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

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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

Copyright Declaration

Abstract

Angelicoin 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).

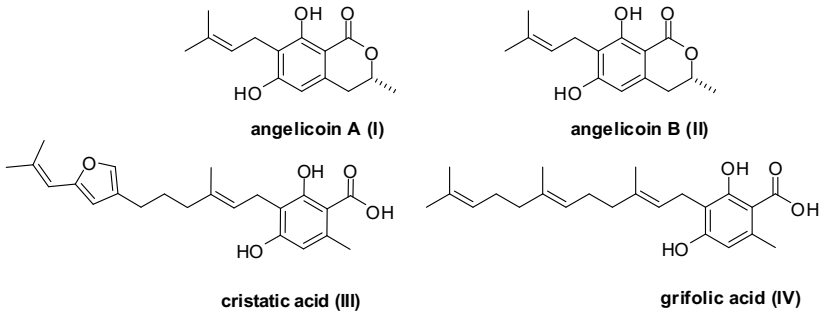
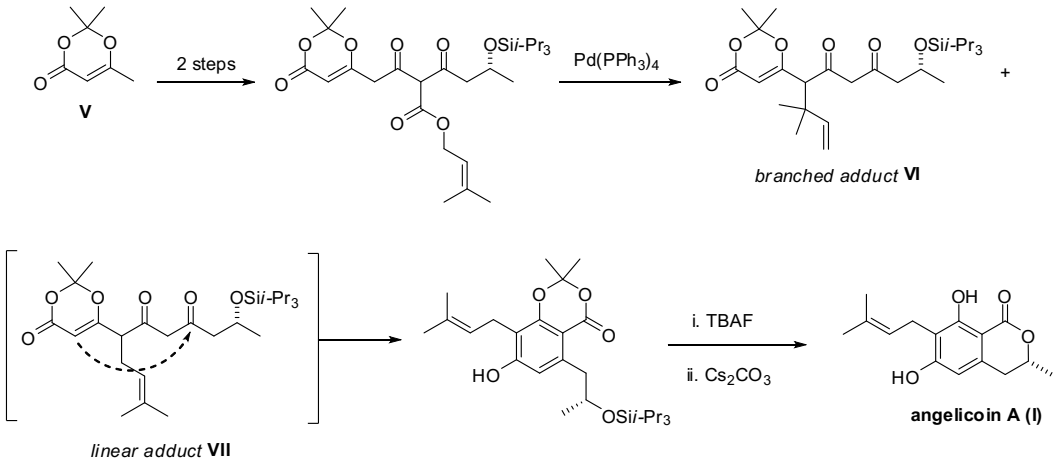


Figure A1

The total syntheses of angelicoin A (**I**) and angelicoin B (**II**) from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **V** are reported using late stage aromatisation reactions *via* diketo-dioxinones 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).[(a)(b)]



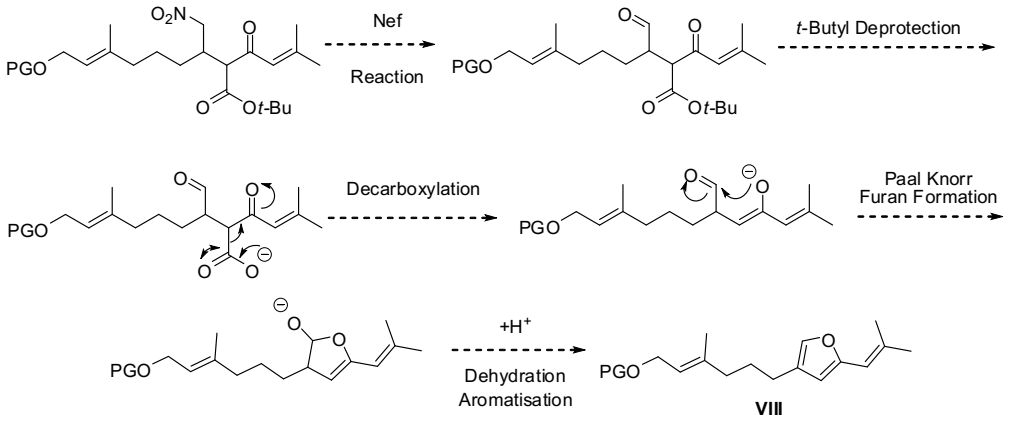
Scheme A1

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.[(a)(c)]

The regioselectivity of this novel palladium(0)-catalysed decarboxylative prenyl migration was determined unambiguously through X-ray crystallographic studies.[(a)(c)] Furthermore, an intermolecular mechanism is proposed after thorough mechanistic studies

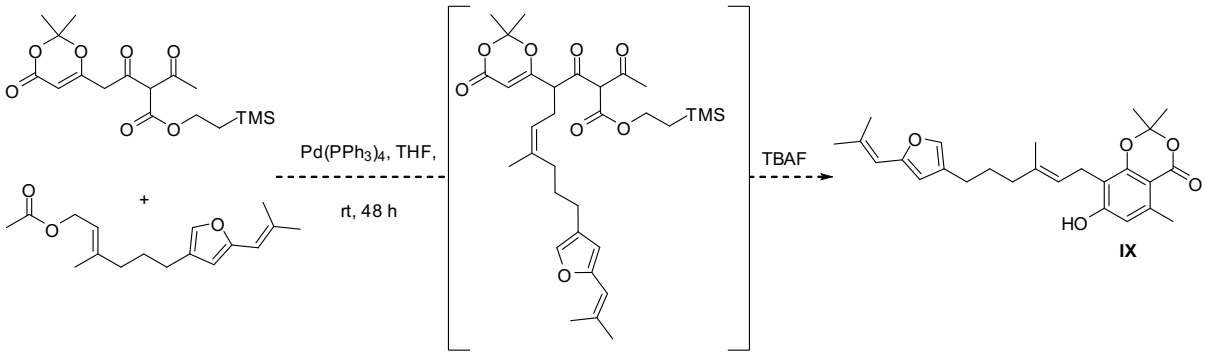
including cross over and variable concentration experiments, base studies, and regioselectivity investigations.

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 **VIII** (Scheme A2), *via* a Nef reaction, deprotection, decarboxylation and furan formation.



Scheme A2

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



Scheme A3

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

References

(a) Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5748- 5750.

(b) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 652-657.

(c) Laclef, S.; Anderson, K.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2012***, 53*, 225-227.

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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
CI	chemical ionisation
cm^{-1}	reciprocal centimetre
COD	1,5-cyclooctadiene
conc.	concentration
COSY	correlation spectroscopy
Cp	cyclopentadienyl
d	doublet
d_6	deuterated

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4 bis(diphenylphosphino)butane
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulphoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBP	di-*tert*-butyl peroxide
DUPHOS	1,2-bis[(2*R*,5*R*)-2,5-diisopropylphospholano]benzene
E	*entgegen* (on opposite sides)
EI	electron impact
equiv.	equivalent
ESI	electrospray ionisation
et al.	*et alii* (and others)
EWG	electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
g	gram
GC	gas chromatography
GPR	G- protein coupled receptor
GSK3	glycogen synthase kinase 3
h	hour
HBTU	*O*-benzotriazole-*N*,*N*,*N*',*N*'-tetramethyl-uronium-hexafluoro-phosphate
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy

HSP90	Heat Shock Protein 90
HSQC	heteronuclear single quantum correlation
HWE	Horner Wadsworth Emmons
Hz	hertz
IR	infrared
J	coupling constant (in NMR)
L	litre
LDA	lithium diisoproplyamine
LiHMDS	lithium bis(trimethylsilyl)amide
m	milli; multiplet (NMR spectroscopy); metre; medium (IR spectroscopy); *meta*
M	molarity; Mega
m.p.	melting point
MAP	mitogen-activated protein
M-CoA	malonyl coenzyme A
m-CPBA	meta-chloroperoxybenzoic acid
Mes	mesitylene
min	minute
mol	mole
MOM	methoxy methyl ether
MOP	2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
MS	mass spectroscopy; molecular sieves
MsCl	methanesulphonyl chloride
n	nano
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	nucleophile
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PG	protecting group
pH	measure of the activity of the (solvated) hydrogen ion
PHOX	phosphinooxazolines
pKa	acid dissociation constant at logarithmic scale

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
ν_{max}	strong and selected absorbances (in IR)
w	weak
wt. %	weight percentage
Z	*Zusammen* (on the same side)
α	alpha
β	beta
γ	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]

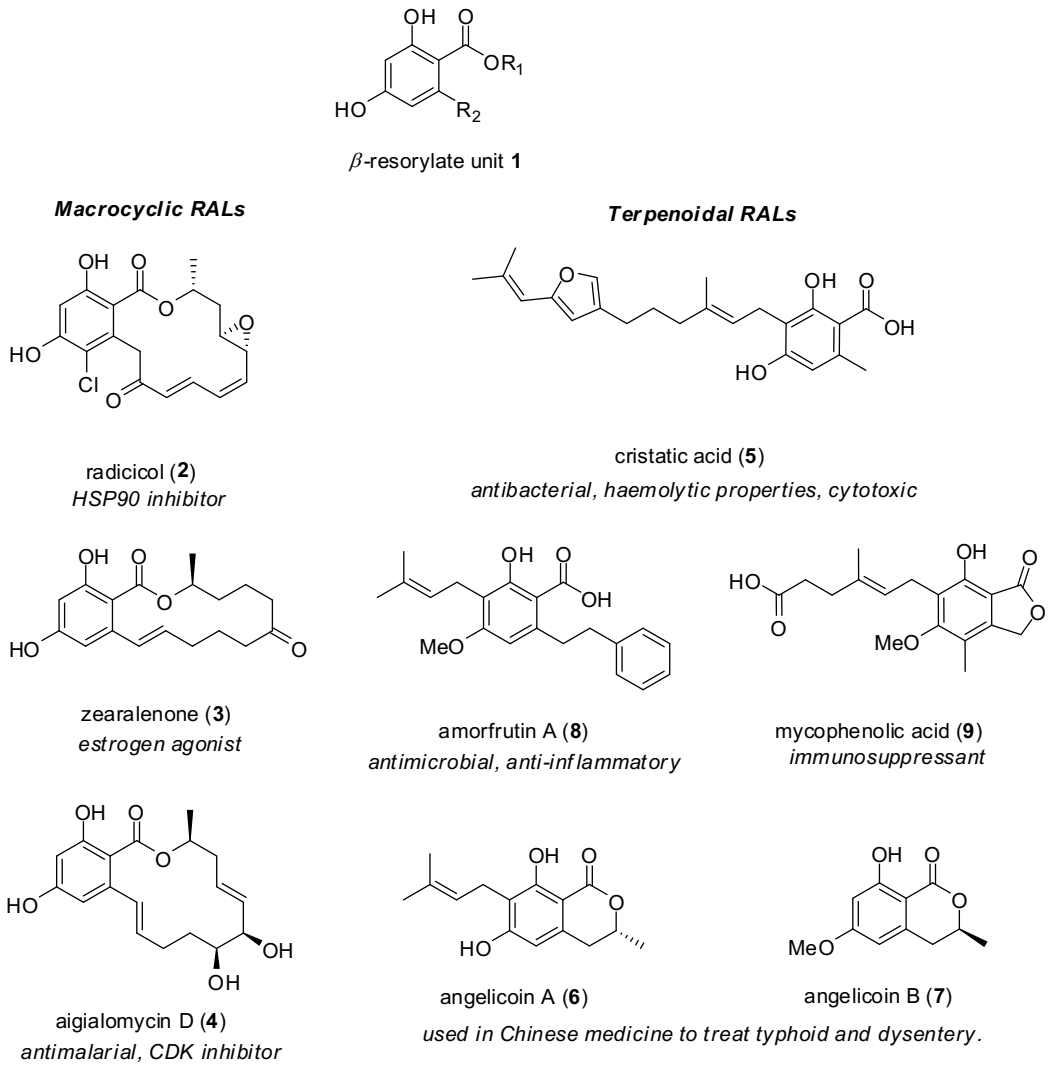


Figure 1: Resorcylic Acid Lactones (RALs)

RALs can vary widely in their structure, for example radicicol (**2**),[2] zearaleone (**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] angelicoin A (**6**),[8][9] angelicoin B (**7**),[8][9] amorfruitin A (**8**)[10] and

mycophenolic acid (**9**)[11] contain the *β*-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).[12] Additionally, the pharmaceutical industry[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).[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 *Humicola fuscoatrais*[2] is a potent and selective inhibitor of Heat Shock Protein 90 (HSP90).[18] HSP90 is upregulated in cancer cells and radicicol (**2**) is a competitive ligand for the ATP binding site.[17] Some RALs such as radicicol (**2**) also inhibit MAP kinases (MAP kinases regulate a cell's response to its environment).[16]

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

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

fruticosa originating in North America, China and Korea.[10] Amorfrutin A (**8**) exhibits narrow spectrum antimicrobial activity against Gram-positive and acid-fast microorganisms.[10]

Cristatic acid (**5**) was isolated in 1981 by Steglich *et al.* from the mushroom *Albatrellus cristatus.*[6] It has been shown to have antibiotic activity against gram-positive bacteria, Haemolytic function and to have an inhibitory effect on the Ehrlich carcinoma.[7][21]

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*.[22] Subsequently, it has been shown to possess many valuable biological properties such as antiviral,[23] antifungal,[24] antibacterial,[25] antitumour[26] and antipsoriasis.[27] 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.[13]

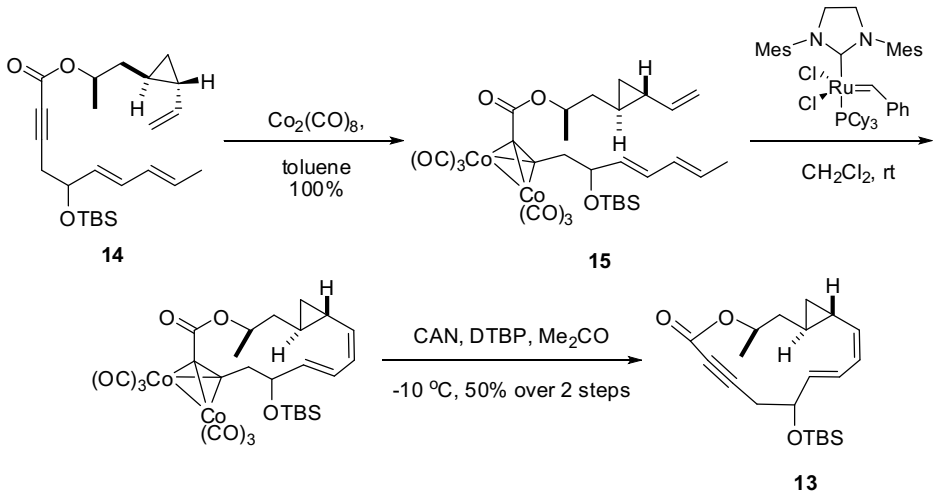
CellCept™ and Myfortic™ work by inhibiting IMPDH (Inosine Monophosphate Dehydrogenase) in purine biosynthesis which is necessary for the growth of T and B cells. Suppressing these cells reduces the risk of organ rejection following a transplant. However, suppression also weakens the body's ability to defend against infection.[13] Myfortic™ and CellCept™ can also be used in the treatment of autoimmune diseases, such as systemic lupus erythematosus and pemphigus vulgaris.[28] Mycophenolic acid (**9**) exemplifies how valuable some resorcylate natural products can be within the pharmaceutical industry.

1.4 Total Syntheses of RALs

*1.4.1 Danishefsky's Approach to Cylcoproparadicicol (**10**)*

Danishefsky *et al.* published the total synthesis of cyclopropara dicicol (**10**) in 2004, utilising a Diels-Alder reaction to put in place the resorcylate core **11**.[29] The Diels-Alder reaction took place between cyclic diene **12** and ynolide **13** (Scheme 2).

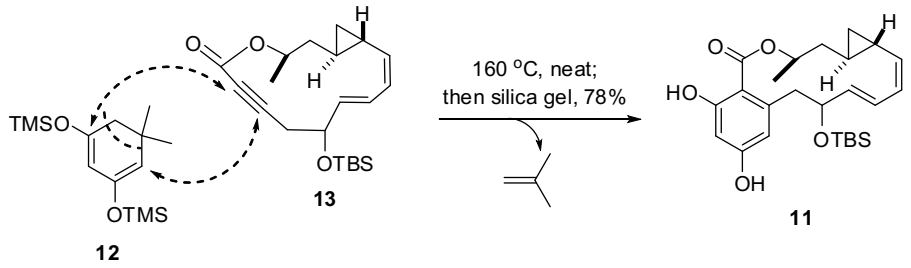
The synthesis of ynolide **13** is shown below in Scheme 1. Ring Closing Metathesis (RCM) was unsuccessful under standard conditions, presumably due to the presence of the acetylene (owing to its linear form thus preventing cyclisation).[29][30] Danishefsky *et al.* employed dicobalt to act as a protecting 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[29]

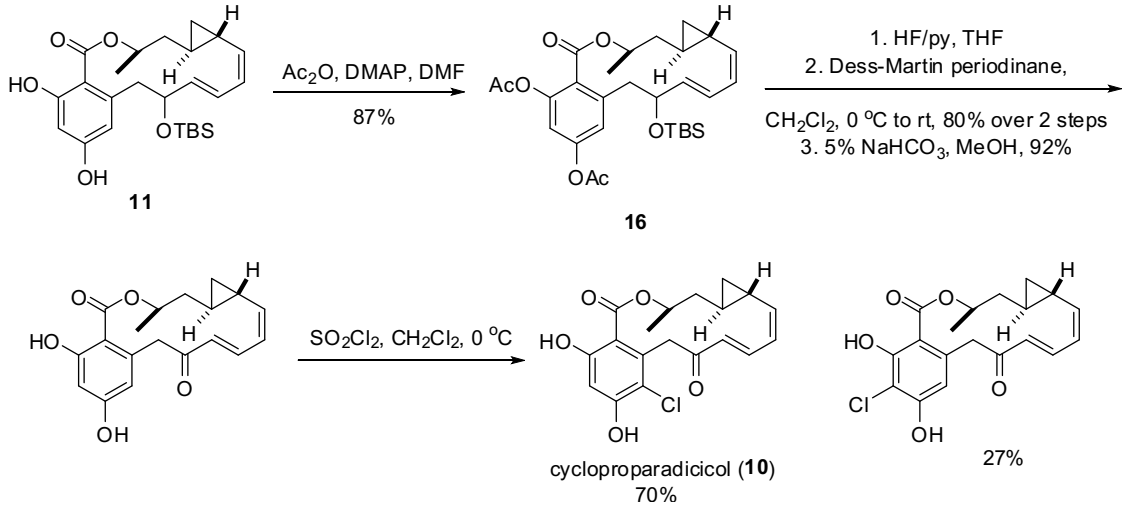
Heating ynolide **13** and cyclic diene **12** facilitated a Diels-Alder reaction; this was followed by selective desilyation of the TMS groups by silica gel chromatography, providing

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[29]

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 oxidiation of the secondary alcohol to a ketone. The acetates were then deprotected, chlorination followed furnishing cyclopropara dicicol (**10**) in a 70% yield.[29] This synthesis exhibits two excellent methodologies which enabled gram quantities of cyclopropara dicicol (**10**) to be produced for biological testing.[29]



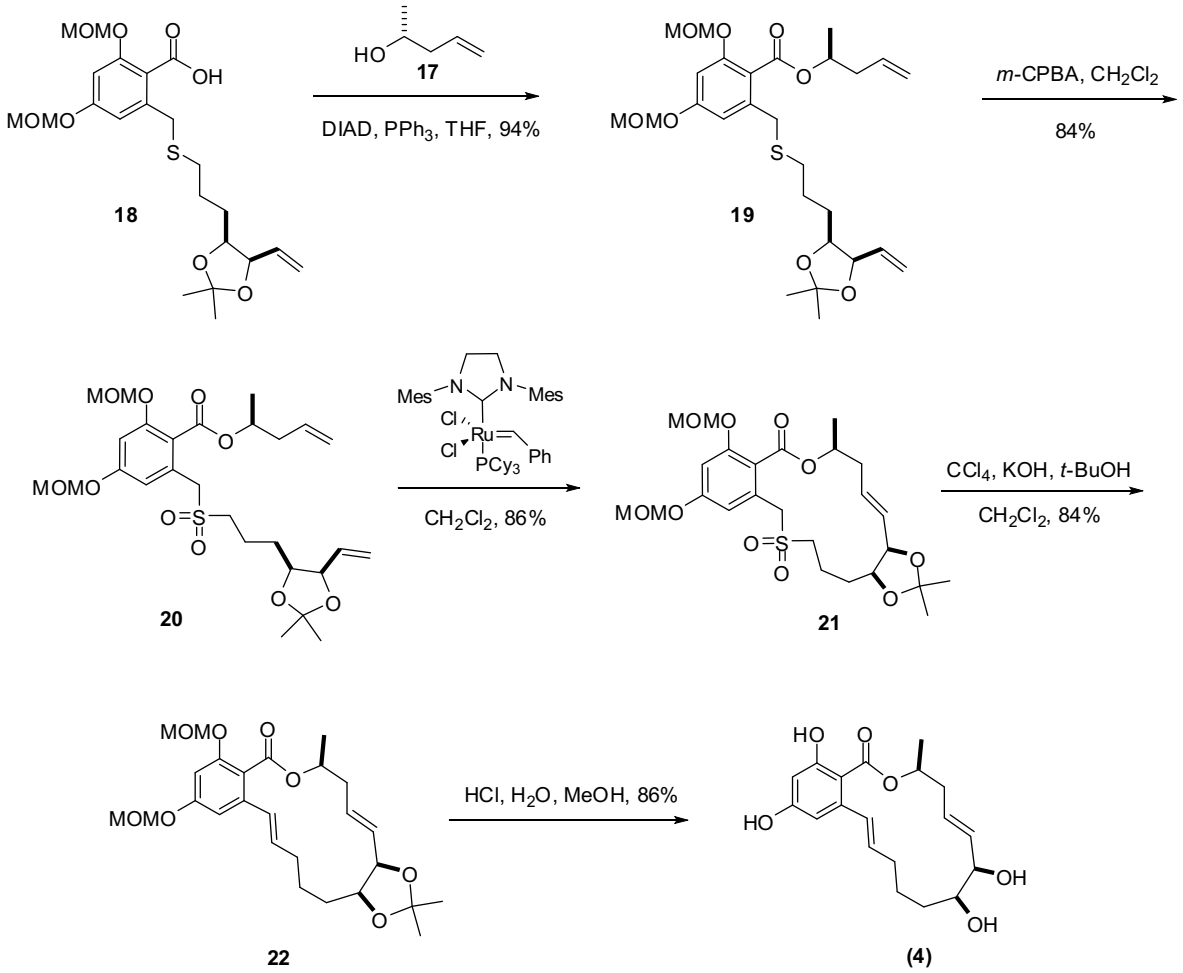
Scheme 3: Final Steps in the Synthesis of Cyclopropara diciol (10)[29]

The synthetic route exemplifies the excellent targets that RALs can be to academic groups. This is shown again in the total synthesis of aigiaolmycin D (**4**) by Harvery *et al.* (Section 1.4.2).[31]

1.4.2 Harvey's Approach to Aigialomycin D (4)

Harvey *et al.* published the total synthesis of aigialomycin D (**4**) in 2008.[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**).[31]



Scheme 4: Synthesis of Aigiaolmycin D (4)[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.

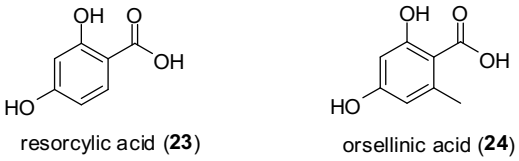
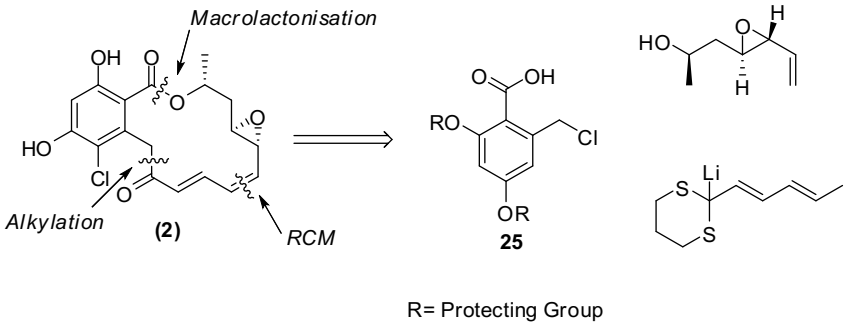


Figure 2: Resorcylic Acid (23) and Orselinic Acid (24)

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.



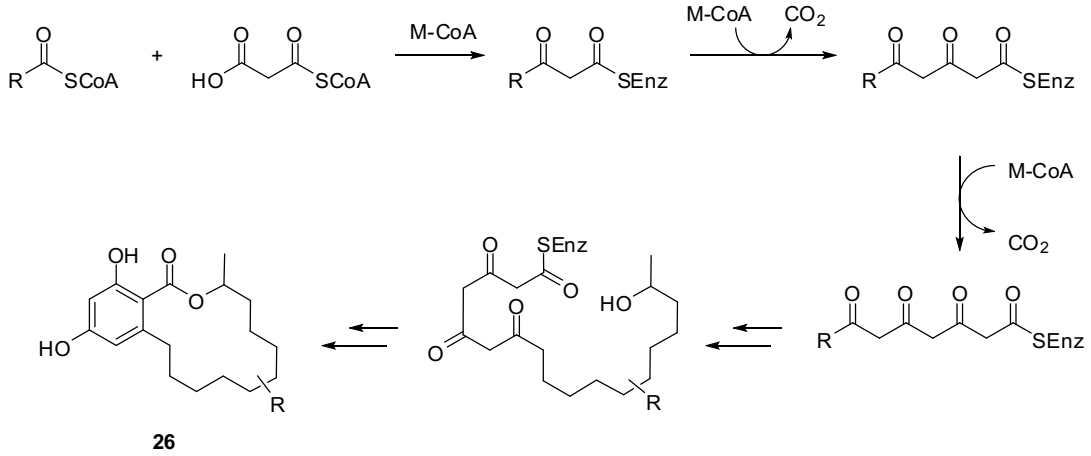
Scheme 5: Retrosynthetic Analysis of Radicicol (2)[32]

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 cyclopropparadicicol (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.[33] Collie's ideas were later revived and formulated by Birch in the 1960's into the polyketide hypothesis, which is still accepted today.[34] 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).[16][35][36]



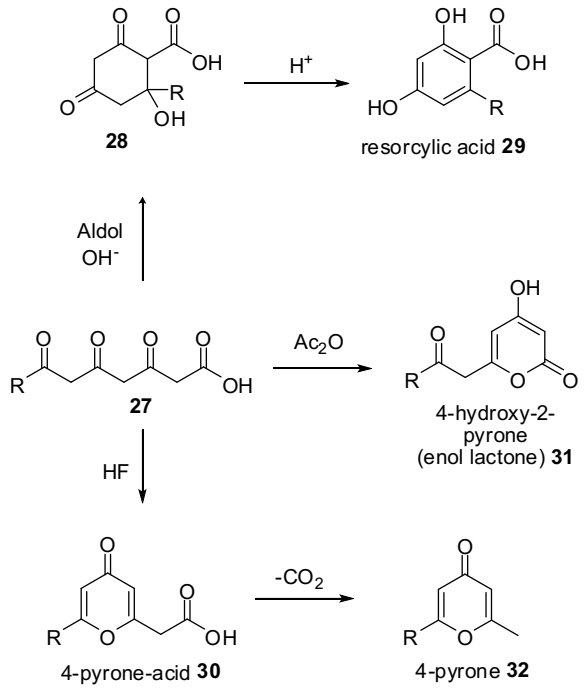
Scheme 6: Biosynthesis of a Polyketide and Aromatisation to an RAL

The biosynthetic pathway is catalysed by polyketide synthases which are large multidomain enzymes found in a variety of fungal strains.[16]

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]



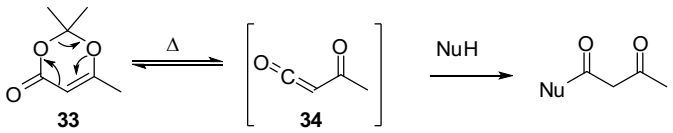
Scheme 7: Cyclisation of Polyketides[37]

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

27 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]

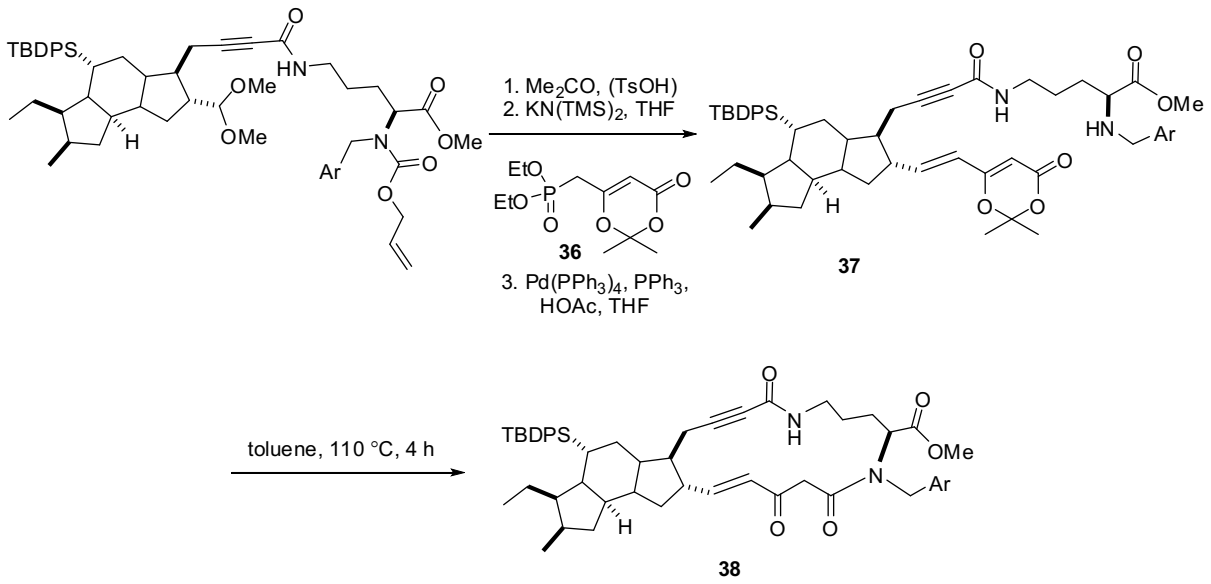
1.8 Dioxinone in Total Synthesis

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 *β*-keto esters or *β*-keto amides (Scheme 8).[39]



Scheme 8: Opening of Dioxinone 33

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 macrocyle **38** (Scheme 9).[41]

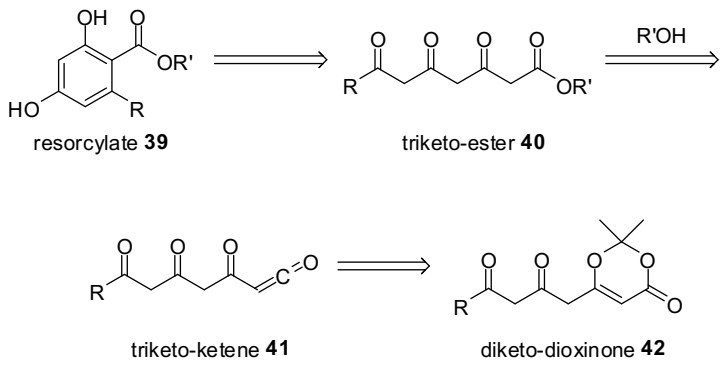


Scheme 9: Dioxinone 36 in the Total Synthesis of (+)-Ikarugamycin[41]

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.,*[34] Harris *et al.*[37] and Hyatt *et al.*[39] 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).



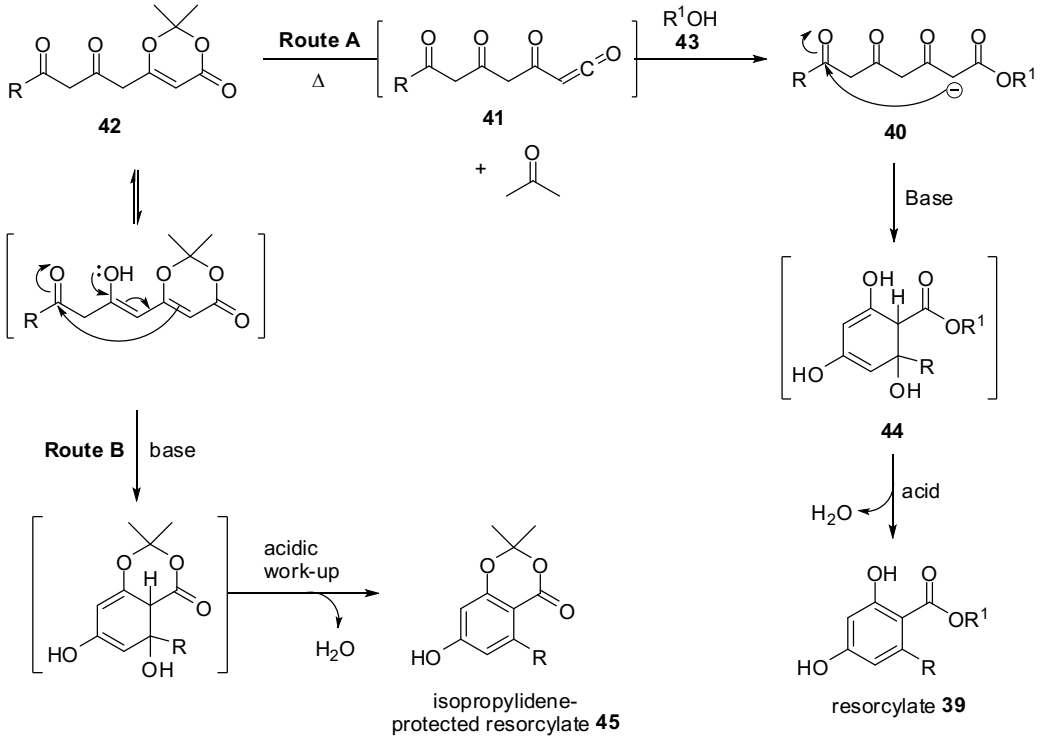
Scheme 10: Retrosynthesis for the Construction of Resorcylate Natural Products

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, Cs_2CO_3 or K_2CO_3 to facilitate the cylcisation. 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 CH_2Cl_2 with Et_3N or alternatively in MeOH with Cs_2CO_3. 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

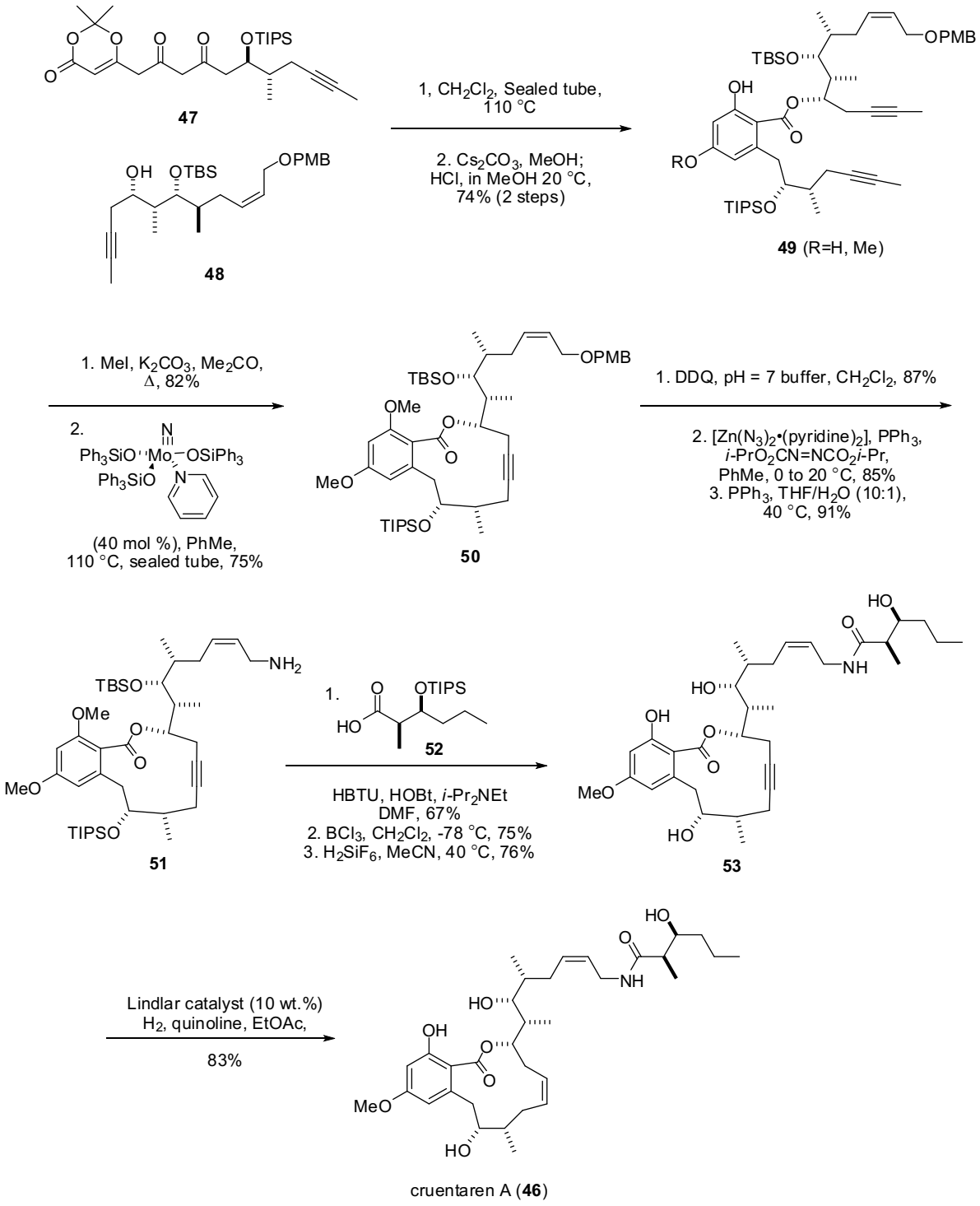
The Barrett approach for the formation of the resorcylate core has been named the '*Late-Stage Aromatisation Strategy.'*

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

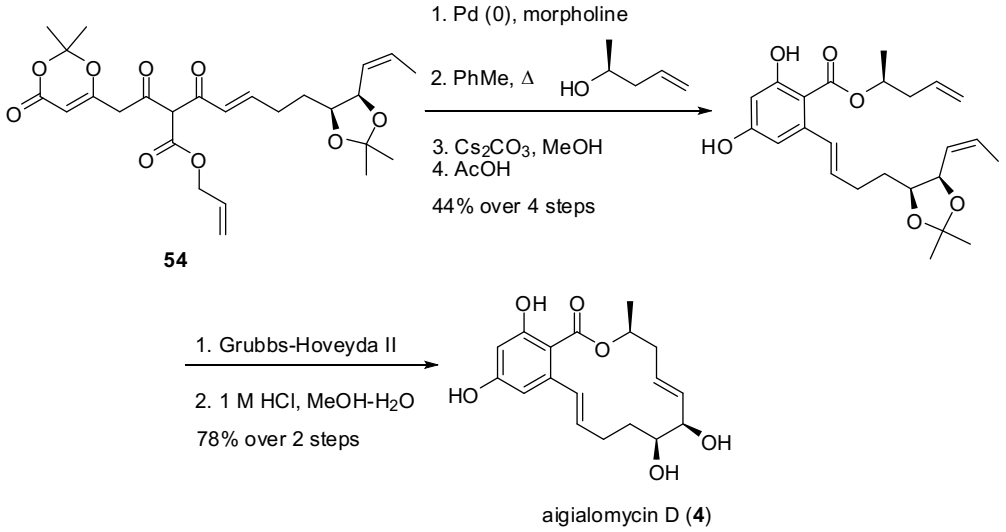
deprotection afforded an alcohol which underwent azide formation *via* a Mitsunobu reaction. Subsequent Staudinger reduction efficiently gave amine **51**. Amide bond formation between amine **51** and carboxylic acid **52** was achieved using HBTU as the coupling reagent. Mono-cleaveage of the methyl group followed by silylether deprotections afforded resorcylate **53**. The final step in the total synthesis involved a Lindlar reduction of the alkyne to give cruentaren A (**46**).[45]



Scheme 12: Synthesis of Cruentaren A (46)[45]

1.12 Discovery of the Decarboxylative Allyl Migration[I]

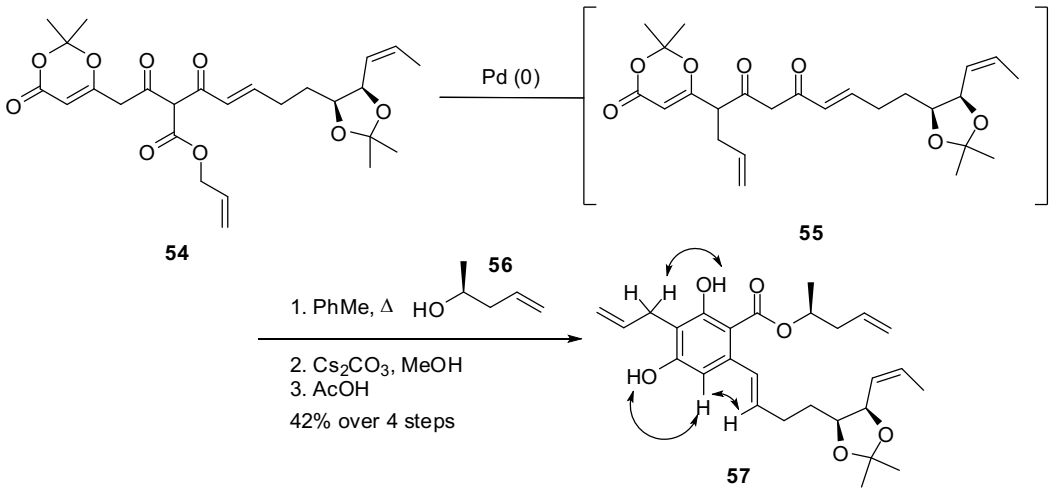
Recently Barrett *et al.* reported the total synthesis of aigialomycin D (**4**).[46] The approach featured a key Pd(0)-catalysed deallylation and decarboxylation of allyl ester **54**, employing morpholine as a nucleophilic palladium π-allyl cation scavenger, to provide the ketene precursor. Subsequent 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)

During these studies Barrett *et al.* observed that reaction of allyl ester **54** with $Pd(PPh_3)_4$ in the absence of mopholine 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).[47]

[I] Section 1.12 has been published: Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. B. *Org. Lett.* **2011**, *13*, 5748-5750.



Scheme 14: Discovery of the Decarboxylative Allyl Migration

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).

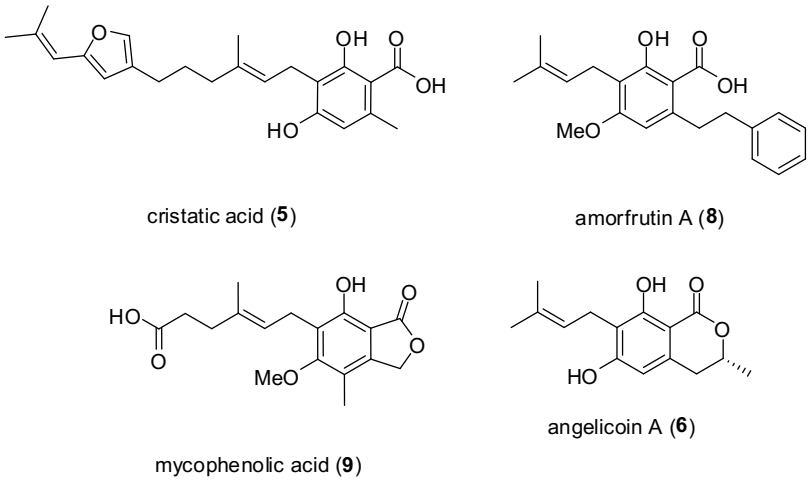
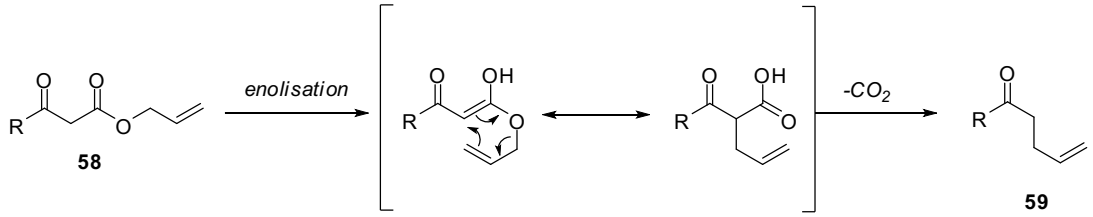


Figure 3: Allylated Resorcylate Natural Products

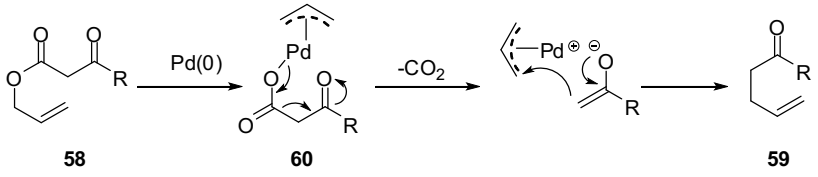
1.13 Decarboxylation and Allylation: The Carroll Rearrangement

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).[48][49] The reaction requires high temperatures, strongly basic conditions and its success can depend on the electronic properties and size of the substrate.[50]



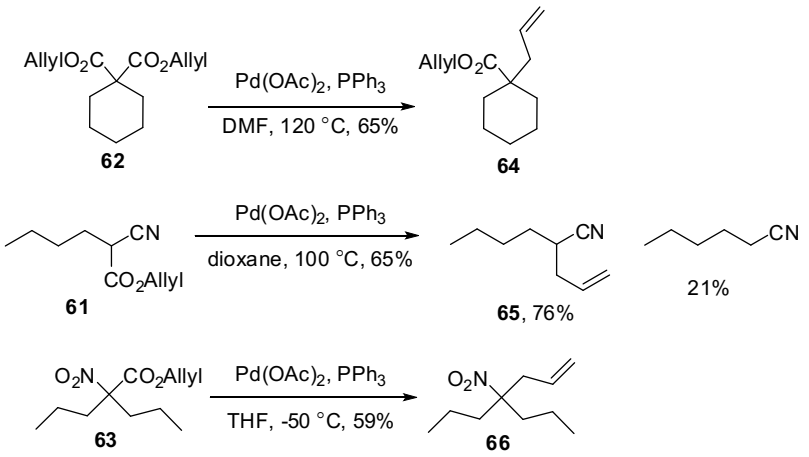
Scheme 15: The Carroll Rearrangement

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).[51] 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**.[52][53][54]



Scheme 16: Tsuji-Trost Reaction

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*-alkylnitro alkane **66** respectively (Scheme 17), presenting the versatility of this transformation.[52]



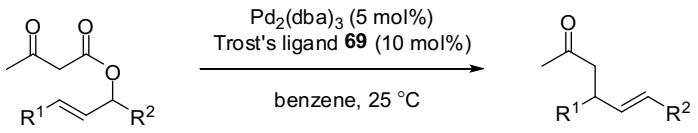
Scheme 17: Versatility of the Tsuji-Trost Reaction[52]

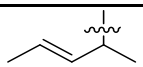
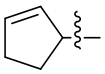
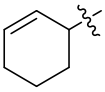
More recently Trost *et al*. and Tunge *et al.* have demonstrated that this pathway can be advanced onto more complicated systems.[55][56][57]

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.[58] In 2004, Tunge *et al.* reported high levels of asymmetric induction through the utilisation of nucleophilic catalysts and chiral ligands.[59] The group investigated the use of $Pd_2(dba)_3$ and Trost's ligand **69**,[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).

