 10%, <strong>124</strong> 10%</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>30 min</td>
<td>Guanidine</td>
<td>RSM (17%)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2 h</td>
<td>4-Ethylmorpholine</td>
<td><strong>123</strong> 10%, <strong>124</strong> 10%</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td>10 min</td>
<td>4-Ethylmorpholine</td>
<td><strong>123</strong> 11%, <strong>124</strong> 10%</td>
<td>1:1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield isolated after column chromatography.
<sup>b</sup>3.0 equivalents of tertiary amine.
2.10 Utilisation of an Inorganic Base

It was known within the Barrett group that Cs$_2$CO$_3$ can be utilised to aid aromatisation in the late-stage aromatisation strategy.$^{[42][43][82]}$ Tunge et al.$^{[90]}$ have also demonstrated increased yields in the decarboxylative allylation reaction through the use of Cs$_2$CO$_3$. Additionally, Cs$_2$CO$_3$ has a high solubility in organic solvents compared with other inorganic bases.$^{[91]}$ For these 3 reasons Cs$_2$CO$_3$ was chosen for this study.

The results were very encouraging with entry 4 (Table 7) giving the highest yield of resorcylate 124 and diketo-dioxinone 123. It was interesting that a longer reaction time of 18 h increased the yield of 123 and 124 (Table 7, Entry 2) compared with a reaction of 1 h (Table 7, Entry 1). This was different to the results shown in Table 6 whereby the reaction had gone to completion after 10 min with 4-ethylmorpholine (Table 6, Entry 5). Surprisingly, the ratio of linear 124 to branched 123 products was different with Cs$_2$CO$_3$ compared to 4-ethylmorpholine.

Pleasingly, the yield of resorcylate 124 was higher than diketo-dioxinone 123 because resorcylate 124 was required in the total synthesis of angelicoin A (6) (Section 47). It was significant that when the number of equivalents of Cs$_2$CO$_3$ was increased from 1 to 3 the yield of both resorcylate 124 and diketo-dioxinone 123 increased indicating that Cs$_2$CO$_3$ may be aiding both the decarboxylation, prenylation and aromatisation steps within the reaction. (The use of Cs$_2$CO$_3$ as a base is discussed in more detail in the mechanistic discussion Section 3.5).
2 The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)

Table 7: Studies Utilising Cs$_2$CO$_3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time/ h</th>
<th>Equiv. of Cs$_2$CO$_3$</th>
<th>Yield$^a$</th>
<th>123:124</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>123 8%, 124 35%</td>
<td>1:4</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>1</td>
<td>123 10%, 124 41%</td>
<td>1:4</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>3</td>
<td>123 9%, 124 48%</td>
<td>1:5</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>Excess</td>
<td>123 8%, 124 49%</td>
<td>1:5</td>
</tr>
</tbody>
</table>

$^a$Isolated yield after column chromatography.

2.11 Catalyst and Ligands Studies

A number of Pd catalysts and ligands were screened in order to observe the effect on both the yield and linear to branched ratio. Some of the Pd sources commonly used by Murakami et al.,$^{[92]}$ Stoltz et al.,$^{[93]}$ Tunge et al.$^{[94]}$ and Trost et al.$^{[95]}$ for decarboxylative-allylations are Pd$_2$(dba)$_3$ 128 and Pd(PPh$_3$)$_4$. Additionally, a number of ligands widely utilised are rac-BINAP 74, Trost 69, Xantphos 129, PPh$_3$ and dppf 130 (Figure 11).$^{[60][64][96]}$ With this information to hand a number of small scale reactions were investigated (Table 8).

It was apparent that Pd(II) sources, PdCl$_2$ and Pd(OAc)$_2$ (Table 8, Entries 7 & 8) failed to catalyse the reaction, whereas Pd(0) sources such as Pd(PPh$_3$)$_4$ and Pd$_2$(dba)$_3$/Xantphos were effective catalysts. It was interesting but not surprising that the type of catalyst and ligand had a significant effect on the linear to branched ratio. This is because the yield of a reaction and linear to branched ratio can vary dramatically depending upon the catalyst and ligands.
being utilised for the transformation. The optimum conditions found were Pd(PPh$_3$)$_4$ at 10 mol% giving resorcylate 124 in a 50% yield and diketo-dioxinone 123 in a 10% yield (Table 8, Entry 2).

Table 8: Catalyst and Ligand Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand (20%)</th>
<th>Yield$^a$</th>
<th>123:124</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh$_3$)$_4$ (2.5 mol%)</td>
<td>-</td>
<td>123 8%, 124 43%,</td>
<td>1:4</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh$_3$)$_4$ (10 mol%)</td>
<td>-</td>
<td>123 10%, 124 50%</td>
<td>1:5</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$ (5 mol%)</td>
<td>Xantphos</td>
<td>123 31%, 124 24%</td>
<td>3:2</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$(dba)$_3$ (5 mol%)</td>
<td>rac-BINAP</td>
<td>123 2%, 124 10%</td>
<td>1:5</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$(dba)$_3$ (5 mol%)</td>
<td>Trost</td>
<td>123 6%, 124 25%</td>
<td>1:4</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$(dba)$_3$ (5 mol%)</td>
<td>dppf</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$ (10 mol%)</td>
<td>PPh$_3$</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>PdCl$_2$ (10 mol%)</td>
<td>PPh$_3$</td>
<td>RSM</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Isolated yield after column chromatography.
2 The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)

Figure 11: Ligands and Palladium Sources Utilised in Table 8
2.12 Temperature Studies

Results from studies towards the temperature of the Pd(0)-decarboxylative prenylation and aromatisation sequence are illustrated in Table 9. The results from the temperature investigations demonstrated that the optimum temperature was to begin the reaction at 0 °C, allow it to warm to rt and stir for 18 h (Table 9, Entry 3). Interestingly, the starting material 111 had been consumed after 1 h at 40 °C (Table 9, Entry 4) but the yield was lower than stirring for 18 h at rt (Table 9, Entry 3). This result indicated the sensitivity of the reaction to heat; the rate increased however, decomposition of diketo-dioxinones 123 and 110 and the starting material 111 also increased.

Table 9: Temperature Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>123:124</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−78 °C</td>
<td>8 h</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0 °C</td>
<td>8 h</td>
<td>123 6%, 124 40%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1:6</td>
</tr>
<tr>
<td>3</td>
<td>0 °C to rt</td>
<td>18 h</td>
<td>123 10%, 124 52%</td>
<td>1:5</td>
</tr>
<tr>
<td>4</td>
<td>40 °C</td>
<td>1 h</td>
<td>123 10%, 124 40%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1:4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after column chromatography.
<sup>b</sup>Consumption of the starting material 111 by TLC after 8 h.
<sup>c</sup>Consumption of the starting material 111 by TLC after 1 h.
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2.13 Solvent Studies

The final study was to look at the solvent effect on the Pd(0)-decarboxylative prenylation and aromatisation sequence. A number of solvents were screened, however, only THF was found to be effective (Table 10, Entry 5).

Table 10: Solvent Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>123:124</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Et₂O</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>RSM</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>123 11%, 124 51%</td>
<td>1:5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after column chromatography.

In conclusion, a thorough optimisation study has taken place whereby the best conditions were found to be Pd(PPh₃)₄ (10 mol%), Cs₂CO₃ (3 equivalents), 0 °C to rt over 18 h in THF, providing resorcylate 124 in a 50% yield and diketo-dioxinone 123 in a 10% yield. With these conditions to hand studies towards the total synthesis of angelicoin A (6) were continued.
2 The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)

2.14 Final Steps in the Synthesis of Angelicoin A (6)

The final steps in the synthesis of angelicoin A (6) are shown in scheme 47. Deprotection of silyl ether 124 was accomplished utilising TBAF furnishing alcohol 128 in an excellent 97% yield. Finally, lactonisation was carried out under basic conditions (to avoid cyclisation of the phenol onto the protonated prenyl moiety which occurs under acidic conditions, see Section 2.5) by heating alcohol 128 with KOH in EtOH affording angelicoin A (6) in a 90% yield.

Scheme 47: Final Steps in the Synthesis of Angelicoin A (6)

The synthesis of angelicoin A (6) was completed in 5 linear steps starting from dioxinone 33 in an overall 33% yield.

2.15 Conclusions and Future Work

The total synthesis of angelicoin B (7) has been completed in 6 linear starting steps from dioxinone 33 in an overall 29% yield. The synthesis exhibits the key Pd(0)-decarboxylative deallylation and aromatisation transformation which provided resorcylate 107 in an excellent 80% yield starting from diketo-ester-dioxinone 104. In addition, the yield of the Claisen condensation between dioxinone 33 and acid chloride 101 was increased from 20% to a good 65%.

The total synthesis of angelicoin A (6) has been carried out in 5 linear steps starting from dixoinone 33 in an overall 33% yield. Thorough optimisation studies were conducted into the novel Pd(0)-decarboxylative prenylation and aromatisation sequence investigating the effects
2 The Total Synthesis of Angelicoin B (7) and Angelicoin A (6)

of catalyst, ligand, solvent, temperature and base. These studies demonstrated that diketoester-dioxinone 111 could be transformed into resorcylate 124 and diketo-dioxinone 123 in an excellent 60% yield and in a 5:1 ratio respectively. Optimised synthetic steps from these total syntheses are currently being utilised successfully within the Barrett group in the synthesis of other resorcylate natural products and other biologically active resorcylate analogues.

In the future it would be interesting to continue studies towards the optimisation of the Pd(0)-decarboxlyative allylation and aromatisation sequence. Tunge et al. have shown that Ruthenium, Iridium and Molybdenum can be efficient catalysts for this transformation.\textsuperscript{[90]} Hence, the reaction could be attempted with these metals utilising a variety of ligands and bases to see if the yield or the linear to branched ratio alters.
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

The last chapter describes the total synthesis of angelicoin A (6) utilising a migratory Pd(0)-decarboxylative prenylation and aromatisation sequence. The next strategy was to prove that the Pd(0)-decarboxylative prenylation was truly migratory. It was postulated that an effective way to prove the migratory nature of this reaction was to obtain an X-ray crystal structure of the intermediates both before and after the decarboxylative prenylation had taken place. The aim was to prove that the prenylester functionality was indeed on C-3 of diketoester-dioxinone 111 prior to treatment with Pd(PPh₃)₄ and that the prenyl moiety migrated to C-1 after treatment with Pd(PPh₃)₄ (Scheme 48).

3.1 X-ray Crystal Structure of Tricycle 130III

Unfortunately, diketo-prenylester-dioxinone 111 was an oil at rt. It was thought that aromatisation and removal of the silylether would provide a crystal suitable for X-ray crystallography. Accordingly, diketo-prenylester 111 was aromatised by treatment with Et₃N affording phenol 129 in a 40% yield. Deprotection of the silylether 130 was implemented utilising TBAF, interestingly lactonisation occurred within the reaction mixture furnishing tricycle 130 in a 63% yield. Gratifyingly, tricycle 130 was a crystalline solid suitable for X-ray crystallography (Scheme 48).

---

III Section 3.1 has been published and therefore has similarity to Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. B. Org. Lett. 2011, 13, 5748-5750.
Scheme 48: Steps in the Synthesis of Tricycle 130

The X-ray crystal structure of tricycle 130 is shown below in Figure 12. The X-ray crystal structure verified the position of the prenyl ester functionality being on C-3 of diketo-prenylester-dioxinone 111 prior to treatment with Pd(PPh$_3$)$_4$.

Figure 12: X-ray Crystal Structure of Tricycle 130
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

3.2 X-ray Crystal Structure of Angelicioin A (6)\textsuperscript{IV}

The next step was to prove the position of the prenyl moiety after the Pd(0)-decarboxylative prenylation had taken place. Sections 2.8 - 2.13 discussed the optimisation studies towards the Pd(0)-decarboxylative prenylation and late stage aromatisation sequence. Two products were obtained from this reaction, the linear product \textbf{110} which aromatised within the reaction mixture to give resorcy late \textbf{124} and the branched product \textbf{123} (Scheme 45). The aim was to prove that the position of the prenyl moiety was on C-1 and not C-3 of resorcy late \textbf{124} (Figure 13). Unfortunately, resorcy late \textbf{124} (Figure 13) was not a crystalline solid and not suitable for X-ray crystallography. However, Angelicoin A (\textbf{6}) (Figure 13) provided an excellent crystalline solid and an X-ray crystal structure was obtained (Figure 14).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{resorcylate_and_angelicioin}
\caption{Resorcy late \textbf{124} and Angelicioin A (\textbf{6})}
\end{figure}

The X-ray crystal structure established that migration had occurred during the Pd(0)-decarboxylative prenylation due to the position of the linear prenyl moiety being on C-1 of the aromatic ring (Figure 14).

\textsuperscript{IV} Section 3.2 has been published and therefore has similarity to Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. B. \textit{Org. Lett.} \textbf{2011}, \textit{13}, 5748-5750.
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

Figure 14: X-ray Crystal Structure of Angelicoin A (6)

3.3 Towards an X-ray Crystal Structure of Branched Resorcylate

The next strategy was to obtain an X-ray crystal structure of the branched isomer 123 from the Pd(0)-decarboxylative prenylation reaction. Regrettably, diketo-dioxinone 123 was an oil at rt and thus investigations into its aromatisation were conducted (Table 11).

Three standard methods utilised within the Barrett group for aromatisation of diketo-dioxinones\textsuperscript{[42][43]} were attempted for diketo-dioxinone 123 (Table 11) (see Section 1.10 of the Introduction). All of these methods furnished residual starting material 123 (Table 11, Entries 1 & 2) or decomposition of the starting material 123 (Table 11, Entry 3). It was thought that aromatisation was not occurring due to the bulky nature of the branched olefin preventing cyclisation (Figure 10).
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

Table 11: Studies Towards the Aromatisation of Diketo-dioxinone 123

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs$_2$CO$_3$ (excess), MeOH, rt to $\Delta$, 18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$N(excess), CH$_2$Cl$_2$, rt to $\Delta$, 18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (excess), PhMe, $\Delta$, 1 h; Cs$_2$CO$_3$ (3.0 equiv.), MeOH, rt, 4h; AcOH (excess), rt, 3h</td>
<td>Decomposition of the SM</td>
</tr>
</tbody>
</table>

It was apparent that the low yield of diketo-dioxinone 123 following the Pd(0)-decarboxylative prenylation was making it hard to bring material through in order to aromatise. Moreover, the separation of resorcylate 124 from diketo-dioxinone 123 was very difficult because the two products had similar $R_f$ values (in a wide range of eluents). Therefore conditions were investigated that could provide a high yield of the branched product 123.

As illustrated previously in Section 2.11 certain Pd catalysts and ligands can provide a higher percentage of branched product 123. Additionally, it has been shown by Tunge et al.$^{[90][94]}$ and Lacour et al.$^{[97][98]}$ that utilising Ruthenium in this transformation can promote formation of branched product. Table 12 below illustrates the Ruthenium catalysts, bases and ligands that were screened. Unfortunately, none of conditions screened (Table 12) yielded the desired products. Presumably, the structure of diketo-prenylester-dioxinone 111 was not suitable for Ruthenium catalysis.
Table 12: Ruthenium Conditions Investigated

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (10 mol%)</th>
<th>Ligand (20 mol%)</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCp(MeCN)_3.PF_6</td>
<td>-</td>
<td>CH_2Cl_2</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>RuCp(MeCN)_3</td>
<td>-</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>3</td>
<td>RuClCp(PPh_3)_2</td>
<td>-</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>48 h</td>
<td>RSM</td>
</tr>
<tr>
<td>4</td>
<td>RuClCp(PPh_3)_2</td>
<td>Py</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>48 h</td>
<td>RSM</td>
</tr>
<tr>
<td>5</td>
<td>RuClCp(PPh_3)_2</td>
<td>Bpy</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>48 h</td>
<td>RSM</td>
</tr>
<tr>
<td>6</td>
<td>RuClCp(PPh_3)_2</td>
<td>TMEDA</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>7</td>
<td>Ru(methylallyl)_2(COD)</td>
<td>-</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>8</td>
<td>Ru(methylallyl)_2(COD)</td>
<td>Py</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>9</td>
<td>Ru(methylallyl)_2(COD)</td>
<td>Bpy</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>10</td>
<td>Ru(methylallyl)_2(COD)</td>
<td>TMEDA</td>
<td>THF</td>
<td>0 °C to r.t.</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>11</td>
<td>[Cp*RuCl]_4</td>
<td>-</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>12</td>
<td>[Cp*RuCl]_4</td>
<td>Py</td>
<td>THF</td>
<td>0 °C to Δ</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>13</td>
<td>[Cp*RuCl]_4</td>
<td>Bpy</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>14</td>
<td>[Cp*RuCl]_4</td>
<td>TMEDA</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>15</td>
<td>[Cp*RuCl]_4</td>
<td>Py</td>
<td>CH_2Cl_2</td>
<td>0 °C to rt</td>
<td>18 h</td>
<td>RSM</td>
</tr>
</tbody>
</table>
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

Consequently, the protecting group was changed from a silyl ether to a benzyl ether. It was postulated that following aromatisation, diketo-dioxinone 132 would not require deprotection because the two aromatic functionalities within the molecule would induce π-stacking providing a solid suitable for X-ray crystallography (Scheme 49).\[99\]

Scheme 49: Possible Synthetic Route Towards Resorcylate 135

The synthetic route towards resorcylate 135 (Scheme 50) began with the benzyl protection of alcohol 136, giving benzyl ether 137 in a 76% yield. Saponification of methyl ester 137 to acid 138 took place using NaOH/THF. Acid chloride 139 was then synthesised in situ utilising oxalyl chloride and catalytic DMF. Formation of diketo-ester-dioxinone 132 was achieved by treating ketoester-dioxinone 113 with MgCl$_2$ and pyridine followed by the addition of acid chloride 139. When diketo-ester-dioxinone 132 was treated with Pd(PPh$_3$)$_4$, the Pd(0)-decarboxylative prenylation took place providing resorcylate 133 in a 35% yield. Unfortunately, branched-diketo-dioxinone 134 could only be seen in the crude $^1$H NMR and was not available in adequate yield to isolate by silica column chromatography.
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

The next approach involved utilising a methyl group as the side chain in diketo-ester-dioxinone. It was assumed that this side chain would enable the synthesis of a solid following aromatisation of the branched-diketo-dioxinone suitable for X-ray crystallography. The synthesis of branched-diketo-dioxinone and its subsequent aromatisation is illustrated in Scheme 51.

Diketoester-dioxinone was formed by pre-stirring ketoester-dioxinone with MgCl₂ and pyridine followed by the addition of acetyl chloride. Treatment of diketoester-dioxinone with Pd(PPh₃)₄ facilitated the Pd(0)-decarboxylative prenylation and aromatisation providing linear resorcylate in a 50% yield and branched-diketo-dioxinone in a 10% yield (Scheme 51).
Scheme 51: Synthesis of Branched-Diketo-Dioxinone 141 and its Subsequent Aromatisation

The final step was to aromatise branched-diketo-dioxinone 141, a number of conditions were screened, and these are shown in Table 13 below. Regrettably, it was not possible to aromatise branched-diketo-dioxinone 141 under basic aromatisation conditions (Table 13). Again, this was presumably due to the bulky nature of the branched prenyl group preventing aromatisation (Figure 10).

Table 13: Conditions Screened for the Aromatisation of 141

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (excess)</td>
<td>CH₂Cl₂</td>
<td>rt to Δ, 72 h</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃ (excess)</td>
<td>MeOH</td>
<td>rt to Δ, 72 h</td>
<td>RSM</td>
</tr>
<tr>
<td>3</td>
<td>LDA (excess)</td>
<td>THF</td>
<td>−78 °C to Δ, 48 h</td>
<td>RSM</td>
</tr>
</tbody>
</table>

It was decided to conduct the late stage aromatisation conditions; accordingly diketo-dioxinone 141 was refluxed in toluene and MeOH (Scheme 52). The reaction was monitored by TLC and consumption of the starting material took 18 h (usually only 1 h of heating is required). Remarkably, the reaction led to the formation of branched-resorcylate 144 (Scheme 52).

---

Scheme 51: Synthesis of Branched-Diketo-Dioxinone 141 and its Subsequent Aromatisation

The final step was to aromatise branched-diketo-dioxinone 141, a number of conditions were screened, and these are shown in Table 13 below. Regrettably, it was not possible to aromatise branched-diketo-dioxinone 141 under basic aromatisation conditions (Table 13). Again, this was presumably due to the bulky nature of the branched prenyl group preventing aromatisation (Figure 10).

Table 13: Conditions Screened for the Aromatisation of 141

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (excess)</td>
<td>CH₂Cl₂</td>
<td>rt to Δ, 72 h</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃ (excess)</td>
<td>MeOH</td>
<td>rt to Δ, 72 h</td>
<td>RSM</td>
</tr>
<tr>
<td>3</td>
<td>LDA (excess)</td>
<td>THF</td>
<td>−78 °C to Δ, 48 h</td>
<td>RSM</td>
</tr>
</tbody>
</table>

It was decided to conduct the late stage aromatisation conditions; accordingly diketo-dioxinone 141 was refluxed in toluene and MeOH (Scheme 52). The reaction was monitored by TLC and consumption of the starting material took 18 h (usually only 1 h of heating is required). Remarkably, the reaction led to the formation of branched-resorcylate 144 (Scheme 52).
Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

Scheme 52: Formation of Branched-Resorcylate 144

Aromatisation of diketo-dioxinones usually requires treatment with acid, base or pressure (sealed tube),[42][43][82] making this result very intriguing. Scheme 53 below illustrates a proposed mechanism for this aromatisation. It was hypothesised that following formation of ketene 145 and subsequent trapping with MeOH to afford triketo-ester, the enol form of triketo-ester 146 would perform an intramolecular cyclisation under elevated temperatures to furnish cycle 147. Finally, dehydration and tautomerisation would afford resorcylate 143.

Scheme 53: Proposed Aromatisation Mechanism at Elevated Temperatures

Unfortunately branched-resorcylate 144 was a gum and thus not crystalline, nevertheless the new aromatisation conditions were noteworthy and are currently being studied further within the Barrett group.
3.4 Synthesis of Branched-Resorcylate 148

During studies towards total synthesis of amorfrutin A (8) it was found that refluxing branched-diketo-dioxinone 148 with Cs$_2$CO$_3$ in THF provided branched-resorcylate 149 in a 68% yield (Scheme 54).

\[
\text{Scheme 54: Synthesis of Branched-Resorcylate 149}
\]

Pleasingly, branched-resorcylate 149 was a crystalline solid and an X-ray crystal structure was obtained (Figure 15). The X-ray structure confirmed the position of the branched prenyl moiety being on C-1 of the aromatic ring (Scheme 54), providing further evidence for the migration of the Pd(0)-decarboxylative prenylation and aromatisation sequence.

\[
\text{Figure 15: X-ray Crystal Structure of Branched-Resorcylate 149}
\]

---

\textsuperscript{V} Work in Section 3.4 has been carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this research. Additionally, this work has been published and therefore has similarity to Laclef, S.; Anderson, K.; White, A. J. P.; Barrett, A. G. M. \textit{Tetrahedron Letters} 2012, 53, 225–227.
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3.5 Mechanistic Investigations

The migration of the Pd(0)-decarboxylative prenylation had been proved unambiguously by X-ray crystallography studies. Hence, the next approach was to conduct mechanistic studies into this intriguing reaction. Initially it was considered that the mechanism could be taking place via a modified Carroll Rearrangement (Scheme 55) through formation of the π-allyl Pd complex 151 followed by decarboxylation to provide diketo-dioxinone 152. Subsequent intermolecular allylation would provide the allylated-diketodioxinone 150, which would readily undergo aromatisation.

Scheme 55: Observed Prenyl Migration and Postulated Reaction Mechanism via a Modified Carroll Rearrangement

3.6 Substrate Investigations

3.6.1 Allyl Group

It was decided to investigate the Pd(0)-decarboxylative allylation and aromatisation sequence in relation to the allyl and crotyl moieties. The aim was to see if these groups would migrate and with the crotyl moiety to see if any branched isomer would be obtained. Diketo-
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

allylester-dioxinone 153 was prepared by treatment of ketoester-dioxinone 102 with MgCl₂ and pyridine followed by the addition of acetyl chloride (Scheme 56).

The Pd(0)-decarboxylative allylation of diketo-ester-dioxinone 153 provided allyl resorcylate 154 and resorcylate 155 in a 1:1 ratio and overall 60% yield. This result demonstrated that the allylation was migratory, though, the yield of allyl-resorcylate 154 was lower than expected (possible reasons for this will be discussed in Section 3.9).

![Scheme 56: Synthesis of Diketo-Ester-Dioxinone 153 and Subsequent Treatment with Pd(PPh₃)₄](image)

3.6.2 Crotyl Group

The synthesis of diketo-crotylester-dioxinone 156 (Scheme 57) was completed utilising the methods discussed previously in Section 2.6. Subsequent reaction of diketo-crotylester-dioxinone 156 with Pd(PPh₃)₄ provided crotyl-resorcylate 157 in a 46% yield. This result provided additional evidence for the migratory nature of this sequence but interestingly, no branched product was observed in this transformation (Scheme 57).
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Scheme 57: Formation of Diketo-Crotylester-Dioxinone 156 and Reaction with Pd(PPh₃)₄

3.7 Concentration Studies

The next approach was to study the effects of reaction concentration on the course of the reaction to determine if any other products would be produced. The optimised conditions for the Pd(0)-decarboxylative-allylation-aromatisation sequence (0.2 M) gave the branched-diketo-dioxinone 141 and linear resorcylate 142. Surprisingly, when the reaction concentration was decreased (0.014 M), two new products, the resorcylates 159 and 155 were formed and isolated in a 1:1 ratio and 83% overall yield (Scheme 58). Interestingly, at this lower concentration (0.014 M), only traces of diketodioxinone 141 and resorcylate 142 were isolated. Similarly, at the higher concentration (0.2 M), only traces of resorcylate 159 and 155 were isolated (Scheme 58). The reaction was repeated on diketo-ester-dioxinone 132 to ensure reproducibility of this unusual result. Delightfully, the same result was obtained with diketo-ester-dioxinone 132 (Scheme 58). Scheme 58 illustrates the results from the concentration studies and highlights the intermediates (in square brackets) that were formed throughout the reaction.
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Scheme 58: Concentration Studies towards Pd(0)-Decarboxylative Prenylation Sequence
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It was postulated that intermolecular trapping of the π-prenyl-palladium(II) cation complex produced from oxidative insertion of a Pd(0) complex into the C-O bond of ester 140 by a second molecule of diketo-ester-dioxinone 140, afforded intermediate dioxinones 158 and 160. Subsequent aromatisation resulted in the formation of the two resorcylates 159 and 155. These results are consistent with the operation of an intermolecular mechanism at low concentration in which diketoester 140 serves as both a π-prenyl donor and acceptor.

Interestingly, at low concentration the branched-diketo-prenylester-dioxinone 167 was not observed (Figure 16). At a high concentration there are a high number of collisions between the enolate (nucleophile) and the π-prenyl-Palladium(II) cation complex (electrophile).\[100\] It was therefore postulated that when the concentration was decreased the number of collisions between the enolate and the π-prenyl-Palladium(II) cation complex would decrease and this was why the branched-diketo-prenylester-dioxinone 166 was not seen.

![Chemical structures](image)

Figure 16: Branched-Diketo-Prenylester-Dioxinone 166 and Branched-Prenylester-Resorcylate 167
Encouraged by these findings, the next study sought to examine a cross-over experiment between unlabelled and deuterium labelled compounds. The study focused on the rearrangements of esters 168 and 169 at a concentration of 0.2 M (Scheme 59). Four resorcylates 170, 171, 172 and 173 were obtained from the cross over experiment with esters 170 and 171 being isolated together in 70% yield and 1:1 ratio and esters 172 and 173 also isolated together in 70% yield and 1:1 ratio (yield is based on using 1.0 equivalent of 168 and 1.0 equivalent of 169). These results are consistent with the prenyl moiety migration occurring via an intermolecular mechanism at a concentration of 0.2 M.

Scheme 59: Cross-Over Experiment between non-Deuterated Ester Diketodioxinone 168 and Deuterated Ester 169

---

VI Work in Section 3.8 has been carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this work.
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3.9 Proposed Mechanism

In consistence with the results of these experiments, the following mechanism was proposed (Scheme 60). It was hypothesised that prenylester-diketodioxinone 140 can enter the catalytic manifold in one of two ways, either as a prenyl donor affording diketodioxinone 160 (Pathway B) or as a prenyl acceptor giving the double prenyl dioxinone 158 (Pathway A). Diketodioxinone 160 can subsequently undergo prenylation to provide prenyl-diketodioxinone 150. Finally, the double prenyl dioxinone 158 can undergo deprenylation and decarboxylation to provide prenyl-diketodioxinone 150, which can readily undergo aromatisation to provide resorcylate 142. Resorcylates 159 and 155 were isolated when the reaction was carried out at low concentration. Under these conditions the intramolecular cyclisation reaction to form resorcylate 155 and prenylated-resorcylate 159 proceeded faster than the intermolecular reactions to form prenyl-diketodioxinone 150. It was hypothesised that the intramolecular reaction proceeded faster than the intermolecular reaction due to the low concentration. At a low concentration an intramolecular reaction is more likely to proceed over an intermolecular one because both of the reactive components are tethered together, whereas with an intermolecular reaction the two reactive components are required to travel through the solvent in order to react.^[101]
Section 3.6.1 above described the reaction of diketo-allylester-dioxinone 153 with Pd(PPh₃)₄ which provided two products allyl-resorcylate 154 and resorcylate 155 in a 60% yield and 1:1 ratio (Scheme 61). Presumably, resorcylate 155 was obtained in a 30% yield because aromatisation of diketo-dioxinone 160 was faster than allylation of diketo-dioxinone 160.
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3.10 Base Studies

The next plan was to formalise the role of Cs$_2$CO$_3$ in the mechanism to establish if it was catalysing the aromatisation step or the decarboxylation and allylation step, or both steps. To explore this question, ethyl ester 174 was allowed to react with allyl chloride as an electrophile in the presence of Pd(PPh$_3$)$_4$ in THF. Interestingly, no product was formed and starting material 174 was recovered confirming that a base is required for this transformation to take place (with an external allylation).

As stated previously in Section 2.8 several intermediates are generated during the course of the reaction including an enolate 175 and/or a carboxylate 176 (Figure 17) that could be acting as a general base. To investigate the topic further ethyl ester 174 (synthesis is shown in Scheme 62) was allowed to react with allyl chloride and CsOAc at 0.2 M, which resulted in the formation of the hexasubstituted resorcylate 177 in an 82% yield (Scheme 62). Reaction using Cs$_2$CO$_3$ in place of CsOAc at 0.2 M resulted in the formation of the same, resorcylate 177 in an 81% yield. The Barrett group have recently utilised this allylation reaction in the synthesis of diverse hexasubstituted benzene derivatives, whereby the acetate anion was generated in situ and acted as a base in the reaction.\[^{102}\]
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

These studies indicated that a general base is required for the transformation, which could be an enolate 175, and/or a carboxylate 176 (Figure 17).

Figure 17: Proposed Aromatisation Bases

3.11 Regioselectivity Investigations

The next strategy was to investigate the regioselectivity of the reaction and to understand why the allylation was migratory. In order to examine this it was decided to treat diketo-dioxinone 179 with allyl acetate and ascertain the regioselectivity of allylation (Scheme 63). Ketodioxinone 178 was prepared via deprotonation of dioxinone 33 followed by the addition of acetyl chloride. Subsequent treatment of keto-dioxinone 178 with LDA followed by Et₂Zn and addition of N-methoxy-N-methylbenzamide (182) furnished diketo-phenyl-dioxinone 179 in a 76% yield. High regioselectivity in the allyl transfer step was observed providing

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VII Work in Section 3.11 was carried out in collaboration with Dr Sylvain Laclef. He is duly thanked for his collaboration and contributions to this work.
diketo-dioxinone 180 which then aromatised to give resorcylate 181 in an 82% yield (Scheme 63).

Scheme 63: Preparation of Diketo-Dioxinone 179 and Subsequent Allylation and Aromatisation

This experiment was consistent with the decarboxylation in Pathway B of the proposed mechanism (Scheme 60) where decarboxylation could be occurring before or after prenylation (allylation). It was therefore postulated that the regioselectivity was not driven by decarboxylation but could be due to the difference in pKa with prenylation (allylation) occurring at C-3 instead of C-5 due to the C-3 methylene having a lower pKa due to the adjacent dioxinone ring.\(^{[104]}\) The mechanistic studies that were conducted are consistent with an intermolecular reaction manifold.
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

3.12 Conclusions and Future Work

3.12.1 Pd(0)-Decarboxylative Allylation and Aromatisation

The migratory Pd(0)-decarboxylative prenylation and aromatisation sequence has been unambiguously verified through the use of X-ray crystallography. An X-ray crystal structure has been obtained proving the position of the ester functionality in diketo-ester-dioxinone \( 111 \) prior to treatment with \( \text{Pd(PPh}_3\text{)}_4 \). X-ray crystal structures of both the linear resorcylate (6) and branched resorcylate \( 149 \) have been obtained confirming the position of the prenyl moiety on the aromatic ring and thus the migratory nature of the Pd(0)-decarboxylative prenylation and aromatisation sequence.

Thorough mechanistic investigations including substrate studies, concentration studies, cross over experiments and base studies have been performed, leading to the proposal of an intermolecular mechanism for the migratory Pd(0)-decarboxylative prenylation. In the future it would be valuable to conduct further mechanistic studies towards Pd(0)-decarboxylative prenylation including in-situ NMR and react IR investigations. The aim of these two investigations would be to monitor the intermediates formed in the Pd(0)-decarboxylative prenylation that cannot be isolated. Prenylated-diketo-prenylester-dioxinone \( 158 \) and diketo-dioxinone \( 160 \) are not isolated however, they should be seen utilising in-situ NMR and react IR and thus provide further evidence for the proposed mechanism (Scheme 64).
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

In addition, it would be advantageous to carry out the decarboxylative prenylation with 1 equivalent of Pd(PPh₃)₄ at a low concentration (0.014 M) in order to observe the products that were produced. Theoretically with 1.0 equivalent of Pd(PPh₃)₄ pathway A of the proposed mechanism (Scheme 64) would be shut down. Therefore at a low concentration only resorcylate 155 should be obtained.

Scheme 64: Proposed Mechanism
3 Verification and Mechanistic Studies Towards the Migratory Pd(0)-Decarboxylative Prenylation

3.12.2 Aromatisation under Elevated Temperatures

Section 3.3 demonstrated that aromatisation could occur at elevated temperatures without the requirement of a base, acid or pressure (sealed tube) (Scheme 65). This initial result could be studied further utilising a variety of alcohols such as ethanol or i-propanol. Moreover, different side chains could be investigated in place of the branched prenyl moiety. These results could be utilised by the Medicinal Section of the Barrett group towards the synthesis of different resorcylate analogues. Recently, the resorcinol scaffold has been shown to be an HSP90 inhibitor.\textsuperscript{105} Therefore new methodologies to generate analogues of the resorcinol scaffold will be invaluable for biological screening/testing.

\begin{equation}
\text{Scheme 65: Aromatisation at Elevated Temperatures}
\end{equation}
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Cristatic acid methyl ester 183 was chosen as a synthetic target to exhibit both the late-stage aromatisation strategy and the Pd(0)-decarboxylative allylation sequence. Cristatic acid (5) was isolated from the fruiting bodies of the higher mushroom *Albatrellus cristatus* by Steglich *et al.* in 1981. Cristatic acid methyl ester 183 was chosen as a synthetic target to exhibit both the late-stage aromatisation strategy and the Pd(0)-decarboxylative allylation sequence. Cristatic acid (5) was isolated from the fruiting bodies of the higher mushroom *Albatrellus cristatus* by Steglich *et al.* in 1981.\textsuperscript{6,7} *Albatrelles cristatus* exhibits a wide range of biological properties including antibiotic activity against gram-positive bacteria, a strong haemolytic function and has a considerable inhibitory effect against cells of the ascites form of the Ehrlich carcinoma.\textsuperscript{6,106}

![Figure 18: Cristatic Acid Methyl Ester 183](image)

The only two previous preparative approaches towards the total synthesis of cristatic acid (5) were published by Fürtner *et al.* in 2000\textsuperscript{106} and Joullié *et al.* in 1988.\textsuperscript{107}
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.1 Approach of Joulié et al.[107]

Joulié et al. published studies towards the total synthesis of cristatic acid (5) in 1988. The group focused on three main sections of the molecule: the resorcylate core 184, the 2,4-disubstitued furan 185 and the intervening terpenoid chain 186 (Scheme 66).[107]

![Scheme 66: Retrosynthetic Analysis](image)

Interestingly, the resorcylate core was prepared using a modified procedure developed by Barrett et al.[38] Allyl bromide was attached to the resorcylate core via an alkylation of the potassium phenolate 184. The 2,4-disubstitued furan 185 was prepared from furfural[108] and attached onto the terpenoid chain via an alkylation to give aldehyde 187. The synthesis was finished by formation of the olefin and deprotection of one of the MOM groups to afford MOM protected cristatic acid 188. Unfortunately the total synthesis was not completed due to problems deprotecting the MOM groups. A number of conditions were screened; however, only one MOM group was finally removed in 25% yield.[107] This illustrates that careful choice of protecting groups is crucial early in a synthesis (Scheme 67).
Scheme 67: Joullié’s Approach to Cristatic Acid (5)
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.2 Fürstner’s Approach[106]

The key disconnections in Fürstner’s approach to cristatic acid methyl ester 183 involved an oxidative cleavage to put in place the furan moiety, a Wittig reaction to install the olefin and a number of alkylation to build the essential benzylic and alkyl bonds (Scheme 68).[106]

![Scheme 68: Retrosynthetic Analysis](image)

The synthesis began through alkylation of sodium phenolate with allyl bromide followed by phenolic SEM protections providing prenyl resorcylate 189. Allylic oxidation and subsequent conversion to the bromide furnished bromide-prenyl-resorcylate 190. Displacement with phenyl sulphonyl 191 then took place followed by a reduction with sodium amalgam to afford resorcylate 192. At the end of the synthesis a number of conditions were screened for the final deprotection.[109] The optimal conditions were found to be TBAF in HMPA[110] which provided the cristatic acid methyl ester 183 in a 60% yield (Scheme 69).[106]
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Scheme 69: Fürstner’s Approach to Cristatic Acid Methyl Ester (183)\(^{[106]}\)

4.3 The Barrett Retrosynthetic Analysis of Cristatic Acid Methyl Ester 183

It was envisaged that opening of isopropylidene protected resorcylate 193 with MeOH could provide cristatic acid methyl ester 183. Resorcylate 193 could be obtained from a Pd(0)-decarboxylative, allylation and aromatisation sequence beginning with diketoester dioxinone 194 which in turn could be available from acylation of ketoester-dioxinone 195. It was thought that a Claisen condensation could be facilitated between acid chloride 196 and dioxinone 33 in order to obtain ketoester dioxinone 195. Finally, it was predicated that deprotection of protected alcohol 198 and subsequent heating with Meldrum’s acid could afford acid 197. It is noteworthy that this strategy does not require phenolic group protection due to the late stage aromatisation to provide the aromatic core.
4.4 Retrosynthetic Analysis for Protected Alcohol 198

The aim of this retrosynthesis was to devise an elegant and novel concept enabling new intermediates for pharmaceutical and biological exploration that had not been utilised previously by Fürstner et al.\textsuperscript{[106]} or Joullié et al.\textsuperscript{[107]} It was hypothesised that the furan moiety could be put in place \textit{via} a one-pot sequence involving a Nef reaction,\textsuperscript{[111]} \textit{t}-butyl deprotection and decarboxylation\textsuperscript{[112]} and Paal-Knorr furan formation.\textsuperscript{[113]} It was envisaged that the nitro compound 199 could be generated \textit{via} a Michael addition between keto-ester 200 and nitro olefin 201. Finally, it was thought that a Henry reaction\textsuperscript{[114]} on aldehyde 202 could facilitate the construction of nitro olefin 201 (Scheme 71).
Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Scheme 71: Strategy for the Protected Alcohol 198

Scheme 72 below illustrates the proposed mechanism for furan formation. It was thought that a Nef reaction on nitro alkane 199 could provide aldehyde 203, under the reaction conditions the t-butyl ester would be removed facilitating decarboxylation. Attack of the ketone onto the aldehyde in a Paal–Knorr fashion could enable the formation of the 5-membered ring 204 and finally dehydration of the hemiacetal would afford furan 198.

Scheme 72: Stepwise Formation of Furan 198
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.5 Synthesis of t-Butyl-Ester-Keto 200

Initially, it was decided to focus on the synthesis of t-butyl-ester-keto 200. t-Butyl ester-keto 200 has previously been synthesised by Lavallée et al. in 1991 (Scheme 73).\[115\] Aldehyde 205 was treated with the zinc enolate of t-butyl acetate generated from zinc and t-butylbromoacetate, the corresponding β-hydroxy ketone was then treated with MnO₂ which provided keto-ester 200 in a 57% yield over the three steps. This reaction was found to be unreliable on scale due to problems generating the zinc enolate species. It was therefore not possible to synthesise the β-hydroxy ketone in significant quantities for the total synthesis.

\[
\text{Br} \quad \overset{1.7 \text{ equiv.}}{\text{Or-Bu}} \quad 205 \\
\overset{2.5 \text{ equiv.}, \text{THF}, \Delta, 5 \text{ min}}{\text{Et}_2\text{O}, 0 ^\circ\text{C to rt, 1 h, 77\% over 2 steps}} \\
\overset{(1.0 \text{ equiv.})}{\text{Or-Bu}} \quad 200
\]

Scheme 73: Synthesis of t-Butyl-Ester-Keto 200 by Lavallée et al.\[115\]

It was hypothesised that formation of enolate 206 followed by the addition of acid chloride 207 would lead to the formation of ketoester 200 (Scheme 74). Unfortunately, only decomposition of the starting materials was observed due to competing reaction pathways. It was therefore decided to utilise a softer leaving group, thus benzotriazole was studied (Scheme 75).\[83\]\[84\]

\[
\overset{2.0 \text{ equiv.}}{\text{Or-Bu}} \quad 206 \\
\overset{-78 ^\circ\text{C, 30 min}}{\text{LDA (2.1 equiv.), THF, -78 \circ\text{C}}} \\
\overset{1.0 \text{ equiv.}}{\text{Cl}} \quad 207 \\
\overset{-78 ^\circ\text{C to rt, 18 h}}{\text{Or-Bu}} \quad 200
\]

Scheme 74: Attempted Synthesis of t-Butyl-Ester-Keto 200

Benzotriazole amide 208 was synthesised from the acid 209 in a 70% yield utilising a procedure developed within the Barrett group.\[82\] The next step involved treating t-butylester 210 with LDA to form the corresponding enolate 206, which was then added to benzotriazole amide 208, furnishing keto-ester 200 in an excellent 70% yield (Scheme 75).
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Scheme 75: Synthetic of Benzotriazole Amide 208 and t-Butyl-Ester-Keto 200

4.6 Studies Towards the Construction of Nitro Olefin 211

4.6.1 Towards the Synthesis of Nitro Olefin 211 Utilising a Horner–Wadsworth–Emmons (HWE) Reaction

A number of different strategies were identified for the introduction of the E-olefin 213. Initially, it was decided to investigate the use of a HWE reaction to install the E-olefin 213. It was envisaged that nitro olefin 211 could be formed via a one step TES deprotection and Swern reaction\(^{[116]}\) of silyl ether 212 followed by a Henry reaction\(^{[114]}\). Silyl ether 212 could be produced by reduction of ester 213 to the alcohol followed by TBS protection. It was postulated that ester 213 could be obtained by performing a HWE reaction on ketone 214. Ketone 214 could be furnished via a TES protection of alcohol 215 and then treatment with MeLi\(^{[117]}\). Finally, it was hypothesised that amide 215 could be afforded by treatment of commercially available \(\delta\)-valerolactone 216 with Weinreb amide (Scheme 76).\(^{[118]}\)
The next step involved a HWE reaction to install the E-olefin 213. A HWE approach for the construction of E-olefin was sought because Joullié et al.\textsuperscript{[107]} had previously reported a high...
yielding and selective HWE procedure for the formation of E-olefin. Accordingly, treatment of ketone 214 with the ylid of ethyl 2-(diethoxyphosphoryl)acetate 218 afforded the product in 98% yield as a 3:1 mixture of E:Z isomers, respectively (Scheme 78). Regrettably, it was not possible to separate the two isomers. Presumably, Joullié et al. were able to separate their isomers due to the presence of different functionalities in the molecule. Scheme 78 demonstrates that a higher yield and selectivity was obtained compared to Joullié et al. and with the knowledge that the two isomers E-213 and Z-213 could be separable with different functionalities it was decided to continue the synthesis and try to separate at a later stage.

![Scheme 78: Horner–Wadsworth–Emmons Reaction](image)

Reduction of the ester 213 proceeded smoothly utilising DIBAL-H, affording alcohol 219 in a 63% yield (E:Z = 3:1). TBS protection of alcohol 219 furnished silyl ether 212, which was then subjected to Swern oxidation conditions facilitating a TES deprotection and subsequent oxidation in one step, providing aldehyde 220 in a 33% yield (E:Z = 3:1) (Scheme 79). Attempts to separate the E:Z mixture of alkenes after every synthetic step proved unsuccessful. Therefore, it was decided to investigate carboalumination for the introduction of the E-olefin because this method is regiospecific and would only provide the E-olefin (Scheme 80).
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.6.2 Carboalumination

The retrosynthesis begins with a one-pot TES deprotection and oxidation\(^{116}\) of silyl ether 212 followed by a Henry reaction\(^{114}\) to afford nitro olefin 211. It was envisaged that silyl ether 212 could be obtained via carboalumination\(^{119}\) of alkyne 221 followed by TBS protection of the subsequent alcohol.

![Scheme 80: Retrosynthetic Strategy Utilising Carboalumination](image)

In 2005, Dussault et al. published the total synthesis of plakinic acid A utilising a carboalumination step which inspired the retrosynthesis above (Scheme 80).\(^{120}\) It was envisaged that the carbometallation should take place in the presence of zircocene dichloride to provide the corresponding alkenyl metal derivative 222 in a high stereoselective and regioselective manner via a syn-addition.\(^{119}\) It has been proposed by Takahashi et al. that the addition of the Me-Al bond to alkynes is assisted by ZrCp\(_2\) and that Me\(_2\)AlCl-Cp\(_2\)ZrCl\(_2\) is a good methylaluminating agent.\(^{121}\) After formation of the Al-Me bond, transmetallation
utilising t-BuLi would occur followed by reaction with paraformaldehyde to provide alcohol 219 (Scheme 81).\(^{120}\)

Prior to commencing with the synthetic Scheme 81 illustrated above it was decided to trap the alkenyl metal derivative 222 with iodine to ensure the selectivity of the reaction (Scheme 82). Protection of alcohol 223 was achieved using TESCl in a 95% yield. Carboalumination commenced by stirring zirconocene dichloride with AlMe\(_3\) and alkyne 221 for 18 h, the reaction was then quenched with iodine (Scheme 82).\(^{122}\) Unfortunately, the reaction yielded the desired product 224 in a 10% yield and the deprotected alcohol 225 in a 50% yield. It was therefore decided to change the protecting group to the bulkier and less sensitive TBDPS (Scheme 83).\(^{123}\)

Scheme 81: Carboalumination Conditions and Mechanism

Scheme 82: Protection of Alcohol 223 and Subsequent Carboalumination
Protection of the alcohol 223 was achieved using TBDPSCl affording silyl ether 226 in 88% yield. Carboalumination\[121]\ commenced as before and trapping with iodine gave E-iodo-olefin 227 in a pleasing 70% yield (Scheme 83).

$$\text{保护的醇} 223 \text{ 通过使用} \text{TBDPSCl\ 得到\ 乙氧基醚} 226 \text{\ 在} 88\% \text{\ 收率。}$$

Scheme 83: Carboalumination with Alkyne 226

Having successfully carried out the reaction with iodine as the electrophile it was decided to transmetallate and quench with paraformaldehyde, facilitating the elegant three step one-pot reaction (Scheme 84).\[120]\ The reaction progressed well giving a mixture of alcohol 228 and olefin 229 in low yield. It was apparent that a longer reaction time was required in order to drive the reaction to completion. Accordingly, the reaction was repeated and stirred for 120 h after the addition of paraformaldehyde. The yield of alcohol 228 increased to 53% and olefin 229 to 22%.

$$\text{在碘化物作为亲电基的情况下成功地进行了反应之后，决定通过异构化和用甲醛终止反应，实现了精美的三条步骤一锅反应 (Scheme 84)。反应进展良好，得到混合物的醇 228 和烯烃 229\ 在低收率。明显的是，反应需要更长的时间来驱动反应到完成。因此，反应被重复并搅拌了 120 h 后添加甲醛。醇 228 的产率增加到 53% \text{和烯烃} 229\ \text{到} 22\%}.$$

Scheme 84: Carboalumination of Alkyne 226

Upon scale-up it was evident that the reaction was not optimal as the yield of both the alcohol 228 to 20% and olefin 229 to 6% were significantly reduced. Presumably, this was due to scaling up effects in particular the exothermic addition of t-BuLi in combination with a decrease in efficient mixing, creating reaction hotspots in the larger vessel which thereby led
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

to unwanted reactions and decomposition.\(^{124}\) It was therefore decided to investigate an alternative strategy for the formation of the E-olefin.

4.6.3 Stereoselective and Regioselective Reduction of Alkynol 230

The next strategy for a high yielding method for the introduction of E-olefin was to utilise a stereoselective and regioselective reduction of alkynol 230 utilising Red-Al.\(^{125}\) It was envisaged that nitro olefin 231 could be available from TBDPS deprotection of silyl ether 232, and then oxidation and a Henry reaction.\(^{114}\) Silyl ether 232 could be obtained via a PMB protection and methylation of vinyl iodide 233. Vinyl iodide 233 could be obtained following a stereoselective and regioselective reduction of alkynol 230 utilising Red-Al.\(^{125}\) Finally, alkynol 230 could be obtained by deprotonation of alkyne 226 followed by coupling with paraformaldehyde (Scheme 85).\(^{126}\)

![Scheme 85: Retrosynthetic Analysis for Nitro-Olefin 231](image.png)

The synthesis began with the TBDPS protection of alcohol 223 obtaining silyl ether 226 in an 88% yield. Deprotonation and subsequent addition of paraformaldehyde to alkyne 226 provided alkynol 230 in 87% yield.\(^{126}\) Treatment of alkynol 230 with Red-Al followed by quenching with NIS afforded olefin 234 in 80% yield (Scheme 86).\(^{125}\) However, this step
also afforded deprotection of the TBDPS group, presumably due to prolonged stirring in Red-Al. Thus it was decided to change the protecting group to PMB (Scheme 87).

Scheme 86: Synthetic Steps in the Construction of Alkene 234

PMB protection of alcohol 223 using PMBCl, provided PMB ether 235 in an excellent 90% yield. Formation of alkynol 236 progressed smoothly in an 81% yield. Subsequent treatment with Red-Al followed by NIS furnished iodide 237 in an 83% yield (Scheme 87).[125]

Scheme 87: Formation of Iodide Utilising the PMB Protecting Group

Having successfully achieved the synthesis of iodide 237 the next step in the synthetic route was displacement of the iodide functionality for a methyl group.
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4.7 Methyl Incorporation Studies

4.7.1 Methyl Incorporation Utilising the Gilman Reagent

The Gilman reagent discovered in 1966 by Henry Gilman has been shown to be extremely effective in exchanging alkyl groups with halides in alkenes.\(^{[127]}\) For this reason it was decided to investigate the use of Me\(_2\)CuLi in the synthesis of olefin 238.\(^{[129]}\) Accordingly, a number of conditions were screened for the formation of olefin 238 utilising Me\(_2\)CuLi these are illustrated below in Table 14.