Table 1: Asymmetric Palladium-Catalysed Rearrangements of $R^1COCH_2CO_2R^2$[61]



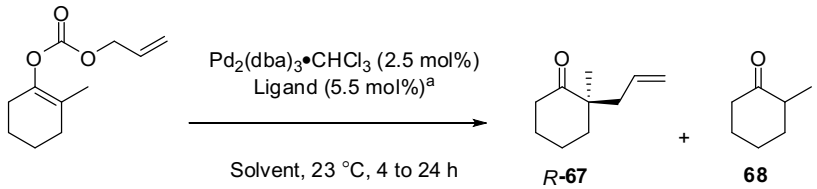
Entry	R^1	R^2	Time/ h	ee[a]	Yield/ %[b]
1	Me		15	86	82
2	Me		15	86	85
3	Me		24	94	75

[a] Measured at 25 °C.
[b] Isolated yield after column chromatography.

1.15 Regio- and Enantioselective Tsuji-Trost Reaction

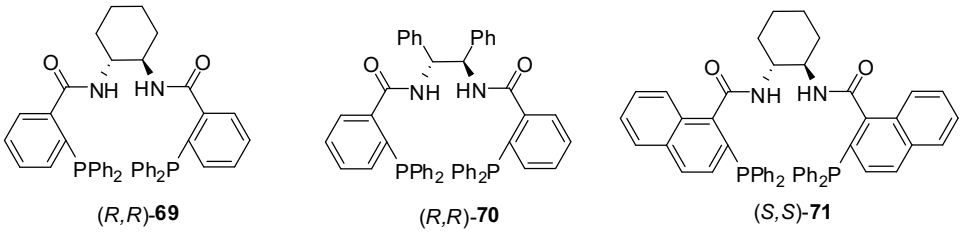
In 2004, Trost *et al.* published studies on a regio- and enantioselective decarboxylative allylic alkylation of ketones through allyl enol carbonates. Table 2 below illustrates some of the optimisation studies for alkylation at the tertiary carbon.[61] The results demonstrated excellent regio- and enantioselectivity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

Table 2: Selected Optimisation Studies[61]



Entry	Ligand	Solvent	ee[b]	Yield of *R*-67/ %[c]	Yield of 68/ %[c]
1	**69**	DME	66	81	8
2	**71**	DME	76	87	2
3	**69**	Toluene	31	73	0
4	**70**	Toluene	61	73	2
5	**71**	Toluene	60	85	1

[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.



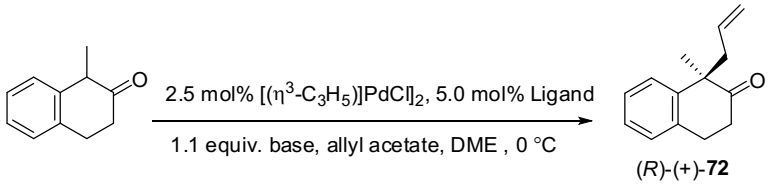
Scheme 18: Chiral Ligands used in Optimisation Studies[61]

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]

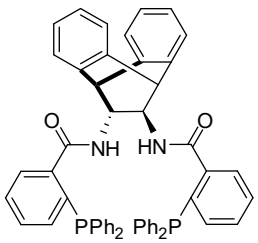
1.16 Counterion Effect in Asymmetric Allylic Alkylation

In 2002, Trost *et al.* published work on the counterion effect in a Pd-catalysed asymmetric allylic alkylation (AAA) (Table 3).[62] 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]



Entry	Base	Ligand	Yield of 72/ %	ee
1	LDA	(*S,S*)-**69**	90%	–33%
2	Cs_2CO_3	(*S,S*)-**69**	91%	+45%
3	Cs_2CO_3	(*S,S*)-**73**	93%	+90%

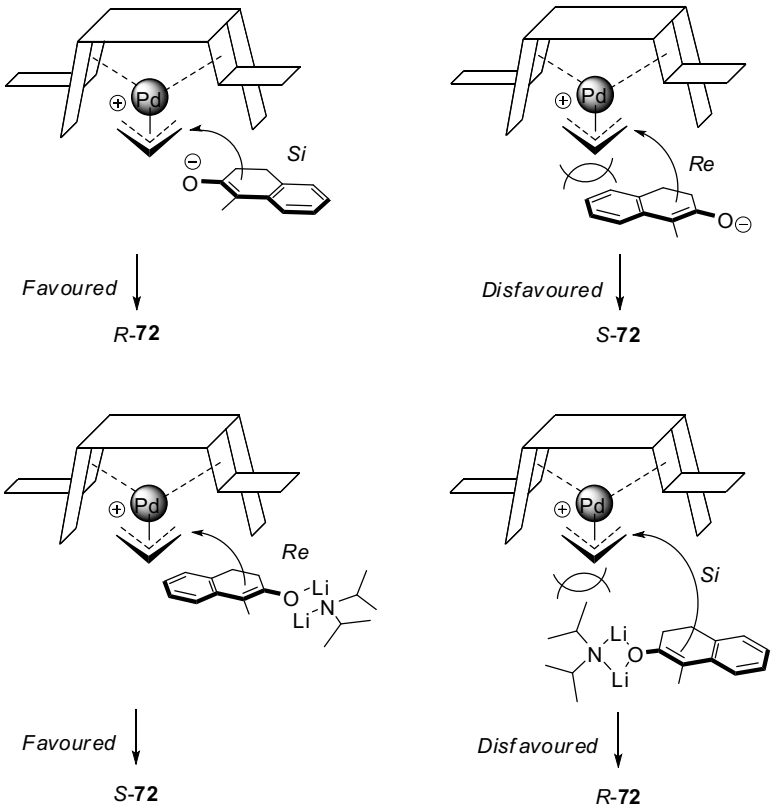


(*R,R*)-**73**

Figure 4: Ligand 73[62]

When non-coordinating Cs_2CO_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).[62][63] Thus enantioselectivity can be explained in this manner depending on the substrate and ligand being used in the transformation.[64]

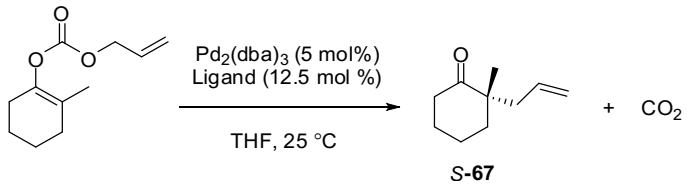


Scheme 19: Cartoon Models for the Alkylation of a Charge Separated Palladium Enolate[63]

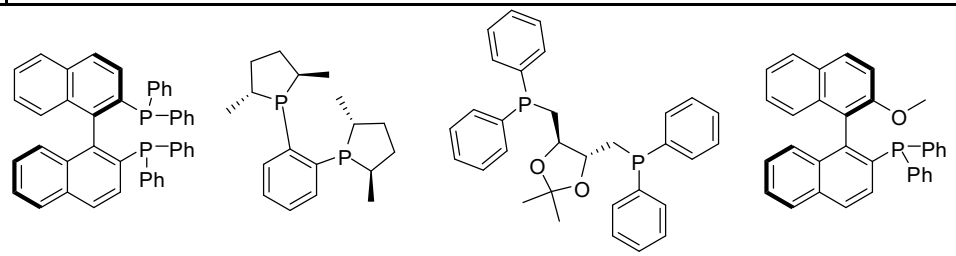
1.17 Enantioselective Ligand Studies

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.[65] These studies showed that in the allylation step the phosphinooxazoline (PHOX) ligands were very good at producing enantioselectivity (Entries 7-10, Table 4).[65]

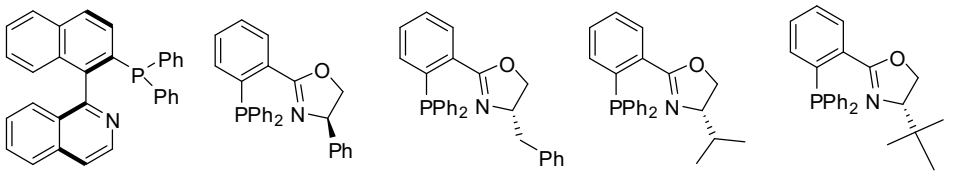
Table 4: Results from Stoltz's Enantioselective Ligand Screening[65]



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



(*R*)-BINAP **74** (*R,R*)-Me-DUPHOS **75** (*R,R*)-DIOP **76** (*R*)-MOP **77**

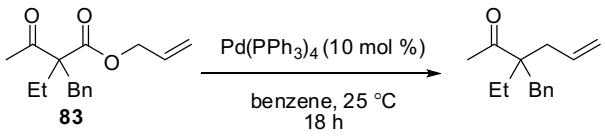


(*R*)-QUINAP **78** (*R*)-Ph-PHOX **79** (*S*)-Bn-PHOX **80** (*S*)-I-Pr-PHOX **81** (*S*)-*t*-Bu-PHOX **82**

Figure 5: Ligands from Table 4[65]

1.18 Mechanistic Studies

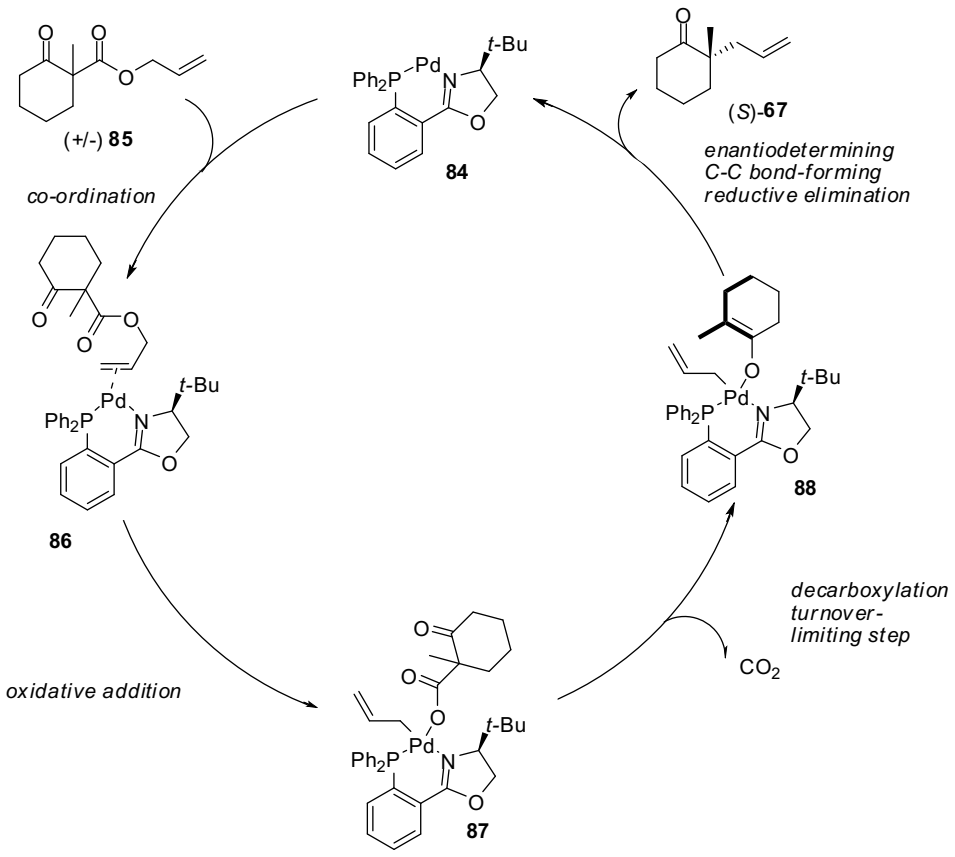
In 2004, Tunge *et al*.[59] performed mechanistic studies to establish the order of decarboxylation and allylation. Through utilisation of a quaternary *α*-carbon **83**, *α*-deprotonation would not be possible therefore the only plausible mechanism would involve decarboxylation followed by allylation (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.[59]



Scheme 20: Substrate and Reaction Conditions Utilised for Tunge's Mechanistic Study[59]

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).[66]

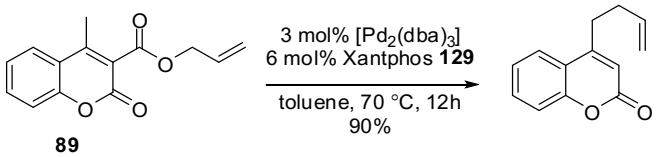
Substrate **84** undergoes coordination to ester **85** to give complex **86** followed by oxidative addition to give carboxylate **87**, (*the resting state of the catalytic cycle*). The next step is decarboxylation (*the turnover limiting step of the catalytic cycle*) affording enolate **88**. Finally, 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**.[66]



Scheme 21: Proposed Mechanism for the Enantioselective Allylic Alkylation[66]

1.19 Decarboxylation, Allylation and Migration

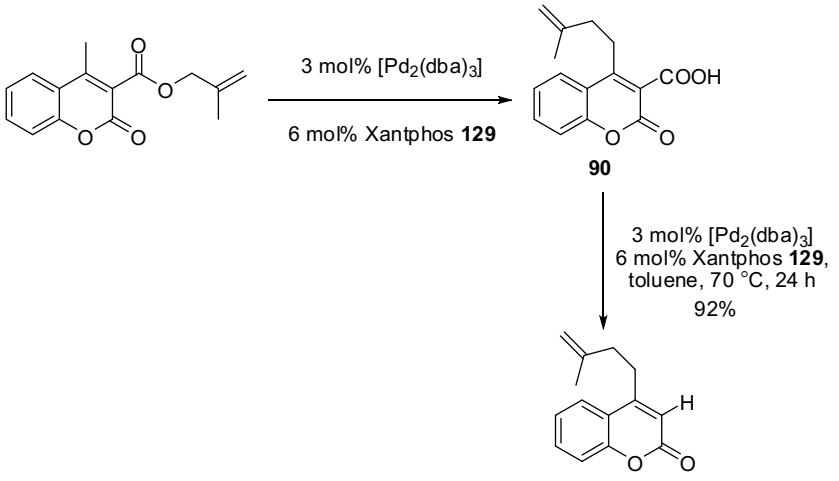
In 2011, Tunge *et al.* published work on a migratory decarboxylative coupling of coumarins. Scheme 22 illustrates optimised conditions for allyl ester **89**.[67]



Scheme 22: Migratory Decarboxylative Allylation[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

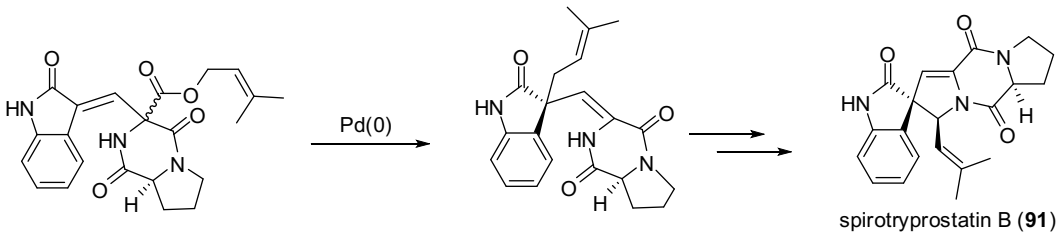
explained why the migration was occurring. This mechanism was deduced because carboxylic acid **90** was isolated in the reaction mixture after 2 h. The acid **90** could then be decarboxylated successfully by treatment with Pd(0) (Scheme 23).[67]



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]



Scheme 24: Synthesis of Spirotryprostatin B (91)[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 resorcylate natural products. Figure 6 illustrates five resorcylate natural products that will be discussed and studied further throughout this thesis.

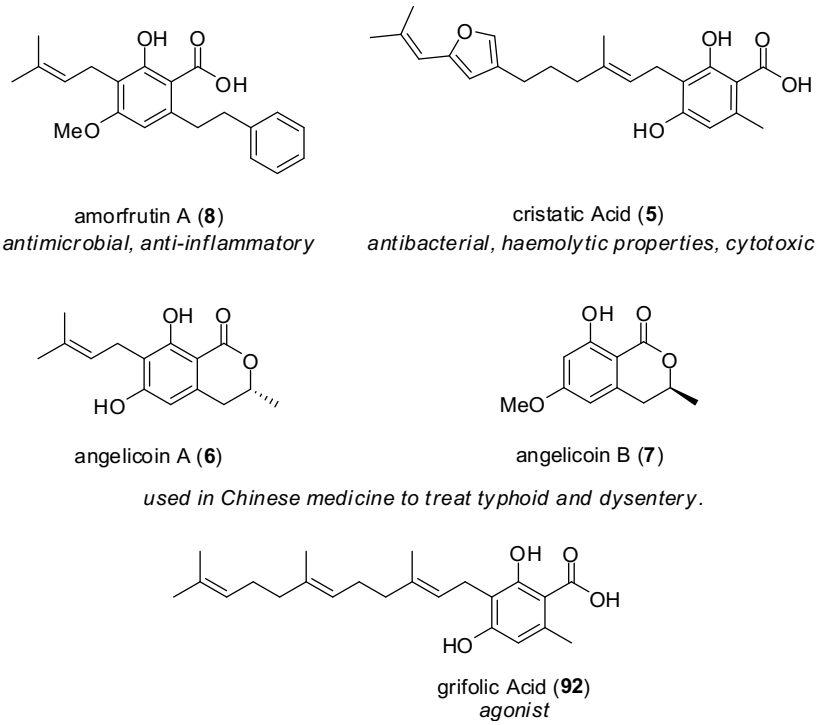


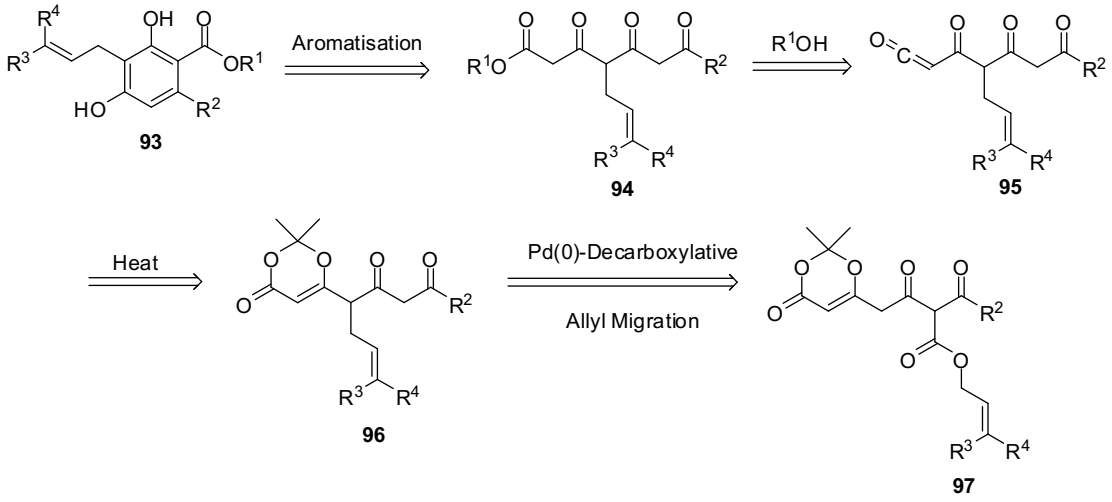
Figure 6: Resorcylate Natural Products

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

(**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.[70]

1.22 General Retrosynthetic Strategy

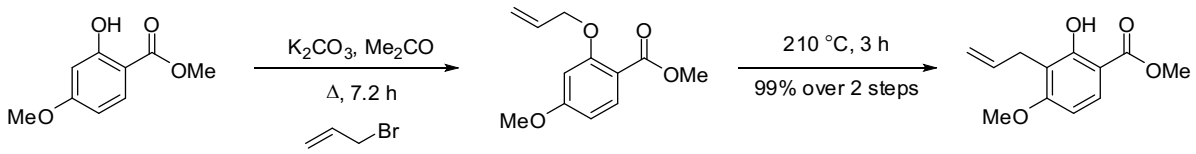
Scheme 25 below illustrates a general retrosynthetic strategy for the construction of angelicoin A (**6**), amorfrutin A (**8**), grifolic acid (**92**) and cristatic acid (**5**) (Figure 6). It was envisaged that resorcylate **93** could be obtained from aromatisation of triketo-acid **94** (R^1=H). 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

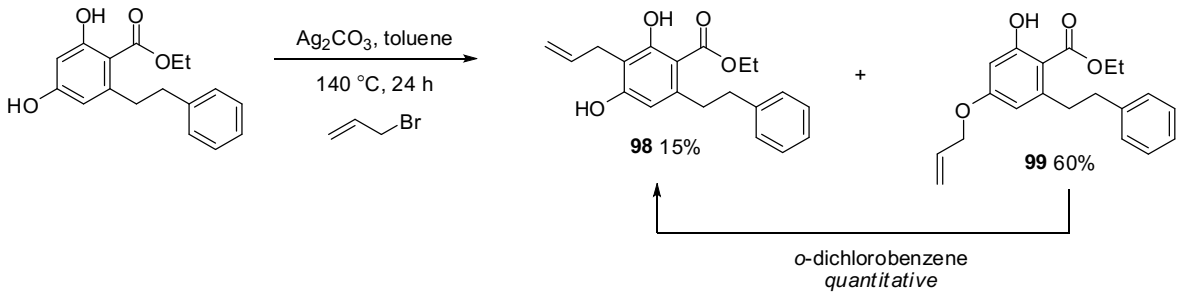
1.23 Alternative Strategies for the Incorporation of an Allyl Moiety onto the Resorcylate Core

The retrosynthetic strategy (Scheme 25) would enable the formation of a substituted aromatic resoryclate 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]

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]

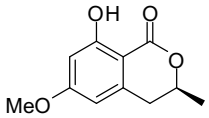
1.24 Research Project Aims

The aim of this research project was to demonstrate a Pd(0)-catalysed regioselective decarboxylative, allylation 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-allylation 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)[II]

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

Angelicoin B (**7**)[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).[42][43]



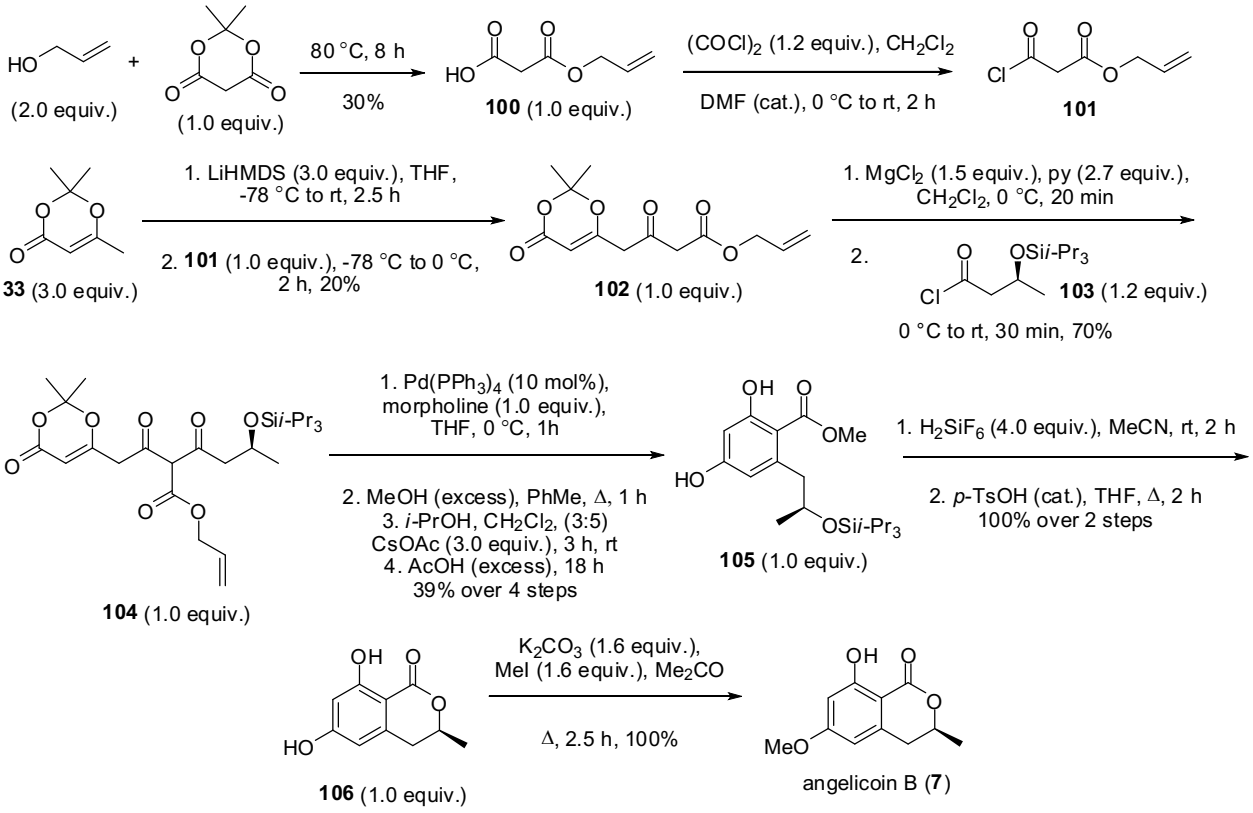
angelicoin B (**7**)

Figure 7: Angelicoin B (7)

Previous studies, within the Barrett group, for the construction of angelicoin B (**7**) are illustrated below in Scheme 28.[73] The first step in the synthesis utilised a similar method first described by Tararov *et al.* in 2006.[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 $MgCl_2$ and pyridine followed by acid chloride **103** furnished diketo-ester dioxinone **104**. Treatment of diketoester-dioxinone **104** with $Pd(PPh_3)_4$ and morpholine followed by late stage aromatisation conditions[42][43] provided resorcylate **105** in 39% yield over 4 steps. Deprotection of the silylether **105** followed by acid mediated

[II] Parts of Chapter 2 have been published and therefore have similarity to Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. B. *Org. Lett.* **2011**, *13*, 5748-5750 and Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.*, **2012**, *77*, 652–657.

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)

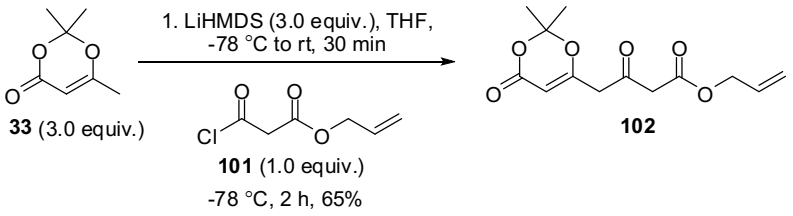
There were a number of key steps that needed attention in the synthesis (Scheme 28): yield optimisation was essential for the thermolysis of allyl alcohol with Meldrum's acid; the Claisen condensation of acid chloride **101** onto dioxinone **33** and the decarboxylation, deallylation and aromatisation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

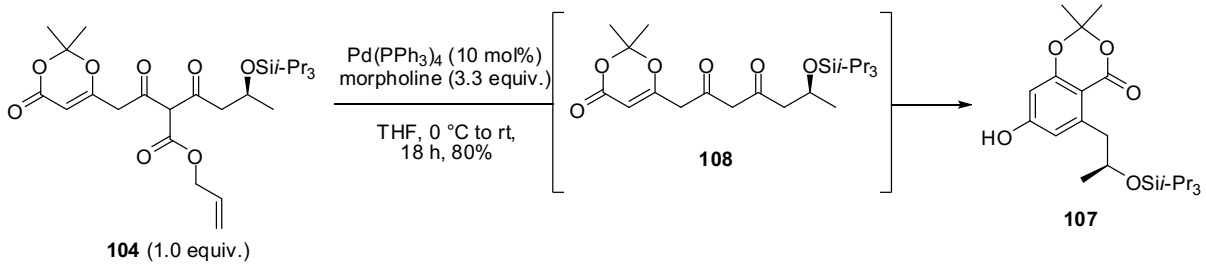
It was hypothesised that the second cause for the low yield of keto-ester-dioxinone **102** was due to the reaction temperature following the addition of acid chloride **101**. The reaction had been allowed to warm from –78 °C to 0 °C over 2 h (following the addition of acid chloride **101**). Generally, 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

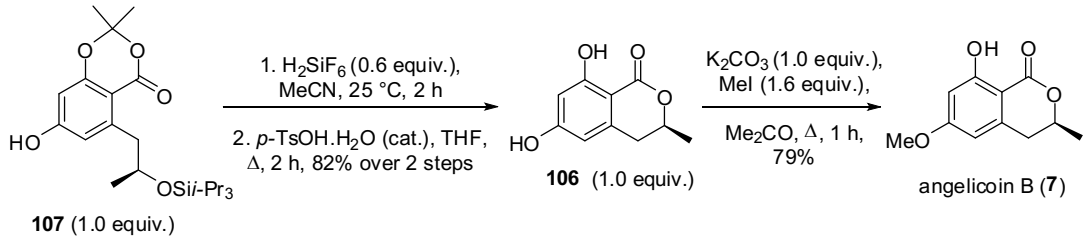
The next step was to optimise the Pd(0)-decarboxylative deallylation and aromatisation sequence. Formerly, the aromatisation had been carried out utilising standard aromatisation conditions providing methyl ester **105** in 39% yield over 4 steps (Scheme 28). However, it was predicted that isoproplyidene 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).[43] Therefore the Pd(0)-decarboxylative deallyation reaction was repeated with an excess of morpholine providing isopropylidene protected resorcylate **107** in a pleasing 80% yield (Scheme 30).



Scheme 30: Pd(0)-Decarboxylative Deallylation and Aromatisation

Deprotection of the silylether **107** was achieved by treatment with H_2SiF_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).



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,[79] 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.[80] 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).

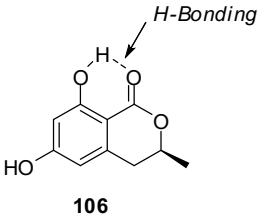
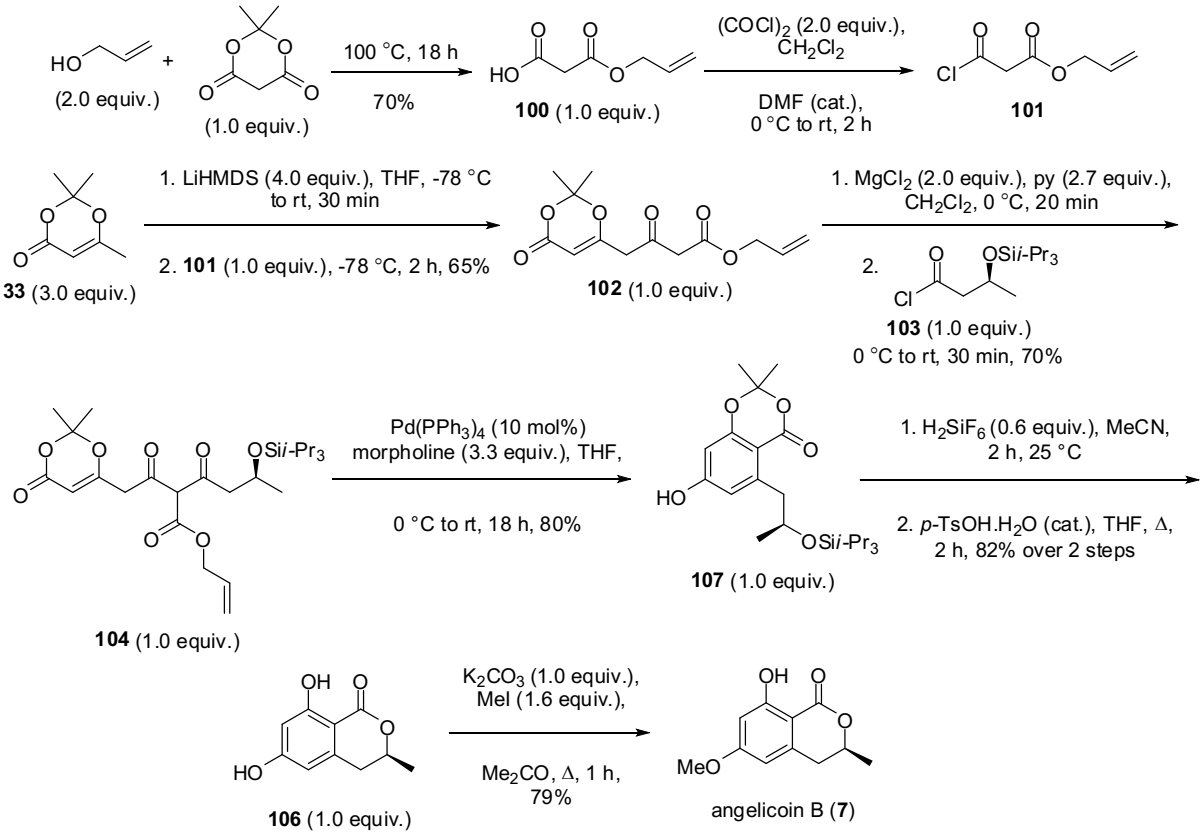


Figure 8: H-Bonding in Lactone 106

2.3 Total Synthesis of Angelicoin B (7)

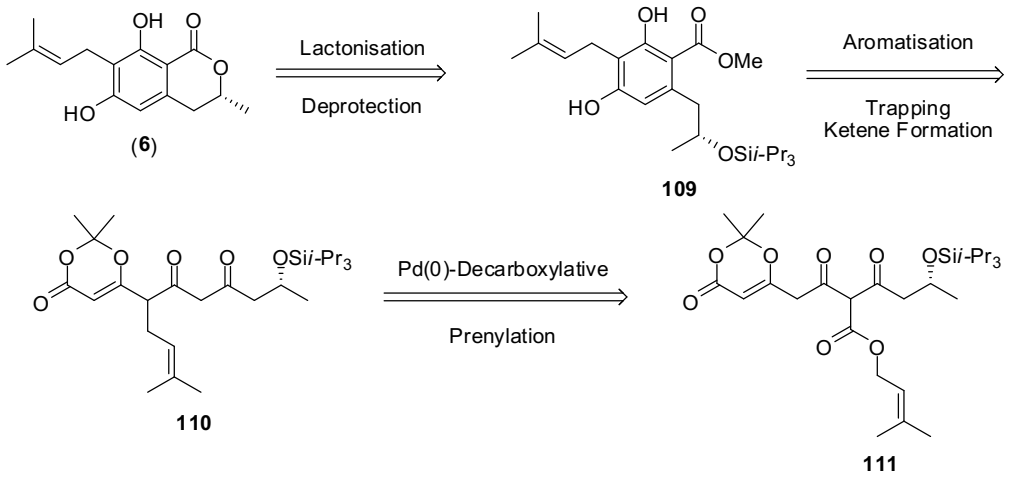
Scheme 32 below illustrates the final synthetic route to angelicoin B (**7**), which was completed in an overall yield of 29% over 6 linear steps starting from dioxinone **33**.



Scheme 32: Enhanced Synthesis of Angelicoin B (7)

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).

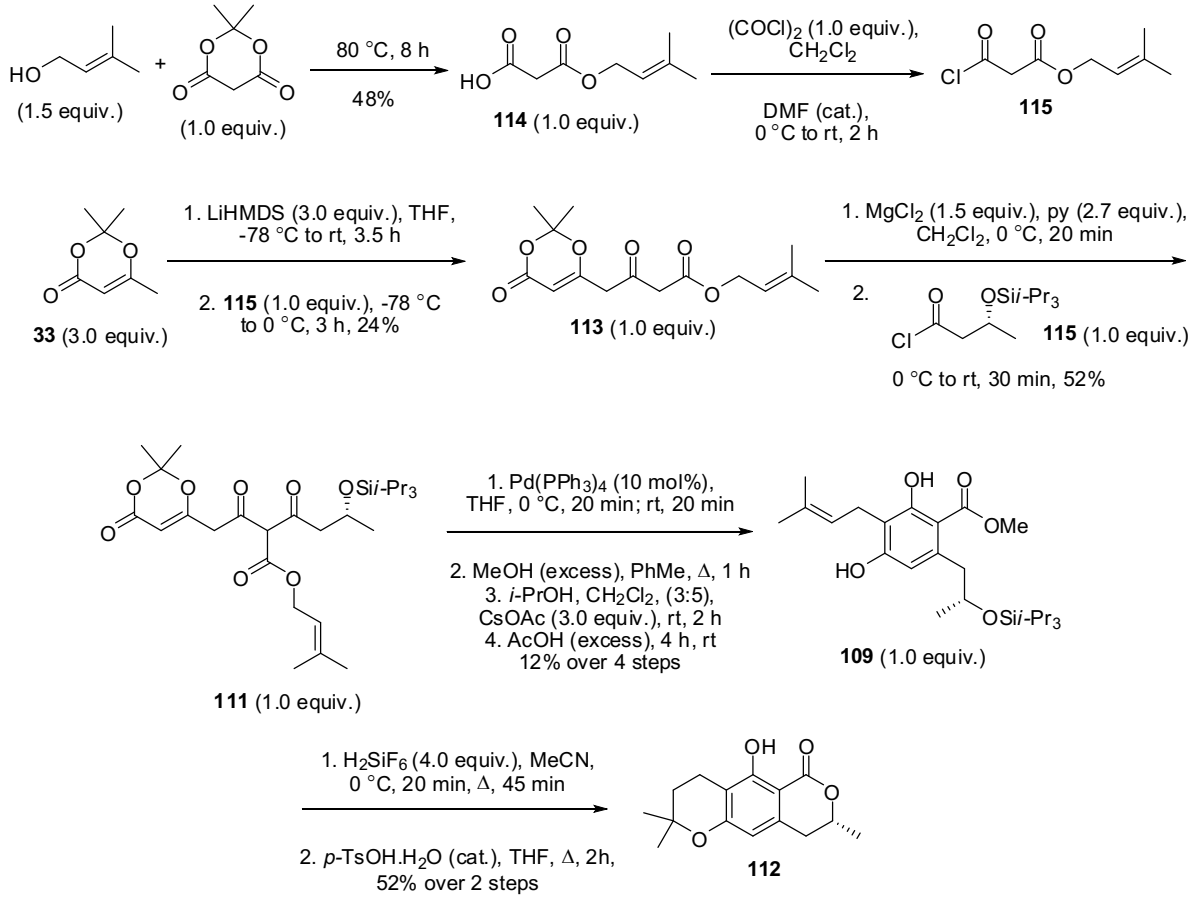


Scheme 33: Retrosynthetic Analysis of Angelicoin A (6)

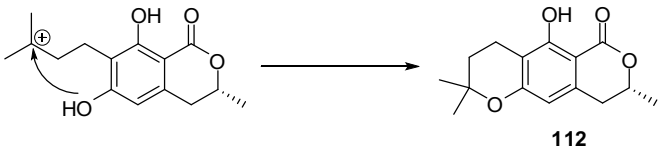
2.5 Previous Studies Towards the Total Synthesis of Angelicoin A (6)

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 $Pd(PPh_3)_4$ 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)



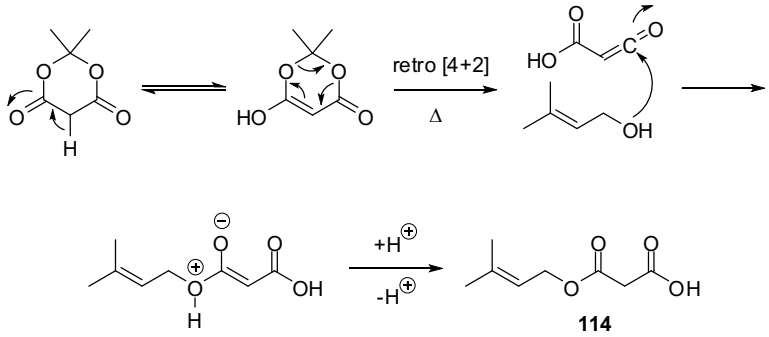
Scheme 35: Cyclisation under Acidic Conditions

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.*[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).



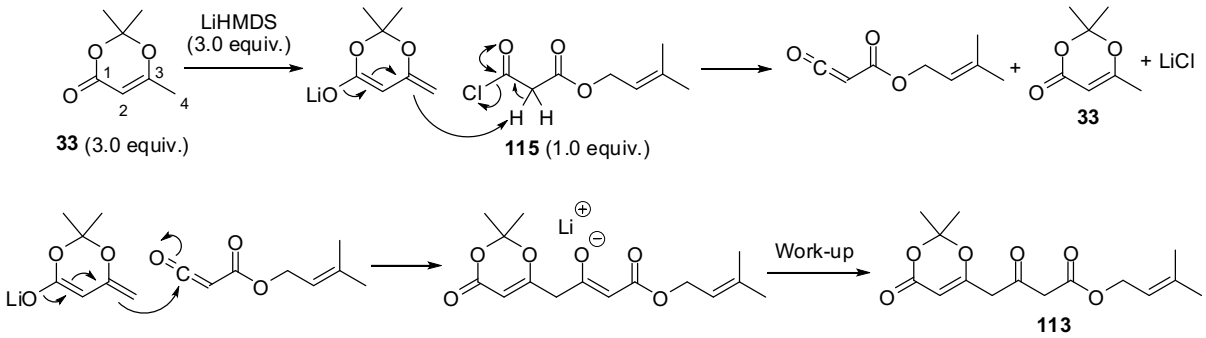
Scheme 36: Proposed Mechanism for the Formation of Acid 114

In order to improve the yield of the reaction it was decided to increase the temperature to 140 ^{o}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 ^{o}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 $NaHCO_3$ 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**

(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

Entry	Concentration/ M	Yield/ %[a]
1	0.046	65
2	0.023	45

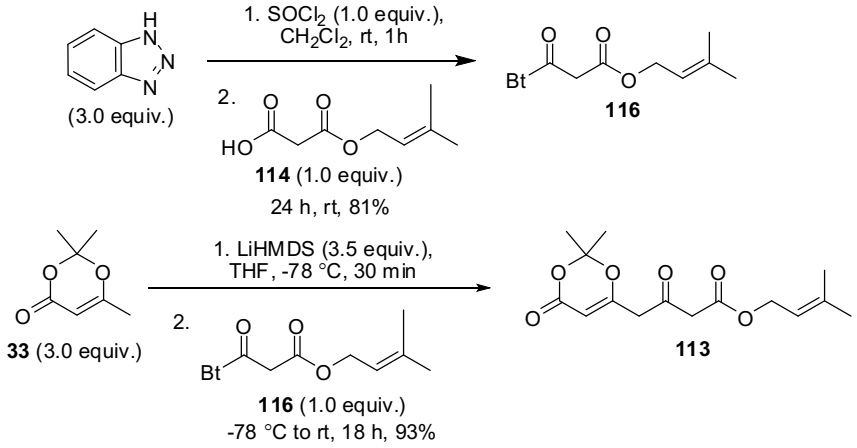
[a]Isolated yield after column chromatography.

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.[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.[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).[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 *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).



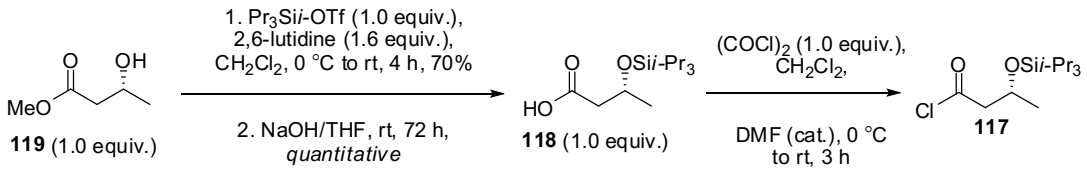
Scheme 38: Formation of Benzotriazole Amide and Subsequent Addition to Dioxinone 33

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 *et al.*[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

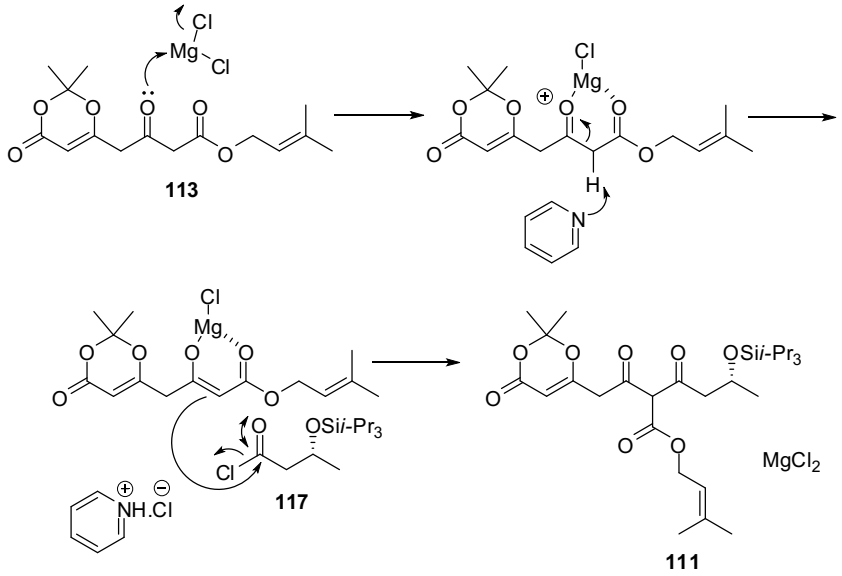
stirred for 18 h, giving only 30% conversion. However, stirring ester in NaOH/THF for 72 h gave full conversion to the acid **118**. Conversion of the acid **118** to the acid chloride **117** was achieved using oxalyl chloride and catalytic DMF (Scheme 39).



Scheme 39: Steps in the Formation of Acid Chloride 117

*2.7.2 Diketo-Prenylester-Dioxinone **111***

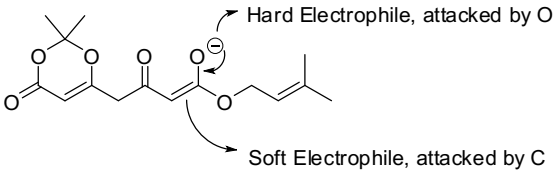
The synthesis of diketo-prenylester-dioxinone **111** was based on a similar procedure reported previously in the Barrett group.[82] Ketoester-dioxinone **113** was treated with $MgCl_2$ and pyridine, with $MgCl_2$ acting as a chelating agent enabling pyridine to deprotonate at the correct position (Scheme 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]

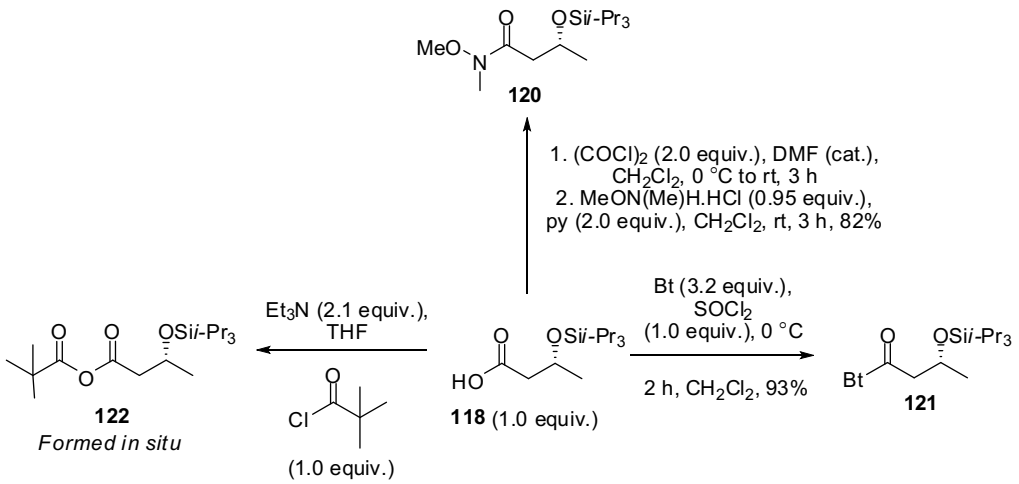
A number of side products, including *O*-acylation were observed during this reaction by ^{1}H NMR spectroscopy. Therefore, it was decided to investigate each step of the reaction in order to further improve the yield. Formation of the acid chloride **117** was monitored by IR spectroscopy to determine 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).[83][84][88]



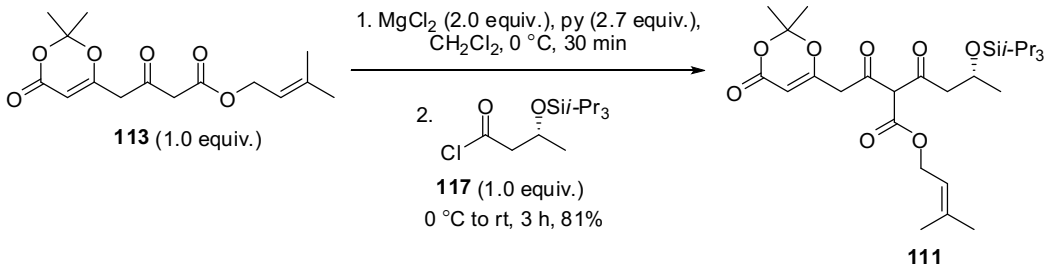
Scheme 41: Diagram showing the Attack of C onto Soft Electrophiles and O onto Hard Electrophiles

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 Et_3N and pivaloyl chloride.



Scheme 42: Formation of Electrophiles 120-122

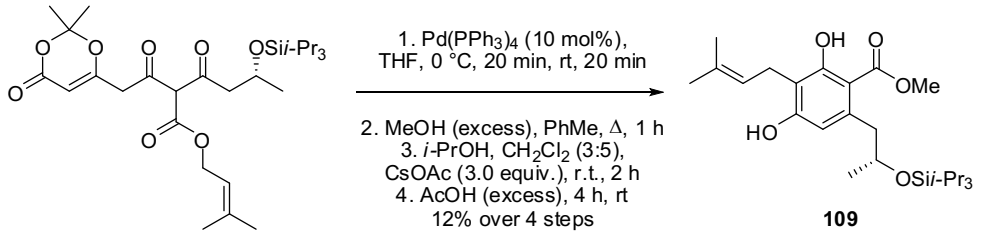
With compounds **120-122** in hand, the addition reaction was investigated. The Weinreb amide **120** and benzotriazole **121** leaving groups returned starting material and the pivilate leaving group **122** gave decomposition of the starting materials. Finally, the reaction was repeated with the acid chloride **177** using two equivalents of $MgCl_2$ (to ensure $MgCl_2$ 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

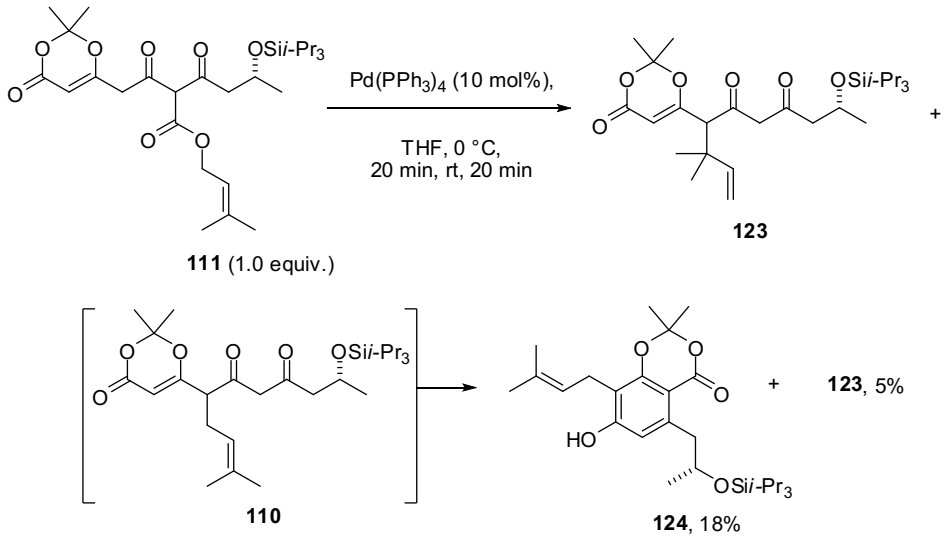
2.8 Pd(0)-Decarboxylative-Prenylation and Late Stage Aromatisation

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 $Pd(PPh_3)_4$ (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.



Scheme 45: Reaction of Diketo-Prenylester-Dioxinone 111 with $Pd(PPh_3)_4$

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).

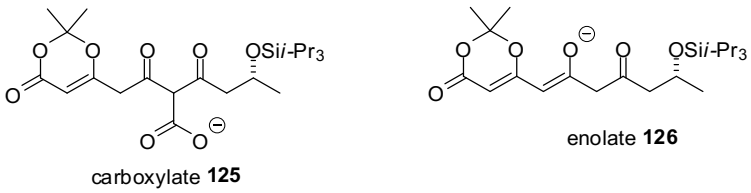
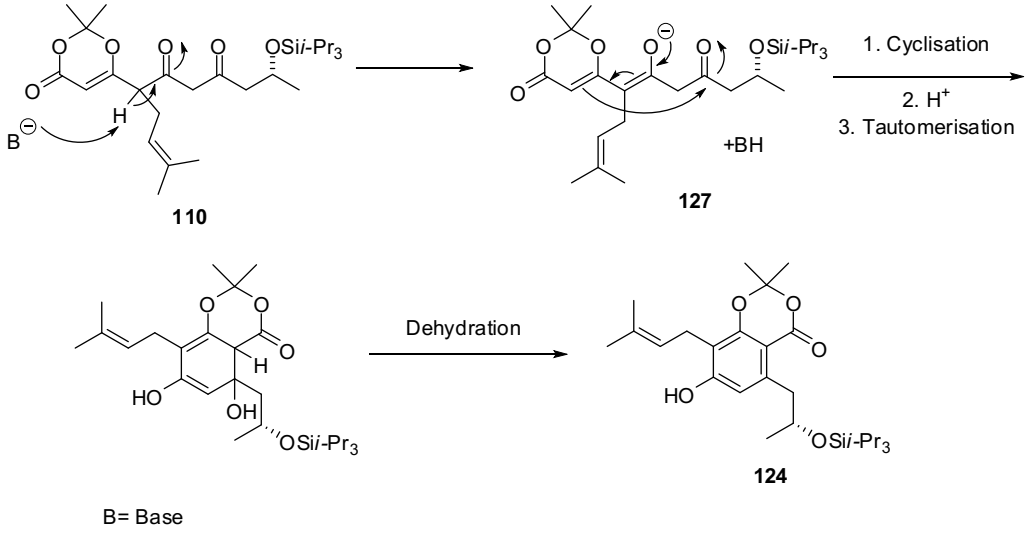


Figure 9: Proposed Aromatisation Bases



Scheme 46: Proposed Aromatisation Mechanism

Finally, branched product **123** did not aromatise within the reaction mixture presumably due to sterics blocking cyclisation from occurring (Figure 10).

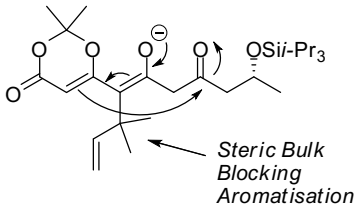


Figure 10: Steric Bulk Blocking Aromatisation

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

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 π-allyl Pd complex enabling deallylation to occur.[46][82] Accordingly, tertiary amines were explored because it was assumed they would facilitate aromatisation but not cause deallylation.[43]

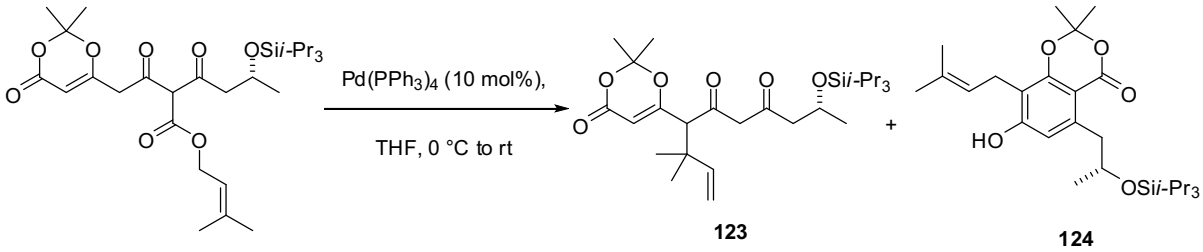
Unfortunately, overall the yield of resorcylate **124** and diketo-dioxinone **123** did not increase following this study (Table 6). However, interestingly the ratio of **123**:**124** did alter depending on the base and the reaction time. The first tertiary amine to be investigated was 4-methylmorpholine (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.*[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 π-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



111 (1.0 equiv.) **123** **124**

Entry	Time	Tertiary Amine[b]	Yield[a]	123:124
1	30 min	4-Methylmorpholine	**123** 5%, **124** 5%	1:1
2	30 min	4-Ethylmorpholine	**123** 10%, **124** 10%	1:1
3	30 min	Guanidine	RSM (17%)	-
4	2 h	4-Ethylmorpholine	**123** 10%, **124** 10%	1:1
5	10 min	4-Ethylmorpholine	**123** 11%, **124** 10%	1:1

[a]Yield isolated after column chromatography.
[b]3.0 equivalents of tertiary amine.

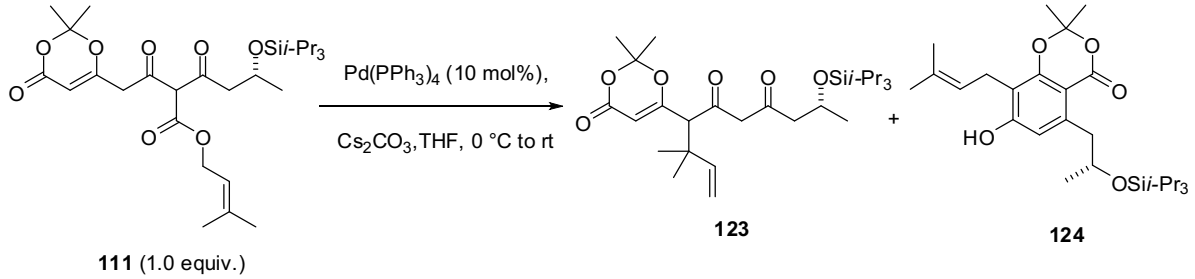
2.10 Utilisation of an Inorganic Base

It was known within the Barrett group that Cs_2CO_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_2CO_3. Additionally, Cs_2CO_3 has a high solubility in organic solvents compared with other inorganic bases.[91] For these 3 reasons Cs_2CO_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_2CO_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_2CO_3 was increased from 1 to 3 the yield of both resorcylate **124** and diketo-dioxinone **123** increased indicating that Cs_2CO_3 may be aiding both the decarboxylation, prenylation and aromatisation steps within the reaction. (The use of Cs_2CO_3 as a base is discussed in more detail in the mechanistic discussion Section 3.5).

Table 7: Studies Utilising Cs_2CO_3



111 (1.0 equiv.) **123** **124**

Entry	Time/ h	Equiv. of Cs_2CO_3	Yield[a]	123:124
1	1	1	**123** 8%, **124** 35%	1:4
2	18	1	**123** 10%, **124** 41%	1:4
3	**18**	**3**	**123 9%, 124 48%**	**1:5**
4	18	Excess	**123** 8%, **124** 49%	1:5

[a] Isolated yield after column chromatography.

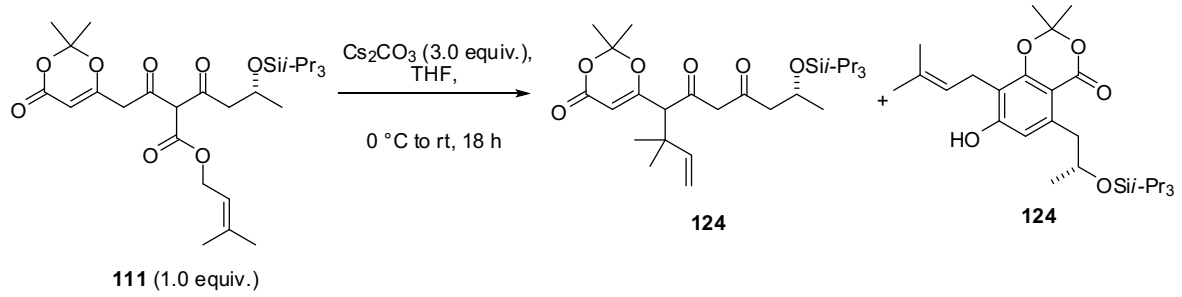
2.11 Catalyst and Ligands Studies

A number of Pd catalysts and ligands were screened in order to observe the effect on both the yield and linear **124** to branched **123** 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.[89] 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



111 (1.0 equiv.) **124** **124**

Entry	Catalyst	Ligand (20%)	Yield[a]	123:124
1	$Pd(PPh_3)_4$ (2.5 mol%)	**-**	**123** 8%, **124** 43%,	1:4
2	**$Pd(PPh_3)_4$ (10 mol%)**	**-**	**123 10%, 124 50%**	**1:5**
3	$Pd_2(dba)_3$ (5 mol%)	Xantphos	**123** 31%, **124** 24%	3:2
4	$Pd_2(dba)_3$ (5 mol%)	*rac*-BINAP	**123** 2%, **124** 10%	1:5
5	$Pd_2(dba)_3$ (5 mol%)	Trost	**123** 6%, **124** 25%	1:4
6	$Pd_2(dba)_3$ (5 mol%)	dppf	RSM	-
7	$Pd(OAc)_2$ (10 mol%)	PPh_3	RSM	-
8	$PdCl_2$ (10 mol%)	PPh_3	RSM	-

[a]Isolated yield after column chromatography.

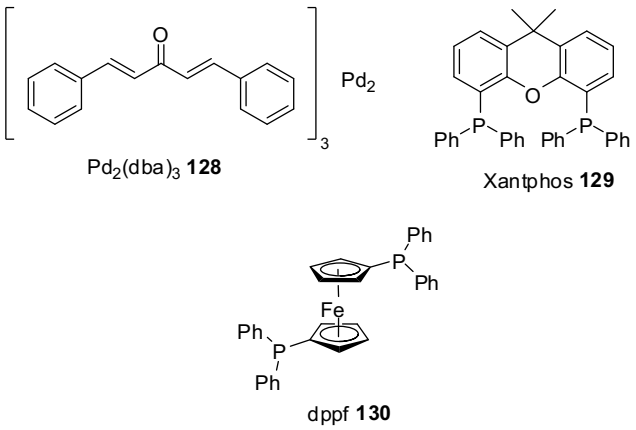
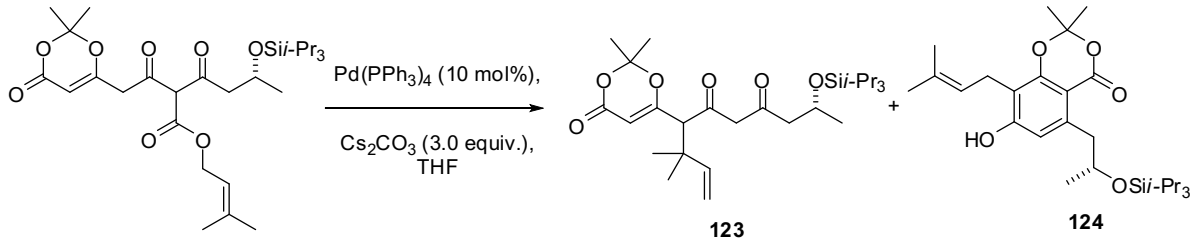


Figure 11: Ligands and Palladium Sources Utilised in Table 8

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



111 (1.0 equiv.) **123** **124**

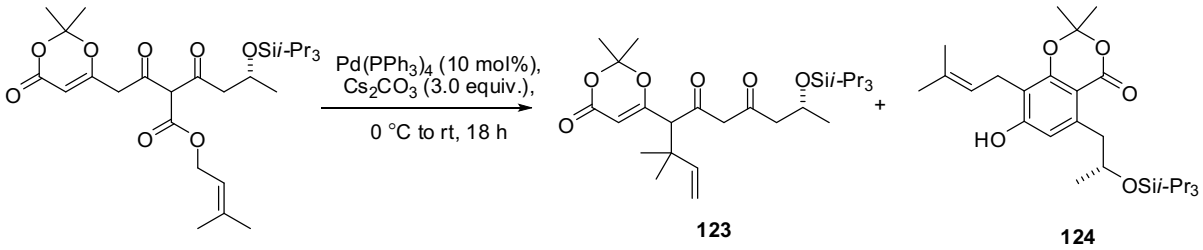
Entry	Temperature	Time	Yield[a]	123:124
1	–78 °C	8 h	RSM	-
2	0 °C	8 h	**123** 6%, **124** 40%[b]	1:6
3	**0 °C to rt**	**18 h**	**123 10%, 124 52%**	**1:5**
4	40 °C	1 h	**123** 10%, **124** 40%[c]	1:4

[a]Isolated yield after column chromatography.
[b]Consumption of the starting material **111** by TLC after 8 h.
[c]Consumption of the starting material **111** by TLC after 1 h.

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



111 (1.0 equiv.) **123** **124**

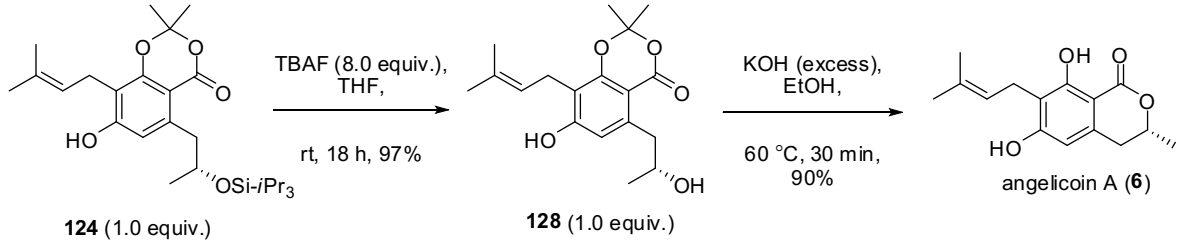
Entry	Solvent	Yield[a]	123:124
1	DMF	RSM	-
2	Et_2O	RSM	-
3	Toluene	RSM	-
4	CH_2Cl_2	RSM	-
5	**THF**	**123 11%, 124 51%**	**1:5**

[a]Isolated yield after column chromatography.

In conclusion, a thorough optimisation study has taken place whereby the best conditions were found to be $Pd(PPh_3)_4$ (10 mol%), Cs_2CO_3 (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.

2.14 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 silylether **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

of catalyst, ligand, solvent, temperature and base. These studies demonstrated that diketo-ester-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.[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.

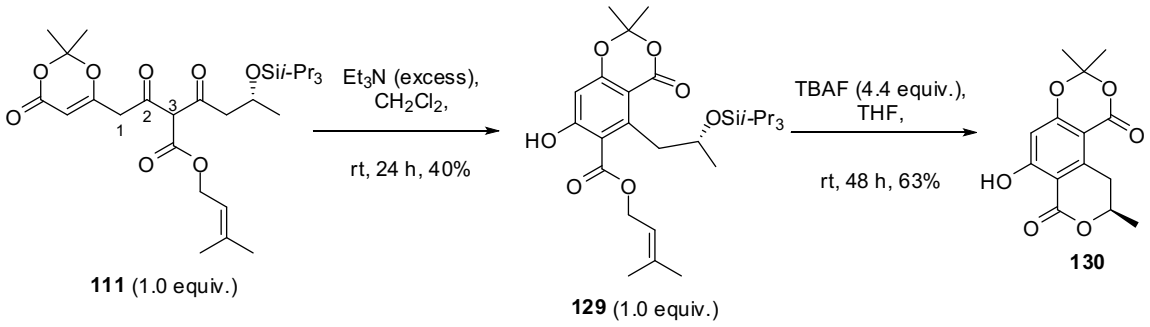
3 Verification and Mechanistic Studies Towards the *Migratory* Pd(0)-Decarboxylative Prenylation

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 $Pd(PPh_3)_4$ and that the prenyl moiety migrated to C-1 after treatment with $Pd(PPh_3)_4$ (Scheme 48).

3.1 X-ray Crystal Structure of Tricyle 130[III]

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 Et_3N 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 prenylester functionality being on C-3 of diketo-prenylester-dioxinone **111** prior to treatment with $Pd(PPh_3)_4$.

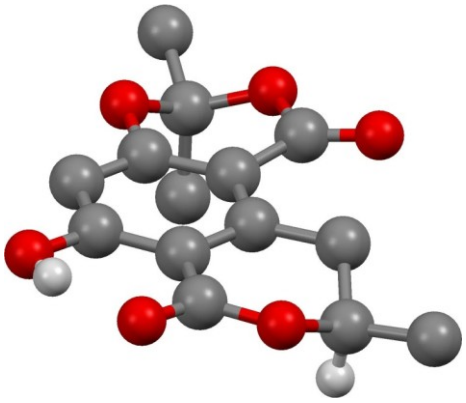


Figure 12: X-ray Crystal Structure of Tricycle 130

3.2 X-ray Crystal Structure of Angelicioin A (6)[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 **110** which aromatised within the reaction mixture to give resorcylate **124** and the branched product **123** (Scheme 45). The aim was to prove that the position of the prenyl moiety was on C-1 and not C-3 of resorcylate **124** (Figure 13). Unfortunately, resorcylate **124** (Figure 13) was not a crystalline solid and not suitable for X-ray crystallography. However, Angelicoin A (**6**) (Figure 13) provided an excellent crystalline solid and an X-ray crystal structure was obtained (Figure 14).

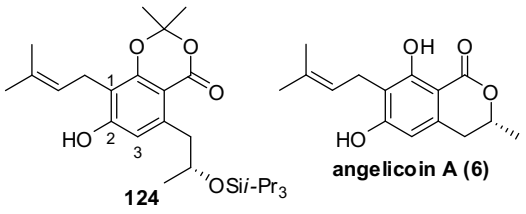


Figure 13: Resorcylate 124 and Angelicoin A (6)

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).

[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. *Org. Lett.* **2011**, *13*, 5748-5750.

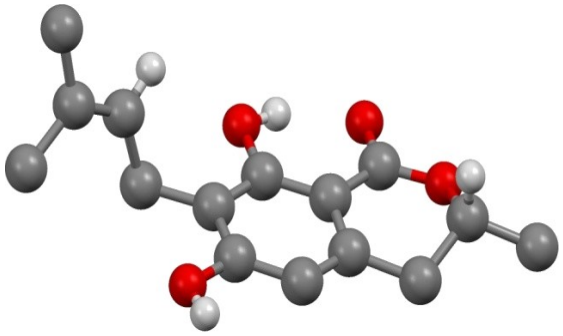


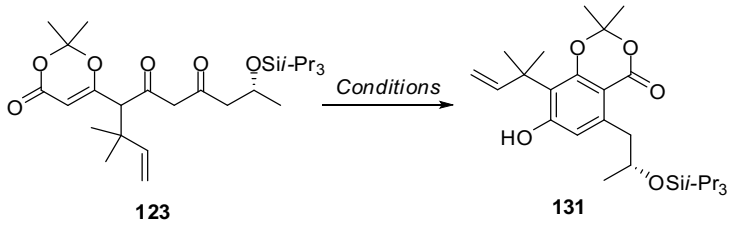
Figure 14: X-ray Crystal Structure of Angelicoin A (6)

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[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).

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



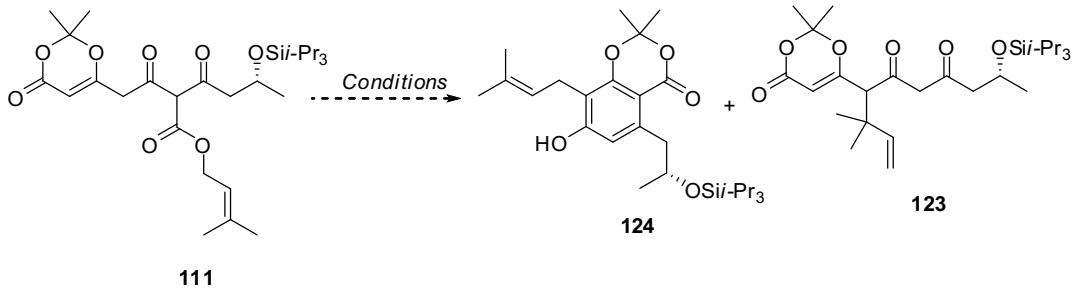
123 **131**

Entry	Reaction Conditions	Product
1	Cs_2CO_3 (excess), MeOH, rt to Δ, 18 h	RSM
2	Et_3N(excess), CH_2Cl_2, rt to Δ, 18 h	RSM
3	MeOH (excess), PhMe, Δ, 1 h; Cs_2CO_3 (3.0 equiv.), MeOH, rt, 4h; AcOH (excess), rt, 3h	Decomposition of the SM

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.

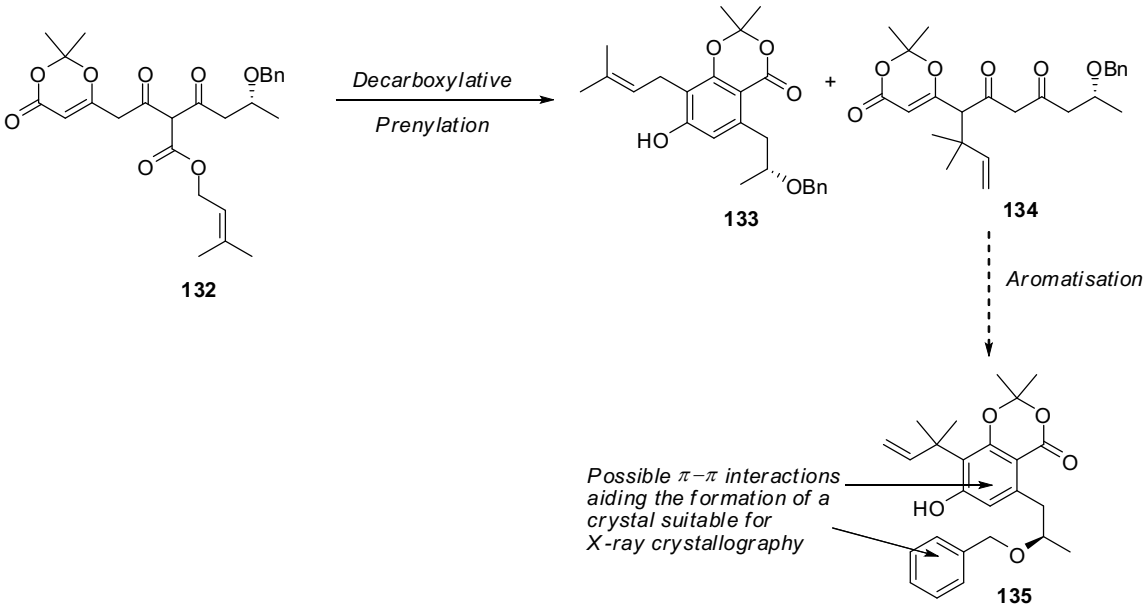
Table 12: Ruthenium Conditions Investigated



111 **124** **123**

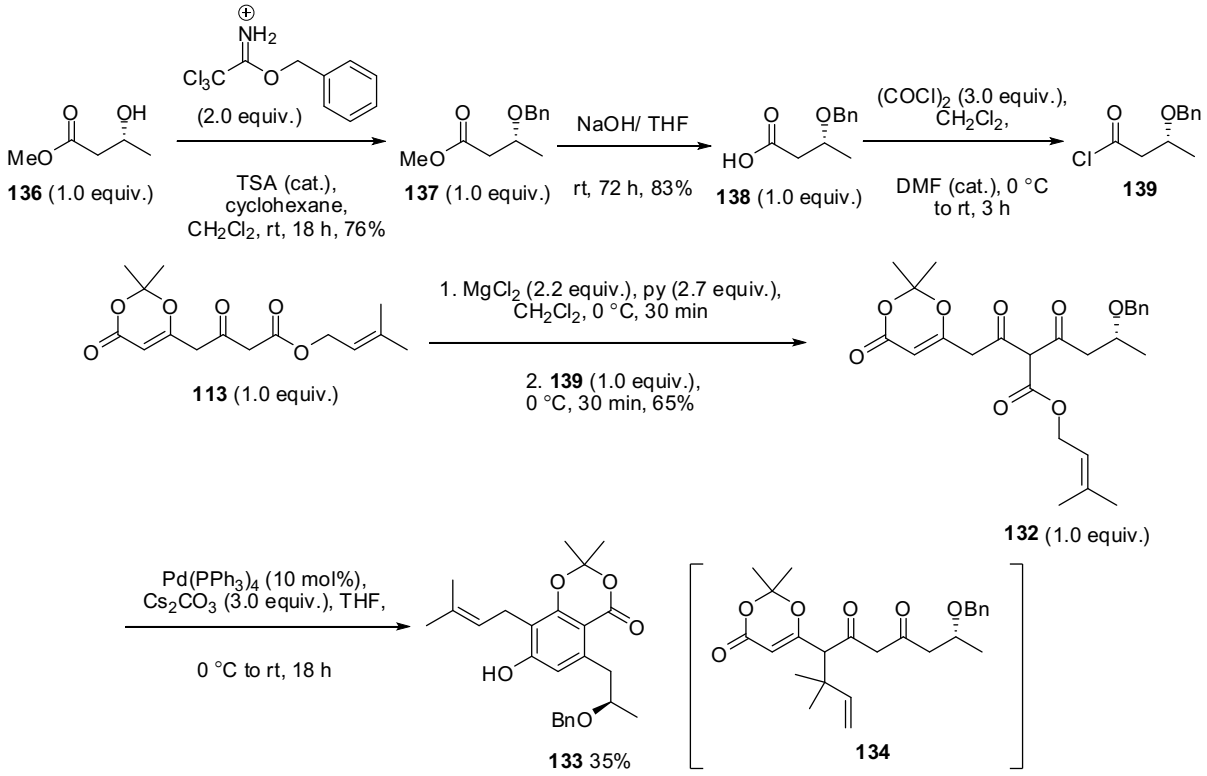
Entry	Catalyst (10 mol%)	Ligand (20 mol%)	Solvent	Temp.	Time	Outcome
1	$RuCp(MeCN)_3.PF_6$	-	CH_2Cl_2	0 °C to Δ	18 h	RSM
2	$RuCp(MeCN)_3$	-	THF	0 °C to Δ	18 h	RSM
3	$RuClCp(PPh_3)_2$	-	THF	0 °C to Δ	48 h	RSM
4	$RuClCp(PPh_3)_2$	Py	THF	0 °C to Δ	48 h	RSM
5	$RuClCp(PPh_3)_2$	Bpy	THF	0 °C to Δ	48 h	RSM
6	$RuClCp(PPh_3)_2$	TMEDA	THF	0 °C to rt	18 h	RSM
7	$Ru(methylallyl)_2(COD)$	-	THF	0 °C to Δ	18 h	RSM
8	$Ru(methylallyl)_2(COD)$	Py	THF	0 °C to Δ	18 h	RSM
9	$Ru(methylallyl)_2(COD)$	Bpy	THF	0 °C to Δ	18 h	RSM
10	$Ru(methylallyl)_2(COD)$	TMEDA	THF	0 °C to r.t.	18 h	RSM
11	$[Cp^*RuCl]_4$	-	THF	0 °C to Δ	18 h	RSM
12	$[Cp^*RuCl]_4$	Py	THF	0 °C to Δ	18 h	RSM
13	$[Cp^*RuCl]_4$	Bpy	THF	0 °C to rt	18 h	RSM
14	$[Cp^*RuCl]_4$	TMEDA	THF	0 °C to rt	18 h	RSM
15	$[Cp^*RuCl]_4$	Py	CH_2Cl_2	0 °C to rt	18 h	RSM

Consequently, the protecting group was changed from a silylether 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

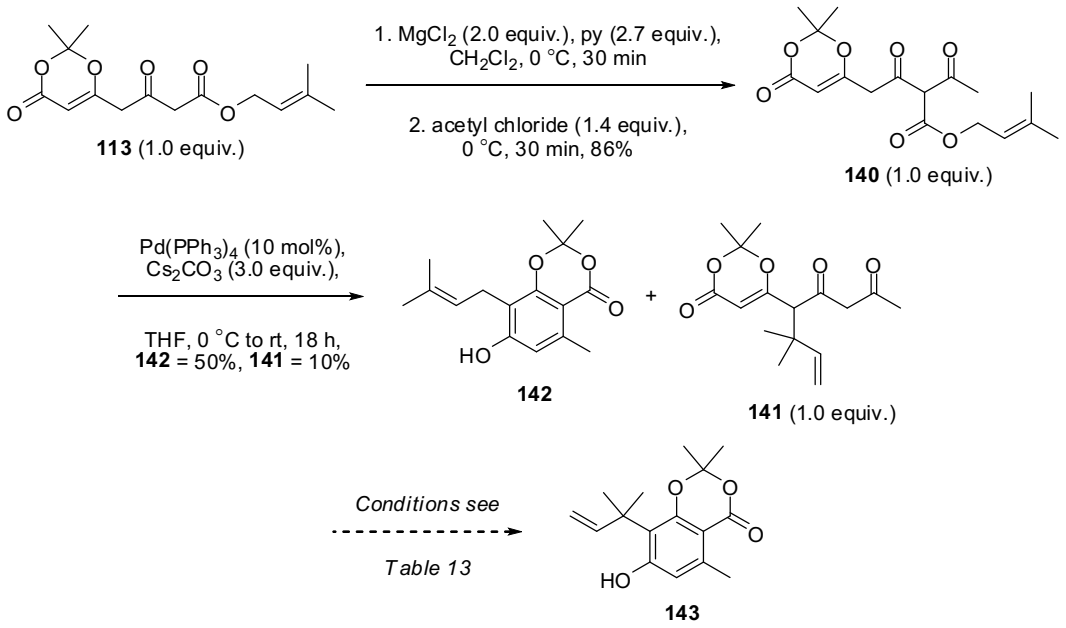
The synthetic route towards resorcylate **135** (Scheme 50) began with the benzyl protection of alcohol **136**, giving benzyl ether **137** in a 76% yield. Saponification of methyl ester **137** to acid **138** took place using NaOH/ THF. Acid chloride **139** was then synthesised *in situ* utilising 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 ^1H NMR and was not available in adequate yield to isolate by silica column chromatography.



Scheme 50: Towards the Synthesis of Branched-Diketo-Dioxinone 134

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 **141** suitable for X-ray crystallography. The synthesis of branched-diketo-dioxinone **141** and its subsequent aromatisation is illustrated in Scheme 51.

Diketoester-dioxinone **140** was formed by prestirring ketoester-dioxinone **113** with $MgCl_2$ and pyridine followed by the addition of acetyl chloride. Treatment of diketoester-dioxinone **140** with $Pd(PPh_3)_4$ facilitated the Pd(0)-decarboxylative prenylation and aromatisation providing linear resorcylate **142** in a 50% yield and branched-diketo-dioxinone **141** in a 10% yield (Scheme 51).



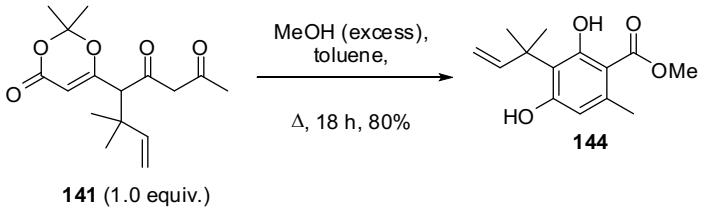
Scheme 51: Synthesis of Branched-Diketo-Dioxinone 141 and its Subsequent Aromatisation

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).[42][43][82] 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

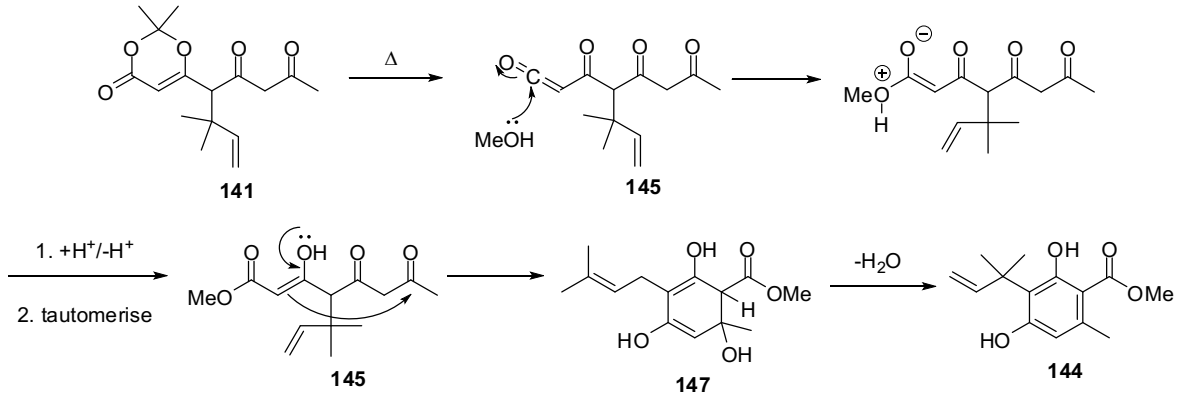
Entry	Base	Solvent	Conditions	Outcome
1	Et_3N (excess)	CH_2Cl_2	rt to Δ, 72 h	RSM
2	Cs_2CO_3 (excess)	MeOH	rt to Δ, 72 h	RSM
3	LDA (excess)	THF	–78 °C to Δ, 48 h	RSM

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 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**.

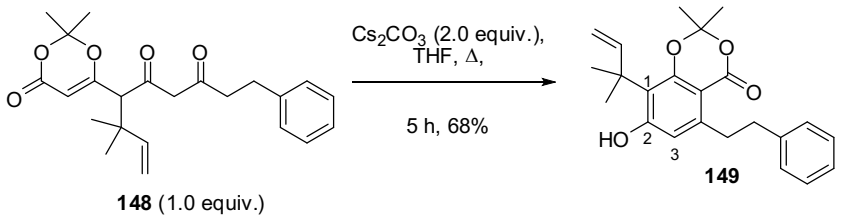


Scheme 53: Proposed Aromatisation Mechanism at Elevated Temperatures

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[V]

During studies towards total synthesis of amorfrutin A (**8**) it was found that refluxing branched-diketo-dioxinone **148** with Cs_2CO_3 in THF provided branched-resorcylate **149** in a 68% yield (Scheme 54).



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.

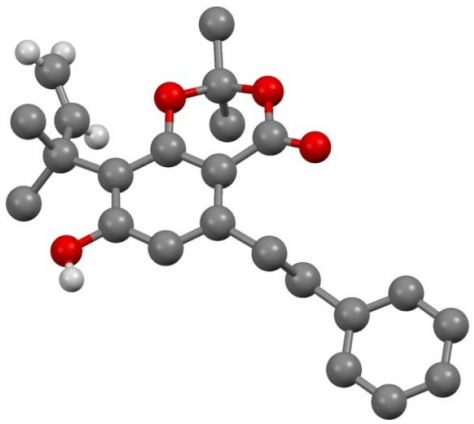
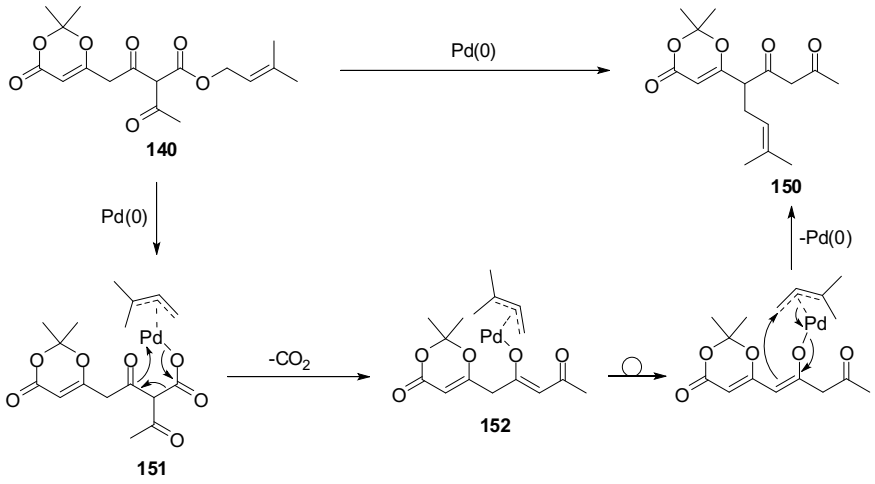


Figure 15: X-ray Crystal Structure of Branched-Resorcylate 149

[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. *Tetrahedron Letters* **2012**, *53*, 225–227.

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)[48] 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

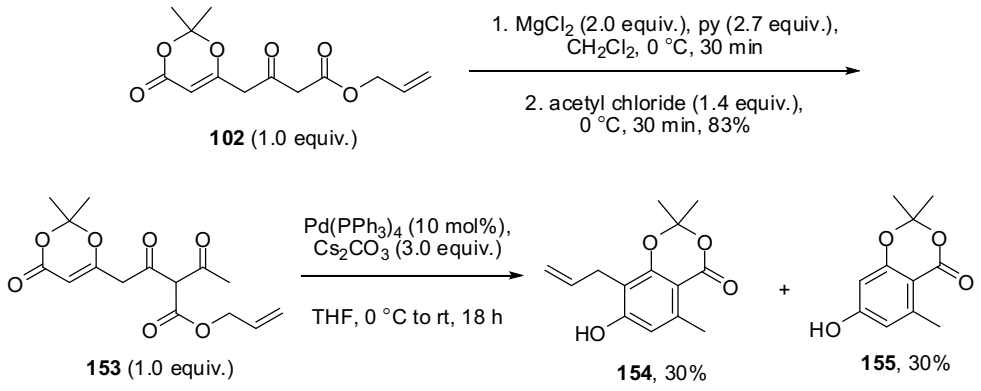
3.6 Substrate Investigations

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-

allylester-dioxinone **153** was prepared by treatment of ketoester-dioxinone **102** with $MgCl_2$ and pyridine followed by the addition of acetyl chloride (Scheme 56).

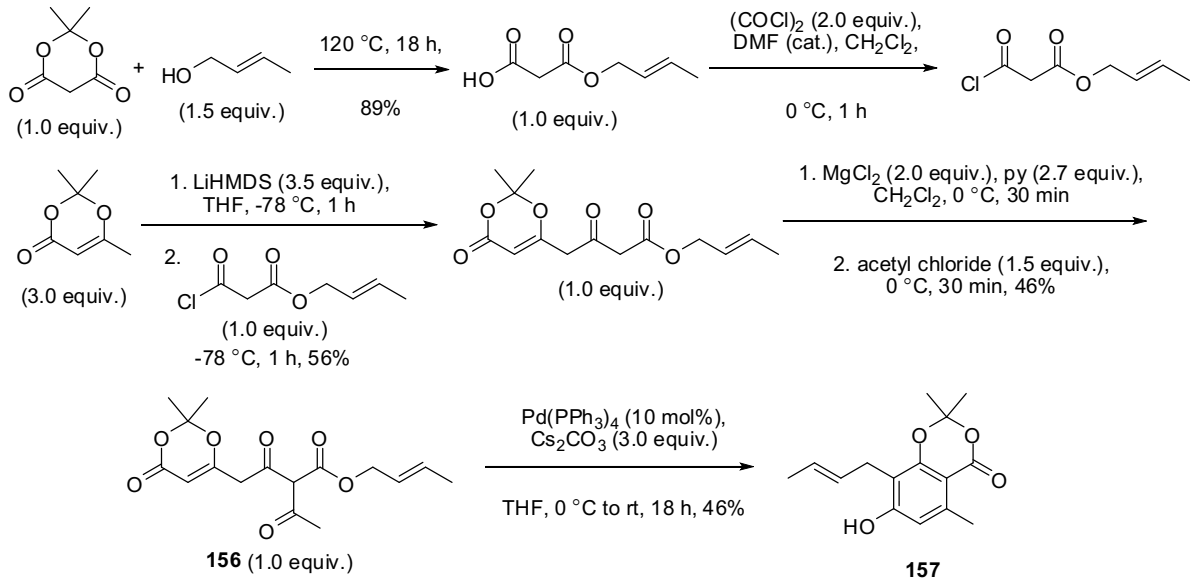
The Pd(0)-decarboxylative allylation of diketo-ester-dioxinone **153** provided allyl resorcylate **154** and resorcylate **155** in a 1:1 ratio and overall 60% yield. This result demonstrated that the allylation was migratory, though, the yield of allyl-resorcylate **154** was lower than expected (possible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



Scheme 56: Synthesis of Diketo-Ester-Dioxinone 153 and Subsequent Treatment with $Pd(PPh_3)_4$

3.6.2 Crotyl Group

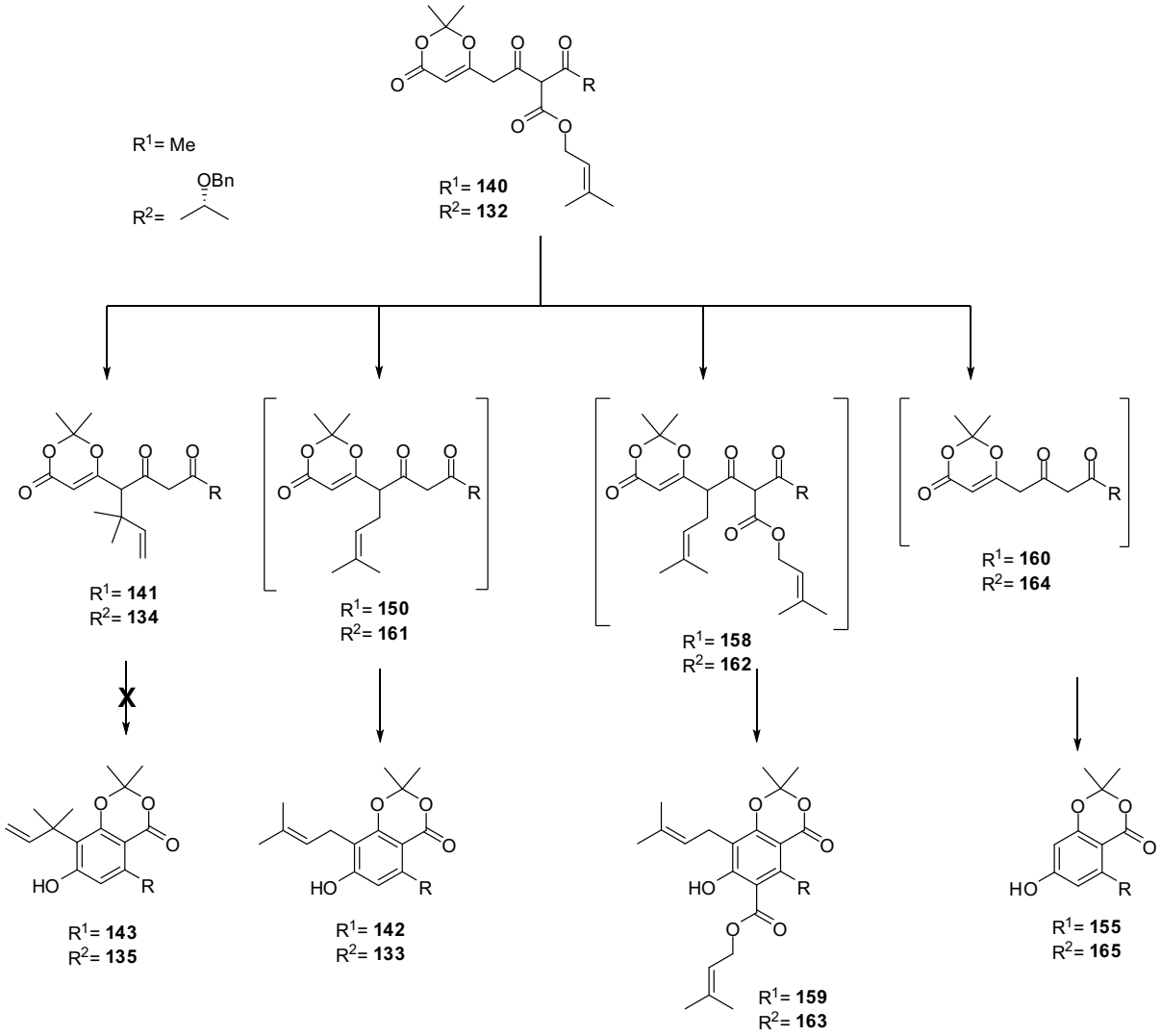
The synthesis of diketo-crotylester-dioxinone **156** (Scheme 57) was completed utilising the methods discussed previously in Section 2.6. Subsequent reaction of diketo-crotylester-dioxinone **156** with $Pd(PPh_3)_4$ provided crotyl-resorcylate **157** in a 46% yield. This result provided additional evidence for the migratory nature of this sequence but interestingly, no branched product was observed in this transformation (Scheme 57).