The reaction was successful on one occasion (Entry 1, Table 14) however olefin 239 was also isolated. It was thought that olefin 239 had arisen due to the reaction not going to completion, thus the reaction was stirred for 24 h (Entry 2, Table 14). Unfortuantely, the yield of olefin 239 increased and methyl-olefin 238 decreased. The next strategy was to use a new bottle of MeLi with a higher concentration (Entry 3, Table 14). Interestingly, this led to the formation of olefin 239 and a new side product, alkyne 240, which was presumably formed via elimination of HI across the double bond. The reaction temperature was thus decreased to –10 °C, nevertheless olefin 239 and alkyne 240 were obtained (Entry 4, Table 14). Finally, the solvent was changed to Et\(_2\)O, but again olefin 239 and alkyne 240 were provided (Entry 5, Table 14).
Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Table 14: Conditions Screened Utilising Me₂CuLi

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp.</th>
<th>Solvent</th>
<th>Time</th>
<th>Conc. Of MeLi</th>
<th>Products¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 °C to rt</td>
<td>THF</td>
<td>6 h</td>
<td>0.3 M</td>
<td>239 10%, 238 60%</td>
</tr>
<tr>
<td>2</td>
<td>0 °C to rt</td>
<td>THF</td>
<td>24 h</td>
<td>0.3 M</td>
<td>239 40%, 238 40%</td>
</tr>
<tr>
<td>3</td>
<td>0 °C to rt</td>
<td>THF</td>
<td>15 h</td>
<td>1.3 M</td>
<td>239 40%, 240 40%</td>
</tr>
<tr>
<td>4</td>
<td>−10 °C</td>
<td>THF</td>
<td>15 h</td>
<td>1.3 M</td>
<td>239 40%, 240 40%</td>
</tr>
<tr>
<td>5</td>
<td>0 °C</td>
<td>Et₂O</td>
<td>15 h</td>
<td>1.3 M</td>
<td>239 40%, 240 40%</td>
</tr>
</tbody>
</table>

¹Isolated yield after column chromatography.

It was hypothesised that the side products may have arisen from the different bottles of MeLi being used or from the coordinating nature of the free alcohol functionality preventing the iodide from being substituted for a methyl group. Consequently, the next strategy was to protect the alcohol as a TBDPS ether and attempt the reaction again (Scheme 88). Alcohol 237 was successfully protected with the TBDPS protecting group. However, treatment with Me₂CuLi unfortunately only led to decomposition of the starting material. Due to the inconsistency and capricious nature of this transformation it was decided to study a different strategy for the incorporation of the methyl group.
4 Towards the Total Synthesis of Crisatic Acid Methyl Ester (183)

Scheme 88: TBDPS Protection Followed by Treatment with Me₂CuLi

4.7.2 Lithium Iodide Exchange Followed by MeI Addition

The next approach for the introduction of the methyl group was to carry out a lithium-iodide exchange followed by the addition of MeI. Hudrlik et al. [129] and Hopkins et al. [130] had previously demonstrated that lithium iodine exchange using n-BuLi or t-BuLi, followed by the addition of MeI led to the incorporation of a methyl group. Treatment of iodide 242 with n-BuLi followed by the addition of MeI afforded only a mixture of olefin 243 and starting material 242 (Scheme 89). The reaction was therefore attempted again with t-BuLi, however this led to decomposition of the starting material.

Scheme 89: Lithium Iodide Exchange and Followed by MeI Addition

The next strategy was to utilise an alternative protecting group to aid the lithiation. Bajwa et al., [131] Jamieson et al. [132] and Winkle et al. [133] have demonstrated the efficient directing group effects of the MOM ether. Therefore, alcohol 237 was protected as the MOM ether 244 in a 98% yield. MOM ether 244 was then treated with n-BuLi followed by MeI and interestingly two new products were obtained; olefin 245 in a 60% yield and alkyne 246 in a 30% yield (Scheme 90).
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Scheme 90: MOM Protection Followed by Lithium-Iodide Exchange and MeI Addition

It was hypothesised that alkyne 246 could have been formed via deprotonation of the olefinic C-H bond followed by elimination of the iodide (Scheme 91). Furthermore, it was postulated that olefin 245 could have been obtained due to the ‘protective sphere’ provided by the coordination of the MOM group\textsuperscript{[133]} preventing attack from MeI (Scheme 91).

Scheme 91: Proposed Mechanisms for the Formation of Alkene 245 and Alkyne 246

It was apparent the utilising lithium in this reaction was leading to formation of unwanted side-products. Hence, it was decided to investigate the use of Pd cross coupling reactions for methyl incorporation.
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.7.3 Studies towards Kumada Cross Coupling

It was hypothesised that the Kumada cross coupling, reported independently in 1972 by Corriu et al.\[134\] and Kumada et al.,\[135\] would be an excellent tool for the incorporation of the methyl group. Iodide 244/241 was treated with i-PrMgCl and Pd(PPh$_3$)$_4$ followed by the addition of MeI (Scheme 92). Pleasingly, the Kumada-type cross coupling conditions provided methyl-olefin 247 in a 47% yield (MOM protecting group) and methyl-olefin 242 in a 50% yield (TBDPS protecting group). Unfortunately, the reaction also afforded olefin 245 (MOM protecting group) and 243 (TBDPS protecting group) and recovered starting material 244 (MOM protecting group) and 241 (TBDPS protecting group) which all had very similar $R_f$ values and as a result were very difficult to separate. Thus, it was decided to conduct studies towards the Negishi Cross Coupling.\[137\]

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 244 \quad (1.0 \text{ equiv.})
\end{align*}
\]

1. i-PrMgCl (2.0 equiv.),
THF, 0 $^\circ$C, 1 h

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 247 \quad 47%
\end{align*}
\]

2. Pd(PPh$_3$)$_4$ (5 mol%), 10 min

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 244 \quad 25%
\end{align*}
\]

3. MeI (10.0 equiv.),
0 $^\circ$C to rt, 18 h

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 243 \quad 10%
\end{align*}
\]

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 245 \quad 8%
\end{align*}
\]

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 244 \quad 25%
\end{align*}
\]

\[
\begin{align*}
\text{RO} & \quad \text{I} \quad \text{OPMB} \\
R^1 = \text{MOM}, & \quad 241 \quad 20%
\end{align*}
\]

Scheme 92: Kumada-Type Cross Coupling
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.7.4 Negishi Cross Coupling

Recent work by Fu et al.\textsuperscript{[136]} has demonstrated successful palladium-catalysed Negishi cross coupling of unactivated alkyl iodides and bromides. Accordingly, ZnBr\(_2\) was prestirred with MeMgBr in Et\(_2\)O, Pd(PPh\(_3\))\(_4\) and iodide 241 were then added and the mixture stirred for 18 h.\textsuperscript{[137]} Unfortunately, only decomposition of the starting material was observed (Scheme 93).

![Scheme 93: Negishi Cross Coupling](image)

The next strategy was to utilise a pre-formed zinc complex, ZnMe\(_2\). Thus, iodide 241 was stirred with Pd(PPh\(_3\))\(_4\) followed by treatment with ZnMe\(_2\). Pleasingly, these reaction conditions afforded alkene 242 in an excellent 95\% yield. It was noteworthy that after the addition of ZnMe\(_2\) there was a colour change from colourless to yellow, presumably, indicating activation of the catalyst.\textsuperscript{[138]} When the reaction was complete the colour changed back to colourless (Scheme 94).

![Scheme 94: Negishi Cross Coupling Utilising ZnMe\(_2\)](image)
4.8 Final Steps Towards the Synthesis of Nitro-Alkene 250

PMB deprotection was achieved using DDQ in CH$_2$Cl$_2$:Buffer pH 7, affording alcohol 248 in a 70% yield. Swern oxidation of alcohol 248 provided aldehyde 249 in a 92% yield (Scheme 95).

Prior to formation of nitro alkene 250 it was decided to conduct a model study in order to obtain optimised conditions for the Henry reaction,$^{[114]}$ Michael Addition and one-pot Nef reaction,$^{[111]}$ deprotection, decarboxylation$^{[112]}$ and furan formation$^{[113]}$ steps (Scheme 95).

Instead of using valuable aldehyde 249 which had taken seven steps to prepare it was decided to conduct a model study using commercially available hexanal.

Scheme 95: Final Steps Towards the Synthesis of Nitro-Alkene 250

![Scheme 95](image-url)
4.9 Model Study into the Furan Formation

Scheme 96 below illustrates the retrosynthesis that the model study would encompass. It was envisaged that a furan 251 could be available following a Nef reaction,\[^{111}\] tert-butyl deprotection, decarboxylation\[^{112}\] and Paal Knorr furan formation\[^{113}\] beginning with nitro alkane 252. Nitro alkane 252 could be obtained via a Michael addition between nitro olefin 253 and ketoester 200 and finally nitro-alkene 253 could be provided through a Henry reaction\[^{114}\] starting with hexanal.

![Scheme 96: Retrosynthesis for the Model Study](image)

4.9.1 Henry Reaction

The Henry reaction\[^{114}\] is a C–C bond forming reaction between a carbonyl compound and a nitro alkane, leading to the formation of $\beta$-hydroxy nitro compounds. If acidic protons are available dehydration will follow resulting in the formation of a $\beta$-nitro alcohol.\[^{119}\] Vergari et al. demonstrated a one-step highly efficient strategy for the preparation of nitro olefins.\[^{140}\] Accordingly, hexanal was treated with nitromethane and piperidine providing nitro-alkene 253 in a 50% yield (Scheme 97).

![Scheme 97: Henry Reaction](image)
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4.9.2 Michael Addition

The next step in the model study was a Michael addition between nitro olefin 253 and ketoester 200. It was decided treat ketoester 200 with a catalytic amount of KOt-Bu for 10 min, followed by the dropwise addition of nitro-alkene 253 in order to prevent polymerisation.[141][142] Delightfully, nitro-alkene 252 was furnished in a 75% yield (Scheme 98).[142]

![Scheme 98: Michael Addition](image)

4.9.3 Nef Reaction, t-Butyl Deprotection, Decarboxylation and Furan Formation

The next step in the model study was to investigate the one-pot Nef reaction,[111] deprotection, decarboxylation[112] and furan formation.[113] A number of academic groups have demonstrated the formation of a furan ring starting from a molecule containing the nitro and dicarbonyl functionalities.[143] For example Lee et al.[144] showed that nitro alkane 254 could be transformed into furan 255 under acidic conditions (Scheme 99). Lee et al. postulated a mechanism that protonation of the nitro group followed by intramolecular attack of the carbonyl oxygen towards the protonated nitro group would generate the allylic carbocation intermediate 256. This would then be followed by an intermolecular Friedel-Crafts reaction with benzene and finally aromatisation to give furan 255.[144][145]
Based on the reported precedent, it was decided to screen a number of conditions for the one-pot reaction to provide the furan 251 (Table 15). The first conditions to be screened were those utilised by Lee et al.\cite{144} (Entry 1, Table 15), however, these harsh conditions led to decomposition of the starting material. Consequently, the next tactic was to utilise \( \text{KMnO}_4 \) to perform an oxidative Nef reaction (Entry 2, Table 15), but this method afforded a complex mixture of products.\cite{146} As a result the use of \( \text{CrCl}_2 \) was studied in order to facilitate a reductive Nef reaction (Entry 3, Table 15).\cite{147} It was also thought that the Lewis acid would aid in furan formation.\cite{113} Nonetheless, this condition yielded a complex mixture of products.

The next strategy was to look at more traditional conditions for the Nef reaction, forming the nitronate salt followed by the addition of strong aqueous acid (Entries 4 & 5, Table 15).\cite{147} Furthermore, it was postulated that the acidic conditions would aid the deprotection, decarboxylation\cite{112} and furan formation steps.\cite{113} Unfortunately, no reaction was observed and only recovered starting material was isolated. Yoshikoshi et al. demonstrated that refluxing a nitro compound and dicarbonyl in KF could lead to the formation of furan rings.\cite{148} Accordingly, these conditions were attempted; however, they led to the isolation of starting material (Entry 6, Table 15). Finally, Fuji et al. demonstrated the use of \( \text{TiCl}_3 \) to facilitate a Nef reaction in the total synthesis of spirotryprostatin B (91).\cite{149} Additionally, it
was thought TiCl₃ would act as Lewis acid aiding furan formation. Nevertheless, these conditions led to the formation of a complex mixture of products (Entry 7, Table 15).

**Table 15: Nef Reaction, Deprotection, Decarboxylation and Furan Formation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄ (excess), TFA (excess), C₆H₆, Δ, 2 h[^144]</td>
<td>Decomposition of 252</td>
</tr>
<tr>
<td>2</td>
<td>NaH (2.0 equiv.), HΟt-Bu, 10 min, 0°C; KMnO₄ (excess), Pentane/H₂O, 30 min, 0°C to rt[^146]</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>NaOMe (2.0 equiv.), MeOH, 30 min, 0°C; NH₄OAc (25.0 equiv.), CrCl₂ (3.0 equiv.), H₂O, 0°C to rt, 3 h[^147]</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>NaH (2.0 equiv.), THF, 0°C, 30 min; 1 M HCl, 0°C to rt, 18 h[^147]</td>
<td>RSM</td>
</tr>
<tr>
<td>5</td>
<td>NaH (2.0 equiv.), THF, 0°C, 30 min; H₂SO₄ (conc.), 0°C to rt, 18 h[^147]</td>
<td>RSM</td>
</tr>
<tr>
<td>6</td>
<td>KF (excess), Xylene, Δ, 18[^148]</td>
<td>RSM</td>
</tr>
<tr>
<td>7</td>
<td>NH₄OAc (excess), MeOH/H₂O, TiCl₃ (20% aq., 4.0 equiv.), 0°C to rt, 5 h[^149]</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Regrettably, formation of furan 251 in a one-pot reaction was not possible. It was apparent that the Nef reaction was not working successfully, either because the aldehyde was being formed and then decomposing (Entries 2, 3 & 7, Table 15) or not being formed at all (Entries
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4, 5 & 6, Table 15). Therefore, it was decided to perform the t-butyl deprotection and decarboxylation reaction to afford nitro alkane 252 and then attempt the Nef reaction followed by furan formation. Accordingly, ester 252 was treated with TsOH and refluxed in benzene affording nitro ketone 257 in a pleasing 91% yield (Scheme 100).\textsuperscript{[150]}

\[ \text{O}_2\text{N} \quad \text{O} \quad \text{O}_2\text{N} \quad \text{O} \]

\[ \text{252 (1.0 equiv.)} \quad \xrightarrow{\text{TsOH (0.2 equiv.), C}_6\text{H}_6, \Delta, 4 \text{ h}, 91\%} \quad \text{257} \]

\textbf{Scheme 100: Deprotection and Decarboxylation of Ester 252}

The next step was to attempt a one-pot Nef reaction\textsuperscript{[111]} and furan formation.\textsuperscript{[113]} The conditions illustrated in Entries 2, 4 and 6 of Table 15 were attempted however only afforded degradation of the starting material. It was apparent that aldehyde 258 was being produced but then decomposing in the reaction mixture. Consequently, it was decided to form the aldehyde 258 \textit{via} the Nef reaction,\textsuperscript{[111]} isolate the product and then perform the furan formation. Scheme 101 below illustrates the traditional Nef conditions utilised to furnish aldehyde 258 in a 71% yield.\textsuperscript{[147]}

\[ \text{O}_2\text{N} \quad \text{O} \quad \text{O}_2\text{N} \quad \text{O} \]

\[ \text{252 (1.0 equiv.)} \quad \xrightarrow{\text{1. NaH (2.2 equiv.), MeOH, 0 \degree\text{C}, 30 \text{ min}}} \quad \text{258} \]

\[ \text{258 (1.0 equiv.)} \quad \xrightarrow{\text{2. HCl:MeOH: H}_2\text{O (1:8:10), 0 \degree\text{C}, 15 \text{ min}, 71\%}} \quad \text{251} \]

\textbf{Scheme 101: Nef Reaction for the Formation of Aldehyde 258}

With aldehyde 258 in hand the Paal Knorr furan formation was attempted. The Paal Knorr furan synthesis proceeds under acidic conditions or by Lewis Acid activation.\textsuperscript{[113]} Under acidic conditions decomposition of the starting material occurred (Scheme 102).

\[ \text{O}_2\text{N} \quad \text{O} \quad \text{O}_2\text{N} \quad \text{O} \]

\[ \text{258 (1.0 equiv.)} \quad \xrightarrow{\text{HCl (conc):H}_2\text{O (1:1), 30 \text{ min, rt}}} \quad \text{251} \]

\textbf{Scheme 102: Attempted Furan Formation under Acidic Conditions}
However, when aldehyde 258 was treated with TiCl₃, furan 251 was isolated in a 3% yield with a complex mixture of side products (Scheme 103). It was apparent that this reaction would require tedious optimisation in order to make a feasible synthetic route towards cristatic acid methyl ester 183. Due to this reason and the large number of steps in the synthesis it was decided to concentrate on an alternative route towards the synthesis of cristatic acid methyl ester 183.

Scheme 103: Furan Formation via Lewis Acid Activation
4.10 Strategy B for Protected Alcohol 198: Silylether 259

Strategy B for the construction of silylether 259 was a more conservative retrosynthesis. It was envisaged that terpenoid 259 could be formed by activation of alcohol 260 as the mesylate followed by hydride addition. Furan 260 could be installed via a lithium halogen exchange on bromo-furan 261 followed by the addition of aldehyde 262. It was thought that oxidative cleavage of epoxide 263 could afford aldehyde 262. Finally, TBDPS protection of geraniol 265 followed by epoxidation of the olefin 264 could provide epoxide 263 (Scheme 104).

4.11 Synthesis of Alcohol 260

4.11.1 Synthesis of Aldehyde 262

The synthesis began with the TBDPS protection of geraniol 265 to provide silyl ether 264. Epoxidation of olefin 264 using m-CPBA afforded epoxide 263 in a 71% yield. Finally, oxidative cleavage of epoxide 263 was achieved furnishing aldehyde 262 in a 74% yield (Scheme 105).
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Scheme 105: Synthesis of Aldehyde 262

4.11.2 Synthesis of Bromo-Furan 261

The next step in the synthetic route was the synthesis of olefin 261 via a Wittig reaction.\[154\]

This was achieved by first treating \(i\)-propyl(triphenyl)phosphonium iodide with \(n\)-BuLi at \(-78\) °C. The solution was then warmed to \(0\) °C, resulting in a colour change from orange to a deep red, presumably indicating the formation of the phosphonium ylide.\[155\] This warming was essential and if it was not done the reaction did not work and decomposition of the starting material occurred. The solution was then cooled to \(-78\) °C and commercially available aldehyde 266 added, after 1 h and consumption of the starting material the reaction was stopped, providing olefin 261 in a 20% yield (Scheme 106).\[107\]

Scheme 106: Formation of Bromo-Furan 261

It was postulated that the yield was low for this reaction due to the unstable nature of olefin 261.\[107\] This was demonstrated further because olefin 261 could only be stored in the freezer for around two weeks before it degraded, presumably via polymerisation. For these reasons it was decided to protect aldehyde 266 prior to the lithium halogen exchange step and then
perform the Wittig reaction following the activation as the mesylate and reduction (Scheme 107). Accordingly, aldehyde 266 was protected as the diethyl acetal 267 in a 77% yield.\\[\textsuperscript{107,156}\]

\[
\begin{align*}
\text{Br} & \quad \text{OEt} \\
\text{266 (1.0 equiv.)} & \quad \text{267}
\end{align*}
\]

\textbf{Scheme 107: Protection of Aldehyde 266}

\subsection*{4.11.3 Lithium-Halogen Exchange Followed by the Addition of Aldehyde 261}

Bromo-furan 267 was treated with n-BuLi in order to facilitate a lithium-bromine exchange, aldehyde 262 was then added to the reaction mixture providing alcohol 268 in a 10% yield and bromo-alcohol 269 in a 2% yield (Scheme 108).\\[\textsuperscript{152}\] While the reaction was low yielding it was interesting that bromo-alcohol 269 was also isolated. Presumably, competition between lithium-bromine exchange and ortho-lithiation upon addition on n-BuLi gave rise to the two different products 268 and 269.\\[\textsuperscript{157}\]

\[
\begin{align*}
\text{Br} & \quad \text{OEt} \\
\text{267 (1.0 equiv.)} & \quad \text{TBDPSO} \\
\text{262 (0.9 equiv.)} & \quad \text{268} 10\% \\
-78 \degree C & \quad \text{269} 2\%
\end{align*}
\]

\textbf{Scheme 108: Addition of Bromo Furan 267 to Aldehyde 269}

Mesylation of alcohol 268 followed by the addition of NaBH\textsubscript{4} was attempted (Scheme 109).\\[\textsuperscript{151,158}\] It was thought that following mesylation and upon addition NaBH\textsubscript{4}, a nucleophilic source of hydride,\\[\textsuperscript{159}\] the mesyl group would readily leave because the partial positive charge $\alpha$ to the furan would be readily stabilised by the aromatic system.
Unfortunately, under these conditions decomposition of the starting material 269 was observed due to the sensitive nature of the furan moiety.

Scheme 109: Mesylation Followed by Reduction

Due to the low yield of alcohol 269 and unsuccessful nature of the mesylation and hydride reaction it was decided to synthesise the iodide 271 and then perform an alkylation with bromo-furan 267. This strategy was chosen because it was previously utilised successfully by Joullié et al.\textsuperscript{[107]}

4.12 Alkylation Approach to Furan 259

4.12.1 Retrosynthetic Analaysis

It was thought that deprotection of diethyl acetate 270 and a subsequent Wittig reaction\textsuperscript{[154]} on the corresponding aldehyde could provide terpenoid 259. An alkylation reaction between bromo-furan 267 and iodide 271 could give access to alkyl-furan 270. Iodide 271 could be available following mesylation of alcohol 272 and a Finkelstein reaction.\textsuperscript{[107]} Finally, alcohol 272 could be obtained via a reduction of aldehyde 262 (Scheme 110).\textsuperscript{[107]}

Scheme 110: Retrosynthesis for Furan 259
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4.12.2 Synthesis of Iodide 271

Reduction of aldehyde 262 utilising NaBH₄ provided alcohol 272 in an 81% yield.\[^{[153]}\] Iodide 271 was then formed *via* mesylation of alcohol 272 followed by an iodide substitution utilising NaI (Scheme 111).\[^{[153]}\] With iodide 271 in hand the cross coupling with bromo-furan 267 was attempted.

Scheme 111: Synthesis of Iodide 271

4.13.2 Alkylation of Bromo-Furan 267 with Iodide 271

Bromo-furan 267 was treated with *n*-BuLi followed by the addition of HMPA. Iodide 271 was then added furnishing furan 270 in a 60% yield and bromo-terpenoid 273 in a 10% yield (Entry 1, Table 16). The addition order was essential for this reaction and when HMPA was added prior to *n*-BuLi the only product obtained was bromo-terpenoid 273 (Entry 3, Table 16). Presumably, this was due to pre-complexation of *n*-BuLi with HMPA\[^{[157]}\] promoting ortho-lithiation and drastically reducing the rate of lithium-halogen exchange.\[^{[157]}\] The reaction was attempted without the use of HMPA, however, the yield of both products 270 and 273 dropped to 30% and 4%, respectively (Entry 2, Table 16).

Scheme 112: Alkylation of Bromo-Furan 267 with Iodide 271
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Due to the coordinating nature of HMPA\cite{[160]} in this reaction it was decided to investigate the alternative reagents DMPU\cite{[161]} and DMI\cite{[162]} (Entries 4 & 5, Table 16). The aim of this investigation was to see if these additives affected the yield or course of this reaction. Unfortunately, the yield of both terpenoid 270 and bromo-terpenoid 273 did not increase and HMPA was found to be the best reagent for this reaction.

Table 16: Alkylation Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions prior to Iodide Addition\textsuperscript{a}</th>
<th>Products\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n)-BuLi (2.0 equiv.), 5 min, (-78^\circ) C; HMPA (2.4 equiv.), 30 min</td>
<td>270 60%, 273 10%</td>
</tr>
<tr>
<td>2</td>
<td>(n)-BuLi (2.0 equiv.), (-78^\circ) C, 30 min</td>
<td>270 30%, 273 4%</td>
</tr>
<tr>
<td>3</td>
<td>HMPA (2.4 equiv.), 5 min, (-78^\circ) C; (n)-BuLi (2.0 equiv.), 30 min</td>
<td>273 71%</td>
</tr>
<tr>
<td>4</td>
<td>(n)-BuLi (2.0 equiv.), 5 min, (-78^\circ) C; DMI (2.4 equiv.), 30 min</td>
<td>270 33%, 273 6%</td>
</tr>
<tr>
<td>5</td>
<td>(n)-BuLi (2.0 equiv.), 5 min, (-78^\circ) C; DMPU (2.4 equiv.), 30 min</td>
<td>270 24%, 273 3%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Iodide 271 was added to all reactions at \(-78^\circ\) C. The reaction was then allowed to warm to rt and stirred for 18h.

\textsuperscript{b}Isolated yield after column chromatography.
4.14 Final Steps in the Synthesis of Alcohol 275

The final steps in the synthesis of alcohol 275 involved deprotection of diethyl acetal 270, a Wittig reaction to install the olefin 259 and deprotection of the silylether (TBDPS).

A number of conditions were investigated for the deprotection of diethyl acetal 270 (Table 17). The first conditions (Entry 1, Table 17) demonstrated by Joullié et al.,\(^\text{[107]}\) involved treating diethyl acetal 270 in CDCl\(_3\) overnight, unfortunately this did not facilitate deprotection and starting material was recovered. Presumably, this reaction only works if the CDCl\(_3\) is acidic in nature. Therefore, the next strategy (Entry 2, Table 17) was to stir diethyl acetal 270 in 1 M HCl for 30 min, this provided aldehyde 274 in an excellent 89% yield. However, interestingly Gregg et al. demonstrated that diethyl acetal’s can be deprotected cleanly and efficiently utilising In(OTf)\(_3\) in acetone.\(^\text{[163]}\) Accordingly, diethyl acetal 270 was treated with In(OTf)\(_3\) and after 5 min the reaction was complete. Pleasingly, the reaction did not require purification and could be used crude in the next step.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl(_3), rt, 18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>1 M HCl, 30 min, rt</td>
<td>274 89%</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)(_3) (0.1 equiv.), Me(_2)CO, 5 min, rt</td>
<td>274 &lt;98%</td>
</tr>
</tbody>
</table>
The Wittig reaction\textsuperscript{[154]} was accomplished utilising the conditions discussed in Section 4.11.2 which provided olefin 259 in a pleasing 70\% yield\textsuperscript{[107]} The deprotection of silylether 259 was achieved in 81\% yield utilising TBAF (Scheme 113).

Scheme 113: Alkene Formation and TBDPS Deprotection

Having successfully completed the synthesis of alcohol 275 the next synthetic step involved heating with Meldrum’s acid to provide acid 259.
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4.15 Towards the Synthesis of Acid 197

The next step towards the synthesis of cristatic acid methyl ester 183 was to heat alcohol 275 with Meldrum’s acid in order to perform a retro Diels-Alder reaction and provide acid 197 (Scheme 114). Hence, alcohol 275 and Meldrum’s Acid were heated at 80 °C for 8 h, following a similar procedure reported by Tararov et al.[74] Acid 197 could be seen by both $^1$H NMR and mass spectrometry, however, the sample was not clean and it was apparent that there were a number of side products present. For this reason the reaction was repeated, however, instead of the usual workup the crude material was put onto silica and purified by chromatography. Unfortunately, due to the nature of the material the separation took a long time and acid 197 could not be purified effectively. The next step in the synthesis involved formation of acid chloride 196 utilising oxalyl chloride (Scheme 114). It was known that this reaction would generate HCl within the reaction mixture. Therefore due to the senstivie nature of the furan moiety and the cumbersome separation it was decided to devise an alternative retrosynthesis.

\[
\text{HO} \text{O} \text{O} \text{O} \text{OO} \text{HO} + \text{toluene, 80 °C, 8 h} \rightarrow \text{HO} \text{O} \text{O} \text{O} \text{OO} \text{197}
\]

\[
\text{(COCl)}_2 (2.0 \text{ equiv.}), \text{DMF (cat.), CHCl}_2 \rightarrow \text{Cl} \text{O} \text{O} \text{O} \text{O} \text{O} \text{196}
\]

Scheme 114: Retro-Diels Alder Reaction of Alcohol 275 and Meldrum's Acid
4.16 Second Retrosynthesis for Cristatic Acid Methyl Ester 183

It was predicted that cristatic acid methyl ester 183 could be available via opening of isopropylidene protected resorcylate 193 with MeOH. Treatment of diketo-ester-dioxinone 276 with acetate 277 and Pd(PPh₃)₄ could facilitate an external Pd(0)-decarboxylative allylation; subsequent ester deprotection and aromatisation could then furnish isopropylidene protected resorcylate 193. It was envisaged that acetate 277 could be obtained from alcohol 275. Formation of diketo-ester-dioxinone 276 could be accomplished utilising standard methodology from within the Barrett group (discussed in Chapter 2) (Scheme 115).

Scheme 115: Alternative Retrosynthesis for Cristatic Acid Methyl Ester 183
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4.17 Synthesis of Diketo-Ester-Dioxinone 276

The synthesis of diketo-ester-dioxinone 276 began by refluxing Meldrum’s Acid with alcohol 280, facilitating a retro Diels-Alder reaction providing acid 281 in a 90% yield.[74] Acid 281 was then transformed into the corresponding acid chloride 279 utilising oxalyl chloride and catalytic DMF. Treatment of dioxinone with LiHMDS followed by the addition of acid chloride 279 afforded keto-ester-dioxinone 278 in a 55% yield. Finally, the synthesis of diketo-ester-dioxide 276 was achieved by acylation of keto-ester-dioxinone 278 with acetyl chloride (Scheme 116).[42][43]

![Scheme 116: Synthesis of Diketo-Ester-Dioxinone 276](image-url)
4.18 Synthesis of Acetate 277 and Subsequent Allylation with Diketo-Ester-Dioxinone 276

Acetate 277 was synthesised utilising a procedure from within the Barrett group.\cite{155}

Treatment of alcohol 275 with acetic anhydride, K$_2$CO$_3$ and DMAP provided acetate 277 in a 60% yield (Scheme 117). With acetate 277 in hand the Pd(0)-catalysed decarboxylative allylation, ester deprotection and aromatisation could be attempted (Scheme 118).

\[
\text{HO-}
\begin{array}{c}
\text{275 (1.0 equiv.)}
\end{array}
\begin{array}{c}
\text{Ac}_2\text{O (2.0 equiv.),}
\text{K}_2\text{CO}_3 (2.0 equiv.),}
\text{DMAP (cat.),}
\text{EtOAc, rt, 18 h, 60%}
\end{array}
\begin{array}{c}
\text{277}
\end{array}
\]

Scheme 117: Synthesis of Acetate 277

Following earlier work from within the Barrett group involving allylation\cite{102} and following the mechanistic studies (Chapter 3) it was envisaged that treatment of diketo-ester-dioxinone 276 and acetate 277 with Pd(PPh$_3$)$_4$ would facilitate a decarboxylative allylation providing intermediate 282 (Scheme 118). The next step in the sequence would involve deprotection of the TMSE ester and subsequent decarboxylation and aromatisation to furnish isopropylidene resorcylate 193. Serrano-Wu \textit{et al}.\cite{164} demonstrated that deprotection of TMSE esters and decarboxylation can take place utilising TBAF. It was further envisaged that the TBAF would provide a basic system enabling aromatisation to take place. Accordingly, diketo-ester 276 and acetate 277 were treated with Pd(PPh$_3$)$_4$ followed by TBAF. Unfortunately, the reaction yielded resorcylate 283, with the TMSE ester still intact (Scheme 118).
Although the desired product 193 was not obtained, the results from the reaction were very encouraging, because the Pd(0)-decarboxylative allylation was successful. Therefore, it was apparent that different conditions were required for the deprotection of the TMSE ester that would enable deprotection prior to aromatisation. A model study was conducted into the Pd(0)-decarboxylative, allylation, deprotection and aromatisation sequence utilising farnesyl acetate 284.
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4.19 Model Study into the Decarboxylative, Allylation, Deprotection and Aromatisation Sequence\textsuperscript{VIII}

Commercially available farnesyl 285 was treated with acetic anhydride to provide the corresponding acetate 284 for the model study in an 85% yield (Scheme 119).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {285 (1.0 equiv.)};
\draw[->] (a) -- (1.5,0) node[midway,above] {Ac_2O (2.0 equiv.), K_2CO_3 (2.0 equiv.), DMAP (cat.), EtOAc, rt, 18 h, 85\%} -- (3,0) node[midway,above] {284};
\end{tikzpicture}
\end{center}

\textbf{Scheme 119: Synthesis of Acetate 284}

The first set of conditions to be screened were those reported by Serrano-Wu \textit{et al.}\textsuperscript{[164] (Entry 1, Table 18). These conditions provided resorcylate 285 with the TMSE ester still present. It was therefore decided to screen TBAF•1H_2O and TBAF•3H_2O to see if an additive of water would positively affect the reaction (Entries 2 & 3, Table 18), however the reaction yielded resorcylate 285. The solvent was then changed from THF to DMF and DMSO respectively (Entries 4 & 5, Table 18), nevertheless resorcylate 285 was recovered again.\textsuperscript{[165]}

Marlowe \textit{et al.} demonstrated in 1993 that SiO_2 in THF could be utilised for deprotection of the TMSE ester.\textsuperscript{[166]} These conditions were attempted but yielded resorcylate 285 (Entry 6, Table 18). The next strategy was to employ a different fluoride source, thus TAS-F,\textsuperscript{[167]} HF•NEt_3 and H_2SiF_6 were screened (Entries 7, 8 & 9, Table 18) but unfortunately yielded resorcylate 285. It was thought that the basic nature of the system was leading to aromatisation prior to deprotection, accordingly, acetic acid was added into the system with TBAF to act as a buffering agent (Entry 10, Table 18),\textsuperscript{[168]} nonetheless resorcylate 285 was

\textsuperscript{VIII}Work in Section 4.19 was carried out in collaboration with Dr. Nicolas George. He is duly thanked for his contribution to the research. Specific experiments carried out by Dr. Nicholas George are clearly stated in Table 18 with an asterisk (*).
obtained. The final set of conditions to be screened was to utilise 1 M NaOH, however this led to the formation of resorcylate 285 (Entry 11, Table 18).

**Table 18: Decarboxylative, Allylation, Deprotection and Aromatisation Sequence**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAF (5.0 equiv.), THF, Δ, 2 h&lt;sup&gt;164&lt;/sup&gt;</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>2</td>
<td>TBAF·1H₂O (5.0 equiv.), Δ, 2 h*</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>3</td>
<td>TBAF·3H₂O (5.0 equiv.), Δ, 2 h*</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>4</td>
<td>TBAF (5.0 equiv.), DMF, Δ, 2 h&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>5</td>
<td>TBAF (5.0 equiv.), DMSO, Δ, 2 h&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>6</td>
<td>SiO₂ (10.0 equiv.), THF, 5 h, rt*&lt;sup&gt;166&lt;/sup&gt;</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>7</td>
<td>TAS-F (5.0 equiv.), THF, 4 h, rt&lt;sup&gt;167&lt;/sup&gt;</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>8</td>
<td>H₂SiF₆ (5.0 equiv.), THF, 8 h, rt</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>9</td>
<td>HF·Et₃N (5.0 equiv.), THF, 1 h, rt*</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>10</td>
<td>Acetic Acid (5.0 equiv.), TBAF (5.0 equiv.), THF, 2 h, rt&lt;sup&gt;168&lt;/sup&gt;</td>
<td>Resorcylate 285</td>
</tr>
<tr>
<td>11</td>
<td>1M NaOH, 1 h, rt*</td>
<td>Resorcylate 285</td>
</tr>
</tbody>
</table>

<sup>a</sup>Crude product isolated after workup.
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

Due to time constrains and the unsuccessful nature of the conditions that were screened (Table 18) it was decided to change the retrosynthetic route for the construction of cristatic acid methyl ester 183 (the strategy is discussed in Section 4.21).

4.20 Conclusions

Studies towards this total synthesis have exhibited a wide range of methodologies developed within the Barrett group, including dioxinone chemistry\textsuperscript{[42][43]} and the Pd(0)-decarboxylative allylation and aromatisation sequence. Unfortunately, some of the more ambitious plans to install the furan were unsuccessful that would have highlighted the development of new chemistry. Nevertheless, it was convenient that it was possible to fall back on the work of Joullié \textit{et al.}\textsuperscript{[107]} in order to install the side-chain fragments. The research investigations have displayed some very interesting results; the competition between ortho-lithiation and lithium halogen exchange (Scheme 112), the colour change in the Negishi cross coupling (Scheme 94) and the Pd(0)-decarboxylative allylation between farnesyl acetate 284 and diketo-ester-dioxinone 276 providing the TMSE resorcylate 285 (Table 18).
4.21 The Synthesis of Cristatic Acid Methyl Ester 183\textsuperscript{IX}

It was postulated that following a methanolysis to form the methyl ester of cristatic acid 183, isopropylidene protected resorcylate 193 could be obtained via a Pd(0)-decarboxylative-allylation and aromatisation sequence beginning with diketo-ester-dioxinone 194. Diketo-ester-dioxinone 194 could be available from acylation of keto-ester-dioxinone 195\textsuperscript{[43]} which in turn could be formed via the coupling of amide 287 and keto-dioxinone 178. Finally, imidazole carboxylate 287 could be obtained by treating alcohol 275 with CDI (Scheme 120).

\textsuperscript{IX} Work in this Section 4.21 was carried out by Dr. Nicolas George. This section has been added into this thesis for clarity and to illustrate the end of the total synthesis of cristatic acid methyl ester 183. Dr. Nicolas George is duly thanked for finishing the total synthesis and for his contribution to this research.
The synthesis began with formation of the imidazole carboxylate 287 utilising standard conditions from within the Barrett group. Amide 287 was then coupled with diketo-dioxinone 178 to furnish keto-ester-dioxinone 195 in a 20% yield. Acylation then took place, followed by the Pd(0)-decarboxylative allylation and aromatisation sequence to afford isopropylidene protected resorcylate 193 in a 42% yield. The final step in the total synthesis involved methanolysis to furnish cristatic acid methyl ester 183 in a 64% yield (Scheme 121).
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.22 Future Work

4.22.1 Pd(0)-Decarboxylation Allylation, Ester Deprotection, Decarboxylation & Aromatisation

It was significant that aromatisation took place prior to removal of the TMSE ester in diketoester-dioxinone 282 providing TMSE resorcylate 283 over resorcylate 193. However, this might not be the case if a different protecting group\(^{[170]}\) was used in place of TMSE. Hence, it would be a good idea to study a number of different protecting groups for this transformation which might enable a number of new natural products to be harnessed where internal Pd(0)-decarboxylative allylation is not possible (Scheme 122).

![Scheme 122: Pd(0)-Decarboxylative Allylation, Deprotection and Aromatisation](image)

There are a number of potential protecting groups that could be studied. Firstly, 2,2,2-trichloroethyl ester (RCO\(_2\)CH\(_2\)CCl\(_3\)), removed with zinc dust\(^{[170][171]}\) could be considered. If zinc dust was added after Pd(0)-decarboxylative allylation had taken place it might allow deprotection prior to aromatisation. Secondly, 2-methylthioethyl ester (RCO\(_2\)CH\(_2\)CH\(_2\)SCH\(_3\)), removed by oxidation (H\(_2\)O\(_2\), (NH\(_4\))\(_6\)Mo\(_7\)O\(_{24}\), Me\(_2\)CO\(^{[170][172]}\)) could be investigated. Thirdly, 2-(p-methoxyphenyl)ethyl ester (p-CH\(_3\)OC\(_6\)H\(_4\)CH\(_2\)CH\(_2\)O\(_2\)CR), removed via treatment with 1% TFA\(^{[170][173]}\) or dichloroacetic acid in CH\(_2\)Cl\(_2\) by DDQ\(^{[170][174]}\) could be studied.
4 Towards the Total Synthesis of Cristatic Acid Methyl Ester (183)

4.22.2 Total Synthesis of Resorcylate Natural Products Utilising the Pd(0)-Decarboxylative Allylation

In the future it would be advantageous to complete the first total synthesis of cristatic acid (5). Chapter five discusses studies towards the opening of the isopropylene protected resorcylate 286 to the corresponding acid (92) which could be applied to cristatic acid methyl ester 183. Additionally, it would be good to apply the Pd(0)-decarboxylative allylation and aromatisation sequence to the total synthesis of other terpenoidal resorcylate natural products. [69]
5 Towards the Total Synthesis of Grifolic Acid (92)

5.1 Aims of the Synthetic Study

Grifolic acid (92) (Figure 19) was isolated in 1981 by Steglich et al. from the mushroom *Albatrellus cristatus*, and has been shown to display GPR120 agonistic activity. The GPR120 is a G-protein-coupled receptor found within the intestinal tract and thought to play an important role in insulin release. Grifolic acid (92) was chosen as a synthetic target to exhibit the Pd(0)-decarboxylative allylation and aromatisation sequence developed in Chapter 2. Furthermore, the target was chosen in order to conduct thorough investigations for the opening of the isopropylidene protecting group to the corresponding acid. This is because a number of terpenoidal resorcylic natural products including cristatic acid (5) contain the acid functionality.

![Figure 19: Grifolic Acid (92)](image)
5 Towards the Total Synthesis of Grifolic Acid (92)

5.2 Retrosynthetic Analysis

Scheme 123 below illustrates the proposed retrosynthetic analysis for the construction of grifolic acid (92). It was envisaged that saponification of isopropylidene resorcylate 286 could afford grifolic acid (92). Resorcylate 286 could in turn be accessed via a Pd(0)-decarboxylative allylation and aromatisation sequence from diketo-ester-dioxinone 292. A Claisen condensation of dioxinone 233 with acid chloride 294 followed by acylation could provide diketo-ester-dioxinone 292. Finally, a retro Diels-Alder reaction between Meldrum’s acid and farnesyl 285 could furnish the acid which subsequently could be transformed into acid chloride 294 (Scheme 123).[42][43]

Scheme 123: Retrosynthetic Analysis of Grifolic Acid (92)
5.3 Synthesis of Isopropylidene Protected Resorcylate 286

The synthesis began by heating Meldrum’s acid with farnesyl 285 in order to perform a retro Diels-Alder reaction affording acid 295[74] which was then transformed into the corresponding acid chloride 294 through treatment with oxalyl chloride and catalytic DMF. In this case amylene was employed in order to mop up excess HCl, preventing addition onto the farnesyl double bonds (Scheme 124).

![Scheme 124: Synthesis of Acid Chloride 294]

Deprotonation of dioxinone 33 with LiHMDS followed by the addition of acid chloride 294 afforded keto-ester-dioxinone 293 in a 65% yield. Subsequent treatment with MgCl2 and pyridine followed by the addition of acetyl chloride furnished diketo-ester-dioxinone 292 in an excellent 98% yield. Finally, facilitation of the Pd(0)-decarboxylative allylation and aromatisation sequence afforded resorcylate 286 in a 66% yield (Scheme 125).
5 Towards the Total Synthesis of Grifolic Acid (92)

![Scheme 125: Synthesis of Resorcylate 286](image)

5.4 Studies Towards the Formation of Grifolic Acid (92)

5.4.1 Saponification of Isopropylidene Resorcylate 286

Having successfully achieved the synthesis of resorcylate 286 the next goal was to conduct investigations into the formation of grifolic acid (92) through opening of the isopropylidene moiety. General conditions for the opening of isopropylidene groups involve treatment with an acid such as TFA.\textsuperscript{[176]} However, during studies towards the total synthesis of angelicoin A (6) it was discovered that the use of acidic conditions (TFA) led to cyclisation of the phenol onto the protonated olefin (Scheme 126) (Chapter 2, Section 2.5). As a result, it was decided to investigate a number of non-acidic conditions for the opening of isopropylidene protected resorcylate 286 (Table 19).

![Scheme 126: Cyclisation under Acidic Conditions](image)
The first conditions to be screened (Entry 1, Table 19) were demonstrated by Fürstner et al. in 2000[177] and involved treating isopropylidene resorcylate 286 with BCl₃. The reaction was started at 0 °C, however, after no consumption of the starting material, the reaction was allowed to warm to rt and stirred for 18 h. Unfortunately, only starting material was afforded indicating that the Lewis acid was not strong enough to activate the hydrolysis.

The next strategy was to utilise the basic conditions reported by Porco, Jr. et al.[178] in 2002 (Entry 2, Table 19). But, after the addition of 1.0 equivalent of KOH there was no reaction, hence the equivalents of KOH was increased from 1.0 to 10.0 while monitoring the reaction and stirring at rt. The starting material was still present; consequently the reaction was gently heated to reflux with monitoring, and then allowed to stir for 72 h. After 72 h the starting material had been consumed, but a complex mixture of products had been obtained. It was postulated after studying the ¹H NMR that one of the products might be the decarboxylated resorcylate 286 (due to the presence of the Ar-H and there being no carboxylic acid proton) (Figure 20).[189]

![Figure 20: Decarboxylated Resorcylate 296](image)

Regrettably, due to the complex nature of products present in the reaction mixture and the small scale of the reaction the decarboxylated product 286 could not be isolated and fully identified. The reaction was repeated with NaOH (Entry 3, Table 19) and LiOH (Entry 4, Table 19), but nevertheless the same outcome occurred as with KOH. Presumably, the reaction did not work because the base deprotonated the free phenol leading to an increased electron density on the carbonyl moiety reducing its reactivity towards hydrolysis (Scheme 127).[180]
The last step in the total synthesis of amorfrutin A (8) involved a saponification utilising KOH (40%) in refluxing DMSO (Scheme 128). These conditions were applied to isopropylidene resorcylate 286 (Entry 5, Table 19) however, led to decomposition of the starting material. Seemingly because in the formation of amorfrutin A (8) the free phenol was methylated preventing deprotonation and so allowing saponification at the carbonyl moiety.

The final strategy was to add TMSCl into the reaction in addition to KOTMS with the intention of protecting the phenol \textit{in situ} allowing the saponification to take place. Regrettably, after the addition of excess TMSCl and KOTMS and heating the reaction to reflux the reaction only yielded starting material (Entry 7, Table 19).

\textbf{Table 19: Conditions Screened Towards the Formation of Grifolic Acid (92)}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BCl$_3$ (1.0 to 10.0 equiv.), CH$_2$Cl$_2$, 0 °C to rt, 18 h$^{[177]}$</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>KOH (1.0 to 10.0 equiv.), THF/H$_2$O (1:1), rt to Δ, 72 h$^{[178]}$</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>NaOH (1.0 to 10.0 equiv.), THF/H$_2$O (1:1), rt to Δ, 72 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>LiOH (1.0 to 10.0 equiv.), THF/H$_2$O (1:1), rt to Δ, 72 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>KOH (40%), DMSO, Δ, 18 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>KOTMS (1.0 to 10.0 equiv.), THF, rt to Δ, 18 h$^{[181]}$</td>
<td>RSM</td>
</tr>
<tr>
<td>7</td>
<td>KOTMS (1.0 to 10.0 equiv.), TMSCl (1.0 to 10.0 equiv.), THF, rt to Δ, 18 h</td>
<td>RSM</td>
</tr>
</tbody>
</table>
5 Towards the Total Synthesis of Grifolic Acid (92)

5.4.2 Formation of Methyl Ester 300 and Subsequent Saponification Attempts

The methyl ester of resorcylate 300 was synthesised utilising previous conditions from within the Barrett group.\textsuperscript{160} Resorcylate 286 was heated with MeOH and Cs\textsubscript{2}CO\textsubscript{3} in a sealed tube providing methyl ester 300 in a 98% yield (Scheme 129). With methyl ester 300 in hand a number of saponification conditions were attempted (Table 20).

![Scheme 129: Preparation of Methyl Ester 300](image)

The first strategy for the conversion of the methyl ester 300 to the corresponding acid (92) was to utilise traditional saponification conditions,\textsuperscript{182} hence methyl ester 300 was treated with LiOH in MeOH/H\textsubscript{2}O at rt. The equivalents of the base were increased but the temperature remained the same because previously this had led to decomposition of the starting material and suspected decarboxylation (Entry 4, Table 20). Unfortunately, the reaction yielded residual starting material, thus NaOH (Entry 2, Table 20) and KOH (Entry 3, Table 20) were investigated, yet the same result was observed. Presumably, the reaction did not work because the base deprotonated the two phenolic moieties leading to an increased electron density on the carbonyl moiety, reducing its reactivity towards hydrolysis (Scheme 127).

The next synthetic approach was to attempt the conditions of Lovrić et al.\textsuperscript{181} hence methyl ester 300 was treated with KOTMS (Entry 4, Table 20). Unfortunately, the reaction yielded residual starting material, and, with \textit{in situ} protection of the phenol moieties with TMSCl in the presence of KOTMS, (Entry 5, Table 20) having no effect.
Table 20: Saponification Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOH (1.0 to 10.0 equiv.), MeOH/H₂O (1:1), rt, 72 h</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>NaOH (1.0 to 10.0 equiv.), MeOH/H₂O (1:1), rt, 72 h</td>
<td>RSM</td>
</tr>
<tr>
<td>3</td>
<td>KOH (1.0 to 10.0 equiv.), MeOH/H₂O (1:1), rt, 18 h</td>
<td>RSM</td>
</tr>
<tr>
<td>4</td>
<td>KOTMS (1.0 to 10.0 equiv.), THF, rt to Δ, 18 h&lt;sup&gt;181&lt;/sup&gt;</td>
<td>RSM</td>
</tr>
<tr>
<td>5</td>
<td>KOTMS (1.0 to 10.0 equiv.), TMSCl (1.0 to 10.0 equiv.) THF, rt to Δ, 18 h</td>
<td>RSM</td>
</tr>
</tbody>
</table>

5.4.3 Protection of Phenol Followed by Saponification

It was apparent that saponification was not effective on either isopropylidene protected resorcylate 286 or methyl ester 300. Thus the next strategy was to protect the free phenol with the sterically stable and bulky TBDPS protecting group.<sup>183</sup> Accordingly, phenol 286 was treated with TBDPSCI and imidazole, providing silyl ether 301 in an 88% yield (Scheme 130).

Scheme 130: Formation of Silyl ether 301

A range of conditions for the saponification of resorcylate 301 were attempted and are illustrated in Table 21. Basic conditions utilising KOH were attempted but led to the
5 Towards the Total Synthesis of Grifolic Acid (92)

deprotection of the silyl ether (Entry 1, Table 21).\textsuperscript{[178]} It was thus decided to utilise the Lewis acid conditions demonstrated by Fürstner et al.,\textsuperscript{[177]} nevertheless treatment of resorcylate 301 with BCl$_3$ led to deprotection of the silyl ether (Entry 2, Table 21). Finally, KOTMS was tried (Entry 3, Table 21),\textsuperscript{[181]} but led to deprotection. These results were interesting considering the inherent stability of the TBDPS group.\textsuperscript{[183][184]}

Table 21: Saponification Conditions of Resorcylate Silylether 301

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH (1.0 to 5.0 equiv.), THF/H$_2$O (1:1), rt, 6 h\textsuperscript{[182]}</td>
<td>Resorcylate 286</td>
</tr>
<tr>
<td>2</td>
<td>BCl$_3$ (1.0 to 10.0 equiv.), CH$_2$Cl$_2$, rt, 18 h\textsuperscript{[177]}</td>
<td>Resorcylate 286</td>
</tr>
<tr>
<td>3</td>
<td>KOTMS (1.0 to 5.0 equiv.), THF, rt, 18 h\textsuperscript{[181]}</td>
<td>Resorcylate 286</td>
</tr>
</tbody>
</table>

5.4.4 Thermal Opening of Isopropylidene 286

Due to the success in the formation of methyl ester 300 via treatment with MeOH in the presence of Cs$_2$CO$_3$ it was decided to utilise these conditions using TMSCH$_2$CH$_2$OH 280 in place of MeOH.\textsuperscript{[169]} The intention of this was to create the protected carboxylic acid 303 and subsequently deprotect in order to furnish griflic acid (92). Hence, silyl ether resorcylate 301 was treated with TMSCH$_2$CH$_2$OH 280 in the presence of Cs$_2$CO$_3$ and delightfully, resorcylate 303 was afforded in a 63% yield. However, deprotection of the silyl ether 302 also occurred, thus the reaction was repeated beginning with resorcylate 286. Pleasingly, the reaction was successful and silyl ether 303 was isolated in a 75% yield (Scheme 131).
5 Towards the Total Synthesis of Grifolic Acid (92)

The last step in the total synthesis was the deprotection of the TMSE protecting group (Scheme 131), however due to time constraints this was not possible. Nonetheless, a very robust route for the opening of isopropylidene resorcylates had been established which with the subsequent deprotection could afford the corresponding acids.