Scheme 57: Formation of Diketo-Crotylester-Dioxinone 156 and Reaction with $Pd(PPh_3)_4$

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.



Entry	Conc.	Diketo-Dioxinone	Prenyl-Resorcylate	Prenylester-Prenyl-Resorcylate	Resorcylate
1	0.2 M	**141**= 10%	**142**= 50%	**159**= 2%	**155**= 3%
		134= 0%	**161**= 65%	**163**= 1%	**165**= 2%
2	0.014 M	**141**= 0.5%	**142**= 3%	**159**= 42%	**155**= 41%
		134= 0%	**133**= 2%	**163**= 32%	**165**=33%

Scheme 58: Concentration Studies towards Pd(0)-Decarboxylative Prenylation Sequence

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.

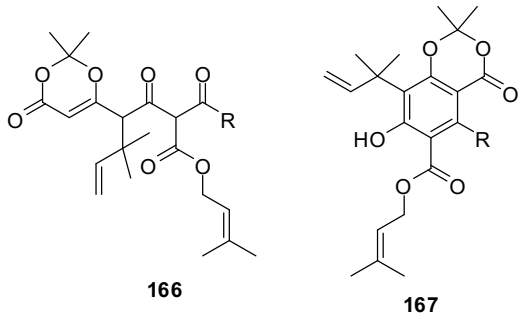
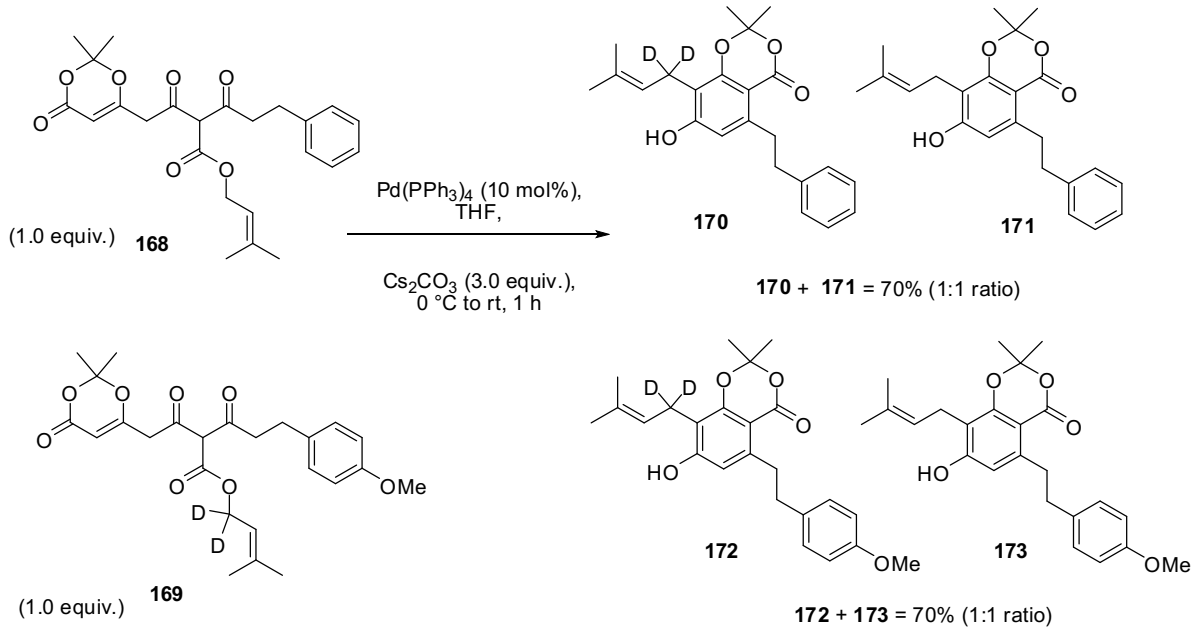


Figure 16: Branched-Diketo-Prenylester-Dioxinone 166 and Branched-Prenylester-Resorcylate 167

3.8 Cross-Over Experiment[VI]

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.

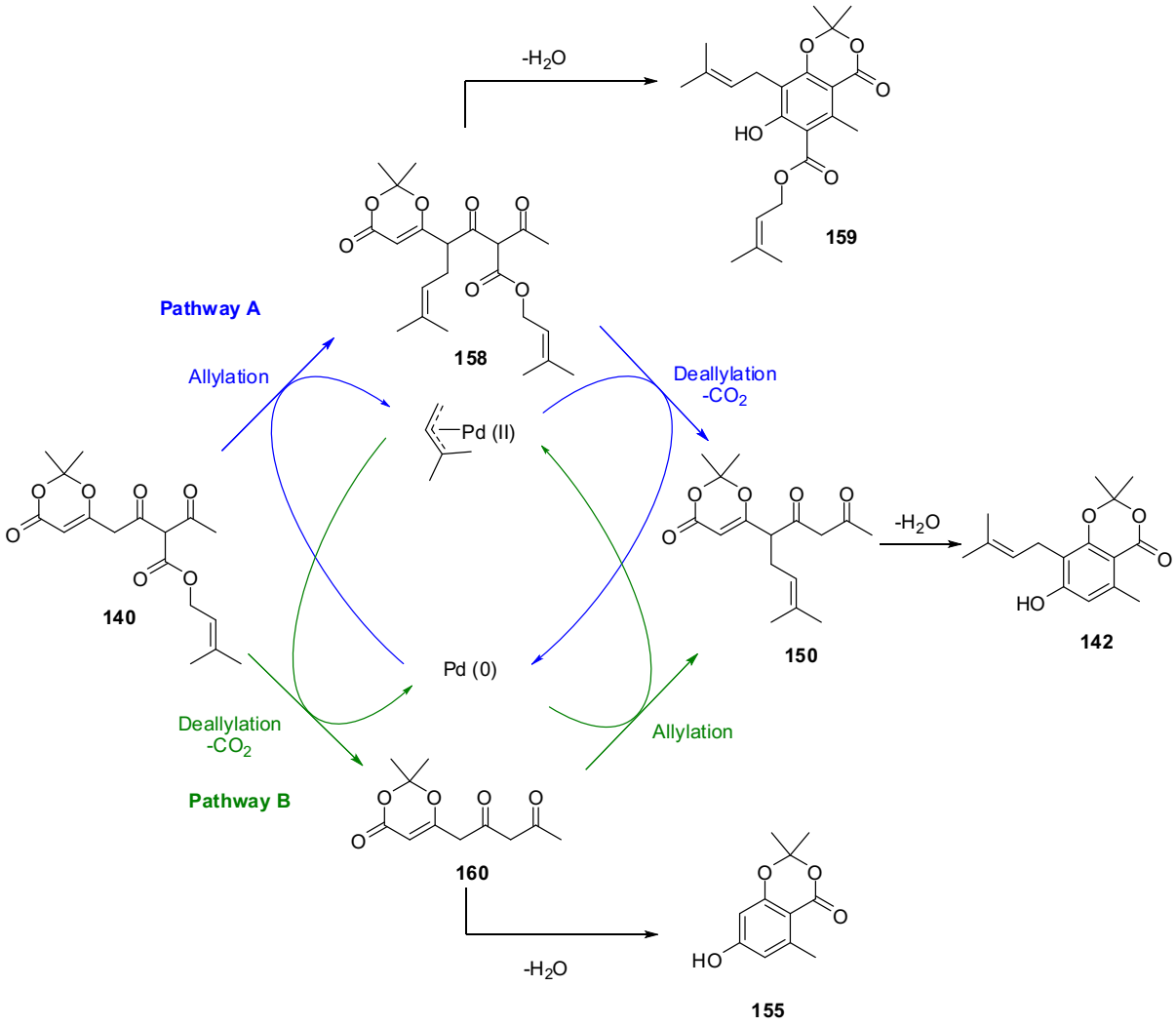


Scheme 59: Cross-Over Experiment between non-Deuterated Ester Diketodioxinone 168 and Deuterated Ester 169

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

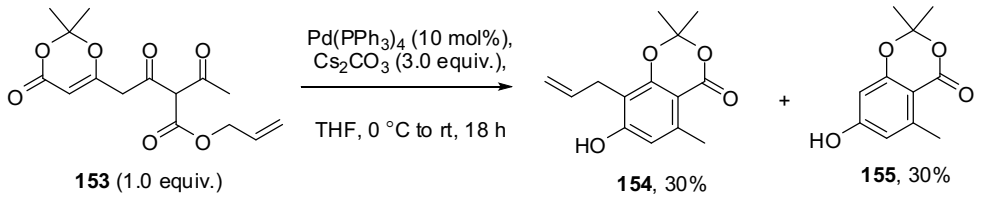
3.9 Proposed Mechanism

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-diketo-dioxinone **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]



Scheme 60: Proposed Mechanism

Section 3.6.1 above described the reaction of diketo-allylester-dioxinone **153** with $Pd(PPh_3)_4$ 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**.



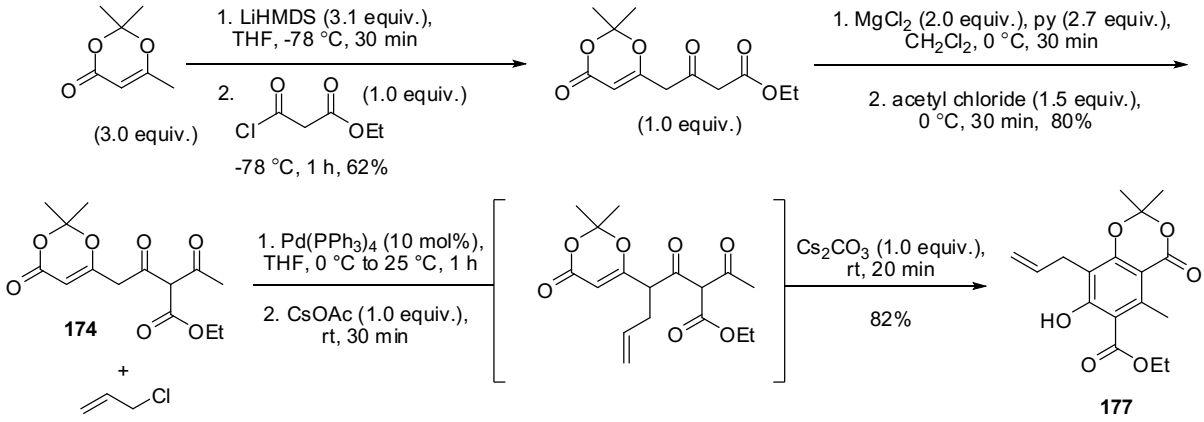
153 (1.0 equiv.) **154**, 30% **155**, 30%

Scheme 61: Reaction of Diketo-Allylester-Dioxinone 153 with $Pd(PPh_3)_4$

3.10 Base Studies

The next plan was to formalise the role of Cs_2CO_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_2CO_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]



Scheme 62: Synthesis of Diketo-Ester-Dioxinone and Subsequent Reaction between Ethyl Ester 174 and Allyl chloride

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).

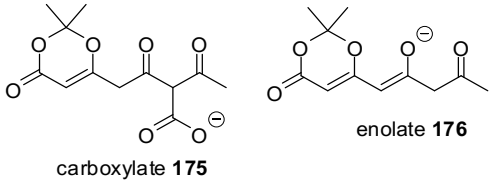


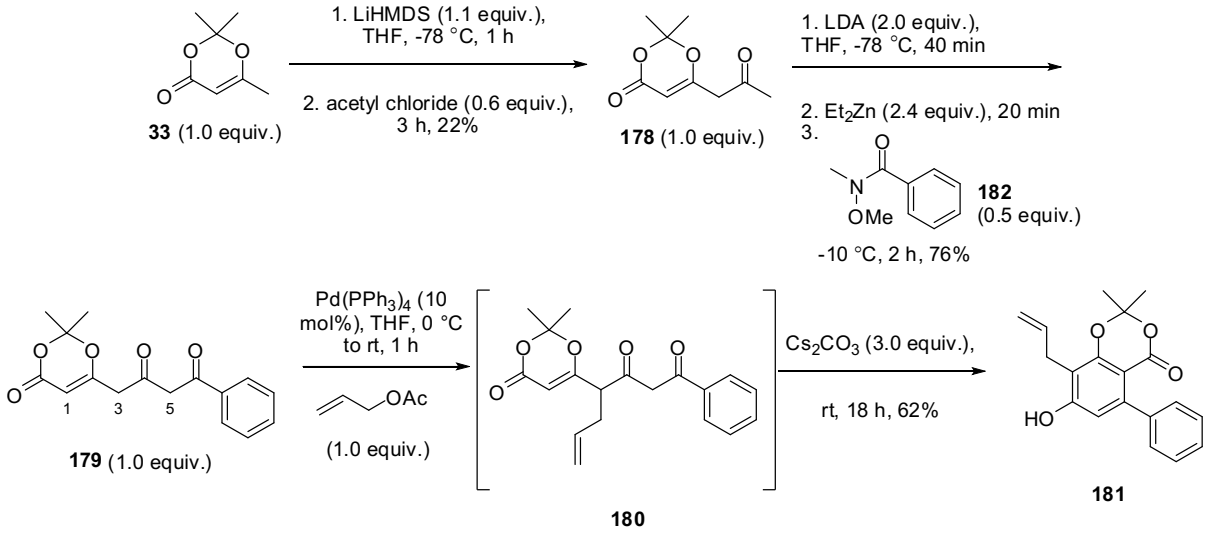
Figure 17: Proposed Aromatisation Bases

3.11 Regioselectivity Investigations[VII]

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). Keto-dioxinone **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 Et_2Zn and addition of *N*-methoxy-*N*-methylbenzamide (**182**) furnished diketo-phenyl-dioxinone **179** in a 76% yield.[103] High regioselectivity in the allyl transfer step was observed providing

[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

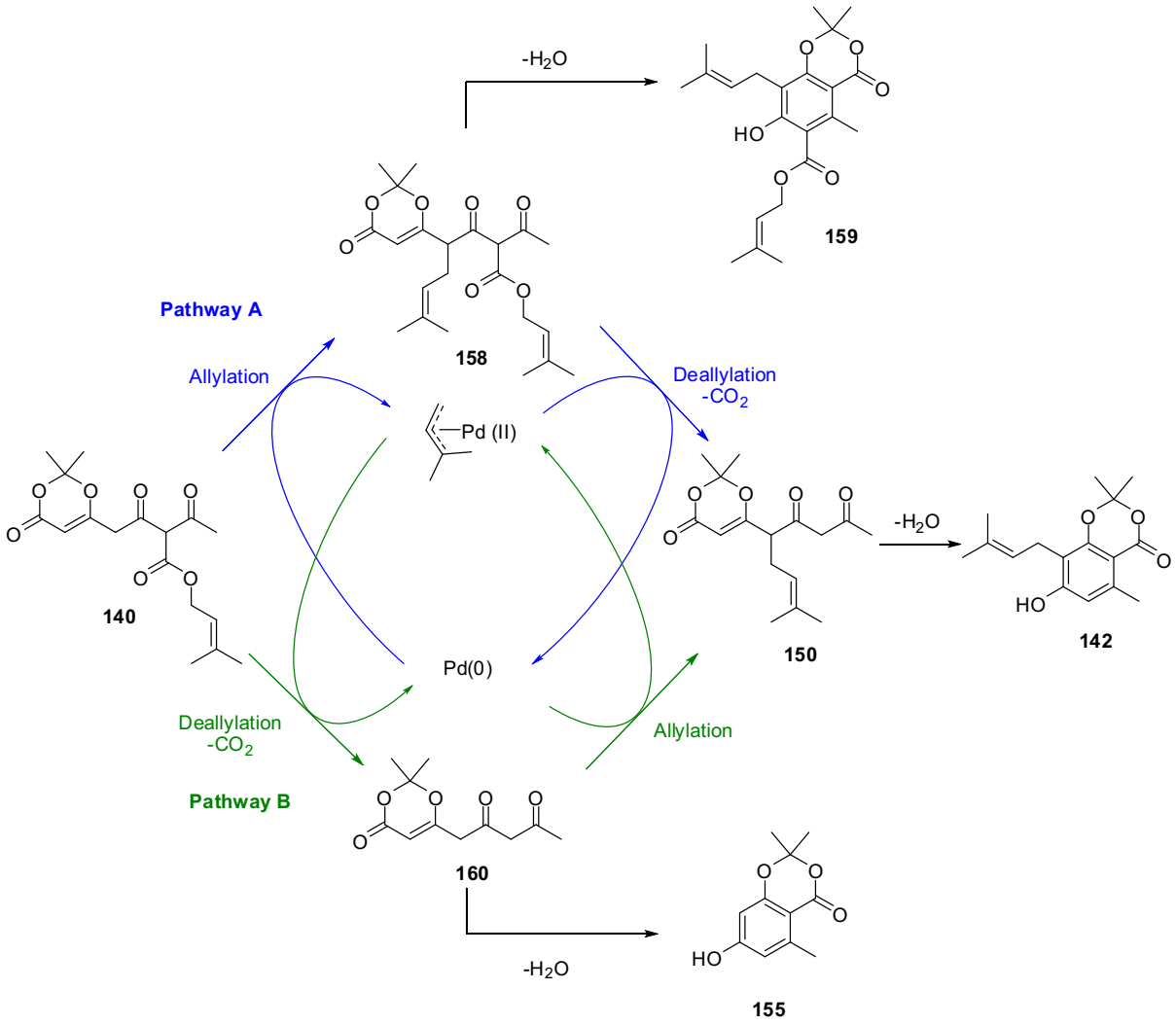
This experiment was consistent with the decarboxylation in Pathway B of the proposed mechanism (Scheme 60) where decarboxylation could be occurring before or after prenylation (allylation). It was therefore postulated that the regioselectivity was not driven by decarboxylation but could be due to the 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.

3.12 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 $Pd(PPh_3)_4$. 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).

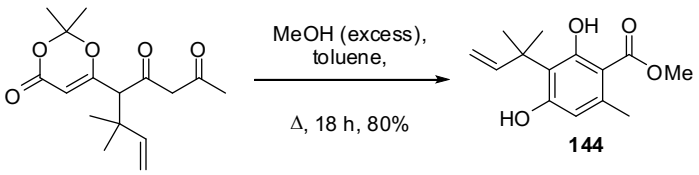


Scheme 64: Proposed Mechanism

In addition, it would be advantageous to carry out the decarboxylative prenylation with 1 equivalent of $Pd(PPh_3)_4$ at a low concentration (0.014 M) in order to observe the products that were produced. Theoretically with 1.0 equivalent of $Pd(PPh_3)_4$ pathway A of the proposed mechanism (Scheme 64) would be shut down. Therefore at a low concentration only resorcylate **155** should be obtained.

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.[105] Therefore new methodologies to generate analogues of the resorcinol scaffold will be invaluable for biological screening/testing.

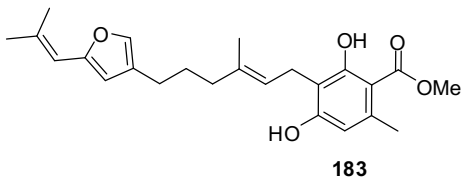


141 **144**

Scheme 65: Aromatisation at Elevated Temperatures

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.[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.[6][106]



183

Figure 18: Cristatic Acid Methyl Ester 183

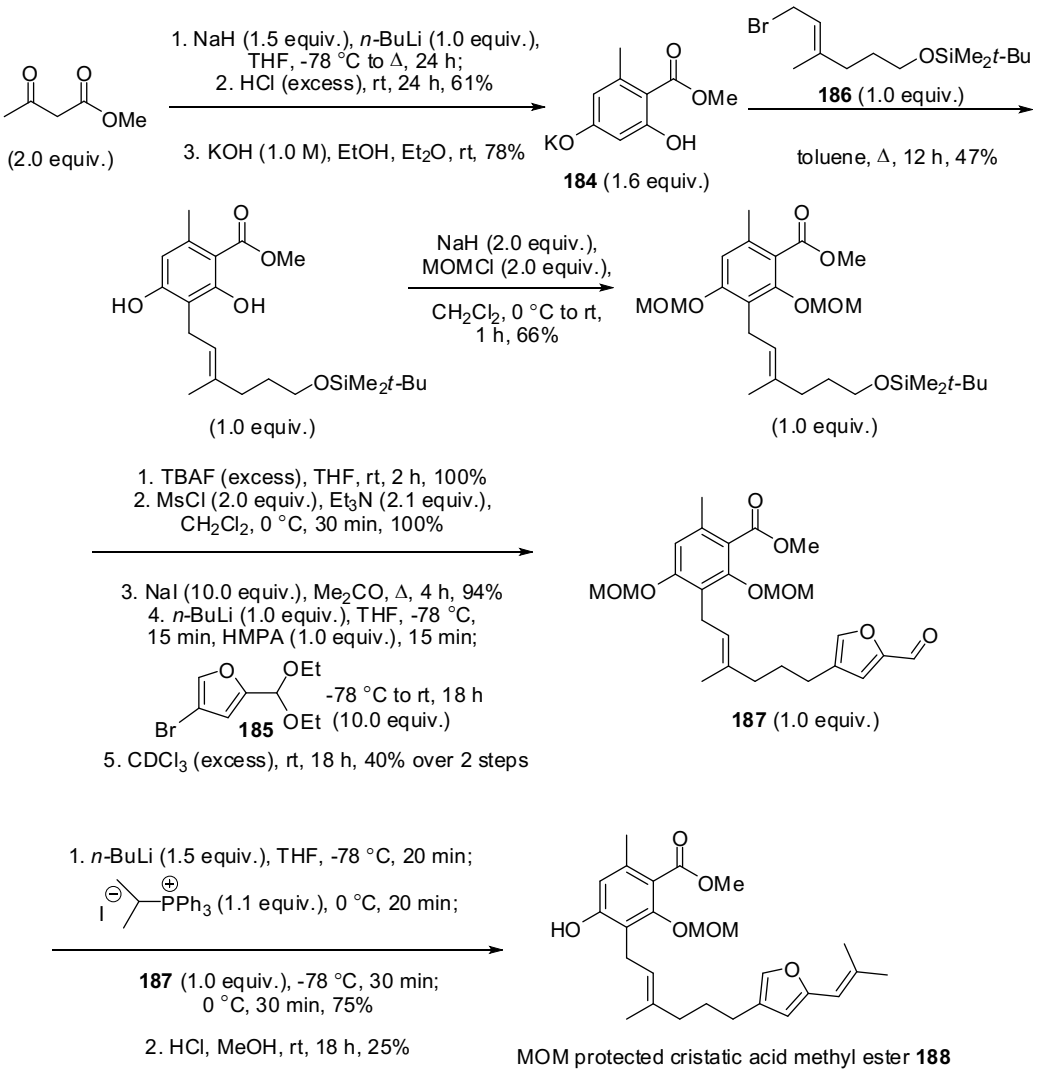
The only two previous preparative approaches towards the total synthesis of cristatic acid (**5**) were published by Fürstner *et al.* in 2000[106] and Joullié *et al.* in 1988.[107]

4.1 Approach of Joullié *et al.*[107]

Joullié *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

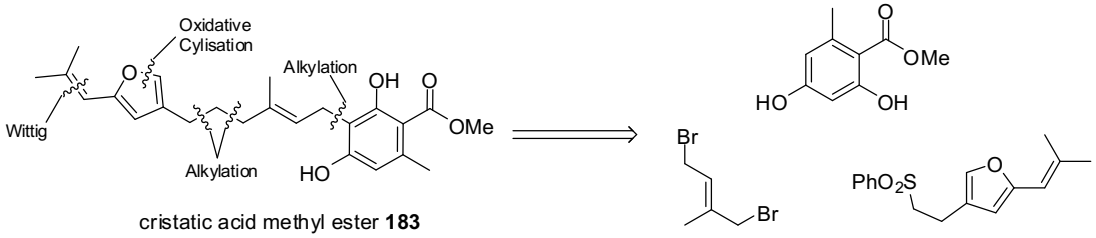
Interestingly, the resorcylate core was prepared using a modified procedure developed by Barrett *et al.*[38] Allyl bromide was attached to the resorcylate core *via* an alkylation of the potassium phenolate **184**. The 2,4-disubstitued furan **185** was prepared from furfural[108] and attached onto 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)[107]

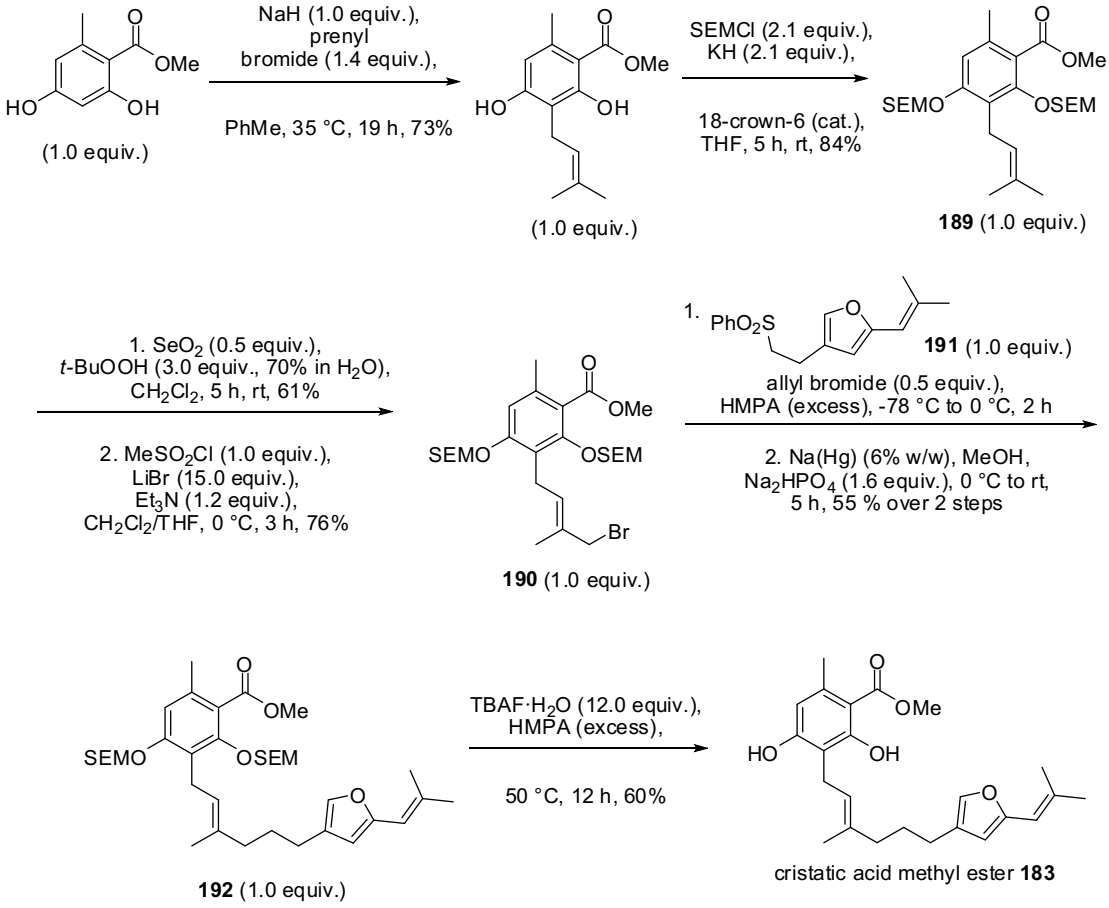
4.2 Fürstner's Approach[106]

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 alkylations to build the essential benzylic and alkyl bonds (Scheme 68).[106]



Scheme 68: Retrosynthetic Analysis

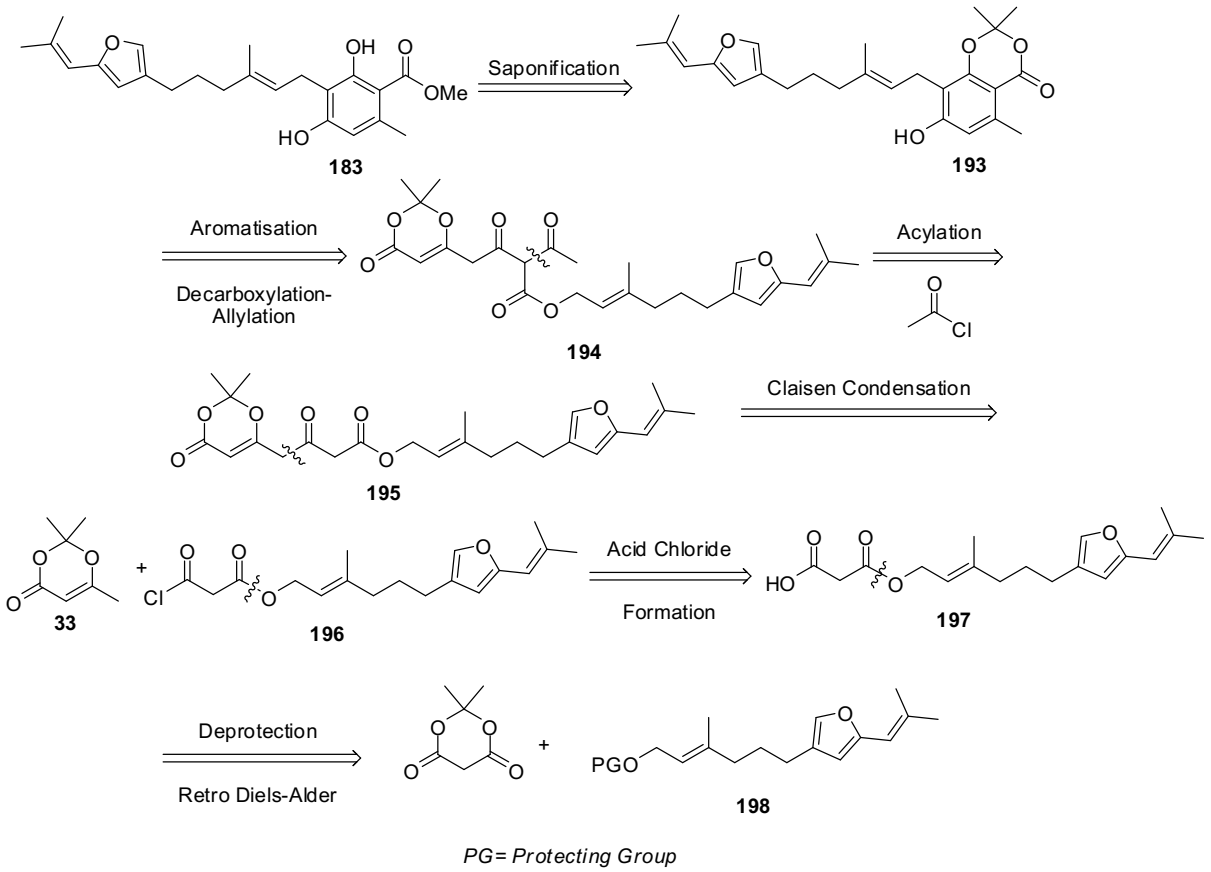
The synthesis began through alkylation of sodium phenolate with allyl bromide followed by phenolic SEM protections providing prenyl resorcylate **189**. Allylic oxidation and subsequent conversion to the bromide furnished bromide-prenyl-resorcylate **190**. Displacement with phenyl sulphonyl **191** 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]



Scheme 69: Fürstner's Approach to Cristatic Acid Methyl Ester (183)[106]

4.3 The Barrett Retrosynthetic Analysis of Cristatic Acid Methyl Ester 183

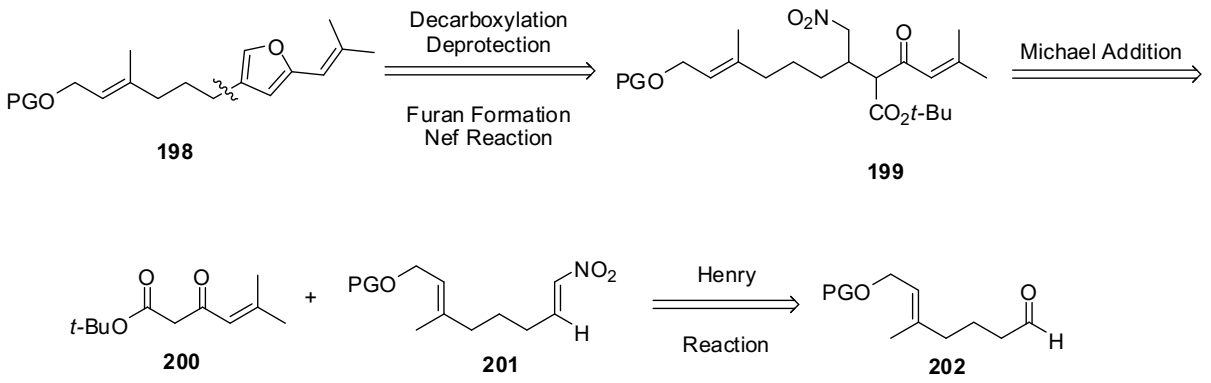
It was envisaged that opening of isopropylidene protected resorcylate **193** with MeOH could provide cristatic acid methyl ester **183**. Resorcylate **193** could be obtained from a Pd(0)-decarboxylative, allylation and aromatisation sequence beginning with diketoester dioxinone **194** which in turn 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.



Scheme 70: Retrosynthetic Analysis of Cristatic Acid Methyl Ester 183

4.4 Retrosynthetic Analysis for Protected Alcohol 198

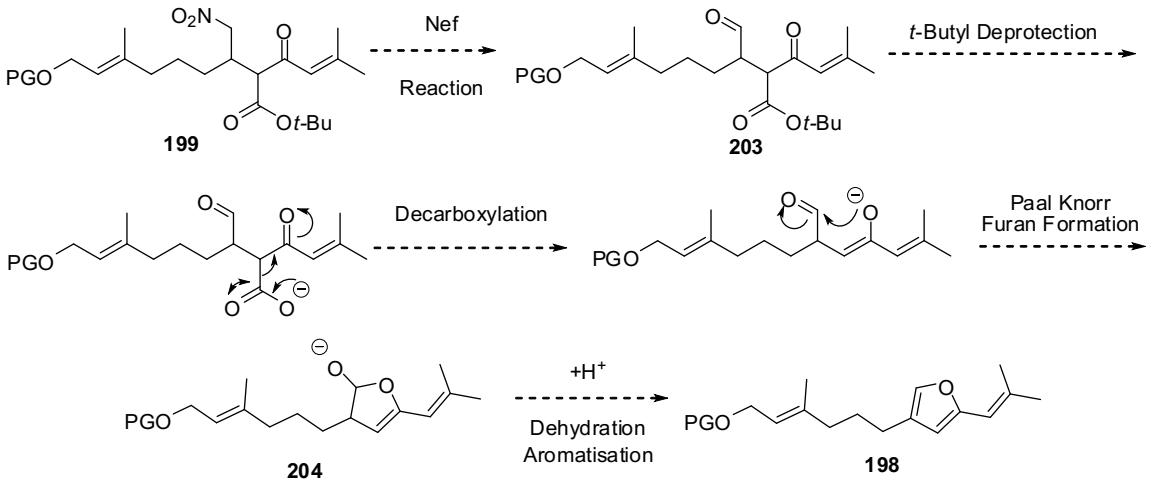
The aim of this retrosynthesis was to devise an elegant and novel concept enabling new intermediates for pharmaceutical and biological exploration that had not been utilised previously by Fürstner *et al.*[106] or Joullié *et al.*[107] It was hypothesised that the furan moiety could be put in place *via*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



PG= Protecting Group

Scheme 71: Strategy for the Protected Alcohol 198

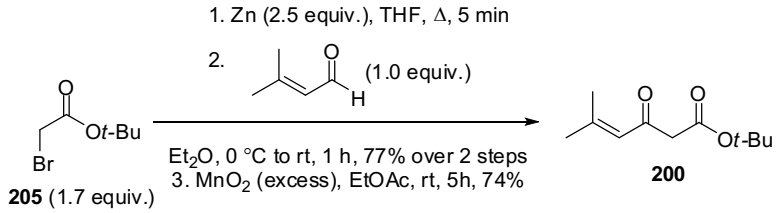
Scheme 72 below illustrates the proposed mechanism for furan formation. It was thought that a Nef reaction on nitro alkane **199** could provide aldehyde **203**, under the reaction conditions the *t*-butyl ester would be removed facilitating decarboxylation. Attack of the ketone onto the aldehyde in 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

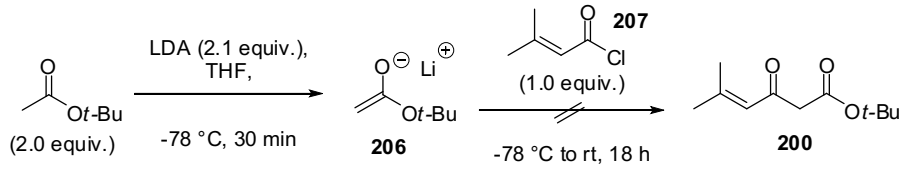
4.5 Synthesis of *t*-Butyl-Ester-Keto 200

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 MnO_2 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.



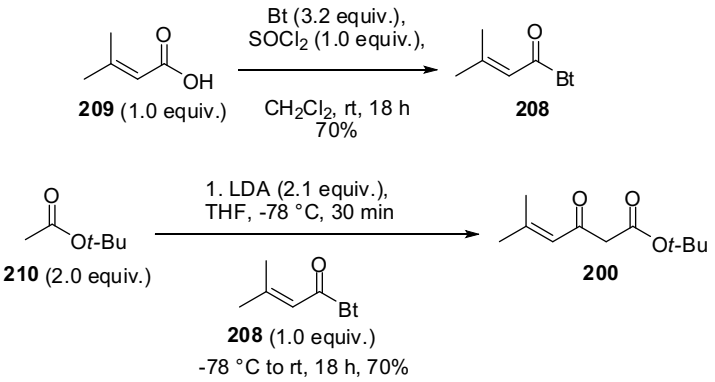
Scheme 73: Synthesis of *t*-Butyl-Ester-Keto 200 by Lavallée *et al.*[115]

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]



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).

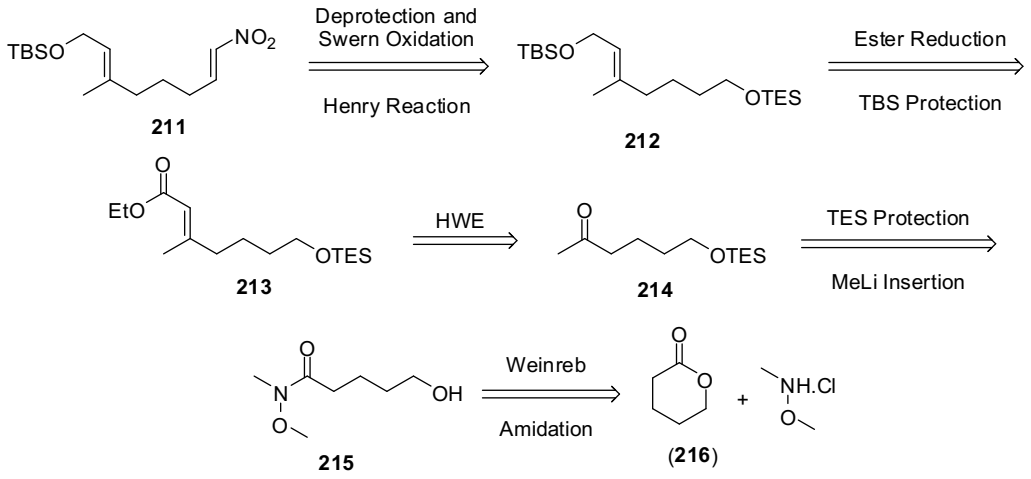


Scheme 75: Synthetic of Benzotriazole Amide 208 and *t*-Butyl-Ester-Keto 200

4.6 Studies Towards the Construction of Nitro Olefin 211

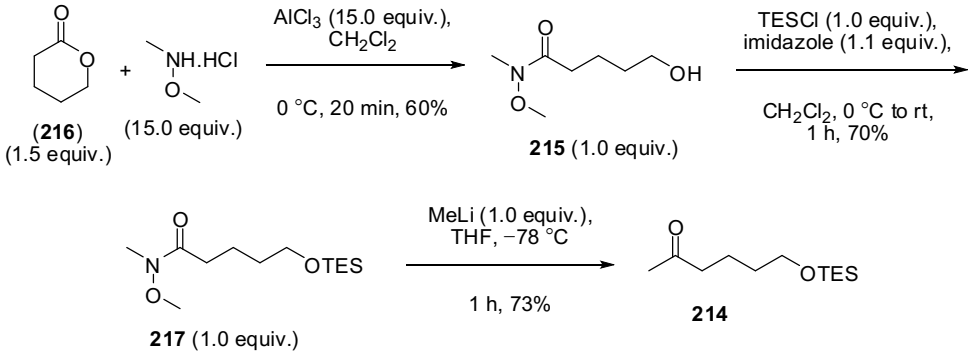
*4.6.1 Towards the Synthesis of Nitro Olefin **211** Utilising a Horner–Wadsworth–Emmons (HWE) Reaction*

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 silylether **212** followed by a Henry reaction.[114] Silylether **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 δ-valerolactone **216** with Weinreb amide (Scheme 76).[118]



Scheme 76: Retrosynthesis for the Construction of Nitro Alkene 211

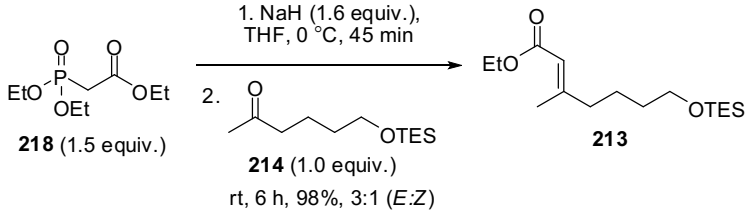
The synthesis began by treating *δ*-valerolactone **216** with *N*-methyl hydroxymethylamine hydrochloride to facilitate a Weinreb amination,[118] utilising $AlCl_3$ as a Lewis acid and providing amide **215** in a 60% yield. This procedure was chosen due to the low cost and commercial availability for the starting materials, the fast reaction time and minimal purification procedure. [118] Subsequent TES protection of alcohol **215** provided silylether **217** in a 70% yield. It was decided to use the TES protecting group because later in the synthesis it was removed under Swern conditions enabling aldehyde **220** (Scheme 79) to be provided *via* a one-pot process.[116] Treatment of amide **217** with MeLi provided ketone **214** in a 73% yield (Scheme 77).[117]



Scheme 77: Synthesis of Silylether 214

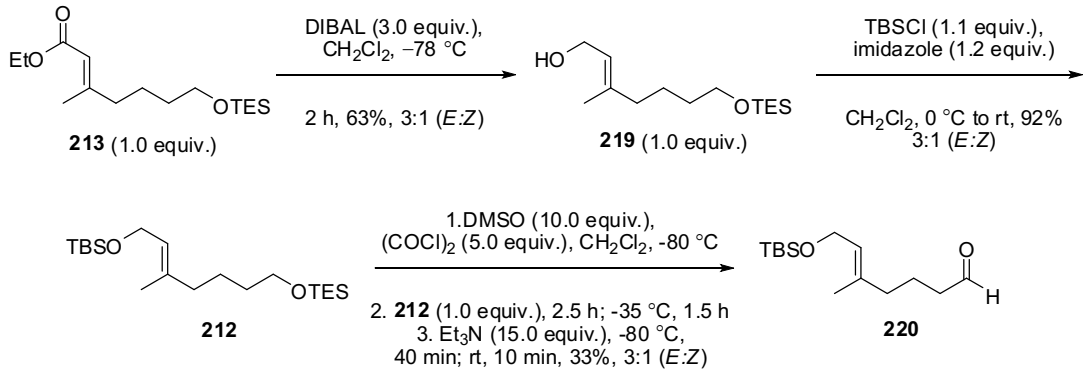
The next step involved a HWE reaction to install the *E*-olefin **213**. A HWE approach for the construction of *E*-olefin was sought because Joullié *et al.*[107] had previously reported a high

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. [107] 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

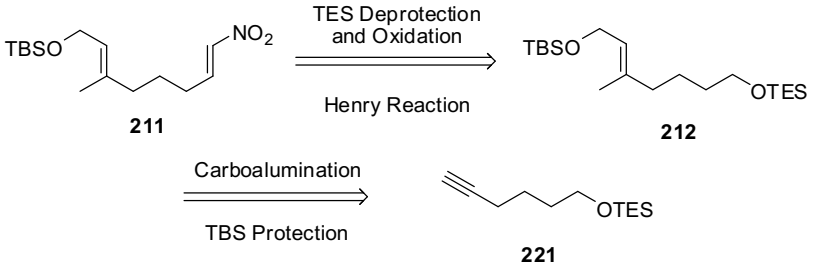
Reduction of the ester **213** proceeded smoothly utilising DIBAL-H, affording alcohol **219** in a 63% yield (*E:Z* = 3:1). TBS protection of alcohol **219** furnished silylether **212**, which was then subjected to Swern oxidation conditions[116] facilitating a TES deprotection and subsequent oxidation 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[119] for the introduction of the *E*-olefin because this method is regiospecific and would only provide the *E*-olefin (Scheme 80).