5.5 Conclusions

In conclusion, the synthesis of resorcylate 286 has been accomplished in four linear steps from dioxinone 33 in an overall yield of 32%. The synthesis has successfully exhibited both dioxinone methodology\(^{[42][43]}\) and the Pd(0)-decarboxylative allylation and aromatisation sequence. The project has demonstrated that the opening of the isopropylidene protected resorcylate 286 is not possible under a number of basic and Lewis acid conditions. This study has established that conversion of the methyl ester 300 to the corresponding acid (92) is not trivial. Nevertheless, the study has discovered that isopropylidene protected resorcylate 286 can be opened upon treatment with TMSCH\(_2\)CH\(_2\)OH 280 in the presence of Cs\(_2\)CO\(_3\) to provide the TMSE protected acid 303 which could in turn be deprotected to furnish the corresponding acid (92). This methodology can now be applied to the synthesis of other resorcylate natural products containing similar functionalities.\(^{[175]}\)
5 Towards the Total Synthesis of Grifolic Acid (92)

5.6 Future Work

5.6.1 Synthesis of the Grifolin Family of Natural Products

The findings from this project can be applied towards the total synthesis of the Grifolin family of natural products (Scheme 132). In 1988, Nozoe et al. conducted a detailed study into the Grifolin family of natural products, isolating and confirming the structure of grifolin (304), o-methylgrifolin (305), grifolic acid (92) and isopentenylphenol (308) from *Polyporus dispansus*. They established that these structures were similar to those of farnesyl phenol (307) and grifolin (304) extracted from the roots of *Grifola confluens*, neogrilin isolated from *Albatrellus confluens*, and cristatic acid (5), isolated from the European *A. Cristatus* and the closely related American *Albatrellus* species.

The work discussed in this chapter would enable the possibility to synthesis grifolin (304), o-methylgrifolin (305), farnesyl phenol (307) and grifolic acid (92) from resorcylate 286 (Scheme 132). It is thought that grifolin (304) could be obtained through formation of the acid followed by decarboxylation under basic conditions at reflux. (It should be noted that the decarboxylation conditions would require optimisation). o-Methylgrifolin (305) could then be provided through selective phenol methylation. Methylation of phenol 286 followed by saponification could afford farnesyl phenol (307) and finally formation of TMSE ether 303 followed by deprotection could furnish grifolic acid (92) (Scheme 132).
5 Towards the Total Synthesis of Grifolic Acid (92)

Scheme 132: Proposed Synthesis Towards the Grifin Family of Natural Products

The grifolin family of natural products have been shown to have a range of biological properties such as antibiotic activity,[6] antimicrobial activity,[179][185] plant growth inhibitory,[186] promotion of melanin synthesis by B16 melanoma cells,[187] anticholesteremic activities level in blood and liver,[188] activity on human and rat vanilloid receptor 1 (VR1)[189] hence their synthesis and biological testing would be desirable.
5 Towards the Total Synthesis of Grifolic Acid (92)

5.6.2 The Synthesis of Isopentenylphenol (308)

As stated above Nozoe et al. isolated isopentenylphenol (308) from the mushroom *Polyporus dispansus*.\(^{[69]}\) It was envisaged that this natural product would be available from resorcylate 142, a product obtained from the mechanistic studies (Section 3.5) into the Pd(0)-deacryboxylative allylation and aromatisation sequence. Hence, resorcylate 142 was treated with MeOH in the presence of Cs\(_2\)CO\(_3\)\(^{[169]}\) and pleasingly, isopentenylphenol (308) was obtained in a 90% yield and is currently awaiting biological testing (Scheme 133).

![Scheme 133: Synthesis of Isopentenylphenol (308)](image)

5.6.3 The Synthesis of Cristatic Acid (5)

Section 4.21 above described the total synthesis of cristatic acid methyl ester 183. In the future it would be exciting to complete the first total synthesis of cristatic acid (5) *via* opening of the isopropylidene protected resorcylate 193 to TMSE ester 309 and subsequent deprotection (Scheme 134).

![Scheme 134: Proposed Synthesis of Cristatic Acid (5)](image)
6 Experimental

6.1 General Experimental Procedures

All reactions were carried out in flame-dried or oven-dried glassware in an atmosphere of dry N₂ or Ar unless otherwise stated. Room temperature was taken as 25 °C and temperatures other than this were recorded as the bath temperature, unless otherwise stated. Prolonged periods of vessel cooling were attained by the use of CryoCool apparatus.

The following reaction solvents were distilled under N₂: Et₂O and THF from Na/Ph₃CO ketyl; PhMe from Na; CH₂Cl₂, MeOH, pyridine and Et₃N from CaH₂. H₂O refers to distilled H₂O. Other solvents and all reagents were obtained from commercial suppliers and were used as obtained, if purity was >98%.

Flash column chromatography was performed using Merck silica gel 60, particle size 40-63 mm (eluants are given in parenthesis). Thin layer chromatography (TLC) was performed on pre-coated aluminum backed plates (Merck Kieselgel 60 F254), visualisation was accomplished under UV light (254 nm) and/or by staining using aqueous potassium permanganate or vanillin followed by gentle heating with a heat gun.

Melting points were obtained using a Reichert-Thermovar melting point apparatus and are uncorrected.

Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 Polarimeter with a path length of 1 dm, using the 589.3 nm Na D-line. Concentrations (c) are quoted in g/100 mL.

Infrared spectra were recorded using a Mattson 5000 FTIR apparatus with automatic background subtraction. The samples were coated on diamond; solid samples were pressed
Experimental

on the diamond at 120 Nm. Indicative features of each spectrum are given with adsorptions ($v_{max}$) reported in wavenumber (cm$^{-1}$). Selected stretches (>1500 cm$^{-1}$) have been assigned.

$^1$H NMR and $^{13}$C NMR spectra were recorded operating at 400 (Bruker DRX-400 spectrometer) or 500 (Bruker AM 500 Spectrometer) and 100 (Bruker DRX-400 spectrometer) or 125 MHz (Bruker AM 500 Spectrometer) respectively with chemical shifts ($\delta$) quoted in parts per million (ppm) and referenced to a residual solvent peak. CDCl$_3$ ($\delta_H$ 7.26, $\delta_C$ 77.16), $d_6$-CD$_3$OD ($\delta_H$ 3.31, $\delta_C$ 49.05), $d_6$-C$_6$D$_6$ ($\delta_H$ 7.16, $\delta_C$ 128.39). Coupling constants ($J$) are quoted in Hertz (Hz) to the nearest 0.1 Hz. Spectra recorded at 500 ($^1$H NMR) and 125 MHz ($^{13}$C NMR) were carried out by the Imperial College Department of Chemistry NMR Service. Proton and carbon assignments have been made for each compound, therefore HSQC, HMBC, 1D NOESY, 2D NOESY, DEPT 135, DEPT 90, DEPT 45 and $^1$H-$^1$H COSY NMR experiments were utilised where necessary.

Microanalysis was determined by the London Metropolitan University Analytical Service.

Low and high resolution mass spectra (EI, CI, ESI) were recorder by Imperial College Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer.

X-ray diffraction data were recorded by the Imperial College Department of Chemistry X-ray diffraction service.
6 Experimental

6.2 Procedures and Compound Characterisation

3-(Allyloxy)-3-oxopropanoic acid (100)

Based on a procedure by Tararov et al.[74] Meldrum's acid (30.0 g, 208 mmol, 1.0 equiv.) and allyl alcohol (27.0 mL, 416 mmol, 2.0 equiv.) were heated at 80 °C for 8 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (200 mL) and the resulting solution stirred for 8 h at rt. The reaction mixture was extracted with Et₂O : hexanes (1 : 1, 3 x 150 mL) and the aqueous acidified to pH 3 using 1 M HCl. The resulting aqueous was extracted with EtOAc (3 x 200 mL), dried (MgSO₄) and rotary evaporated to afford carboxylic acid 100[82] as a colourless oil (20.0 g, 70%):

Rf 0.43 (1 : 1 hexanes : EtOAc);

IR (neat) νₘₐₓ 3300 (br., H-O), 2949 (m, C-H), 1713 (s, C=O), 1651 (m, C=C), 1369 (m), 1312 (w), 1201 (w), 1150 (s), 1092 (w) cm⁻¹;

HRMS (CI) calc. for C₆H₁₂O₄N [M+NH₄]⁺: requires 162.0766, found 162.0759 (Δ –4.3 ppm);

¹H NMR (400 MHz, CDCl₃) 8.00 (br. s, 1H, 1), 5.99-5.90 (m, 1H, 6), 5.41-5.36 (m, 1H, 7a), 5.33-5.29 (m, 1H, 7b), 4.71 (dt, J = 6.0, 0.5 Hz, 2H, 5), 3.50 (s, 2H, 3);

¹³C NMR (100 MHz, CDCl₃) δ 170.6 (2), 166.7 (4), 131.2 (6), 119.2 (7), 65.9 (5), 40.6 (3);

Anal. Calc. for C₆H₈O₄: C, 50.00; H, 5.59. Found: C, 49.97; H, 5.44.
Based on a procedure by Navarro et al.[82] Carboxylic acid 100 (900 mg, 6.25 mmol, 0.8 equiv.) was stirred in CH$_2$Cl$_2$ (10 mL) at 0 °C. Oxalyl chloride (1.40 mL, 16.0 mmol, 2.0 equiv.) and 3 drops of DMF (cat.) were added and the reaction mixture stirred for 30 min at 0 °C followed by 30 min at rt. The reaction mixture was rotary evaporated to afford acid chloride 101 as a yellow oil which was used without further purification.

HMDS (6.9 mL, 33 mmol, 4.1 equiv.) was stirred in THF (250 mL) at –78 °C. n-BuLi in hexanes (16 mL, 32 mmol, 2.3 M, 4.0 equiv.) was added dropwise and the mixture stirred for 30 min. Dioxinone 33 (3.2 mL, 24 mmol, 3.0 equiv.) was added dropwise to the stirring solution which was stirred for a total of 1 h. Acid chloride 101 in THF (10 mL) was added dropwise to the stirring solution. The reaction mixture was stirred for 2 h and then quenched with a saturated aqueous solution of NH$_4$Cl (150 mL), acidified to pH 3 utilising 1 M HCl and extracted with EtOAc (3 x 100 mL). The organics were combined, washed with brine (100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (7 : 3 hexanes : Et$_2$O) to afford keto-allylester-dioxinone 102$^{[82]}$ (1.06 g, 65%) as a yellow oil:

$\textbf{R}_f 0.30 \ (1 : 2 \text{ hexanes : Et}_2\text{O);}$

$\textbf{IR} \ (\text{neat}) \nu_{\text{max}} 2999 \ (w, \text{ C-H}), 2947 \ (w, \text{ C-H}), 1721 \ (s, \text{ C=O}), 1637 \ (m, \text{ C=C}), 1376 \ (m), 1273 \ (m), 1254 \ (sh.), 1202 \ (sh.), 1016 \ (w), 1091 \ (w), 1062 \ (w) \ \text{cm}^{-1};$

$\textbf{HRMS} \ (\text{ESI}) \text{ calc. for } C_{13}H_{17}O_6 [M+H]^+: \text{ requires } 269.1025, \text{ found } 269.1031 \ (\Delta +2.2 \text{ ppm});$
6 Experimental

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.99-5.89 (m, 1H, 12), 5.40 (s, 1H, 2), 5.35-5.31 (m, 2H, 13a & 13b), 4.68 (d, $J = 6.0$ Hz, 2H, 11), 3.58 (s, 2H, 9), 3.53 (s, 2H, 7), 1.74 (s, 6H, 5 & 6);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 195.4 (8), 166.0 (1), 163.4 (10), 160.4 (3), 131.2 (12), 119.4 (13), 107.4 (4), 97.2 (2), 66.3 (11), 49.0 (9), 47.0 (7), 25.0 (2C, 5 & 6).

(S)-3-(Tri-Isopropylsilyloxy)butanoic acid (311)

Based on a procedure by Tschaen et al.$^{[85]}$ 2,6-Lutidine (11.0 mL, 94.8 mmol, 1.6 equiv.) followed by TIPSOTf (16.0 mL, 59.3 mmol, 1.0 equiv.) were added with stirring to alcohol 310 (7.00 g, 59.3 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (90 mL) at 0 °C and stirred for an additional 1 h at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was quenched with 1 M HCl (200 mL) and stirred for 10 min. The resulting solution was extracted with Et$_2$O (2 x 200 mL), the organics combined, washed with H$_2$O (2 x 200 mL), dried (MgSO$_4$) and rotary evaporated to afford silyl ether 311 as a colourless oil which was used without further purification.

Methyl ester 311 was added with stirring to aqueous NaOH (1 M; 110 mL, 109 mmol, 1.8 equiv.) and THF (100 mL) and stirred for 72 h. The resulting solution was acidified to pH 3 using 1 M HCl and extracted with CH$_2$Cl$_2$ (3 x 200 mL). The combined organic layers were washed with brine (2 x 250 mL), dried (MgSO$_4$) and rotary evaporated to afford carboxylic acid 310$^{[85]}$ (11.5 g, 77%) as a pale yellow oil:

$\text{R}_f$ 0.52 (1 : 9 MeOH : CH$_2$Cl$_2$);

$[\alpha]_{D}^{25} = -0.5$ (c 0.2, CHCl$_3$);
6 Experimental

IR (neat) $v_{\text{max}}$ 3250 (br., O-H), 2942 (m, C-H), 2866 (m, C-H), 1710 (sh., C=O), 1463 (w), 1412 (w), 1381 (w), 1247 (w), 1203 (w), 1128 (w), 1096 (sh.), 1005 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{13}$H$_{27}$O$_3$Si [M+H]$^+$: requires 259.1729, found 259.1743 ($\Delta$ +5.4 ppm);

$^1$H NMR (400 MHz, CDCl$_3$) 10.28 (br. s, 1H, 1), 4.42 (app. sextet, $J = 4.0$ Hz, 1H, 4), 2.64 - 2.54 (m, 2H, 3), 1.34 (d, $J = 4.0$ Hz, 3H, 5), 1.12 - 1.08 (m, 21H, 6 & 7);

$^{13}$C NMR (100 MHz, CDCl$_3$) 175.2 (2), 65.8 (4), 44.0 (3), 23.5 (5), 17.9 (6C, 7), 12.3 (3C, 6);

Anal. Calc. for C$_{13}$H$_{28}$O$_3$Si: C, 59.95; H, 10.84. Found: C, 60.02; H, 10.77.

(5S)-Allyl 2-(2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl)-3-oxo-5-(tri-isopropylsilyloxy)hexanoate (104)

Based on a procedure by Navarro et al.$^{[82]}$ Oxalyl chloride (0.50 mL, 5.30 mmol, 2.0 equiv.) and 3 drops of DMF (cat.) were added sequentially with stirring to carboxylic acid 312 (823 mg, 2.70 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (10 mL) at 0 °C and stirred for 1 h. The resulting solution was rotary evaporated to afford acid chloride 103 as a pale yellow oil which was used without further purification.

Keto-allylester-dioxinone 102 (710 mg, 2.60 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (3 mL) was added to MgCl$_2$ (500 mg, 5.30 mmol, 2.0 equiv.) and pyridine (0.60 mL, 7.10 mmol, 2.7 equiv.) in
CH₂Cl₂ (20 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Acid chloride 103 in CH₂Cl₂ (3 mL) was added dropwise and the resulting solution stirred for 1 h at 0 °C. The reaction was quenched with brine (200 mL), extracted with EtOAc (2 x 200 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 4 EtOAc : hexanes) to afford diketo-allylester-dioxinone 104[82] (942 mg, 70%) as a pale yellow oil:

Rf 0.66 (2 : 1 Et₂O : hexanes);

[α] D 25 = +17.48 (c 1.2, CHCl₃);

IR (neat) ν max 2944 (m, C-H), 2867 (m, C-H), 1734 (s, C=O), 1665 (m, C=C), 1378 (m), 1272 (m), 1206 (m), 1160 (m), 1128 (w), 1067 (w) cm⁻¹;

HRMS (ESI) calc. for C₂₆H₄₃O₈Si [M+H]⁺: requires 511.2727, found 511.2720 (Δ -1.4 ppm);

¹H NMR (400 MHz, CDCl₃) δ 17.56 (s, 1H, 16), 6.05 - 5.95 (m, 1H, 19), 5.44 - 5.33 (m, 2H, 20a & 20b), 5.36 (s, 1H, 2), 4.74 (d, J = 8.0 Hz, 2H, 18), 4.53 - 4.45 (app. sextet, J = 8.0 Hz, 1H, 12), 3.70 (s, 2H, 7), 3.02 (dd, J = 12.0, 8.0 Hz, 1H, 11b), 2.83 (dd, J = 12.0, 4.0 Hz, 1H, 11a), 1.71 (s, 6H, 5 & 6), 1.26 (d, J = 8.0 Hz, 3H, 13), 1.05 (br. s, 21H, 14 & 15);

¹³C NMR (125 MHz, CDCl₃) δ 195.5 (8), 193.2 (10), 166.0 (1), 165.0 (17), 160.7 (3), 131.4 (4), 119.8 (19), 109.3 (20), 107.2 (9), 96.6 (2), 66.5 (12), 66.0 (18), 47.2 (7), 43.0 (11), 25.0 (2C, 5 & 6), 24.3 (13), 18.0 (6C, 15), 12.3 (3C, 14);

Morpholine (0.10 mL, 0.96 mmol, 3.3 equiv.) was added with stirring to diketo-allyl ester-dioxinone 104 (150 mg, 0.29 mmol, 1.0 equiv.) in THF (1.5 mL) at 0 °C, followed immediately by the addition of Pd(PPh₃)₄ (33 mg, 0.03 mmol, 10 mol%) in THF (1.5 mL). After 25 min at 0 °C, the mixture was allowed to warm to rt and stirred for 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (5 mL), followed by H₂O (10 mL) and was then acidified to pH 4 using 1 M HCl. The resulting aqueous layer was extracted with EtOAc (3 x 20 mL), the organics combined, dried (MgSO₄) and rotary evaporated to afford polyketide 108 as a colourless oil which was used without further purification.

Polyketide 108 was dissolved in toluene (2 mL) and MeOH (30 μL, 0.73 mmol, 2.5 equiv.) and heated to reflux for 1 h. The resulting solution was rotary evaporated, the crude residue dissolved in MeOH (5 mL), Cs₂CO₃ (472 mg, 1.45 mmol, 5.0 equiv.) in MeOH (1 mL) added and the resulting mixture stirred at rt for 3 h. AcOH (0.20 mL, 2.90 mmol, 10.0 equiv.) was added and the resulting mixture stirred for 18 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (10 mL), extracted with Et₂O (3 x 20 mL), the organics combined, washed with brine (15 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 2 Et₂O : hexanes) to give resorcylate 105 (43.0 mg, 39% over 4 steps) as a colourless solid:
Experimental

m.p. 50-52 °C (hexanes);

R_f 0.38 (1 : 3 Et_2O : hexanes);

[α]_D^{25} = +35.5 (c 0.3, CHCl_3);

IR (neat) \nu_{max} 3365 (br., O-H), 2926 (m, C-H), 2865 (m, C-H), 1652 (m, C=C), 1625 (sh., C=C), 1586 (m, C=C), 1462 (m), 1386 (sh.), 1318 (m), 1263 (sh.), 1194 (sh.), 1173 (w), 1134 (sh.), 1108 (m), 1082 (w), 1025 (w) cm^{-1};

HRMS (ESI) calc. for C_{20}H_{35}O_{5}Si [M+H]^+ requires 383.2254, found 383.2236 (Δ = -4.70 ppm);

^1H NMR (500 MHz, CDCl_3) δ 11.63 (s, 1H, 15), 6.31 (d, J = 2.0 Hz, 1H, 5), 6.29 (d, J = 2.0 Hz, 1H, 3), 5.37 (s, 1H, 14), 4.17 - 4.11 (m, 1H, 10), 3.92 (s, 3H, 8), 3.14 (dd, J = 12.0, 4.0 Hz, 1H, 9b), 2.93 (dd, J = 12.0, 8.0 Hz, 1H, 9a), 1.17 (d, J = 4.0 Hz, 3H, 11), 0.98 (br. s, 3H, 12) 0.97 (br. s, 18H, 13);

^13C NMR (125 MHz, CDCl_3) δ 171.8 (7), 165.2 (2), 160.0 (4), 145.0 (6), 113.2 (5), 105.4 (3), 101.8 (1), 69.8 (10), 52.0 (8), 46.7 (9), 24.4 (11), 18.1 (6C, 13), 12.6 (3C, 12).

(S)-7-Hydroxy-2,2-dimethyl-5-(2-(triisopropylsilyloxy)propyl)-4H-benzo[d][1,3]dioxin-4-one (107)

Diketo-allylester-resorcylate 104 (30 mg, 0.10 mmol, 1.0 equiv.) was stirred with Pd(PPh_3)_4 (6.0 mg, 4.85 µmol, 10 mol%) and morpholine (100 µL, 0.32 mmol, 3.3 equiv.) in THF (0.5
mL) at 0 °C for 30 min and then allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (10 mL), extracted with Et₂O (2 x 10 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 1 Et₂O : hexanes) to afford isopropylidene protected resorcylate 107 as a white solid (20 mg, 80%): m.p. = 98-100 °C (pentane);
Rf 0.5 (1 : 1 EtOAc : hexanes);
[α]²⁵ = +4.4 (c 1.0, CHCl₃);
**IR** (neat) νmax 3365 (s, O-H), 2941 (m, C-H), 2891 (m, C-H), 2866 (m, C-H), 1691 (sh., C=O), 1614 (sh., C=O), 1581 (sh., C=O), 1462 (w), 1387 (w), 1293 (m), 1283 (m), 1257 (w), 1192 (sh.), 1172 (sh.), 1133 (w), 1099 (w) cm⁻¹; **HRMS** (ESI) calc. for C₂₂H₃₇O₅Si [M+H]⁺: requires 409.2410, found 409.2403 (Δ –1.7 ppm);
**¹H NMR** (500 MHz, CDCl₃) δ 6.34 (d, J = 2.0 Hz, 1H, 5), 6.17 (d, J = 2.0 Hz, 1H, 3), 5.42 (br. s, 1H, 12), 4.58-4.51 (m, 1H, 8), 3.51 (dd, J = 15.0, 4.0 Hz, 1H, 7b), 3.24 (dd, J = 15.0, 8.0 Hz, 1H, 7a), 1.35 (s, 3H, 9), 1.32-1.31 (m, 6H, 15 & 16), 1.10 (br. s, 3H, 10), 1.09 (br. s, 18H, 11);
**¹³C NMR** (125 MHz, CDCl₃) δ 161.9 (13), 160.2 (4), 159.5 (2), 147.3 (6), 115.9 (1), 105.5 (5), 104.7 (14), 102.1 (3), 69.4 (8), 45.6 (7), 25.5 (9), 25.3, 24.6 (15 & 16), 18.3 (6C, 11), 12.9 (3C, 10);
**Anal.** Calc. for C₂₂H₃₆O₅Si: C, 64.67; H, 8.88. Found: C, 64.58; H, 9.03.
**Experimental**

(S)-6,8-Dihydroxy-3-methylisochroman-1-one (106)

H$_2$SiF$_6$ in H$_2$O (20% w/w; 60 µL, 90 µmol, 0.6 equiv.) was added to silyl ether 107 (53 mg, 0.14 mmol, 1.0 equiv.) in MeCN (2.1 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with H$_2$O (20 mL), extracted with EtOAc (2 x 20 mL), dried (MgSO$_4$) and rotary evaporated to give alcohol 313 as a colourless solid which was used without further purification.

One micro spatula tip of p-TsOH.H$_2$O (∼3 mg, cat.) was added to isopropylidene protected resorcylate 313 (32 mg, 0.14 mmol, 1.0 equiv.) in THF (5 mL) and the mixture heated at reflux for 2 h. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$ (10 mL), extracted with Et$_2$O (3 x 25 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 1 Et$_2$O : hexanes) to give lactone 106$^{[100]}$ (21 mg, 80% over 2 steps) as a white solid:

**m.p.** = 138-140 °C (benzene);

**R$_f$** 0.32 (1 : 1 Et$_2$O : hexanes);

[$\alpha$]$^\circ_{D}$ = $+3.31$ (c 0.016, CHCl$_3$);

**IR** (neat) $\nu_{max}$ 3206 (m, O-H), 2924 (m, C-H), 2855 (m, C-H), 1739 (w, C=O), 1634 (sh., C=C), 1440 (w), 1366 (m), 1229 (w), 1217 (sh.), 1209 (sh.) cm$^{-1}$;

**HRMS** (ESI) calc. for C$_{10}$H$_{11}$O$_4$[M+H]$^+$: requires 195.0657, found 195.0663 (Δ +3.1 ppm);
6 Experimental

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 6.21 (s, 1H, 5), 6.19-6.17 (m, 1H, 3), 4.83 (br. s, 2H, 10 & 11), 4.68 - 4.62 (m, 1H, 8), 2.91-2.89 (m, 1H, 7b), 2.79-2.78 (m, 1H, 7a), 1.46 (d, $J$ = 6.0 Hz, 3H, 12);

$^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 171.7 (9), 166.2 (2), 165.6 (4), 143.5 (6), 107.9 (3), 102.2 (5), 101.5 (1), 77.2 (8), 35.5 (7), 20.9 (12);


**Angelicoin B: (S)-8-Hydroxy-6-methoxy-3-methylisochroman-1-one (7)**

Lactone 106 (18 mg, 90 µmol, 1.0 equiv.) was stirred in Me$_2$CO (3.72 mL) for 2 min. MeI (9 µL, 0.15 mmol, 1.6 equiv.) and K$_2$CO$_3$ (13 mg, 90 µmol, 1.0 equiv.) were then added and the resulting solution heated at reflux for 1 h. The reaction was quenched with water (5 mL), extracted with EtOAc (2 x 20 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 2 Et$_2$O : hexanes) to afford Angelicoin B (7)$^{[9]}$ (15 mg, 79%) as a white solid:

- **m.p.** 58-60 °C (pentane);
- **Rf** 0.25 (1 : 3 Et$_2$O : hexanes);
- $[\alpha]_{D}^{25} = +30.6$ (c 0.5, MeOH), lit. $[\alpha]_{D}^{25} = +31.5$ (c 0.5, MeOH);
- **IR** (neat) $\nu_{max}$ 2980 (w, C-H), 2929 (w, C-H), 1664 (s, C=C), 1627 (m, C=C), 1440 (w), 1371 (w), 1250 (sh.), 1203 (w), 1159 (m), 1118 (w), 1069 (w) cm$^{-1}$;
- **HRMS** (ESI) calc. for C$_{11}$H$_{13}$O$_4$ [M+H]$^+$: requires 209.0814, found 209.0811 (Δ +1.4 ppm);
Experimental

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.25 (s, 1H, 11), 6.37 (d, $J = 2.0$ Hz, 1H, 5), 6.25 - 6.24 (m, 1H, 3), 4.71 - 4.64 (m, 1H, 8), 3.83 (s, 3H, 12), 2.91 - 2.84 (m, 2H, 7a & b), 1.51 (d, $J = 6.0$ Hz, 3H, 9);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.8 (10), 165.8 (4), 164.6 (2), 140.9 (6), 106.2 (5), 101.6 (1), 99.4 (3), 75.5 (8), 55.6 (12), 34.9 (7), 20.7 (9);

Anal. Calc. for C$_{11}$H$_{12}$O$_4$: C, 63.45; H, 5.81. Found: C, 63.56; H, 5.78.

3-(3-Methyl-2-but-1-enyl) malonate 114

Based on a procedure by Tararov et al.$^{[74]}$ Prenyl alcohol (14.3 mL, 141 mmol, 1.5 equiv.) and Meldrum’s acid (13.6 g, 94.0 mmol, 1.0 equiv.) were stirred at 120 °C for 12 h. The mixture was poured into a saturated aqueous solution NaHCO$_3$ (400 mL) and stirred for 6 h. The aqueous layer was extracted with EtOAc (3 x 200 mL) and then acidified to pH 3.0 using 1 M HCl. The resulting aqueous layer was extracted with EtOAc (2 x 400 mL), the organic layers combined, dried (MgSO$_4$) and rotary evaporated to afford carboxylic acid 114 (15.3 g, 94%) as a pale yellow solid:

m.p. 34-36 °C (hexanes);

R$_f$ 0.40 (1 : 9 MeOH : CH$_2$Cl$_2$);

IR (neat) $\nu_{\text{max}}$ 3350 (br. O-H), 2978 (w, C-H), 2937 (w, C-H), 1714 (s, C=O), 1416 (w), 1378 (w), 1339 (m), 1312 (w), 1277 (m), 1151 (sh.), 1048 (m) cm$^{-1}$;

HRMS (Cl) calc. for C$_8$H$_{16}$NO$_4$ [M+H]$^+$: requires 190.1079, found 190.1077 ($\Delta \pm 1.1$ ppm);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (br. s, 1H, 1) 5.38 (t, $J = 8.0$ Hz, 1H, 6), 4.71 (d, $J = 8.0$ Hz, 2H, 5), 3.47 (s, 2H, 3), 1.80 (s, 3H, 9), 1.75 (s, 3H, 8);
6 Experimental

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.1 (2), 167.2 (4), 140.4 (7), 117.6 (6), 62.9 (5), 40.6 (3), 25.7 (9), 18.0 (8);

Anal. Calc. for C$_8$H$_{12}$O$_4$: C, 55.81; H 7.02. Found: C, 55.87; H, 7.18.

3-Methylbut-2-enyl 3-(1H-benzo[d][1,2,3]triazol-1-yl)-3-oxopropanoate (116)

Based on a procedure by Navarro et al.$^{[82]}$ SOCl$_2$ (0.84 mL, 11.6 mmol, 1.0 equiv.) was added to benzotriazole (4.40 g, 36.6 mmol, 3.0 equiv.) in CH$_2$Cl$_2$ (47 mL) and the resulting mixture was stirred for 1 h. Carboxylic acid 114 (2.0 g, 11.6 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (20 mL) was added and the resulting mixture stirred for 24 h. The mixture was filtered and the filtrate was rotary evaporated. The crude residue was dissolved in CH$_2$Cl$_2$ (300 mL), washed with NaOH (0.5 M) (3 x 150 mL) and then pH 9 buffer (2 x 250 mL). The combined organic layers were dried (MgSO$_4$) and rotary evaporated to afford benzotriazole amide 116 (2.5 g, 81%) as a colourless oil:

$R_f$ 0.70 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes);

IR (neat) $v_{max}$ 2962 (w, C-H), 1726 (s, C=O), 1380 (s), 1267 (m), 1209 (m), 1146 (w) cm$^{-1}$;

HRMS (Cl) calc. for C$_{14}$H$_{16}$N$_3$O$_3$ [M+H]$^+$: required 274.1192, found 274.1197 (Δ +1.8 ppm);

$^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 8.22 (d, $J = 8.0$ Hz, 1H, 2 / 5), 7.84 (d, $J = 8.0$ Hz, 1H, 2 / 5), 7.13 - 7.09 (m, 1H, 3 / 4), 6.99 - 6.95 (m, 1H, 3 / 4), 5.36 - 5.33 (m, 1H, 11), 4.62 (d, $J = 8.0$ Hz, 2H, 10), 4.06 (s, 2H, 8), 1.54 (s, 3H, 14), 1.46 (s, 3H, 13);

$^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 165.7 (7), 164.9 (14), 146.6 (5), 139.3 (12), 131.0 (1), 130.1 (3), 125.9 (4), 120.1 (5), 118.4 (11), 114.2 (2), 62.4 (10), 42.6 (8), 25.3 (14), 17.5 (13).
3-Methylbut-2-enyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (113)

Based on a procedure by Navarro et al.[82] Dioxinone 33 (2.40 mL, 17.4 mmol, 3.0 equiv.) in THF (5 mL) was added dropwise to a freshly prepared solution of LiN(SiMe$_3$) in THF (1 M; 20.3 mL, 20.3 mmol, 3.5 equiv.) in THF (250 mL) at −78 °C and the resulting solution stirred for 1 h. Benzotriazole amide 116 (684 mg, 5.80 mmol, 1.0 equiv.) in THF (20 mL) was then added dropwise and the resulting mixture stirred for 2 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (300 mL) and acidified to pH 3 with 1 M HCl. The resulting solution was extracted with EtOAc (3 x 200 mL), the organics combined, washed with brine (100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (7 : 3 hexanes : Et$_2$O) to afford keto-prenylester-dioxinone 113 (1.58 g, 93%) as a yellow oil:

$\text{R}_f$ 0.31 (2 : 1 Et$_2$O : hexanes);

$\text{IR}$ (neat) $\nu_{\text{max}}$ 3381 (br., O-H), 2831 (w, C-H), 1738 (sh., C=O), 1730 (sh., C=O), 1640 (m, C=C), 1376 (m), 1274 (m), 1217(w), 1017 (sh.), 903 (w) cm$^{-1}$;

$\text{HRMS}$ (ESI) calc. for C$_{15}$H$_{21}$O$_6$ [M+H]$^+$: required 297.1338, found 297.1329 ($\Delta$ −3.0 ppm);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.37 (s, 1H, 2), 5.36 - 5.33 (m, 1H, 12), 4.66 (d, $J = 8.0$ Hz, 2H, 15), 3.53 (s, 2H, 9), 3.52 (s, 2H, 7), 1.78 (s, 3H, 11), 1.72 (s, 9H, 5, 6 & 14);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 195.7 (7), 166.3 (1), 163.6 (10), 160.4 (13), 140.3 (3), 117.6 (12), 107.3 (4), 97.0 (2), 62.5 (11), 49.1 (9), 46.9 (8), 25.7 (2C, 5 & 6), 24.9 (15), 18.0 (14);

$\text{Anal.}$ Calc. for C$_{15}$H$_{20}$O$_6$: C, 60.80; H, 6.80. Found: C, 60.89; H, 6.81.
Experimental

(R)-3-(Triisopropylsilyloxy)butanoic acid (118)

Based on a procedure by Tschaen et al.\textsuperscript{[74]} Alcohol 119 (5.0 g, 42 mmol, 1.0 equiv.) was stirred in CH\textsubscript{2}Cl\textsubscript{2} (100 mL) at 0 °C. 2,6-Lutidine (7.9 mL, 68 mmol, 1.6 equiv.) was added dropwise followed by TIPSOTf (11.4 mL, 42.3 mmol, 1.0 equiv.) dropwise and the resulting solution stirred for 1 h at 0 °C, allowed to warm to rt and stirred for 3 h. The reaction mixture was quenched with 1 M HCl (200 mL), stirred for 10 min and extracted with Et\textsubscript{2}O (2 x 200 mL). The organics were combined, washed with H\textsubscript{2}O (2 x 200mL), dried (MgSO\textsubscript{4}) and rotary evaporated to afford silyl ether 314 which was used without further purification.

Methyl ester 314 was added to a solution of 1 M NaOH (50 mL) and THF (50 mL). The reaction mixture was allowed to stir at rt for 72 h before being acidified to pH 3.0 using 1 M HCl and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 200 mL). The organics were combined, washed with brine (2 x 250 mL), dried (MgSO\textsubscript{4}) and rotary evaporated to afford carboxylic acid 118 (7.22 g, 90% over 2 steps) as a pale yellow oil:

\[ \text{Rf } 0.52 \text{ (1 : 9 MeOH : CH}_2\text{Cl}_2); \]
\[ [\alpha]_D^{25} = +3.3 \text{ (c 0.875, CHCl}_3); \]
\[ \text{IR (neat) } \nu_{\text{max}} 2940 \text{ (m, C-H), 2867 (m, C-H), 1710 (sh., C=O), 1463 (w), 1129 (m), 1096 (w), 1004 (m) cm}^{-1}; \]
\[ \text{HRMS (ESI) calc. for C}_{13}\text{H}_{28}\text{O}_3\text{Si [M+H]}^+: \text{requires 261.1886, found 261.1874 (Δ –4.6 ppm)}; \]
Experimental

$^1$H NMR (400 MHz, CDCl$_3$) 10.75 (br. s, 1H, 1), 4.43-4.41 (m, 1H, 4), 2.63 (dd, $J = 10.0, 6.0$ Hz, 2H, 3b), 2.57 (dd, $J = 10.0, 3.0$ Hz, 2H, 3a), 1.35 (d, $J = 4.0$ Hz, 3H, 5), 1.11 (br. s, 18H, 7), 1.10 (br. s, 3H, 6);

$^{13}$C NMR (100 MHz, CDCl$_3$) 174.5 (2), 65.9 (4), 43.8 (3), 23.4 (5), 18.0 (6C, 7), 12.3 (3C, 6).

(R)-N-Methoxy-N-methyl-3-(triisopropylsilyloxy)butanamide (120)

Carboxylic acid 118 (1.00 g, 3.25 mmol, 1.0 equiv.) was stirred in CH$_2$Cl$_2$ (10 mL) at 0 °C. Oxalyl chloride (0.60 mL, 7.17 mmol, 2.0 equiv.) and DMF (25 μL, 0.30 mmol, 0.1 equiv.) were added and the reaction mixture stirred for 1 h at 0 °C followed by 2 h at rt. The reaction mixture was rotary evaporated to afford acid chloride 117 as an orange oil which was used without further purification.

$N,O$-Dimethylhydroxylamine hydrochloride (332 mg, 3.40 mmol, 0.95 equiv.) was stirred with pyridine (0.60 mL, 7.16 mmol, 2.0 equiv.) in CH$_2$Cl$_2$ (10 mL) for 30 min, acid chloride 117 was then added and the reaction mixture stirred at rt for 3 h. The reaction mixture was poured into brine (50 mL), extracted with Et$_2$O and CH$_2$Cl$_2$ (1 : 1), dried (MgSO$_4$) and rotary evaporated to afford Weinreb amide 120 (900 mg, 82%) as a pale yellow oil:

$R_f$ 0.5 (EtOAc);

$[\alpha]_{D}^{25} = -11.23$ (c 3.08, CHCl$_3$);
6 Experimental

IR (neat) \( \nu_{\text{max}} \) 2944 (s, C-H), 2867 (s, C-H), 1667 (m, C=O), 1463 (m), 1179 (m), 1122 (sh.), 1092 (w) cm\(^{-1}\);

MS (CI) [M+H]\(^+\): requires 304, found 304;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.53-4.46 (m, 1H, 5), 3.72 (s, 3H, 2), 3.20 (s, 3H, 1), 2.79 (dd, \( J = 15.0, 5.0 \) Hz, 1H, 4b), 2.49 (dd, \( J = 15.0, 7.0 \) Hz, 1H, 4a), 1.29 (d, \( J = 6.0 \) Hz, 3H, 6), 1.09 (br. s, 18H, 8), 1.08 (br. s, 3H, 7);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 189.2 (3), 65.9 (5), 61.3 (2), 42.2 (4), 24.3 (1), 18.1 (6), 17.7 (6C, 8), 12.4 (3C, 7).

\((5R)-3\text{-Methylbut}-2\text{-enyl} \text{ 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl}-3\text{-oxo-5-(tri-isopropylsilyloxy)hexanoate (111)}\)

Based on a procedure by Navarro et al.\cite{82} Oxalyl chloride (1.50 mL, 16.9 mmol, 2.0 equiv.) and DMF (30 \( \mu \)L, 0.44 mmol, 0.1 equiv.) were added to carboxylic acid 118 (2.20 g, 8.40 mmol, 1.0 equiv.) in CH\(_2\)Cl\(_2\) (50 mL) at 0 °C and stirred for 1 h. The reaction mixture was rotary evaporated to afford acid chloride 117 as a pale yellow oil, which was used without further purification.

Keto-prenylester-dioxinone 113 (100 mg, 0.34 mmol, 1.0 equiv.) in CH\(_2\)Cl\(_2\) (1 mL) was added dropwise to a mixture of MgCl\(_2\) (64 mg, 0.67 mmol, 2.0 equiv.) and pyridine (80 \( \mu \)L, 0.92 mmol, 2.7 equiv.) in CH\(_2\)Cl\(_2\) (2 mL) at 0 °C. The resulting solution was stirred for 30
min and then acid chloride 117 in CH₂Cl₂ (0.5 mL) was added dropwise and the resulting solution stirred for 1 h. The reaction mixture was quenched with brine (20 mL), extracted with EtOAc (2 x 50 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 4 Et₂O : hexanes) to afford diketo-prenylester-dioxinone 111 (148 mg, 81\%) as a yellow oil:

**Rf** 0.74 (2 : 1 Et₂O : hexanes);

\[ [\alpha]_{D}^{25} = -6.7 \ (c \ 0.82, \text{CHCl}_3) ; \]

**IR** (neat) \( \nu \text{max} \), 2941 (m, C-H), 2867 (m, C-H), 1733 (sh., C=O), 1712 (sh., C=O), 1641 (w, C=C), 1464 (m), 1391 (m), 1273 (w), 1250 (sh.), 1204 (w), 1126 (sh.), 1068 (sh.), 1015 (w) cm⁻¹;

**HRMS** (ESI) calc. for C₂₈H₄₇O₈Si [M+H⁺]: requires 539.3032, found 539.3040 (Δ –1.5 ppm);

1H NMR (400 MHz, CDCl₃) δ 17.47 (s, 1H, 22), 5.45 - 5.41 (m, 1H, 18), 5.37 (s, 1H, 2), 4.74 (d, \( J = 8.0 \) Hz, 2H, 17), 4.49-4.47 (m, 1H, 12), 3.70 (s, 2H, 7), 2.98 (dd, \( J = 14.0, 7.0 \) Hz, 1H, 11b), 2.84 (dd, \( J = 14.0, 4.0 \) Hz, 1H, 11a), 1.81 (s, 3H, 20), 1.78 (s, 3H, 21), 1.72 (s, 6H, 5 & 6), 1.25 (d, \( J = 6.0 \) Hz, 3H, 13), 1.06 (br. s, 21H, 14 & 15);

13C NMR (100 MHz, CDCl₃) δ 195.2 (8), 193.0 (10), 166.3 (1), 165.0 (16), 160.7 (19), 140.4 (3), 117.7 (18), 109.6 (4), 107.1 (9), 96.5 (2), 66.5 (12), 62.0 (17), 47.1 (7), 42.9 (11), 25.7 (20), 24.9 (2C, 5 & 6), 24.8 (13), 24.3 (21), 18.0 (6C, 15), 12.4 (3C, 14);

**Anal.** Calc. for C₂₈H₄₆O₈Si: C, 62.42; H, 8.61. Found: C, 62.36; H, 8.64.
Based on a procedure by Navarro et al. [82] Benzotriazole (720 mg, 6.05 mmol, 3.2 equiv.) was stirred in CH$_2$Cl$_2$ (12 mL) at rt. Thionyl chloride (0.14 mL, 1.92 mmol, 1.0 equiv.) was added and the mixture stirred for 45 min. Carboxylic acid 118 (500 mg, 1.92 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (8 mL) was added and the mixture allowed to stir for 2 h. The reaction mixture was filtered and the filtrate rotary evaporated to afford benzotriazole amide 121 (643 mg, 93%) as a yellow oil:

R$_f$ 0.64 (2 : 1 hexanes : EtOAc);

$[\alpha]_{D}^{25}$ = -0.301 (c 1.06, CHCl$_3$);

IR (neat) $\nu_{\text{max}}$ 2943 (m, C-H), 2867 (m, C-H), 1736 (sh., C=O), 1450 (w), 1375 (sh.), 1128 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{19}$H$_{31}$N$_3$O$_2$Si [M+NH]$^+$ requires 361.2264, found 362.2257 ($\Delta$ –1.9 ppm);

$^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 8.41 (d, J = 8.0 Hz, 1H, 2 / 5), 7.92 (d, J = 8.0 Hz, 1H, 2 / 5), 7.21-7.14 (m, 1H, 3 / 4), 7.04-7.01 (m, 1H, 3 / 4), 4.82-4.76 (m, 1H, 9), 3.67 (dd, J = 8.0, 5.0 Hz, 1H, 8b), 3.24 (dd, J = 8.0, 2.5 Hz, 1H, 8a), 1.31 (d, J = 3.0 Hz, 3H, 10), 1.15 (br. s, 3H, 11), 1.13 (br. s, 18H, 12);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.4 (7), 170.3 (6), 130.7 (1), 129.9 (3), 125.8 (4), 120.1 (5), 114.4 (2), 66.2 (9), 45.5 (8), 24.1 (10), 18.0 (6C, 12), 12.5 (3C, 11)
6 Experimental

(R)-7-Hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-5-(2-(tri-isopropylsilyloxy)propyl)-4H-benzo[d][1,3]dioxin-4-one (124) and (2R)-7-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-8,8-dimethyl-2-(tri-isopropylsilyloxy)dec-9-ene-4,6-dione (123)

Pd(PPh$_3$)$_4$ (38 mg, 33 μmol, 10 mol%) and Cs$_2$CO$_3$ (348 mg, 0.99 mmol, 3.0 equiv.) were stirred in THF (1 mL) for 10 min at 0 °C. Diketo-prenylester-dioxinone 111 (150 mg, 0.33 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise and the resulting solution stirred for 18 h at rt. The reaction was quenched with brine (20 mL), extracted with EtOAc (2 x 50 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 : 12 CH$_2$Cl$_2$ : EtOAc : hexanes) to give prenyl-resorcylate 124 as a white solid (79 mg, 50%) and diketo-dioxinone 123 as a colourless oil (16 mg, 10%).

**Prenyl-resorcylate 124:**

m.p. 79-81 °C (benzene);

R$_f$ 0.60 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes);

[α]$_D$$_{25}$ = −31.33 (c 1.0, CHCl$_3$);

IR (neat) $\nu_{\text{max}}$ 3286 (br., O-H), 2941 (m, C-H), 2866 (m, C-H), 1702 (sh., C=O), 1695 (sh. C=O), 1594 (m), 1375 (w), 1298 (w), 1108 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{27}$H$_{45}$O$_5$Si [M+H]$^+$: requires 477.3028, found 477.3036 (Δ −1.7 ppm).
*Experimental*

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.52 (s, 1H, 5), 6.47 (s, 1H, 21), 5.18 (t, $J = 8.0$ Hz, 1H, 17), 4.30-4.28 (m, 1H, 8), 3.33 (d, $J = 8.0$ Hz, 2H, 16), 3.26 (dd, $J = 12.0$, 5.0 Hz, 1H, 7a), 3.09 (dd, $J = 12.0$, 7.0 Hz, 1H, 7b), 1.81 (s, 3H, 20), 1.74 (s, 3H, 19), 1.70 (s, 6H, 14 & 15), 1.20 (d, $J = 5.0$ Hz, 3H, 9), 1.0 (br. s, 21H, 10 & 11);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.9 (12), 159.6 (2), 156.1 (4), 143.8 (6), 134.3 (18), 121.1 (17), 115.4 (3), 113.6 (5), 105.1 (13), 104.7 (1), 69.0 (8), 44.7 (7), 25.8 (9), 25.6 (20), 24.2 (2C, 14 & 15), 22.0 (16), 18.1 (19), 17.9 (6C, 11), 12.5 (3C, 10);

**Anal.** Calc. for C$_{27}$H$_{44}$O$_5$Si: C, 68.02; H, 9.30. Found: C, 67.95; H, 9.17.

*Diketo-dioxinone 123:* (Mixture of diastereoisomers in a 1:1 ratio)

R$_f$ 0.55 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes);

IR (neat) $\nu_{max}$ 2943 (m, C-H), 2867 (m, C-H), 1731 (sh., C=O), 1612 (m, C=C), 1463 (w), 1376 (m), 1250 (w), 1068 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{27}$H$_{47}$O$_6$Si [M+H]$^+$ requires 495.3146, found 495.3155 ($\Delta$ –1.8 ppm);

$^1$H NMR (400 MHz, CDCl$_3$) δ 15.44 (br. s, 1H, 21), 6.03 (dd, $J = 17.0$, 10.0 Hz, 0.5 H, 11), 5.99 (dd, $J = 17.0$, 10.0 Hz, 0.5 H, 11), 5.59 (s, 0.5 H, 14), 5.58 (s, 0.5 H, 14), 5.53 (s, 0.5 H, 2), 5.52 (s, 0.5 H, 2), 5.05 (d, $J = 10.0$ Hz, 1 H, 12a), 5.03 (d, $J = 17.0$ Hz, 1 H, 12b), 4.41-4.39 (m, 1H, 17), 2.94 (s, 1H, 7), 2.52 (dd, $J = 14.0$, 5.0 Hz, 1H, 16b), 2.41 - 2.35 (m, 1H, 16a), 1.71 (s, 3H, 5 / 6), 1.69 (s, 3H, 5 / 6), 1.26 (d, $J = 5.0$ Hz, 3H, 18), 1.22 (s, 6H, 9 & 10), 1.07 (br. s, 3H, 19), 1.06 (br. s, 18H, 20);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 191.6 (13), 189.4 (15), 166.9 (1), 160.8 (3), 144.5 (11), 112.7 (12), 106.6 (4), 102.9 (14), 96.6 (2), 66.3 (17), 62.6 (7), 48.2 (16), 40.5 (8), 25.9 (2C, 9 & 10), 25.6 (2C, 5 & 6), 24.6 (18), 18.0 (6C, 20), 12.4 (3C, 19).
Bu₄NF in THF (1 M; 2.18 mL, 2.18 mmol, 8.0 equiv.) was added to silyl ether 124 (130 mg, 0.27 mmol, 1.0 equiv.) in THF (4 mL) and stirred for 48 h. The reaction was quenched with H₂O (20 mL), extracted with EtOAc (2 x 30 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 6 hexanes : EtOAc) to give alcohol 128 (87 mg, 97%) as a colourless gum:

R_f 0.64 (EtOAc);

[α]_D^25 = −23.7 (c 1.5, CHCl₃);

IR (neat) ν_max 3204 (br., O-H), 2981 (w, C-H), 2930 (w, C-H), 1723 (m, C=O), 1606 (m, C=C), 1420 (w), 1374 (m), 1274 (sh.), 1237 (sh.), 1166 (w), 1043 (m) cm⁻¹;

HRMS (ESI) calc. for C_{18}H_{25}O_{5} [M+H]^+: requires 321.1711, found 321.1702 (Δ +2.8 ppm);

^1H NMR (400 MHz, CDCl₃) δ 7.97 (br. s, 1H, 20), 6.42 (s, 1H, 5), 5.14 (t, J = 8.0 Hz, 1H, 12), 4.18 - 4.09 (m, 1H, 8), 3.48 (s, 1H, 10), 3.24 (d, J = 8.0 Hz, 2H, 11), 2.99 (dd, J = 12.0, 8.0 Hz, 2H, 7), 1.78 (s, 3H, 15), 1.72 (s, 3H, 14), 1.70 (s, 3H, 18 / 19), 1.68 (s, 3H, 18 / 19), 1.35 (d, J = 8.0 Hz, 3H, 9);

^13C NMR (125 MHz, CDCl₃) δ 162.4 (16), 160.7 (2), 156.4 (4), 142.3 (6), 133.1 (13), 121.1 (12), 114.8 (3), 114.3 (5), 105.0 (1), 104.9 (17), 69.8 (8), 43.1 (7), 26.0 (18 / 19), 25.8 (18 / 19), 25.2 (15), 23.5 (9), 21.9 (11), 17.9 (14).
KOH in EtOH (1 M; 8.70 mL, 8.70 mmol, 56.0 equiv.) was added to alcohol 128 (50 mg, 0.16 mmol, 1.0 equiv.) and the mixture heated to reflux for 30 min, allowed to cool, and acidified to pH 2.0 using 1 M HCl. The aqueous phase was extracted with EtOAc (2 x 50 mL) and the combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (1 : 2 hexanes : EtOAc) to afford angelicoin A 6⁹ (37 mg, 90%) as a white solid:
m.p. 118-120 °C (pentane);
R_f 0.38 (1 : 2 EtOAc : hexanes);
[α]_D^25 = −32.3 (c 0.37, MeOH), lit. [α]_D^25 = −37.1 (c 0.50, MeOH)
IR (neat) ν_max 3161 (br., O-H), 2988 (w, C-H), 1746 (m, C=O), 1614 (sh., C=C), 1365 (m), 1222 (m), 1216 (sh.), 1205 (w) cm⁻¹;
HRMS (ESI) calc. for C₁₅H₁₇O₄ [M+H]⁺: requires 261.1127, found 261.1133 (Δ +2.3 ppm);
¹H NMR (400 MHz, CDCl₃) δ 11.55 (s, 1H, 17), 6.40 (br. s, 1H, 16), 6.35 (s, 1H, 5), 5.28 (t, 1H, J = 7.0 Hz, 1H, 12), 4.72-4.64 (m, 1H, 8), 3.44 (d, J = 7.0 Hz, 2H, 11), 2.86-2.84 (m, 2H, 7), 1.85 (s, 3H, 15), 1.78 (s, 3H, 14), 1.50 (d, J = 8.0 Hz, 3H, 10);
¹³C NMR (105 MHz, CDCl₆) δ 170.3 (9), 161.7 (4), 161.2 (2), 138.6 (6), 136.0 (13), 121.0 (12), 112.4 (3), 106.4 (5), 101.4 (1), 75.6 (8), 34.6 (7), 25.8 (15), 21.8 (11), 20.7 (10), 17.9 (14);
(R)-3-Methylbut-2-enyl 7-hydroxy-2,2-dimethyl-4-oxo-5-(2-(tri-
ispopylsilyloxy)propyl)-4H-benzo[d][1,3]dioxine-6-carboxylate (129)

Et₃N (1.50 mL, 10.6 mmol, 20.0 equiv.) was added to diketo-prenylester-dioxinone 111 (285 mg, 0.53 mmol, 1.0 equiv.) in CH₂Cl₂ (50 mL) and stirred for 24 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (10 mL) and acidified to pH 2 using 1 M HCl. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (10 : 1 : 1 hexanes : EtOAc : CH₂Cl₂) to afford isopropylidene-protected resorcylate 129 (110 mg, 40%) as a clear oil:

Rᶠ 0.62 (1 : 1 : 6 EtOAc : CH₂Cl₂ : hexanes);

[α]_D^25 = +17.21 (c 0.83, CHCl₃);

IR (neat) νₓmax 2968 (w, C-H), 2866 (w, C-H), 1735 (s, C=O), 1659 (m, C=C), 1594 (m, C-C), 1450 (w), 1377 (m), 1233 (sh.), 1209 (sh.), 1123 (w), 1105 (w), 1038 (w) cm⁻¹;

HRMS (ESI) calc. for C₂₈H₄₅O₇Si [M+H]^+: requires 521.2935, found 521.2938 (Δ +0.6 ppm);

¹H NMR (500 MHz, CDCl₃) δ 11.22 (br. s, 1H, 21), 6.41 (s, 1H, 3), 5.49 (app. t of quin, J = 7.0, 0.5, 1H, 14), 4.92-4.88 (m, 2H, 13), 4.85-4.83 (m, 1H, 8), 4.18 - 4.12 (m, 1H, 7a), 4.00
Experimental

6 Experimental

(b. s, 1H, 7b), 1.80 (s, 3H, 17), 1.78 (s, 3H, 16), 1.69 (s, 3H, 19 / 20), 1.66 (s, 3H, 19 / 20), 1.21 (b. s, 3H, 9), 0.92 (b. s, 18H, 11), 0.91 (b. s, 3H, 10);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.9 (16), 166.2 (4), 160.7 (12), 159.6 (2), 151.1 (6), 140.9 (15), 117.4 (14), 113.0 (1), 106.0 (5), 104.7 (18), 103.5 (3), 70.5 (8), 62.9 (13), 39.5 (7), 26.0 (9), 25.8 (2C, 19 & 20), 25.4 (17), 18.1 (16), 17.9 (6C, 11), 12.6 (3C, 10).