Scheme 79: Synthesis of Aldehyde 220

4.6.2 Carboalumination

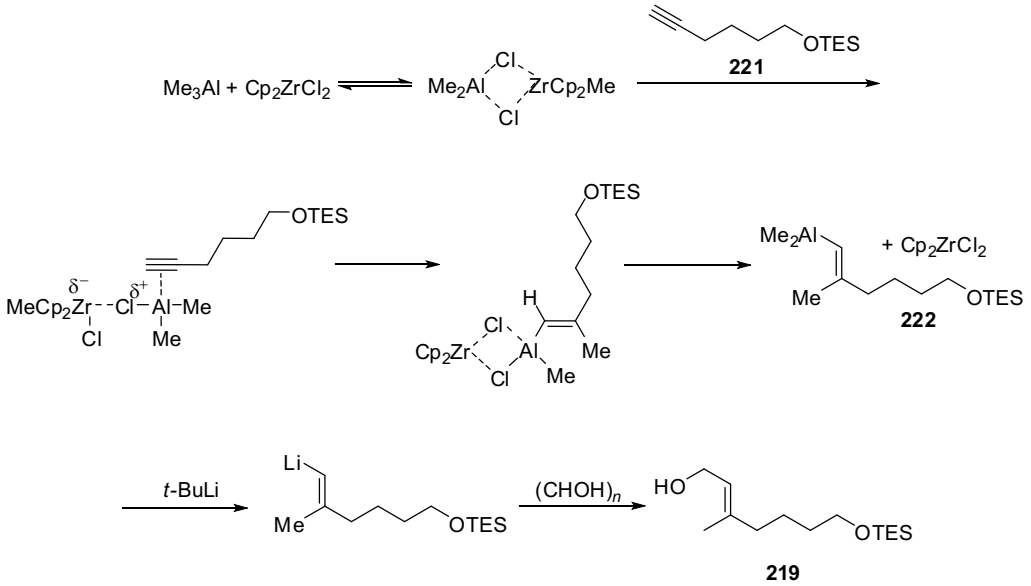
The retrosynthesis begins with a one-pot TES deprotection and oxidation[116] of silylether **212** followed by a Henry reaction[114] to afford nitro olefin **211**. It was envisaged that silylether **212** could be obtained *via* carboalumination[119] of alkyne **221** followed by TBS protection of the subsequent alcohol.



Scheme 80: Retrosynthetic Strategy Utilising Carboalumination

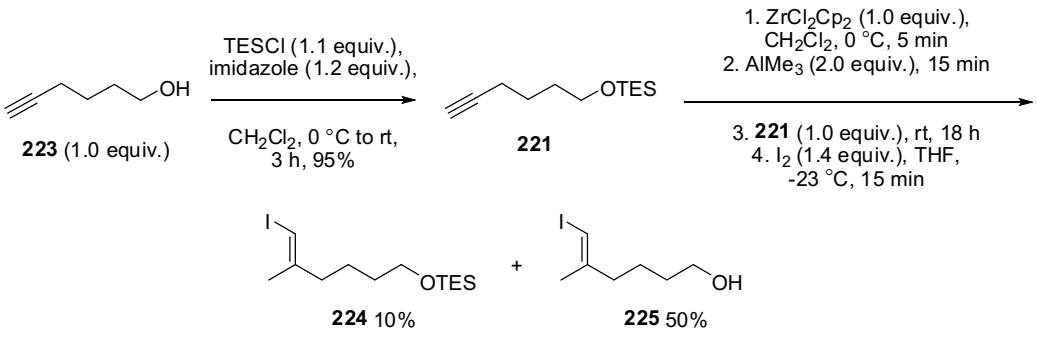
In 2005, Dussault *et al.* published the total synthesis of plakinic acid A utilising a carboalumination step which inspired the retrosynthesis above (Scheme 80).[120] It was envisaged that the carbometallation should take place in the presence of zirocene dichloride to provide the corresponding alkenyl 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_2AlCl-Cp_2ZrCl_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]



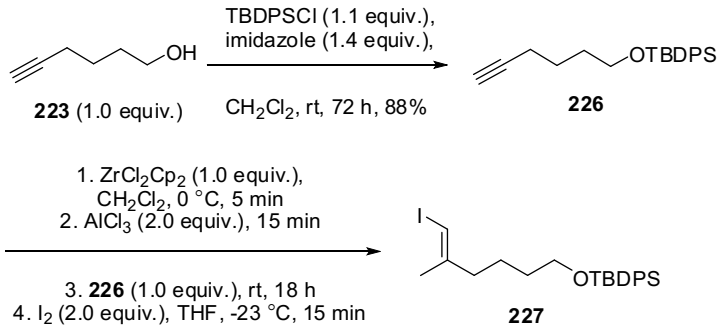
Scheme 81: Carboalumination Conditions and Mechanism

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 zirconcene 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]



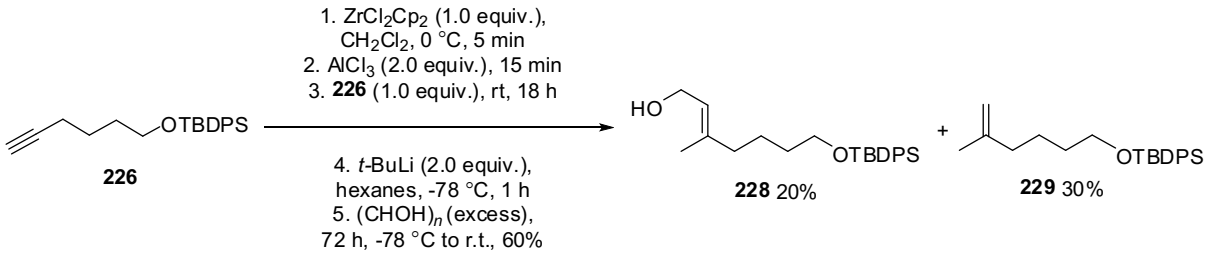
Scheme 82: Protection of Alcohol 223 and Subsequent Carboalumination

Protection of the alcohol **223** was achieved using TBDPSCl affording silylether **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).



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%.



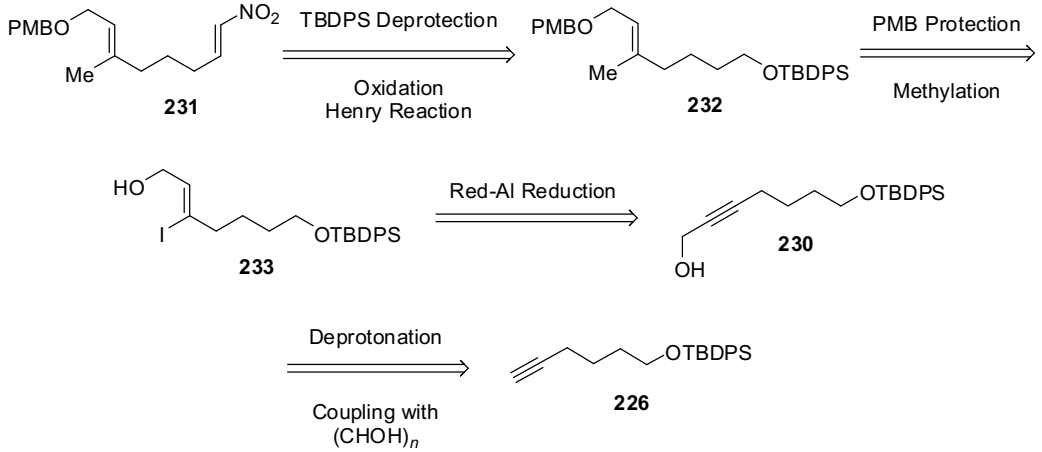
Scheme 84: Carboalumination of Alkyne 226

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

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***

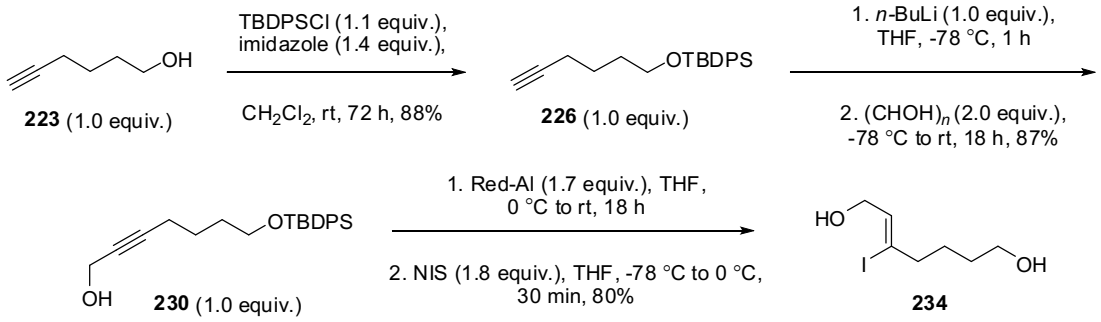
The next strategy for a high yielding method for the introduction of *E*-olefin was to utilise a stereoselective and regioselective reduction of alkynol **230** utilising Red-Al.[125] It was envisaged that nitro olefin **231** could be available from TBDPS deprotection of silylether **232**, and then oxidation and a Henry reaction.[114] Silylether **232** could be obtained *via* a PMB protection and methylation of vinyl iodide **233**. Vinyl iodide **233** could be available following a stereoselctive 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

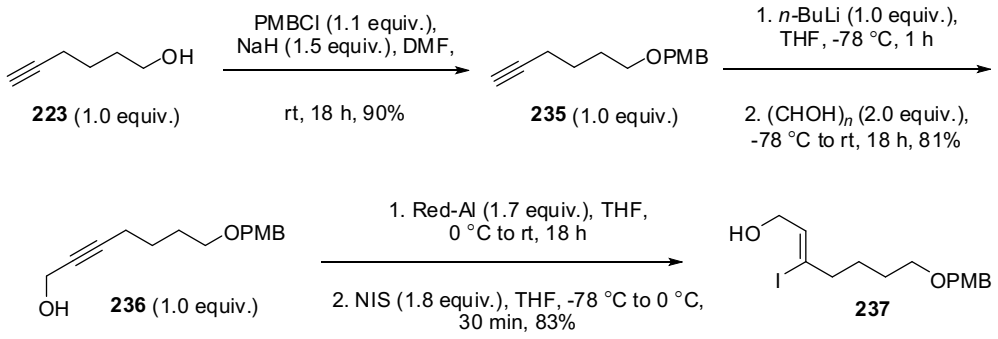
The synthesis began with the TBDPS protection of alcohol **223** obtaining silylether **226** in an 88% yield. Deprotonation and subsequent addition of paraformaldehyde to alkyne **226** provided alkynol **230** in 87% yield.[126] Treatment of alkynol **230** with Red-Al followed by quenching with NIS 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.

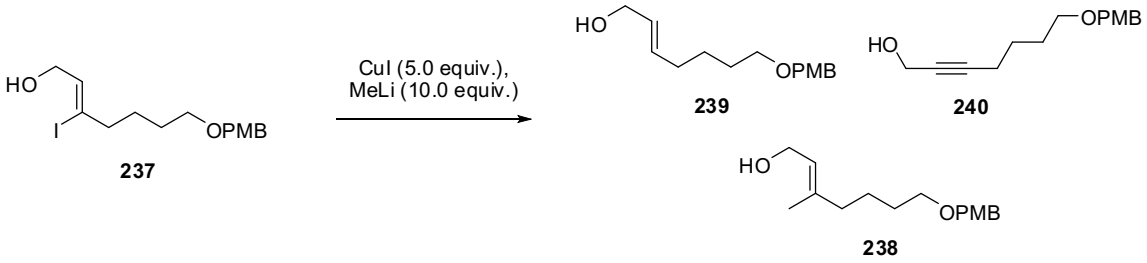
4.7 Methyl Incorporation Studies

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_2CuLi in the synthesis of olefin **238**.[129] Accordingly, a number of conditions were screened for the formation of olefin **238** utilising Me_2CuLi 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 alykne **240** were obtained (Entry 4, Table 14). Finally, the solvent was changed to Et_2O, but again olefin **239** and alkyne **240** were provided (Entry 5, Table 14).

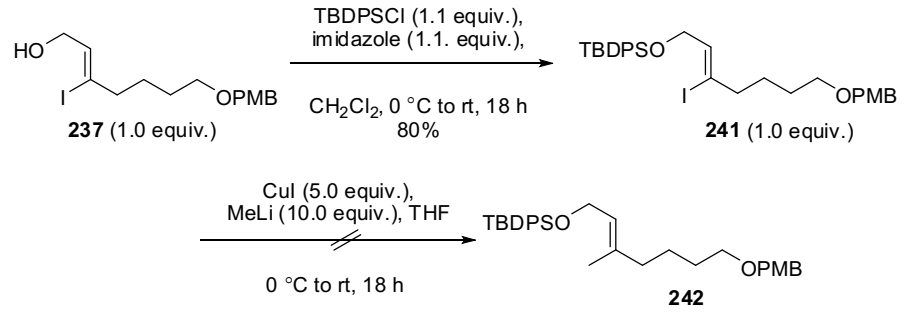
Table 14: Conditions Screened Utilising Me_2CuLi



Entry	Temp.	Solvent	Time	Conc. Of MeLi	Products[a]
1	0 °C to rt	THF	6 h	0.3 M	**239** 10%, **238** 60%
2	0 °C to rt	THF	24 h	0.3 M	**239** 40%, **238** 40%
3	0 °C to rt	THF	15 h	1.3 M	**239** 40%, **240** 40%
4	–10 °C	THF	15 h	1.3 M	**239** 40%, **240** 40%
5	0 °C	Et_2O	15 h	1.3 M	**239** 40%, **240** 40%

[a]Isolated yield after column chromatography.

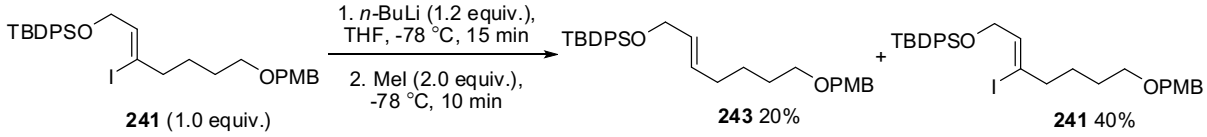
It was hypothesised that the side products may have arisen from the different bottles of MeLi being used or from the coordinating nature of the free alcohol functionality preventing the iodide from being substituted for a methyl group. Consequently, the next strategy was to protect the alcohol as a TBDPS ether and attempt the reaction again (Scheme 88). Alcohol **237** was successfully protected with the TBDPS protecting group. However, treatment with Me_2CuLi 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.



Scheme 88: TBDPS Protection Followed by Treatment with Me_2CuLi

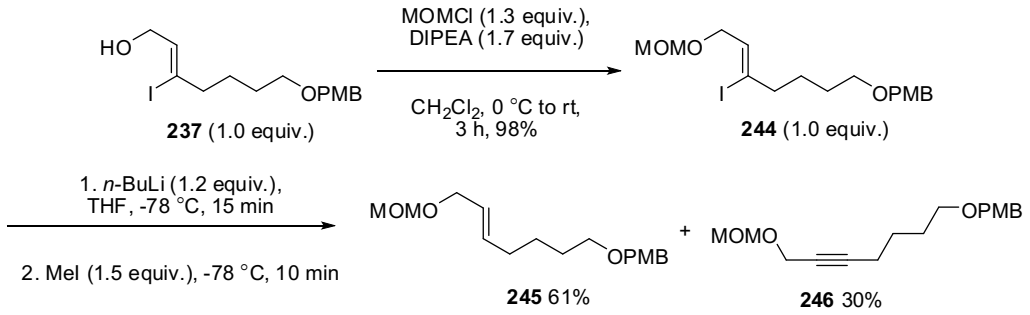
4.7.2 Lithium Iodide Exchange Followed by MeI Addition

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.



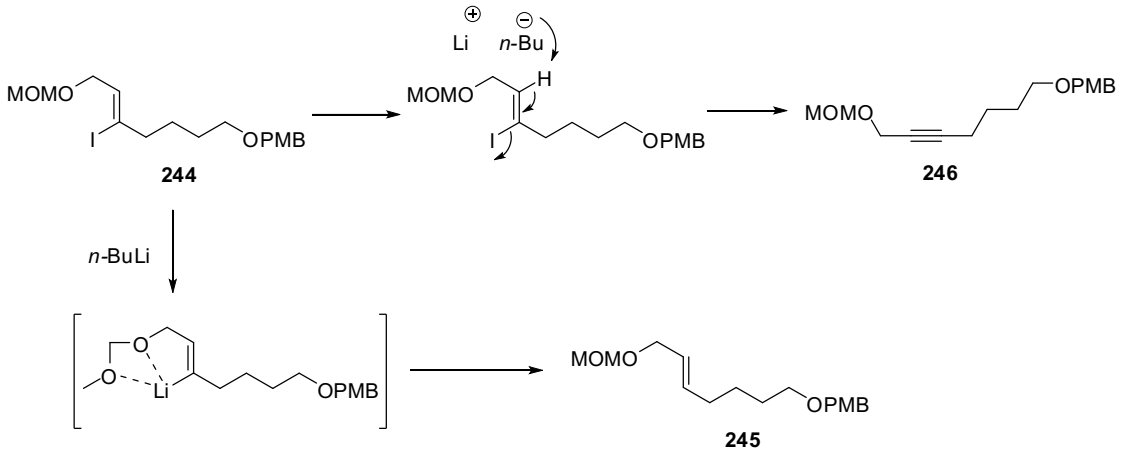
Scheme 89: Lithium Iodide Exchange and Followed by MeI Addition

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).



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[133] preventing attack from MeI (Scheme 91).

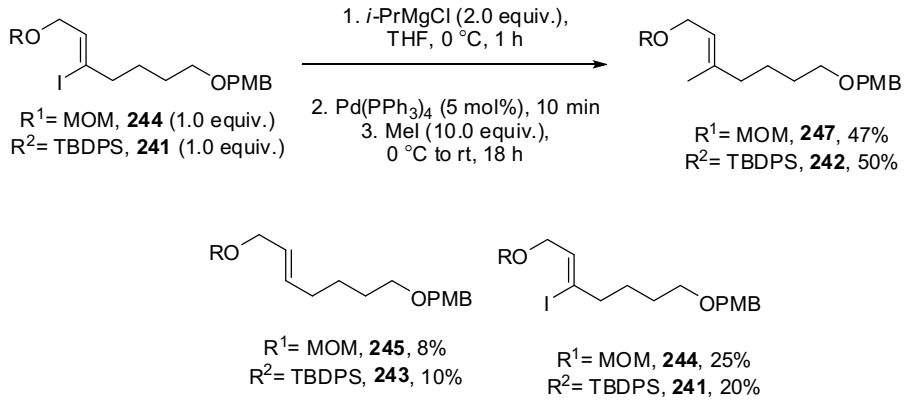


Scheme 91: Proposed Mechanisms for the Formation of Alkene 245 and Alkyne 246

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.

4.7.3 Studies towards Kumada Cross Coupling

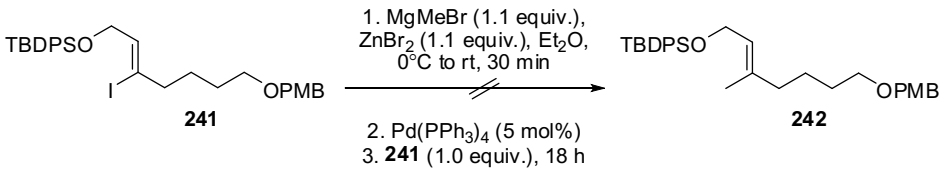
It was hypothesised that the Kumada cross coupling, reported independently in 1972 by Corriu *et al.*[134] and Kumada *et al.*,[135] would be an excellent tool for the incorporation of the methyl group. Iodide **244/241** was treated with *i*-PrMgCl and $Pd(PPh_3)_4$ followed by the addition of MeI (Scheme 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]



Scheme 92: Kumada-Type Cross Coupling

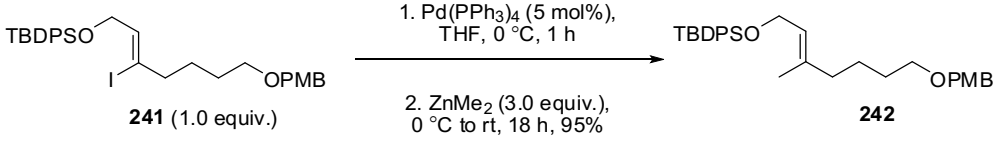
4.7.4 Negishi Cross Coupling

Recent work by Fu *et al*.[136] has demonstrated successful palladium-catalysed Negishi cross coupling of unactivated alkyl iodides and bromides. Accordingly, $ZnBr_2$ was prestirred with MeMgBr in Et_2O, $Pd(PPh_3)_4$ and iodide **241** were then added and the mixture stirred for 18 h.[137] Unfortunately, only decomposition of the starting material was observed (Scheme 93).



Scheme 93: Negishi Cross Coupling

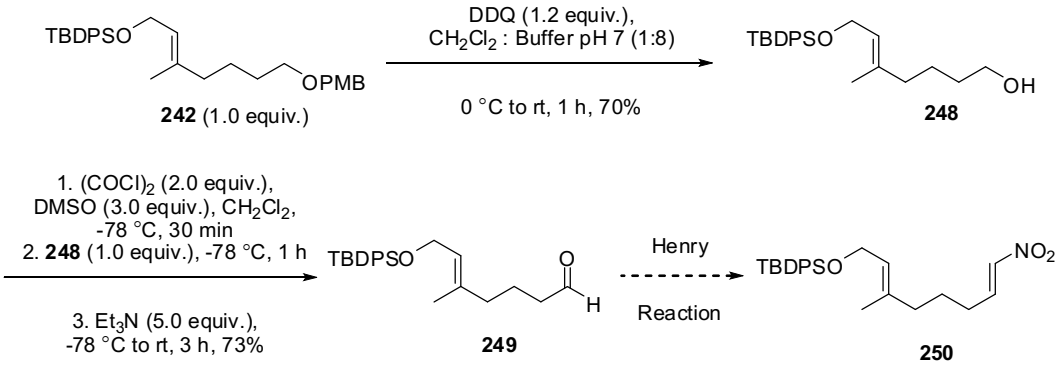
The next strategy was to utilise a pre-formed zinc complex, $ZnMe_2$. Thus, iodide **241** was stirred with $Pd(PPh_3)_4$ followed by treatment with $ZnMe_2$. Pleasingly, these reaction conditions afforded alkene **242** in an excellent 95% yield. It was noteworthy that after the addition of $ZnMe_2$ there was a colour change from colourless to yellow, presumably, indicating activation of the catalyst.[138] When the reaction was complete the colour changed back to colourless (Scheme 94).



Scheme 94: Negishi Cross Coupling Utilising $ZnMe_2$

4.8 Final Steps Towards the Synthesis of Nitro-Alkene 250

PMB deprotection was achieved using DDQ in CH_2Cl_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).

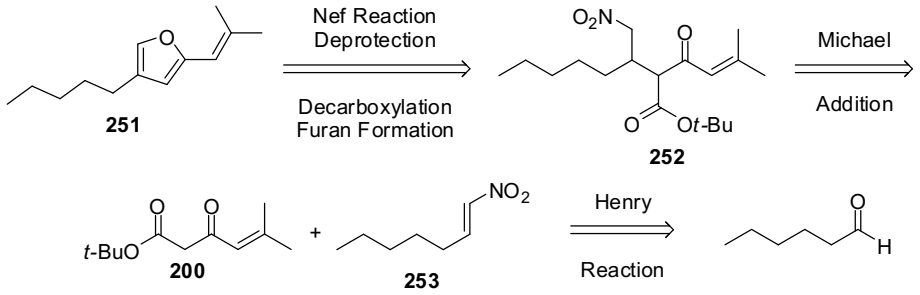


Scheme 95: Final Steps Towards the Synthesis of Nitro-Alkene 250

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.

4.9 Model Study into the Furan Formation

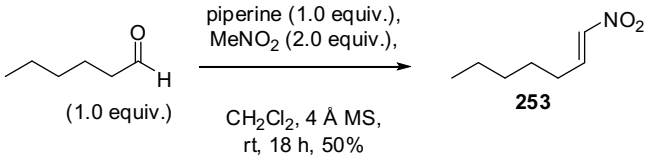
Scheme 96 below illustrates the retrosynthesis that the model study would encompass. It was envisaged that a furan **251** could be available following a Nef reaction,[111] *tert*-butyl deprotection, decarboxylation[112] and Paal Knorr furan formation[113] beginning with nitro alkane **252**. Nitro alkane **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

4.9.1 Henry Reaction

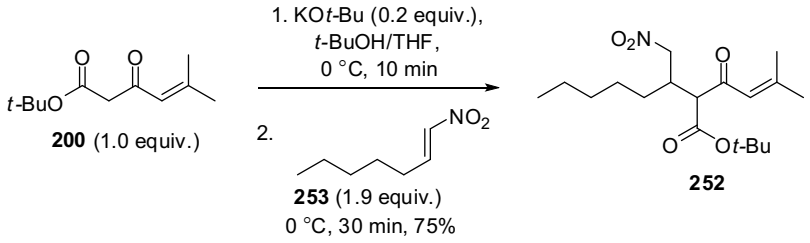
The Henry reaction[114] is a C–C bond forming reaction between a carbonyl compound and a nitro alkane, leading to the formation of *β*-hydroxy nitro compounds. If acidic protons are available dehydration will follow resulting in the formation of a *β*-nitro alcohol.[139] Vergari *et al.* demonstrated 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

4.9.2 Michael Addition

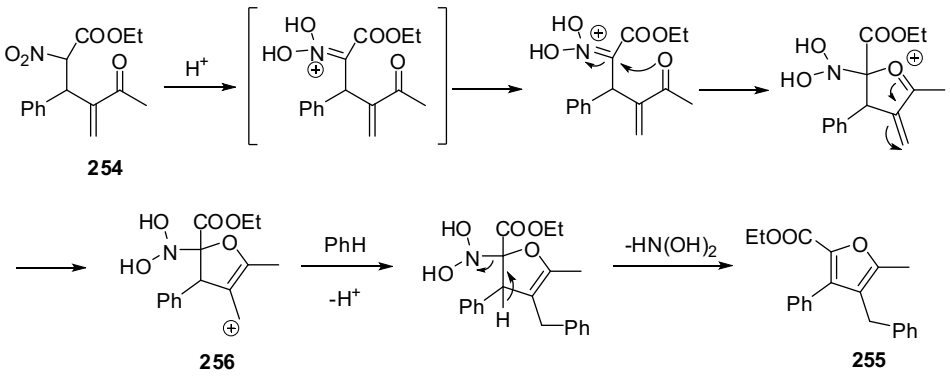
The next step in the model study was a Michael addition between nitro olefin **253** and ketoester **200**. It was decided treat ketoester **200** with a catalytic amount of KO*t*-Bu for 10 min, followed by the dropwise addition of nitro-alkene **253** in order to prevent polymerisation.[141][142] Delightfully,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



Scheme 98: Michael Addition

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]



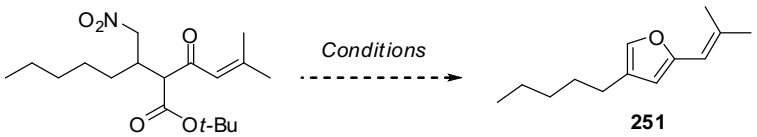
Scheme 99: Formation of Furan 255[144]

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.*[144] (Entry 1, Table 15), however, these harsh conditions led to decomposition of the starting material. Consequently, the next tactic was to utilise $KMnO_4$ to perform an oxidative Nef reaction (Entry 2, Table 15), but this method afforded a complex mixture of products.[146] As a result the use of $CrCl_2$ was studied in order to facilitate a reductive Nef reaction (Entry 3, Table 15).[147] It was also thought that the Lewis acid would aid in furan formation.[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). [147] Furthermore, it was postulated that the acidic conditions would aid the deprotection, decarboxylation[112] and furan formation steps. [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.[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 $TiCl_3$ to facilitate a Nef reaction in the total synthesis of spirotryprostatin B (**91**).[149] Additionally, it

was thought $TiCl_3$ would act as Lewis acid aiding furan formation.[113] 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

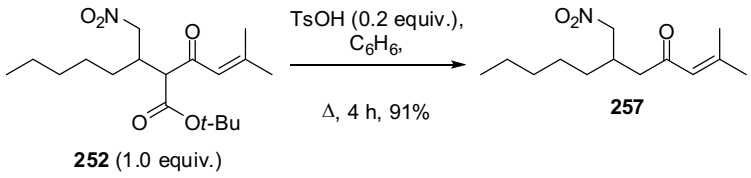


252 **251**

Entry	Conditions	Outcome
1	H_2SO_4 (excess), TFA (excess), C_6H_6, Δ, 2 h[144]	Decomposition of **252**
2	NaH (2.0 equiv.), HO*t*-Bu, 10 min, 0°C; $KMnO_4$ (excess), Pentane/H_2O, 30 min, 0 °C to rt[146]	Complex mixture
3	NaOMe (2.0 equiv.), MeOH, 30 min, 0 °C; NH_4OAc (25.0 equiv.), $CrCl_2$ (3.0 equiv.), H_2O, 0 °C to rt, 3 h[147]	Complex mixture
4	NaH (2.0 equiv.), THF, 0 °C, 30 min; 1 M HCl, 0 °C to rt, 18 h[147]	RSM
5	NaH (2.0 equiv.), THF, 0 °C, 30 min; H_2SO_4 (conc.), 0 °C to rt, 18 h[147]	RSM
6	KF (excess), Xylene, Δ, 18 [148]	RSM
7	NH_4OAc (excess), MeOH/H_2O, $TiCl_3$ (20% aq., 4.0 equiv.), 0 °C to rt, 5 h[149]	Complex mixture

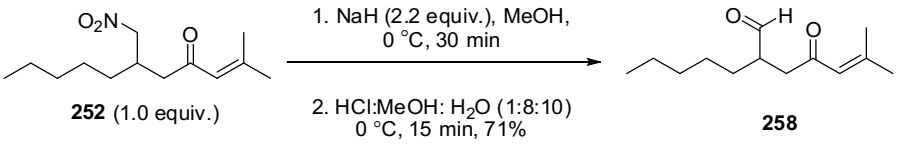
Regrettably, formation of furan **251** in a one-pot reaction was not possible. It was apparent that the Nef reaction was not working successfully, either because the aldehyde was being formed and then decomposing (Entries 2, 3 & 7, Table 15) or not being formed at all (Entries

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).[150]



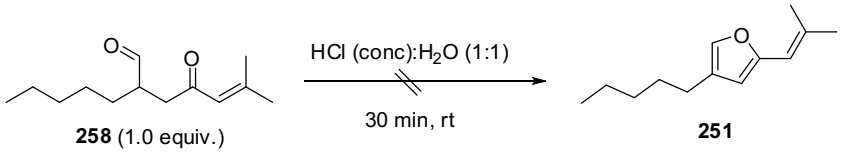
Scheme 100: Deprotection and Decarboxylation of Ester 252

The next step was to attempt a one-pot Nef reaction[111] and furan formation.[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** *via* the Nef reaction,[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.[147]



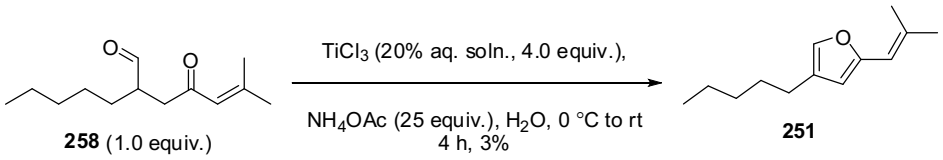
Scheme 101: Nef Reaction for the Formation of Aldehyde 258

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.[113] Under acidic conditions decomposition of the starting material occurred (Scheme 102).



Scheme 102: Attempted Furan Formation under Acidic Conditions

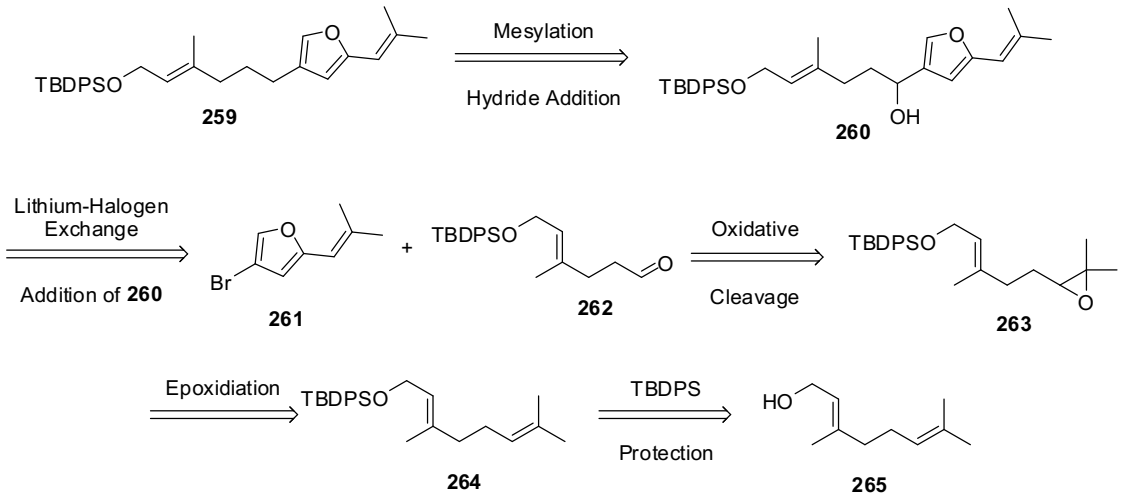
However, when aldehyde **258** was treated with $TiCl_3$, furan **251** was isolated in a 3% yield with a complex mixture of side products (Scheme 103). It was apparent that this reaction would require tedious optimisation in order to make a feasible synthetic route towards cristatic acid methyl ester **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.[151] Furan **260** could be installed *via* a lithium halogen exchange on bromo-furan **261** followed by the addition of aldehyde **262**.[152] 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).[107][153]

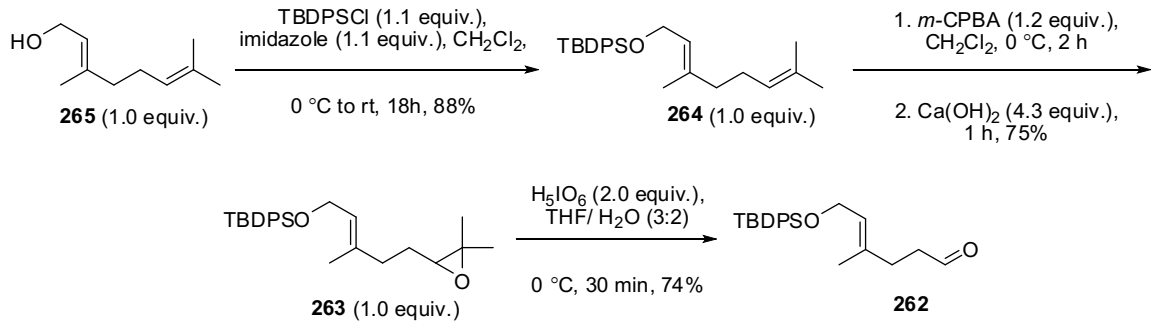


Scheme 104: Strategy B for the Construction of Silylether 259

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 silylether **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).[151][153]



265 (1.0 equiv.)

264 (1.0 equiv.)

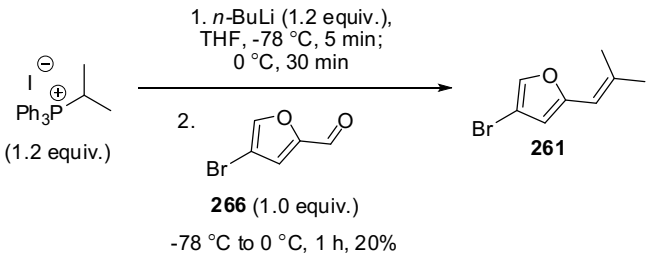
263 (1.0 equiv.)

262

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 stating material the reaction was stopped, providing olefin **261** in a 20% yield (Scheme 106).[107]



(1.2 equiv.)

266 (1.0 equiv.)

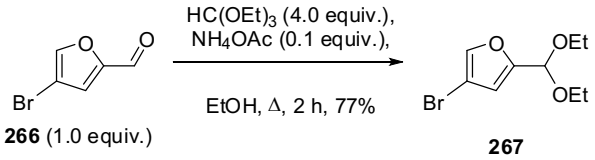
-78 °C to 0 °C, 1 h, 20%

261

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

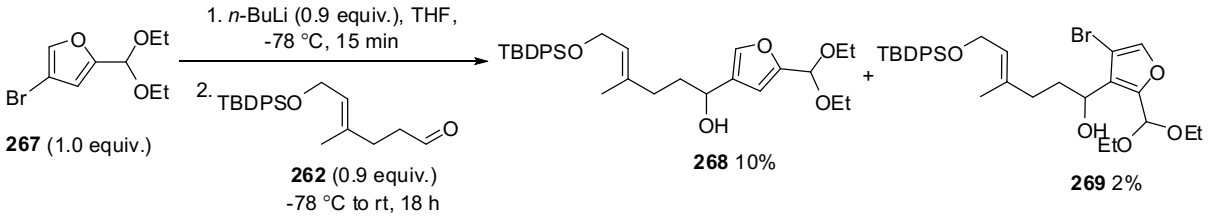
perform the Wittig reaction following the activation as the mesylate and reduction (Scheme 107). Accordingly, aldehyde **266** was protected as the diethyl acetal **267** in a 77% yield.[107][156]



Scheme 107: Protection of Aldehyde 266

*4.11.3 Lithium-Halogen Exchange Followed by the Addition of Aldehyde **261***

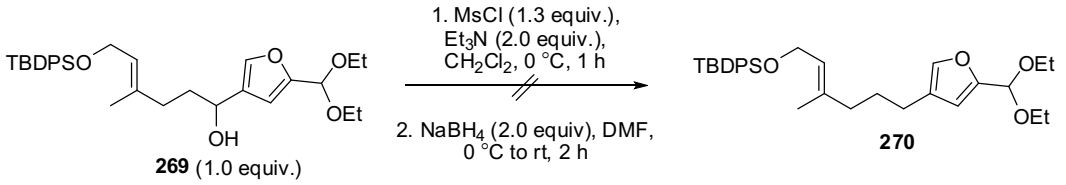
Bromo-furan **267** was treated with *n*-BuLi in order to facilitate a lithium-bromine exchange, aldehyde **262** was then added to the reaction mixture providing alcohol **268** in a 10% yield and bromo-alcohol **269** in a 2% yield (Scheme 108).[152] While the reaction was low yielding it was interesting 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**.[157]



Scheme 108: Addition of Bromo Furan 267 to Aldehyde 269

Mesylation of alcohol **268** followed by the addition of $NaBH_4$ was attempted (Scheme 109).[151][158] It was thought that following mesylation and upon addition $NaBH_4$, a nucleophilic source of hydride,[159] the mesyl group would readily leave because the partial positive charge α 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.



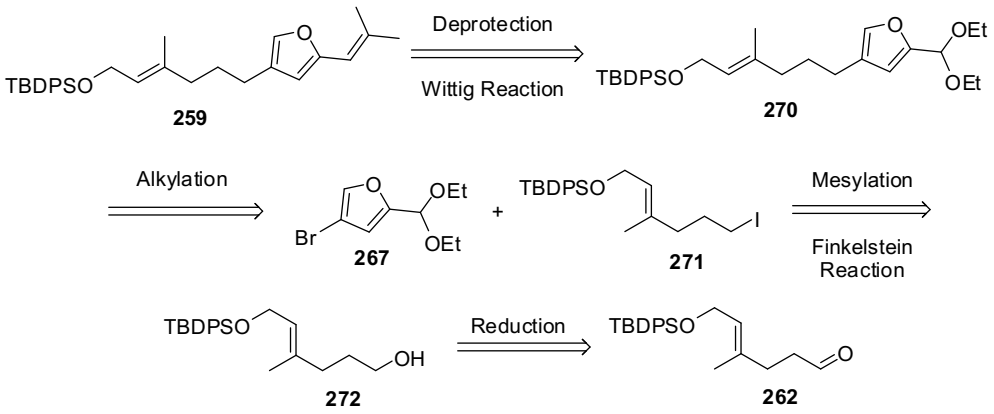
Scheme 109: Mesylation Followed by Reduction

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.*[107]

4.12 Alkylation Approach to Furan 259

4.12.1 Retrosynthetic Analaysis

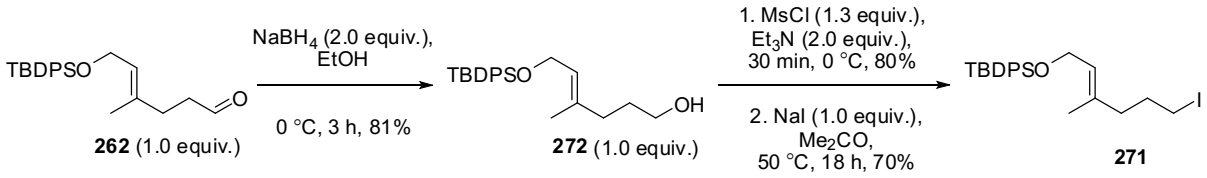
It was thought that deprotection of diethyl acetate **270** and a subsequent Wittig reaction[154] on the corresponding aldehyde could provide terpenoid **259**. An alkylation reaction between bromo-furan **267** and iodide **271** could give access to alkyl-furan **270**. Iodide **271** could be available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



Scheme 110: Retrosynthesis for Furan 259

*4.12.2 Synthesis of Iodide **271***

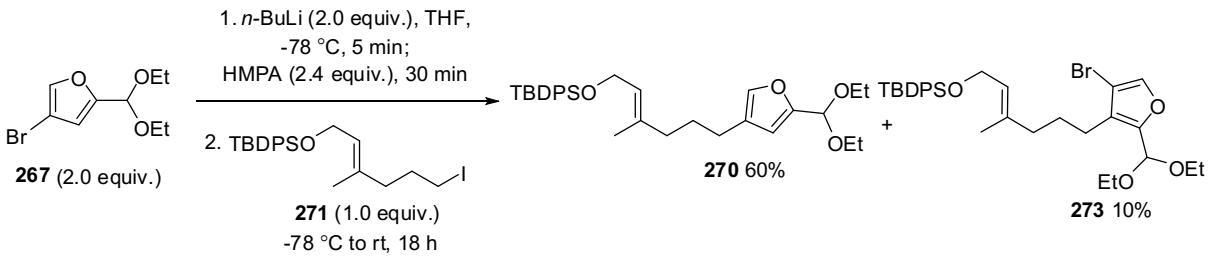
Reduction of aldehyde **262** utilising $NaBH_4$ provided alcohol **272** in an 81% yield.[153] Iodide **271** was then formed *via* mesylation of alcohol **272** followed by an iodide substitution utilising NaI (Scheme 111).[153] With iodide **271** in hand the cross coupling with bromo-furan **267** 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[160] 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

Due to the coordinating nature of HMPA[160] in this reaction it was decided to investigate the alternative reagents DMPU[161] and DMI[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

Entry	Conditions prior to Iodide Addition[a]	Products[b]
1	*n*-BuLi (2.0 equiv.), 5 min, –78 °C; HMPA (2.4 equiv.), 30 min	**270** 60%, **273** 10%
2	*n*-BuLi (2.0 equiv.), –78 °C, 30 min	**270** 30%, **273** 4%
3	HMPA (2.4 equiv.), 5 min, –78 °C; *n*-BuLi (2.0 equiv.), 30 min	**273** 71%
4	*n*-BuLi (2.0 equiv.), 5 min, –78 °C; DMI (2.4 equiv.), 30 min	**270** 33%, **273** 6%
5	*n*-BuLi (2.0 equiv.), 5 min, –78 °C; DMPU (2.4 equiv.), 30 min	**270** 24%, **273** 3%

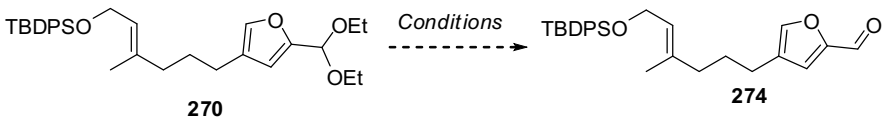
[a]Iodide **271** was added to all reactions at –78 °C. The reaction was then allowed to warm to rt and stirred for 18h.
[b]Isolated yield after column chromatography.

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 acetate **270** (Table 17). The first conditions (Entry 1, Table 17) demonstrated by Joullié *et al*.,[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.[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.

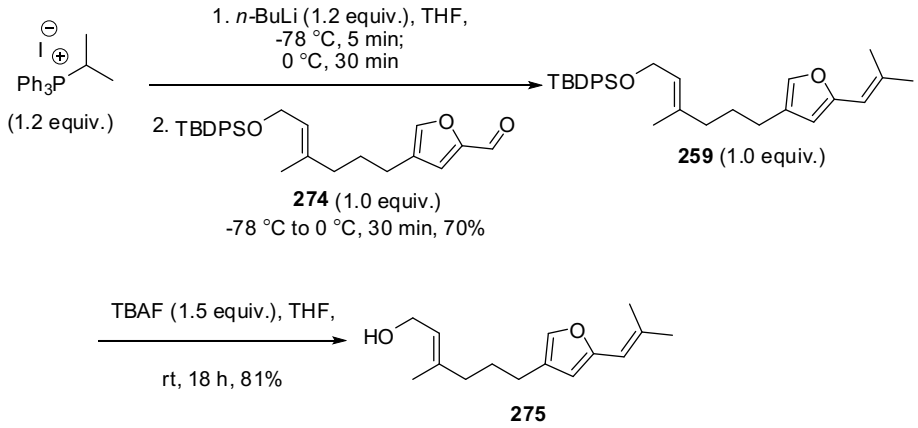
Table 17: Conditions for the Deprotection of Diethyl Acetate 270



270 **274**

Entry	Conditions	Products
1	$CDCl_3$, rt, 18 h	RSM
2	1 M HCl, 30 min, rt	**274** 89%
3	$In(OTf)_3$ (0.1 equiv.), Me_2CO, 5 min, rt	**274** <98%

The Wittig reaction[154] was accomplished utilising the conditions discussed in Section 4.11.2 which provided olefin **259** in a pleasing 70% yield,[107] The deprotection of silylether **259** was achieved in 81% yield utilising TBAF (Scheme 113).

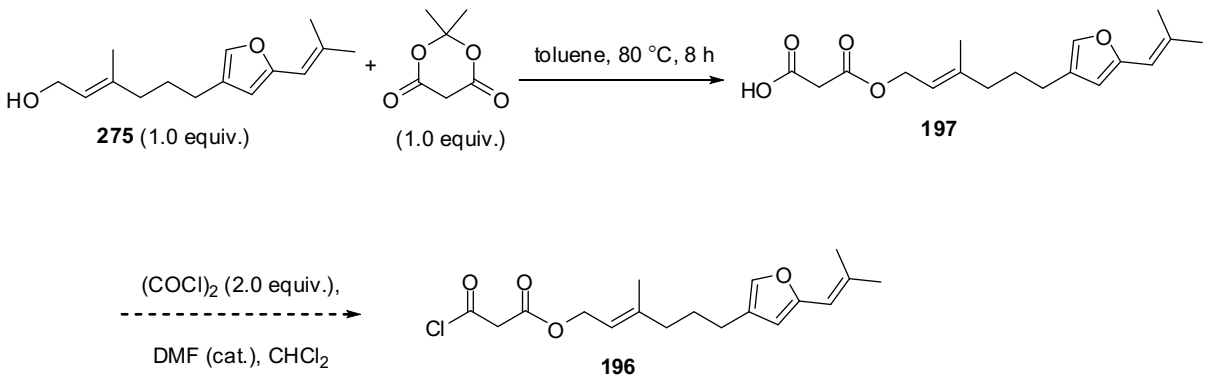


Scheme 113: Alkene Formation and TBDPS Deprotection

Having successfully completed the synthesis of alcohol **275** the next synthetic step involved heating with Meldrum's acid to provide acid **259**.

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.

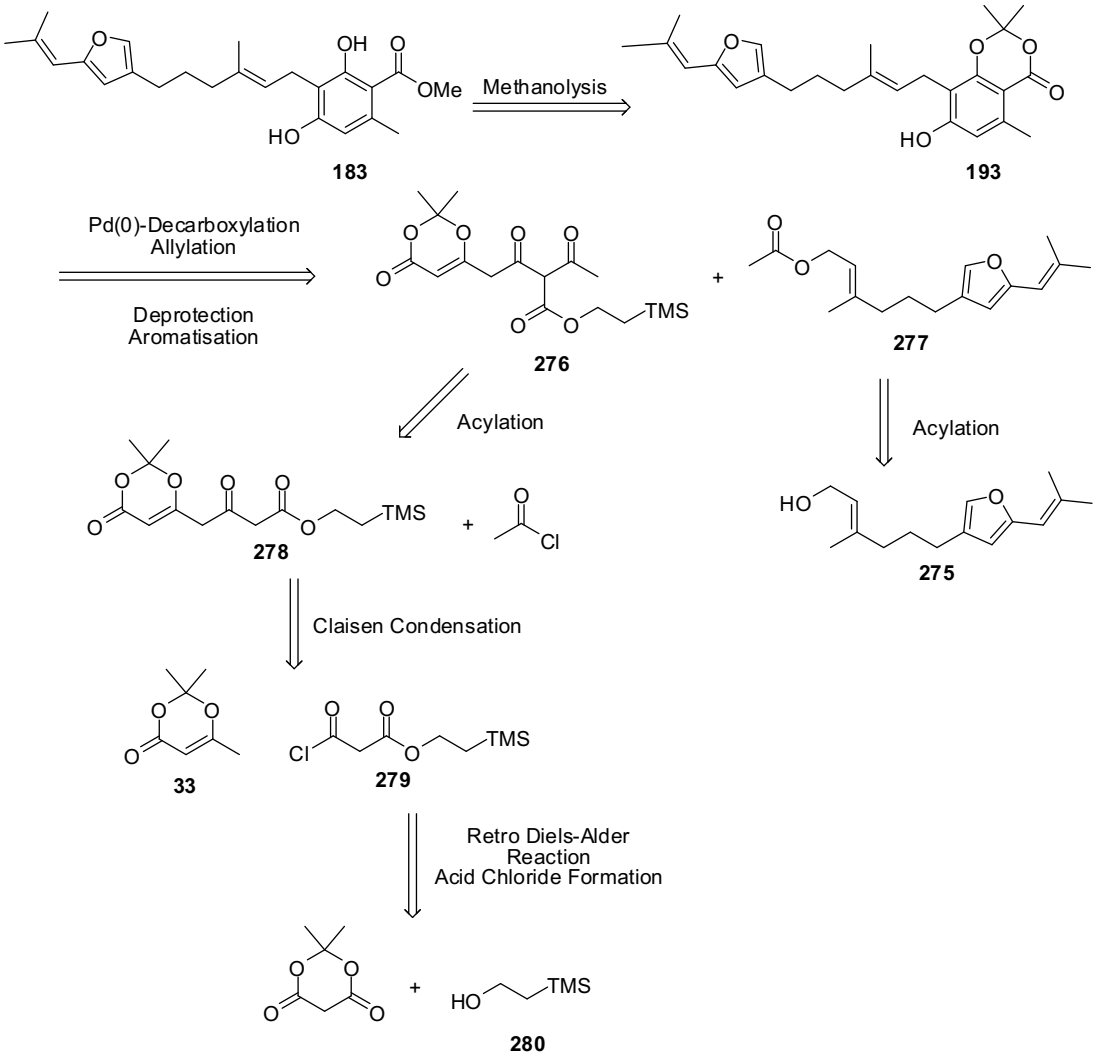


275 (1.0 equiv.) (1.0 equiv.) **197** **196**

Scheme 114: Retro-Diels Alder Reaction of Alcohol 275 and Meldrum's Acid

4.16 Second Retrosynthesis for Cristatic Acid Methyl Ester 183

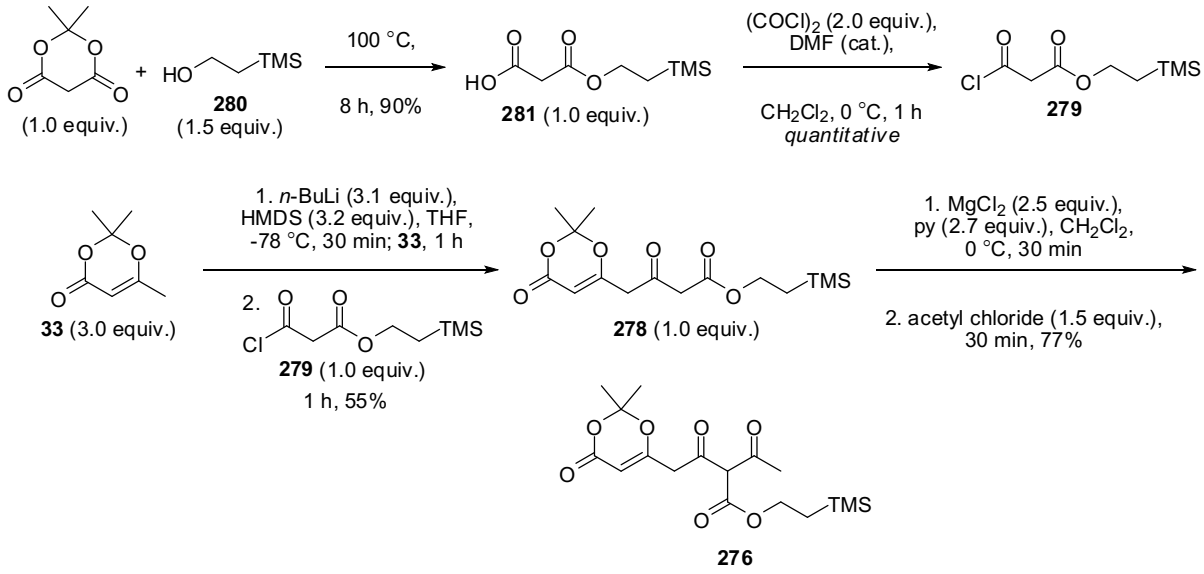
It was predicted that cristatic acid methyl ester **183** could be available *via* opening of isopropylidene protected resorcylate **193** with MeOH. Treatment of diketo-ester-dioxinone **276** with acetate **277** and $Pd(PPh_3)_4$ could facilitate an external Pd(0)-decarboxylative allylation; subsequent ester deprotection and aromatisation could then furnish isopropylidene protected resorcylate **193**.[102][164] 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).[42][43]



Scheme 115: Alternative Retrosynthesis for Cristatic Acid Methyl Ester 183

4.17 Synthesis of Diketo-Ester-Dioxinone 276

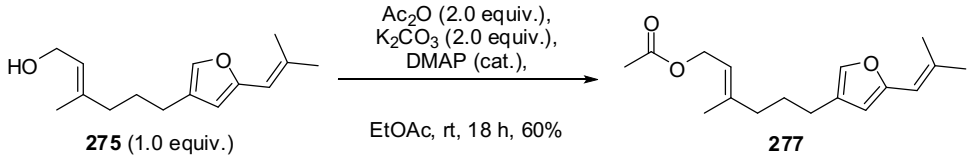
The synthesis of diketo-ester-dioxinone **276** began by refluxing Meldrum's Acid with alcohol **280**, facilitating a retro Diels-Alder reaction providing acid **281** in a 90% yield.[74] Acid **281** was then transformed into the corresponding acid chloride **279** utilising oxalyl chloride and catalytic 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-dioxine **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

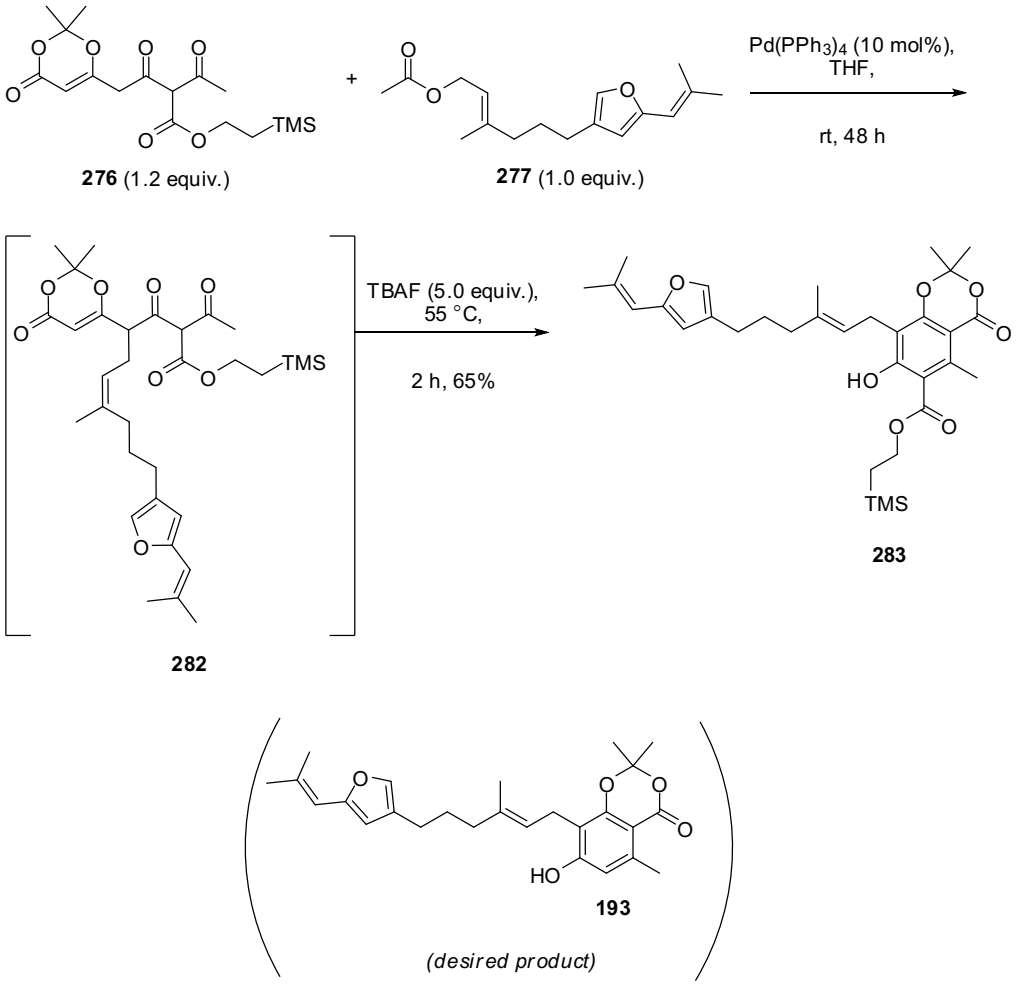
4.18 Synthesis of Acetate 277 and Subsequent Allylation with Diketo-Ester-Dioxinone 276

Acetate **277** was synthesised utilising a procedure from within the Barrett group.[153] Treatment of alcohol **275** with acetic anhydride, K_2CO_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).



Scheme 117: Synthesis of Acetate 277

Following earlier work from within the Barrett group involving allylation[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 *et al.*[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).

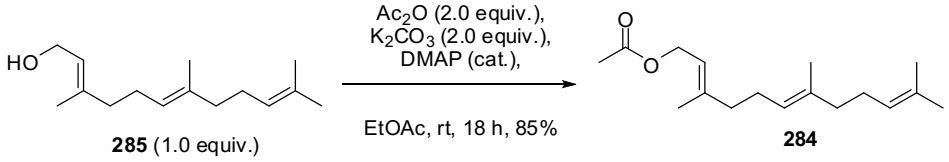


Scheme 118: Treatment of Diketo-Ester-Dioxinone 276 and Acetate 277 with $Pd(PPh_3)_4$

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**.

4.19 Model Study into the Decarboxylative, Allylation, Deprotection and Aromatisation Sequence[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).



Scheme 119: Synthesis of Acetate 284

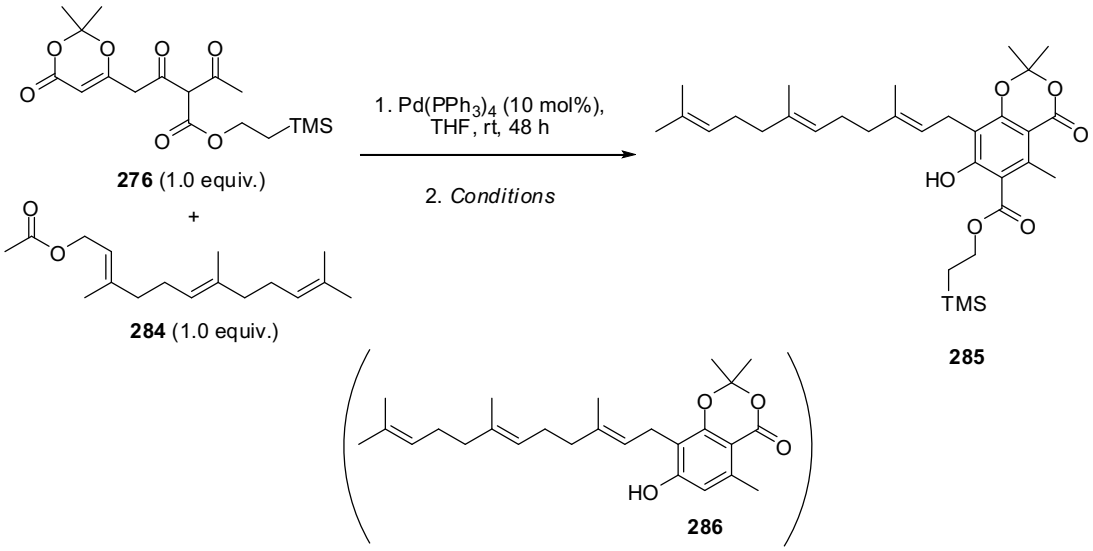
The first set of conditions to be screened were those reported by Serrano-Wu *et al*.[164] (Entry 1, Table 18). These conditions provided resorcylate **285** with the TMSE ester still present. It was therefore decided to screen TBAF•1H_2O and TBAF•3H_2O to see if an additive of water would positively 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.[165]

Marlowe *et al.* demonstrated in 1993 that SiO_2 in THF could be utilised for deprotection of the TMSE ester.[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,[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),[168] nonetheless resorcylate **285** was

[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



Entry	Conditions	Product[a]
1	TBAF (5.0 equiv.), THF, Δ, 2 h[164]	Resorcylate **285**
2	TBAF•1H_2O (5.0 equiv.), Δ, 2 h*	Resorcylate **285**
3	TBAF•3H_2O (5.0 equiv.), Δ, 2 h*	Resorcylate **285**
4	TBAF (5.0 equiv.), DMF, Δ, 2 h[165]	Resorcylate **285**
5	TBAF (5.0 equiv.), DMSO, Δ, 2 h[165]	Resorcylate **285**
6	SiO_2 (10.0 equiv.), THF, 5 h, rt*[166]	Resorcylate **285**
7	TAS-F (5.0 equiv.), THF, 4 h, rt[167]	Resorcylate **285**
8	H_2SiF_6 (5.0 equiv.), THF, 8 h, rt	Resorcylate **285**
9	HF•Et_3N (5.0 equiv.), THF, 1 h, rt*	Resorcylate **285**
10	Acetic Acid (5.0 equiv.), TBAF (5.0 equiv.), THF, 2 h, rt[168]	Resorcylate **285**
11	1M NaOH, 1 h, rt*	Resorcylate **285**

[a]Crude product isolated after workup.

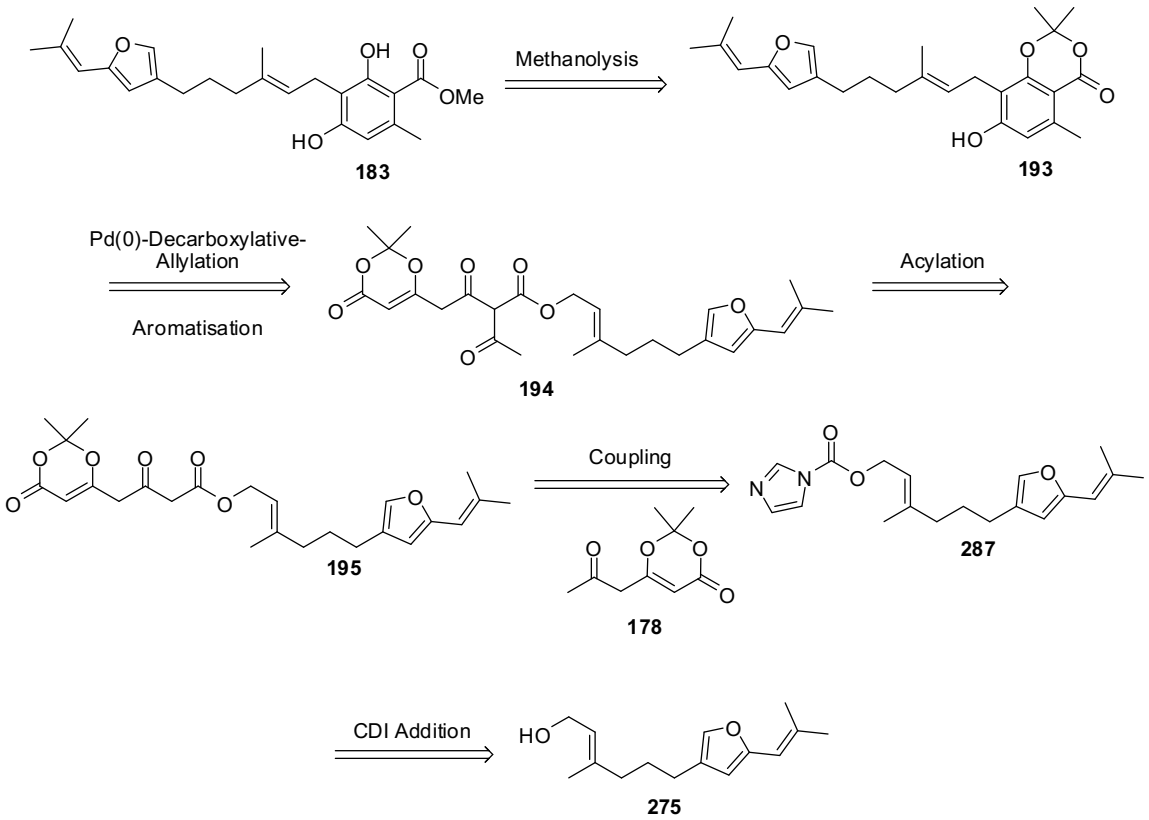
Due to time constrains and the unsuccessful nature of the conditions that were screened (Table 18) it was decided to change the retrosynthetic route for the construction of cristatic acid methyl ester **183** (the strategy is discussed in Section 4.21).

4.20 Conclusions

Studies towards this total synthesis have exhibited a wide range of methodologies developed within the Barrett group, including dioxinone chemistry[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 *et al.*[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[IX]

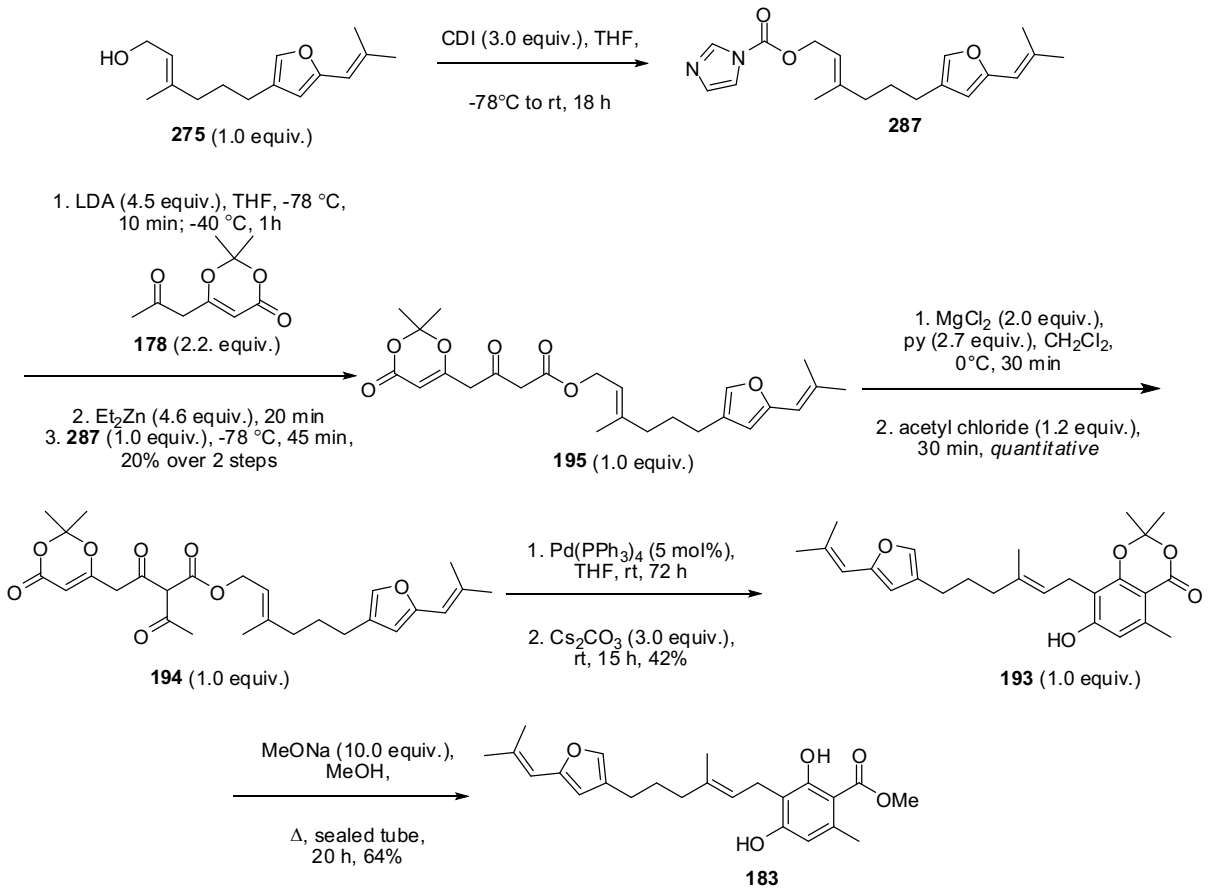
It was postulated that following a methanolysis to form the methyl ester of cristatic acid **183**, isopropylidene protected resorcylate **193** could be obtained *via* a Pd(0)-decarboxylative-allylation and aromatisation sequence beginning with diketo-ester-dioxinone **194**. Diketo-ester-dioxinone **194** could be available from acylation of keto-ester-dioxinone **195**[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).[169]



Scheme 120: Retrosynthetic Analysis of Cristatic Acid Methyl Ester 183

[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.[82] Amide **287** was then coupled with diketo-dioxinone **178** to furnish keto-ester-dioxinone **195** in a 20% yield.[169] 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).

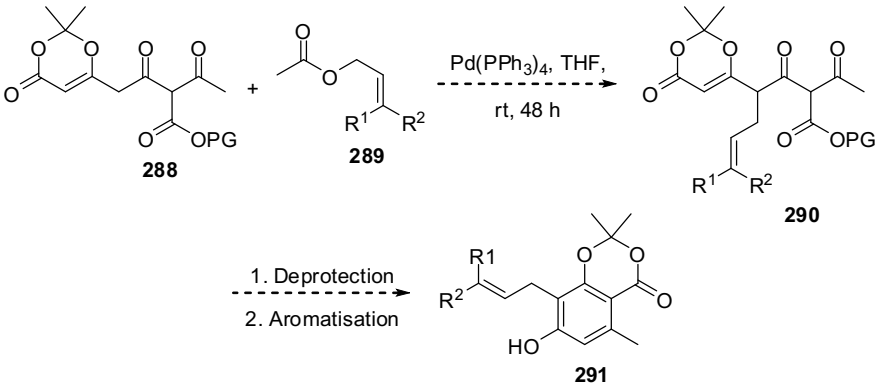


Scheme 121: Synthesis of Cristatic Acid Methyl Ester 183

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 diketo-ester-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

There are a number of potential protecting groups that could be studied. Firstly, 2,2,2-trichloroethyl ester ($RCO_2CH_2CCl_3$), 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 ($RCO_2CH_2CH_2SCH_3$), removed by oxidation (H_2O_2, $(NH_4)_6Mo_7O_{24}$, Me_2CO)[170][172] could be investigated. Thirdly, 2-(*p*-methoxyphenyl)ethyl ester (*p*-$CH_3OC_6H_4CH_2CH_2O_2CR$), removed *via* treatment with 1% TFA[170][173] or dichloroacetic acid in CH_2Cl_2 by DDQ[170][174] could be studied.

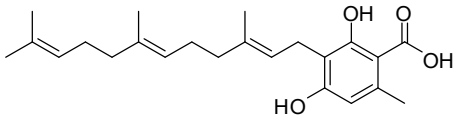
4.22.2 Total Synthesis of Resorcylate Natural Products Utilising the Pd(0)-Decarboxylative Allylation

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 isopropyliene 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*,[6][69] 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.[70] 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 resorcylate natural products including cristatic acid (**5**) contain the acid functionality.[175]

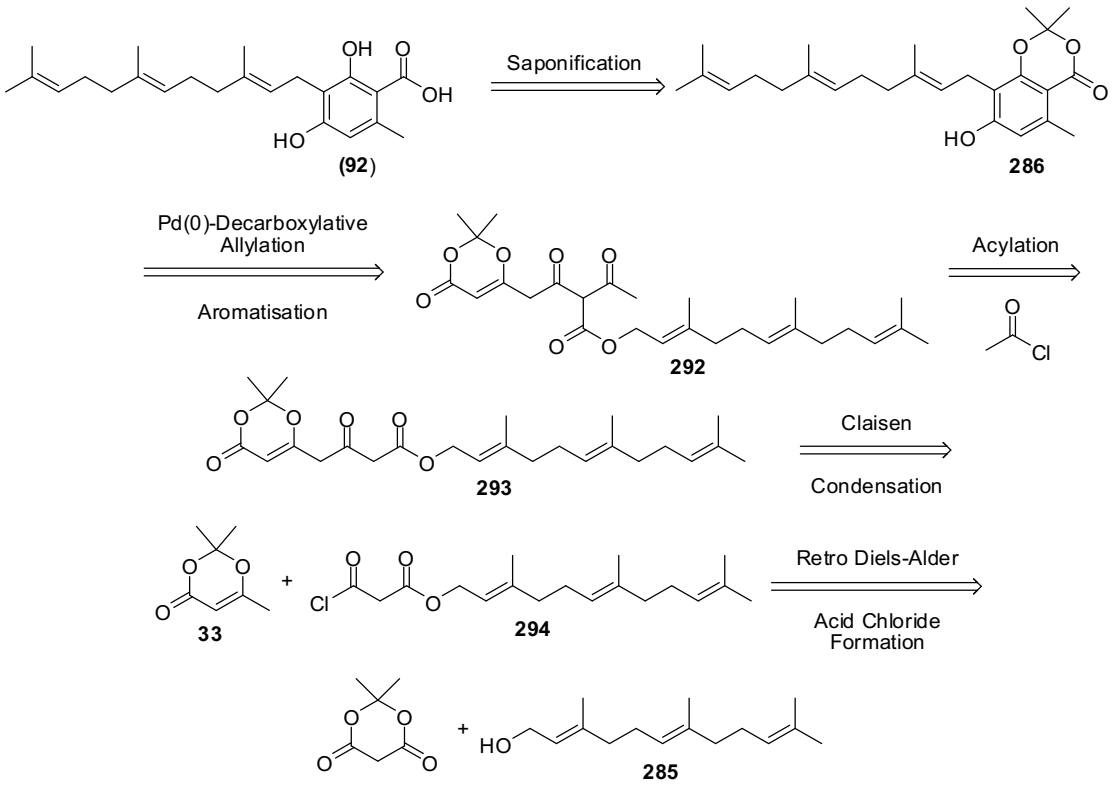


grifolic acid (**92**)

Figure 19: Grifolic Acid (92)

5.2 Retrosynthetic Analysis

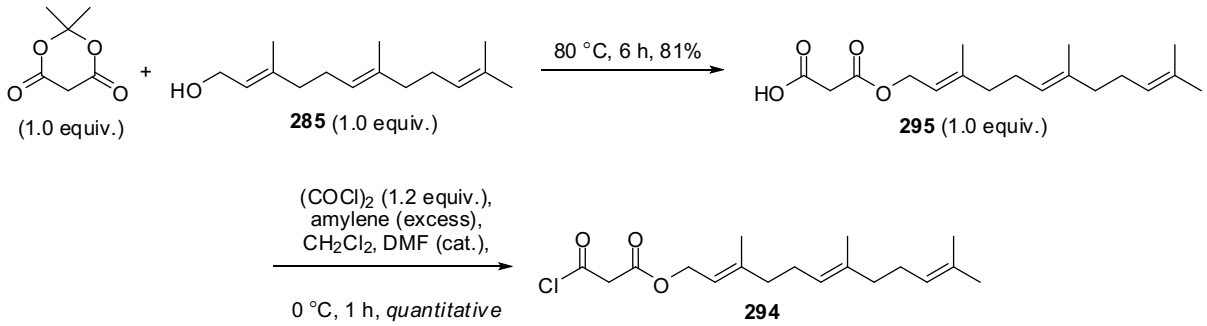
Scheme 123 below illustrates the proposed retrosynthetic analysis for the construction of grifolic acid (**92**). It was envisaged that saponification of isopropylidene resorcylate **286** could afford grifolic acid (**92**). Resorcylate **286** could in turn be accessed *via* a Pd(0)-decarboxylative 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)

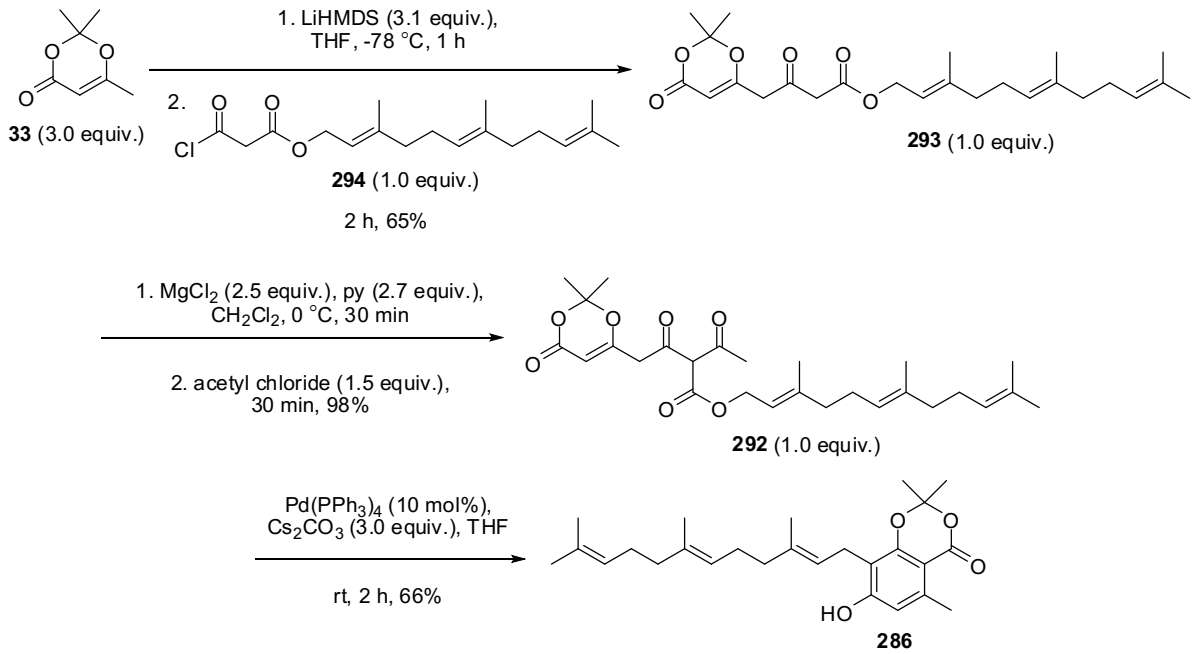
5.3 Synthesis of Isopropylidence Protected Resorcylate 286

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 $MgCl_2$ 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).

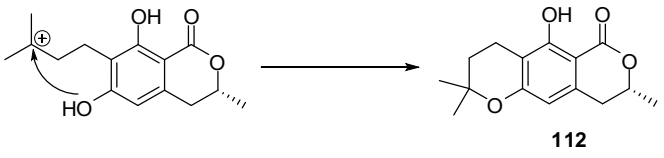


Scheme 125: Synthesis of Resorcylate 286

5.4 Studies Towards the Formation of Grifolic Acid (92)

*5.4.1 Saponification of Isopropylidene Resorcylate **286***

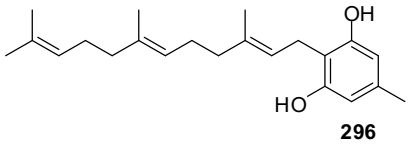
Having successfully achieved the synthesis of resorcylate **286** the next goal was to conduct investigations into the formation of grifolic acid (**92**) through opening of the isopropylidene moiety. General conditions for the opening of isopropylidene groups involve treatment with an acid such as TFA.[176] 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

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 BCl_3. 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.

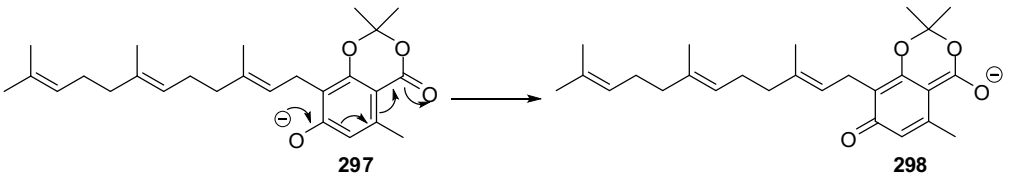
The next strategy was to utilise the basic conditions reported by Porco, Jr. *et al.*[178] in 2002 (Entry 2, Table 19). But, after the addition of 1.0 equivalent of KOH there was no reaction, hence the equivalents of KOH was increased from 1.0 to 10.0 while monitoring the reaction and stirring at rt. 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 ^{1}H 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]



296

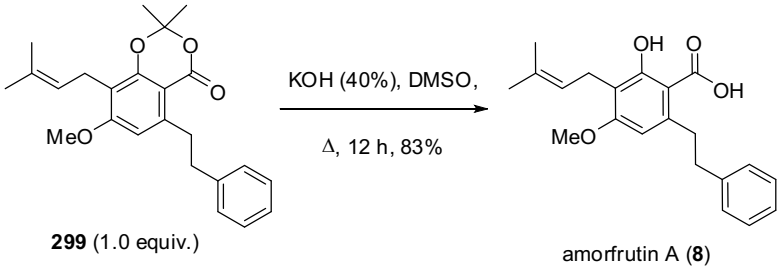
Figure 20: Decarboxylated Resorcylate 296

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]



Scheme 127: Phenolate Production

The last step in the total synthesis of amorfrutin A (**8**) involved a saponifaction utilising KOH (40%) in refluxing DMSO (Scheme 128).[X] 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.



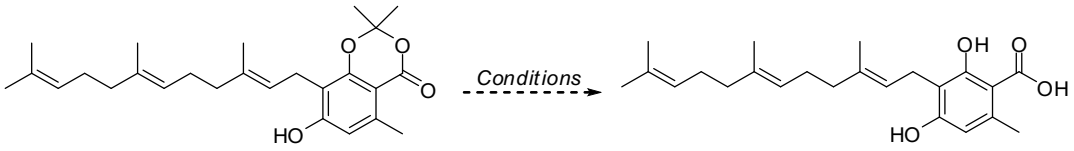
Scheme 128: Formation of Amorfrutin A (8) *via* Saponification

The next approach was inspired by the work of Lovrić *et al.*[181] who revealed that treatment of esters with KOTMS led to the formation of the corresponding carboxylic acid. Accordingly, isopropylidene protected resorcylate **286** was treated with 1.0 equivalent of KOTMS, which was gradually increased to 10.0 equivalents after there was no initial consumption of the starting material (Entry 6, Table 19). The reaction mixture was then allowed to slowly heat to reflux and stirred for 18 h, but residual starting material was observed indicating that the nucleophilicity of KOTMS was not strong enough to open the isopropylidene group. Alternatively, KOTMS could have been deprotonating the phenol and preventing the carboxyl moiety from reacting (Scheme 127).

[X] The total synthesis of amorfrutin A (**8**) has been published, please see Laclef, S.; Anderson, K.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2012**, *53*, 225–227.

The final strategy was to add TMSCl into the reaction in addition to KOTMS with the intention of protecting the phenol *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).

Table 19: Conditions Screened Towards the Formation of Grifolic Acid (92)

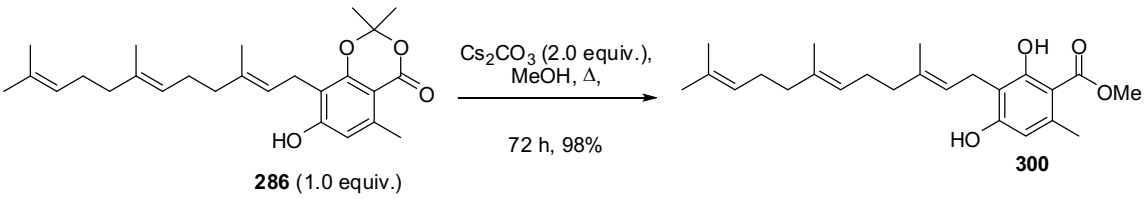


286 (**92**)

Entry	Conditions	Outcome
1	BCl_3 (1.0 to 10.0 equiv.), CH_2Cl_2, 0 °C to rt, 18 h[177]	RSM
2	KOH (1.0 to 10.0 equiv.), THF/H_2O (1:1), rt to Δ, 72 h[178]	Complex mixture
3	NaOH (1.0 to 10.0 equiv.), THF/H_2O (1:1), rt to Δ, 72 h	Complex mixture
4	LiOH (1.0 to 10.0 equiv.), THF/H_2O (1:1), rt to Δ, 72 h	Complex mixture
5	KOH (40%), DMSO, Δ, 18 h	Decomposition
6	KOTMS (1.0 to 10.0 equiv.), THF, rt to Δ, 18 h[181]	RSM
7	KOTMS (1.0 to 10.0 equiv.), TMSCl (1.0 to 10.0 equiv.), THF, rt to Δ, 18 h	RSM

*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.[169] Resorcylate **286** was heated with MeOH and Cs_2CO_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).

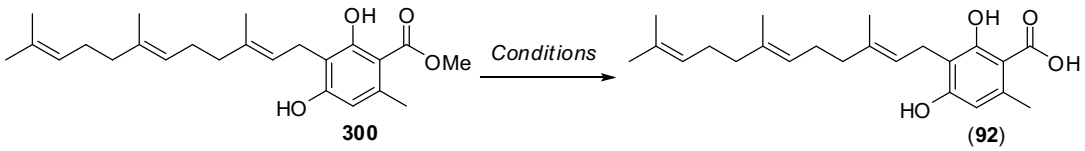


Scheme 129: Preparation of Methyl Ester 300

The first strategy for the conversion of the methyl ester **300** to the corresponding acid (**92**) was to utilise traditional saponification conditions,[182] hence methyl ester **300** was treated with LiOH in $MeOH/H_2O$ 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.* [181] hence methyl ester **300** was treated with KOTMS (Entry 4, Table 20). Unfortunately, the reaction yielded residual starting material, and, with *in situ* protection of the phenol moieties with TMSCl in the presence of KOTMS, (Entry 5, Table 20) having no effect.

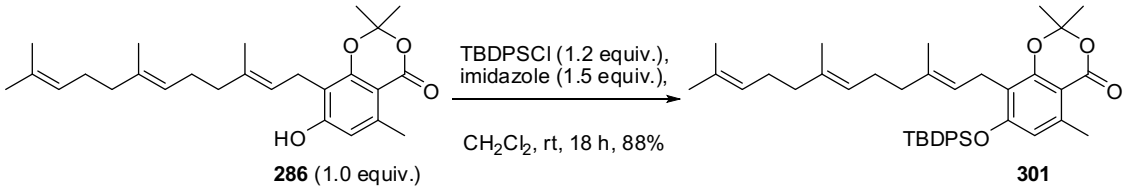
Table 20: Saponification Conditions



Entry	Conditions	Outcome
1	LiOH (1.0 to 10.0 equiv.), MeOH/H_2O (1:1), rt, 72 h	RSM
2	NaOH (1.0 to 10.0 equiv.), MeOH/H_2O (1:1), rt, 72 h	RSM
3	KOH (1.0 to 10.0 equiv.), MeOH/H_2O (1:1), rt, 18 h	RSM
4	KOTMS (1.0 to 10.0 equiv.), THF, rt to Δ, 18 h[181]	RSM
5	KOTMS (1.0 to 10.0 equiv.), TMSCl (1.0 to 10.0 equiv.) THF, rt to Δ, 18 h	RSM

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.[183] Accordingly, phenol **286** was treated with TBDPSCl and imidazole, providing silylether **301** in an 88% yield (Scheme 130).

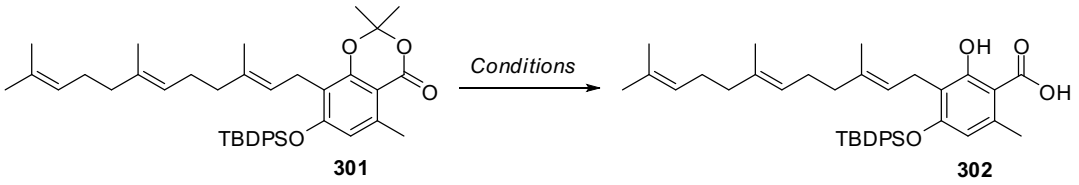


Scheme 130: Formation of Silylether 301

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

deprotection of the silylether (Entry 1, Table 21).[178] It was thus decided to utilise the Lewis acid conditions demonstrated by Fürstner *et al.,*[177] nevertheless treatment of resorcylate **301** with BCl_3 led to deprotection of the silylether (Entry 2, Table 21). Finally, KOTMS was tried (Entry 3, Table 21),[181] but led to deprotection. These results were interesting considering the inherent stability of the TBDPS group.[183][184]

Table 21: Saponification Conditions of Resorcylate Silylether 301

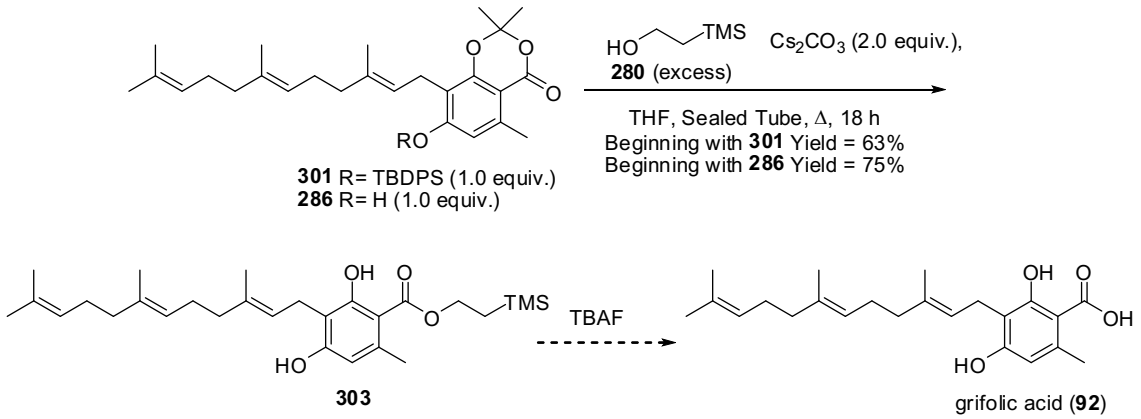


301 **302**

Entry	Conditions	Outcome
1	KOH (1.0 to 5.0 equiv.), THF/H_2O (1:1), rt, 6 h[182]	Resorcylate **286**
2	BCl_3 (1.0 to 10.0 equiv.), CH_2Cl_2, rt, 18 h[177]	Resorcylate **286**
3	KOTMS (1.0 to 5.0 equiv.), THF, rt, 18 h[181]	Resorcylate **286**

*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_2CO_3 it was decided to utilise these conditions using $TMSCH_2CH_2OH$ **280** in place of MeOH.[169] The intention of this was to create the protected carboxylic acid **303** and subsequently deprotect in order to furnish griflic acid (**92**). Hence, silylether resorcylate **301** was treated with $TMSCH_2CH_2OH$ **280** in the presence of Cs_2CO_3 and delightfully, resorcylate **303** was afforded in a 63% yield. However, deprotection of the silylether **302** also occurred, thus the reaction was repeated beginning with resorcylate **286**. Pleasingly, the reaction was successful and silylether **303** was isolated in a 75% yield (Scheme 131).



Scheme 131: Synthesis of Resorcylate 303

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 resoryclates had been established which with the subsequent deprotection could afford the corresponding acids.

5.5 Conclusions

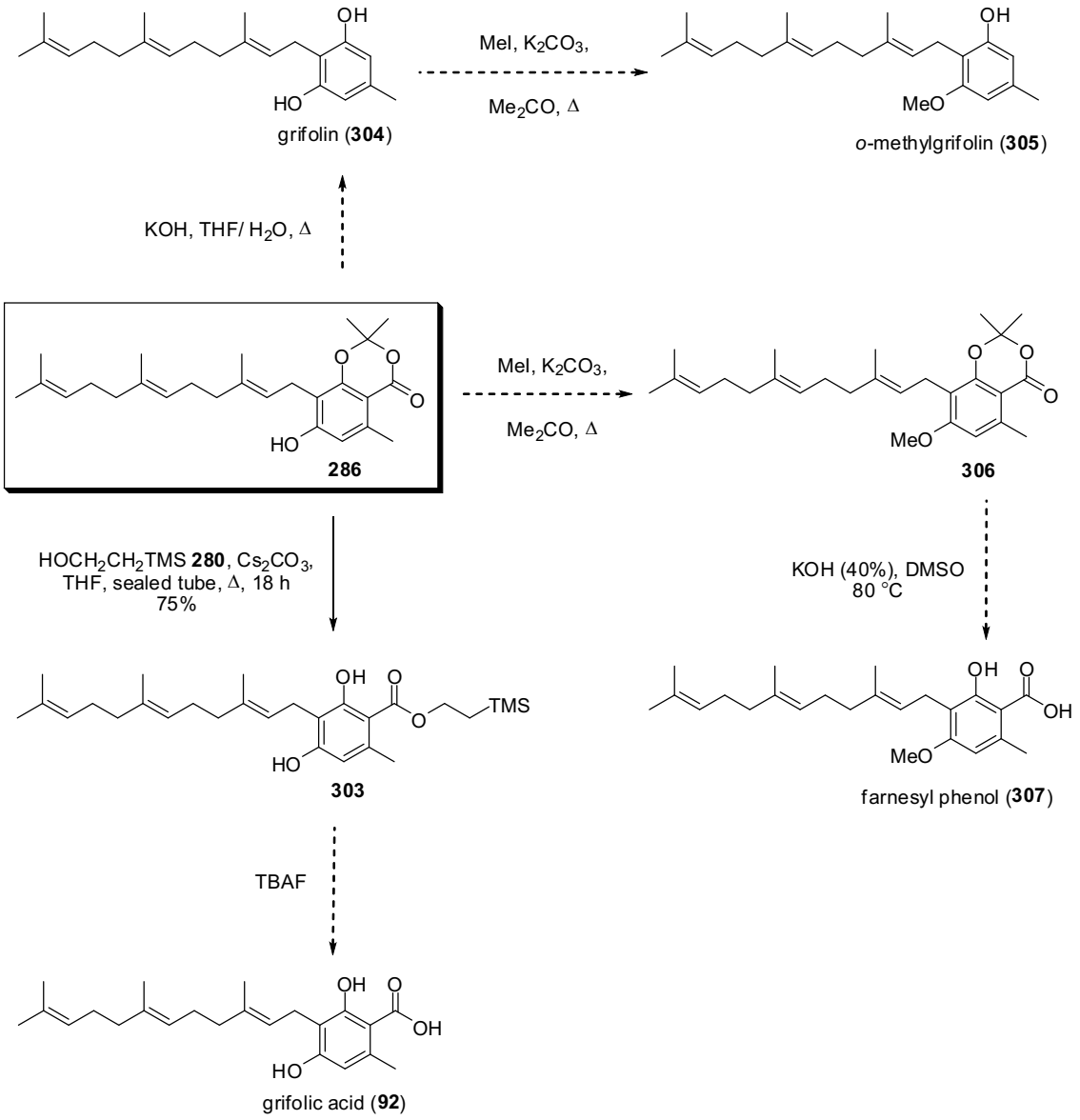
In conclusion, the synthesis of resorcylate **286** has been accomplished in four linear steps from dioxinone **33** in an overall yield of 32%. The synthesis has successfully exhibited both dioxinone methodology[42][43] and the Pd(0)-decarboxylative allylation and aromatisation sequence. The project 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 $TMSCH_2CH_2OH$ **280** in the presence of Cs_2CO_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]

5.6 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).[69] 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*.[69] They established that these structures were similar to those of farnesyl phenol (**307**) and grifolin (**304**) extracted from the roots of *Grifola confluens*,[6] neogriflin isolated from *Albatrellus confluens*,[6] and cristatic acid (**5**), isolated from the European *A. Cristatus* and the closely related American *Albatrellus* species.[6]

The work discussed in this chapter would enable the possiblity 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).