(S)-6-Hydroxy-3,3,9-trimethyl-9,10-dihydro-[1,3]dioxino[5,4-f]isochromene-1,7-dione

(130)

Bu$_4$NF in THF (1 M; 0.80 mL, 0.40 mmol, 4.4 equiv.) was added to silyl ether-resorcylate 129 (46 mg, 90 μmol, 1.0 equiv.) in THF (1 mL) and stirred for 48 h at rt. The reaction was quenched with brine (10 mL), extracted with EtOAc (2 x 20 mL), the organic layers combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 hexanes : EtOAc) to afford tricycle 130 (15 mg, 63%) as a white solid:

m.p. = 178-180 °C (pentane);

R$_f$ 0.30 (1 : 1 EtOAc : hexanes);

[α]$^2_{D} = -13.24$ (c 0.73, CHCl$_3$);

IR (neat) ν$_{max}$ 2922 (m, C-H), 1738 (s, C=O), 1679 (w, C=C), 1596 (w, C-C), 1371 (m), 1230 (m) cm$^{-1}$;

HRMS (EI) calc. for C$_{14}$H$_{16}$O$_6$ [M+H]$^+$: requires 279.0869, found 279.0865 (Δ –1.4 ppm);
Experimental

$^1$H NMR (500 MHz, CDCl$_3$) δ 12.77 (br. s, 1H, 15), 6.35 (d, $J = 0.5$ Hz, 1H, 3), 3.74 - 3.67 (m, 1H, 8), 2.46 - 2.40 (m, 2H, 7), 1.27 (s, 3H, 13 / 14), 1.24 (s, 3H, 13 / 14), 0.89 (d, $J = 8.0$ Hz, 3H, 9);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.6 (10), 168.5 (11), 162.3 (4), 158.7 (2), 147.4 (6), 105.7 (1), 105.4 (5), 103.5 (12), 103.0 (3), 74.6 (8), 32.4 (7), 25.9 (13 / 14), 25.0 (13 / 14), 20.2 (9);

**Anal.** Calc. for C$_{14}$H$_{15}$O$_6$: C, 60.43; H, 5.07. Found: C, 60.88; H, 4.65.

(R)-Methyl 3-(benzyloxy)butanoate (138)

Alcohol 136 (2.0 g, 17.0 mmol, 1.0 equiv.) was stirred in cyclohexane (113 mL) and CH$_2$Cl$_2$ (56 mL). Benzyl 2,2,2-trichloroacetimidate (8.56 g, 33.9 mmol, 2.0 equiv.) followed by TSA (10 μL, 0.85 mmol, 0.1 equiv.) were added and the mixture stirred at rt for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO$_3$ (100 mL), extracted with CH$_2$Cl$_2$ (3 x 100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford benzyl-protected alcohol 137 (2.66 g, 76%) as a clear oil which was used without further purification.

Methyl ester 137 was stirred in NaOH (1 M, 22.0 mL, 22.1 mmol, 1.8 equiv.) and THF (20 mL) for 72 h. The reaction was acidified to pH 3 using 1 M HCl, extracted with CH$_2$Cl$_2$ (3 x 200 mL), the organics combined, washed with brine (150 mL), dried (MgSO$_4$) and rotary evaporated to afford carboxylic acid 138 (1.94 g, 83%) as a clear oil:

R$_f$ 0.4 (1 : 9 MeOH : CH$_2$Cl$_2$);
Experimental

\[ \alpha \]_D = -0.83 (c 0.113, CHCl_3);

IR (neat) \( \nu_{\text{max}} \) 3029 (br., O-H), 2975 (w, C-H), 2930 (w, C-H), 1706 (sh., C=O), 1454 (w), 1377 (w), 1305 (w), 1134 (w), 1075 (m) cm\(^{-1}\);

HRMS (CI) calc. for C\(_{11}\)H\(_{18}\)NO \([\text{M+NH}]^+\): requires 212.1287, found 212.1297 (\(\Delta +4.7 \text{ ppm}\));

\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \( \delta \) 7.25-7.24 (m, 2H, 8), 7.17-7.14 (m, 2H, 7), 7.08-7.05 (m, 1H, 9), 4.27 (q, \( J = 13.0 \text{ Hz} \), 2H, 5), 3.80-3.74 (m, 1H, 3), 2.44 (dd, \( J = 15.0, 7.0 \text{ Hz} \), 1H, 2b), 2.13 (dd, \( J = 15.0, 5.0 \text{ Hz} \), 1H, 2a), 0.96 (d, \( J = 6.0 \text{ Hz} \), 3H, 4);

\(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)) \( \delta \) 177.3 (1), 139.1 (6), 128.2 (8), 128.0 (9), 127.8 (7), 71.7 (5), 70.8 (3), 41.8 (2), 19.6 (4);


(5R)-3-Methylbut-2-enyl 5-(benzyloxy)-2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl)-3-oxohexanoate (132)

Based on a procedure by Navarro et al.\(^{[82]}\) Carboxylic acid 138 (490 mg, 2.52 mmol, 1.5 equiv.) was stirred in CH\(_2\)Cl\(_2\) (10 mL). Oxalyl chloride (0.45 mL, 5.04 mmol, 3.0 equiv.) and 2 drops of DMF (cat.) were added and the mixture stirred at 0 °C for 30 min. The reaction mixture was rotary evaporated to afford acid chloride 139 which was used without further purification.
Keto-prenylester-dioxinone 113 (500 mg, 1.68 mmol, 1.0 equiv.), MgCl$_2$ (352 mg, 3.7 mmol, 2.2 equiv.) and pyridine (0.4 mL, 4.54 mmol, 2.7 equiv.) were stirred in CH$_2$Cl$_2$ (10 mL) for 30 min. Acid chloride 139 in CH$_2$Cl$_2$ (5 mL) was added to the reaction mixture which was stirred for 30 min at 0 °C. The reaction mixture was quenched with brine (50 mL), extracted with EtOAc (2 x 100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 : 4 CH$_2$Cl$_2$ : EtOAc : hexanes) affording diketo-prenylester-dioxinone 132 (500 mg, 65%) as a pale yellow oil:

R$_f$ 0.60 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes);

[$\alpha$]$_D^{25}$ = −40.95 (c 0.61, CHCl$_3$);

IR (neat) $\nu_{\text{max}}$ 2975 (w, C-H), 2937 (w, C-H), 1728 (s, C=O), 1638 (w, C=C), 1374 (s), 1271 (m), 1250 (m), 1202 (w), 1126 (w), 1065 (m), 1015 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{26}$H$_{32}$O$_8$Na [M+Na]$^+$: requires 495.1995, found 495.1993 (Δ −0.4 ppm);

$^1$H NMR (500 MHz, C$_6$D$_6$) δ 17.50 (s, 1H, 25), 7.25-7.23 (m, 3H, 16 & 18), 7.07 (tt, J = 7.5, 1.0 Hz, 2H, 17), 5.29 (app. t of quin. J = 7.0, 0.5 Hz, 1H, 21), 5.2 (s, 1H, 2), 4.56-4.53 (m, 2H, 20), 4.34 (d, J = 12.0 Hz, 1H, 14), 4.25 (d, J = 12.0 Hz, 1H, 14), 3.91-3.87 (m, 1H, 12), 3.34 (s, 2H, 7), 3.15 (dd, J = 14.0, 3.0 Hz, 1H, 11a), 2.65 (dd, J = 14.0, 5.5 Hz, 1H, 11b), 1.51 (d, J = 0.5 Hz, 3H, 24), 1.45 (d, J = 0.5 Hz, 3H, 23), 1.31 (s, 6H, 5 & 6), 1.04 (d, J = 6.0 Hz, 3H, 13);

$^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 195.8 (8), 193.5 (10), 166.1 (1), 164.2 (19), 159.6 (22), 139.9 (3), 139.1 (15), 127.5 (2C, 17), 127.3 (3C, 16 & 18), 118.6 (21), 110.1 (4), 106.7 (9), 97.4 (2), 72.6 (12), 70.8 (14), 61.8 (20), 44.6 (11), 42.9 (7), 25.6 (2C, 5 & 6), 24.7 (23), 20.0 (24), 17.8 (13);

Anal. Calc. for C$_{26}$H$_{32}$O$_8$: C, 66.09; H, 6.83. Found: C, 66.22; H, 6.74.
Experimental

(R)-5-(2-(benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-ENYL)-4H-benzo[d][1,3]dioxin-4-one (133)

Pd(PPh₃)₄ (91 mg, 79 μmol, 0.1 equiv.) and Cs₂CO₃ (770 mg, 2.37 mmol, 3.0 equiv.) were stirred in THF (4 mL) at 0 °C for 2 min. Diketo-prenylester-dioxinone 132 (375 mg, 0.79 mmol, 1.0 equiv.) in THF (1 mL) was added to the stirring solution which was then allowed for stir for 20 min. The reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (50 mL), extracted with EtOAc (2 x 50 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 1 : 4 CH₂Cl₂ : EtOAc : hexanes) affording prenyl resorcylate 133 (100 mg, 31%) as a white solid: (traces of diketo-dioxinone 134 could be seen by crude NMR but could not be isolated)

m.p. 72-74 °C (pentane);

Rₓ 0.6 (1 : 1 : 6 CH₂Cl₂ : EtOAc : hexanes);

[α]D²⁵ = -31.5 (c 0.21, CHCl₃);

IR (neat) νmax 3264 (br., O-H), 2971 (w, C-H), 2929 (w, C-H), 1724 (sh., C=O), 1693 (m, C=C), 1606 (m, C=C), 1419 (m), 1376 (s), 1285 (sh.), 1207 (s), 1166 (w), 1108 (m) cm⁻¹;

HRMS (ESI) calc. for C₂₅H₃₁O₅ [M+H]⁺: requires 411.2157, found 411.2171 (Δ –1.5 ppm);

¹H NMR (500 MHz, C₆D₆) δ 7.18-7.15 (m, 2H, 12), 7.12-7.09 (m, 2H, 13), 7.04-7.01 (m, 1H, 14), 6.36 (s, 1H, 24), 6.31 (s, 1H, 5), 5.37 (app. t of quin., J = 7.0, 0.5 Hz, 1H, 20), 4.45
6 Experimental

(d, \( J = 12.0 \text{ Hz}, 1H, 10 \)), 4.29 (d, \( J = 12.0 \text{ Hz}, 1H, 10 \)), 4.01-3.95 (m, 1H, 8), 3.52 (dd, \( J = 12.0, 4.0 \text{ Hz}, 1H, 7b \)), 3.43 (d, \( J = 7.0 \text{ Hz}, 2H, 19 \)), 3.28 (dd, \( J = 12.0, 7.0 \text{ Hz}, 1H, 7a \)), 1.69 (d, \( J = 0.5 \text{ Hz}, 3H, 23 \)), 1.61 (d, \( J = 0.5 \text{ Hz}, 3H, 22 \)), 1.33 (s, 6H, 17 & 18), 1.29 (d, \( J = 6.0 \text{ Hz}, 3H, 9 \);

\(^{13}\text{C NMR}\) (125 MHz, C\(_6\)D\(_6\)) 160.7 (15), 159.8 (4), 156.8 (2), 143.5 (6), 139.6 (11), 132.2 (21), 129.2 (2C, 13), 128.6 (14), 127.4 (2C, 12), 122.4 (20), 115.1 (1), 114.7 (3), 105.6 (16), 104.6 (5), 76.3 (8), 70.9 (10), 42.3 (7), 25.6 (22), 22.4 (17 & 18), 21.5 (19), 20.4 (9), 17.8 (23).

3-Methylbut-2-enyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4\(H\)-1,3-dioxin-6-yl)-3-oxobutanoate

(140)

Based on a procedure by Navarro et al.\(^{[82]}\) Keto-prenylester-dioxinone 113 (450 mg, 1.52 mmol, 1.0 equiv.) was added to MgCl\(_2\) (173 mg, 1.82 mmol, 2.0 equiv.) and pyridine (0.3 mL, 3.9 mmol, 2.7 equiv.) in CH\(_2\)Cl\(_2\) (40 mL) at 0 °C and stirred for 30 min. Acetyl chloride (0.15 mL, 2.13 mmol, 1.4 equiv.) was added and the resulting solution stirred for 1 h at 0 °C. The reaction mixture was quenched with brine (100 mL), extracted with EtOAc (2 x 100 mL), the organics combined, dried (MgSO\(_4\)), rotary evaporated and chromatographed (3 : 7 Et\(_2\)O : hexanes to Et\(_2\)O) to afford diketo-prenylester-dioxinone 140 (301 mg, 86%) as a yellow oil:

\( R_f 0.50 \) (2 : 1 Et\(_2\)O : hexanes);
6 Experimental

IR (neat) $\nu_{\text{max}}$ 2934 (w, C-H), 1722 (s, C=O), 1706 (s, C=O), 1636 (m, C=C), 1375 (m), 1272 (sh.), 1201 (m) cm$^{-1}$;

HRMS (ESI) calc. for C$_9$H$_{12}$O$_4$[M+H]$^+$: requires 339.1444, found 339.1440 (Δ –1.2 ppm);

$^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 18.00 (s, 1H, 18), 5.28-5.25 (m, 1H, 14), 5.20 (s, 1H, 2), 4.54 (d, $J$ = 7.5 Hz, 2H, 13), 3.38 (s, 2H, 7), 2.03 (s, 3H, 11), 1.53 (s, 3H, 17), 1.45 (s, 3H, 16), 1.31 (s, 6H, 5 & 6);

$^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$ 195.9 (8), 194.2 (10), 165.9 (1), 164.4 (12), 159.6 (15), 139.6 (3), 118.7 (14), 108.8 (4), 106.7 (9), 97.3 (2), 61.6 (13), 43.1 (7), 25.6 (17), 25.1 (11), 24.68 (2C, 5 & 6), 17.77 (16);

Anal. Calc. for C$_{17}$H$_{22}$O$_7$: C, 60.43; H, 6.50. Found: C, 60.43; H, 6.50.

5-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-6,6-dimethyloct-7-ene-2,4-dione (141), 7-Hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-enyl)-4H-benzo[d][1,3]dioxin-4-one (142), 3-Methylbut-2-enyl 7-hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-enyl)-4-oxo-4H-benzo[d][1,3]dioxine-6-carboxylate (159) and 7-Hydroxy-2,2,5-trimethyl-4H-benzo[d][1,3]dioxin-4-one (155)

Pd(PPh$_3$)$_4$ (164 mg, 142 μmol, 0.1 equiv.) and Cs$_2$CO$_3$ (1.40 g, 4.26 mmol, 3.0 equiv.) were stirred in THF (7.1 mL for a concentration of 0.2 M and 100 mL for a concentration of 0.014 M) at 0 °C, diketo-prenylester-dioxinone 140 (480 mg, 1.42 mmol, 1.0 equiv.) was added and
the resulting solution stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (10 mL), extracted with EtOAc (2 x 50 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 1 : 10 to 1 : 1 : 5 CH₂Cl₂ : EtOAc : hexanes) to afford diketo-dioxinone 141 (42 mg, 10% at 0.2 M, 2 mg, 0.5% at 0.014 M) as a yellow oil, prenyl-resorcyline 142 (195 mg, 50% at 0.2 M, 12 mg, 3% at 0.014 M) as a white solid, prenylester-prenyl-resorcyline 159 (11 mg, 2% at 0.2 M, 231 mg, 42% at 0.014 M) as a clear oil and resorcyline 155[42] (9 mg, 3% at 0.2 M, 121 mg, 41% at 0.014 M) as a colourless oil.

**Diketo-dioxinone 141:**

\( R_f \) 0.5 (1 : 1 : 6 EtOAc : CH₂Cl₂ : hexanes);

\[ \text{IR (neat) } v_{\text{max}} = 2979, 2961, 1740, 1395, 1365 \, \text{cm}^{-1}; \]

\[ \text{HRMS (ESI) calc. for } C_{16}H_{23}O_5 [M+H]^+ : \text{requires } 295.1545, \text{found } 295.1530 (\Delta -5.1 \text{ ppm}); \]

\[ \text{^1H NMR (500 MHz, CD}_6D_6) \delta = 5.91, 5.52, 4.88, 4.85, 5.04, 2.60, 1.50, 1.27, 1.04 \, \text{ppm}; \]

\[ \text{^13C NMR (125 MHz, CD}_6D_6) \delta = 192.1, 188.7, 166.3, 159.8, 145.1, 122.4, 106.4, 101.7, 97.6, 62.5, 40.4, 25.7, 23.4 \, \text{ppm}; \]

**Prenyl-resorcyline 142:**

m.p. 121-124 °C (pentane);

\( R_f \) 0.55 (1 : 1 : 6 EtOAc : CH₂Cl₂ : hexanes);

\[ \text{IR (neat) } v_{\text{max}} = 3213, 2998, 1689, 1605, 1518, 1378, 1324, 1296, 1240, 1167, 1048 \, \text{cm}^{-1}; \]

\[ \text{HRMS (ESI) calc. for } C_{16}H_{21}O_4 [M+H]^+ : \text{requires } 277.1440, \text{found } 277.1437 (\Delta -1.1 \text{ ppm}); \]

203
6 Experimental

$^1$H NMR (500 MHz, C$_6$D$_6$) δ 5.94 (s, 1H, 17), 5.63 (s, 1H, 5), 5.29 (app. t of quin., $J = 7.0$, 0.5 Hz, 1H, 13), 3.36 (d, $J = 7.0$ Hz, 2H, 12), 2.70 (s, 3H, 7), 1.65 (d, $J = 0.5$ Hz, 3H, 16), 1.58 (d, $J = 0.5$ Hz, 3H, 15), 1.33 (s, 6H, 10 & 11);

$^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 160.6 (8), 159.8 (4), 156.6 (2), 142.6 (6), 132.6 (14), 122.2 (13), 113.7 (3), 113.5 (5), 106.0 (1), 104.6 (9), 30.4 (16), 22.3 (12), 22.2 (7), 17.8 (15);

Anal. Calc. for C$_{16}$H$_{20}$O$_4$: C, 69.54; H, 7.30. Found: C, 68.01; H, 7.53.

Prenylester-prenyl-resorcylate 159:

R$_f$ 0.85 (1 : 1 : 6 EtOAc : CH$_2$Cl$_2$ : hexanes);

IR (neat) $\nu_{max}$ 2924 (w, C-H), 1736 (s, C=O), 1654 (w, C=C), 1586 (C-C), 1447 (w), 1376 (m), 1266 (m), 1034 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{22}$H$_{29}$O$_6$ [M+H]$^+$: requires 389.1964, found 389.1960 (Δ –1.0 ppm);

$^1$H NMR (500 MHz, C$_6$D$_6$) δ 12.48 (s, 1H, 23), 5.43 (app. t of quin., $J = 7.0$, 0.5 Hz, 1H, 13), 5.25 (app. t of quin., $J = 7.0$, 0.5 Hz, 1H, 19), 4.54 (d, $J = 7.0$ Hz, 2H, 18), 3.50 (d, $J = 7.0$ Hz, 2H, 12), 3.06 (s, 3H, 7), 1.75 (d, $J = 0.5$ Hz, 3H, 22), 1.65 (d, $J = 0.5$ Hz, 3H, 16), 1.46 (d, $J = 0.5$ Hz, 3H, 21), 1.39 (d, $J = 0.5$ Hz, 3H, 15), 1.30 (s, 6H, 10 & 11);

$^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 171.9 (8), 165.2 (17), 159.4 (2), 158.5 (4), 147.1 (6), 140.3 (20), 131.8 (14), 122.1 (13), 118.1 (19), 115.7 (3), 110.8 (5), 107.3 (1), 104.3 (9), 62.6 (18), 25.8 (2C, 10 & 11), 25.5 (2C, 16 & 22), 22.4 (12), 20.5 (2C, 15 & 21), 17.89 (7).

Resorcylate 155:

R$_f$ 0.2 (1 : 3 Et$_2$O : hexanes);

IR (neat) $\nu_{max}$ 3328 (br., O-H), 2989 (w, C-H), 1684 (s, C=O), 1615 (s, C=C), 1578 (m, C-C), 1480 (m), 1654 (m), 1286 (sh.), 1199 (m), 1066 (m) cm$^{-1}$;
6 Experimental

**HRMS (ESI)** calc. for C$_{11}$H$_{13}$O$_{4}$ [M+H]$^+$: requires 209.0814, found 209.0809 ($\Delta$ –2.4 ppm);

**$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.56 (s, 1H, 12), 6.37 (s, 1H, 5), 6.22 (d, $J$ = 2.0 Hz, 1H, 3), 2.58 (s, 3H, 7), 1.66 (s, 6H, 10 & 11);

**$^{13}$C NMR** (125MHz, CDCl$_3$) $\delta$ 165.6 (8), 162.8 (4), 160.5 (2), 146.7 (6), 114.9 (5), 106.2 (1), 104.9 (9), 102.2 (3), 25.7 (2C, 10 & 11), 22.3 (7);

**Anal.** Calc. for C$_{11}$H$_{13}$O$_{4}$: C, 63.45; H, 5.81. Found: C, 63.56; H, 5.92.

**Methyl 2,4-dihydroxy-6-methyl-3-(2-methylbut-3-en-2-yl)benzoate (144)**

![Structure of 144]

Diketo-allylester-dioxinone 141 (20 mg, 66 μmol, 1.0 equiv.) was refluxed in MeOH (2 mL) and toluene (5 mL) for 18 h. The resulting mixture was rotary evaporated and chromatographed (1 : 7 Et$_2$O : pentane) to afford allyl-resorcylate 144 (12 mg, 80%) as a colourless gum:

**R$_f$** 0.85 (1 : 3 : 4 CH$_2$Cl$_2$ : EtOAc : hexanes);

**IR (neat)** $\nu_{\text{max}}$ 2926 (m, C-H), 1739 (s, C=O), 1654 (w, C=C), 1439 (w), 1366 (m), 1217 (m), 1230 (m) cm$^{-1}$;

**HRMS (ESI)** calc. for C$_{14}$H$_{119}$O$_{4}$ [M+H]$^+$: requires 251.1283, found 251.1278 ($\Delta$ –2.0 ppm);

**$^1$H NMR** (500 MHz, C$_6$D$_6$) $\delta$ 13.22 (s, 1H, 16), 7.21 (s, 1H, 15), 6.42 (s, 1H, 5), 6.20 (dd, $J$ = 17.0, 10.0 Hz, 1H, 11), 5.02 (d, $J$ = 17.0 Hz, 1H, 12a), 4.81 (d, $J$ = 10.0 Hz, 1H, 12b), 3.26 (s, 3H, 9), 2.28 (s, 3H, 7), 1.62 (s, 6H, 13 & 14);

**$^{13}$C NMR** (125 MHz, C$_6$D$_6$) $\delta$ 173.39 (8), 165.6 (4), 160.4 (2), 150.3 (11), 141.2 (6), 119.8 (1), 116.2 (3), 113.6 (5), 112.5 (12), 51.2 (9), 30.2 (10), 27.0 (2C, 13 & 14), 24.1 (7).
Based on a procedure by Navarro et al.[82] Keto-allylester-dioxinone 102 (700 mg, 2.60 mmol, 1.0 equiv.) was added to MgCl₂ (300 mg, 3.12 mmol, 2.0 equiv.) and pyridine (500 mg, 0.50 mL, 6.76 mmol, 2.7 equiv.) in CH₂Cl₂ (50 mL) at 0 °C and stirred for 30 min. Acetyl chloride (332 mg, 3.64 mmol, 1.4 equiv.) was added and the resulting solution stirred for 1 h at 0 °C. The reaction mixture was quenched with brine (100 mL), extracted with EtOAc (2 x 50 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (2 : 8 Et₂O : hexanes to Et₂O) to afford diketo-allylester-dioxinone 153 (665 mg, 83%) as a yellow oil (665 mg, 83%):

\[ R_f \text{ 0.36 (2 : 1 Et}_2\text{O : hexanes);} \]

\[ \text{IR (neat) } \nu_{\text{max}} \text{ 2990 (w, C-H), 2870 (w, C-H), 1724 (s, C=O), 1637 (m, C=C), 1564 (m, C-C), 1270 (sh.), 1074 (sh.) cm}^{-1}; \]

\[ \text{HRMS (ESI) calc. for C}_{15}\text{H}_{19}\text{O}_{7}[M+H]^+: \text{requires 311.1131, found 311.1123 (} \Delta-2.6 \text{ ppm);} \]

\[ ^{1}\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ 17.81 (s, 1H, 16), 6.03–5.92 (m, 1H, 14), 5.41–5.30 (m, 3H, 2 & 15), 4.71 (d, } J = 6.0 \text{ Hz, 2H, 13), 3.74 (s, 2H, 7), 2.43 (s, 3H, 11), 1.70 (s, 6H, 5 & 6);} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta \text{ 196.1 (8), 193.8 (10), 165.9 (1), 165.1 (12), 160.7 (3), 131.5 (14), 119.7 (15), 108.2 (4), 107.2 (9), 96.5 (2), 65.9 (13), 43.2 (7), 25.6 (2C, 5 & 6), 24.9 (11).} \]
Experimental

8- Allyl-7-hydroxy-2,2,5-trimethyl-4H-benzo[d][1,3]dioxin-4-one (154) and 7-Hydroxy-2,2,5-trimethyl-4H-benzo[d][1,3]dioxin-4-one (155)

Pd(PPh₃)₄ (37 mg, 32 μmol, 0.1 equiv.) and Cs₂CO₃ (313 mg, 0.96 mmol, 3.0 equiv.) were stirred in THF (3 mL) at 0 °C for 5 min. Diketo-allylester-dioxinone 153 (100 mg, 0.32 mmol, 1.0 equiv.) in THF (1 mL) was added to the stirring solution which was allowed to warm from 0 °C to rt and stirred for 18 h. The mixture was quenched with a saturated aqueous solution of NaHCO₃ (10 mL), extracted with Et₂O (2 x 50 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 20 to 1 : 5 Et₂O : hexanes) to afford a mixture of allyl-resorcylate 154 and resorcylate 155[42] (44 mg, 60%) in a 1:1 ratio as a white solid:

Rᵥ 0.2 (1 : 3 Et₂O : hexanes);

**Allyl-resorcylate 154:**

IR (neat) νmax 3243 (br., O-H), 2989 (w, C-H), 1710 (m, C=O), 1694 (m, C=C), 1611 (sh. C=C), 1591 (m, C=C), 1274 (sh.), 1207 (s), 1126 (m) cm⁻¹;

HRMS (ESI) calc. for C₁₄H₁₇O₄ [M+H]^+: requires 249.1127, found 249.1120 (Δ –2.8 ppm);

¹H NMR (500 MHz, C₆D₆) δ 5.87-5.79 (m, 1H, 13), 5.73 (s, 1H, 15), 5.00-4.91 (m, 2H, 14), 4.81 (s, 1H, 3), 3.26 (dt, J = 5.0, 0.5 Hz, 12), 2.68 (s, 3H, 11), 1.30 (s, 6 H, 8 & 9);

¹³C NMR (125 MHz, C₆D₆) δ 160.2 (10), 159.3 (4), 156.7 (6), 143.1 (2), 135.7 (13), 115.3 (14), 113.3 (5), 111.7 (3), 106.2 (1), 104.6 (7), 27.1 (12), 25.4 (8 & 9), 22.2 (11).

**Resorcylate 155:** characterised as described earlier.
Based on a procedure by Tararov et al.\textsuperscript{[74]} E-crotyl-alcohol (17.2 mL, 208 mmol, 1.5 equiv.) and Meldrum’s acid (20.0 g, 139 mmol, 1.0 equiv.) were stirred at 120 °C for 18 h. The reaction mixture was poured into a saturated aqueous solution of NaHCO\textsubscript{3} (400 mL) and washed with EtOAc (3 x 200 mL). The aqueous layer was acidified to pH 3.0 using 1 M HCl and extracted with EtOAc (2 x 400 mL). The organics were combined and rotary evaporated to afford crotylester-carboxylic acid \textit{315}[191] (19.5 g, 89%) as a pale yellow oil:

$$R_f$$ 0.42 (1 : 9 MeOH : CH\textsubscript{2}Cl\textsubscript{2});

\textbf{IR} (neat) \( \nu_{max} \) 3501 (br., O-H), 2948 (w, C-H), 1731 (sh. C=O), 1378 (m), 1146 (sh.), 965 (sh.) cm\textsuperscript{-1};

\textbf{MS} (CI) [M+NH\textsubscript{4}]\textsuperscript{+}: requires 176, found 176;

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.00 (br. s, 1H, 1), 5.80 - 5.91 (m, 1H, 7), 5.57 - 5.66 (m, 1H, 6), 4.62 (d, \( J = 7.0 \) Hz, 2H, 5), 3.44 (s, 2H, 3), 1.74-1.73 (m, 3H, 8);

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 169.8 (4), 165.0 (2), 132.1 (7), 124.5 (6), 66.8 (5), 40.1 (3), 17.8 (8).
(E)-But-2-enyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (317)

Based on a procedure by Navarro et al.\textsuperscript{[82]} Crotylester-carboxylic acid 315 (4.0 g, 25.3 mmol, 1.0 equiv.) was stirred in CH\textsubscript{2}Cl\textsubscript{2} (20 mL) at 0 °C. Oxalyl chloride (4.40 mL, 50.6 mmol, 2.0 equiv.) and 4 drops of DMF (cat.) were added and the reaction mixture stirred for 1 h at 0 °C. The reaction mixture was rotary evaporated to afford acid chloride 316 as a brown oil which was used without further purification.

\textit{n-}BuLi in hexanes (63.5 mL, 1.4 M, 88.6 mmol, 3.5 equiv.) and HMDS (18.5 mL, 88.6 mmol, 3.5 equiv.) was stirred in THF (100 mL) at −78 °C for 20 min. Dioxinone 33 (11.7 mL, 88.6 mmol, 3.0 equiv.) was added dropwise to the stirring solution which was stirred for 1 h. Acid chloride 316 in THF (10 mL) was added dropwise to the stirring solution. The resulting solution was stirred for 1 h. The reaction mixture was poured into a saturated aqueous solution of NH\textsubscript{4}Cl (250 mL), acidified to pH 3 utilising 1 M HCl and extracted with EtOAc (3 x 200 mL). The organics were combined, washed with brine (100 mL), dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (7 : 3 hexanes : Et\textsubscript{2}O) to afford diketo-crotylester-dioxinone 317 (4.0 g, 56%) as a yellow oil:

\[ R_f \] 0.32 (2 : 1 Et\textsubscript{2}O : hexanes);
6 Experimental

IR (neat) $\nu_{\text{max}}$ 2943 (w, C-H), 1719 (m, C=O), 1635 (m, C=C), 1272 (sh.), 1201 (sh.), 1015 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{14}$H$_{19}$O$_6$ [M+H]$^+$: requires 283.1182, found 283.1185 (Δ +1.1 ppm);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.88-5.79 (m, 1H, 13), 5.62-5.55 (m, 1H, 12), 5.40 (s, 1H, 2), 4.57 (d, $J$ = 6.0 Hz, 2H, 11), 3.53 (s, 2H, 9), 3.51 (s, 2H, 7), 1.74 (d, $J$ = 6.0 Hz, 3H, 14), 1.71 (s, 6H, 5 & 6);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 195.6 (8), 166.2 (1), 163.6 (10), 160.6 (3), 132.7 (13), 124.2 (12), 107.4 (4), 97.1 (2), 66.5 (11), 49.1 (7), 47.0 (9), 25.0 (2C, 5 & 6), 17.8 (14).

(E)-But-2-enyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (156)

Based on a procedure by Navarro et al.$^{[82]}$ Keto-crotylester-dioxinone 317 (500 mg, 1.77 mmol, 1.0 equiv.) was added to MgCl$_2$ (333 mg, 3.50 mmol, 2.0 equiv.) and pyridine (0.14 mL, 4.77 mmol, 2.7 equiv.) in CH$_2$Cl$_2$ (20 mL) at 0 °C and stirred for 30 min. Acetyl chloride (0.2 mL, 2.66 mmol, 1.5 equiv.) was added to the reaction mixture which was stirred for 1 h hour at 0 °C. The reaction mixture was quenched with brine (50 mL), extracted with EtOAc (2 x 100 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (3 : 7 Et$_2$O : hexanes to Et$_2$O) to afford diketo-crotylester-dioxinone 156 (260 mg, 46%) as a pale yellow oil:

$R_f$ 0.40 (2 : 1 hexanes : Et$_2$O);

IR (neat) $\nu_{\text{max}}$ 2943 (w, C-H), 1727 (sh., C=O), 1638 (m, C=C), 1564 (m, C-C), 1390 (m), 1201 (sh.), 1070 (sh.) cm$^{-1}$;

210
6 Experimental

HRMS (ESI) calc. for C_{16}H_{20}O_{7}[M+H]^+: requires 325.1287, found 325.1280 (Δ = 2.2 ppm);

^1H NMR (400 MHz, CDCl$_3$) δ 17.0 (s, 1H, 17), 5.94-5.58 (m, 1H, 15), 5.99-5.63 (m, 1H, 14), 5.37 (s, 1H, 12), 4.67 (d, J = 6.0 Hz, 2H, 13), 3.76 (s, 2H, 7), 2.44 (s, 3H, 11), 1.77 (d, J = 6.0 Hz, 3H, 16), 1.72 (s, 6H, 5 & 6);

^13C NMR (100 MHz, CDCl$_3$) δ 195.9 (8), 193.6 (10), 165.2 (1), 132.7 (12), 129.0 (3), 125.3 (15), 124.4 (14), 96.5 (4), 67.9 (9), 65.9 (2), 53.4 (13), 43.2 (7), 29.4 (2C, 5 & 6), 25.6 (11), 17.8 (16).

(E)-8-(But-2-enyl)-7-hydroxy-2,2,5-trimethyl-4H-benzo[d][1,3]dioxin-4-one (157)

Pd(PPh$_3$)$_4$ (70 mg, 60 μmol, 0.1 equiv.) and Cs$_2$CO$_3$ (606 mg, 1.86 mmol, 3.0 equiv.) were stirred in THF (1 mL) for 5 min at 0 °C. Diketo-crotylester-dioxinone 156 (200 mg, 0.62 mmol, 1.0 equiv.) in THF (1 mL) was added and the reaction was allowed to warm from 0 °C to rt and stirred for 18 h. The reaction mixture was quenched with brine (20 mL), extracted with EtOAc (2 x 50 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 EtOAc : hexanes) to afford crotyl-resorcylate 157 (50 mg, 30%) as a colourless gum:

R$_f$ 0.45 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes);

IR (neat) $\nu_{\text{max}}$ 3255 (br., O-H), 2995 (w, C-H), 1692 (m, C=C), 1607 (m, C=C), 1592 (w, C-C), 1452 (m), 1322 (w), 1284 (sh.), 1209 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{15}$H$_{18}$O$_4$[M+H]$^+$: requires 263.1283, found 263.1287 (Δ +1.5 ppm);

^1H NMR (500 MHz, C$_6$D$_6$) δ 8.21 (s, 1H, 16), 6.52 (s, 1H, 5), 5.50-5.38 (m, 2H, 13 & 14), 3.27 (d, J = 5.0 Hz, 2H, 12), 3.16 (s, 3H, 7), 1.48-1.49 (m, 3H, 15), 1.31 (s, 6H, 10 & 11);
6 Experimental

$^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 160.5 (8), 159.8 (4), 156.6 (2), 143.0 (6), 126.2 (13), 114.4 (3), 113.5 (5), 112.6 (14), 106.1 (1), 104.6 (9), 26.0 (12), 25.5 (2C, 10 & 11), 22.2 (7), 17.8 (15).

(R)-5-(2-(Benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-4H-benzo[d][1,3]dioxin-4-one (163), (R)-5-(2-(Benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (165) and (R)-5-(2-(benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-4H-benzo[d][1,3]dioxin-4-one (133)

Diketo-prenylester-dioxinone 132 (100 mg, 0.21 mmol, 1.0 equiv.), Pd(PPh$_3$)$_4$ (12 mg, 10 µmol, 5 mol%) and Cs$_2$CO$_3$ (205 mg, 0.63 mmol, 3.0 equiv.) were stirred in THF (15 mL) at 0 °C for 30 min. The reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (50 mL), extracted with EtOAc (2 x 50 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 : 4 CH$_2$Cl$_2$ : EtOAc : hexanes) to afford prenylester-prenyl-resorcylate 163 (35 mg, 32%) as a colourless oil, resorcylate 365 (24 mg, 33%) as a colourless gum and prenyl-resorcylate 133 (2 mg, 2%) as a white solid:

**Prenylester-prenyl-resorcylate 163:**

R$_f$ 0.90 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes);

[α]$_D^{25}$ = −33.3 (c 0.46, CHCl$_3$);

212
6 Experimental

IR (neat) $v_{\text{max}}$ 2970 (w, C-H), 1730 (m, C=O), 1655 (w, C=C), 1585 (w, C-H), 1452 (w), 1376 (m), 1266 (sh.), 1207 (s), 1118 (w), 1042 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{31}$H$_{39}$O$_7$ [M+H]$^+$: requires 523.2696, found 523.2701 ($\Delta +1.0$ ppm);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.30 (br. s, 1H, 30), 7.22-7.17 (m, 3H, 16 & 18), 7.10-7.04 (m, 2H, 17), 5.43 (app. t of quin., $J = 7.0$, 0.5 Hz, 1H, 21), 5.20 (app. t of quin., $J = 7.0$, 0.5 Hz, 1H, 14), 4.80 (d, $J = 7.0$ Hz, 2H, 20), 4.40 (d, $J = 12.0$ Hz, 1H, 14), 4.19 (d, $J = 12.0$ Hz, 1H, 14), 4.10 (q, $J = 7.0$, 1H, 12), 3.75 (br. s, 1H, 11a), 3.54 (br. s, 1H, 11b), 3.31 (d, $J = 7.0$, 2H, 25), 1.78 (s, 6H, 9 & 10), 1.74 (br. s, 3H, 24), 1.70 (br. s, 3H, 29), 1.62 (br. s, 3H, 23), 1.53 (br. s, 3H, 28), 1.21 (d, $J = 7.0$ Hz, 3H, 13);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.3 (7), 163.5 (19), 160.4 (4), 157.8 (2), 146.7 (22), 140.7 (15), 138.9 (6), 132.2 (27), 128.3 (5), 128.0 (2C, 17), 127.7 (18), 127.3 (2C, 16), 121.2 (21), 117.5 (26), 115.7 (3), 104.4 (2C, 8 & 1), 76.5 (12), 70.5 (14), 62.7 (20), 36.3 (11), 26.5 (2C, 9 & 10), 25.8 (24), 24.8 (29), 22.0 (28), 19.9 (23), 18.1 (25), 17.8 (13).

Resorcylate 165:

R$_f$ 0.4 (1 : 1 : 6 CH$_2$Cl$_2$ : EtOAc : hexanes); $[\alpha]_{D}^{25} = -3.0$ (c 0.3, CHCl$_3$);

IR (neat) $v_{\text{max}}$ 2971 (w, C-H), 1738 (s, C=O), 1366 (m), 1217 (m) cm$^{-1}$.

HRMS (ESI) calc. for C$_{20}$H$_{23}$O$_5$ [M+H]$^+$: requires 343.1545, found 3431552 ($\Delta +2.0$ ppm);

$^1$H NMR (500 MHz, CD$_6$D$_6$) $\delta$ 7.21-7.19 (m, 2H, 17), 7.13-7.10 (m, 2H, 16), 7.05-7.02 (m, 1H, 18), 6.28 (d, $J = 2.5$ Hz, 1H, 5), 6.24 (d, $J = 2.5$ Hz, 3), 5.74 (s, 1H, 19), 4.47 (d, $J = 12.0$ Hz, 1H, 14), 4.30 (d, $J = 12.0$ Hz, 1H, 14), 3.97-3.91 (m, 1H, 12), 3.48 (dd, $J = 12.0$, 6.0 Hz, 1H, 11b), 3.30 (dd, $J = 12.0$, 3.0 Hz, 1H, 11a), 1.30 (s, 3H, 9 / 10), 1.29 (s, 3H, 9 / 10), 1.26 (d, $J = 6.0$ Hz, 13);
Experimental

$^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 161.9 (7), 160.2 (4), 159.5 (2), 147.0 (6), 139.7 (15), 128.5 (2C, 17), 127.5 (18), 127.4 (2C, 16), 115.4 (5), 105.5 (1), 104.7 (8), 102.1 (3), 76.0 (12), 70.9 (14), 42.3 (11), 25.6 (9 / 10), 25.2 (9 / 10), 20.3 (13).

Prenyl-Resorcylate 133: characterised as described earlier.

Ethyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (318)

Based on a procedure by Navarro et al.$^{[82]}$ n-BuLi in hexanes (4.10 mL, 10.2 mmol, 3.1 equiv.; 2.5 M) was slowly added to HMDS (2.20 mL, 10.6 mmol, 3.2 equiv.) in THF (160 mL) at −78 °C and stirred for 30 min. Dioxinone 33 (1.30 mL, 10.0 mmol, 3.0 equiv.) was added dropwise to the stirring solution which was then allowed to stir for 1 h at −78 °C. Ethyl 3-chloro-3-oxopropanoate (319) (500 mg, 3.30 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise to the stirring solution. The reaction mixture was stirred at −78 °C for a 1 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (20 mL), acidified to pH 3 utilising 1 M HCl and extracted with EtOAc (3 x 200 mL). The organics were combined, washed with brine (100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed eluting with (7 : 3 hexanes : Et$_2$O) to afford keto-ethylester-dioxinone 318$^{[102]}$ (512 mg, 62%) as a yellow oil:

- $R_f$ 0.20 (2 : 1 Et$_2$O : hexanes);
- IR (neat) $\nu_{max}$ 2994 (w, C-H), 1720 (s, C=O), 1638 (w, C=C), 1375 (w), 1271 (sh.), 1202 (sh.), 1015 (w) cm$^{-1}$;
- HRMS (ESI) calc. for C$_{12}$H$_{17}$O$_6$ [M+H]$^+$: requires 257.1025, found 257.1024 (Δ –0.4 ppm);
Experimental

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.36 (s, 1H, 2), 4.22 (q, $J = 5.0$ Hz, 2H, 11), 3.51 (s, 2H, 9), 3.50 (s, 2H, 7), 1.71 (s, 6H, 5 & 6), 1.29 (t, $J = 5.0$ Hz, 3H, 12);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 195.7 (8), 166.3 (1), 163.5 (10), 160.7 (3), 107.3 (4), 97.1 (2), 61.8 (11), 49.1 (9), 47.0 (7), 25.0 (2C, 5 & 6), 14.2 (12).

Ethyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (174)

Based on a procedure by Navarro et al.$^{[82]}$ Pyridine (0.42 mL, 5.13 mmol, 2.7 equiv.) and MgCl$_2$ (450 mg, 4.69 mmol, 2.5 equiv.) were stirred in CH$_2$Cl$_2$ (15 mL) for 2 min at 0 °C for 2 min. Keto-ethylester-dioxinone 318 (480 mg, 1.90 mmol, 1.0 equiv.) was added in CH$_2$Cl$_2$ (1.5 mL) and the resulting solution stirred for 30 min. Acetyl chloride (0.21 mL, 2.90 mmol, 1.5 equiv.) was added dropwise and the mixture stirred at 0 °C for 30 min. The reaction was quenched with brine (100 mL), extracted with EtOAc (2 x 200 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 : 10 EtOAc : CH$_2$Cl$_2$ : hexanes) to afford diketo-ethylester-dioxinone 174$^{[102]}$ (451 mg, 80%) as a pale yellow oil:

R$_f$ 0.80 (2 : 1 : 5 EtOAc : CH$_2$Cl$_2$ : hexanes);

IR (neat) $v_{max}$ 2995 (w, C-H), 1725 (s, C=O), 1637 (m, C=C), 1565 (m, C-C), 1373 (sh.), 1270 (sh.), 1250 (sh.), 1201 (s), 1103 (sh), 1077 (sh.), 901 (w), 810 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{14}$H$_{19}$O$_7$[M+H]$^+$: requires 299.1131, found 299.1137 (Δ +2.0 ppm);

$^1$H NMR (500 MHz, CDCl$_3$) δ 18.00 (s, 1H, 15), 5.34 (s, 1H, 2), 4.29 (q, $J = 6.0$ Hz, 2H, 11), 3.74 (s, 2H, 7), 2.42 (s, 3H, 14), 1.70 (s, 6H, 5 & 6), 1.35 (t, $J = 6.0$ Hz, 3H, 12);
Experimental

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 195.9 (8), 193.6 (13), 166.2 (1), 165.2 (10), 160.8 (9), 180.5 (3), 107.2 (4), 96.4 (2), 61.1 (11), 43.2 (7). 25.6 (14), 24.9 (2C, 5 & 6), 14.2 (12).

Ethyl 8-allyl-7-hydroxy-2,2,5-trimethyl-4-oxo-4H-benzo[d][1,3]dioxine-6-carboxylate

(177)

Diketo-ethylester-dioxinone 174 (96 mg, 0.32 mmol, 1.0 equiv.) and allyl chloride (29 µL, 0.35 mmol, 1.1 equiv.) were stirred in THF (1.6 mL) at 0 °C. Pd(PPh$_3$)$_4$ (37 mg, 32 µmol, 0.1 equiv.) was added followed by Cs$_2$CO$_3$ (105 mg, 0.32 mmol, 1.0 equiv.) and the resulting solution stirred for 1 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (20 mL), extracted with Et$_2$O (2 x 20 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 Et$_2$O : pentane) to afford allyl-resorcylate 177$^{[102]}$ (90 mg, 88%) as a white solid:

m.p. = 42-45 °C (hexanes)

R$_f$ 0.65 (Et$_2$O : pentane 3 : 9);

HRMS (ESI) calc. for C$_{17}$H$_{21}$O$_6$[M+H]$^+$: requires 321.1338, found 321.1349 (Δ +3.4 ppm);

IR $v_{max}$ 2987 (w, C-H), 1730 (m, C=O), 1653 (m, C=C), 1583 (w, C=C), 1377 (w), 1264 (m), 1233 (s), 1208 (sh.), 1028 (m), 1013 (m), 901 (w) cm$^{-1}$;

$^1$H NMR (C$_6$D$_6$, 400 MHz) δ 12.53 (s, 1H, 18), 6.03-5.93 (m, 1H, 13), 5.14-5.09 (m, 1H, 14a), 5.02-4.98 (m, 1H, 14b), 3.82 (q, $J = 6.0$ Hz, 2H, 16), 3.46 (dt, $J = 8.0$, 0.5 Hz, 2H, 12), 2.99 (s, 3H, 7), 1.29 (s, 6H, 10 & 11), 0.81 (t, $J = 6.0$ Hz, 3H, 17);
Experimental

$^{13}$C NMR (CD$_6$, 100 MHz) δ 171.4 (15), 165.3 (8), 159.4 (2), 158.7 (4), 147.6 (6), 135.0 (13), 115.3 (14), 113.8 (3), 110.6 (5), 107.2 (1), 104.4 (9), 62.0 (16), 27.2 (12), 25.4 (2C, 10 & 11), 20.5 (7), 13.7 (17).

2,2-Dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (178)

Based on a procedure by Navarro et al.[82] n-BuLi in hexanes (1.6 M; 29.0 mL, 46.4 mmol, 1.1 equiv.) and HMDS (9.7 mL, 46.4 mmol, 1.1 equiv.) were stirred in THF (50mL) at –78 °C for 30 min. Dioxinone 33 (6.0 g, 5.6 mL, 42.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution and the resulting reaction mixture was stirred for 1 h. Acetyl chloride (1.8 mL, 25.3 mmol, 0.6 equiv.) was added dropwise and the resulting solution stirred for 3 h. The reaction mixture was poured into a saturated aqueous solution of NH$_4$Cl and 1 M HCl (1 : 1, 100 mL) and stirred for 30 min at rt. The pH was adjusted to pH 2 using 1 M HCl and the aqueous was extracted with Et$_2$O (2 x 250mL). The organics were combined, dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 1 to 1 : 1 hexanes : Et$_2$O) to afford keto-dioxinone 178[82] (900 mg, 22%) as a pale yellow solid:

**m.p.** 47 – 50 °C (pentane);

R$_f$ 0.30 (2 : 1 Et$_2$O : hexanes);

IR (neat) $\nu_{max}$ 2997 (w, C-H), 1721 (sh., C=O), 1637 (m, C=C), 1376 (sh.), 1272 (sh.), 1201 (sh.), 1012 (w) cm$^{-1}$;

MS (Cl) [M+H]$^+$: requires 185, found 185;
6 Experimental

$^1H$ NMR (400 MHz, CDCl$_3$) δ 5.36 (s, 1H, 2), 3.37 (s, 2H, 7), 2.26 (s, 3H, 9), 1.73 (s, 6H, 5 & 6);

$^{13}C$ NMR (100 MHz, CDCl$_3$) δ 200.9 (8), 164.3 (1), 160.6 (3), 107.2 (4), 96.7 (2), 48.0 (7), 30.2 (9), 25.0 (5 & 6).

4-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-1-phenylbutane-1,3-dione (179)

$n$-BuLi in hexanes (2.5 M, 3.6 mL, 8.4 mmol, 2.0 equiv.) was added dropwise with stirring to $i$-Pr$_2$NH (1.2 mL, 8.4 mmol, 2.0 equiv.) in THF (20 mL) at $-78^\circ$C and the resulting solution stirred for 20 min. Keto-dioxinone 178 (0.74 g, 4.0 mmol, 1.0 equiv.) in THF (2.0 mL) was added dropwise and the mixture stirred for 40 min. Et$_2$Zn in hexanes (1.0 M, 8.4 mL, 8.4 mmol, 2.4 equiv.) was added slowly and after 20 min, the reaction mixture was allowed to warm to $-20^\circ$C. N-Methoxy-N-methylbenzamide (182) (0.33 g, 2.0 mmol, 0.5 equiv.) in THF (3.0 mL) was added and the mixture stirred at $-10^\circ$C for 2 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (30 mL) and 1.0 M HCl (10 mL) and the aqueous layer acidified to pH 2 using 1.0 M HCl. The product was extracted with EtOAc (2 x 50 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (5: 1 to 2 : 1 hexanes : EtOAc) to afford diketo-phenyl-dioxinone 179 (0.44 g, 76%) as a pale yellow solid:

m.p. 59 - 60°C (hexanes);

R$_f$ 0.71 (1 : 1 EtOAc : hexanes);

IR (neat) $\nu_{\max}$ 2988 (w, C-H), 1725 (sh., C=O), 1602 (m, C=C), 1571 (m, C-C), 1456 (w), 1373 (sh.), 1252 (m), 1017 (m), 927 (w) cm$^{-1}$;
6 Experimental

HRMS (ESI) calc. for C_{16}H_{17}O_{5} [M+H]^+: requires 289.1076, found 289.1086 (Δ +3.4 ppm);

^{1}H NMR (CDCl_{3}, 400 MHz) δ 15.73 (s, 1H, 15), 7.87 (d, J = 7.5 Hz, 2H, 12), 7.57 (t, J = 7.5 Hz, 1H, 14), 7.47 (t, J = 7.5 Hz, 2H, 13), 6.21 (s, 1H, 9), 5.45 (s, 1H, 2), 3.36 (s, 2H, 7), 1.71 (s, 6H, 5 & 6);

^{13}C NMR (CDCl_{3}, 100 MHz) δ 190.2 (8), 182.4 (10), 165.0 (1), 160.7 (3), 133.7 (11), 132.9 (14), 128.8 (2C, 13), 127.0 (2C, 12), 107.2 (4), 96.5 (9), 96.4 (2), 44.1 (7), 24.9 (2C, 5 & 6).

8-Allyl-7-hydroxy-2,2-dimethyl-5-phenyl-4H-benzo[d][1,3]dioxin-4-one (181)

Allyl acetate (69 mg, 0.69 mmol, 1.0 equiv.) and Pd(PPh_{3})_{4} (20 mg, 17 μmol, 2.5 mol%) were stirred in THF (3.5 mL) at rt for 2 min. Diketo-phenyl-dioxinone 179 (200 mg, 0.69 mmol, 1.0 equiv.) was added in THF (0.5 mL) and the resulting solution stirred for 2 h. After consumption of the starting material by TLC, Cs_{2}CO_{3} (678 mg, 2.07 mmol, 3.0 equiv.) was added and stirring continued for 12 h. The reaction was quenched with a saturated aqueous solution of NH_{4}Cl (20 mL), extracted with EtOAc (2 x 30 mL), the organics combined, dried (MgSO_{4}), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to give allyl-resorcylate 181 (148 mg, 69%) as a white solid:

m.p. 72 - 75 °C (pentane);

R_{f} 0.55 (1 : 3 EtOAc : hexanes);

IR (neat) ν_{max} 3016 (m, C-H), 2970 (m, C-H), 1740 (s, C=O), 1435 (w), 1366 (sh.), 1228 (sh.), 1206 (sh.) cm^{-1};
6 Experimental

HRMS (ESI) calc. for C_{19}H_{18}O_{4} [M+H]^+ : requires 311.1283, found 311.1280 (Δ −1.0 ppm);

^1H NMR (CDCl₃, 400 MHz) δ 7.85-7.83 (m, 2H, 16), 7.55 (t, J = 7.5 Hz, 1H, 17), 7.47 (t, J = 7.5 Hz, 2H, 15), 6.21 (s, 1H, 18), 5.67-60 (m, 1H, 12), 5.51 (s, 1H, 5), 5.17 (br. s, 1H, 13a), 5.15 (br. s, 1H, 13b), 2.64 (d, J = 6.0 Hz, 2H, 11), 1.65 (s, 6H, 9 & 10);

^13C NMR (CDCl₃, 100 MHz) δ 170.8 (7), 160.9 (2), 135.2 (4), 133.7 (6), 132.7 (14), 131.3 (12), 128.8 (2C, 16), 126.9 (2C, 15), 120.0 (17), 115.9 (13), 106.8 (3), 95.6 (5 / 8), 95.1 (5 / 8), 94.2 (1), 35.2 (11), 25.0 (2C, 9 & 10).

1-(1H-Benzoz[d][1,2,3]triazol-1-yl)-3-methylbut-2-en-1-one (208)

Based on a procedure by Navarro et al.\textsuperscript{[82]} Benzotriazole (19.0 g, 160 mmol, 3.2 equiv.) was stirred in CH₂Cl₂ (260 mL) for 5 min. Thionyl chloride (3.6 mL, 50 mmol, 1.0 equiv.) was added to the mixture which was stirred for 1 h. 3-Methylbut-2-enoic acid (209) (5.0 g, 50 mmol, 1.0 equiv.) was added in CH₂Cl₂ (100 mL) quickly into the stirring mixture which was then stirred for 18 h. The reaction mixture was filtered, the filtrate rotary evaporated, the resulting oil suspended in CH₂Cl₂ (500 mL), washed with buffer pH 9 (4 x 250 mL), water (2 x 100 mL) and then brine (300 mL). The organics were combined, dried (MgSO₄) and rotary evaporated to afford benzotriazole amide 208\textsuperscript{[102]} (7.0 g, 70%) as an off white solid:

m.p. 97 - 98 °C (CH₂Cl₂ : hexanes);

R_f 0.60 (1 : 7 EtOAc : hexanes);

IR (neat) ν_max 2979 (w, C-H), 1740 (s, C=O), 1623 (m, N-H), 1449 (sh.), 1222 (sh.), 1067 (w) cm⁻¹;
6 Experimental

HRMS (ESI) calc. for C_{11}H_{12}N_{3}O [M+H]^+ requires 202.0982, found 202.0980 (Δ +1.0 ppm);

^1H NMR (400 MHz, MeOD) δ 8.38 (d, J = 8.0 Hz, 1H, 11 / 8), 8.13 (d, J = 8.0 Hz, 1H, 11 / 8), 7.74-7.71 (m, 1H, 9 / 10), 7.60-7.56 (m, 1H, 9 / 10), 4.92 (s, 1H, 4), 2.45 (s, 3H, 2), 2.20 (s, 3H, 1);

^13C NMR (100 MHz, MeOD) δ 166.2 (5), 164.5 (3), 147.3 (7), 132.8 (6), 131.3 (10), 127.3 (9), 120.7 (8), 115.7 (4), 115.4 (11), 28.5 (2), 21.7 (1);

Anal. Calc. for C_{11}H_{11}N_{3}: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.54; H, 5.48; N, 20.79.

**t-Butyl 5-methyl-3-oxohex-4-enoate (200)**

![Structural formula of 200](image)

i-Pr₂NH (10.0 mL, 71.1 mmol, 2.2 equiv.) was added into THF (200 mL) followed by the addition of n-BuLi in hexanes (27.1 mL, 2.5 M, 67.8 mmol, 2.1 equiv.) and the resulting mixture was stirred for 30 min at −78 °C. t-Butylacetate (8.7 mL, 64.6 mmol, 2.0 equiv.) was added and the mixture stirred for 1 h. Benzotriazole amide 208 (6.5 g, 32.3 mmol, 1.0 equiv.) in THF (20 mL) was added and the mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (200 mL), acidified to pH 2 using 1 M HCl and extracted with EtOAc (2 x 150 mL). The organics were combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to give t-butyl ester-keto-olefin 200[^115] (9.0 g, 70%) as an orange oil:

R_f 0.60 (1 : 7 EtOAc : hexanes);

IR (neat) ν_max 2979 (w, C-H), 2933 (w, C-H), 1731 (m, C=O), 1688 (m, C=C), 1620 (m, C=O), 1254 (w), 1142 (w) cm⁻¹;
HRMS (CI) calc. for C_{11}H_{22}NO_{3} [M+NH_{4}]^{+}: requires 216.1602, found 216.1600 (Δ +0.9 ppm);

^{1}H NMR (400 MHz, CDCl_{3}) δ 6.14 (s, 1H, 4), 3.37 (s, 2H, 6), 2.19 (s, 3H, 2), 1.94 (s, 3H, 1), 1.49 (s, 9H, 9);

^{13}C NMR (125 MHz, CDCl_{3}) δ 192.5 (5), 167.1 (7), 157.7 (3), 122.8 (4), 81.5 (8), 52.0 (6), 28.0 (3C, 9), 27.7 (2), 21.0 (1).

5-Hydroxy-N-methoxy-N-methylpentanamide (215)

Based on a procedure by Flick et al.\textsuperscript{[118]} Weinreb amide hydrochloride salt (22.0 g, 22.5 mmol, 15.0 equiv.) was stirred in CH_{2}Cl_{2} (5 mL) at 0 °C for 5 min. AlCl_{3} in CH_{2}Cl_{2} (12.5 mL, 1.8 M, 22.5 mmol, 15.0 equiv.) was added dropwise and the mixture stirred for 20 min. Tetrahydro-2H-pyran-2-one (216) (1.40 mL, 14.9 mmol, 1.5 equiv.) was added dropwise to the stirring solution which was then stirred for 20 min at 0 °C. The mixture was dried (MgSO_{4}) and rotary evaporated to afford amide 215\textsuperscript{[191]} (1.11 g, 50%) as a colourless oil:

R_{f} 0.20 (EtOAc);

IR (neat) ν_{max} 3399 (br., O-H), 2969 (w, C-H), 2941 (m, C-H), 2871 (m, C-H), 1736 (s, C=O), 1637 (s), 1419 (m), 1382 (m), 1228 (m), 1203 (sh.), 1179 (sh.), 1068 (w) cm\textsuperscript{-1};

HRMS (ESI) calc. for C_{7}H_{16}NO_{3} [M+H]^{+}: requires 162.1130, found 162.1123 (Δ –4.3 ppm);

^{1}H NMR (400 MHz, CDCl_{3}) δ 3.68 (s, 3H, 2), 3.64 (t, J = 8.0 Hz, 2H, 7), 3.18 (s, 3H, 1), 2.47 (t, J = 8.0 Hz, 2H, 4), 1.74 (quin., J = 8.0 Hz, 2H, 5), 1.64-1.58 (m, 2H, 6);

^{13}C NMR (100 MHz, CDCl_{3}) δ 174.6 (3), 62.1 (2), 61.2 (7), 32.3 (2C, 1 & 4), 31.3 (6), 20.3 (5);
**6 Experimental**

**Anal.** Calc. for $\text{C}_7\text{H}_{15}\text{NO}_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.17; H, 9.37; N, 8.62.

*N-Methoxy-N-methyl-5-(triethylsilyloxy)pentanamide (217)*

Alcohol 215 (6.10 g, 37.9 mmol, 1.0 equiv.) was stirred in $\text{CH}_2\text{Cl}_2$ (130 mL) and imidazole (2.84 g, 41.7 mmol, 1.1 equiv.) was added followed by TESCl (6.40 mL, 37.9 mmol, 1.0 equiv.) dropwise at 0 °C, the resulting mixture was then stirred for 1 h. The reaction was quenched with $\text{H}_2\text{O}$ (100 mL), extracted with $\text{CH}_2\text{Cl}_2$ (2 x 200 mL), washed with brine (100 mL), the organics combined, dried ($\text{MgSO}_4$), rotary evaporated and chromatographed (2 : 6 to 1 : 1 EtOAc : hexanes) to afford silylether 217 (6.7 g, 70%) as a colourless oil:

- $\text{R}_f$ 0.5 (2 : 6 EtOAc : hexanes);
- **IR** (neat) $\nu_{\text{max}}$ 2911 (w, C-H), 2876 (m, C-H), 1739 (m, C=O), 1668 (s), 1459 (m), 1414 (m), 1381 (sh.), 1320 (w), 1231 (w), 1216 (w), 1177 (sh.) cm$^{-1}$;
- **HRMS** (ESI) calc. for $\text{C}_{13}\text{H}_{30}\text{NO}_3\text{Si}$ [M+H]$^+$: requires 276.1995, found 276.1998 ($\Delta$ 1.1 ppm);

$^1\text{H NMR}$ (400 MHz, CDCl$_3$) $\delta$ 3.70 (s, 3H, 2), 3.65 (t, $J = 8.0$ Hz, 2H, 7), 3.20 (s, 3H, 1), 2.47 (t, $J = 8.0$ Hz, 2H, 4), 1.75-1.68 (m, 2H, 5), 1.64-1.57 (m, 2H, 6), 0.98 (t, $J = 7.0$ Hz, 9H, 9), 0.62 (q, $J = 7.0$ Hz, 6H, 8);

$^{13}\text{C NMR}$ (125 MHz, CDCl$_3$) $\delta$ 174.5 (3), 62.6 (2), 61.1 (7), 32.5 (2C, 1 & 4), 31.7 (6), 21.1 (5), 6.76 (3C, 9), 4.4 (3C, 8);

**Anal.** Calc. for $\text{C}_{13}\text{H}_{29}\text{NO}_3\text{Si}$: C, 56.68; H, 10.61; N, 5.08. Found: C, 56.79; H, 10.70; N, 5.02.
Based on a procedure by Zanardi et al.\textsuperscript{[117]} Amide 217 (6.70 g, 24.3 mmol, 1.0 equiv.) was stirred in THF (120 mL) at −78 °C, MeLi in hexanes (16.2 mL, 24.3 mmol, 1.5 M, 1.0 equiv.) was added dropwise to the stirring solution which was then stirred for 1 h. The reaction was quenched with water (150 mL), extracted with EtOAc (2 x 200mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 8 EtOAc : hexanes) giving ketone 214\textsuperscript{[193]} (4.0 g, 73%) as a colourless oil:

$R_f$ 0.81 (1 : 1 EtOAc : hexanes);

IR (neat) $v_{max}$ 2953 (m, C-H), 2911 (m, C-H), 2876 (m, C-H), 1717 (sh. C=O), 1459 (w), 1414 (w), 1358 (w), 1237 (w), 1006 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{12}$H$_{27}$O$_2$Si [M+H]$^+$: requires 231.1780, found 231.1777 ($\Delta$ –1.3 ppm);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.64 (t, $J$ = 6.0 Hz, 2H, 6), 2.49 (t, $J$ = 6.0 Hz, 2H, 3), 2.70 (s, 3H, 1), 1.70-1.60 (m, 2H, 5), 1.59-1.52 (m, 2H, 4), 0.98 (t, $J$ = 7.0 Hz, 9H, 8), 0.62 (q, $J$ = 7.0 Hz, 6H, 7);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.0 (2), 62.5 (6), 43.5 (3), 32.2 (5), 29.8 (1), 20.3 (4), 6.8 (3C, 8), 4.4 (3C, 7);

**Anal.** Calc. for C$_{12}$H$_{26}$O$_2$Si: C, 62.04; H, 10.41. Found: C, 62.17; H, 10.37.
(E)-Ethyl 3-methyl-7-(triethylsilyloxy)hept-2-enoate (E-213) and (Z)-Ethyl 3-methyl-7-(triethylsilyloxy)hept-2-enoate (Z-213)

Based on a procedure by Joullié et al.\textsuperscript{[107]} Diethyl 2-oxobutylphosphonate 218 (1.1 mL, 5.4 mmol, 1.5 equiv.) was stirred in THF (20 mL) and NaH (232 mg (60% suspension in oil), 5.8 mmol, 1.6 equiv.) was added at 0 °C for 45 min. Ketone 214 (1.0 g, 3.6 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise and the mixture stirred at rt for 6 h. The mixture was quenched with H\textsubscript{2}O (50 mL), extracted with Et\textsubscript{2}O (2 x 100 mL), dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (2 : 8 to 1 : 1 EtOAc : hexanes) giving (E)-olefin E-213 and (Z)-olefin Z-213 in a 3 : 1 ratio (1.04 g, 98%) as a colourless oil:

\( R_f \) 0.85 (1 : 1 EtOAc : hexanes);

\textbf{IR} (neat) \( \nu_{\text{max}} \) 2952 (m, C-H), 2937 (w, C-H), 2876 (m, C-H), 1717 (sh., C=O), 1649 (w, C=C), 1459 (w), 1416 (w), 1221 (sh.), 1144 (sh.), 1095 (sh.), 1007 (w) cm\textsuperscript{-1};

\textbf{HRMS} (ESI) calc. for C\textsubscript{16}H\textsubscript{33}O\textsubscript{3}Si [M+H]\textsuperscript{+}: requires 301.2199, found 301.2201 (\( \Delta +0.7 \) ppm).

(E)-Olefin E-213:

\( ^1\text{H NMR} \) (400 MHz, C\textsubscript{6}D\textsubscript{6}) \( \delta \) 5.82-5.81 (m, 1H, 4), 4.04 (q, \( J = 7.0 \) Hz, 2H, 2), 3.46-3.43 (m, 2H, 10), 2.20 (s, 3H, 6), 1.83 (t, \( J = 7.0 \) Hz, 2H, 7), 1.38-1.35 (m, 4H, 8 & 9), 1.03-0.98 (m, 12H, 1 & 12), 0.63-0.56 (m, 6H, 11);

\( ^{13}\text{C NMR} \) (125 MHz, C\textsubscript{6}D\textsubscript{6}) \( \delta \) 166.4 (3), 159.4 (5), 116.3 (4), 62.5 (10), 59.3 (2), 40.6 (7), 32.6 (9), 23.9 (8), 18.6 (6), 14.4 (1), 7.1 (3C, 12), 4.8 (3C, 11).
6 Experimental

(Z)-Olefin Z-213:

^1^H NMR (400 MHz, C_6D_6) δ 5.75 (br. s, 1H, 4), 4.03-4.01 (m, 2H, 2), 3.58 (t, J = 7.0 Hz, 2H, 10), 2.76 (t, J = 7.0 Hz, 2H, 7), 2.20 (s, 3H, 6), 1.60-1.58 (m, 2H, 9), 1.36-1.34 (m, 2H, 8), 1.03-0.98 (m, 12H, 1 & 12), 0.63-0.56 (m, 6H, 11);

^1^3^C NMR (125 MHz, C_6D_6) δ 166.4 (3), 160.2 (5), 116.9 (4), 62.7 (10), 59.3 (2), 40.6 (7), 33.1 (9), 24.8 (8), 18.6 (6), 14.4 (1), 7.1 (3C, 12), 4.8 (3C, 11).

(E)-3-Methyl-7-(triethylsilyloxy)hept-2-en-1-ol (E-219) and (Z)-3-Methyl-7-(triethylsilyloxy)hept-2-en-1-ol (Z-219)

A mixture of (E)-olefin E-213 and (Z)-olefin Z-213 in a 3 : 1 ratio (500 mg, 1.67 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (15 mL) at -78 °C. DIBAL in CH_2Cl_2 (5.0 mL, 1 M, 5.0 mmol, 3.0 equiv.) was added dropwise and the mixture stirred for 2 h. The reaction was poured into a saturated aqueous solution of Rochelle’s salt (50 mL) and MeOH (1 : 1 200 mL). The aqueous layer was extracted with EtOAc, dried (Na_2SO_4), rotary evaporated and chromatographed (1 : 1 EtOAc : hexanes) to give (E)-olefin-alcohol E-219 and (Z)-olefin-alcohol E-219 in a 3 : 1 ratio (267 mg, 63%) as a colourless oil:

**R_f** 0.70 (2 : 1 EtOAc : hexanes);

**IR** (neat) v_max 3326 (br., O-H), 2936 (m, C-H), 2911 (m, C-H), 2876 (m, C-H), 1669 (w, C=C), 1458 (w), 1238 (w), 1096 (w), 1003 (sh.) cm^{-1};
**6 Experimental**

**HRMS (ESI) calc. for C_{14}H_{31}O_{2}Si [M+H]^+:** requires 259.2093, found 259.2094 (Δ +0.4 ppm).

**(E)-Olefin-alcohol E-219:**

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 5.42-5.39 \text{ (m, 1H, 3), 4.15 (d, } J = 7.0 \text{ Hz, 2H, 2), 3.60 (t, } J = 8.0 \text{ Hz, 2H, 9), 2.03 (t, } J = 8.0 \text{ Hz, 2H, 6), 1.66 (s, 3H, 5), 1.55-1.42 \text{ (m, 4H, 7 & 8), 1.17 (br. s, 1H, 1), 0.95 (t, } J = 7.0 \text{ Hz, 9H, 11), 0.59 (q, } J = 7.0 \text{ Hz, 6H, 10);} \\
\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 139.9 (4), 123.4 (3), 62.7 (9), 59.4 (2), 39.3 (6), 32.4 (8), 23.8 (7), 16.1 (5), 6.8 (3C, 11), 4.4 (3C, 10).\]

**(Z)-Olefin-alcohol Z-219:**

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 5.44-5.39 \text{ (m, 1H, 3), 4.14 (d, } J = 7.0 \text{ Hz, 2H, 2), 3.60 (t, } J = 8.0 \text{ Hz, 2H, 9), 2.09 (t, } J = 8.0 \text{ Hz, 2H, 6), 1.73 (s, 3H, 5), 1.55-1.42 \text{ (m, 4H, 7 & 8), 1.17 (br. s, 1H, 1), 0.95 (t, } J = 7.0 \text{ Hz, 9H, 11), 0.59 (q, } J = 7.0 \text{ Hz, 6H, 10);} \\
\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 139.9 (4), 123.4 (3), 62.7 (9), 59.4 (2), 39.3 (6), 32.4 (8), 23.8 (7), 16.1 (5), 6.8 (3C, 11), 4.4 (3C, 10).\]
Experimental

\((E)-13,13\text{-Diethyl-2,2,3,3,7-pentamethyl-4,12-dioxo-3,13-disilapentadec-6-ene (E-212)}\)
and \((Z)-13,13\text{-Diethyl-2,2,3,3,7-pentamethyl-4,12-dioxo-3,13-disilapentadec-6-ene (Z-212)}\)

\begin{align*}
\text{E-212} & \quad \text{Z-212}
\end{align*}

A mixture of \((E)\)-olefin-alcohol \textbf{E-219} and \((Z)\)-olefin-alcohol \textbf{Z-219} in a 3 : 1 ratio (267 mg, 1.03 mmol, 1.0 equiv.) were added to a solution of imidazole (84 mg, 1.24 mmol, 1.2 equiv.) and TBSCI (171 mg, 1.13 mmol, 1.1 equiv.) in DMF (1 mL) and stirred at rt for 12 h. The reaction mixture was quenched with H\textsubscript{2}O (100 mL) and extracted with a mixture of pentane and CH\textsubscript{2}Cl\textsubscript{2} (9 : 1, 2 x 200 mL). The organics were combined, dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (1 : 9 Et\textsubscript{2}O : pentane) to afford \((E)\)-olefin-silyl ether \textbf{E-212} and \((Z)\)-olefin-silyl ether \textbf{Z-212} in a 3 : 1 ratio (350 mg, 92%) as a colourless oil:

\[\text{Rf} 0.82 (1 : 9 \text{ EtOAc} : \text{hexanes});\]

\[\text{IR (neat)} \nu_{\text{max}} 2952 (m, C-H), 2932 (m, C-H), 2877 (m, C-H), 2858 (m, C-H), 1670 (w, C=C), 1461 (w), 1381 (w), 1252 (sh.), 1089 (s) \text{ cm}^{-1};\]

\[\text{HRMS (CI)} \text{ calc. for C}_{20}\text{H}_{48}\text{NO}_2\text{Si}_2\text{[M+NH}_4]^+: requires 390.3234, found 390.3216 (\Delta \approx 2.0 \text{ ppm});\]

\((E)\)-Olefin-silyl ether \textbf{E-212}:

\[\text{^1H NMR (400 MHz, CDCl}_3\text{)} \delta 5.31-5.28 (m, 1H, 5), 4.17 (d, J = 7.0 Hz, 2H, 4), 3.60 (t, J = 8.0 Hz, 2H, 11), 2.05 (t, J = 8.0 Hz, 2H, 8), 1.61 (s, 3H, 7), 1.54-1.39 (m, 4H, 9 & 10), 0.95 (t, J = 7.0 Hz, 9H, 13), 0.90 (s, 9H, 1), 0.60 (q, J = 7.0 Hz, 6H, 12), 0.06 (s, 6H, 3);\]
6 Experimental

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.0 (6), 124.4 (5), 62.8 (11), 60.3 (4), 39.3 (8), 32.5 (10), 26.0 (3C, 1), 23.3 (9), 18.43 (2), 16.2 (7), 6.8 (3C, 13), 4.4 (3C, 12), $\delta$5.1 (2C, 3).

(Z)-Olefin-silyl ether Z-212:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.33-5.31 (m, 1H, 5), 4.15 (d, $J = 7.0$ Hz, 2H, 4), (t, $J = 8.0$ Hz, 2H, 11), 2.03 (t, $J = 8.0$ Hz, 2H, 8), 1.59 (s, 3H, 7), 1.54-1.39 (m, 4H, 9 & 10), 0.95 (t, $J = 7.0$ Hz, 9H, 13), 0.90 (s, 9H, 1), 0.60 (q, $J = 7.0$ Hz, 6H, 12), 0.06 (s, 6H, 3);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.7 (6), 125.1 (5), 63.1 (11), 59.9 (4), 39.3 (8), 32.7 (10), 26.0 (3C, 1), 24.4 (9), 18.43 (2), 16.2 (7), 6.8 (3C, 13), 4.4 (3C, 12), $\delta$5.1 (2C, 3).

(E)-7-(t-Butyldimethylsilyloxy)-5-methylhept-5-enal (E-220) and (Z)-7-(t-Butyldimethylsilyloxy)-5-methylhept-5-enal (Z-220)

Based on a procedure by Zanoni et al.[116] DMSO (0.95 ml, 13.4 mmol, 10.0 equiv.) was added dropwise to a stirring solution of oxalyl chloride (0.58 ml, 6.70 mmol, 5.0 equiv.) in CH$_2$Cl$_2$ (3.35 mL) at $-80$ °C and stirred for 1 h. A solution of (E)-olefin silyl ether E-212 and (Z)-olefin silyl ether E-212 in a 3 : 1 ratio (500 mg, 1.34 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (18 mL) was added dropwise and the resulting solution stirred for 2.5 h. The temperature was warmed to $-35$ °C and the reaction mixture stirred for 1.5 h. The mixture was cooled to $-80$ °C and Et$_3$N (2.8 mL, 20.1 mmol, 15.0 equiv.) was added dropwise and the resulting mixture stirred for 40 min. The mixture was allowed to warm to rt and quenched with brine (100 ml), extracted with EtOAc (2 x 100 ml), the organics combined, dried (MgSO$_4$), rotary evaporated
Experimental

and chromatographed (1 : 8 EtOAc : hexanes to EtOAc) giving \((E)\)-olefin aldehyde **E-220** and \((Z)\)-olefin aldehyde **Z-220** in a 3 : 1 ratio (130 mg, 33%) as a colourless oil:

- **R<sub>f</sub>** 0.65 (1 : 7 EtOAc : hexanes);
- **IR** (neat) \(\nu_{\text{max}}\) 2930 (m, C-H), 2856 (m, C-H), 1726 (sh., C=O), 1462 (w), 1253 (sh.), 1056 (s) cm\(^{-1}\);
- **HRMS** (ESI) calc. for C\(_{14}\)H\(_{29}\)O\(_2\)Si [M+H]: requires 257.1937, found 257.1932 (\(\Delta -1.9\) ppm);
- **Anal.** Calc. for C\(_{14}\)H\(_{28}\)O\(_2\)Si: C, 65.57; H, 11.00. Found: C, 65.46; H, 10.92.

**(E)-Olefin-aldehyde E-220:**

\(^1\)H **NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 9.76 (t, \(J = 1.0\) Hz, 1H, 12), 5.33-5.30 (m, 1H, 5), 4.18 (d, \(J = 8.0\) Hz, 2H, 4), 2.41 (dt, \(J = 8.0, 1.0\) Hz, 2H, 10), 2.03 (t, \(J = 8.0\) Hz, 2H, 8), 1.76 (quin., \(J = 8.0\) Hz, 2H, 9), 1.61 (s, 3H, 7), 0.90 (s, 9H, 1), 0.06 (s, 6H, 3);

\(^{13}\)C **NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 202.2 (11), 135.6 (6), 125.5 (5), 60.1 (4), 43.1 (10), 38.6 (8), 25.9 (3C, 1), 20.2 (9), 19.9 (2), 15.9 (7), –5.2 (2C, 3).

**(Z)-Olefin-aldehyde Z-220:**

\(^1\)H **NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 9.76 (t, \(J = 1.0\) Hz, 1H, 12), 5.35-5.32 (m, 1H, 5), 4.10 (d, \(J = 8.0\) Hz, 2H, 4), 2.41 (dt, \(J = 8.0, 1.0\) Hz, 2H, 10), 2.04 (t, \(J = 8.0\) Hz, 2H, 8), 1.72-1.70 (m, 2H, 9), 1.61 (s, 3H, 7), 0.90 (s, 9H, 1), 0.06 (s, 6H, 3);

\(^{13}\)C **NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 202.0 (11), 136.4 (6), 126.1 (5), 59.6 (4), 43.2 (10), 38.6 (8), 31.0 (9), 25.9 (3C, 1), 23.1 (2), 20.17 (7), –5.17 (2C, 3).
**Experimental**

**Triethyl(hex-5-ynyloxy)silane (221)**

![Structural formula of triethyl(hex-5-ynyloxy)silane (221)](image)

Hex-5-yn-1-ol 223 (6.90 mL, 62.7 mmol, 1.0 equiv.) was stirred in CH₂Cl₂ (186 mL) for 2 min. Imidazole (4.50 g, 75.2 mmol, 1.2 equiv.) was added followed by TESCl (10.2 mL, 69.0 mmol, 1.1 equiv.) and the resulting mixture stirred for 3 h. The reaction mixture was quenched with H₂O (300 mL), extracted with CH₂Cl₂ (2 x 100 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 15 EtOAc : hexanes) to afford triethyl(hex-5-ynyloxy)silane (221)[194] as a colourless oil (13.0 g, 95%):

- **Rf** 0.90 (1 : 1 EtOAc : hexanes);

- **IR** (neat) \( \nu_{\text{max}} \) 3311 (w, C≡CH), 2954 (m, C-H), 2877 (m, C-H), 1459 (w), 1216 (w), 1237 (w), 1103 (sh.), 1006 (sh.) cm\(^{-1}\);

- **HRMS** (Cl) calc. for C\(_{12}\)H\(_{25}\)OSi [M+H]+: requires 213.1675, found 213.1677 (\( \Delta +0.9 \) ppm);

- **\(^1\)H NMR** (400 MHz, CDCl₃) \( \delta \) 3.66 (t, \( J = 8.0 \) Hz, 2H, 6), 2.25 (td, \( J = 8.0, 0.5 \) Hz, 2H, 3), 1.97 (t, \( J = 0.5 \) Hz, 1H, 1), 1.70-1.58 (m, 4H, 4 & 5), 0.98 (t, \( J = 7.0 \) Hz, 9H, 8), 0.62 (q, \( J = 7.0 \) Hz, 6H, 7);

- **\(^{13}\)C NMR** (100 MHz, CDCl₃) \( \delta \) 84.5 (2), 68.3 (1), 62.3 (6), 31.8 (5), 24.9 (4), 18.2 (3), 6.8 (3C, 8), 4.4 (3C, 7).
(E)-Triethyl(6-iodo-5-methylhex-5-enyloxy)silane (224) and (E)-6-Iodo-5-methylhex-5-en-1-ol (225)

Based on a procedure by Welzel et al.[122] Zirconocene dichloride (1.4 g, 4.7 mmol, 1.0 equiv.) was stirred in CH₂Cl₂ (22 mL) at 0 °C. AlMe₃ in CH₂Cl₂ (4.72 mL, 2.0 M, 9.44 mmol, 2.0 equiv.) was added dropwise and the reaction mixture stirred for 15 min. Alkyne 221 (1.0 g, 4.7 mmol, 1.0 equiv.) was added in CH₂Cl₂ (3 mL) and the mixture was allowed to warm to rt and stirred for 18 h. Iodine (840 mg, 6.61 mmol, 1.4 equiv.) in THF (4 mL) was added at −18 °C and the mixture stirred for 5 min. The reaction was quenched with a saturated aqueous solution of NH₄Cl (8 mL) and a saturated aqueous solution of Na₂S₂O₃ (4 mL), extracted with CH₂Cl₂ (1 x 500 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (29 : 1 EtOAc : hexanes) to afford (E)-olefin silyl ether 224 (170 mg, 10%) and (E)-olefin alcohol 225[195] (840 mg, 50%) as colourless oils.

(E)-Olefin-silyl ether 224:

\[
R_f 0.9 \quad (1 : 7 \text{ EtOAc : hexanes});
\]

\[
\text{IR (neat) } v_{\text{max}} 2952 \text{ (m, C-H)}, \ 2910 \text{ (m, C-H)}, \ 2875 \text{ (m, C-H)}, \ 1457 \text{ (m), } 1413 \text{ (m), } 1377 \text{ (w), } 1235 \text{ (m), } 1072 \text{ (s), } 1003 \text{ (s) cm}^{-1};
\]

\[
\text{HRMS (CI) calc. for } C_{13}H_{28}OSiI [M+H]^+: \text{ requires } 355.0954, \text{ found } 355.0954 (\Delta 0.0 \text{ ppm});
\]

\[
^1H \text{ NMR (500 MHz, } C_6D_6) \delta 5.69 \text{ (sextet, } J = 0.5 \text{ Hz, 1H, 1}), \ 3.45 \text{ (t, } J = 7.0 \text{ Hz, 2H, 7), } 1.86-1.83 \text{ (m, 2H, 4), } 1.64 \text{ (d, } J = 0.5 \text{ Hz, 3H, 3), } 1.36-1.26 \text{ (m, 4H, 5 & 6), } 1.0 \text{ (t, } J = 8.0 \text{ Hz, 9H, 9), } 0.60 \text{ (q, } J = 8.0 \text{ Hz, 6H, 8});
\]
6 Experimental

$^{13}$C NMR (500 MHz, C$_6$D$_6$) δ 147.89 (2), 75.13 (1), 62.48 (7), 39.24 (4), 32.42 (6), 24.14 (5), 23.62 (3), 7.09 (3C, 9), 4.83 (3C, 8);

Anal. Calc. for C$_{13}$H$_{27}$OISi: C, 44.06; H, 7.68. Found: C, 43.94; H, 7.51.

(E)-Olefin-alcohol 225:

R$_f$ 0.2 (1 : 7 EtOAc : hexanes);

IR (neat) $v_{max}$ 3321 (br., O-H), 2934 (s, C-H), 2862 (m, C-H), 1739 (w), 1616 (w, C=C), 1433 (w), 1375 (m), 1271 (sh.), 1141 (sh.), 1033 (sh.), 1058 (sh.) cm$^{-1}$;

HRMS (CI) calc. for C$_7$H$_{17}$NOI [M+NH$_4$]$^+$: requires 258.0355, found 258.0352 (Δ -1.2 ppm);

$^1$H NMR (500 MHz, C$_6$D$_6$) δ 5.64 (s, 1H, 1), 3.19 (t, J = 6.0 Hz, 2H, 7), 1.76 (t, J = 6.0 Hz, 2H, 4), 1.61 (s, 3H, 3), 1.11 (quin., J = 6.0 Hz, 4H, 5 & 6);

$^{13}$C NMR (500 MHz, C$_6$D$_6$) δ 147.8 (2), 75.1 (1), 62.2 (7), 39.2 (4), 32.2 (6), 23.9 (5), 23.6 (3);

Anal. Calc. for C$_7$H$_{13}$OI: C, 35.02; H, 5.46. Found: C, 35.01; H, 5.39
**Experimental**

**t-Butyl(hex-5-ynyloxy)diphenylsilane (226)**

Hex-5-yn-1-ol 223 (5.5 mL, 51 mmol, 1.0 equiv.) and imidazole (4.86 g, 71.4 mmol, 1.4 equiv.) were stirred in CH₂Cl₂ (150 mL) at 0 °C, TBDPSCl (14.6 mL, 56.1 mmol, 1.1 equiv.) was added and the reaction mixture was allowed to warm to rt and stirred for 72 h. The reaction was quenched with H₂O (300 mL), extracted with CH₂Cl₂ (2 x 300 mL), the organics combined, washed with brine (200 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 99 Et₂O : hexanes) affording silyl ether 226[196] (15.0 g, 88%) as a colourless oil:

R<sub>f</sub> 0.95 (1 : 7 EtOAc : hexanes);

IR (neat) ν<sub>max</sub> 3309 (w, C≡CH), 2932 (w, C-H), 2858 (w, C-H), 1472 (w), 1427 (sh.), 1106 (w) cm⁻¹;

HRMS (ESI) calc. for C₂₂H₂₉OSi [M+H]<sup>+</sup>: requires 337.1988, found 337.1997 (∆ +2.7 ppm);

H NMR (500 MHz, C₆D₆) δ 7.75-7.73 (m, 4H, 11), 7.23-7.21 (m, 6H, 10 & 12), 3.55 (t, J = 6.0 Hz, 2H, 6), 1.92 (td, J = 6.0, 1.0 Hz, 2H, 3), 1.74 (t, J = 1.0 Hz, 1H, 1), 1.57-1.51 (m, 2H, 5), 1.49-1.43 (m, 2H, 4), 1.15 (s, 9H, 8);

C NMR (125 MHz, C₆D₆) δ 136.0 (6C, 10 & 12), 134.3 (2C, 9), 129.9 (4C, 11), 84.3 (1), 68.9 (2), 63.6 (6), 31.8 (5), 27.1 (3C, 8), 25.2 (4), 19.4 (7), 18.3 (3);

Anal. Calc. for C₂₂H₂₉OSi: C, 78.51; H, 8.39. Found: C, 78.61; H, 8.29.
Based on a procedure by Welzel et al.\textsuperscript{[122]} Zirconene dichloride (2.6 g, 8.9 mmol, 1.0 equiv.) was stirred in CH$_2$Cl$_2$ (45 mL) at 0 °C. AlMe$_3$ in CH$_2$Cl$_2$ (10.0 mL, 1.8 M, 18.0 mmol, 2.0 equiv.) was added dropwise and the reaction mixture allowed to stir for 15 min. Alkyne 226 (3.0 g, 8.9 mmol, 1.0 equiv.) was added in CH$_2$Cl$_2$ (10 mL) and the mixture was allowed to warm to rt and stirred for 18 h. Iodine (4.5 g, 18.0 mmol, 2.0 equiv.) in THF (60 mL) was added at −23 °C and the mixture allowed to warm to 0 °C and stirred for 15 min. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (15 mL) and a saturated aqueous solution of Na$_2$S$_2$O$_3$ (8 mL) and extracted with CH$_2$Cl$_2$ (2 x 200 mL). The organics were combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 99 Et$_2$O : hexanes) to afford (E)-olefin 227 (2.6 g, 63%) as a colourless oil:

**R$_f$** 0.9 (1 : 7 Et$_2$O : hexanes);

**IR** (neat) $\nu_{max}$ 2930 (w, C-H), 2857 (w, C-H), 1472 (w), 1427 (sh.), 1105 (s) cm$^{-1}$;

**HRMS** (CI) calc. for C$_{23}$H$_{32}$OSi [M+H]$^+$: requires 479.1267, found 479.1269 ($\Delta$ +0.4 ppm);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70-7.65 (m, 4H, 11), 7.44-7.37 (m, 6H, 10 & 12), 5.83 (app. sextet, $J = 0.5$ Hz, 1H, 9), 3.66 (t, $J = 6.0$ Hz, 2H, 6), 2.19-2.17 (m, 2H, 3), 1.80 (d, $J = 0.5$ Hz, 3H, 1), 1.52 (quin., $J = 6.0$ Hz, 4H, 4 & 5), 1.05 (s, 9H, 8);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 148.0 (2), 135.6 (4C, 11), 134.0 (2C, 13), 129.6 (4C, 12), 127.6 (2C, 10), 74.6 (9), 63.5 (6), 39.2 (3), 31.8 (5), 23.9 (3C, 8), 23.9 (4), 23.7 (7), 19.2 (1);

**Anal.** Calc. for C$_{23}$H$_{31}$OSi: C, 57.73; H, 6.53. Found: C, 57.89; H, 6.60.
Based on a procedure by Dai et al.\cite{120} Zirconocene dichloride (2.6 g, 8.9 mmol, 1.0 equiv.) was stirred in CH$_2$Cl$_2$ (45 mL) at 0 °C. AlMe$_3$ in CH$_2$Cl$_2$ (18 mL, 1.0 M, 18 mmol, 2.0 equiv.) was added dropwise and the reaction mixture allowed to stir for 15 min. Alkyne 226 (3.0 g, 8.9 mmol, 1.0 equiv.) was added in CH$_2$Cl$_2$ (10 mL) and the mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was rotary evaporated and the resulting residue triturated with hexanes (3 x 20 mL) under an inert atmosphere. The resulting solution was cooled to –78 °C and t-BuLi in hexanes (11.3 mL, 1.6 M, 18.0 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was allowed to stir for 2 h and then transferred by cannula into paraformaldehyde (8.04 g, 268 mmol, 30.0 equiv.) in hexanes (20 mL). The resulting solution was allowed to warm to rt and stirred for 120 h. The reaction was quenched with H$_2$O (100 mL), extracted with Et$_2$O (300 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford olefin alcohol 228\cite{197} (1.8 g, 53%) and olefin 229\cite{198} (650 mg, 22%) both as colourless oils.

Olefin alcohol 228:

R$_f$ 0.5 (3 : 5 EtOAc : hexanes);

IR (neat) $\nu_{max}$ 3335 (br., O-H), 2931 (m, C-H), 2858 (m, C-H), 1472 (sh.), 1427 (sh.), 1388 (w), 1361 (w), 1106 (s) cm$^{-1}$;
**Experimental**

HRMS (CI) calc. for C_{24}H_{38}NO_{2}Si [M+NH_{4}]^{+}: requires 400.2672, found 400.2677 (Δ +1.2 ppm);

_{1}H NMR (500 MHz, CDCl_{3}) δ 7.69-7.67 (m, 4H, 14), 7.44-7.37 (m, 6H, 13 & 15), 5.39 (app. t of sextet, J = 7.0, 0.5 Hz, 1H, 3), 4.15 (d, J = 7.0 Hz, 2H, 2), 3.68 (t, J = 6.0 Hz, 2H, 9), 2.01 (t, J = 6.0 Hz, 2H, 6), 1.66 (br. s, 3H, 5), 1.58-1.47 (m, 4H, 7 & 8), 1.06 (s, 9H, 11);

_{13}C NMR (125 MHz, CDCl_{3}) δ 139.9 (4135.6 (4C, 14), 134.1 (2C, 12), 129.5 (2C, 15), 127.6 (4C, 13), 123.3 (3), 63.7 (9), 59.4 (2), 39.1 (6), 32.1 (8), 26.9 (3C, 11), 23.8 (7), 19.2 (10), 16.1 (5);

Anal. Calc. for C_{24}H_{34}O_{2}Si: C, 75.27; H, 8.96. Found: C, 75.34; H, 9.03.

**Olefin 229:**

R_f 0.95 (3 : 5 EtOAc : hexanes);

IR (neat) ν_{max} 2931 (m, C-H), 2858 (m, C-H), 1462 (sh.), 1428 (sh.), 1106 (s) cm^{-1};

HRMS (CI) calc. for C_{23}H_{33}OSi [M+H]^{+}: requires 353.2301, found 353.2305 (Δ +1.1 ppm);

_{1}H NMR (500 MHz, CDCl_{3}) δ 7.69-7.67 (m, 4H, 12), 7.44-7.37 (m, 6H, 11 & 13), 4.70 (br. s, 1H, 1a), 4.66 (br. s, 1H, 1b), 3.86 (t, J = 6.0 Hz, 2H, 7), 2.00 (t, J = 6.0 Hz, 2H, 4), 1.71 (s, 3H, 3), 1.60-1.49 (m, 4H, 5 & 6), 1.06 (s, 9H, 11);

_{13}C NMR (125 MHz, CDCl_{3}) δ 146.0 (2), 135.6 (2C, 10), 129.5 (6C, 11 & 13), 127.6 (4C, 12), 109.8 (1), 63.4 (7), 37.5 (4), 32.2 (6), 26.9 (3C, 9), 23.8 (5), 22.3 (3), 19.2 (3C, 8);

Anal. Calc. for C_{24}H_{34}O_{2}Si: C, 78.35, H, 9.15. Found: C, 78.43; H, 9.21.
**Experimental**

7-(t-Butyldiphenylsilyloxy)hept-2-yn-1-ol (230)

Based on a procedure by Lindsay *et al.*[126] Alykne 226 (1.50 g, 3.58 mmol, 1.0 equiv.) was stirred in THF (4 mL) at –78 °C. *n*-BuLi in hexanes (1.50 mL, 0.48 mmol, 1.0 equiv., 2.4 M) was added dropwise and the solution stirred for 1 h. The reaction mixture was transferred by cannula into paraformaldehyde (215 mg, 7.16 mmol, 2.0 equiv.). The reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL), extracted with Et₂O (2 x 30 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford alkyne alcohol 230[199] (1.4 g, 87%) as a colourless oil:

R_f 0.4 (1 : 1 EtOAc : hexanes);

**IR** (neat) ν_max, 3370 (br., O-H), 2931 (w, C-H), 2856 (w, C-H), 1472 (w), 1428 (sh.), 1389 (w), 1187 (w), 1106 (m), 1007 (m), 999 (w) cm⁻¹;

**HRMS** (Cl) calc. for C_{23}H_{34}NO_2Si [M+NH_4]^+: requires 384.2359, found 384.2368 (Δ +2.3 ppm);

**¹H NMR** (500 MHz, CDCl₃) δ 7.67-7.66 (m, 4H, 13), 7.44-7.36 (m, 6H, 12 & 14), 4.24 (d, J = 6.0 Hz, 2H, 2), 3.68 (t, J = 7.0 Hz, 2H, 8), 2.24-2.21 (m, 2H, 5), 1.69-1.58 (m, 4H, 6 & 7), 1.42 (t, J = 6.0 Hz, 1H, 1), 1.06 (s, 9H, 10);

**¹³C NMR** (125 MHz, CDCl₃) δ 135.6 (4C, 13), 134.0 (2C, 11), 129.5 (4C, 12), 127.6 (2C, 14), 86.4 (4), 78.5 (3), 63.4 (8), 51.4 (2), 31.7 (7), 26.9 (3C, 10), 25.0 (6), 19.2 (9), 18.5 (5);

**Anal.** Calc. for C_{23}H_{30}O_2Si: C, 75.36; H, 8.25. Found: C, 75.27; H, 8.35.
6 Experimental

(Z)-3-Iodohept-2-ene-1,7-diol (234)

Based on a procedure by Yamazaki et al.[125] Alkyne 230 (750 mg, 2.0 mmol, 1.0 equiv.) was stirred in THF (5 mL) and Red-Al (1.0 mL, 3.32 mmol, 1.7 equiv., 65 w.t.% in toluene) was added at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 18 h. NIS (810 mg, 3.6 mmol, 1.8 equiv.) in THF (3 mL) was added dropwise to the stirring solution at –78 °C over 20 min. The reaction mixture was warmed to 0 °C and stirred for 30 min. The reaction was quenched with a saturated aqueous solution of Rochelle’s salt (10 mL) and a saturated aqueous solution of Na2S2O3 (10 mL), extracted with Et2O (2 x 50 mL), the organics combined, dried (MgSO4), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes to EtOAc) to afford (Z)-3-iodohept-2-ene-1,7-diol (234) (400 mg, 80%) as a colourless oil:

Rf 0.2 (7 : 3 EtOAc : hexanes);

IR (neat) νmax, 3313 (br., O-H), 2935 (w, C-H), 2861 (w, C-H), 1738 (m), 1644 (w, C=C, 1451 (w), 1366 (w), 1228 (w), 1217 (w), 1060 (w), 1018 (w) cm⁻¹;

1H NMR (400 MHz, CDCl3) δ 5.90 (t, J = 7.0 Hz, 1H, 3), 4.24 (d, J = 7.0 Hz, 2H, 2), 3.70 (t, J = 7.5 Hz, 2H, 8), 2.57 (t, J = 7.5 Hz, 2H, 5), 1.70-1.56 (m, 5H, 6, 7 & 9), 1.36 (br. s, 1H, 1);

13C NMR (125 MHz, CDCl3) δ 133.9 (3), 110.1 (4), 67.2 (2), 62.6 (8), 44.8 (5), 31.2 (7), 25.4 (6);

1-((Hex-5-ynoxy)methyl)-4-methoxybenzene (235)

Hex-5-yn-1-ol (223) (5.0 g, 51 mmol, 1.0 equiv.) and NaH (2.91 g, 76.5 mmol, 1.5 equiv., (60% suspension in oil)) were stirred in DMF (50 mL) at 0 °C for 1 h. PMBCl (7.6 mL, 56 mmol, 1.1 equiv.) was added dropwise and the solution was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (100 mL), extracted with Et₂O (2 x 200 mL), the organics combined and washed with brine (3 x 300 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford PMB ether 235[196] (10 g, 90%) as a colourless oil:

R_f 0.55 (3 : 7 EtOAc : hexanes);

HRMS (ESI) calc. for C₁₄H₁₈O₂Na [M+Na]^+: requires 241.1204, found 241.1231 (Δ +11.2 ppm);

IR (neat) ν_max 3293 (w, C≡CH), 2938 (w, C-H), 2859 (w, C-H), 1612 (sh., C=C), 1511 (sh., C-C), 1301 (w), 1244 (sh.), 1093 (sh.), 1034 (sh.) cm⁻¹;

¹H NMR (CDCl₃, 500 MHz) δ 7.26 (d, J = 9.0 Hz, 2H, 9), 6.88 (d, J = 9.0 Hz, 2H, 10), 4.43 (s, 2H, 7), 3.81 (s, 3H, 12), 3.47 (t, J = 6.0 Hz, 2H, 6), 2.21 (td, J = 6.0, 1.0 Hz, 2H, 3), 1.94 (t, J = 1.0 Hz, 1H, 1), 1.75-1.69 (m, 2H, 5), 1.64-1.59 (m, 2H, 4);

¹³C NMR (CDCl₃, 125 MHz) δ 159.1 (11), 130.7 (8), 129.2 (2C, 9), 113.8 (2C, 10), 84.4 (2), 72.5 (7), 69.4 (6), 68.34 (1), 55.3 (12), 28.8 (5), 25.2 (4), 18.2 (3);

Anal. Calc. for C₁₄H₁₈O₂: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.23.
Based on a procedure by Lindsay et al.\textsuperscript{[126]} Alkyne 235 (6.80 g, 29.8 mmol, 1.0 equiv.) was stirred in THF (150 mL) at –78 °C. \textit{n}-BuLi in hexanes (13.1 mL, 32.8 mmol, 1.1 equiv., 2.5 M) was added dropwise and the solution stirred for 1 h. The reaction mixture was transferred by cannula into paraformaldehyde (4.50 g, 149 mmol, 5.0 equiv.). The reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction was quenched with a saturated aqueous solution of NH\textsubscript{4}Cl (300 mL), extracted with Et\textsubscript{2}O (2 x 200 mL), the organics combined, dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (3 : 7 EtOAc : hexanes) to afford alcohol 236\textsuperscript{[126]} (6.0 g, 81\%) as a colourless oil:

\[ \text{R}_F \text{ 0.48 (1 : 1 EtOAc : hexanes);} \]

\[ \text{IR (neat)} \nu_{\text{max}} 3399 \text{ (br., O-H)}, 2938 \text{ (w, C-H)}, 2862 \text{ (w, C-H)}, 1738 \text{ (sh., C=C)}, 1511 \text{ (sh., C-C)}, 1365 \text{ (w), 1244 \text{ (sh.), 1078 (m), 1030 \text{ (sh.), 1011 (sh.) cm}^{-1};} \]

\[ \text{HRMS (ESI) calc. for C}_{15}\text{H}_{20}\text{O}_{3}\text{Na [M+Na]}^{+} \text{: requires 271.1310, found 271.1309 (\Delta -0.4 ppm);} \]

\[ ^{1}H \text{ NMR (CDCl} _{3}, 500 \text{ MHz)} \delta 7.25 \text{ (d, } J = 9.0 \text{ Hz, 2H, 11), 6.88 \text{ (d, } J = 9.0 \text{ Hz, 2H, 12), 4.43 (s, 2H, 9), 4.24-4.22 \text{ (m, 2H, 2), 3.81 (s, 3H, 14), 3.46 (t, } J = 6.0 \text{ Hz, 2H, 8), 2.24 (t, } J = 6.0 \text{ Hz, 2H, 5), 1.73-1.68 \text{ (m, 2H, 6), 1.63-1.57 (m, 3H, 1 & 7);} \]

\[ ^{13}C \text{ NMR (CDCl} _{3}, 125 \text{ MHz)} \delta 159.1 \text{ (13), 130.6 (10), 129.2 (2C, 8), 113.8 (2C, 9), 86.2 (4), 78.6 (3), 72.5 (9), 69.5 (8), 55.3 (14), 51.4 (2), 28.9 (6), 25.3 (7), 18.5 (5);} \]

\[ \text{Anal. Calc. for C}_{15}\text{H}_{20}\text{O}_{3}; \text{ C, 72.55; H, 8.12. Found: C, 71.96; H, 8.32.} \]
Based on a procedure by Yamazaki et al.\textsuperscript{[125a]} Alkyne 236 (280 mg, 1.13 mmol, 1.0 equiv.) was stirred in THF (3 mL) at 0 °C for 2 min and then Red-Al (0.60 mL, 1.79 mmol, 1.7 equiv., 60 w.t.% in toluene) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 18 h. NIS (440 mg, 2.0 mmol, 1.8 equiv.) in THF (2 mL) was added dropwise to the stirring solution at −78 °C over 20 min. The reaction mixture was warmed to 0 °C and stirred for 30 min. The reaction was quenched with a saturated aqueous solution of Rochelle’s salt (3 mL) and a saturated aqueous solution of Na$_2$S$_2$O$_3$ (4 mL), extracted with Et$_2$O (2 x 20 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (3 : 7 EtOAc : hexanes) to afford olefin alcohol 237 (400 mg, 83%) as a colourless oil:

$\text{R}_f$ 0.5 (1 : 1 EtOAc : hexanes);

IR (neat) $\nu_{\text{max}}$ 3409 (br., O-H), 2935 (w, C-H), 2858 (w, C-H), 1611 (w, C=C), 1512 (sh., C-C), 1454 (w), 1360 (w), 1244 (sh.), 1172 (w), 1080 (sh.), 1032 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{15}$H$_{21}$O$_3$NaI [M+Na]$^+$: requires 399.0433, found 399.0444 ($\Delta$ +2.8 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.27 (d, $J$ = 9.0 Hz, 2H, 11), 6.88 (d, $J$ = 9.0 Hz, 2H, 12), 5.83 (tt, $J$ = 6.0, 0.5 Hz, 1H, 3), 4.43 (s, 2H, 9), 4.18 (d, $J$ = 6.0, 2H, 2), 3.81 (s, 3H, 14), 3.45 (t, $J$ = 6.0 Hz, 2H, 8), 2.51 (t, $J$ = 6.0 Hz, 2H, 5), 1.62-1.58 (m, 5H, 1, 6 & 7);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2 (13), 133.8 (3), 130.6 (10), 129.3 (2C, 11), 133.8 (2C, 12), 110.3 (4), 72.6 (9), 69.6 (8), 67.3 (2), 55.3 (14), 44.9 (5), 28.3 (7), 25.8 (6).
Based on a procedure by Holler et al., MeLi in hexanes (8.06 mL, 2.66 mmol, 10.0 equiv. 0.33 M) was added dropwise to a solution of CuI (253 mg, 1.33 mmol, 5.0 equiv.) in THF (3 mL) at 0 °C. The solution went yellow followed by grey and was stirred for 30 min at 0 °C. Alkyne alcohol 236 (100 mg, 0.27 mmol, 1.0 equiv.) in THF (0.5 mL) was added dropwise to the reaction mixture which was stirred for 5 h at rt. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (10 mL), extracted with Et₂O (20 mL), dried (MgSO₄), rotary evaporated and chromatographed (3 : 7 EtOAc : hexanes) to afford methylhept-2-en-1-ol 238 (43 mg, 60%) and hept-2-en-1-ol 239 (6 mg, 9%) both as a colourless oils:

**Methylhept-2-en-1-ol 238:**

\[ R_f 0.48 \text{ (1 : 1 EtOAc : hexanes); } \]

\[ \text{IR (neat) } \nu_{\text{max}} 3385 \text{ (br., } \text{O-H}), \quad 2935 \text{ (m, } \text{C-H}), \quad 2858 \text{ (m, } \text{C-H}), \quad 1612 \text{ (w, C=C)}, \quad 1512 \text{ (sh., C-C)}, \quad 1245 \text{ (sh.), } 1173 \text{ (w), } 1097 \text{ (sh.), } 1034 \text{ (sh.), } 1010 \text{ (w) } \text{cm}^{-1}; \]

**HRMS (ESI) calc. for C₁₆H₂₅O₃ [M+H][⁺]:** requires 265.1804, found 265.1799 (Δ –1.9 ppm);

\[ \text{¹H NMR (CDCl₃, 500 MHz) } \delta 7.26 \text{ (d, } J = 9.0 \text{ Hz, 2H, 12)}, \quad 6.88 \text{ (d, } J = 9.0 \text{ Hz, 2H, 13)}, \]

\[ 5.41-5.37 \text{ (m, 1H, 3)}, \quad 4.43 \text{ (s, 2H, 10)}, \quad 4.14 \text{ (d, } J = 6.0 \text{ Hz, 2H, 2)}, \quad 3.80 \text{ (s, 3H, 15)}, \quad 3.44 \text{ (t, } J = 6.0 \text{ Hz, 2H, 9)}, \quad 2.02 \text{ (t, } J = 6.0 \text{ Hz, 2H, 6)}, \quad 1.66 \text{ (s, 3H, 5)}, \quad 1.61-1.56 \text{ (m, 2H, 8)}, \quad 1.52-1.46 \text{ (m, 2H, 7)}, \quad 1.26 \text{ (br. s, 1H, 1)}; \]

**¹³C NMR (CDCl₃, 125 MHz) \( \delta \):** 159.1 (14), 139.7 (4), 130.7 (11), 129.2 (2C, 12), 123.5 (3), 113.7 (2C, 13), 72.5 (10), 69.9 (9), 63.7 (2), 55.2 (15), 39.2 (6), 29.2 (8), 24.2 (7), 16.1 (5).
Alcohol: 239:

Rf 0.52 (1:1 EtOAc: hexanes);

IR (neat) \(\nu_{\text{max}}\) 3399 (br., O-H), 2934 (m, C-H), 2856 (m, C-H), 1611 (w, C=C), 1512 (sh., C-C), 1457 (w), 1363 (w), 1301 (w), 1244 (sh.), 1173 (w), 1087 (m), 1033 (sh.) cm\(^{-1}\);

HRMS (ESI) calc. for C\(_{15}\)H\(_{23}\)O\(_3\) [M+H]\(^+\): requires 251.1647, found 251.1648 (\(\Delta \pm 0.4\) ppm).