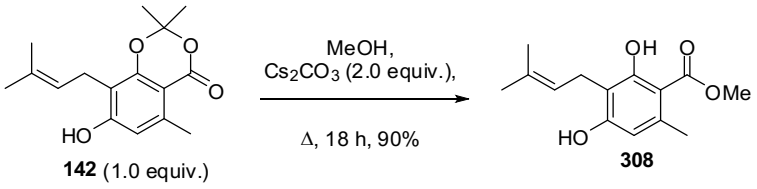


Scheme 132: Proposed Synthesis Towards the Griflin Family of Natural Products

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.

*5.6.2 The Synthesis of Isopentenylphenol (**308**)*

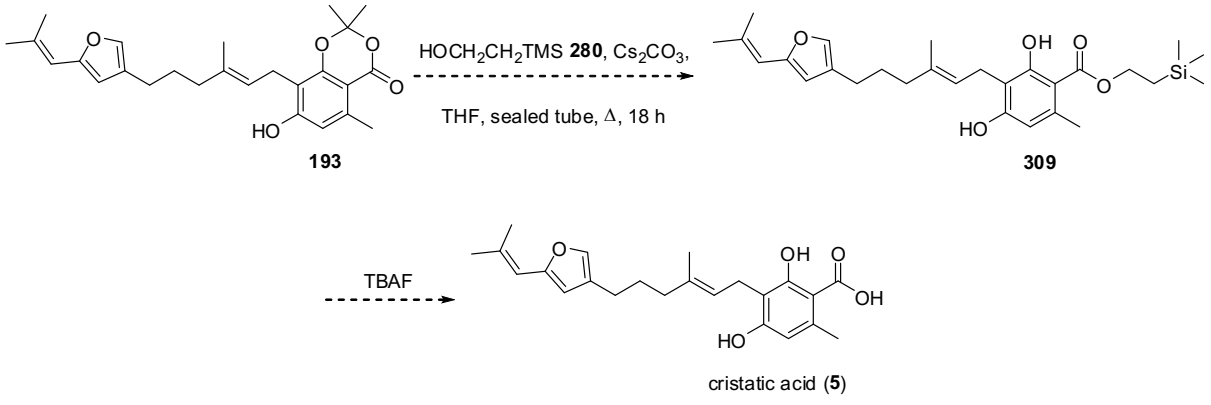
As stated above Nozoe *et al.* isolated isopentenylphenol (**308**) from the mushroom *Polyporus dispansus*.[69] It was envisaged that this natural product would be available from resorcylate **142**, a product obtained from the mechanistic studies (Section 3.5) into the Pd(0)-deacrboxylative allylation and aromatisation sequence. Hence, resorcylate **142** was treated with MeOH in the presence of Cs_2CO_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)

*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)

6 Experimental

6.1 General Experimental Procedures

All reactions were carried out in flame-dried or oven-dried glassware in an atmosphere of dry N_2 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 N_2: Et_2O and THF from Na/Ph_2CO ketyl; PhMe from Na; CH_2Cl_2, MeOH, pyridine and Et_3N from CaH_2. H_2O refers to distilled H_2O. 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

on the diamond at 120 Nm. Indicative features of each spectrum are given with adsorptions (ν_{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 (δ) quoted in parts per million (ppm) and referenced to a residual solvent peak. $CDCl_3$ (δ_H 7.26, δ_C 77.16), d_6-CD_3OD (δ_H 3.31, δ_C 49.05), d_6-C_6D_6 (δ_H 7.16, δ_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.

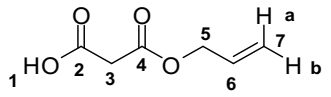
Microanalysis was determined by the London Metropolitan University Analytical Service.

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.

6.2 Procedures and Compound Characterisation

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



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 $NaHCO_3$ (200 mL) and the resulting solution stirred for 8 h at rt. The reaction mixture was extracted with Et_2O : 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 ($MgSO_4$) and rotary evaporated to afford carboxylic acid **100**[82] as a colourless oil (20.0 g, 70%):

$\mathbf{R}_f$ 0.43 (1 : 1 hexanes : EtOAc);

IR (neat) ν_{max} 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};

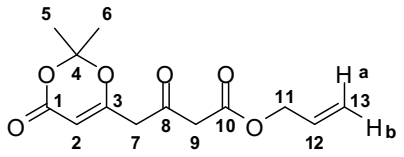
HRMS (CI) calc. for $C_6H_{12}O_4N$ $[M+NH_4]^+$: requires 162.0766, found 162.0759 (Δ –4.3 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) 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**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (**2**), 166.7 (**4**), 131.2 (**6**), 119.2 (**7**), 65.9 (**5**), 40.6 (**3**);

Anal. Calc. for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.97; H, 5.44.

Allyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (102)



102

Based on a procedure by Navarro *et al.*[82] Carboxylic acid **100** (900 mg, 6.25 mmol, 0.8 equiv.) was stirred in CH_2Cl_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_4Cl (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_2O) to afford keto-allylester-dioxinone **102**[82] (1.06 g, 65%) as a yellow oil:

R_f 0.30 (1 : 2 hexanes : Et_2O);

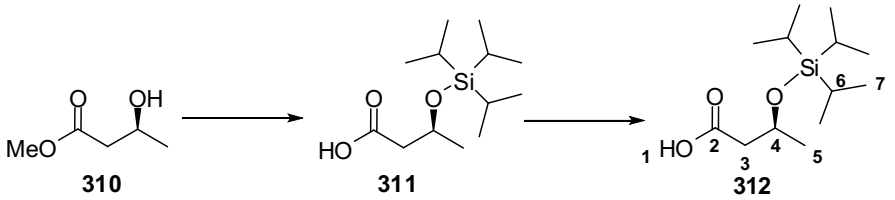
IR (neat) ν_{max} 2999 (w, **C-H**), 2947 (w, **C-H**), 1721 (s, **C=O**), 1637 (m, **C=C**), 1376 (m), 1273 (m), 1254 (sh.), 1202 (sh.), 1016 (w), 1091 (w), 1062 (w) cm^{-1};

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2Cl_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_2O (2 x 200 mL), the organics combined, washed with H_2O (2 x 200 mL), dried ($MgSO_4$) and rotary evaporated to afford silylether **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_2Cl_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:

R_f 0.52 (1 : 9 MeOH : CH_2Cl_2);

$[\alpha]_D^{25} = -0.5$ (*c* 0.2, $CHCl_3$);

IR (neat) ν_{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};

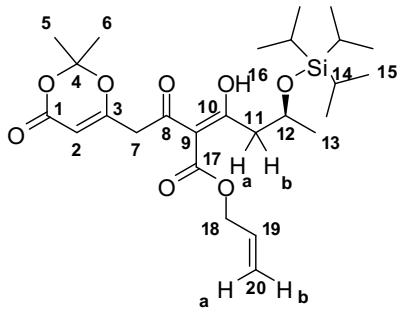
HRMS (ESI) calc. for $C_{13}H_{27}O_3Si$ $[M+H]^+$: requires 259.1729, found 259.1743 (Δ +5.4 ppm);

^{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 $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 60.02; H, 10.77.

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



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_2Cl_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_2Cl_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

CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Acid chloride **103** in CH_2Cl_2 (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 ($MgSO_4$), rotary evaporated and chromatographed (1 : 4 EtOAc : hexanes) to afford diketo-allylester-dioxinone **104**[82] (942 mg, 70%) as a pale yellow oil:

R_f 0.66 (2 : 1 Et_2O : hexanes);

$[\alpha]_D^{25} = +17.48$ (*c* 1.2, $CHCl_3$);

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};

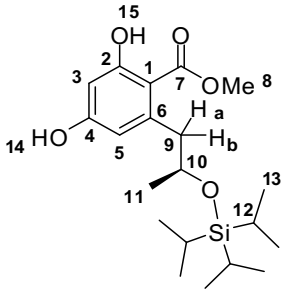
HRMS (ESI) calc. for $C_{26}H_{43}O_8Si$ $[M+H]^+$: requires 511.2727, found 511.2720 (Δ –1.4 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) 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**);

^{13}C NMR (125 MHz, $CDCl_3$) 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**);

Anal. Calc. for $C_{26}H_{42}O_8Si$: C, 61.15; H, 8.29. Found: C, 61.01; H, 8.22.

(*S*)-Methyl 2,4-dihydroxy-6-(2-(tri-isopropylsilyloxy)propyl)benzoate (105)



105

Morpholine (0.10 mL, 0.96 mmol, 3.3 equiv.) was added with stirring to diketo-allylester-dioxinone **104** (150 mg, 0.29 mmol, 1.0 equiv.) in THF (1.5 mL) at 0 °C, followed immediately by the addition of $Pd(PPh_3)_4$ (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 NH_4Cl (5 mL), followed by H_2O (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 ($MgSO_4$) 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), Cs_2CO_3 (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 $NaHCO_3$ (10 mL), extracted with Et_2O (3 x 20 mL), the organics combined, washed with brine (15 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 2 Et_2O : hexanes) to give resorcylate **105** (43.0 mg, 39% over 4 steps) as a colourless solid:

m.p. 50-52 °C (hexanes);

R_f 0.38 (1 : 3 Et_2O : hexanes);

$[\alpha]_D^{25}$ = +35.5 (*c* 0.3, $CHCl_3$);

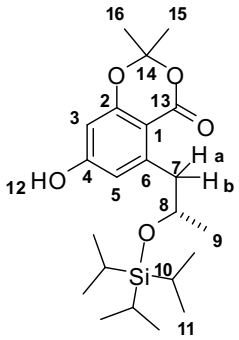
IR (neat) ν_{max} 3365 (br., **O-H**), 2926 (m, **C-H**), 2865 (m, **C-H**), 1652 (m, **C=C**), 1625 (sh., **C=C**), 1586 (m, **C=C**), 1462 (m), 1386 (sh.), 1318 (m), 1263 (sh.), 1194 (sh.), 1173 (w), 1134 (sh.), 1108 (m), 1082 (w), 1025 (w) cm^{-1};

HRMS (ESI) calc. for $C_{20}H_{35}O_5Si$ $[M+H]^+$: requires 383.2254, found 383.2236 (Δ –4.70 ppm);

^{1}H 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**);

^{13}C 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)-4*H*-benzo[*d*][1,3]dioxin-4-one (107)



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 NH_4Cl (10 mL), extracted with Et_2O (2 x 10 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 Et_2O : hexanes) to afford isopropylidene protected resorcylate **107** as a white solid (20 mg, 80%):

m.p. = 98-100 °C (pentane);

$\mathbf{R_f}$ 0.5 (1 : 1 EtOAc : hexanes);

$[\alpha]_D^{25}$ = +4.4 (*c* 1.0, $CHCl_3$);

IR (neat) ν_{max} 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};

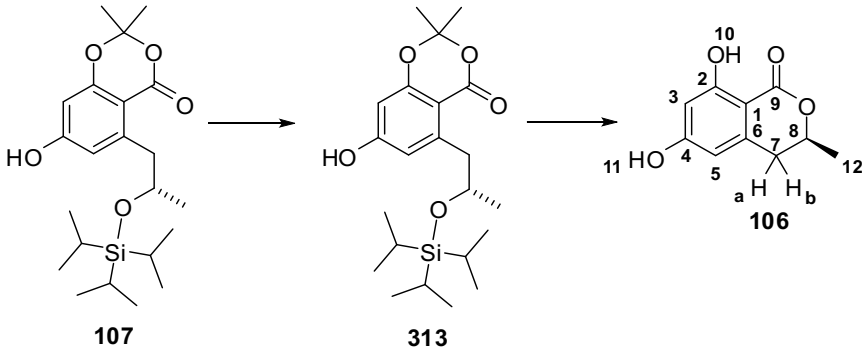
HRMS (ESI) calc. for $C_{22}H_{37}O_5Si$ $[M+H]^+$: requires 409.2410, found 409.2403 (Δ –1.7 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) 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**);

^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{22}H_{36}O_5Si$: C, 64.67; H, 8.88. Found: C, 64.58; H, 9.03.

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



H_2SiF_6 in H_2O (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_2O (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_2O (~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_2O (3 x 25 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 1 Et_2O : hexanes) to give lactone **106**[190] (21 mg, 80% over 2 steps) as a white solid:

m.p. = 138-140 °C (benzene);

$\mathbf{R}_f$ 0.32 (1 : 1 Et_2O : hexanes);

$[\alpha]_D^{25}$ = +3.31 (*c* 0.016, $CHCl_3$);

IR (neat) ν_{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};

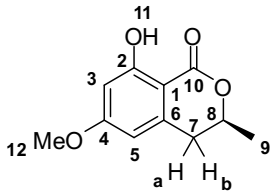
HRMS (ESI) calc. for $C_{10}H_{11}O_4$ $[M+H]^+$: requires 195.0657, found 195.0663 (Δ +3.1 ppm);

^{1}H NMR (500 MHz, CD_3OD) δ 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_3OD) δ 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**);

Anal. Calc. for $C_{10}H_{10}O_4$: C 61.85; H 5.19. Found: C, 61.90; H 5.21.

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



(**7**)

Lactone **106** (18 mg, 90 μmol, 1.0 equiv.) was stirred in Me_2CO (3.72 mL) for 2 min. MeI (9 μL, 0.15 mmol, 1.6 equiv.) and K_2CO_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_2O : hexanes) to afford Angelicoin B (**7**)[9] (15 mg, 79%) as a white solid:

m.p. 58-60 °C (pentane);

R_f 0.25 (1 : 3 Et_2O : hexanes);

$[\alpha]_D^{25}$ = +30.6 (*c* 0.5, MeOH), lit. $[\alpha]_D^{25}$ = +31.5 (*c* 0.5, MeOH);

IR (neat) ν_{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};

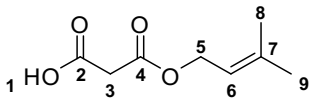
HRMS (ESI) calc. for $C_{11}H_{13}O_4$ $[M+H]^+$: requires 209.0814, found 209.0811 (Δ +1.4 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-buten-1-yl) malonate 114



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_2Cl_2);

IR (neat) ν_{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};

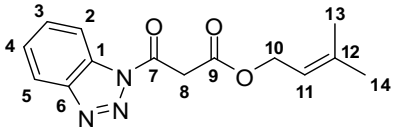
HRMS (CI) calc. for $C_8H_{16}NO_4$ $[M+H]^+$: requires 190.1079, found 190.1077 (Δ –1.1 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) δ 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**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_8H_{12}O_4$: C, 55.81; H 7.02. Found: C, 55.87; H, 7.18.

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



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_2Cl_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_2Cl_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_2Cl_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_2Cl_2 : EtOAc : hexanes);

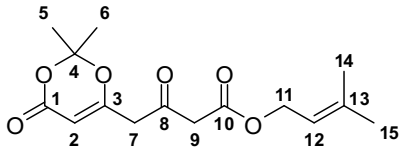
IR (neat) ν_{max} 2962 (w, **C-H**), 1726 (s, **C=O**), 1380 (s), 1267 (m), 1209 (m), 1146 (w) cm^{-1};

HRMS (CI) calc. for $C_{14}H_{16}N_3O_3$ $[M+H]^+$: required 274.1192, found 274.1197 (Δ +1.8 ppm);

^{1}H NMR (400 MHz, C_6D_6) δ 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_3OD) δ 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-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (113)



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_4Cl (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_2O) to afford keto-prenylester-dioxinone **113** (1.58 g, 93%) as a yellow oil:

R_f 0.31 (2 : 1 Et_2O : hexanes);

IR (neat) ν_{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};

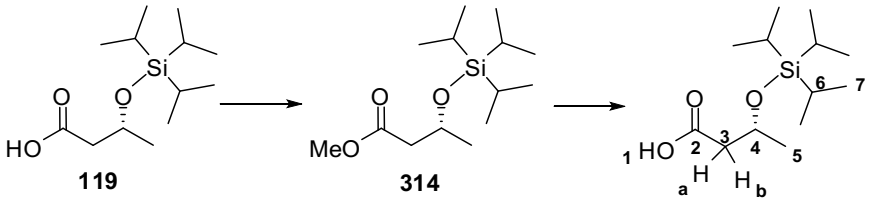
HRMS (ESI) calc. for $C_{15}H_{21}O_6$ $[M+H]^+$: required 297.1338, found 297.1329 (Δ –3.0 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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**);

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.89; H, 6.81.

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



Based on a procedure by Tschaen *et al.*[74] Alcohol **119** (5.0 g, 42 mmol, 1.0 equiv.) was stirred in CH_2Cl_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_2O (2 x 200 mL). The organics were combined, washed with H_2O (2 x 200mL), dried ($MgSO_4$) and rotary evaporated to afford silylether **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_2Cl_2 (3 x 200 mL). The organics were combined, washed with brine (2 x 250 mL), dried ($MgSO_4$) and rotary evaporated to afford carboxylic acid **118** (7.22 g, 90% over 2 steps) as a pale yellow oil:

R$_f$ 0.52 (1 : 9 MeOH : CH_2Cl_2);

$[\alpha]_D^{25} = +3.3$ (*c* 0.875, $CHCl_3$);

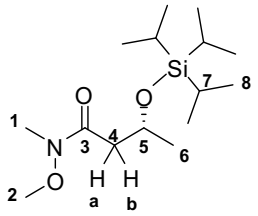
IR (neat) ν_{max} 2940 (m, **C-H**), 2867 (m, **C-H**), 1710 (sh., **C=O**), 1463 (w), 1129 (m), 1096 (w), 1004 (m) cm^{-1};

HRMS (ESI) calc. for $C_{13}H_{28}O_3Si$ $[M+H]^+$: requires 261.1886, found 261.1874 (Δ –4.6 ppm);

^{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)



120

Carboxylic acid **118** (1.00 g, 3.25 mmol, 1.0 equiv.) was stirred in CH_2Cl_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_2Cl_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_2O and CH_2Cl_2 (1 : 1), dried ($MgSO_4$) and rotary evaporated to afford Weinreb amide **120** (900 mg, 82%) as a pale yellow oil:

$\mathbf{R}_f$ 0.5 (EtOAc);

$[\alpha]_D^{25} = -11.23$ (*c* 3.08, $CHCl_3$);

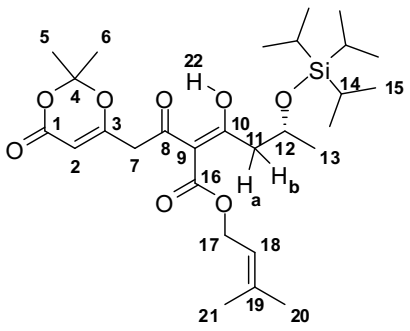
IR (neat) ν_{max} 2944 (s, **C-H**), 2867 (s, **C-H**), 1667 (m, **C=O**), 1463 (m), 1179 (m), 1122 (sh.), 1092 (w) cm^{-1};

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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**).

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



111

Based on a procedure by Navarro *et al*.[82] Oxalyl chloride (1.50 mL, 16.9 mmol, 2.0 equiv.) and DMF (30 µL, 0.44 mmol, 0.1 equiv.) were added to carboxylic acid **118** (2.20 g, 8.40 mmol, 1.0 equiv.) in CH_2Cl_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_2Cl_2 (1 mL) was added dropwise to a mixture of $MgCl_2$ (64 mg, 0.67 mmol, 2.0 equiv.) and pyridine (80 µL, 0.92 mmol, 2.7 equiv.) in CH_2Cl_2 (2 mL) at 0 °C. The resulting solution was stirred for 30

min and then acid chloride **117** in CH_2Cl_2 (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 ($MgSO_4$), rotary evaporated and chromatographed (1 : 4 Et_2O : hexanes) to afford diketo-prenylester-dioxinone **111** (148 mg, 81%) as a yellow oil:

R_f 0.74 (2 : 1 Et_2O : hexanes);

$[\alpha]_D^{25} = -6.7$ (*c* 0.82, $CHCl_3$);

IR (neat) ν_{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};

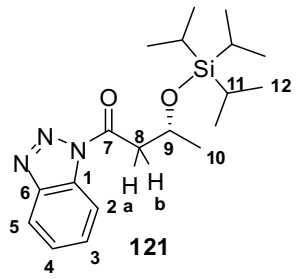
HRMS (ESI) calc. for $C_{28}H_{47}O_8Si$ $[M+H]^+$: requires 539.3032, found 539.3040 (Δ –1.5 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) 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**);

^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{28}H_{46}O_8Si$: C, 62.42; H, 8.61. Found: C, 62.36; H, 8.64.

(*R*)-1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-(triisopropylsilyloxy)butan-1-one (121)



121

Based on a procedure by Navarro *et al.*[82] Benzotriazole (720 mg, 6.05 mmol, 3.2 equiv.) was stirred in CH_2Cl_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_2Cl_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, $CHCl_3$);

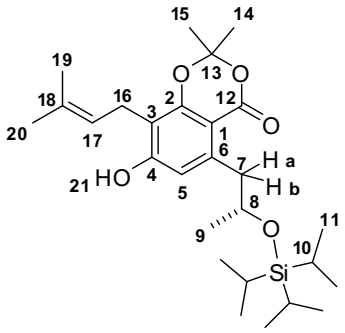
IR (neat) ν_{max} 2943 (m, **C-H**), 2867 (m, **C-H**), 1736 (sh., **C=O**), 1450 (w), 1375 (sh.), 1128 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{19}H_{31}N_3O_2Si$ $[M+NH]^+$: requires 361.2264, found 362.2257 (Δ –1.9 ppm);

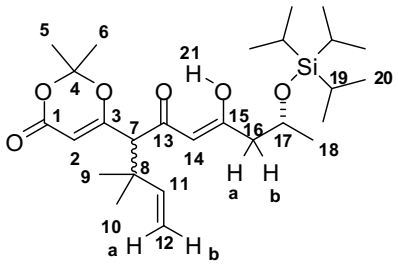
^{1}H NMR (400 MHz, C_6D_6) δ 8.41 (d, *J* = 8.0 Hz, 1H, **2** / **5**), 7.92 (d, *J* = 8.0 Hz, 1H, **2** / **5**), 7.21-7.14 (m, 1H, **3** / **4**), 7.04-7.01 (m, 1H, **3** / **4**), 4.82-4.76 (m, 1H, **9**), 3.67 (dd, *J* = 8.0, 5.0 Hz, 1H, **8b**), 3.24 (dd, *J* = 8.0, 2.5 Hz, 1H, **8a**), 1.31 (d, *J* = 3.0 Hz, 3H, **10**), 1.15 (br. s, 3H, **11**), 1.13 (br. s, 18H, **12**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 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**)

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



124



123

$Pd(PPh_3)_4$ (38 mg, 33 μmol, 10 mol%) and Cs_2CO_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_2Cl_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_2Cl_2 : EtOAc : hexanes);

$[\alpha]_D^{25} = -31.33$ (*c* 1.0, $CHCl_3$);

IR (neat) ν_{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 $C_{27}H_{45}O_5Si$ $[M+H]^+$: requires 477.3028, found 477.3036 (Δ –1.7 ppm);

^{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 $C_{27}H_{44}O_5Si$: 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_2Cl_2 : EtOAc : hexanes);

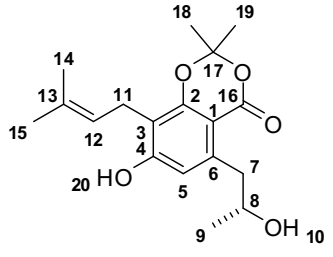
IR (neat) ν_{max} 2943 (m, **C-H**), 2867 (m, **C-H**), 1731 (sh., **C=O**), 1612 (m, **C=C**), 1463 (w), 1376 (m), 1250 (w), 1068 (w) cm^{-1};

HRMS (ESI) calc. for $C_{27}H_{47}O_6Si$ $[M+H]^+$: requires 495.3146, found 495.3155 (Δ –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**).

(*R*)-7-Hydroxy-5-(2-hydroxypropyl)-2,2-dimethyl-8-(3-methylbut-2-enyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (128)



128

Bu_4NF in THF (1 M; 2.18 mL, 2.18 mmol, 8.0 equiv.) was added to silylether **124** (130 mg, 0.27 mmol, 1.0 equiv.) in THF (4 mL) and stirred for 48 h. The reaction was quenched with H_2O (20 mL), extracted with EtOAc (2 x 30 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 6 hexanes : EtOAc) to give alcohol **128** (87 mg, 97%) as a colourless gum:

$\mathbf{R}_f$ 0.64 (EtOAc);

$[\alpha]_D^{25} = -23.7$ (*c* 1.5, $CHCl_3$);

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};

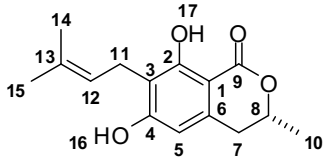
HRMS (ESI) calc. for $C_{18}H_{25}O_5$ $[M+H]^+$: requires 321.1711, found 321.1702 (Δ +2.8 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) 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**);

^{13}C NMR (125 MHz, $CDCl_3$) 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**).

Angelicoin A: ((*R*)-6,8-Dihydroxy-3-methyl-7-(3-methylbut-2-enyl)isochroman-1-one)

(6)



(**6**)

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 ($MgSO_4$), rotary evaporated and chromatographed (1 : 2 hexanes : EtOAc) to afford angelicoin A **6**[9] (37 mg, 90%) as a white solid:

m.p. 118-120 °C (pentane);

R_f 0.38 (1 : 2 EtOAc : hexanes);

$[\alpha]_D^{25} = -32.3$ (*c* 0.37, MeOH), lit. $[\alpha]_D^{25} = -37.1$ (*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};

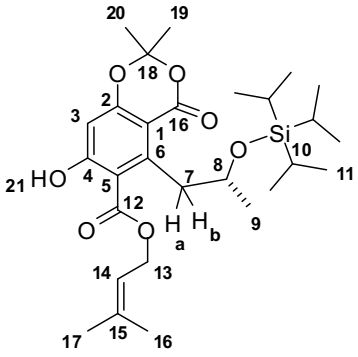
HRMS (ESI) calc. for $C_{15}H_{17}O_4$ $[M+H]^+$: requires 261.1127, found 261.1133 (Δ +2.3 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) 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**);

^{13}C NMR (105 MHz, $CDCl_6$) 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**);

Anal. Calc. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.63; H, 6.83.

(*R*)-3-Methylbut-2-enyl 7-hydroxy-2,2-dimethyl-4-oxo-5-(2-(tri-isopropylsilyloxy)propyl)-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (129)



129

Et_3N (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 CH_2Cl_2 (50 mL) and stirred for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (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 ($MgSO_4$), rotary evaporated and chromatographed (10 : 1 : 1 hexanes : EtOAc : CH_2Cl_2) to afford isopropylidene-protected resorcylate **129** (110 mg, 40%) as a clear oil:

R_f 0.62 (1 : 1 : 6 EtOAc : CH_2Cl_2 : hexanes);

$[\alpha]_D^{25}$ = +17.21 (*c* 0.83, $CHCl_3$);

IR (neat) ν_{max} 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};

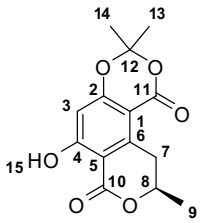
HRMS (ESI) calc. for $C_{28}H_{45}O_7Si$ $[M+H]^+$: requires 521.2935, found 521.2938 (Δ +0.6 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) 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

(br. 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 (br. s, 3H, **9**), 0.92 (br. s, 18H, **11**), 0.91 (br. 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)



130

Bu_4NF in THF (1 M; 0.80 mL, 0.40 mmol, 4.4 equiv.) was added to silylether-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);

$[\alpha]_D^{25} = -13.24$ (*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};

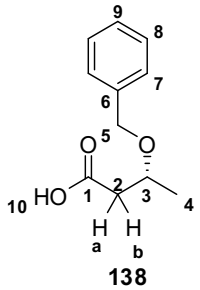
HRMS (EI) calc. for $C_{14}H_{16}O_6$ $[M+H]^+$: requires 279.0869, found 279.0865 (Δ –1.4 ppm);

^{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)



138

Alcohol **136** (2.0 g, 17.0 mmol, 1.0 equiv.) was stirred in cyclohexane (113 mL) and CH_2Cl_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_2Cl_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_2Cl_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_2Cl_2);

$[\alpha]_D^{25} = -0.83$ (*c* 0.113, $CHCl_3$);

IR (neat) ν_{max} 3029 (br., **O-H**), 2975 (w, **C-H**), 2930 (w, **C-H**), 1706 (sh., **C=O**), 1454 (w), 1377 (w), 1305 (w), 1204 (m), 1134 (w), 1075 (m) cm^{-1};

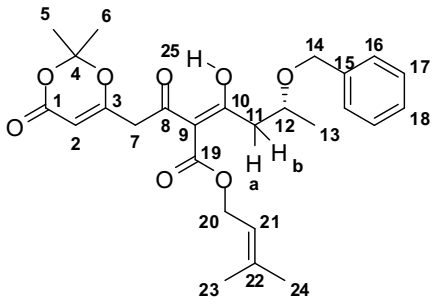
HRMS (CI) calc. for $C_{11}H_{18}NO$ $[M+NH]^+$: requires 212.1287, found 212.1297 (Δ +4.7 ppm);

^{1}H NMR (500 MHz, C_6D_6) δ 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 Hz, 2H, **5**), 3.80-3.74 (m, 1H, **3**), 2.44 (dd, *J* = 15.0, 7.0 Hz, 1H, **2b**), 2.13 (dd, *J* = 15.0, 5.0 Hz, 1H, **2a**), 0.96 (d, *J* = 6.0 Hz, 3H, **4**);

^{13}C NMR (125 MHz, C_6D_6) δ 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**);

Anal. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.13; H, 7.14.

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



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_2Cl_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_2Cl_2 (10 mL) for 30 min. Acid chloride **139** in CH_2Cl_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_2Cl_2 : EtOAc : hexanes) affording diketo-prenylester-dioxinone **132** (500 mg, 65%) as a pale yellow oil:

R_f 0.60 (1 : 1 : 6 CH_2Cl_2 : EtOAc : hexanes);

$[\alpha]_D^{25} = -40.95$ (*c* 0.61, $CHCl_3$);

IR (neat) ν_{max} 2975 (w, **C-H**), 2937 (w, **C-H**), 1728 (s, **C=O**), 1638 (m, **C=C**), 1564 (w, **C-C**), 1374 (s), 1271 (m), 1250 (m), 1202 (w), 1126 (w), 1065 (m), 1015 (w) cm^{-1};

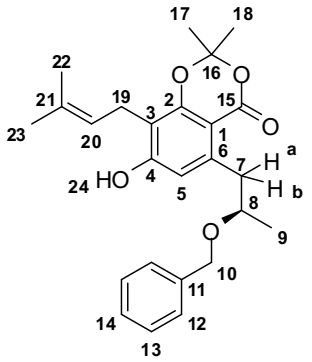
HRMS (ESI) calc. for $C_{26}H_{32}O_8Na$ $[M+Na]^+$: requires 495.1995, found 495.1993 (Δ –0.4 ppm);

^{1}H NMR (500 MHz, C_6D_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_6D_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.

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



133

$Pd(PPh_3)_4$ (91 mg, 79 μmol, 0.1 equiv.) and Cs_2CO_3 (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 NH_4Cl (50 mL), extracted with EtOAc (2 x 50 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 : 4 CH_2Cl_2 : 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);

$\mathbf{R}_f$ 0.6 (1 : 1 : 6 CH_2Cl_2 : EtOAc : hexanes);

$[\alpha]_D^{25} = -31.5$ (*c* 0.21, $CHCl_3$);

IR (neat) ν_{max} 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};

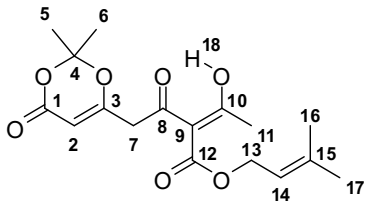
HRMS (ESI) calc. for $C_{25}H_{31}O_5$ $[M+H]^+$: requires 411.2157, found 411.2171 (Δ –1.5 ppm);

^{1}H NMR (500 MHz, C_6D_6) 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

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

^{13}C NMR (125 MHz, C_6D_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)



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_2Cl_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_2O : hexanes to Et_2O) to afford diketo-prenylester-dioxinone **140** (301 mg, 86%) as a yellow oil:

R_f 0.50 (2 : 1 Et_2O : hexanes);

IR (neat) ν_{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};

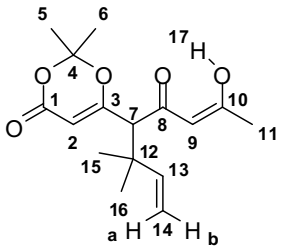
HRMS (ESI) calc. for $C_9H_{12}O_4$ $[M+H]^+$: requires 339.1444, found 339.1440 (Δ –1.2 ppm);

^{1}H NMR (500 MHz, C_6D_6) δ 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**);

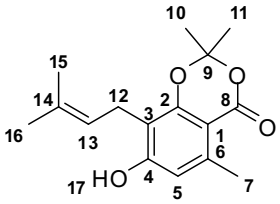
^{13}C NMR (125 MHz, C_6D_6) δ 195.9 (**8**), 194.2 (**10**), 165.9 (**1**), 164.4 (**12**), 159.6 (**15**), 139.6 (**3**), 118.7 (**14**), 108.8 (**4**), 106.7 (**9**), 97.3 (**2**), 61.6 (**13**), 43.1 (**7**), 25.6 (**17**), 25.1 (**11**), 24.68 (**2C, 5** & **6**), 17.77 (**16**);

Anal. Calc. for $C_{17}H_{22}O_7$: C, 6.035; H, 6.55. Found: C, 60.43; H, 6.50.

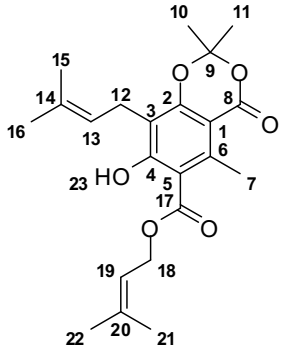
5-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-6,6-dimethyloct-7-ene-2,4-dione (141), 7-Hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-enyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (142), 3-Methylbut-2-enyl 7-hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-enyl)-4-oxo-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (159) and 7-Hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one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



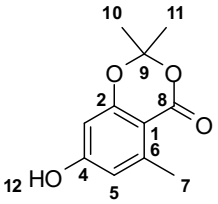
141



142



159



155

$Pd(PPh_3)_4$ (164 mg, 142 μmol, 0.1 equiv.) and Cs_2CO_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 NH_4Cl (10 mL), extracted with EtOAc (2 x 50 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 : 10 to 1 : 1 : 5 CH_2Cl_2 : 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-resorcylate **142** (195 mg, 50% at 0.2 M, 12 mg, 3% at 0.014 M) as a white solid, prenylester-prenyl-resorcylate **159** (11 mg, 2% at 0.2 M, 231 mg, 42% at 0.014 M) as a clear oil and resorcylate **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 : CH_2Cl_2 : hexanes);

IR (neat) ν_{max} 2979 (w, **C-H**), 2961 (w, **C-H**), 1740 (s, **C=O**), 1395 (w), 1365 (m), 1217 (sh.), 1222 (m), 1019 (w) cm^{-1};

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

^{1}H NMR (500 MHz, C_6D_6) δ 16.0 (br. s, 1H, **17**), 5.91 (dd, *J* = 17.0, 11.0 Hz, 1H, **13**), 5.52 (s, 1H, **2**), 5.04 (s, 1H, **9**), 4.88 (dd, *J* = 11.0, 2.0 Hz, 1H, **14a**), 4.85 (dd, *J* = 17.0, 2.0 Hz, 1H, **14b**), 2.60 (s, 1H, **7**), 1.50 (s, 3H, **11**), 1.27 (s, 6H, **15** & **16**), 1.04 (s, 6H, **5** & **6**);

^{13}C NMR (125 MHz, C_6D_6) δ 192.1 (**8**), 188.7 (**10**), 166.3 (**1**), 159.8 (**3**), 145.1 (**13**), 122.4 (**14**), 106.4 (**4**), 101.7 (**9**), 97.6 (**2**), 62.5 (**7**), 40.4 (**12**), 25.7 (2C, **15** & **16**), 25.3 (2C, **5** & **6**), 23.4 (**11**).

*Prenyl- resorcylate **142**:*

m.p. 121-124 °C (pentane);

R_f 0.55 (1 : 1 : 6 EtOAc : CH_2Cl_2 : hexanes);

IR (neat) ν_{max} 3213 (br., **O-H**), 2998 (w, **C-H**), 1689 (sh., **C=C**), 1605 (sh., **C=C**), 1518 (w, **C-C**), 1378 (w), 1324 (m), 1296 (sh.), 1279 (sh.), 1240 (w), 1167 (m), 1048 (w) cm^{-1};

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

^{1}H NMR (500 MHz, C_6D_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_6D_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**), 25.5 (2C, **10** & **11**), 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_2Cl_2 : hexanes);

IR (neat) ν_{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_6D_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_6D_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_2O : hexanes);

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

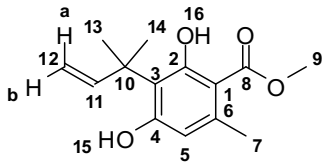
HRMS (ESI) calc. for $C_{11}H_{13}O_4$ $[M+H]^+$: requires 209.0814, found 209.0809 (Δ –2.4 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



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_2O : pentane) to afford allyl-resorcylate **144** (12 mg, 80%) as a colourless gum:

R_f 0.85 (1 : 3 : 4 CH_2Cl_2 : EtOAc : hexanes);

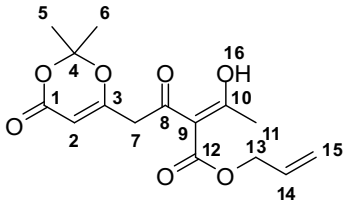
IR (neat) ν_{max} 2926 (m, **C-H**), 1739 (s, **C=O**), 1654 (w, **C=C**), 1439 (w), 1366 (m), 1217 (m), 1230 (m) cm^{-1};

HRMS (ESI) calc. for $C_{14}H_{119}O_4$ $[M+H]^+$: requires 251.1283, found 251.1278 (Δ –2.0 ppm);

^{1}H NMR (500 MHz, C_6D_6) δ 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_6D_6) δ 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**).

Allyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate 153



153

Based on a procedure by Navarro *et al.*[82] Keto-allylester-dioxinone **102** (700 mg, 2.60 mmol, 1.0 equiv.) was added to $MgCl_2$ (300 mg, 3.12 mmol, 2.0 equiv.) and pyridine (500 mg, 0.50 mL, 6.76 mmol, 2.7 equiv.) in CH_2Cl_2 (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 ($MgSO_4$), rotary evaporated and chromatographed (2 : 8 Et_2O : hexanes to Et_2O) to afford diketo-allylester-dioxinone **153** (665 mg, 83%) as a yellow oil (665 mg, 83%):

R_f 0.36 (2 : 1 Et_2O : hexanes);

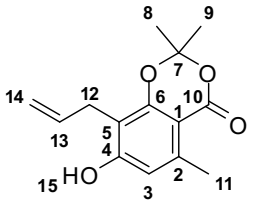
IR (neat) ν_{max} 2990 (w, **C-H**), 2870 (w, **C-H**), 1724 (s, **C=O**), 1637 (m, **C=C**), 1564 (m, **C-C**), 1270 (sh.), 1074 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{15}H_{19}O_7$ $[M+H]^+$: requires 311.1131, found 311.1123 (Δ –2.6 ppm);

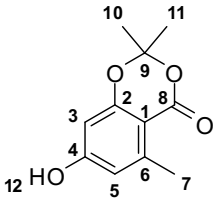
^{1}H NMR (400 MHz, $CDCl_3$) δ 17.81 (s, 1H, **16**), 6.03–5.92 (m, 1H, **14**), 5.41–5.30 (m, 3H, **2** & **15**), 4.71 (d, J = 6.0 Hz, 2H, **13**), 3.74 (s, 2H, **7**), 2.43 (s, 3H, **11**), 1.70 (s, 6H, **5** & **6**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 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**).

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



154



155

$Pd(PPh_3)_4$ (37 mg, 32 μmol, 0.1 equiv.) and Cs_2CO_3 (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 $NaHCO_3$ (10 mL), extracted with Et_2O (2 x 50 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 20 to 1 : 5 Et_2O : 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:

R_f 0.2 (1 : 3 Et_2O : hexanes);

*Allyl-resorcylate **154**:*

IR (neat) ν_{max} 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};

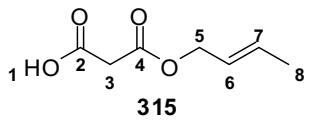
HRMS (ESI) calc. for $C_{14}H_{17}O_4$ $[M+H]^+$: requires 249.1127, found 249.1120 (Δ –2.8 ppm);

^{1}H NMR (500 MHz, C_6D_6) 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**);

^{13}C NMR (125 MHz, C_6D_6) 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.

(*E*)-3-(But-2-enyloxy)-3-oxopropanoic acid (315)



315

Based on a procedure by Tararov *et al.*[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 $NaHCO_3$ (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 **315**[191] (19.5 g, 89%) as a pale yellow oil:

$\mathbf{R_f}$ 0.42 (1 : 9 MeOH : CH_2Cl_2);

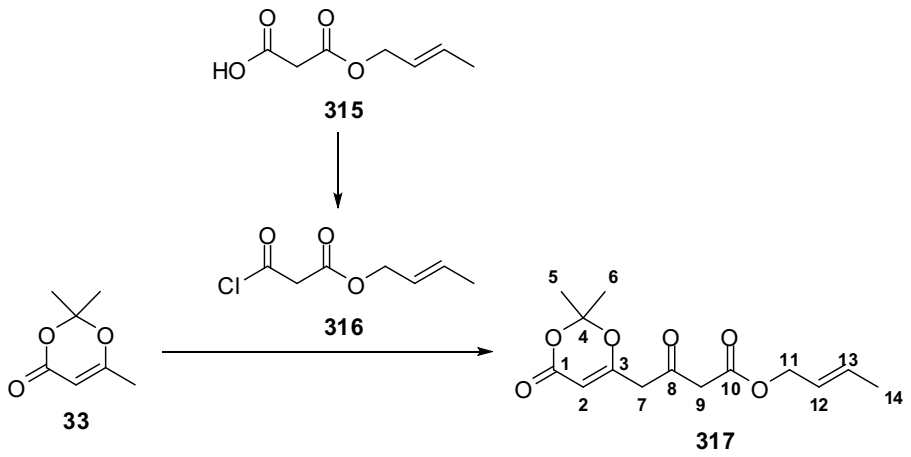
IR (neat) ν_{max} 3501 (br., **O-H**), 2948 (w, **C-H**), 1731 (sh. **C=O**), 1378 (m), 1146 (sh.), 965 (sh.) cm^{-1};

MS (CI) $[M+NH_4]^+$: requires 176, found 176;

^{1}H NMR (400 MHz, $CDCl_3$) δ 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**);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 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-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (317)



Based on a procedure by Navarro *et al.*[82] Crotylester-carboxylic acid **315** (4.0 g, 25.3 mmol, 1.0 equiv.) was stirred in CH_2Cl_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.

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_4Cl (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 ($MgSO_4$), rotary evaporated and chromatographed (7 : 3 hexanes : Et_2O) to afford diketo-crotylester-dioxinone **317** (4.0 g, 56%) as a yellow oil:

R_f 0.32 (2 : 1 Et_2O : hexanes);

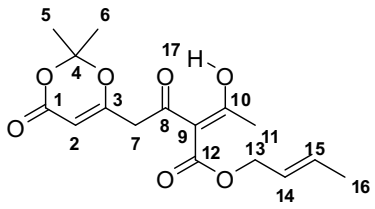
IR (neat) ν_{max} 2945 (w, **C-H**), 1719 (m, **C=O**), 1635 (m, **C=C**), 1272 (sh.), 1201 (sh.), 1015 (w) cm^{-1};

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (156)



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_2Cl_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_2O : hexanes to Et_2O) to afford diketo-crotylester-dioxinone **156** (260 mg, 46%) as a pale yellow oil:

R_f 0.40 (2 : 1 hexanes : Et_2O);

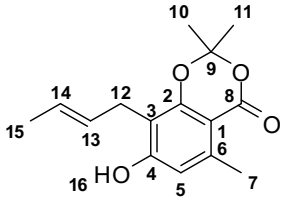
IR (neat) ν_{max} 2943 (w, **C-H**), 1727 (sh., **C=O**), 1638 (m, **C=C**), 1564 (m, **C-C**), 1390 (m), 1201 (sh.), 1070 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{16}H_{20}O_7$ $[M+H]^+$: requires 325.1287, found 325.1280 (Δ –2.2 ppm);

^{1}H 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, **2**), 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**);

^{13}C 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-4*H*-benzo[*d*][1,3]dioxin-4-one (157)



157

$Pd(PPh_3)_4$ (70 mg, 60 μmol, 0.1 equiv.) and Cs_2CO_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_2Cl_2 : EtOAc : hexanes);

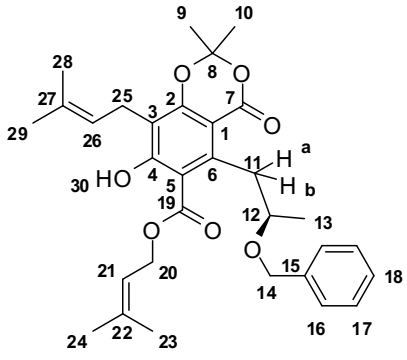
IR (neat) ν_{max} 3255 (br., **O-H**), 2995 (w, **C-H**), 1692 (m, **C=C**), 1607 (m, **C=C**), 1592 (w, **C-C**), 1452 (m), 1322 (w), 1284 (sh.), 1209 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{15}H_{18}O_4$ $[M+H]^+$: requires 263.1283, found 263.1287 (Δ +1.5 ppm);

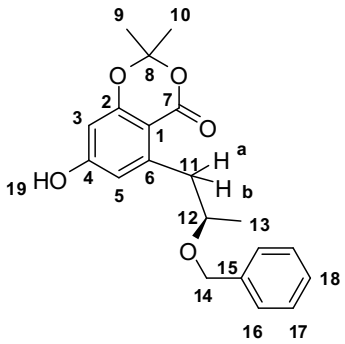
^{1}H NMR (500 MHz, C_6D_6) δ 8.21 (s, 1H, **16**), 5.95 (s, 1H, **5**), 5.50-5.38 (m, 2H, **13** & **14**), 3.27 (d, *J* = 5.0 Hz, 2H, **12**), 3.16 (s, 3H, **7**), 1.48-1.49 (m, 3H, **15**), 1.31 (s, 6H, **10** & **11**);

^{13}C NMR (125 MHz, C_6D_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**).