\(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz) \(\delta\) 7.26 (d, \(J = 9.0\) Hz, 2H, 11), 6.86 (d, \(J = 9.0\) Hz, 2H, 12), 5.71-5.60 (m, 2H, 3 & 4), 4.43 (s, 2H, 9), 4.08 (t, \(J = 6.0\) Hz, 2H, 2), 3.80 (s, 3H, 14), 3.44 (t, \(J = 6.0\) Hz, 2H, 8), 2.08-2.04 (m, 2H, 5), 1.64-1.58 (m, 2H, 6), 1.49-1.43 (m, 2H, 7), 1.29-1.25 (m, 1H, 1);

\(^{13}\text{C NMR}\) (CDCl\(_3\), 125 MHz) \(\delta\) 159.1 (13), 133.0 (4), 130.7 (10), 129.2 (3C, 3 & 11), 133.7 (2C, 12), 72.5 (9), 69.9 (8), 63.8 (2), 55.3 (14), 31.9 (5), 29.2 (6), 25.7 (7);

Anal. Calc. for C\(_{15}\)H\(_{22}\)O\(_3\): C, 71.97; H, 8.86; found: C, 71.83; H, 8.77.
Alcohol 237 (540 mg, 1.44 mmol, 1.0 equiv.) was stirred in CH₂Cl₂ (7.2 mL) at 0 °C for 5 min and imidazole (107 mg, 1.58 mmol, 1.1 equiv.) was added at 0 °C and the resulting solution stirred for 10 min. TBDPSCI (0.41 mL, 1.58 mmol, 1.1 equiv.) was added dropwise and the solution was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (20 mL), extracted with Et₂O (2 x 20 mL), the organics combined, dried (MgSO₄), rotary evaporated chromatographed (1 : 9 EtOAc : hexanes) affording silylether 241 (700 mg, 80%) as a colourless oil:

Rₐ 0.8 (3 : 7 EtOAc : hexanes);
IR (neat) νmax 2931 (w, C-H), 2856 (w, C-H), 1612 (w, C=C), 1472 (w), 1427 (sh.), 1246 (w), 1172 (w), 1104 (m), 1037 (sh.) cm⁻¹;
HRMS (ESI) calc. for C₃₁H₄₃NO₃Si [M+NH₄]⁺: requires 632.2057, found 632.2040 (Δ +11.5 ppm);

¹H NMR (CDCl₃, 500 MHz) δ 7.68-7.67 (m, 4H, 5), 7.44-7.37 (m, 6H, 4 & 6), 7.27 (d, J = 9.0 Hz, 2H, 16), 6.89 (d, J = 9.0 Hz, 2H, 17), 5.84 (tt, J = 6.0, 0.5 Hz, 1H, 8), 4.44 (s, 2H, 14), 4.26 (d, J = 6.0 Hz, 2H, 7), 3.80 (s, 3H, 19), 3.45 (t, J = 7.0 Hz, 2H, 13), 2.46-2.44 (m, 2H, 10), 1.59-1.56 (m, 4H, 11 & 12), 1.06 (s, 9H, 2);

¹³C NMR (CDCl₃, 125 MHz) δ 159.1 (18), 135.6 (4C, 5), 134.7 (7), 133.5 (2C, 3), 130.7 (15), 129.7 (6C, 4 & 6), 127.7 (2C, 16), 113.8 (2C, 17), 107.1 (9), 72.6 (14), 69.7 (13), 69.0 (8), 55.3 (19), 44.7 (10), 28.3 (12), 26.8 (3C, 2), 25.9 (11), 19.2 (1);
Experimental

Anal. Calc. for C$_{31}$H$_{39}$O$_3$Si: C, 60.58; H, 6.40. Found: C, 60.62; H, 6.47.

(E)-t-Butyl(7-(4-methoxybenzyl)oxy)-3-methylhept-2-enyloxy)diphenylsilane (242) and (E)-t-Butyl(7-(4-methoxybenzyl)oxy)hept-2-enyloxy)diphenylsilane (243)

^tPrMgCl in hexanes (0.25 mL, 0.29 mmol, 2.0 equiv.; 1.3 M) was added to iodo-olefin 241 (90 mg, 0.15 mmol, 1.0 equiv.) in THF (0.5 mL) at 0 °C and the solution stirred for 1 h. Pd(PPh$_3$)$_4$ (9 mg, 7.0 μmol, 5 mol%) in THF (0.5 mL) was added and the solution stirred for 10 min. MeI in hexanes (0.15 M; 0.1 mL, 1.5 mmol, 10.0 equiv.) was added and the reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL), extracted with Et$_2$O (2 x 20 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford methyl-olefin 242 (37 mg, 50%) and olefin 243 (7 mg, 10%) and iodo-olefin 241 (starting material) (18 mg, 20%) as colourless oils:

Methyl-olefin 242:

R$_f$0.81 (3 : 7 EtOAc : hexanes);

IR (neat) $\nu_{max}$ 2932 (w, C-H), 2856 (w, C-H), 1613 (w, C=C), 1512 (m, C-C), 1462 (w), 1423 (w), 1361 (w), 1246 (m), 1111 (m), 1036 (m) cm$^{-1}$;

HRMS (ESI) calc. for C$_{32}$H$_{42}$O$_3$SiNa [M+Na]$^+$: requires 525.2801, found 525.2780 (Δ -4.0 ppm);
Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.70-7.68 (m, 4H, 5), 7.42-7.35 (m, 6H, 4 & 6), 7.27 (d, $J = 9.0$ Hz, 2H, 17), 6.87 (d, $J = 9.0$ Hz, 2H, 18), 5.38-5.35 (m, 1H, 8), 4.43 (s, 2H, 15), 4.22 (d, $J = 6.0$ Hz, 2H, 7), 3.80 (s, 3H, 20), 3.44 (t, $J = 6.0$ Hz, 2H, 14), 1.97 (t, $J = 6.0$ Hz, 2H, 11), 1.60-1.56 (m, 2H, 13), 1.48-1.43 (m, 2H, 12), 1.42 (s, 3H, 10), 1.04 (s, 9H, 1);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1 (19), 137.0 (9), 135.6 (2C, 3), 134.1 (2C, 5), 130.8 (16), 129.3 (6C, 4 & 6), 127.6 (2C, 17), 124.2 (8), 113.8 (18), 72.5 (15), 70.0 (14), 61.1 (7), 55.3 (20), 39.2 (11), 29.3 (13), 26.8 (3C, 1), 24.2 (12), 19.2 (2), 16.2 (10);

Anal. Calc. for C$_{32}$H$_{42}$O$_3$Si: C, 76.45%; H, 8.42, found: C, 76.39; H, 8.42.

Olefin 243:

$R_f$ 0.80 (3 : 7 EtOAc : hexanes);

IR (neat) $\nu$ max 2931 (w, C-H), 2856 (w, C-H), 1612 (w, C=C), 1512 (w, C-C), 1427 (w), 1246 (s), 1105 (m), 1037 (sh.) cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71-7.70 (m, 4H, 5), 7.46-7.38 (m, 6H, 4 & 6), 7.28 (d, $J = 9.0$ Hz, 2H, 16), 6.90 (d, $J = 9.0$ Hz, 2H, 17), 5.70-5.53 (m, 2H, 8 & 9), 4.46 (s, 2H, 14), 4.17 (d, $J = 6.0$ Hz, 2H, 7), 3.82 (s, 3H, 19), 3.46 (t, $J = 6.0$ Hz, 2H, 13), 2.07-2.05 (m, 2H, 10), 1.66-1.57 (m, 2H, 11), 1.49-1.42 (m, 2H, 12), 1.07 (s, 9H, 1);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1 (18), 135.6 (2C, 4), 134.8 (2C, 3), 133.9 (9), 130.9 (8), 130.8 (15), 129.6 (2C, 16), 129.5 (2C, 6), 128.9 (4C, 5), 113.7 (2C, 17), 72.5 (14), 69.9 (13), 64.6 (7), 55.3 (19), 31.9 (10), 29.3 (12), 26.8 (3C, 1), 25.8 (11), 19.2 (2);

Anal. Calc. for C$_{31}$H$_{40}$O$_3$Si; C76.18, H 8.25; found C, 76.13; H, 8.26.

Method 2 for the preparation of (E)-t-Butyl(7-(4-methoxybenzyloxy)-3-methylhept-2-enyloxy)diphenylsilane (242): Iodo-olefin 241 (120 mg, 0.20 mmol, 1.0 equiv.) was stirred in THF (1 mL) at 0 °C for 2 min and Pd(PPh$_3$)$_4$ (9.5 mg, 0.8 µmol, 5 mol%) was added. The
resulting solution was stirred for 1 h. ZnMe$_2$ in hexanes (0.5 mL, 0.48 mmol, 3.0 equiv., 1.0 M) was added to the stirring solution which went from colourless to yellow after warming to rt and stirring for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL), extracted with Et$_2$O (2 x 20 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford methyl-olefin 242 (95 mg, 95%) as a colourless oil. Characterisation as described above.

Method 2 for the preparation of (E)-t-Butyl(7-(4-methoxybenzyl)oxy)hept-2-enyloxy)diphenylsilane 243: Iodo-olefin 241 (50 mg, 80 μmol, 1.0 equiv.) was stirred in THF (0.5 mL) at –78 °C. n-BuLi in hexanes (60 μL, 1.6 M, 0.96 mmol, 1.2 equiv.) was added and the resulting solution stirred for 15 min. MeI (10 μL, 0.16 mmol, 2.0 equiv.) was added to the mixture which was stirred for 10 min. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (5 mL), extracted with Et$_2$O (2 x 10 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford olefin 243 (8 mg, 20%) and iodo-olefin 241 (starting material) (16 mg, 40%) as colourless oils. Characterisation as described above.
6 Experimental

(Z)-1-((5-Iodo-7-(methoxymethoxy)hept-5-enyloxy)methyl)-4-methoxybenzene (244)

Hunig’s base (0.3 mL, 1.8 mmol, 1.7 equiv.) was added into a stirring solution of alcohol 237 (400 mg, 1.06 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (5 mL) at 0 °C, MOMCl (0.11 mL, 1.38 mmol, 1.3 equiv.) was added and the resulting solution stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL) and a saturated aqueous solution of NaHCO$_3$ (20 mL), extracted with Et$_2$O (3 x 20 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford MOM ether 244 (440 mg, 98%) as a colourless oil:

$R_f$ 0.6 (3 : 7 EtOAc : hexanes);

IR (neat) $v_{max}$ 2935 (w, C-H), 2857 (w, C-H), 1738 (w), 1612 (w, C=C), 1512 (sh., C-C), 1455 (w), 1365 (w), 1301 (w), 1245 (m), 1150 (w), 1099 (m), 1033 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{17}$H$_{25}$O$_4$NaI [M+Na]$^+$: requires 443.0695, found 443.0698 ($\Delta$ +0.7 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.26 (d, $J$ = 9.0 Hz, 2H, 12), 6.88 (d, $J$ = 9.0 Hz, 2H, 13), 5.80 (tt, $J$ = 6.0, 0.5 Hz, 1H, 4), 4.64 (s, 2H, 10), 4.43 (s, 2H, 2), 4.12 (d, $J$ = 6.0 Hz, 2H, 3), 3.81 (s, 3H, 15), 3.45 (t, $J$ = 6.0 Hz, 2H, 9), 3.39 (s, 3H, 1), 2.52 (t, $J$ = 6.0 Hz, 2H, 6), 1.65-1.57 (m, 4H, 7 & 8);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1 (14), 131.5 (4), 130.6 (11), 129.2 (2C, 12), 113.8 (2C, 13), 110.6 (2), 96.1 (5), 72.6 (10), 71.8 (3), 69.6 (9), 55.4 (15), 55.2 (1), 45.0 (6), 28.3 (8), 25.9 (7).
Iodo-olefin 244 (130 mg, 0.31 mmol, 1.0 equiv.) in THF (1 mL) was allowed to stir at –78 °C. \( n \)-BuLi in hexanes (0.15 mL, 0.37 mmol, 1.2 equiv.; 2.5 M) was added dropwise and the mixture stirred for 15 min. MeI in hexanes (0.29 mL, 0.47 mmol, 1.5 equiv.; 1.6 M) was added and the reaction mixture stirred for 15 min. The reaction mixture was quenched with a saturated aqueous solution of NH\(_4\)Cl (5 mL), extracted with Et\(_2\)O (2 x 10 mL), the organics combined, dried (MgSO\(_4\)), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford alkyne 246 (29 mg, 30%) and olefin 245 (56 mg, 61%) as colourless oils.

**Olefin 245:**

\( R_f \) 0.70 (3 : 7 EtOAc : hexanes);

\( \text{IR (neat) } \nu_{\text{max}} \): 2934 (w, C-H), 2857 (w, C-H), 1739 (m), 1612 (w, C=C), 1512 (sh., C-C), 1365 (w), 1245 (sh.), 1099 (m), 1034 (sh.) cm\(^{-1}\);

\( \text{HRMS (ESI) calc. for } C_{17}H_{26}O_4Na [M+Na]^+ : requires } 317.1729, \text{ found } 317.1718 (\Delta -3.5 \text{ ppm}); \)

\( ^1H \text{ NMR (400 MHz, CDCl}_3) \): 7.28 (d, \( J = 9.0 \text{ Hz, 2H, 12} \)), 6.90 (d, \( J = 9.0 \text{ Hz, 2H, 13} \)), 5.77-5.70 (m, 1H, 4), 5.61-5.51 (m, 1H, 5), 4.65 (s, 2H, 10), 4.45 (s, 2H, 2), 4.02 (d, \( J = 6.0 \text{ Hz, 2H, 3} \)), 3.82 (s, 3H, 15), 3.46 (t, \( J = 7.0 \text{ Hz, 2H, 9} \)), 3.39 (s, 3H, 1), 2.10-2.08 (m, 2H, 6), 1.67-1.60 (m, 2H, 7), 1.52-1.45 (m, 2H, 8);
Experimental

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1 (14), 134.7 (5), 130.7 (11), 129.2 (2C, 12), 126.0 (4), 113.7 (2C, 13), 95.4 (2), 72.5 (10), 69.9 (3), 67.9 (9), 55.3 (15), 55.2 (1), 32.0 (6), 29.3 (8), 25.7 (7);

Anal. Calc. for C$_{17}$H$_{26}$O$_4$: C, 69.36; H, 8.90. Found C, 69.42; found 8.98.

Alkyne 246:

R$_f$ 0.75 (3 : 7 EtOAc : hexanes);

IR (neat) $v_{max}$ 2938 (w, C-H), 2862 (w, C-H), 1738 (w), 1612 (w, C=C), 1512 (sh., C-C), 1361 (w), 1245 (sh.), 1148 (w), 1097 (sh.), 1039 (m) cm$^{-1}$;

HRMS (ESI) calc. for C$_{17}$H$_{24}$O$_4$Na [M+Na]$^+$: requires 315.1572, found 315.1566 ($\Delta$ –1.9 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.26 (d, $J$ = 9.0 Hz, 2H, 12), 6.88 (d, $J$ = 9.0 Hz, 2H, 13), 4.70 (s, 2H, 10), 4.43 (s, 2H, 2), 4.16 (br. s, 2H, 3), 3.80 (s, 3H, 15), 3.46 (t, $J$ = 7.0 Hz, 2H, 9), 3.37 (s, 3H, 1), 2.26-2.23 (m, 2H, 6), 1.73-1.68 (m, 2H, 7), 1.63-1.57 (m, 2H, 8);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1 (14), 130.7 (11), 129.2 (2C, 12), 113.8 (2C, 13), 94.6 (2), 86.7 (5), 75.6 (4), 72.5 (3), 69.5 (10), 55.5 (9), 55.3 (1), 54.7 (15), 28.9 (8), 25.3 (7), 18.6 (6).
(E)-1-Methoxy-4-((7-(methoxymethoxy)-5-methylhept-5-enyloxy)methyl)benzene (247) and (E)-1-Methoxy-4-((7-(methoxymethoxy)hept-5-enyloxy)methyl)benzene (245)

i-PrMgCl in hexanes (1.6 mL, 0.5 mmol, 2.0 equiv.; 0.3 M) was added to iodo-olefin 241 (100 mg, 0.24 mmol, 1.0 equiv.) in THF (1.2 mL) at 0 °C and the resulting solution stirred for 1 h. Pd(PPh₃)₄ (14 mg, 12 μmol, 5 mol%) in THF (0.5 mL) was added and the solution stirred for 10 min. MeI in hexanes (0.15 mL, 0.24 mmol, 10.0 equiv.; 1.6 M) was added and the reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (10 mL), extracted with Et₂O (2 x 20 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford methyl-olefin 247 (35 mg, 47%), iodo-olefin 241 (25 mg, 25%) (starting material) and olefin 245 (6 mg, 8%) as colourless oils.

**Methyl-olefin 247:**

Rf 0.62 (3 : 7 EtOAc : hexanes);

IR (neat) νmax 2935 (w, C-H), 2858 (w, C-H), 1739 (w), 1612 (w, C=C), 1512 (sh., C-C), 1442 (w), 1364 (w), 1301 (w), 1245 (sh.), 1097 (sh.), 1033 (sh.) cm⁻¹;

HRMS (ESI) calc. for C₁₈H₂₈O₄Na [M+Na]⁺: requires 331.1885, found 331.1872 (Δ +0.9 ppm);

¹H NMR (CDCl₃, 500 MHz) δ 7.26 (d, J = 9.0 Hz, 2H, 13), 6.87 (d, J = 9.0 Hz, 2H, 14), 5.36-5.33 (m, 1H, 4), 4.63 (s, 2H, 11), 4.43 (s, 2H, 2), 4.07 (d, J = 6.0 Hz, 2H, 3), 3.80 (s, 3H, 16), 3.44 (t, J = 7.0 Hz, 2H, 10), 3.38 (s, 3H, 1), 2.04 (t, J = 7.0 Hz, 2H, 7), 1.67 (s, 3H, 6), 1.62-1.56 (m, 2H, 8), 1.53-1.47 (m, 2H, 7);
6 Experimental

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 159.1 (15), 140.9 (5), 130.7 (12), 129.2 (2C, 13), 120.3 (4), 113.7 (2C, 14), 95.5 (2), 72.5 (11), 69.9 (10), 63.6 (3), 55.2 (2C, 1 & 16), 39.3 (7), 29.4 (9), 24.3 (8), 16.2 (6).

Olefin 245: Characterised as described earlier.

$^{(E)}$-7-(t-Butyldiphenylsilyloxy)-5-methylhept-5-en-1-ol (248)

PMB ether 242 (200 mg, 0.40 mmol, 1.0 equiv.) was stirred in a solution of CH$_2$Cl$_2$ : Buffer pH 7 (10:1) (4.5 mL) at 0 °C. DDQ (108 mg, 0.48 mmol, 1.2 equiv.) was added and the resulting solution was stirred for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (20 mL) and filtered through celite. The resulting solution was extracted with Et$_2$O (2 x 50 mL), the organics combined, dried (MgSO$_4$) and chromatographed (1 : 1 EtOAc : hexanes) to afford alcohol 248 (107 mg, 70%) as a colourless oil:

$R_f$ 0.4 (1 : 1 EtOAc : hexanes);

IR (neat) $\nu_{\text{max}}$ 3347 (br., O-H), 2932 (m, C-H), 2857 (m, C-H), 1473 (w), 1428 (sh.), 1389 (w), 1112 (s), 1054 (m) cm$^{-1}$;

HRMS (CI) calc. for C$_{24}$H$_{38}$NO$_2$Si [M+NH$_4$]$^+$: requires 400.2673, found 400.2673 (Δ +0.2 ppm);
Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.80-7.79 (m, 4H, 5), 7.23-7.22 (m, 6H, 4 & 6), 5.35-5.42 (m, 1H, 8), 4.22 (d, $J = 5.0$ Hz, 2H, 7), 3.65 (br. s, 2H, 14), 1.98 (t, $J = 5.0$, 2H, 11), 1.51-1.63 (m, 4H, 12 & 13), 1.50 (s, 3H, 10), 1.20 (br. s, 1H, 15), 1.05 (s, 9H, 1);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 136.9 (9), 135.6 (4C, 5), 134.0 (2C, 3), 129.5 (4C, 4), 127.6 (2C, 6), 124.2 (8), 62.9 (14), 61.1 (7), 39.1 (11), 32.3 (13), 26.8 (3C, 1), 23.8 (12), 19.2 (2), 16.1 (10).

Anal. Calc. for C$_{24}$H$_{34}$O$_2$Si: C, 75.34; H, 8.96. Found: C, 75.28; H, 8.97.

$(E)$-7-(t-Butyldiphenylsilyloxy)-5-methylhept-5-enal (249)

Oxalyl chloride (30 $\mu$L, 0.36 mmol, 2.0 equiv.) and DMSO (40 $\mu$L, 0.54 mmol, 3.0 equiv.) were stirred in CH$_2$Cl$_2$ (1.2 mL) at $-78$ °C for 30 min. Alcohol 248 (70 mg, 0.18 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (0.2 mL) was added dropwise and the resulting solution stirred for 1 h. Et$_3$N (0.15 mL, 0.90 mmol, 5.0 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched with H$_2$O (2 mL), extracted with Et$_2$O (2 x 10 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford aldehyde 249 (50 mg, 73%) as a colourless oil:

$R_f$ 0.45 (1 : 9 EtOAc : hexanes);

IR (neat) $\nu_{max}$ 2931 (m, C-H), 2857 (m, C-H), 1673 (sh., C=O), 1428 (sh.), 1107 (sh.) cm$^{-1}$;

HRMS (CI) calc. for C$_{24}$H$_{36}$NO$_2$Si [M+NH$_4$]$^+$: requires 398.2515, found 398.2529 (\Delta +3.5 ppm);
6 Experimental

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 9.28 (t, \(J = 2.0\) Hz, 1H, 15), 7.82-7.80 (m, 4H, 5), 7.24-7.23 (m, 6H, 4 & 6), 5.47-5.45 (m, 1H, 8), 4.28 (d, \(J = 5.0\) Hz, 2H, 7), 1.74 (td, \(J = 5.0\), 2.0 Hz, 2H, 13), 1.67 (t, \(J = 5.0\) Hz, 2H, 11), 1.37 (quin. \(J = 5.0\) Hz, 2H, 12), 1.19 (s, 3H, 10), 1.18 (s, 9H, 1);

\(^1\)H NMR (CDCl\(_3\), 125 MHz) \(\delta\) 200.5 (14), 136.2 (9), 136.0 (4C, 5), 134.4 (2C, 3), 129.9 (6C, 4 & 6), 125.4 (8), 61.3 (7), 43.0 (13), 38.7 (11), 27.0 (3C, 1), 20.0 (12), 19.4 (2), 15.9 (10).

\(\text{(E)-1-Nitrohept-1-ene (253)}\)

\[\text{\begin{center}
\begin{tikzpicture}
\node at (0,0) {1};
\node at (1,0) {2};
\node at (2,0) {3};
\node at (3,0) {4};
\node at (4,0) {5};
\node at (5,0) {6};
\node at (6,0) {7};
\node at (5,1) {NO_2};
\end{tikzpicture}
\end{center}}\]

Based on a procedure by Vergari et al.\([140]\) Hexanal (0.50 mL, 4.16 mmol, 1.0 equiv.) was stirred in CH\(_2\)Cl\(_2\) (8 mL) with molecular sieves (4 Å, 5 g) at rt for 2 min. Piperidine (0.45 mL, 4.16 mmol, 1.0 equiv.) was added followed by MeNO\(_2\) (0.45 mL, 8.32 mmol, 2.0 equiv.) and the resulting solution was stirred for 12 h. The reaction mixture was filtered and the resulting filtrate rotary evaporated. The resulting residue was chromatographed (1 : 6 Et\(_2\)O : pentane) to afford \(\text{(E)-1-nitrohept-1-ene (253)}\)\([201]\) (400 mg, 50%) as a yellow oil:

\(R_f\) 0.85 (1 : 9 Et\(_2\)O : pentane);

IR (neat) \(\nu_{\text{max}}\) 2958 (m, C-H), 2931 (m, C-H), 2861 (w, C-H), 1649 (w, C=C), 1523 (s, N-O), 1350 (s, N-O) cm\(^{-1}\);

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.31-7.25 (m, 1H, 6), 6.98 (dt, \(J = 11.0\), 0.5, 1H, 7), 2.27 (app. td, \(J = 7.0\), 4.0 Hz, 2H, 5), 1.53-1.50 (m, 2H, 2), 1.35-1.31 (m, 4H, 3 & 4), 0.92-0.89 (m, 3H, 1);
13C NMR (CDCl₃, 125 MHz) δ 124.8 (7), 139.5 (6), 31.2 (3), 28.4 (5), 27.4 (4), 22.3 (2), 13.9 (1);

Anal. Calc. for C₇H₁₃NO₂: C, 58.72; H, 9.15; N, 9.78. Found: C, 57.63; H, 7.82; N, 7.66.

*t*-Butyl 2-(3-methylbut-2-enoyl)-3-(nitromethyl)octanoate (252)

Keto *t*-butylester 200 (270 mg, 1.86 mmol, 1.0 equiv.) was added into a stirring solution of KOt-Bu (42 mg, 0.37 mmol, 0.2 equiv.) in *t*-BuOH (10 mL) and THF (10 mL) at 0 °C and the resulting solution stirred for 30 min. (*E*)-1-Nitrohept-1-ene (253) (370 mg, 1.86 mmol, 1.0 equiv.) in THF (2 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h and then quenched with a saturated aqueous solution of NH₄Cl (50 mL) and extracted with Et₂O (2 x 50 mL). The organics were combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 Et₂O : pentane) to afford nitro-ketoester 252 (560 mg, 88%) as a pale yellow oil (*mixture of diastereoisomers in a 1 : 1 ratio*):

Rᵣ0.70 (1 : 9 Et₂O : pentane);

IR (neat) νmax 2933 (m, C-H), 2862 (m, C-H), 1730 (m, C=O), 1687 (w, C=C), 1616 (w, C=C), 1551 (s, N-O), 1445 (w), 1369 (m, N-O), 1154 (s), 1035 (w) cm⁻¹;

HRMS (ESI) calc. for C₁₈H₃₁NO₅Na [M+Na]^+: requires 364.2100, found 364.2098 (Δ –0.5 ppm);

¹H NMR (CDCl₃, 500 MHz) δ 6.17 (app. t, J = 1.0 Hz, 0.5H, 13), 6.15 (app. t, J = 1.0 Hz, 0.5H, 13), 4.68-4.61 (m, 0.5H, 7), 4.55-4.51 (m, 0.5H, 7), 3.62 (d, J = 5.0 Hz, 0.5H, 8), 3.58 (d, J = 5.0 Hz, 0.5H, 8), 2.87-2.81 (m, 1H, 6), 2.17 (d, J = 0.5 Hz, 1.5H, 16), 2.16 (d, J = 0.5
6 Experimental

Hz, 1.5H, 16), 1.94 (d, J = 0.5 Hz, 1.5H, 15), 1.93 (d, J = 0.5 Hz, 1.5H, 15), 1.46 (s, 4.5H, 11), 1.44 (s, 4.5H, 11), 1.37-1.25 (m, 8H, 2, 3, 4 & 5), 0.87 (t, J = 8.0Hz, 3H, 1);

13C NMR (CDCl3, 125 MHz) δ 193.4, 193.3 (12), 167.9, 167.8 (9), 159.4, 159.0 (14), 123.1, 122.5 (13), 82.5 (10), 76.5 (7), 61.4, 61.1 (8), 36.6, 36.5 (3), 31.6 (5), 30.0 (3C, 11), 29.4 (15), 27.9, 27.9 (4), 26.2, 26.1 (2), 22.4 (6), 21.2, 21.1 (16), 13.9 (1);

Anal. Calc. for C18H31NO5: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.26; H, 9.05; N, 4.10.

2-Methyl-6-(nitromethyl)undec-2-en-4-one (257)

Based on a procedure by Geach et al.[150] t-Butylester 252 (250 mg, 0.73 mmol, 1.0 equiv.) was refluxed with TsOH (28 mg, 0.15 mmol, 0.2 equiv.) in benzene (20 mL) for 4 h. The reaction mixture was allowed to cool to rt, rotary evaporated and chromatographed (1 : 9 Et2O : pentane) to afford nitro-ketone 257 (125 mg, 72%) as a colourless oil:

\[ R_f 0.65 \] (1 : 9 Et2O : pentane);

IR (neat) \( \nu_{max} \) 2930 (m, C-H), 2860 (w, C-H), 1686 (sh., C=O), 1618 (sh., C=C), 1547 (s, N-O), 1439 (w), 1379 (m, N-O), 1125 (w), 1038 (w), 1100 (w) cm\(^{-1}\);

HRMS (ESI) calc. for C13H24NO3: requires 242.1756, found 242.1766 (\( \Delta +4.1 \) ppm);

\(^1\)H NMR (CDCl3, 500 MHz) δ 6.05 (app. quin. J = 0.5 Hz, 1H, 10), 4.49-4.40 (m, 2H, 7), 2.67 (app. septet, J = 5.0 Hz, 1H, 6), 2.54 (dd, J = 10.0, 5.0 Hz, 2H, 8), 2.16 (d, J = 0.5 Hz, 3H, 12), 1.90 (d, J = 0.5 Hz, 3H, 13), 1.40-1.24 (m, 8H, 2, 3, 4 & 5), 0.88 (t, J = 5.0 Hz, 3H, 1);
6 Experimental

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 198.3 (9), 156.7 (11), 123.5 (10), 78.7 (7), 45.1 (8), 33.4 (5), 31.6 (3), 31.5 (12), 27.8 (4), 26.2 (6), 22.4 (2), 20.9 (13), 14.0 (1).

6-Methyl-4-oxo-2-pentylhept-5-enal (258)

Nitro compound 257 (18 mg, 75 μmol, 1.0 equiv.) was stirred with NaH (7 mg, 0.17 mmol, 2.2 equiv. (60% suspension in oil)) in MeOH (0.4 mL) at 0 °C for 30 min. A solution of (HCl (conc.) : MeOH : H$_2$O 1 : 8 : 10) (1.9 mL) was then added dropwise and the reaction was stirred for 15 min. The reaction mixture was quenched with a saturated aqueous solution of NaHCO$_3$ (10 mL), extracted with Et$_2$O (2 x 10 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 Et$_2$O : pentane) to afford aldehyde 258 (10 mg, 71%) as a clear gum:

$R_f$ 0.55 (1 : 9 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2930 (s, C-H), 2858 (m, C-H), 1726 (w, C=O), 1687 (s, C=O), 1622 (s, C=C), 1445 (m), 1379 (w), 1114 (m), 1074 (m) cm$^{-1}$;

HRMS (EI) calc. for C$_{13}$H$_{22}$O$_2$: requires 210.1620, found 210.1622 ($\Delta$ +1.0 ppm);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.72 (br. s, 1H, 14), 6.04 (app. quin. $J = 0.5$ Hz, 10), 2.88-2.82 (m, 1H, 8b), 2.57-2.46 (m, 1H, 8a), 2.30-2.26 (m, 1H, 6), 1.87 (d, $J = 0.5$ Hz, 3H, 12), 1.85 (d, $J = 0.5$ Hz, 3H, 13), 1.32-1.21 (m, 8H, 2, 3, 4 & 5), 0.85 (t, $J = 6.0$ Hz, 3H, 1);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 203.8 (7), 200.5 (9), 156.1 (11), 124.4 (10), 46.9 (6), 43.8 (8), 37.1 (3), 28.6 (5), 27.6 (12), 26.6 (4), 22.5 (2), 20.8 (13), 13.9 (1).
2-(2-Methylprop-1-enyl)-4-pentylfuran (251)

Aldehyde 258 (292 mg, 1.39 mmol, 1.0 equiv.) in MeOH (1 mL) was added dropwise to a stirring solution of TiCl$_3$ (20% aqueous solution, 1.54 mL, 5.56 mmol, 4.0 equiv.) and NH$_4$OAc (2.68 g, 35.0 mmol, 25.0 equiv.) in H$_2$O (1.5 mL). The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$ (10 mL), extracted with Et$_2$O (2 x 10 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 8 Et$_2$O : pentane) to afford 2-(2-methylprop-1-enyl)-4-pentylfuran (251) (5 mg, 3%) as a colourless gum:

$R_f$ 0.95 (1 : 9 Et$_2$O : pentane);

IR (neat) $v_{max}$ 2928 (w, C-H), 2858 (w, C-H), 1720 (s, C=O (furan)), 1376 (m), 1142 (m) cm$^{-1}$;

HRMS (EI) calc. for C$_{13}$H$_{20}$O [M+H]$^+$: requires 192.1514, found 192.1524 (Δ +5.2 ppm);

$^1$H NMR (CDCl$_3$, 400 MHz) δ 7.12 (s, 1H, 7), 6.08 (s, 1H, 8), 6.04 (s, 1H, 10), 2.40 (t, $J$ = 7.0 Hz, 2H, 5), 2.00 (s, 3H, 12 / 13), 1.91 (s, 3H, 12 / 13), 1.61-1.54 (m, 2H, 4), 1.39-1.28 (m, 4H, 2 & 3), 0.94-0.90 (m, 3H, 1);

$^{13}$C NMR (CDCl$_3$, 100 MHz) δ 153.6 (9), 136.7 (11), 134.7 (7), 125.8 (6), 114.6 (10), 108.8 (8), 31.5 (4), 29.7 (3), 27.0 (5), 24.9 (13), 22.5 (2), 20.0 (12), 14.1 (1).
Geraniol (265) (2.70 g, 17.3 mmol, 1.0 equiv.) was stirred in CH₂Cl₂ (90 mL) at 0 °C, imidazole (1.30 g, 19.0 mmol, 1.1 equiv.) was then added followed by TBDPSCl (5.0 mL, 19.0 mmol, 1.1 equiv.) and the reaction mixture was allowed to warm to rt and stirred for 12 h. The reaction mixture was quenched with H₂O (100 mL), extracted with CH₂Cl₂ (2 x 100 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 to 2 : 8 EtOAc : hexanes) to afford silyl ether 264[202] (6.0 g, 88%) as a colourless oil:

\[ \text{Rf} 0.8 (2 : 8 \text{ EtOAc} : \text{hexanes}); \]

\[ \text{IR (neat) } v_{\text{max}} 2960 (\text{w, C-H}), 2930 (\text{m, C-H}), 2857 (\text{m, C-H}), 1473 (\text{w}), 1428 (\text{sh.}), 1379 (\text{w}), 1110 (\text{s}), 1056 (\text{sh.}) \text{ cm}^{-1}; \]

\[ \text{HRMS (CI) calc. for } C_{26}H_{40}NO_2Si [M+NH}_4^+ : \text{ requires } 426.2828, \text{ found } 426.2842 (\Delta +3.3 \text{ ppm}); \]

\[ \text{\textsuperscript{1}H NMR (CDCl}_3, 400 MHz) } \delta 7.71-7.68 (\text{m, 4H, 5}), 7.44-7.35 (\text{m, 6H, 4 & 6}), 5.40-5.36 (\text{m, 1H, 8}), 5.12-5.08 (\text{m, 1H, 13}), 4.22 (d, J = 8.0 Hz, 2H, 7), 2.09-1.96 (\text{m, 4H, 11 & 12}), 1.68 (d, J = 0.5 Hz, 3H, 15), 1.61 (s, 3H, 16), 1.43 (s, 3H, 10), 1.04 (s, 9H, 1); \]

\[ \text{\textsuperscript{13}C NMR (CDCl}_3, 100 MHz) } \delta 137.0 (9), 135.6 (4C, 5), 135.2 (2C, 3), 134.1 (14), 131.5 (2C, 6), 129.5 (4C, 4), 124.1, 124.0 (2C, 8 & 13), 61.2 (7), 39.5 (11), 26.8 (3C, 1), 26.4 (12), 25.7 (16), 19.2 (2), 17.7 (15), 16.3 (10); \]

\[ \text{Anal. Calc. for } C_{26}H_{36}OSi: C, 79.53; \text{ H, 9.24. Found: C, 74.07; H, 8.76.} \]

260
(E)-t-Butyl(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enyloxy)diphenylsilane (263)

Based on a procedure by Tago et al.\textsuperscript{153} Olefin 264 (5.20 g, 13.2 mmol, 1.0 equiv.) was stirred in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) at 0 °C. m-CPBA (3.60 g, 15.8 mmol, 1.2 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) was added dropwise and the reaction mixture stirred for 2 h. The mixture was filtered and Ca(OH)\textsubscript{2} (4.20 g, 56.8 mmol, 4.3 equiv.) was added and the resulting solution stirred for 1 h. The reaction mixture was filtered, rotary evaporated and chromatographed (3 : 7 Et\textsubscript{2}O : pentane) to afford epoxide 263\textsuperscript{202} (4.0 g, 75%) as a colourless oil:

\textbf{R}\textsubscript{f} 0.65 (3 : 7 Et\textsubscript{2}O : pentane);

\textbf{IR} (neat) \(\nu_{\text{max}}\) 2931 (m, C-H), 2959 (m, C-H), 2857 (m, C-H), 1473 (w), 1428 (sh.), 1378 (w), 1112 (s), 1057 (m) cm\textsuperscript{-1};

\textbf{HRMS} (ESI) calc. for C\textsubscript{26}H\textsubscript{36}O\textsubscript{2}NaSi [M+Na]\textsuperscript{+} requires 431.2382, found 431.2369 (\(\Delta = 3.0\) ppm);

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.70-7.67 (m, 4H, 5), 7.44-7.35 (m, 6H, 4 & 6), 5.43-5.39 (m, 1H, 8), 4.22 (d, J = 6.0, 2H, 7), 2.71 (t, J = 5.0 Hz, 1H, 13), 2.19-2.03 (m, 2H, 11), 1.71-1.59 (m, 2H, 12), 1.46 (s, 3H, 10), 1.30 (s, 3H, 15), 1.26 (s, 3H, 14), 1.07 (s, 9H, 1);

\textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 136.1 (9), 135.6 (4C, 5), 134.0 (2C, 3), 129.5 (2C, 6), 127.6 (4C, 4), 124.6 (8), 64.0 (13), 61.0 (7), 58.4 (16), 36.1 (11), 27.2 (12), 26.8 (2C, 1), 24.9 (15), 19.2 (2), 18.7 (14), 16.3 (10).
6 Experimental

(E)-6-(t-Butyldiphenylsilyloxy)-4-methylhex-4-enal (262)

Based on a procedure by Tago et al.\textsuperscript{[153]} Epoxide 263 (4.0 g, 9.8 mmol, 1.0 equiv.) was stirred in THF (32 mL). H\textsubscript{2}O\textsubscript{6} (4.14 g, 19.5 mmol, 2.0 equiv.) in H\textsubscript{2}O (20 mL) was added dropwise to the stirring solution at 0 °C and stirred for 30 min. The reaction mixture was quenched with a saturated aqueous solution of NaHCO\textsubscript{3} (50 mL), extracted with Et\textsubscript{2}O (2 x 200 mL), the organics combined, dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (3 : 7 Et\textsubscript{2}O : pentane) to afford aldehyde 262\textsuperscript{[202]} (2.0 g, 60%) as a colourless oil:

R\textsubscript{f} 0.60 (3 : 7 Et\textsubscript{2}O : pentane);

IR (neat) \( \nu_{\text{max}} \) 2931 (m, C-H), 2857 (m, C-H), 1722 (w, C=O), 1472 (w), 1428 (sh.), 1390 (w), 1111 (s), 1069 (m) cm\textsuperscript{-1};

MS (Cl) [M+NH\textsubscript{4}]\textsuperscript{+}: requires 340, found 340; [M+H]\textsuperscript{+}: requires 323, found 323;

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \( \delta \) 9.75 (t, \( J = 1.0 \) Hz, 1H, 14), 7.69-7.67 (m, 4H, 5), 7.42-7.36 (m, 6H, 4 & 6), 5.40-5.37 (m, 1H, 8), 4.22 (d, \( J = 6.0 \) Hz, 2H, 7), 2.50 (td, \( J = 6.0, 1.0 \) Hz, 2H, 12), 2.30 (t, \( J = 6.0 \) Hz, 2H, 11), 1.45 (s, 3H, 10), 1.04 (s, 9H, 1);

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \( \delta \) 202.2 (13), 135.6 (2C, 3), 134.9 (9), 133.9 (4C, 4), 129.6 (2C, 6), 127.6 (4C, 5), 125.0 (8), 60.9 (7), 41.8 (12), 31.5 (11), 26.8 (3C, 1), 19.1 (2), 16.4 (10).
4-Bromo-2-(2-methylprop-1-enyl)furan (261)

Based on a procedure by Joullié et al.[107] Isopropyl(triphenyl)phosphonium iodide (164 mg, 0.38 mmol, 1.2 equiv.) was stirred in THF (2.5 mL) at −78 °C. n-BuLi in hexanes (0.15 mL, 0.38 mmol, 1.2 equiv.) was added dropwise. The solution was allowed to stir at 0 °C for 30 min and then cooled to −78 °C. 4-Bromofuran-2-carbaldehyde (266) (50 mg, 0.31 mmol, 1.0 equiv.) in THF (0.6 mL) was added dropwise and the resulting solution stirred for 1 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL), extracted with Et₂O (2 x 20 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 19 Et₂O : pentane) to afford olefin 261[107] (12 mg, 20%) as a colourless oil:

Rₛ 0.90 (1 : 9 Et₂O : pentane);

IR (neat) νₑₓₘₐₓ 2971 (m, C-H), 2870 (w, C-H), 1738 (m, C-O (furan)), 1365 (m), 1227 (m), 1143 (sh.), 1002 (sh.) cm⁻¹;

HRMS (CI) calc. for C₈H₁₀OBr [M+H]⁺: requires 200.9915, found 200.9907 (Δ –4.0 ppm);

¹H NMR (CDCl₃, 400 MHz) δ 7.33 (s, 1H, 1), 6.22 (s, 1H, 3), 6.02 (s, 1H, 5), 1.97 (s, 3H, 8), 1.93 (s, 3H, 7);

¹³C NMR (CDCl₃, 125 MHz) δ 175.1 (4), 138.5 (1), 137.5 (6), 113.7 (3), 110.1 (5), 100.8 (2), 27.0 (8), 20.1 (7).
6 Experimental

4-Bromo-2-(diethoxymethyl)furan (267)

Based on a procedure by Joullié et al.[107] Aldehyde 266 (100 mg, 0.63 mmol, 1.0 equiv.) was refluxed in EtOH (3.15 mL) with NH₄NO₃ (3 mg, 32 μmol, 5 mol%) and HC(OEt₃) (0.42 mL, 2.52 mmol, 4.0 equiv.) for 2 h. The reaction mixture was allowed to cool to rt and rotary evaporated. The resulting material was suspended between brine (50 mL) and Et₂O (50 mL). The organics were combined, dried (MgSO₄), rotary evaporated and chromatographed (1 : 49 Et₂O : pentane) to afford 4-bromo-2-(diethoxymethyl)furan (267)[107] (120 mg, 77%) as a pale yellow oil:

**Rf** 0.90 (1 : 9 Et₂O : pentane);

**IR** (neat) νmax 2975 (w, C-H), 2885 (w, C-H), 1737 (m, C-O (furan), 1372 (m), 1320 (m), 1218 (m), 1138 (s), 1050 (m) cm⁻¹;

**HRMS** (EI) calc. for C₉H₁₃O₃Br [M+H]+: requires 248.0048, found 248.0041 (Δ –2.8 ppm);

**¹H NMR** (CDCl₃, 400 MHz) δ 7.40 (d, J = 0.5 Hz, 1H, 1), 6.47 (d, J = 0.5 Hz, 1H, 3), 5.49 (s, 1H, 5), 3.66-3.54 (m, 4H, 6), 1.23 (t, J = 8.0 Hz, 6H, 7);

**¹³C NMR** (CDCl₃, 100 MHz) δ 152.8 (4), 140.5 (1), 111.6 (3), 100.0 (2), 95.8 (5), 61.4 (2C, 6), 15.1 (2C, 7);

(E)-6-(t-Butyldiphenylsilyloxy)-1-(5-(diethoxymethyl)furan-3-yl)-4-methylhex-4-en-1-ol (269) and (E)-1-(4-Bromo-2-(diethoxymethyl)furan-3-yl)-6-(t-butyldiphenylsilyloxy)-4-methylhex-4-en-1-ol (268)

4-Bromo-2-(diethoxymethyl)furan (267) (180 mg, 0.73 mmol, 1.0 equiv.) was stirred in THF (2 mL) at –78 °C for 5 min. n-BuLi in hexanes (260 μL, 2.5 M, 0.65 mmol, 0.9 equiv.) was added dropwise and the solution stirred for 15 min. Aldehyde 262 (240 mg, 0.65 mmol, 0.9 equiv.) in THF (0.5 mL) was added dropwise and the resulting solution allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (40 mL), extracted with Et₂O (2 x 30 mL), dried (MgSO₄), rotary evaporated and chromatographed (1 : 9 Et₂O : pentane) to afford alcohol furan 268 (40 mg, 10%) as a clear gum and bromo-alcohol furan 269 (10 mg, 2%) as a colourless oil.

Alcohol-furan 268:

\[ R_f 0.60 \ (4 : 6 \text{ Et}_2\text{O} : \text{pentane}) \]

\[ \text{IR (neat) } v_{\text{max}} 3016 (m, C-H), 2971 (m, C-H), 2945 (m, C-H), 2858 (w, C-H), 1746 (s, C-O (furan)), 1428 (m), 1366 (s), 1229 (s), 1111 (m), 1051 (m) \text{ cm}^{-1}; \]

\[ \text{HRMS (ESI) calc. for C}_{32}\text{H}_{44}\text{O}_5\text{NaSi \ [M+Na]^+}: requires 559.2856, found 559.2863 (Δ +1.3 ppm); \]

\[ ^1\text{H NMR (CDCl}_3, 500 \text{ MHz) } \delta 7.70-7.67 (m, 4H, 3), 7.43-7.36 (m, 6H, 2 & 4), 6.44 (d, } J = 0.5 \text{ Hz, 1H, 15), 5.48 (d, } J = 5.0 \text{ Hz, 1H, 17), 5.41-5.39 (m, 1H, 8), 4.76-4.72 (m, 1H, 21), \]

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4.21 (d, J = 6.0 Hz, 2H, 7), 3.67-3.54 (m, 5H, 13 & 19), 2.09-1.91 (m, 4H, 11 & 12), 1.45 (s, 3H, 9), 1.26-1.20 (m, 6H, 20), 1.05 (s, 9H, 6);

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 151.9 (16), 151.6 (15), 135.9 (10), 135.6 (4C, 2), 134.0 (2C, 1), 129.5 (4C, 3), 127.6 (2C, 4), 124.9 (14), 112.1 (8), 97.7 (17), 95.9 (18), 65.7 (13), 61.6 (2C, 19), 61.0 (7), 35.3 (12), 33.2 (11), 26.8 (3C, 6), 19.2 (5), 16.2 (9), 15.1 (2C, 20).

Bromo-alcohol furan 269:

R$_f$ 0.65 (4 : 6 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2970 (m, C-H), 2930 (m, C-H), 2857 (w, C-H), 1738 (s, C-O (furan)), 1428 (w), 1366 (m), 1217 (sh.), 1110 (sh.), 1047 (m) cm$^{-1}$;

HRMS (ESI) calc. for C$_{32}$H$_{43}$O$_2$NaBrSi [M+Na]$^+$: requires 637.1961, found 637.1953 (Δ – 1.3 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) δ 7.74-7.73 (m, 4H, 3), 7.43-7.39 (m, 6H, 2 & 4), 6.48 (s, 1H, 16), 5.54 (s, 1H, 18), 5.45 (br. s, 1H, 8), 4.60 (m, 1H, 21), 4.27-4.25 (m, 3H, 7 & 13), 3.71-3.60 (m, 4H, 19), 2.57-2.00 (m, 2H, 11), 1.91-1.77 (m, 2H, 12), 1.48 (s, 3H, 10), 1.27 (t, J = 8.0 Hz, 6H, 20), 1.09 (s, 9H, 6);

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 152.4 (17), 138.6 (16), 136.4 (2C, 1), 135.4 (4C, 2), 133.8 (9), 129.4 (2C, 4), 127.5 (4C, 3), 124.3 (8), 106.8 (14), 96.2 (2C, 15 & 18), 66.3 (13), 60.9 (2C, 19), 58.0 (7), 35.4 (11), 35.3 (12), 19.0 (3C, 6), 18.2 (5), 16.2 (10), 15.0 (2C, 20).
Based on a procedure by Tago et al.\textsuperscript{[153]} Aldehyde 262 (1.60 g, 4.34 mmol, 1.0 equiv.) was stirred with NaBH\(_4\) (330 mg, 8.67 mmol, 2.0 equiv.) in EtOH (80 mL) at 0 °C for 3 h. The reaction mixture was rotary evaporated and then quenched with a saturated aqueous solution of NaHCO\(_3\) (100 mL), extracted with EtOAc (2 x 200 mL), the organics combined, dried (MgSO\(_4\)), rotary evaporated and chromatographed (2 : 1 Et\(_2\)O : pentane) to afford alcohol 272 (1.3 g, 81%) as a colourless oil:

\( R_f \) 0.55 (2 : 1 Et\(_2\)O : pentane);

IR (neat) \( \nu_{\text{max}} \) 3343 (br., O-H), 2931 (m, C-H), 2857 (m, C-H), 1473 (sh.), 1428 (sh.), 1112 (sh.), 1052 (s) cm\(^{-1}\);

HRMS (ESI) calc. for C\(_{23}\)H\(_{36}\)NO\(_2\)Si [M+NH\(_4\)]\(^+\): requires 386.2515, found 386.2517 (\( \Delta +0.5\) ppm);

\( ^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 7.70-7.68 (m, 4H, 5), 7.44-7.36 (m, 6H, 4 & 6), 5.43-5.40 (m, 1H, 8), 4.22 (d, \( J = 7.0 \) Hz, 2H, 7), 4.63 (app. q, \( J = 6.0 \) Hz, 2H, 13), 2.05 (t, \( J = 6.0 \) Hz, 2H, 11), 1.69-1.63 (m, 2H, 12), 1.46 (s, 3H, 10), 1.28 (t, \( J = 6.0 \) Hz, 1H, 14), 1.04 (s, 9H, 1);

\( ^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 136.8 (9), 135.6 (2C, 3), 134.0 (4C, 4), 129.5 (2C, 6), 127.6 (4C, 5), 124.4 (8), 62.7 (13), 61.0 (7), 35.7 (11), 30.5 (12), 26.8 (3C, 1), 19.1 (2), 16.2 (10);

Anal. Calc. for C\(_{23}\)H\(_{32}\)O\(_2\)Si: C, 74.95; H, 8.75. Found: C, 74.87; H, 8.75.
Based on a procedure by Joullié et al.\textsuperscript{[107]} Alcohol 272 (1.6 g, 4.3 mmol, 1.0 equiv.) was stirred in CH\textsubscript{2}Cl\textsubscript{2} (25 mL) at 0 °C. Et\textsubscript{3}N (1.2 mL, 8.6 mmol, 2.0 equiv.) was added dropwise followed by MsCl (0.5 mL, 5.64 mmol, 1.3 equiv.) dropwise. The resulting solution was stirred for 30 min and then quenched with a saturated aqueous solution of NH\textsubscript{4}Cl (100 mL), extracted with Et\textsubscript{2}O (2 x 100 mL), the organics combined, washed with brine (100 mL), dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (1 : 1 Et\textsubscript{2}O : pentane) to afford mesylate 320 (1.5 g, 80%) as a colourless oil:

\( R_f \) 0.5 (1 : 1 Et\textsubscript{2}O: pentane);

\textbf{IR} (neat) \( \nu_{max} \) 2931 (w, C-H), 2857 (w, C-H), 1428 (w), 1355 (m), 1173 (m), 1111 (sh.), 1051 (m) cm\textsuperscript{-1};

\textbf{HRMS} (ESI) calc. for C\textsubscript{24}H\textsubscript{34}O\textsubscript{4}NaSi [M+Na]\textsuperscript{+}: requires 469.1845, found 469.1837 (\( \Delta \) –0.2 ppm);

\textbf{\(^1\)H NMR} (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 7.71-7.69 (m, 4H, 3), 7.47-7.39 (m, 6H, 2 & 4), 5.42 (app. td, \( J = 6.0, 0.5 \) Hz, 1H, 8), 4.25-4.19 (m, 4H, 7 & 13), 3.01 (s, 3H, 14), 2.10 (t, \( J = 8.0 \) Hz, 2H, 11), 1.86 (quin. \( J = 8.0 \) Hz, 2H, 12), 1.47 (s, 3H, 9), 1.06 (s, 9H, 6);

\textbf{\(^{13}\)C NMR} (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 135.6 (4C, 2), 135.0 (10), 133.9 (2C, 1), 129.6 (2C, 4), 127.6 (4C, 3), 125.4 (8), 69.5 (13), 60.9 (7), 37.3 (14), 34.9 (11), 26.9 (12), 26.8 (3C, 6), 19.2 (5), 16.1 (9).
Based on a procedure by Joullé et al.\textsuperscript{[107]} Methanesulphonate 320 (1.5 g, 3.4 mmol, 1.0 equiv.) and NaI (504 mg, 3.36 mmol, 1.0 equiv.) were heated at 50 °C in acetone (20 mL) for 18 h. The reaction mixture was quenched with a 1 : 1 mixture of a saturated aqueous solution of Na$_2$S$_2$O$_3$ and a saturated aqueous solution of NaHCO$_3$ (100 mL), extracted with Et$_2$O (2 x 100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 99 Et$_2$O : pentane) to afford iodide 271 (1.15 g, 70%) as a colourless oil.

$R_f 0.90$ (1 : 9 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2930 (m, C-H), 2856 (m, C-H), 1427 (sh.), 1388 (w), 1217 (w), 1110 (s), 1051 (m) cm$^{-1}$;

HRMS (CI) calc. for C$_{23}$H$_{35}$NOSi$[M+\text{NH}_4]^+$: requires 496.1533, found 496.1542 (Å +1.8 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.72-7.71 (m, 4H, 5), 7.46-7.39 (m, 6H, 4 & 6), 5.46-5.43 (m, 1H, 8), 4.25 (d, $J$ = 6.0 Hz, 2H, 7), 3.14 (t, $J$ = 7.0 Hz, 2H, 13), 2.08 (t, $J$ = 7.0 Hz, 2H, 11), 1.91 (quin., $J$ = 7.0 Hz, 2H, 12), 1.44 (s, 3H, 10), 1.07 (s, 9H, 1);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 135.6 (9), 134.9 (2C, 10), 133.9 (4C, 4), 129.5 (2C, 6), 127.6 (4C, 5), 125.4 (8), 61.0 (7), 39.8 (11), 31.3 (12), 26.8 (3C, 1), 19.1 (2), 16.1 (10), 6.4 (13);

Anal. Calc. for C$_{23}$H$_{31}$SiO: C, 57.73; H, 6.53. Found: C, 57.85; H, 6.62.
Based on a procedure by Joullié et al.\textsuperscript{[107]} 4-Bromo-2-(diethoxymethyl)furan (267) (270 mg, 1.09 mmol, 2.0 equiv.) was stirred in THF (4 mL) at \(-78 \, ^\circ C\) for 5 min. \(n\)-BuLi in hexanes (0.9 mL, 1.2 M, 1.09 mmol, 2.0 equiv.) was added dropwise and the solution stirred for 5 min. HMPA (0.25 mL, 1.42 mmol, 2.6 equiv.) was added dropwise and the solution stirred for 30 min. Iodide-olefin 271 (261 mg, 0.55 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise and the resulting solution allowed to warm to rt and stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH\(_4\)Cl (50 mL), extracted with Et\(_2\)O (2 x 50 mL), dried (MgSO\(_4\)), rotary evaporated and chromatographed (1 : 29 to 3 : 27 Et\(_2\)O : pentane) to afford furan 270 (175 mg, 60\%) as a clear gum and bromo-furan 273 (32 mg, 10\%) as a clear oil:

**Furan 270:**

\[ R_f 0.70 (1 : 9 \text{ Et}_2\text{O} : \text{pentane}); \]

\[ \text{IR (neat)} \ \nu_{\text{max}} \ 2930 \, (w, \ \text{C-H}), \ 2857 \, (w, \ \text{C-H}), \ 1683 \, (w), \ 1461 \, (w), \ 1427 \, (w), \ 1361 \, (s), \ 1109 \, (s), \ 1051 \, (s), \ 1005 \, (m) \ \text{cm}^{-1}; \]

\[ \text{HRMS (ESI) calc. for C}_{32}\text{H}_{40}\text{O}_3\text{NaSi} [\text{M+Na}]^+: \text{requires 559.2856, found 599.2856 (}\Delta 0.0 \text{ ppm)}; \]
6 Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.71-7.69 (m, 4H, 3), 7.42-7.36 (m, 6H, 2 & 4), 7.17 (d, $J = 0.5$ Hz, 1H, 15), 6.30 (br. s, 1H, 17), 5.50 (s, 1H, 18), 5.40-5.37 (m, 1H, 8), 4.24 (d, $J = 6.0$ Hz, 2H, 7), 3.67-3.58 (m, 4H, 19), 2.35 (t, $J = 7.0$ Hz, 2H, 13), 2.00 (d, $J = 7.0$ Hz, 2H, 11), 1.63 (quin. $J = 7.0$ Hz, 2H, 12), 1.44 (s, 3H, 9), 1.25 (t, $J = 8.0$ Hz, 6H, 20), 1.05 (s, 9H, 6);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 151.8 (16), 138.6 (15), 136.7 (10), 135.6 (4C, 3), 134.1 (2C, 1), 129.5 (2C, 4), 127.6 (4C, 2), 125.5 (14), 124.4 (8), 109.4 (17), 96.4 (18), 61.3 (2C, 19), 61.1 (7), 38.9 (11), 27.7 (12), 26.8 (3C, 6), 24.3 (13), 19.2 (5), 19.2 (9), 15.15 (2C, 20).

Bromo-furan 273:

R$_f$ 0.75 (1 : 9 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2930 (w, C-H), 2856(w, C-H), 1684 (m, C=O (furan)), 1518 (w), 1427 (w), 1283 (w), 1109 (m), 1057 (m) cm$^{-1}$;

HRMS (ESI) C$_{32}$H$_{43}$O$_3$NaSiBr [M+Na]$^+$: requires 621.2012, found 621.2013 ($\Delta$ +0.2 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.70-7.68 (m, 4H, 3), 7.41-7.36 (m, 6H, 2 & 4), 6.38 (s, 1H, 16), 5.45 (s, 1H, 18), 5.40-5.38 (m, 1H, 8), 4.22 (d, $J = 6.0$ Hz, 2H, 7), 3.65-3.54 (m, 4H, 19), 2.59 (t, $J = 7.0$ Hz, 2H, 13), 1.99 (t, $J = 7.0$ Hz, 2H, 11), 1.72 (quin, $J = 7.0$ Hz, 2H, 12), 1.42 (s, 3H, 10), 1.22 (t, $J = 8.0$ Hz, 6H, 20), 1.04 (s, 9H, 6);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 152.8 (17), 150.1 (16), 136.2 (9), 135.6 (4C, 2), 134.0 (2C, 1), 129.5 (2C, 4), 127.6 (4C, 3), 124.7 (14), 111.8 (15), 96.3 (8), 96.0 (18), 61.3 (2C, 19), 61.1 (11), 38.7 (7), 26.8 (3C, 6), 25.7 (12), 25.6 (13), 19.2 (5), 16.1 (10), 15.1 (2C, 20).
(E)-4-(6-(t-Butyldiphenylsilyloxy)-4-methylhex-4-enyl)furan-2-carbaldehyde (274)

Method 1: Diethoxymethyl-furan 270 (190 mg, 0.35 mmol, 1.0 equiv.) was stirred in 1 M HCl (1 mL) and THF (1 mL) at rt for 30 min. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (10 mL), extracted with Et₂O (2 x 10 mL), dried (MgSO₄) and rotary evaporated to afford aldehyde 274 (141 mg, 89%) as a colourless oil:

Rf 0.40 (2 : 9 Et₂O : pentane);

IR (neat) νmax 2931 (m, C-H), 2856 (m, C-H), 1683 (s, C=O), 1504 (sh.), 1428 (sh.), 1384 (w), 1110 (s), 1059 (m) cm⁻¹;

HRMS calc. for C₂₈H₃₈NO₃Si [M+NH₄]⁺: requires 464.2621, found 464.2638 (Δ +3.7 ppm);

¹H NMR (CDCl₃, 500 MHz) δ 9.60 (s, 1H, 19), 7.70-7.68 (m, 4H, 3), 7.45 (s, 1H, 15) 7.42-7.35 (m, 6H, 2 & 4), 7.11 (s, 1H, 17), 5.39-5.36 (m, 1H, 8), 4.24 (d, J = 6.0 Hz, 2H, 7), 2.42 (t, J = 7.0 Hz, 2H, 13), 2.01 (t, J = 7.0 Hz, 2H, 11), 1.67 (quin. J = 7.0 Hz, 2H, 12), 1.44 (s, 3H, 9), 1.05 (s, 9H, 6);

¹³C NMR (CDCl₃, 125 MHz) δ 177.9 (18), 152.9 (16), 144.9 (15), 136.1 (10), 135.6 (4C, 2), 133.9 (2C, 1), 129.5 (2C, 4), 128.2 (14), 127.6 (4C, 3), 124.8 (2C, 8 & 17), 61.0 (7), 38.6 (11), 27.5 (12), 26.8 (3C, 6), 23.8 (13), 19.2 (5), 16.1 (9).

Method 2: Based on a procedure by Gregg et al.[¹⁶³] Diethoxymethyl-furan 270 (500 mg, 0.91 mmol, 1.0 equiv.) was stirred in acetone (18.2 mL) for 5 min. In(OTf)₃ (51 mg, 90 μmol, 0.1 equiv.) was added and the resulting solution stirred for 5 min. The reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL), extracted with Et₂O (2 x 50 mL), the
organics combined, dried (MgSO$_4$) and rotary evaporated to afford aldehyde 274 (380 mg, 93%) as a colourless oil. The product was used without further purification. Characterised as described previously.

\[(E)-t\text{-Butyl}(3\text{-methyl}-6-(5-(2\text{-methylprop-1-}t\text{-enyl)furan-3-yl})\text{hex-2-}t\text{enyloxy)diphenylsilane (259)}\]

Based on a procedure by Joullié et al.$^{[107]}$ Isopropyltriphenylphosphonium iodide (182 mg, 0.42 mmol, 1.2 equiv.) was stirred in THF (3.5 mL) at –78 °C. n-BuLi in hexanes (0.35 mL, 1.2 M, 0.42 mmol, 1.2 equiv.) was added dropwise and the solution turned orange. The resulting solution was stirred at 0 °C for 30 min and the colour turned deep red. The reaction mixture was cooled to –78 °C and aldehyde 274 (141 mg, 0.32 mmol, 1.0 equiv.) in THF (0.5 mL) was added dropwise and the resulting solution stirred for 30 min. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (20 mL), extracted with Et$_2$O (2 x 40 mL), the organics combined, washed with brine (30 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 98 Et$_2$O : pentane) to afford olefin 259 (120 mg, 70%) as a colourless oil:

$R_f$ 0.95 (1:9 Et$_2$O : pentane);

IR (neat) $v_{\text{max}}$, 2930 (m, C-H), 2856 (m, C-H), 1472 (w), 1428 (w), 1261 (w), 1111 (sh.), 1059 (m) cm$^{-1}$;

HRMS (CI) calc. for C$_{31}$H$_{41}$O$_2$Si [M+H]$^+$: requires 473.2876, found 473.2874 (Δ –0.4 ppm);
6 Experimental

$^1$H NMR (CDCl$_3$, 400 MHz) δ 7.72-7.70 (m, 4H, 3), 7.44-7.38 (m, 6H, 2 & 4), 7.11 (s, 1H, 15), 6.07 (s, 1H, 17), 6.04 (s, 1H, 18), 5.40 (t, J = 6.0 Hz, 1H, 8), 4.25 (d, J = 6.0 Hz, 2H, 7), 2.37 (t, J = 8.0 Hz, 2H, 13), 2.02 (t, J = 8.0 Hz, 2H, 11), 2.00 (s, 3H, 19 / 20), 1.91 (s, 3H, 19 / 20), 1.65 (quin. J = 8.0 Hz, 2H, 12), 1.45 (s, 3H, 9), 1.06 (s, 9H, 6);

$^{13}$C NMR (CDCl$_3$, 100 MHz) δ 153.7 (16), 136.8 (21), 135.6 (4C, 2), 134.8 (2C, 1), 134.1 (2C, 10 & 15), 129.5 (2C, 4), 127.6 (4C, 3), 126.4 (14), 124.4 (8), 114.6 (18), 108.7 (17), 61.13 (7), 38.9 (11), 27.9 (12), 27.0 (13), 26.9 (3C, 6), 24.4 (20), 20.1 (5), 19.2 (19), 16.2 (9).

$(E)$-3-Methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-en-1-ol (275)

Silylether 259 (60 mg, 0.12 mmol, 1.0 equiv.) was stirred in THF (0.6 mL) and TBAF (0.2 mL, 0.18 mmol, 1.5 equiv.) was added dropwise. The resulting solution was stirred for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO$_3$ (20 mL), extracted with Et$_2$O, the organics combined, washed with brine (10 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 Et$_2$O : pentane) to afford alcohol 275 (25 mg, 81%) as a colourless gum:

R$_f$ 0.42 (1 : 1 Et$_2$O : pentane);

IR (neat) $\nu_{\text{max}}$ 3453 (br., O-H) 2970 (m, C-H), 2937 (m, C-H), 2867 (w, C-H), 1739 (s, C=O (furan)), 1441 (w), 1366 (m), 1217 (m), 1229 (m), 1206 (m) cm$^{-1}$;

HRMS (EI) calc. for C$_{15}$H$_{22}$O$_2$ [M+H]$^+$: requires 234.1620, found 234.1635 (Δ +6.4 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) δ 7.10 (s, 1H, 10), 6.04 (s, 1H, 11), 6.01 (s, 1H, 13), 5.43-5.40 (m, 1H, 3), 2.31 (d, J = 6.0 Hz, 2H, 2), 2.59 (br. s, 1H, 1), 2.37 (t, J = 8.0 Hz, 2H, 8), 2.09-
Experimental

2.04 (m, 2H, 6), 1.96 (s, 3H, 15 / 16), 1.88 (s, 3H, 15 / 16), 1.80-1.70 (m, 2H, 7), 1.67 (s, 3H, 5);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 153.7 (12), 139.6 (14), 136.8 (10), 134.9 (4), 126.3 (3), 123.5 (9), 114.5 (13), 108.6 (11), 59.4 (2), 39.0 (6), 27.9 (7), 27.0 (8), 24.5 (16), 20.1 (15), 16.2 (5).

3-Oxo-3-(2-(trimethylsilyl)ethoxy)propanoic acid (281)

Based on a procedure by Tararov et al.$^{[74]}$ Meldrum's acid (30.0 g, 208 mmol, 1.0 equiv.) and 2-(trimethylsilyl)ethanol (280) (36.8 g, 312 mmol, 1.5 equiv.) were heated at 100 °C for 8 h. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$ (200 mL) and the resulting solution stirred for 8 h at rt. The reaction mixture was extracted with Et$_2$O : hexanes (1:1, 3 x 150 mL), the aqueous acidified to pH 3 using 1 M HCl, extracted with EtOAc (3 x 200 mL), dried (MgSO$_4$) and rotary evaporated to afford carboxylic acid 281$^{[203]}$ (38.0 g, 90%) as a yellow oil:

R$_f$ 0.45 (1 : 1 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2954 (m, C-H), 1736 (s, C=O), 1380 (w), 1322 (w), 1249 (m), 1217 (w), 1151 (m) cm$^{-1}$;

HRMS (El) calc. for C$_8$H$_{16}$O$_3$Si [M+H]$^+$: requires 204.0818, found 204.0826 ($\Delta$ +3.9 ppm);

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 9.68 (br. s, 1H, 1), 4.30 (t, $J = 8.0$ Hz, 2H, 5), 3.44 (s, 2H, 4), 1.06 (t, $J = 8.0$ Hz, 2H, 6), 0.07 (s, 9H, 7);

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 167.8 (2), 166.9 (4), 64.7 (5), 40.3 (3), 17.2 (6), −1.6 (3C, 7).
Experimental

2-(Trimethylsilyl)ethyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (278)

![Structural formula of 278]

Based on a procedure by Navarro et al.\textsuperscript{[82]} Carboxylic acid 281 (3.0 g, 14.4 mmol, 1.0 equiv.) was stirred in CH\textsubscript{2}Cl\textsubscript{2} (30 mL) for 1 min. Oxalyl chloride (2.5 mL, 28.8 mmol, 2.0 equiv.) and DMF (60 μL, 1.44 mmol, 0.1 equiv.) were added at 0 °C and the reaction mixture stirred for 30 min. The reaction mixture was rotary evaporated to afford acid chloride 279 (3.0 g, 93%) which was used crude in the next step.

n-BuLi in hexanes (18.0 mL, 44.6 mmol, 2.5 M, 3.1 equiv.) was added to HMDS (9.6 mL, 46.1 mmol, 3.2 equiv.) in THF (500 mL) at −78 °C and the resulting solution stirred for 30 min. Dioxinone 33 (5.7 mL, 43.2 mmol, 3.0 equiv.) was added dropwise and the resulting solution stirred for 1 h. Acid chloride 279 was added in THF (20 mL) and the resulting solution stirred for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NH\textsubscript{4}Cl (20 mL), acidified to pH 2 using 1 M HCl, extracted with Et\textsubscript{2}O (2 x 300 mL), the organics combined, washed with brine (200 mL), dried (MgSO\textsubscript{4}), rotary evaporated and chromatographed (2 : 8 to 1 : 1 Et\textsubscript{2}O : pentane) to afford ketoester-dioxinone 278 (2.6 g, 55%) as a yellow oil:

\begin{align*}
R_f & 0.45 (1 : 1 \text{ Et}_2\text{O} : \text{pentane}); \\
\text{IR} \ (\text{neat}) & \nu_{\text{max}} 2954 \ (\text{w, C-H}), 1719 \ (\text{s, C=O}), 1638 \ (\text{m, C=C}), 1390 \ (\text{m}), 1319 \ (\text{m}), 1271 \ (\text{m}), 1249 \ (\text{m}), 1201 \ (\text{m}), 1176 \ (\text{sh.}), 1015 \ (\text{sh.}) \ \text{cm}^{-1}; \\
\text{HRMS (ESI) calc. for C}_{15}\text{H}_{23}\text{O}_6\text{Si} [M+H]^+: & \text{requires 327.1264, found 327.1287 (}\Delta +7.0 \ \text{ppm});
\end{align*}
6 Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.34 (s, 1H, 2), 4.23-4.19 (m, 2H, 11), 3.48 (s, 2H, 9), 3.47 (s, 2H, 7), 1.68 (s, 6H, 5 & 6), 1.00-0.97 (m, 2H, 12), 0.02 (s, 9H, 13);

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 195.7 (8), 166.4 (1), 163.6 (10), 160.4 (3), 107.2 (4), 96.9 (2), 64.1 (11), 49.2 (9), 46.9 (7), 24.9 (2C, 5 & 6), 17.2 (12), –1.4 (3C, 13).

Based on a procedure by Navarro et al.$^{[82]}$ Ketoester-dioxinone 278 (470 mg, 1.41 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (2 mL) was added to MgCl$_2$ (353 mg, 2.50 mmol, 2.5 equiv.) and pyridine (0.31 mL, 3.81 mmol, 2.7 mmol) in CH$_2$Cl$_2$ (7 mL) at 0 °C for 20 min. Acetyl chloride (150 $\mu$L, 2.12 mmol, 1.5 equiv.) was added dropwise and the resulting solution stirred for 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (50 mL), extracted with Et$_2$O (2 x 50 mL), dried (MgSO$_4$), rotary evaporated, chromatographed (1 : 1 : 4 CH$_2$Cl$_2$ : EtOAc : pentane) to afford diketo-ester-dioxinone 276 (402 mg, 77%) as a yellow oil:

$R_F$ 0.65 (1 : 1 Et$_2$O : pentane);

IR (neat) $\nu_{\text{max}}$ 2954 (w, C-H), 1730 (s, C=O), 1639 (m, C=C), 1391 (m), 1376 (m), 1272 (m), 1250 (m), 1204 (w), 1071 (w), 1016 (w) cm$^{-1}$;

HRMS (Cl) calc. for C$_{17}$H$_{27}$O$_7$Si [M+H]$^+$: 388.1792, found 388.1798 ($\Delta$ +1.5 ppm);
Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 17.58 (s, 1H, 16), 5.34 (s, 1H, 2), 4.31-4.28 (m, 2H, 11), 3.73 (s, 2H, 7), 2.42 (s, 3H, 15), 1.70 (s, 6H, 5 & 6), 1.09-1.05 (m, 2H, 12), 0.07 (s, 9H, 13);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 195.7 (14), 193.4 (8), 166.4 (1), 165.2 (10), 160.7 (3), 108.7 (4), 107.2 (9), 96.5 (2), 63.5 (11), 43.1 (7), 25.5 (15), 24.9 (2C, 5 & 6), 17.6 (12), -1.6 (3C, 13).

$(E)$-3-Methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-enyl acetate (277)

Based on a procedure by Tago et al.$^{[153]}$ Alcohol 275 (30 mg, 0.13 mmol, 1.0 equiv.) was stirred in EtOAc (1.0 mL). K$_2$CO$_3$ (36 mg, 0.26 mmol, 2.0 equiv.), 1 micro stapula head tip of DMAP and Ac$_2$O (24 μL, 0.26 mmol, 2.0 equiv.) were added and the resulting solution stirred for 2 h. The reaction mixture was filtered and the filtrate rotary evaporated. The resulting residue was suspended between EtOAc (20 mL) and a saturated aqueous solution of NaHCO$_3$ (20 mL), the organics combined, washed with brine (10 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (3 : 7 Et$_2$O : pentane) to afford acetate 277 (20 mg, 60%) as a clear gum:

R$_f$ 0.52 (2 : 8 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2938 (w, C-H), 1736 (s, C=O), 1442 (w), 1382 (w), 1233 (m), 1166 (w), 1023 (m) cm$^{-1}$;

HRMS (EI) calc. for C$_{17}$H$_{24}$O$_3$ [M+H]$^+$: requires 276.1725, found 276.1739 ($\Delta$ +5.1 ppm);
6 Experimental

$^1$H NMR (CDCl$_3$, 400 MHz) δ 7.12 (s, 1H, 11), 6.06 (s, 1H, 12), 6.03 (s, 1H, 14), 5.37 (t, $J = 7.0$ Hz, 1H, 4), 4.61 (d, $J = 7.0$ Hz, 2H, 3), 2.39 (t, $J = 8.0$ Hz, 2H, 9), 2.11-2.07 (m, 5H, 1 & 7), 1.99 (s, 3H, 16 / 17), 1.91 (s, 3H, 16 / 17), 1.74-1.66 (m, 5H, 6 & 8);

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 171.1 (2), 153.7 (13), 142.0 (15), 136.8 (11), 134.9 (5), 126.2 (10), 119.3 (4), 114.5 (14), 108.6 (12), 60.4 (3), 38.7 (7), 26.9 (8), 25.8 (9), 25.3 (17), 24.6 (1), 24.4 (16), 22.2 (6).

(E)-2-(Trimethylsilyl)ethyl 7-hydroxy-2,2,5-trimethyl-8-(3-methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-enyl)-4-oxo-4H-benzo[d][1,3]dioxine-6-carboxylate (283)

Furan acetate 277 (80 mg, 0.29 mmol, 1.0 equiv.) and diketo-ester-dioxinone 276 (90 mg, 0.24 mmol, 1.2 equiv.) were stirred in THF (3 mL). Pd(PPh$_3$)$_4$ (27 mg, 24 μmol, 0.1 equiv.) was added and the resulting solution stirred for 48 h. TBAF in THF (1.45 mL, 1.0 M, 1.45 mmol, 5.0 equiv.) was added and the resulting solution heated at 55 °C for 2 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (50 mL), extracted with Et$_2$O (2 x 50 mL), the organics combined, washed with brine (20 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 8 Et$_2$O : pentane) to afford furan-resorcylate 283 (89 mg, 65%) as a colourless oil:

$R_f$ 0.70 (3 : 7 Et$_2$O : pentane);
6 Experimental

IR (neat) $v_{\text{max}}$ 2933 (m, C-H), 1733 (sh., C=O), 1653 (sh., C=C), 1584 (sh., C=C), 1448 (w), 1387 (w), 1265 (sh.), 1234 (sh.), 1173 (w), 1031 (w) cm$^{-1}$;

HRMS (Cl) calc. for C$_{32}$H$_{45}$O$_7$Si [M+H]$^+$: requires 425.2328, found 425.2319 (Δ –2.1 ppm);

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 11.92 (s, 1H, 31), 7.05 (s, 1H, 24), 6.01 (s, 1H, 25), 5.99 (br. s, 1H, 27), 5.16-5.12 (m, 1H, 17), 4.49-4.45 (m, 2H, 13), 3.31 (d, $J$ = 7.0 Hz, 2H, 16), 2.88 (s, 3H, 7), 2.32 (t, $J$ = 8.0 Hz, 2H, 22), 1.99 (t, $J$ = 8.0 Hz, 2H, 20), 1.88 (s, 3H, 30), 1.76 (s, 3H, 29), 1.69 (s, 3H, 19), 1.68 (s, 6H, 10 & 11), 1.60-1.56 (m, 2H, 21), 1.21-1.15 (m, 2H, 14), 0.09 (s, 9H, 15);

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 171.7 (12), 164.6 (8), 160.3 (2), 158.0 (4), 153.6 (26), 146.7 (28), 136.7 (6), 135.5 (24), 134.8 (18), 126.4 (23), 121.3 (17), 115.4 (3), 114.5 (27), 110.8 (25), 108.7 (5), 106.4 (1), 104.6 (9), 64.8 (13), 39.2 (20), 28.1 (21 / 22), 26.9 (22 / 21), 25.8 (2C, 10 & 11), 24.4 (29), 20.3 (30), 20.1 (2C, 7 & 16), 17.5 (14), 16.0 (19), -1.6 (3C, 15).

$(2E,6E)$-3,7,11-Trimethyldodeca-2,6,10-trienyl acetate (284)

Based on a procedure by Tago et al.$^{[153]}$ Farnesyl alcohol 285 (1.0 g, 4.5 mmol, 1.0 equiv.) was stirred in EtOAc (35 mL), K$_2$CO$_3$ (1.24 g, 9.0 mmol, 2.0 equiv.), 1 micro spatula head tip of DMAP (cat.) and Ac$_2$O (0.85 mL, 9.0 mmol, 2.0 equiv.) were added and the resulting solution stirred for 18 h. The reaction mixture was filtered and the filtrate rotary evaporated. The resulting residue was suspended between EtOAc (100 mL) and a saturated aqueous solution of NaHCO$_3$ (100 mL), the organics combined, washed with brine (50 mL), dried (MgSO$_4$) and rotary evaporated to afford acetate 284$^{[203]}$ (1.0 g, 85%) as a colourless oil: $R_f$ 0.9 (1 : 9 Et$_2$O : pentane);
**6 Experimental**

IR (neat) $v_{\text{max}}$ 2970 (m, C-H), 2924 (m, C-H), 1740 (s, C=O), 1441 (w), 1365 (m), 1228 (s), 1021 (w), 954 (w) cm$^{-1}$;

**HRMS (EI)** calc. for C$_{17}$H$_{28}$O$_2$ [M+H]$^+$: requires 264.2089, found 264.2094 (Δ +1.9 ppm);

**$^1$H NMR** (CDCl$_3$, 400 MHz) $\delta$ 5.36 (t, $J = 7.0$ Hz, 1H, 4), 5.12 (br. s, 2H, 9 & 14), 4.61 (d, $J = 7.0$ Hz, 2H, 3), 2.15-2.05 (m, 9H, 1, 7, 8, 12, 13), 1.73 (s, 3H, 6), 1.70 (s, 3H, 11), 1.62 (s, 6H, 16 & 17);

**$^{13}$C NMR** (CDCl$_3$, 100 MHz) $\delta$ 171.1 (2), 142.3 (5), 135.5 (10), 131.3 (15), 124.3 (9), 123. (14), 118.2 (4), 61.4 (3), 39.7 (12), 39.5 (7), 26.7 (8), 26.2 (13), 25.7 (17), 21.1 (1), 17.7 (16), 16.5 (11), 16.0 (6).

**2-(Trimethylsilyl)ethyl 7-hydroxy-2,2,5-trimethyl-4-oxo-8-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)-4H-benzo[d][1,3]dioxine-6-carboxylate (285)**

Acetate 284 (120 mg, 0.45 mmol, 1.0 equiv.) and diketo-ester-dioxinone 276 (200 mg, 0.54 mmol, 1.2 equiv.) were stirred in THF (3 mL). Pd(PPh$_3$)$_4$ (52 mg, 45 μmol, 0.1 equiv.) was added and the resulting solution stirred for 36 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (50 mL), extracted with Et$_2$O (2 x 50 mL), the organics combined, washed with brine (20 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (2 : 8 Et$_2$O : pentane) to afford silylester-farnesyl-resorcylate 285 (150 mg, 60%) as a colourless oil:
Based on a procedure by Tararov et al.\textsuperscript{[74]} Meldrum’s acid (6.5 g, 45 mmol, 1.0 equiv.) and farnesyl 285 (11 mL, 45 mmol, 1.0 equiv.) were heated at 80 °C for 6 h. The reaction was quenched with a saturated aqueous solution of NaHCO\textsubscript{3} (100 mL) and the resulting solution stirred for 30 min at rt. The reaction mixture was extracted with EtOAc (2 x 200 mL) and the aqueous acidified to pH 3 using 1 M HCl. The resulting aqueous was extracted with EtOAc (3 x 200 mL), the organics combined, dried (MgSO\textsubscript{4}) and rotary evaporated to afford carboxylic acid 295\textsuperscript{[204]} (11.0 g, 81%) as a colourless oil:
6 Experimental

**IR** (neat) $v_{\text{max}}$ 3521 (br. O-H), 2922 (m, C-H), 1719 (s, C=O), 1382 (m), 1151 (s) cm$^{-1}$;

**HRMS** (CI) calc. for C$_{18}$H$_{32}$NO$_4$ [M+NH$_4]^+$: requires 326.2331, found 326.2328 (Δ –0.9 ppm);

**$^{1}$H NMR** (CDCl$_3$, 400 MHz) $\delta$ 10.25 (br. s, 1H, 1), 5.37 (t, $J$ = 7.0 Hz, 1H, 6), 5.11 (t, $J$ = 7.0 Hz, 2H, 11 & 16), 4.73 (d, $J$ = 7.0 Hz, 2H, 5), 3.46 (s, 2H, 3), 2.14-1.97 (m, 8H, 9, 10, 14 & 15), 1.71 (s, 3H, 19), 1.70 (s, 3H, 8 / 13), 1.62 (s, 6H, 8 / 13 & 18);

**$^{13}$C NMR** (CDCl$_3$, 100 MHz) $\delta$ 172.0 (2), 168.2 (4), 143.8 (7), 135.6 (12), 131.4 (17), 124.3 (11), 123.5 (16), 117.2 (6), 63.0 (5), 40.1 (3), 39.7 (14), 39.5 (9), 26.7 (15), 26.1 (10), 25.7 (19), 17.7 (18), 16.5 (13), 16.0 (8).

(2$^E$,6$^E$)-3,7,11-Trimetyldodeca-2,6,10-trienyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (293)

Based on a procedure by Navarro et al.$^{[82]}$ Acid 295 (4.0 g, 13 mmol, 1.0 equiv.) was stirred in CH$_2$Cl$_2$ (40 mL) and amylene (44.0 mL, 400 mmol, 30 equiv.) at 0 °C for 5 min. Oxalyl chloride (1.4 mL, 16 mmol, 1.2 equiv.) and 4 small drops of DMF (cat.) were added and the reaction mixture stirred for 30 min at 0 °C followed by 30 min at rt. The reaction mixture was rotary evaporated to afford acid chloride 294 as a yellow oil which was used without further purification.

HMDS (8.7 mL, 42 mmol, 3.2 equiv.) was stirred in THF (300 mL) at –78 °C. n-BuLi in hexanes (16.2 mL, 41.0 mmol, 2.5 M, 3.1 equiv.) was added dropwise and the mixture stirred
6 Experimental

for 30 min. Dioxinone 33 (5.2 mL, 40 mmol, 3.0 equiv.) was added dropwise and the solution was stirred for 1 h. Acid chloride 294 in THF (10 mL) was added dropwise to the stirring solution. The reaction mixture was stirred for 2 h and then quenched with a saturated aqueous solution of NH₄Cl (150 mL), acidified to pH 3 utilising 1 M HCl and extracted with EtOAc (3 x 100 mL). The organics were combined, washed with brine (100 mL), dried (MgSO₄), rotary evaporated and chromatographed (7 : 3 hexanes : Et₂O) to afford keto-farnesylester-dioxinone 293 (1.09 g, 65%) as a yellow oil:

Rf 0.35 (1 : 2 hexanes : Et₂O);

IR (neat) v max 2917 (w, C-H), 1722 (sh., C=O), 1638 (m, C=C), 1374 (m), 1203 (sh.), 1015 (sh.) cm⁻¹;

HRMS (EI) calc. for C₂₅H₃₆O₆ [M+H]+: requires 432.2512, found 432.2518 (Δ +1.4 ppm);

¹H NMR (CDCl₃, 400 MHz) δ 5.38-5.32 (m, 2H, 2 & 12), 5.12-5.09 (m, 2H, 17 & 22), 4.69 (d, J = 7.0 Hz, 2H, 11), 3.53 (s, 2H, 9), 3.52 (s, 2H, 7), 2.14-1.97 (m, 8H, 15, 16, 20 & 21), 1.73 (s, 9H, 14, 19 & 25), 1.70 (s, 3H, 24), 1.62 (s, 6H, 5 & 6);

¹³C NMR (CDCl₃, 100 MHz) δ 195.7 (8), 166.4 (1), 163.5 (10), 143.7 (13), 135.6 (3), 131.4 (18), 124.3 (23), 123.4 (17), 117.8 (22), 117.3 (12), 107.2 (4), 97.1 (2), 62.6 (11), 49.1 (9), 46.9 (7), 39.5 (20), 39.4 (15), 26.7 (16), 26.2 (21), 25.7 (25), 24.9 (2C, 5 & 6), 17.7 (24), 16.5 (19), 16.0 (14).
Based on a procedure by Navarro et al.\textsuperscript{[82]} Keto-farnesylester-dioxinone 293 (2.0 g, 4.6 mmol, 1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) was added to a solution of MgCl\textsubscript{2} (1.10 g, 11.5 mmol, 2.5 equiv.) and pyridine (1.0 mL, 12.5 mmol, 2.7 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (13 mL) and the resulting solution stirred at 0 °C for 20 min. Acetyl chloride (0.5 mL, 7.0 mmol, 1.5 equiv.) was added and the mixture stirred for 30 min at 0 °C and 30 min at rt. The reaction mixture was quenched with a saturated aqueous solution of NH\textsubscript{4}Cl (100 mL), extracted with Et\textsubscript{2}O (2 x 100 mL), the organics combined, dried (MgSO\textsubscript{4}) and rotary evaporated to afford diketo-farnesylester-dioxinone 292 (2.1 g, 98%) as a yellow oil:

\[ \text{Rf} 0.61 (7 : 3 \text{Et}_2\text{O} : \text{pentane}); \]

\[ \text{IR (neat)} \nu_{\text{max}} 3923 (w, \text{C}-\text{H}), 1729 (s, \text{C}=\text{O}), 1709 (s, \text{C}=\text{O}), 1638 (m, \text{C}=\text{C}), 1390 (m), 1374 (s), 1270 (sh.), 1203 (sh.), 1069 (m), 1014 (sh.) \text{cm}^{-1}; \]

HRMS (ESI) calc. for C\textsubscript{27}H\textsubscript{38}O\textsubscript{7}Na [M+Na]\textsuperscript{+}: requires 497.2515, found 497.2516 (Δ +0.2 ppm);

\[ ^1\text{H NMR} (\text{CDCl}_3, 400 \text{MHz}) \delta 17.61 (s, 1\text{H}, 28), 5.42 (t, 1\text{H}, J = 7.0 \text{Hz}, 12), 5.36 (s, 1\text{H}, 2), 5.11 (br. s, 2\text{H}, 17 \& 22), 4.77 (d, J = 7.0 \text{Hz}, 2\text{H}, 11), 3.75 (s, 2\text{H}, 7), 2.43 (s, 3\text{H}, 27), 2.16-1.97 (m, 8\text{H}, 15, 16, 20 \& 21), 1.77 (s, 3\text{H}, 25), 1.72 (s, 6\text{H}, 14 \& 19), 1.70 (s, 3\text{H}, 24), 1.62 (s, 6\text{H}, 5 \& 6); \]

\[ ^{13}\text{C NMR} (\text{CDCl}_3, 100 \text{MHz}) \delta 195.8 (26), 193.5 (26), 165.2 (1), 160.8 (10), 143.6 (13), 135.7 (3), 132.5 (18), 124.2 (23), 123.4 (17), 117.6 (22), 108.5 (12), 107.2 (4), 96.5 (2\text{C}, 2 \& 9), \]
6 Experimental

61.9 (11), 43.1 (7), 39.5 (2C, 15 & 20), 26.7 (27), 26.2 (16), 25.7 (21), 25.5 (25), 25.0 (2C, 5 & 6), 17.7 (24), 16.6 (14 / 19), 16.0 (14 / 19).

7-Hydroxy-2,2,5-trimethyl-8-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)-4H-benzo[d][1,3]dioxin-4-one (286)

Diketo-farnesylester-dioxinone 292 (900 mg, 2.11 mmol, 1.0 equiv.) was stirred in THF (20 mL), Pd(PPh₃)₄ (244 mg, 0.21 mmol, 0.1 equiv.) and Cs₂CO₃ (2.1 g, 6.3 mmol, 3.0 equiv.) were added and the resulting solution stirred at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (100 mL), extracted with Et₂O (2 x 50 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (3 : 7 Et₂O : pentane) to afford farnesyl-resorcylate 286 (574 mg, 66%) as a pale yellow solid.

m.p. 180-184 °C (pentane);
Rₚ 0.40 (1 : 1 Et₂O : pentane);
IR (neat) vₘₐₓ 3282 (br., O-H), 2924 (m, C-H), 2854 (m, C-H), 1728 (sh., C=O), 1696 (sh., C=O), 1607 (sh., C=C), 1514 (sh., C=C), 1451 (m), 1410 (m), 1376 (m), 1275 (s), 1209 (s), 1166 sh.), 1107 (sh.), 1044 (w) cm⁻¹;
HRMS (ESI) calc. for C₂₆H₃₅O₄ [M+H]⁺: requires 411.2542, found 411.2535 (Δ +1.7 ppm);
¹H NMR (CDCl₃, 400 MHz) δ 6.39 (s, 1H, 12), 5.86 (s, 1H, 5), 5.21-5.19 (m, 1H, 14), 5.09-5.05 (m, 2H, 19 & 24), 3.33 (d, J = 8.0 Hz, 2H, 13), 2.59 (s, 3H, 7), 2.13-1.94 (m, 8H, 17, 18,
Experimental

22, & 23), 1.80 (s, 3H, 16), 1.68 (s, 6H, 21 & 27), 1.67 (s, 3H, 26), 1.59 (s, 3H, 10 / 11), 1.58 (s, 3H, 10 / 11);

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 160.9 (8), 160.0 (4), 156.0 (2), 142.9 (6), 139.0 (15), 135.7 (20), 131.3 (25), 124.3 (19), 123.5 (24), 120.7 (14), 113.6 (3), 112.5 (5), 105.5 (1), 104.8 (9), 39.7 (2C, 17 & 22), 26.7 (2C, 18 & 23), 26.3 (27), 25.7 (2C, 10 & 11), 21.9 (2C, 7 & 13), 17.7 (26), 16.2 (2C, 16 & 21).

Methyl 2,4-dihydroxy-6-methyl-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)benzoate (300)

Diketo-farnesyl-resorcylate 286 (70 mg, 0.17 mmol, 1.0 equiv.) and Cs$_2$CO$_3$ (110 mg, 0.34 mmol, 2.0 equiv.) in MeOH (2 mL) were heated at 60 °C in a sealed tube for 72 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL), extracted with Et$_2$O (2 x 10 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 1 Et$_2$O : pentane) to afford farnesyl-resorcylate 300 (68 mg, 94%) as a yellow oil:

R$_f$ 0.66 (7 : 3 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 3408 (br., O-H), 2916 (m, C-H), 2854 (m, C-H), 1649 (sh., C=C), 1618 (sh., C=C), 1438 (m), 1318 (m), 1270 (s), 1196 (m), 1155 (sh.) cm$^{-1}$;

HRMS (ESI) calc. for C$_{24}$H$_{33}$O$_4$[M+H]$^+$: requires 385.2379, found 385.2377 (Δ –0.5 ppm);

$^1$H NMR (CDCl$_3$, 500 MHz) δ 12.08 (s, 1H, 25), 6.22 (s, 1H, 26), 5.78 (s, 1H, 5), 5.29-5.26 (m, 1H, 11), 5.10-5.05 (m, 2H, 16 & 21), 3.43 (d, J = 7.0 Hz, 2H, 10), 3.02 (s, 3H, 9), 2.46 (s, 3H, 7), 2.14-1.95 (m, 8H, 14, 15, 19 & 20), 1.81 (s, 3H, 24), 1.67 (23), 1.59 (2C, 13 & 18);

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$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 172.7 (8), 162.6 (4), 159.5 (2), 140.8 (6), 139.2 (12), 135.6 (17), 131.3 (22), 124.4 (16), 123.6 (21), 121.4 (11), 111.4 (3), 111.3 (1), 105.1 (5), 51.8 (9), 39.7 (2C, 14 & 19), 26.7 (15), 26.3 (20), 25.7 (24), 24.1 (7), 22.0 (10), 17.7 (23), 16.3, 16.0 (2C, 13 & 18).

7-(t-Butylidiphenylsilyloxy)-2,2,5-trimethyl-8-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)-4H-benzo[d][1,3]dioxin-4-one (301)

Resorcylate 286 (260 mg, 0.63 mmol, 1.0 equiv.) and imidazole (65 mg, 0.94 mmol, 1.5 equiv.) were stirred in CH$_2$Cl$_2$ (4 mL), TBDPSCl (0.2 mL, 0.76 mmol, 1.2 equiv.) was added dropwise and the resulting solution stirred for 12 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (50 mL), extracted with Et$_2$O (2 x 50 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (1 : 9 Et$_2$O : pentane) to afford silyl ether 301 (360 mg, 88%) as a colourless oil:

R$_f$ 0.70 (1 : 9 Et$_2$O : pentane);

IR (neat) $\nu_{max}$ 2930 (w, C-H), 2857 (w, C-H), 1733 (w, C=O), 1606 (sh., C=C), 1569 (sh., C=C), 1428 (w), 1319 (w), 1113 (s), 1169 (w) cm$^{-1}$;

HRMS (ESI) calc. for C$_{42}$H$_{55}$O$_4$Si [M+H]$^+$: requires 651.3870, found 651.3878 ($\Delta$ +1.2 ppm);

$^1$H NMR (CDCl$_3$, 400 MHz) δ 7.74-7.71 (m, 4H, 32), 7.43-7.39 (m, 6H, 31 & 33), 5.99 (s, 1H, 5), 5.27 (t, $J$ = 7.0 Hz, 1H, 14), 5.14-5.07 (m, 2H, 19 & 24), 3.47 (d, $J$ = 7.0 Hz, 2H, 13),
Experimental

2.23 (s, 3H, 7), 2.13-1.96 (m, 8H, 17, 18, 22 & 23), 1.81 (s, 3H, 27), 1.69 (br. s, 9H, 10, 11 & 26), 1.60 (br. s, 16 & 21), 1.13 (s, 9H, 29);

13C NMR (CDCl₃, 100 MHz) δ 160.9 (8), 158.7 (4), 156.2 (2), 141.5 (6), 132.0 (15), 131.3 (20), 130.2 (25), 129.7 (2C, 30), 128.0 (4C, 32), 127.7 (6C, 31 & 33), 124.3 (19), 124.1 (24), 121.9 (14), 118.0 (3), 106.0 (5), 104.7 (2C, 9 & 1), 39.7 (2C, 17 & 22), 26.5 (3C, 29), 25.8 (18), 25.7 (23), 22.4 (27), 21.8 (2C, 10 & 11), 19.6 (2C, 7 & 13), 19.0 (28), 17.7 (26), 16.4 (16 / 21), 16.0 (16 / 21).

2-(Trimethylsilyl)ethyl 2,4-dihydroxy-6-methyl-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)benzoate (303)

![Structural formula of 303]

Isopropylidene protected resorcylate 286 (16 mg, 40 μmol, 1.0 equiv.) and Cs₂CO₃ (25 mg, 76 μmol, 2.0 equiv.) were heated in a sealed tube with HOCH₂CH₂OTMS 280 (0.5 mL) and THF (0.25 mL) for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (20 mL), extracted with Et₂O (2 x 20 mL), the organics combined, dried (MgSO₄), rotary evaporated and chromatographed (2 : 8 Et₂O : hexanes to Et₂O) to afford resorcylate 303 (19 mg, 75%) as a colourless oil:

R_f 0.85 (2 : 8 Et₂O : hexanes);

IR (neat) ν max 3460 (w, O-H), 2970 (m, C-H), 2947 (m, C-H), 1738 (s, C=O), 1436 (w), 1366 (s), 1217 (s), 1206 (m) cm⁻¹;

HRMS (ESI) calc. for C₂₅H₄₅O₄Si [M+H]^+: requires 473.3087, found 473.3081 (Δ –1.3 ppm);
Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) δ 12.02 (s, 1H, 27), 6.21 (s, 1H, 28), 5.76 (s, 1H, 5), 5.28-5.26 (m, 1H, 13), 5.09-5.05 (m, 2H, 18 & 23), 4.43-4.40 (m, 2H, 9), 3.44 (d, J = 7.0 Hz, 2H, 12), 2.48 (s, 3H, 7), 2.12-1.95 (m, 8H, 16, 17, 21 & 22), 1.81 (s, 3H, 26), 1.67 (s, 3H, 25), 1.59 (s, 3H, 15 / 20), 1.58 (s, 3H, 15 / 20), 1.18-1.14 (m, 2H, 10), 0.08 (s, 9H, 11);

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 172.4 (8), 162.6 (4), 159.3 (2), 140.9 (6), 138.9 (14), 135.6 (19), 131.3 (24), 124.4 (18), 123.6 (23), 121.5 (13), 111.3 (3C, 1, 3 & 5), 63.6 (9), 39.7 (2C, 16 & 21), 26.7 (17), 26.3 (22), 25.7 (26), 24.3 (7), 22.0 (12), 17.7 (25), 16.3 (10), 16.1 (2C, 15 & 20), -1.5 (3C, 11).

Methyl 2,4-dihydroxy-6-methyl-3-(3-methylbut-2-enyl)benzoate (308)

Isopropylidene protected resorcylate 142 (50 mg, 0.17 mmol, 1.0 equiv.) and Cs$_2$CO$_3$ (110 mg, 0.34 mmol, 2.0 equiv.) were heated in a sealed tube with MeOH (1 mL) for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (20 mL), extracted with Et$_2$O (2 x 20 mL), the organics combined, dried (MgSO$_4$), rotary evaporated and chromatographed (3 : 7 Et$_2$O : hexanes) to afford methylester 308$^{[69]}$ (38 mg, 90%) as a white solid:

m.p. 75 - 77 °C (pentane);

R$_f$ 0.55 (1 : 1 Et$_2$O : hexanes);

IR (neat) $v_{max}$ 2988 (w, C-H), 1746 (m, C=O), 1372 (m), 1216 (sh.) cm$^{-1}$;

HRMS (CI) calc. for C$_{14}$H$_{16}$O$_4$ [M+H]$^+$: requires 251.1283, found 251.1287 (Δ +1.6 ppm);
6 Experimental

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 12.11 (s, 1H, 16), 6.24 (s, 1H, 15), 5.75 (s, 1H, 5), 5.28 (t, $J$ = 7.0 Hz, 1H, 11), 3.94 (s, 3H, 9), 3.44 (d, $J$ = 7.0 Hz, 2H, 10), 2.48 (s, 3H, 7), 1.84 (s, 3H, 14), 1.77 (s, 3H, 13).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 172.6 (8), 162.6 (4), 159.2 (2), 140.8 (6), 135.1 (12), 121.6 (11), 111.4, 111.3 (3C, 1, 3 & 5) 51.8 (9), 25.8 (14), 24.1 (7), 22.1 (10), 17.9 (13).
6 Experimental

6.3 Additional Experimental Procedures

\((R)-5\text{-Hydroxy-2,2,8-trimethyl-3,4,9-tetrahydropyrano[3,4-g]chromen-6(2H)-one}\) 

\((122)\)

\(\text{H}_2\text{SiF}_6\) in \(\text{H}_2\text{O}\) (20% w/w; 50 \(\mu\text{L}, 80 \mu\text{mol}, 4.0\) equiv.) was added with stirring to a solution of resorcylate \(109\) (10 mg, 20 \(\mu\text{mol}, 1.0\) equiv.) in MeCN (4 mL) at 0 °C. After 15 min, the reaction mixture was heated at reflux for 45 min after which 1 micro spatula tip head of \(p\)-TsOH (cat.) was added and the mixture heated at reflux for 2 h. The reaction was cooled to rt and quenched with a saturated aqueous solution of \(\text{NaHCO}_3\) (20 mL). The mixture was extracted with \(\text{Et}_2\text{O}\) (3 x 25 mL), dried (\(\text{MgSO}_4\)), concentrated by rotary evaporation and chromatographed (3 : 1 hexanes : \(\text{Et}_2\text{O}\)) to afford tricyclic resorcylate \(122\) (3 mg, 51%) as a colourless solid:

\(R_f 0.49 \ (3 : 1 \text{hexanes : } \text{Et}_2\text{O});\)

\([\alpha]^{25}_D = +33.00 \ (c 0.2, \text{CHCl}_3);\)

\(\text{IR (neat) } \nu_{\text{max}} 3432 (\text{O-H}), 2925 (\text{C-H}), 1659 (\text{C=C}), 1634 (\text{C=C}), 1584 (\text{C=C}), 1434, 1370, 1311, 1253, 1235, 1157, 1118, 1041 \text{ cm}^{-1};\)

\(\text{HRMS (ESI) calc. for } C_{15}H_{19}O_4 [M + H]^+: \text{requires 263.1283; found 263.1294};\)

\(\text{XI}\) The additional experimental procedures were carried out by colleagues within the Barrett group. They have been added into this thesis for clarity and to aid the reader. Each experiment is clearly labelled with the name of the person that conducted it. These colleagues are duly thanked for their contribution to this research.

\(\text{XII}\) This experiment was carried out by Toni Pfaffeneder under the supervision of Dr Frederick Calo. They are duly thanked for their contribution to this research.
6 Experimental

**H NMR** (400 MHz, CDCl\textsubscript{3}) \(\delta\) 11.47 (s, 1H), 6.14 (s, 1H), 4.67 – 4.61 (m, 1H), 2.82 – 2.80 (m, 2H), 2.68 – 2.65 (m, 2H), 1.82 - 1.80 (m, 2H), 1.49 (d, \(J = 6.4\) Hz, 3H), 1.34 (s, 3H), 1.33 (s, 3H);

**C NMR** (100 MHz, CDCl\textsubscript{3}) \(\delta\) 161.8 (2C), 137.8 (2C), 107.5, 100.1 (2C), 75.6 (2C), 34.6, 31.8, 26.8, 26.6, 20.8, 16.3.

**7-Hydroxy-2,2-dimethyl-8-(2-methylbut-3-en-2-yl)-5-phenethyl-4H-benzo[**

\(d\)[1,3]dioxin-4-one (149)**

Diketo-dioxinone 148 (50 mg, 0.13 mmol, 1.0 equiv.) and Cs\textsubscript{2}CO\textsubscript{3} (85 mg, 0.26 mmol, 2.0 equiv.) in THF (5 mL) were heated to reflux for 5 h. The reaction was quenched with H\textsubscript{2}O (10 mL), and the mixture acidified to pH 3 with 1 M HCl and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), filtered, rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford phenol 149 (32 mg, 68%) as a white solid:

**m.p.** = 103-105 °C (hexanes);

**R\(_f\)** 0.64 (1 : 4 EtOAc : hexanes);

**IR** (neat) \(\nu\textsubscript{max} \) 3213 (O-H), 2986 (C-H), 1693 (C=O), 1684 (C=C), 1593 (C-C), 1497, 1400, 1298, 1209, 1070, 884 cm\(^{-1}\);

**HRMS** (ESI) calc. for C\textsubscript{23}H\textsubscript{27}O\textsubscript{4} [M+H]\(^{+}\): requires 367.1904; found [M+H]\(^{+}\) 367.1896;

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\(^{\text{XIII}}\) This experiment was carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this research.
Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) δ 7.29 - 7.27 (m, 4H), 7.18 (m, 1H), 7.11 (s, 1H), 6.41 (dd, $J$ = 10.6, 17.8 Hz, 1H), 6.41 (s, 1H), 5.44 (d, $J$ = 17.8 Hz, 1H), 5.37 (d, $J$ = 10.6 Hz, 1H), 3.26 (m, 2H), 2.87 (m, 2H), 1.70 (s, 6H), 1.53 (s, 6H);

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 160.5, 160.4, 157.1, 148.9, 146.7, 142.0, 128.6, 128.3 (2C), 125.8 (2C), 117.6, 115.3, 113.6, 106.1, 104.0, 40.9, 37.1, 36.6, 27.5 (2C), 25.5 (2C).

Amorfrutin A: 2-Hydroxy-4-methoxy-3-(3-methyl-2-buten-1-yl)-6-phenethylbenzoic acid (8)$^{xiv}$

KOH (48%, 0.62 mL, 5.3 mmol, 10.0 equiv.) was added to lactone 299 (200 mg, 0.52 mmol, 1.0 equiv.) in DMSO (1 mL) and the mixture was heated at 80 °C for 12 h. After cooling, the mixture was acidified to pH 1 using 1 M HCl and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried (MgSO$_4$), filtered, rotary evaporated and chromatographed (1 : 1 hexanes : EtOAc) to afford amorfrutin A (8)$^{[10a]}$(149 mg, 83%) as a white solid:

m.p. = 139-141 °C (cyclohexane);

R$_f$ 0.43 (EtOAc : hexanes 1 : 1);

IR (neat) $\tilde{\nu}_{\text{max}}$ 2867 (C-H), 1630 (C=O), 1611 (C=C), 1571 (C-C), 1496, 1454 1436, 1226, 1112 cm$^{-1}$;

HRMS (ESI) calc. for C$_{21}$H$_{24}$O$_4$ [M + H]$^+$: requires 341.1753, found 341.1753;

$xiv$ This experiment was carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this research.
6 Experimental

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 11.6 (s, 1H), 7.34 - 7.20 (m, 5H), 6.22 (s, 1H), 5.20 (m, 1H), 3.80 (s, 3H), 3.35 (d, $J=7.1$ Hz, 2H), 3.26 (d, 2H), 2.92 (m, 2H), 1.79 (s, 3H), 1.68 (s, 3H);
$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 175.4, 162.9, 162.1, 145.7, 141.9, 131.8, 128.5 (2C), 128.3 (2C), 125.9, 122.2, 115.3, 106.4, 103.6, 55.5, 39.2, 38.1, 25.8, 22.0, 17.8;

Anal. Calc. for C$_{21}$H$_{24}$O$_4$: C, 74.09; H, 7.11. Found C, 73.94; H, 7.02.

7-Hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-5-phenethyl-$4H$-benzo[d][1,3]dioxin-4-one (171) and 7-hydroxy-2,2-dimethyl-8-([1-$^2$H$_2$]-3-methylbut-2-enyl)-5-phenethyl-$4H$-benzo[d][1,3]dioxin-4-one (170) and 7-hydroxy-5-(4-methoxyphenethyl)-2,2-dimethyl-8-([1-$^2$H$_2$]-3-methylbut-2-enyl)-$4H$-benzo[d][1,3]dioxin-4-one (172) and 7-hydroxy-5-(4-methoxyphenethyl)-2,2-dimethyl-8-(3-methylbut-2-enyl)-$4H$-benzo[d][1,3]dioxin-4-one (173)$^{xv}$

Diketo-ester-dioxinone 168 (186 mg, 0.43 mmol, 1.0 equiv.) and deuterated-diketo-ester-dioxinone 169 (200 mg, 0.43 mmol, 1.0 equiv.) were added to a stirring solution of Pd(PPh$_3$)$_4$ (25 mg, 20 $\mu$mol, 5 mol%) and Cs$_2$CO$_3$ (42 mg, 0.13 mmol, 3.0 equiv.) in THF (2 mL) at 0 $^\circ$C. The resulting mixture was allowed to warm to rt and stirred for 12 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL) and extracted with Et$_2$O (2 x 10 mL). The organics were combined, dried (MgSO$_4$) and rotary evaporated. The crude

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$xv$ This experiment was carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this research.
residue was chromatographed (1 : 9 EtOAc : hexanes) to afford prenyl-phenyl-resorcylate 170 and deuterated-prenyl-phenyl-resorcylate 171 (110 mg, 70%) in a 1:1 ratio as a white solid and deuterated-prenyl-methoxy-resorcylate 172 and prenyl-methoxy-resorcylate 173 (119 mg, 70%) as a 1:1 ratio as a white solid.

Prenyl-phenyl-resorcylate 170 and deuterated-prenyl-phenyl-resorcylate 171:

m.p. 119-120 °C (hexanes);

R_f 0.81 (3 : 1 EtOAc : hexanes);

IR (neat) ν_{max} 2997 (C-H), 2930 (C-H), 1689 (C=O), 1593 (C=C), 1512 (C-C), 1419, 1300, 1213, 909 cm⁻¹;

171: HRMS (ESI) cal. for C_{23}H_{24}D_{2}O_{4}, requires 369.1957, found 369.1957 (Δ = 0.0 ppm);

170: HRMS (ESI) cal. for C_{23}H_{26}O_{4}, requires 367.1909, found 367.1914 (Δ = 1.4 ppm);

^1H NMR (CDCl₃, 400 MHz) δ 7.29-7.28 (m, 8H), 7.22-7.17 (m, 2H), 6.43 (s, 2H), 6.30 (s, 2H), 5.22 (s, 2H), 3.35 (d, J = 8.0 Hz, 2H), 3.31-3.29 (m, 4H), 2.91-2.87 (m, 4H), 1.83 (s, 6H), 1.77 (s, 6H), 1.71 (s, 6H);

^13C NMR (CDCl₃, 100 MHz) δ 166.9, 160.9, 144.5, 140.2, 128.6, 126.4, 124.6, 120.4, 112.8, 110.2, 106.7, 101.7, 96.6, 62.5, 40.5, 39.5, 31.7, 27.6, 25.9 (2C), 25.8, 25.6, 24.7.

Deuterated-prenyl-methoxy-resorcylate 172 and prenyl-methoxy-resorcylate 173:

m.p. 84-86 °C (pentane);

R_f 0.43 (2 : 8 EtOAc : hexanes);

IR (neat) ν_{max} 2924 (C-H), 2256 (C-H), 1718 (C=O), 1625 (C=C), 1592 (C=C), 1512 (C-C), 1416, 1393, 1351, 1291, 1244, 1038 cm⁻¹;

172: HRMS (ESI) cal. for C_{24}H_{26}D_{2}O_{5}, 399.2135, found 399.2131 (Δ = 1.0 ppm);

173: HRMS (ESI) cal. for C_{24}H_{28}O_{5}, 397.2015, found 397.1992 (Δ = 5.8 ppm);
Experimental

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.19 (d, $J = 8.5$ Hz, 4H), 6.82 (d, $J = 8.5$ Hz, 4H), 6.42 (s, 2H), 6.37 (s, 2H), 5.21 (br. s, 2H), 3.80 (s, 6H), 3.34 (d, $J = 8.0$ Hz, 2H), 3.24 (m, 4H), 2.82 (m, 4H), 1.80 (s, 6H), 1.74 (s, 6H), 1.68 (s, 12H);

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 160.6, 160.0, 157.8, 156.2, 146.5, 134.9, 134.1, 129.6 (2C), 120.9, 113.7 (2C), 113.1, 105.0, 104.7, 55.3, 37.0, 36.5, 25.8, 25.7, 22.0, 17.9.

(E)-3-Methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-enyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (195)$^\text{XVI}$

![Image](195)

To a solution of CDI (413 mg, 2.55 mmol, 3.0 equiv.) in THF (11 mL) was added alcohol 275 (200 mg, 0.85 mmol, 1.0 equiv.) in THF (6 mL) at $-78^\circ$C. The reaction was allowed to warm to rt and stirred for 18 h. The reaction was quenched with H$_2$O (50 mL), extracted with Et$_2$O (3 x 50 mL), the organics combined, dried (MgSO$_4$) and concentrated by rotary evaporation to afford imidazole carboxylate 287 which was used without further purification.

$i$-Pr$_2$NH (0.51 mL, 3.88 mmol, 4.5 equiv.) was stirred in THF (5 mL), $n$-BuLi in hexanes (1.6 mL, 2.5 M, 3.88 mmol, 4.5 equiv.) was added dropwise at $-78^\circ$C and the resultant solution stirred for 30 min. A solution of diketo-dioxinone 178 (344 mg, 1.87 mmol, 2.2 equiv.) in THF (2 mL) was added and after 10 min, the reaction (which solidified) was allowed to warm to $-40^\circ$C and stirred for 1 h. A solution of ZnEt$_2$ in hexanes (3.9 mL, 1.0 M, 3.9 mmol, 4.6 equiv.) was added and after 20 min, the reaction was cooled to $-78^\circ$C and a solution of imidazole carboxylate 287 (280 mg, 0.85 mmol, 1.0 equiv.) in THF (3 mL) was added.

$^\text{XVI}$ This experiment was carried out by Dr Nicolas George. He is duly thanked for his contribution to this research.
Experimental

The reaction was stirred at –78°C for 45 min and the reaction was quenched with a saturated aqueous solution of NH₄Cl (5 mL). The solution was allowed to warm to rt, H₂O (40 mL) added and the pH adjusted to 3 using 1 M HCl. The two layers were separated and the aqueous phase was extracted with Et₂O (3 × 50 mL). The combined organic layers were dried (MgSO₄), concentrated by rotary evaporation and chromatographed (7 : 3 hexanes : EtOAc) to afford ketoester-dioxinone **195** (228 mg, 60% over 2 steps) as a light yellow oil:

R_f 0.44 (6 : 4 hexanes : EtOAc);

**IR** (neat) _ν_{max} 2987 (C-H), 1722 (C=O), 1639 (C=C), 1390, 1375, 1272, 1253, 1203, 1016 cm⁻¹;

**HRMS** (ES) calc. for C_{25}H_{33}O₇ [M + H]^+: requires 445.2226; found 445.2229;

**¹H NMR** (CDCl₃, 400 MHz) δ 7.11 (s, 1H), 6.98 (s, 1H), 6.05 (s, 1H), 5.38 (s, 1H), 5.36 (m, 1H), 4.68 (d, _J_ = 7.2 Hz, 2H), 3.53 (s, 2H), 3.51 (s, 2H), 2.38 (t, _J_ = 7.5 Hz, 2H), 2.09 (t, _J_ = 7.4 Hz, 2H), 1.98 (s, 3H), 1.90 (s, 3H), 1.72–1.67 (m, 11H);

**¹³C NMR** (CDCl₃, 100 MHz) δ 195.7, 166.4, 163.6, 160.5, 153.7, 143.4, 136.8, 135.0, 126.1, 117.6, 114.5, 108.6, 107.4, 97.1, 62.6, 49.1, 47.0, 38.9, 27.8, 27.0, 25.0 (2C), 24.4, 20.1, 16.4.
(E)-7-Hydroxy-2,2,5-trimethyl-8-(3-methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-enyl)-4H-benzo[d][1,3]dioxin-4-one (193)\textsuperscript{XVII}

![Chemical Structure]

To a solution of the ketoester-dioxinone 195 (192 mg, 0.43 mmol, 1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) was added MgCl\textsubscript{2} (82 mg, 0.86 mmol, 2.0 equiv.) at –10 °C. After 5 min, pyridine (0.93 mL, 1.16 mmol, 2.6 equiv.) was added dropwise and the resultant solution stirred for 30 min. Acetyl chloride (0.37 mL, 0.52 mmol, 1.15 equiv.) was added dropwise and the resultant solution stirred for 30 min. The reaction was quenched with a saturated aqueous solution of NH\textsubscript{4}Cl (25 mL), extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 25 mL), the organics combined, washed with brine (30 mL), dried (MgSO\textsubscript{4}) and concentrated by rotary evaporation to afford diketo-ester-dioxinone 194 which was used without further purification.

Diketo-ester-dioxinone 194 (159 mg, 0.43 mmol, 1.0 equiv.) was stirred in THF, Pd(PPh\textsubscript{3})\textsubscript{4} (24 mg, 22 μmol, 5 mol%) was added and the resultant solution was stirred at rt for 70 h. Cs\textsubscript{2}CO\textsubscript{3} (420 mg, 1.29 mmol, 3.0 equiv.) was added and the reaction stirred for 15 h. The reaction was quenched with H\textsubscript{2}O (5 mL) and EtOAc (25 mL) and the pH adjusted to 5 using 0.1 M HCl. The two layers were separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO\textsubscript{4}), concentrated by rotary evaporation and chromatographed (8 : 2 hexanes : EtOAc) affording isopropylidene protected resorcylate 193 (77 mg, 42% over 2 steps) as a yellow oil:

\[ R_f 0.52 \quad (7 : 3 \text{ hexanes} : \text{EtOAc}) \]

\textsuperscript{XVII} This experiment was carried out by Dr Nicolas George. He is duly thanked for his contribution to this research.
6 Experimental

IR (neat) $v_{\text{max}}$ 2768 (C-H), 1692 (C=O), 1607 (C=C), 1592 (C=C), 1294, 1276, 1208, 1166, 1107, 1042, 908, 730 cm$^{-1}$;

HRMS (ES) calc. for C$_{26}$H$_{33}$O$_5$ [M+H]$^+$: requires 425.2328, found: 425.2322;

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.08 (s, 1H), 6.97 (br. s, 1H), 6.49 (s, 1H), 6.04 (s, 1H), 6.01 (s, 1H), 5.21 (t, $J = 7.2$ Hz, 1H), 3.33 (t, $J = 7.5$ Hz, 2H), 2.60 (s, 3H), 2.36 (t, $J = 7.5$ Hz, 2H), 2.05 (t, $J = 7.4$ Hz, 2H), 1.97 (s, 3H), 1.89 (s, 3H), 1.80 (s, 3H), 1.72–1.67 (m, 8H);

$^3$C NMR (CDCl$_3$, 100 MHz) $\delta$ 161.7, 160.4, 156.2, 153.7, 142.6, 137.0, 136.8, 134.8, 126.3, 121.4, 114.5, 113.6, 113.3, 108.7, 104.9 (2C), 39.2, 28.1, 27.0, 25.7 (2C), 24.4, 22.0, 21.8, 20.1, 16.1.
Resorcylate 193 (11 mg, 26 μmol, 1.0 equiv.) was added a solution of NaOMe (6 mg, 0.26 mmol, 10.0 equiv.) with in methanol (1 mL). The reaction was heated at 65 °C in a sealed tube for 20 h. The reaction was quenched with 0.1 M HCl (15 mL) and EtOAc (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO₄), concentrated by rotary evaporation and chromatographed (6 : 1 hexanes : EtOAc) affording Cristatic cid methyl ester 183[6] (7 mg, 64%) as a colourless oil:

\[ \text{Rf} 0.42 (4 : 1 \text{hexanes : EtOAc}); \]

\[ \text{IR} \text{ (neat)} \nu_{\text{max}} 2865 (\text{C-H}), 1651 (\text{C=C}), 1620 (\text{C=C}), 1455, 1419, 1378, 1272, 1195, 808 \text{ cm}^{-1} \];

\[ \text{HRMS} \text{ (ES) calc. for C}_{24}\text{H}_{31}\text{O}_{5}\text{[M+H]}^{+} : \text{requires } 399.2171; \text{found: } 399.2186 \];

\[ ^{1}\text{H NMR} \text{ (CDCl}_3, 400 \text{ MHz}) \delta 12.13 (s, 1H), 7.10 (s, 1H) 6.25 (s, 1H), 6.06 (s, 1H), 6.03 (m, 1H), 5.75 (s, 1H), 5.31 (t, J = 7.2 Hz, 1H), 3.95 (s, 3H), 3.45 (d, J = 7.3 Hz, 2H), 2.49 (s, 3H), 2.37 (t, J = 7.5 Hz, 2H), 2.09 (t, J = 7.5 Hz, 2H), 1.98 (s, 3H) 1.91 (s, 3H) 1.83 (s, 3H), 1.69 (m, J = 7.6 Hz, 2H); \]

\[ ^{13}\text{C NMR} \text{ (CDCl}_3, 100 \text{ MHz}) \delta 173.1, 163.0, 159.4, 154.0, 141.3, 138.3, 137.1, 135.2, 127.0, 122.1, 114.8, 112.1, 111.4, 109.1, 105.6, 52.1, 39.5, 28.6, 27.0, 24.7, 24.2, 22.2, 20.2, 16.3. \]

---

XVIII This experiment was carried out by Dr Nicolas George. He is duly thanked for his contribution to this research.
6 Experimental

6.4 X-Ray Date

6.4.1 Tricyle 130

(S)-6-Hydroxy-3,3,9-trimethyl-9,10-dihydro-[1,3]dioxino[5,4-f]isochromene-1,7-dione (130)

Cambridge CCDC code: SANSIL


Table 22. Crystal data and structure refinement for 130

<table>
<thead>
<tr>
<th>Identification code</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>Formula weight</td>
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<tr>
<td>Temperature</td>
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</tr>
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<td>Diffractometer, wavelength</td>
<td>OD Xcalibur PX Ultra, 1.54184 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)</td>
</tr>
</tbody>
</table>
| Unit cell dimensions | \( a = 7.72443(17) \text{ Å} \) \( \alpha = 90^\circ \) 
|                     | \( b = 8.2531(3) \text{ Å} \) \( \beta = 96.121(3)^\circ \) 
|                     | \( c = 19.2848(7) \text{ Å} \) \( \gamma = 90^\circ \) |
| Volume, Z           | 1222.41(7) \text{ Å}^3, 4 |
| Density (calculated) | 1.512 Mg/m\text{^3} |
| Absorption coefficient | 1.012 mm\text{^{-1}} |
| F(000)              | 584            |
| Crystal colour / morphology | Colourless plates |
| Crystal size        | 0.13 x 0.04 x 0.01 mm\text{^3} |
| θ range for data collection | 2.30 to 72.24° |
| Index ranges        | -9<=h<=6, -10<=k<=10, -23<=l<=23 |
| Reflns collected / unique | 8496 / 4644 [R(int) = 0.0608] |
| Reflns observed [F>4\text{\sigma}(F)] | 2902 |
| Absorption correction | Analytical |
6 Experimental

Max. and min. transmission 0.990 and 0.935
Refinement method Full-matrix least-squares on $F^2$
Data / restraints / parameters 4644 / 3 / 370
Goodness-of-fit on $F^2$ 0.947
Final R indices [$F>4\sigma(F)$] $R_1 = 0.0531$, $wR_2 = 0.0933$
 $R_1^+ = 0.0531$, $wR_2^+ = 0.0933$
 $R_1^- = 0.0532$, $wR_2^- = 0.0935$
R indices (all data) $R_1 = 0.1073$, $wR_2 = 0.1089$
Absolute structure parameter $x^+ = 0.1(2)$, $x^- = 0.9(2)$
Extinction coefficient 0.00056(12)
Largest diff. peak, hole 0.252, -0.242 eÅ$^{-3}$
Mean and maximum shift/error 0.000 and 0.000

Table 23. Bond lengths [Å] and angles [°] for 130

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Bond</th>
<th>Length [Å]</th>
<th>Bond</th>
<th>Length [Å]</th>
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<td>C(11A)-C(12A)</td>
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<tr>
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<td>C(5B)-O(4B)-C(3B)</td>
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<td>O(17B)-C(7B)-C(6B)</td>
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<td>C(13B)-C(8B)-C(7B)</td>
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<td>C(13B)-C(8B)-C(9B)</td>
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<td>O(9A)-C(9A)-C(8A)</td>
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<tr>
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<td>O(9B)-C(9B)-O(10B)</td>
<td>117.3(4)</td>
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<td></td>
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</tbody>
</table>
6 Experimental

O(9B)-C(9B)-C(8B)  123.0(4)  C(8B)-C(13B)-C(14B)  119.8(4)
O(10B)-C(9B)-C(8B)  119.7(4)  C(8B)-C(13B)-C(12B)  116.4(3)
C(9B)-O(10B)-C(11B)  117.9(3)  C(14B)-C(13B)-C(12B)  123.8(3)
O(10B)-C(11B)-C(12B)  111.3(3)  C(13B)-C(14B)-C(5B)  118.3(4)
O(10B)-C(11B)-C(18B)  106.0(3)  C(13B)-C(14B)-C(1B)  123.7(4)
C(12B)-C(11B)-C(18B)  113.5(3)  C(5B)-C(14B)-C(1B)  117.8(3)
C(11B)-C(12B)-C(13B)  110.9(3)

Figure 21: X-ray Crystal Structure One of Tricycle 130
6.4.2 Angelicoi A (6)

((R)-6,8-Dihydroxy-3-methyl-7-(3-methylbut-2-enyl)isochroman-1-one) (6)

Cambridge CCDC code: SANSEH


Table 24. Crystal Data and Structure Refinement for 6

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<td>Temperature</td>
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<tr>
<td>Diffractometer, wavelength</td>
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</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, C2</td>
</tr>
</tbody>
</table>
| Unit cell dimensions | a = 10.00787(16) Å  
                      | b = 26.3372(5) Å  
                      | α = 90°  
                      | β = 99.8553(16)° |
Experimental

Volume, Z

2805.97(9) Å³, 8

Density (calculated)

1.242 Mg/m³

Absorption coefficient

0.735 mm⁻¹

F(000)

1120

Crystal colour / morphology

Colourless tablets

Crystal size

0.18 x 0.09 x 0.04 mm³

θ range for data collection

3.36 to 72.55°

Index ranges

-12<=h<=9, -31<=k<=32, -

12<=l<=13

Reflns collected / unique

11153 / 5262 [R(int) = 0.0211]

Reflns observed [F>4σ(F)]

4840

Absorption correction

Analytical

Max. and min. transmission

0.970 and 0.909

Refinement method

Full-matrix least-squares on F²

Data / restraints / parameters

5262 / 5 / 364

Goodness-of-fit on F²

1.049

Final R indices [F>4σ(F)]

R1 = 0.0356, wR2 = 0.0958

R1+ = 0.0356, wR2+ = 0.0958

R1- = 0.0358, wR2- = 0.0966

R indices (all data)

R1 = 0.0391, wR2 = 0.0993

Absolute structure parameter

x+ = -0.00(15), x- = 1.33(15)

Extinction coefficient

0.00037(6)

Largest diff. peak, hole

0.158, -0.127 eÅ⁻³

Mean and maximum shift/error

0.000 and 0.001

Table 25. Bond Lengths [Å] and Angles [°] for 6

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<th>Bond</th>
<th>Length</th>
<th>Bond</th>
<th>Length</th>
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<td>1.504(3)</td>
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<td>C(1A)-O(2A)</td>
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<td>C(3A)-C(4A)</td>
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<tr>
<td>O(2A)-C(3A)</td>
<td>1.465(2)</td>
<td>C(5A)-C(6A)</td>
<td>1.372(3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
C(5A)-C(10A) 1.415(2)  O(1A)-C(1A)-C(10A)  123.27(19)
C(6A)-C(7A)  1.405(3)  O(2A)-C(1A)-C(10A)  120.79(17)
C(7A)-O(12A) 1.348(2)  C(1A)-O(2A)-C(3A)  119.00(15)
C(7A)-C(8A)  1.397(2)  O(2A)-C(3A)-C(11A) 105.02(16)
C(8A)-C(9A)  1.392(3)  O(2A)-C(3A)-C(4A)  110.78(14)
C(8A)-C(13A) 1.506(3)  C(1A)-C(3A)-C(4A)  114.19(17)
C(9A)-O(18A) 1.356(2)  C(5A)-C(4A)-C(3A)  111.38(15)
C(9A)-C(10A) 1.403(3)  C(6A)-C(5A)-C(10A) 119.54(18)
C(13A)-C(14A) 1.501(3)  C(6A)-C(5A)-C(4A)  122.85(17)
C(14A)-C(15A) 1.331(3)  C(10A)-C(5A)-C(4A) 117.55(17)
C(15A)-C(16A) 1.499(3)  C(5A)-C(6A)-C(7A)  120.30(17)
C(15A)-C(17A) 1.507(3)  O(12A)-C(7A)-C(8A) 116.57(18)
O(1B)-C(1B)  1.241(2)  O(12A)-C(7A)-C(6A)  122.12(16)
C(1B)-O(2B)  1.328(2)  C(8A)-C(7A)-C(6A)  121.31(17)
C(1B)-C(10B) 1.447(2)  C(9A)-C(8A)-C(7A)  118.00(18)
O(2B)-C(3B)  1.469(2)  C(9A)-C(8A)-C(13A) 120.74(17)
C(3B)-C(4B)  1.508(3)  C(7A)-C(8A)-C(13A) 121.26(17)
C(3B)-C(11B) 1.512(3)  O(18A)-C(9A)-C(8A) 117.09(17)
C(4B)-C(5B)  1.504(3)  O(18A)-C(9A)-C(10A) 121.52(17)
C(5B)-C(6B)  1.376(3)  C(8A)-C(9A)-C(10A) 121.38(16)
C(5B)-C(10B) 1.404(2)  C(9A)-C(10A)-C(5A)  119.41(17)
C(6B)-C(7B)  1.403(3)  C(9A)-C(10A)-C(1A)  120.45(16)
C(7B)-O(12B) 1.347(2)  C(5A)-C(10A)-C(1A)  120.09(18)
C(7B)-C(8B)  1.398(3)  C(14A)-C(13A)-C(8A) 111.58(17)
C(8B)-C(9B)  1.393(3)  C(15A)-C(14A)-C(13A) 127.3(2)
C(8B)-C(13B) 1.508(3)  C(14A)-C(15A)-C(16A) 123.8(2)
C(9B)-O(18B) 1.359(2)  C(14A)-C(15A)-C(17A) 121.1(2)
C(9B)-C(10B) 1.416(3)  C(16A)-C(15A)-C(17A) 115.1(2)
C(13B)-C(14B) 1.500(3)  O(1B)-C(1B)-O(2B)  116.93(17)
C(14B)-C(15B) 1.329(3)  O(1B)-C(1B)-C(10B)  122.69(18)
C(15B)-C(16B) 1.497(3)  O(2B)-C(1B)-C(10B)  120.38(16)
C(15B)-C(17B) 1.500(3)  C(1B)-O(2B)-C(3B)  119.65(14)
O(1A)-C(1A)-O(2A) 115.93(18)  O(2B)-C(3B)-C(4B)  110.92(14)
6 Experimental

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2B)-C(3B)-C(11B)</td>
<td>104.93(15)</td>
</tr>
<tr>
<td>C(4B)-C(3B)-C(11B)</td>
<td>113.63(17)</td>
</tr>
<tr>
<td>C(5B)-C(4B)-C(3B)</td>
<td>111.41(15)</td>
</tr>
<tr>
<td>C(6B)-C(5B)-C(10B)</td>
<td>119.81(18)</td>
</tr>
<tr>
<td>C(6B)-C(5B)-C(4B)</td>
<td>122.42(16)</td>
</tr>
<tr>
<td>C(10B)-C(5B)-C(4B)</td>
<td>117.71(16)</td>
</tr>
<tr>
<td>C(5B)-C(6B)-C(7B)</td>
<td>120.10(17)</td>
</tr>
<tr>
<td>O(12B)-C(7B)-C(8B)</td>
<td>116.69(17)</td>
</tr>
<tr>
<td>O(12B)-C(7B)-C(6B)</td>
<td>121.51(16)</td>
</tr>
<tr>
<td>C(8B)-C(7B)-C(6B)</td>
<td>121.80(16)</td>
</tr>
<tr>
<td>C(9B)-C(8B)-C(7B)</td>
<td>117.47(18)</td>
</tr>
<tr>
<td>C(9B)-C(8B)-C(13B)</td>
<td>121.12(17)</td>
</tr>
<tr>
<td>C(10B)-C(9B)-C(8B)</td>
<td>117.26(17)</td>
</tr>
<tr>
<td>O(18B)-C(9B)-C(8B)</td>
<td>121.22(16)</td>
</tr>
<tr>
<td>C(8B)-C(9B)-C(10B)</td>
<td>121.51(16)</td>
</tr>
<tr>
<td>C(5B)-C(10B)-C(9B)</td>
<td>119.19(16)</td>
</tr>
<tr>
<td>C(5B)-C(10B)-C(1B)</td>
<td>120.45(17)</td>
</tr>
<tr>
<td>C(9B)-C(10B)-C(1B)</td>
<td>120.31(16)</td>
</tr>
<tr>
<td>C(14B)-C(13B)-C(8B)</td>
<td>112.22(15)</td>
</tr>
<tr>
<td>C(15B)-C(14B)-C(13B)</td>
<td>126.96(18)</td>
</tr>
<tr>
<td>C(14B)-C(15B)-C(16B)</td>
<td>124.20(18)</td>
</tr>
<tr>
<td>C(14B)-C(15B)-C(17B)</td>
<td>120.67(19)</td>
</tr>
<tr>
<td>C(16B)-C(15B)-C(17B)</td>
<td>115.12(19)</td>
</tr>
</tbody>
</table>

Figure 23: X-ray Crystal Structure of Angelicoin A (6)
6 Experimental

6.4.3 Resorcylate 155

7-Hydroxy-2,2,5-trimethyl-4H-benzo[d][1,3]dioxin-4-one (155)

Table 26. Crystal Data and Structure Refinement for 155

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>155</td>
</tr>
<tr>
<td>Formula</td>
<td>C_{11}H_{12}O_{4}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>208.21</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 K</td>
</tr>
<tr>
<td>Diffractometer, wavelength</td>
<td>OD Xcalibur PX Ultra, 1.54184 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.1052(2) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 10.0123(2) Å, β = 90.567(2)°</td>
</tr>
<tr>
<td></td>
<td>c = 11.9529(3) Å, γ = 90°</td>
</tr>
<tr>
<td>Volume, Z</td>
<td>969.95(4) Å, 4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.426 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.913 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>440</td>
</tr>
<tr>
<td>Crystal colour / morphology</td>
<td>Colourless platy needles</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.11 x 0.03 x 0.01 mm³</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>5.46 to 72.19°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9&lt;=h&lt;=9, -9&lt;=k&lt;=12, -11&lt;=l&lt;=14</td>
</tr>
<tr>
<td>Reflns collected / unique</td>
<td>6427 / 1869 [R(int) = 0.0302]</td>
</tr>
<tr>
<td>Reflns observed [F&gt;4σ(F)]</td>
<td>1599</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Analytical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.997 and 0.943</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
</tbody>
</table>
6 Experimental

Data / restraints / parameters 1869 / 1 / 141

Goodness-of-fit on $F^2$ 1.198

Final R indices [F>4 σ (F)]

R1 = 0.0463, wR2 = 0.1269

R indices (all data)

R1 = 0.0540, wR2 = 0.1297

Largest diff. peak, hole 0.296, -0.225 eÅ$^{-3}$

Mean and maximum shift/error 0.000 and 0.000

<table>
<thead>
<tr>
<th>Bond Lengths [Å] and Angles [°] for 155</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(10) 1.371(3) O(3)-C(2)-C(11) 109.73(19)</td>
</tr>
<tr>
<td>O(1)-C(2) 1.427(3) C(12)-C(2)-C(11) 113.3(2)</td>
</tr>
<tr>
<td>C(2)-O(3) 1.446(3) C(4)-O(3)-C(2) 118.98(17)</td>
</tr>
<tr>
<td>C(2)-C(12) 1.509(3) O(4)-C(4)-O(3) 116.0(2)</td>
</tr>
<tr>
<td>C(2)-C(11) 1.519(3) O(4)-C(4)-C(5) 127.0(2)</td>
</tr>
<tr>
<td>O(3)-C(4) 1.359(3) O(3)-C(4)-C(5) 116.83(19)</td>
</tr>
<tr>
<td>O(4)-C(4) 1.217(3) C(10)-C(5)-C(6) 118.4(2)</td>
</tr>
<tr>
<td>C(4)-C(5) 1.455(3) C(10)-C(5)-C(4) 118.0(2)</td>
</tr>
<tr>
<td>C(5)-C(10) 1.398(3) C(6)-C(5)-C(4) 123.5(2)</td>
</tr>
<tr>
<td>C(5)-C(6) 1.422(3) C(7)-C(6)-C(5) 118.5(2)</td>
</tr>
<tr>
<td>C(6)-C(7) 1.378(3) C(7)-C(6)-C(13) 118.9(2)</td>
</tr>
<tr>
<td>C(6)-C(13) 1.501(3) C(5)-C(6)-C(13) 122.6(2)</td>
</tr>
<tr>
<td>C(7)-C(8) 1.399(3) C(6)-C(7)-C(8) 121.8(2)</td>
</tr>
<tr>
<td>C(8)-O(14) 1.354(3) O(14)-C(8)-C(9) 122.3(2)</td>
</tr>
<tr>
<td>C(8)-C(9) 1.388(3) O(14)-C(8)-C(7) 117.5(2)</td>
</tr>
<tr>
<td>C(9)-C(10) 1.381(3) C(9)-C(8)-C(7) 120.3(2)</td>
</tr>
<tr>
<td>C(10)-O(1)-C(2) 115.08(17) C(10)-C(9)-C(8) 118.1(2)</td>
</tr>
<tr>
<td>O(1)-C(2)-O(3) 109.41(17) O(1)-C(10)-C(9) 116.8(2)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(12) 106.47(18) O(1)-C(10)-C(5) 120.4(2)</td>
</tr>
<tr>
<td>O(3)-C(2)-C(12) 106.24(19) O(1)-C(10)-C(5) 122.8(2)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(11) 111.44(19)</td>
</tr>
</tbody>
</table>

Table 27. Bond Lengths [Å] and Angles [°] for 155
6.4.4 Branched Isomer Crystal Structure (149)

7-Hydroxy-2,2-dimethyl-8-(2-methylbut-3-en-2-yl)-5-phenethyl-4H/benzo[ 

\[
\text{d}][1,3] \text{dioxin-4-one (149)}
\]

**Cambridge CCDC code:** NAQBOY


**Table 28. Crystal data and structure refinement for 149**

<table>
<thead>
<tr>
<th>Identification code</th>
<th>149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{23}H_{26}O_{4}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>366.44</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 K</td>
</tr>
<tr>
<td>Diffractometer, wavelength</td>
<td>OD Xcalibur PX Ultra, 1.54184 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 15.26657(8) \text{ Å}) (\alpha = 90^\circ) (\beta = 94.2348(5)^\circ)</td>
</tr>
<tr>
<td></td>
<td>(b = 11.06990(8) \text{ Å})</td>
</tr>
</tbody>
</table>
Volume, $Z$  
$4034.94(4)$ Å$^3$, 8
Density (calculated)  
$1.206$ Mg/m$^3$
Absorption coefficient  
$0.654$ mm$^{-1}$
$F(000)$  
$1568$
Crystal colour / morphology  
Colourless needles
Crystal size  
$0.26 \times 0.09 \times 0.04$ mm$^3$
$\theta$ range for data collection  
$2.90$ to $72.47^\circ$
Index ranges  
$-18 \leq h \leq 18$, $-13 \leq k \leq 13$, $-29 \leq l \leq 19$
Reflns collected / unique  
$32362 / 7923$ [R(int) = 0.0206]
Reflns observed [$F > 4 \sigma (F)$]  
$6771$
Absorption correction  
Analytical
Max. and min. transmission  
$0.977$ and $0.896$
Refinement method  
Full-matrix least-squares on $F^2$
Data / restraints / parameters  
$7923 / 121 / 535$
Goodness-of-fit on $F^2$  
$1.074$
Final R indices [$F > 4 \sigma (F)$]  
$R1 = 0.0483$, $wR2 = 0.1340$
R indices (all data)  
$R1 = 0.0559$, $wR2 = 0.1404$
Extinction coefficient  
$0.00069(12)$
Largest diff. peak, hole  
$0.592$, $-0.324$ eÅ$^{-3}$
Mean and maximum shift/error

### Table 29. Bond Lengths [Å] and Angles [°] for 149

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Bond</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1A)-C(1A)</td>
<td>1.221(2)</td>
<td>O(4A)-C(5A)</td>
<td>1.3678(19)</td>
</tr>
<tr>
<td>C(1A)-O(2A)</td>
<td>1.350(2)</td>
<td>C(5A)-C(6A)</td>
<td>1.397(2)</td>
</tr>
<tr>
<td>C(1A)-C(10A)</td>
<td>1.462(2)</td>
<td>C(5A)-C(10A)</td>
<td>1.410(2)</td>
</tr>
<tr>
<td>O(2A)-C(3A)</td>
<td>1.450(2)</td>
<td>C(6A)-C(7A)</td>
<td>1.408(2)</td>
</tr>
<tr>
<td>C(3A)-O(4A)</td>
<td>1.4118(19)</td>
<td>C(6A)-C(13')</td>
<td>1.540(10)</td>
</tr>
<tr>
<td>C(3A)-C(12A)</td>
<td>1.506(2)</td>
<td>C(6A)-C(13A)</td>
<td>1.566(5)</td>
</tr>
<tr>
<td>C(3A)-C(11A)</td>
<td>1.508(2)</td>
<td>C(7A)-O(18A)</td>
<td>1.3506(19)</td>
</tr>
</tbody>
</table>
C(7A)-C(8A) 1.399(2) C(6B)-C(13B) 1.570(6)
C(8A)-C(9A) 1.378(2) C(7B)-O(18B) 1.348(2)
C(9A)-C(10A) 1.414(2) C(7B)-C(8B) 1.396(2)
C(9A)-C(19A) 1.514(2) C(8B)-C(9B) 1.379(2)
C(13A)-C(14A) 1.520(6) C(9B)-C(10B) 1.405(2)
C(13A)-C(16A) 1.530(6) C(9B)-C(19B) 1.511(2)
C(13A)-C(17A) 1.541(7) C(13B)-C(17B) 1.505(9)
C(14A)-C(15A) 1.290(9) C(13B)-C(16B) 1.509(7)
C(13')-C(14') 1.493(9) C(13B)-C(14B) 1.571(9)
C(13')-C(16') 1.519(10) C(14B)-C(15B) 1.279(8)
C(13')-C(17') 1.549(9) C(13")-C(14") 1.529(15)
C(14')-C(15') 1.309(12) C(13")-C(16") 1.532(15)
C(19A)-C(20A) 1.536(2) C(13")-C(17") 1.546(12)
C(20A)-C(21A) 1.505(3) C(14")-C(15") 1.246(10)
C(21A)-C(22A) 1.385(3) C(13")-C(14") 1.480(11)
C(21A)-C(26A) 1.386(2) C(13")-C(17") 1.504(10)
C(22A)-C(23A) 1.388(3) C(13")-C(16") 1.610(10)
C(23A)-C(24A) 1.378(4) C(14")-C(15") 1.294(11)
C(24A)-C(25A) 1.367(3) C(19B)-C(20B) 1.538(2)
C(25A)-C(26A) 1.383(3) C(20B)-C(21B) 1.509(2)
O(1B)-C(1B) 1.217(2) C(21B)-C(22B) 1.381(3)
C(1B)-O(2B) 1.348(2) C(21B)-C(26B) 1.391(2)
C(1B)-C(10B) 1.462(2) C(22B)-C(23B) 1.381(3)
O(2B)-C(3B) 1.451(2) C(23B)-C(24B) 1.376(3)
C(3B)-O(4B) 1.417(2) C(24B)-C(25B) 1.377(3)
C(3B)-C(11B) 1.505(3) C(25B)-C(26B) 1.386(3)
C(3B)-C(12B) 1.510(3) O(1A)-C(1A)-O(2A) 116.90(15)
O(4B)-C(5B) 1.370(2) O(1A)-C(1A)-C(10A) 125.16(16)
C(5B)-C(6B) 1.399(2) O(2A)-C(1A)-C(10A) 117.91(15)
C(5B)-C(10B) 1.407(2) C(1A)-O(2A)-C(3A) 118.15(13)
C(6B)-C(7B) 1.408(2) O(4A)-C(3A)-O(2A) 109.08(13)
C(6B)-C(13") 1.529(7) O(4A)-C(3A)-C(12A) 106.14(14)
C(6B)-C(13") 1.555(12) O(2A)-C(3A)-C(12A) 106.66(14)
6 Experimental

O(4A)-C(3A)-C(11A) 111.75(14) C(16')-C(13')-C(17') 109.4(7)
O(2A)-C(3A)-C(11A) 109.53(14) C(6A)-C(13')-C(17') 100.5(6)
C(12A)-C(3A)-C(11A) 113.45(15) C(15')-C(14')-C(13') 128.9(10)
C(5A)-O(4A)-C(3A) 115.67(13) C(9A)-C(19A)-C(20A) 111.19(14)
O(4A)-C(5A)-C(6A) 117.36(15) C(21A)-C(20A)-C(19A) 112.69(14)
O(4A)-C(5A)-C(10A) 117.73(14) C(22A)-C(21A)-C(26A) 117.87(18)
C(6A)-C(5A)-C(10A) 124.85(15) C(22A)-C(21A)-C(20A) 120.96(17)
C(5A)-C(6A)-C(7A) 114.06(15) C(26A)-C(21A)-C(20A) 121.16(16)
C(5A)-C(6A)-C(13') 122.1(4) C(21A)-C(22A)-C(23A) 120.9(2)
C(7A)-C(6A)-C(13') 123.3(4) C(24A)-C(23A)-C(22A) 120.2(2)
C(5A)-C(6A)-C(13A) 124.9(2) C(25A)-C(24A)-C(23A) 119.4(2)
C(7A)-C(6A)-C(13A) 120.9(2) C(24A)-C(25A)-C(26A) 120.5(2)
O(18A)-C(7A)-C(8A) 119.27(14) C(25A)-C(26A)-C(21A) 121.07(18)
O(18A)-C(7A)-C(6A) 118.55(15) O(1B)-C(1B)-O(2B) 116.90(15)
C(8A)-C(7A)-C(6A) 122.18(15) O(1B)-C(1B)-C(10B) 125.40(17)
C(9A)-C(8A)-C(7A) 122.56(15) O(2B)-C(1B)-C(10B) 117.69(15)
C(8A)-C(9A)-C(10A) 117.30(15) C(1B)-O(2B)-C(3B) 118.29(13)
C(8A)-C(9A)-C(19A) 118.27(14) O(4B)-C(3B)-O(2B) 109.06(15)
C(10A)-C(9A)-C(19A) 124.38(15) O(4B)-C(3B)-C(11B) 106.16(18)
C(5A)-C(10A)-C(9A) 118.82(15) O(2B)-C(3B)-C(11B) 106.19(16)
C(5A)-C(10A)-C(1A) 118.12(15) O(4B)-C(3B)-C(12B) 112.02(16)
C(9A)-C(10A)-C(1A) 123.00(15) O(2B)-C(3B)-C(12B) 109.38(18)
C(14A)-C(13A)-C(16A) 111.4(4) C(11B)-C(3B)-C(12B) 113.78(19)
C(14A)-C(13A)-C(17A) 102.0(4) C(5B)-O(4B)-C(3B) 115.04(14)
C(16A)-C(13A)-C(17A) 110.5(4) O(4B)-C(5B)-C(6B) 117.32(15)
C(14A)-C(13A)-C(6A) 113.5(3) O(4B)-C(5B)-C(10B) 117.79(15)
C(16A)-C(13A)-C(6A) 104.9(4) C(6B)-C(5B)-C(10B) 124.86(16)
C(17A)-C(13A)-C(6A) 114.6(4) C(5B)-C(6B)-C(7B) 114.09(15)
C(15A)-C(14A)-C(13A) 128.6(6) C(5B)-C(6B)-C(13*) 117.5(3)
C(14')-C(13')-C(16') 106.4(6) C(7B)-C(6B)-C(13*) 127.6(3)
C(14')-C(13')-C(6A) 117.5(7) C(5B)-C(6B)-C(13") 121.7(5)
C(16')-C(13')-C(6A) 113.5(6) C(7B)-C(6B)-C(13") 124.3(5)
C(14')-C(13')-C(17') 109.3(6) C(5B)-C(6B)-C(13B) 122.1(3)

315
C(7B)-C(6B)-C(13B) 123.7(3)  C(16")-C(13")-C(6B) 105.3(9)
O(18B)-C(7B)-C(8B) 119.13(15)  C(17")-C(13")-C(6B) 115.6(7)
O(18B)-C(7B)-C(6B) 119.11(15)  C(15")-C(14")-C(13") 128.1(8)
C(8B)-C(7B)-C(6B) 121.76(15)  C(14")-C(13")-C(17") 109.0(7)
C(9B)-C(8B)-C(7B) 122.89(15)  C(14")-C(13")-C(6B) 111.6(6)
C(8B)-C(9B)-C(10B) 117.31(15)  C(17*)-C(13*)-C(6B) 121.8(6)
C(8B)-C(9B)-C(19B) 118.01(15)  C(14*)-C(13*)-C(16*) 107.3(6)
C(10B)-C(9B)-C(19B) 124.66(14)  C(17*)-C(13*)-C(16*) 102.8(7)
C(9B)-C(10B)-C(5B) 118.85(15)  C(6B)-C(13*)-C(16*) 102.8(6)
C(9B)-C(10B)-C(1B) 123.01(15)  C(15*)-C(14*)-C(13*) 118.2(8)
C(5B)-C(10B)-C(1B) 118.06(15)  C(9B)-C(19B)-C(20B) 109.47(14)
C(17B)-C(13B)-C(16B) 111.5(6)  C(21B)-C(20B)-C(19B) 113.90(15)
C(17B)-C(13B)-C(6B) 110.3(5)  C(22B)-C(21B)-C(26B) 118.12(16)
C(16B)-C(13B)-C(6B) 116.9(4)  C(22B)-C(21B)-C(20B) 120.97(16)
C(17B)-C(13B)-C(14B) 111.9(5)  C(26B)-C(21B)-C(20B) 120.90(17)
C(16B)-C(13B)-C(14B) 100.5(5)  C(23B)-C(22B)-C(21B) 121.21(17)
C(6B)-C(13B)-C(14B) 105.2(5)  C(24B)-C(23B)-C(22B) 120.06(18)
C(15B)-C(14B)-C(13B) 125.5(6)  C(23B)-C(24B)-C(25B) 119.82(17)
C(14")-C(13")-C(16") 110.3(8)  C(24B)-C(25B)-C(26B) 119.97(17)
C(14")-C(13")-C(17") 105.6(9)  C(25B)-C(26B)-C(21B) 120.77(18)
C(16")-C(13")-C(17") 110.3(10)  C(16")-C(13")-C(6B) 109.8(9)
Figure 25: X-ray Crystal Structure One of Branched Isomer 149

Figure 26: X-ray Crystal Structure Two of Branched Isomer 149
7 Bibliography


7 Bibliography


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[73] Studies for the construction of angelicoin B (7) and angelicoin A (6) had previously been carried out by Toni Pfaffeneder under the supervision of Dr Frederick Calo.


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