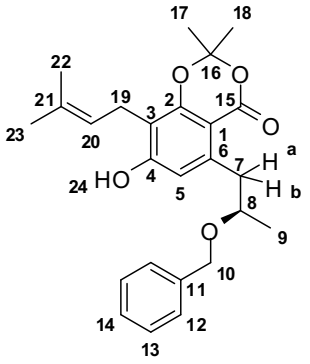
(*R*)-5-(2-(Benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (163), (*R*)-5-(2-(Benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (165) and (*R*)-5-(2-(benzyloxy)propyl)-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-4*H*-benzo[*d*][1,3]dioxin-4-one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



163



165



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_2CO_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_4Cl (50 mL), extracted with EtOAc (2 x 50 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 : 4 CH_2Cl_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_2Cl_2 : EtOAc : hexanes);

$[\alpha]_D^{25} = -33.3$ (*c* 0.46, $CHCl_3$);

IR (neat) ν_{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 (Δ +1.0 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, **26**), 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, $CDCl_3$) δ 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_2Cl_2 : EtOAc : hexanes);

$[\alpha]_D^{25} = -3.0$ (*c* 0.3, $CHCl_3$);

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

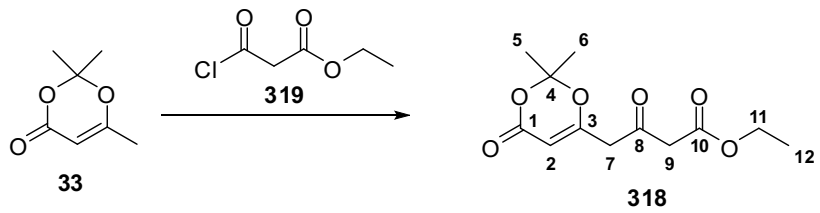
HRMS (ESI) calc. for $C_{20}H_{23}O_5$ $[M+H]^+$: requires 343.1545, found 3431552 (Δ +2.0 ppm);

^{1}H NMR (500 MHz, C_6D_6) δ 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**);

^{13}C NMR (125 MHz, C_6D_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-4*H*-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_4Cl (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_2O) to afford keto-ethylester-dioxinone **318**[102] (512 mg, 62%) as a yellow oil:

R_f 0.20 (2 : 1 Et_2O : hexanes);

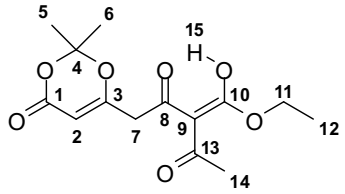
IR (neat) ν_{max} 2994 (w, **C-H**), 1720 (s, **C=O**), 1638 (w, **C=C**), 1375 (w), 1271 (sh.), 1202 (sh.), 1015 (w) cm^{-1};

HRMS (ESI) calc. for $C_{12}H_{17}O_6$ $[M+H]^+$: requires 257.1025, found 257.1024 (Δ –0.4 ppm);

^{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-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (174)



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_2Cl_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_2Cl_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_2Cl_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_2Cl_2 : hexanes);

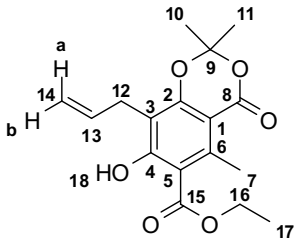
IR (neat) ν_{max} 2995 (w, **C-H**), 1725 (s, **C=O**), 1637 (m, **C=C**), 1565 (m, **C-C**), 1373 (sh.), 1270 (sh.), 1250 (sh.), 1201 (s), 1103 (sh), 1077 (sh.), 901 (w), 810 (w) cm^{-1};

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**);

^{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-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (177)



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_2CO_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_4Cl (20 mL), extracted with Et_2O (2 x 20 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 Et_2O : 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_2O : pentane 3 : 9);

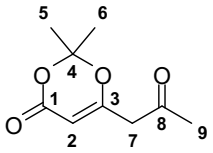
HRMS (ESI) calc. for $C_{17}H_{21}O_6$ $[M+H]^+$: requires 321.1338, found 321.1349 (Δ +3.4 ppm);

IR ν_{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_6D_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**);

^{13}C NMR (C_6D_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)-4*H*-1,3-dioxin-4-one (178)



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_4Cl 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_2O (2 x 250mL). The organics were combined, dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 1 to 1 : 1 hexanes : Et_2O) 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_2O : hexanes);

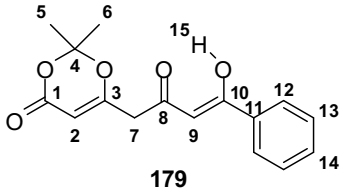
IR (neat) ν_{max} 2997 (w, **C-H**), 1721 (sh., **C=O**), 1637 (m, **C=C**), 1376 (sh.), 1272 (sh.), 1201 (sh.), 1012 (w) cm^{-1};

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

^{1}H 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-4*H*-1,3-dioxin-6-yl)-1-phenylbutane-1,3-dione (179)



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_2NH (1.2 mL, 8.4 mmol, 2.0 equiv.) in THF (20 mL) at –78 °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_2Zn 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 °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 °C for 2 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (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);

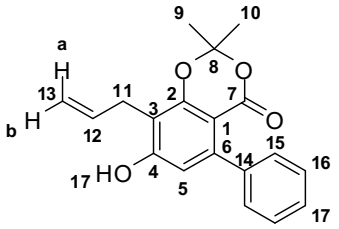
IR (neat) ν_{max} 2988 (w, **C-H**), 1725 (sh., **C=O**), 1602 (m, **C=C**), 1571 (m, **C-C**), 1456 (w), 1373 (sh.), 1252 (m), 1017 (m), 927 (w) cm^{-1};

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-4*H*-benzo[*d*][1,3]dioxin-4-one (181)



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_2CO_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_4Cl (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);

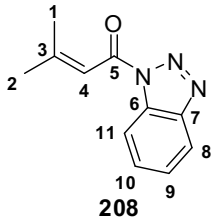
IR (neat) ν_{max} 3016 (m, **C-H**), 2970 (m, **C-H**), 1740 (s, **C=O**), 1435 (w), 1366 (m), 1228 (sh.), 1206 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{19}H_{18}O_4$ $[M+H]^+$: requires 311.1283, found 311.1280 (Δ –1.0 ppm);

^{1}H NMR ($CDCl_3$, 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**);

^{13}C NMR ($CDCl_3$, 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-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-methylbut-2-en-1-one (208)



208

Based on a procedure by Navarro *et al.*[82] Benzotriazole (19.0 g, 160 mmol, 3.2 equiv.) was stirred in CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 (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 ($MgSO_4$) and rotary evaporated to afford benzotriazole amide **208**[192] (7.0 g, 70%) as an off white solid:

m.p. 97 - 98 °C (CH_2Cl_2 : 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};

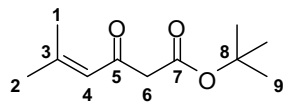
HRMS (ESI) calc. for $C_{11}H_{12}N_3O$ $[M+H]^+$: requires 202.0982, found 202.0980 (Δ +1.0 ppm);

^{1}H 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**);

^{13}C 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 $C_{11}H_{11}ON_3$: 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)



200

i-Pr_2NH (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 NH_4Cl (200 mL), acidified to pH 2 using 1 M HCl and extracted with EtOAc (2 x 150 mL). The organics were combined, dried ($MgSO_4$), 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);

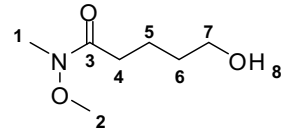
IR (neat) ν_{max} 2979 (w, **C-H**), 2933 (w, **C-H**), 1731 (m, **C=O**), 1688 (m, **C=C**), 1620 (m, **C=O**), 1254 (w), 1142 (w) cm^{-1};

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)



215

Based on a procedure by Flick *et al.*[118] Weinreb amide hydrochloride salt (22 .0g, 22.5 mmol, 15.0 equiv.) was stirred in CH_2Cl_2 (5 mL) at 0 °C for 5 min. $AlCl_3$ in CH_2Cl_2 (12.5 mL, 1.8 M, 22.5 mmol, 15.0 equiv.) was added dropwise and the mixture stirred for 20 min. Tetrahydro-2*H*-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**[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^{-1};

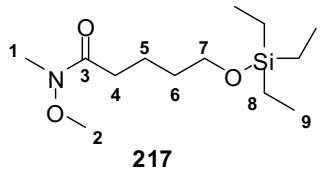
HRMS (ESI) calc. for $C_7H_{16}NO_3$ $[M+H]^+$: requires 162.1130, found 162.1123 (Δ –4.3 ppm);

^{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**);

Anal. Calc. for $C_7H_{15}NO_3$: 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)



217

Alcohol **215** (6.10 g, 37.9 mmol, 1.0 equiv.) was stirred in CH_2Cl_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 H_2O (100 mL), extracted with CH_2Cl_2 (2 x 200 mL), washed with brine (100 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 6 to 1 : 1 EtOAc : hexanes) to afford silylether **217** (6.7 g, 70%) as a colourless oil:

R_f 0.5 (2 : 6 EtOAc : hexanes);

IR (neat) ν_{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};

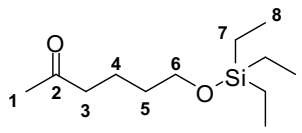
HRMS (ESI) calc. for $C_{13}H_{30}NO_3Si$ $[M+H]^+$: requires 276.1995, found 276.1998 (Δ +1.1 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{13}H_{29}NO_3Si$: C, 56.68; H, 10.61; N, 5.08. Found: C, 56.79; H, 10.70; N, 5.02.

6-(Triethylsilyloxy)hexan-2-one (214)



214

Based on a procedure by Zanardi *et al.*[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**[193] (4.0 g, 73%) as a colourless oil:

R_f 0.81 (1 : 1 EtOAc : hexanes);

IR (neat) ν_{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};

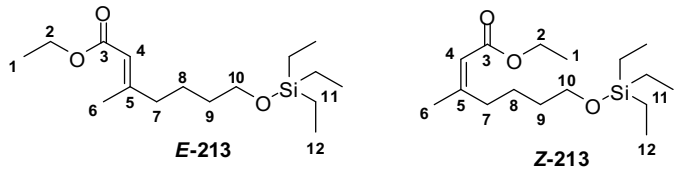
HRMS (ESI) calc. for $C_{12}H_{27}O_2Si$ $[M+H]^+$: requires 231.1780, found 231.1777 (Δ –1.3 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{26}O_2Si$: 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.*[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_2O (50 mL), extracted with Et_2O (2 x 100 mL), dried ($MgSO_4$), 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);

IR (neat) ν_{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^{-1};

HRMS (ESI) calc. for $C_{16}H_{33}O_3Si$ $[M+H]^+$: requires 301.2199, found 301.2201 (Δ +0.7 ppm).

(*E*)-*Olefin* ***E*-213**:

^{1}H NMR (400 MHz, C_6D_6) δ 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**);

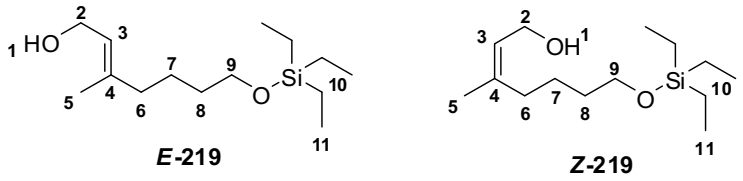
^{13}C NMR (125 MHz, C_6D_6) δ 166.4 (**3**), 159.4 (**5**), 116.3 (**4**), 62.5 (**10**), 59.3 (**2**), 40.6 (**7**), 32.6 (**9**), 23.9 (**8**), 18.6 (**6**), 14.4 (**1**), 7.1 (3C, **12**), 4.8 (3C, **11**).

(*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**);

^{13}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) ν_{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};

HRMS (ESI) calc. for $C_{14}H_{31}O_2Si$ $[M+H]^+$: requires 259.2093, found 259.2094 (Δ +0.4 ppm).

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42-5.39 (m, 1H, **3**), 4.15 (d, *J* = 7.0 Hz, 2H, **2**), 3.60 (t, *J* = 8.0 Hz, 2H, **9**), 2.03 (t, *J* = 8.0 Hz, 2H, **6**), 1.66 (s, 3H, **5**), 1.55-1.42 (m, 4H, **7** & **8**), 1.17 (br. s, 1H, **1**), 0.95 (t, *J* = 7.0 Hz, 9H, **11**), 0.59 (q, *J* = 7.0 Hz, 6H, **10**);

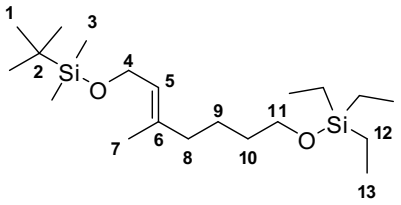
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (**4**), 123.4 (**3**), 62.7 (**9**), 59.4 (**2**), 39.3 (**6**), 32.4 (**8**), 23.8 9 (**7**), 16.1 (**5**), 6.8 (3C, **11**), 4.4 (3C, **10**).

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

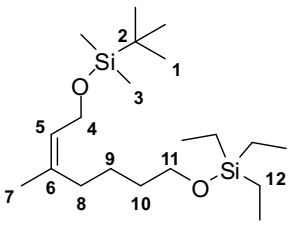
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44-5.39 (m, 1H, **3**), 4.14 (d, *J* = 7.0 Hz, 2H, **2**), 3.60 (t, *J* = 8.0 Hz, 2H, **9**), 2.09 (t, *J* = 8.0 Hz, 2H, **6**), 1.73 (s, 3H, **5**), 1.55-1.42 (m, 4H, **7** & **8**), 1.17 (br. s, 1H, **1**), 0.95 (t, *J* = 7.0 Hz, 9H, **11**), 0.59 (q, *J* = 7.0 Hz, 6H, **10**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (**4**), 123.4 (**3**), 62.7 (**9**), 59.4 (**2**), 39.3 (**6**), 32.4 (**8**), 23.8 9 (**7**), 16.1 (**5**), 6.8 (3C, **11**), 4.4 (3C, **10**).

(*E*)-13,13-Diethyl-2,2,3,3,7-pentamethyl-4,12-dioxa-3,13-disilapentadec-6-ene (*E*-212) and (*Z*)-13,13-Diethyl-2,2,3,3,7-pentamethyl-4,12-dioxa-3,13-disilapentadec-6-ene (*Z*-212)



***E*-212**



***Z*-212**

A mixture of (*E*)-olefin-alcohol ***E*-219** and (*Z*)-olefin-alcohol ***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 TBSCl (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_2O (100 mL) and extracted with a mixture of pentane and CH_2Cl_2 (9 : 1, 2 x 200 mL). The organics were combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 Et_2O : pentane) to afford (*E*)-olefin-silylether ***E*-212** and (*Z*)-olefin-silylether ***Z*-212** in a 3 : 1 ratio (350 mg, 92%) as a colourless oil:

R_f 0.82 (1 : 9 EtOAc : hexanes);

IR (neat) ν_{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) cm^{-1};

HRMS (CI) calc. for $C_{20}H_{48}NO_2Si_2$ $[M+NH_4]^+$: requires 390.3234, found 390.3216 (Δ –2.0 ppm);

(*E*)-*Olefin-silylether* ***E*-212***:*

^{1}H NMR (400 MHz, $CDCl_3$) δ 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**);

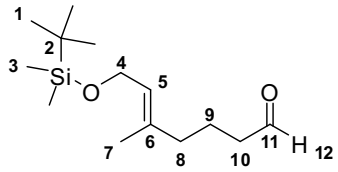
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (**6**), 124.4 (**5**), 62.8 (**11**), 60.3 (**4**), 39.3 (**8**), 32.5 (**10**), 26.0 (3C, **1**), 23.3 (**9**), 18.43 (**2**), 16.2 (**7**), 6.8 (3C, **13**), 4.4 (3C, **12**), –5.1 (2C, **3**).

(*Z*)-*Olefin-silylether* ***Z*-212***:*

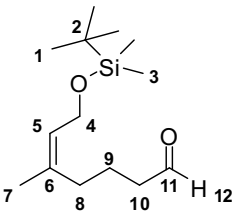
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33-5.31 (m, 1H, **5**), 4.15 (d, *J* = 7.0 Hz, 2H, **4**), (t, *J* = 8.0 Hz, 2H, **11**), 2.03 (t, *J* = 8.0 Hz, 2H, **8**), 1.59 (s, 3H, **7**), 1.54-1.39 (m, 4H, **9** & **10**), 0.95 (t, *J* = 7.0 Hz, 9H, **13**), 0.90 (s, 9H, **1**), 0.60 (q, *J* = 7.0 Hz, 6H, **12**), 0.06 (s, 6H, **3**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 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**), –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)



***E*-220**



***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_2Cl_2 (3.35 mL) at –80 °C and stirred for 1 h. A solution of (*E*)-olefin silylether ***E*-212** and (*Z*)-olefin silylether ***E*-212** in a 3 : 1 ratio (500 mg, 1.34 mmol, 1.0 equiv.) in CH_2Cl_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_3N (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

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_f 0.65 (1 : 7 EtOAc : hexanes);

IR (neat) ν_{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 $C_{14}H_{29}O_2Si$ $[M+H]^+$: requires 257.1937, found 257.1932 (Δ –1.9 ppm);

Anal. Calc. for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.46; H, 10.92.

(E)-Olefin-aldehyde ***E*-220:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 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**);

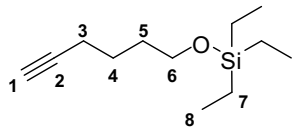
^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2 (**11**), 135.6 (**6**), 125.5 (**5**), 60.1 (**4**), 43.1 (**10**), 38.6 (**8**), 25.9 (3C, **1**), 20.2 (**9**), 19.9 (**2**), 15.9 (**7**), –5.2 (2C, **3**).

(Z)-Olefin-aldehyde ***Z*-220:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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**).

Triethyl(hex-5-ynyloxy)silane (221)



221

Hex-5-yn-1-ol **223** (6.90 mL, 62.7 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (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 H_2O (300 mL), extracted with CH_2Cl_2 (2 x 100 mL), dried ($MgSO_4$), 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%):

R_f 0.90 (1 : 1 EtOAc : hexanes);

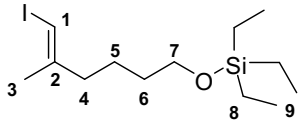
IR (neat) ν_{max} 3311 (w, C≡**CH**), 2954 (m, **C-H**), 2877 (m, **C-H**), 1459 (w), 1216 (w), 1237 (w), 1103 (sh.), 1006 (sh.) cm^{-1};

HRMS (CI) calc. for $C_{12}H_{25}OSi$ $[M+H]^+$: requires 213.1675, found 213.1677 (Δ +0.9 ppm);

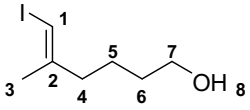
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (t, *J* = 8.0 Hz, 2H, **6**), 2.25 (td, *J* = 8.0, 0.5 Hz, 2H, **3**), 1.97 (t, *J* = 0.5 Hz, 1H, **1**), 1.70-1.58 (m, 4H, **4** & **5**), 0.98 (t, *J* = 7.0 Hz, 9H, **8**), 0.62 (q, *J* = 7.0 Hz, 6H, **7**);

^{13}C NMR (100 MHz, $CDCl_3$) δ 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)



224



225

Based on a procedure by Welzel *et al*.[122] Zirocene dichloride (1.4 g, 4.7 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (22 mL) at 0 °C. $AlMe_3$ in CH_2Cl_2 (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 CH_2Cl_2 (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 NH_4Cl (8 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (4 mL), extracted with CH_2Cl_2 (1 x 500 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (29 : 1 EtOAc : hexanes) to afford (*E*)-olefin silylether **224** (170 mg, 10%) and (*E*)-olefin alcohol **225**[195] (840 mg, 50%) as colourless oils.

*(E)-Olefin-silylether **224:***

R_f 0.9 (1 : 7 EtOAc : hexanes);

IR (neat) ν_{max} 2952 (m, **C-H**), 2910 (m, **C-H**), 2875 (m, **C-H**), 1457 (m), 1413 (m), 1377 (w), 1235 (m), 1072 (s), 1003 (s) cm^{-1};

HRMS (CI) calc. for $C_{13}H_{28}OSiI$ $[M+H]^+$: requires 355.0954, found 355.0954 (Δ 0.0 ppm);

^{1}H NMR (500 MHz, C_6D_6) δ 5.69 (sextet, *J* = 0.5 Hz, 1H, **1**), 3.45 (t, *J* = 7.0 Hz, 2H, **7**), 1.86-1.83 (m, 2H, **4**), 1.64 (d, *J* = 0.5 Hz, 3H, **3**), 1.36-1.26 (m, 4H, **5** & **6**), 1.0 (t, *J* = 8.0 Hz, 9H, **9**), 0.60 (q, *J* = 8.0 Hz, 6H, **8**);

^{13}C NMR (500 MHz, C_6D_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) ν_{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};

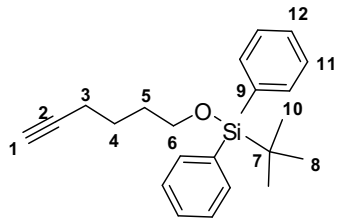
HRMS (CI) calc. for $C_7H_{17}NOI$ $[M+NH_4]^+$: requires 258.0355, found 258.0352 (Δ –1.2 ppm);

^{1}H NMR (500 MHz, C_6D_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_6D_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 $C_7H_{13}OI$: C, 35.02; H, 5.46. Found: C, 35.01; H, 5.39

_t_-Butyl(hex-5-ynyloxy)diphenylsilane (226)



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 CH_2Cl_2 (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 H_2O (300 mL), extracted with CH_2Cl_2 (2 x 300 mL), the organics combined, washed with brine (200 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 99 Et_2O : hexanes) affording silylether **226**[196] (15.0 g, 88%) as a colourless oil:

R_f 0.95 (1 : 7 EtOAc : hexanes);

IR (neat) ν_{max} 3309 (w, C≡**C**H**)**, 2932 (w, **C-H**), 2858 (w, **C-H**), 1472 (w), 1427 (sh.), 1106 (w) cm^{-1};

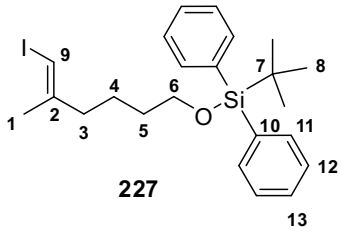
HRMS (ESI) calc. for $C_{22}H_{29}OSi$ $[M+H]^+$: requires 337.1988, found 337.1997 (Δ +2.7 ppm);

^{1}H NMR (500 MHz, C_6D_6) 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**);

^{13}C NMR (125 MHz, C_6D_6) 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 $C_{22}H_{28}OSi$: C, 78.51; H, 8.39. Found: C, 78.61; H, 8.29.

(*E*)-*t*-Butyl(6-iodo-5-methylhex-5-enyloxy)diphenylsilane (227)



227

Based on a procedure by Welzel *et al*.[122] Zirocene dichloride (2.6 g, 8.9 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (45 mL) at 0 °C. $AlMe_3$ in CH_2Cl_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_2Cl_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_4Cl (15 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (8 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The organics were combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 99 Et_2O : hexanes) to afford (*E*)-olefin **227** (2.6 g, 63%) as a colourless oil:

R_f 0.9 (1 : 7 Et_2O : hexanes);

IR (neat) ν_{max} 2930 (w, **C-H**), 2857 (w, **C-H**), 1472 (w), 1427 (sh.), 1105 (s) cm^{-1};

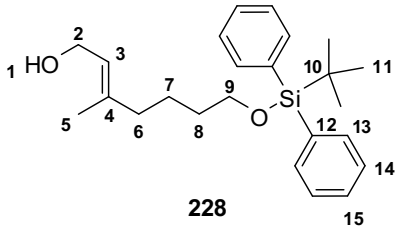
HRMS (CI) calc. for $C_{23}H_{32}OSiI$ $[M+H]^+$: requires 479.1267, found 479.1269 (Δ +0.4 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) δ 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**);

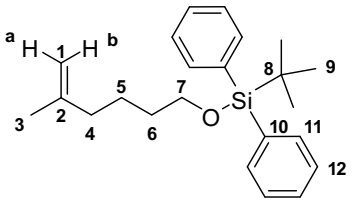
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (**2**), 135.6 (4C, **11**), 134.0 (2C, **13**), 129.6 (4C, **12**), 127.6 (2C, **10**), 74.6 (**9**), 63.5 (**6**), 39.2 (**3**), 31.8 (**5**), 23.9 (3C, **8**), 23.9 (**4**), 23.7 (**7**), 19.2 (**1**);

Anal. Calc. for $C_{23}H_{31}IOSi$: C, 57.73; H, 6.53. Found: C, 57.89; H, 6.60.

(*E*)-7-(*t*-Butyldiphenylsilyloxy)-3-methylhept-2-en-1-ol (228) and *t*-Butyl(5-methylhex-5-enyloxy)diphenylsilane (229)



228



229

Based on a procedure by Dai *et al.*[120] Zirocene dichloride (2.6 g, 8.9 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (45 mL) at 0 °C. $AlMe_3$ in CH_2Cl_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_2Cl_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_2O (100 mL), extracted with Et_2O (300 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford olefin alcohol **228**[197] (1.8 g, 53%) and olefin **229**[198] (650 mg, 22%) both as colourless oils.

*Olefin alcohol **228:***

R_f 0.5 (3 : 5 EtOAc : hexanes);

IR (neat) ν_{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};

HRMS (CI) calc. for $C_{24}H_{38}NO_2Si$ $[M+NH_4]^+$: 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 $C_{24}H_{34}O_2Si$: 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};

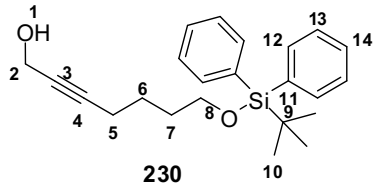
HRMS (CI) calc. for $C_{23}H_{33}OSi$ $[M+H]^+$: requires 353.2301, found 353.2305 (Δ +1.1 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H, **12**), 7.44-7.67 (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 $C_{24}H_{34}O_2Si$: C, 78.35, H, 9.15. Found: C, 78.43; H, 9.21.

7-(*t*-Butyldiphenylsilyloxy)hept-2-yn-1-ol (230)



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 NH_4Cl (20 mL), extracted with Et_2O (2 x 30 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford alkyne alcohol **230**[199] (1.4 g, 87%) as a colourless oil:

$\mathbf{R_f}$ 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};

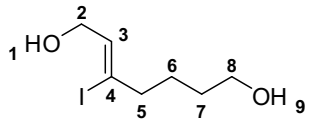
HRMS (CI) calc. for $C_{23}H_{34}NO_2Si$ $[M+NH_4]^+$: requires 384.2359, found 384.2368 (Δ +2.3 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) 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**);

^{13}C NMR (125 MHz, $CDCl_3$) 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.

(*Z*)-3-Iodohept-2-ene-1,7-diol (234)



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 ^{o}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 $Na_2S_2O_3$ (10 mL), extracted with Et_2O (2 x 50 mL), the organics combined, dried ($MgSO_4$), 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:

R$_f$ 0.2 (7 : 3 EtOAc : hexanes);

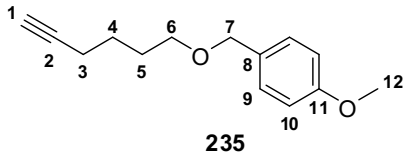
IR (neat) ν_{max} 3313 (br., **O-H**), 2935 (w, **C-H**), 2861 (w, **C-H**), 1738 (m), 1644 (w, **C=C**), 1451 (w), 1366 (w), 1228 (w), 1217 (w), 1060 (w), 1018 (w) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 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**);

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9 (**3**), 110.1 (**4**), 67.2 (**2**), 62.6 (**8**), 44.8 (**5**), 31.2 (**7**), 25.4 (**6**);

Anal. Calc. for $C_7H_{13}IO_2$: C, 32.83; H, 5.12. Found: C, 25.15; H, 4.85.

1-((Hex-5-ynyloxy)methyl)-4-methoxybenzene (235)



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 NH_4Cl (100 mL), extracted with Et_2O (2 x 200 mL), the organics combined and washed with brine (3 x 300 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 EtOAc : hexanes) to afford PMB ether **235**[196] (10 g, 90%) as a colourless oil:

$\mathbf{R_f}$ 0.55 (3 : 7 EtOAc : hexanes);

HRMS (ESI) calc. for $C_{14}H_{18}O_2Na$ $[M+Na]^+$: requires 241.1204, found 241.1231 (Δ +11.2 ppm);

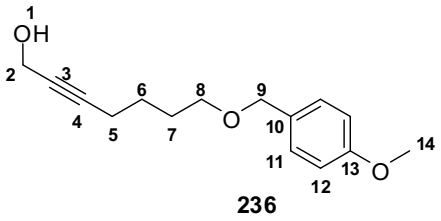
IR (neat) ν_{max} 3293 (w, C≡**CH**), 2938 (w, **C-H**), 2859 (w, **C-H**), 1612 (sh., **C=C**), 1511 (sh., C-C), 1301 (w), 1244 (sh.), 1093 (sh.), 1034 (sh.) cm^{-1};

^{1}H NMR ($CDCl_3$, 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**);

^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.23.

7-(4-Methoxybenzyloxy)hept-2-yn-1-ol (236)



236

Based on a procedure by Lindsay *et al.*[126] Alkyne **235** (6.80 g, 29.8 mmol, 1.0 equiv.) was stirred in THF (150 mL) at –78 °C. *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_4Cl (300 mL), extracted with Et_2O (2 x 200 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (3 : 7 EtOAc : hexanes) to afford alcohol **236**[126] (6.0 g, 81%) as a colourless oil:

$\mathbf{R}_f$ 0.48 (1 : 1 EtOAc : hexanes);

IR (neat) ν_{max} 3399 (br., **O-H**), 2938 (w, **C-H**), 2862 (w, **C-H**), 1738 (sh.), 1611 (sh., **C=C**), 1511 (sh., **C-C**), 1365 (w), 1244 (sh.), 1078 (m), 1030 (sh.), 1011 (sh.) cm^{-1};

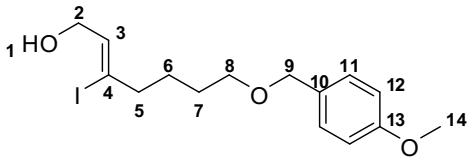
HRMS (ESI) calc. for $C_{15}H_{20}O_3Na$ $[M+Na]^+$: requires 271.1310, found 271.1309 (Δ –0.4 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 9.0 Hz, 2H, **11**), 6.88 (d, J = 9.0 Hz, 2H, **12**), 4.43 (s, 2H, **9**), 4.24-4.22 (m, 2H, **2**), 3.81 (s, 3H, **14**), 3.46 (t, J = 6.0 Hz, 2H, **8**), 2.24 (t, J = 6.0 Hz, 2H, **5**), 1.73-1.68 (m, 2H, **6**), 1.63-1.57 (m, 3H, **1** & **7**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1 (**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**);

Anal. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 71.96; H, 8.32.

(*Z*)-3-Iodo-7-(4-methoxybenzyloxy)hept-2-en-1-ol (237)



237

Based on a procedure by Yamazaki *et al.*[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 $Na_2S_2O_3$ (4 mL), extracted with Et_2O (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:

R_f 0.5 (1 : 1 EtOAc : hexanes);

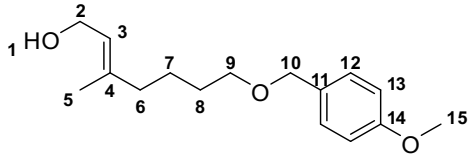
IR (neat) ν_{max} 3409 (br., **O-H**), 2935 (w, **C-H**), 2858 (w, **C-H**), 1611 (w, **C=C**), 1512 (sh., **C-C**), 1454 (w), 1360 (w), 1301 (w), 1244 (sh.), 1172 (w), 1080 (sh.), 1032 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{15}H_{21}O_3NaI$ $[M+Na]^+$: requires 399.0433, found 399.0444 (Δ +2.8 ppm);

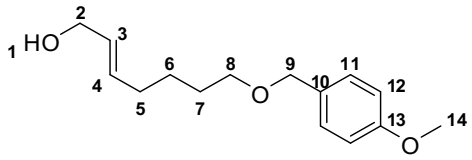
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, *J* = 9.0 Hz, 2H, **11**), 6.88 (d, *J* = 9.0 Hz, 2H, **12**), 5.83 (tt, *J* = 6.0, 0.5 Hz, 1H, **3**), 4.43 (s, 2H, **9**), 4.18 (d, *J* = 6.0, 2H, **2**), 3.81 (s, 3H, **14**), 3.45 (t, *J* = 6.0 Hz, 2H, **8**), 2.51 (t, *J* = 6.0 Hz, 2H, **5**), 1.62-1.58 (m, 5H, **1**, **6** & **7**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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**).

(*E*)-7-(4-Methoxybenzyloxy)-3-methylhept-2-en-1-ol (238) and (*E*)-7-(4-Methoxybenzyloxy)hept-2-en-1-ol (239)



238



239

Based on a procedure by Holler *et al*.[130] 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 NH_4Cl (10 mL), extracted with Et_2O (20 mL), dried ($MgSO_4$), 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**[200] (6 mg, 9%) both as a colourless oils:

*Methylhept-2-en-1-ol **238:***

R_f 0.48 (1 : 1 EtOAc : hexanes);

IR (neat) ν_{max} 3385 (br., **O-H**), 2935 (m, **C-H**), 2858 (m, **C-H**), 1612 (w, **C=C**), 1512 (sh., **C-C**), 1245 (sh.), 1173 (w), 1097 (sh.), 1034 (sh.), 1010 (w) cm^{-1};

HRMS (ESI) calc. for $C_{16}H_{25}O_3$ $[M+H]^+$: requires 265.1804, found 265.1799 (Δ –1.9 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, *J* = 9.0 Hz, 2H, **12**), 6.88 (d, *J* = 9.0 Hz, 2H, **13**), 5.41-5.37 (m, 1H, **3**), 4.43 (s, 2H, **10**), 4.14 (d, *J* = 6.0 Hz, 2H, **2**), 3.80 (s, 3H, **15**), 3.44 (t, *J* = 6.0 Hz, 2H, **9**), 2.02 (t, *J* = 6.0 Hz, 2H, **6**), 1.66 (s, 3H, **5**), 1.61-1.56 (m, 2H, **8**), 1.52-1.46 (m, 2H, **7**), 1.26 (br. s, 1H, **1**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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:***

R_f 0.52 (1 : 1 EtOAc : hexanes);

IR (neat) ν_{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};

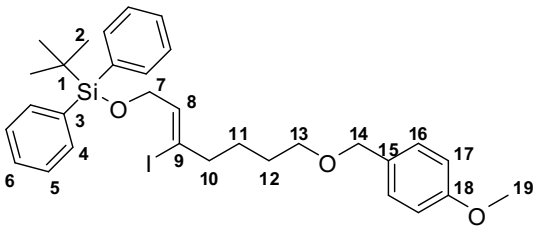
HRMS (ESI) calc. for $C_{15}H_{23}O_3$ $[M+H]^+$: requires 251.1647, found 251.1648 (Δ +0.4 ppm).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, *J* = 9.0 Hz, 2H, **11**), 6.88 (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}C NMR ($CDCl_3$, 125 MHz) δ 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.

(*Z*)-*tert*-Butyl(3-iodo-7-(4-methoxybenzyloxy)hept-2-enyloxy)diphenylsilane (241)



241

Alcohol **237** (540 mg, 1.44 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (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. TBDPSCl (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 NH_4Cl (20 mL), extracted with Et_2O (2 x 20 mL), the organics combined, dried ($MgSO_4$), rotary evaporated chromatographed (1 : 9 EtOAc : hexanes) affording silylether **241** (700 mg, 80%) as a colourless oil:

R_f 0.8 (3 : 7 EtOAc : hexanes);

IR (neat) ν_{max} 2931 (w, **C-H**), 2856 (w, **C-H**), 1612 (w, **C=C**), 1512 (w, **C-C**), 1472 (w), 1427 (sh.), 1246 (w), 1172 (w), 1104 (m), 1037 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{31}H_{43}NO_3SiI$ $[M+NH_4]^+$: requires 632.2057, found 632.2040 (Δ +11.5 ppm);

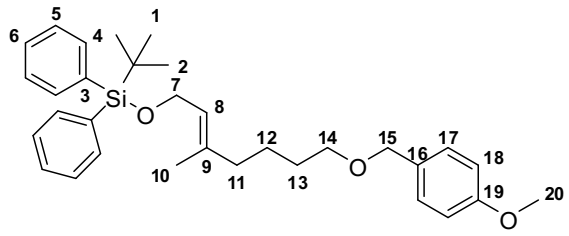
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68-7.67 (m, 4H, **5**), 7.44-7.37 (m, 6H, **4** & **6**), 7.27 (d, *J* = 9.0 Hz, 2H, **16**), 6.89 (d, *J* = 9.0 Hz, 2H, **17**), 5.84 (tt, *J* = 6.0, 0.5 Hz, 1H, **8**), 4.44 (s, 2H, **14**), 4.26 (d, *J* = 6.0 Hz, 2H, **7**), 3.80 (s, 3H, **19**), 3.45 (t, *J* = 7.0 Hz, 2H, **13**), 2.46-2.44 (m, 2H, **10**), 1.59-1.56 (m, 4H, **11** & **12**), 1.06 (s, 9H, **2**);

^{13}C NMR ($CDCl_3$, 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**);

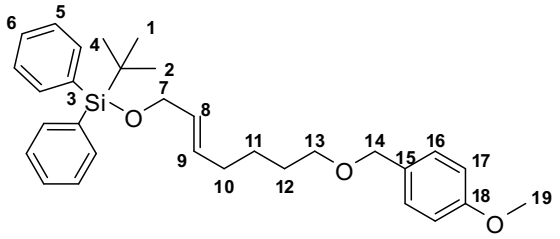
Anal. Calc. for $C_{31}H_{39}IO_3Si$: C, 60.58; H, 6.40. Found: C, 60.62; H, 6.47.

(*E*)-*t*-Butyl(7-(4-methoxybenzyloxy)-3-methylhept-2-enyloxy)diphenylsilane (242) and

(*E*)-*t*-Butyl(7-(4-methoxybenzyloxy)hept-2-enyloxy)diphenylsilane (243)



242



243

^{i}PrMgCl 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_4Cl (10 mL), extracted with Et_2O (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) ν_{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 $C_{32}H_{42}O_3SiNa$ $[M+Na]^+$: requires 525.2801, found 525.2780 (Δ –4.0 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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 $C_{32}H_{42}O_3Si$: 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) ν_{max} 2931 (w, **C-H**), 2856 (w, **C-H**), 1612 (w, **C=C**), 1512 (w, **C-C**), 1427 (w), 1246 (sh.), 1105 (m), 1037 (sh.) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 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) δ 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**);

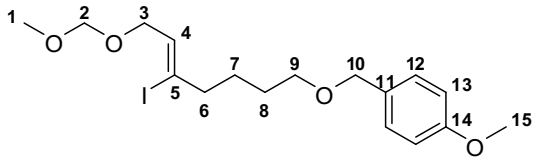
Anal. Calc. for $C_{31}H_{40}O_3Si$; C76.18, H 8.25; found C, 76.13; H, 8.26.

*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_4Cl (10 mL), extracted with Et_2O (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-methoxybenzyloxy)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_4Cl (5 mL), extracted with Et_2O (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.*

(*Z*)-1-((5-Iodo-7-(methoxymethoxy)hept-5-enyloxy)methyl)-4-methoxybenzene (244)



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_2Cl_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_4Cl (10 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL), extracted with Et_2O (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);

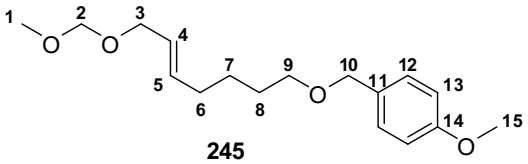
IR (neat) ν_{max} 2935 (w, **C-H**), 2857 (w, **C-H**), 1738 (w), 1612 (w, **C=C**), 1512 (sh., **C-C**), 1455 (w), 1365 (w), 1301 (w), 1245 (m), 1150 (w), 1099 (m), 1033 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{17}H_{25}O_4NaI$ $[M+Na]^+$: requires 443.0695, found 443.0698 (Δ +0.7 ppm);

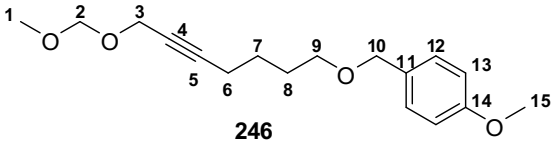
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J = 9.0 Hz, 2H, **12**), 6.88 (d, J = 9.0 Hz, 2H, **13**), 5.80 (tt, J = 6.0, 0.5 Hz, 1H, **4**), 4.64 (s, 2H, **10**), 4.43 (s, 2H, **2**), 4.12 (d, J = 6.0 Hz, 2H, **3**), 3.81 (s, 3H, **15**), 3.45 (t, J = 6.0 Hz, 2H, **9**), 3.39 (s, 3H, **1**), 2.52 (t, J = 6.0 Hz, 2H, **6**), 1.65-1.57 (m, 4H, **7** & **8**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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**).

1-Methoxy-4-((7-(methoxymethoxy)hept-5-ynyloxy)methyl)benzene (245) and (*E*)-1-Methoxy-4-((7-(methoxymethoxy)hept-5-enyloxy)methyl)benzene (246)



245



246

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_4Cl (5 mL), extracted with Et_2O (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);

IR (neat) ν_{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};

HRMS (ESI) calc. for $C_{17}H_{26}O_4Na$ $[M+Na]^+$: requires 317.1729, found 317.1718 (Δ –3.5 ppm);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H, **12**), 6.90 (d, *J* = 9.0 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 Hz, 2H, **3**), 3.82 (s, 3H, **15**), 3.46 (t, *J* = 7.0 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**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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);

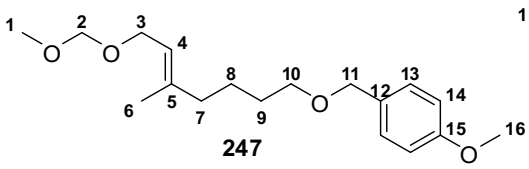
IR (neat) ν_{max} 2938 (w, **C-H**), 2862 (w, **C-H**), 1738 (w), 1612 (w, **C=C**), 1512 (sh., **C-C**), 1361 (w), 1245 (sh.), 1148 (w), 1097 (sh.), 1039 (m) cm^{-1};

HRMS (ESI) calc. for $C_{17}H_{24}O_4Na$ $[M+Na]^+$: requires 315.1572, found 315.1566 (Δ –1.9 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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 ^{o}C and the resulting solution stirred for 1 h. $Pd(PPh_3)_4$ (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 NH_4Cl (10 mL), extracted with Et_2O (2 x 20 mL), the organics combined, dried ($MgSO_4$), 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**:*

R_f 0.62 (3 : 7 EtOAc : hexanes);

IR (neat) ν_{max} 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};

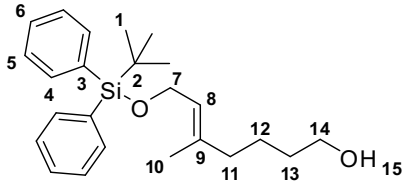
HRMS (ESI) calc. for $C_{18}H_{28}O_4Na$ $[M+Na]^+$: requires 331.1885, found 331.1872 (Δ +0.9 ppm);

^{1}H NMR ($CDCl_3$, 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**);

^{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)



248

PMB ether **242** (200 mg, 0.40 mmol, 1.0 equiv.) was stirred in a solution of CH_2Cl_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_4Cl (20 mL) and filtered through celite. The resulting solution was extracted with Et_2O (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) ν_{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};

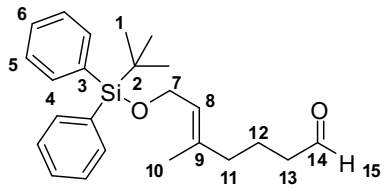
HRMS (CI) calc. for $C_{24}H_{38}NO_2Si$ $[M+NH_4]^+$: requires 400.2672, found 400.2673 (Δ +0.2 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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 $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.28; H, 8.97.

(*E*)-7-(*t*-Butyldiphenylsilyloxy)-5-methylhept-5-enal (249)



249

Oxalyl chloride (30 μL, 0.36 mmol, 2.0 equiv.) and DMSO (40 μL, 0.54 mmol, 3.0 equiv.) were stirred in CH_2Cl_2 (1.2 mL) at –78 °C for 30 min. Alcohol **248** (70 mg, 0.18 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL) was added dropwise and the resulting solution stirred for 1 h. Et_3N (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_2O (2 mL), extracted with Et_2O (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);

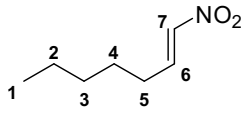
IR (neat) ν_{max} 2931 (m, **C-H**), 2857 (m, **C-H**), 1673 (sh., **C=O**), 1428 (sh.), 1107 (sh.) cm^{-1};

HRMS (CI) calc. for $C_{24}H_{36}NO_2Si$ $[M+NH_4]^+$: requires 398.2515, found 398.2529 (Δ +3.5 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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**).

(*E*)-1-Nitrohept-1-ene (253)



253

Based on a procedure by Vergari *et al*.[140] Hexanal (0.50 mL, 4.16 mmol, 1.0 equiv.) was stirred in CH_2Cl_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_2O : pentane) to afford (*E*)-1-nitrohept-1-ene (**253**)[201] (400 mg, 50%) as a yellow oil:

R_f 0.85 (1 : 9 Et_2O : pentane);

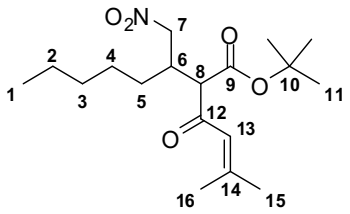
IR (neat) ν_{max} 2958 (m, **C-H**), 2931 (m, **C-H**), 2861 (w, **C-H**), 1649 (w, **C=C**), 1523 (s, **N-O**), 1350 (s, **N-O**) cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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**);

^{13}C NMR ($CDCl_3$, 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 $C_7H_{13}NO_2$: 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)



252

Keto *t*-butylester **200** (270 mg, 1.86 mmol, 1.0 equiv.) was added into a stirring solution of KO*t*-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 NH_4Cl (50 mL) and extracted with Et_2O (2 x 50 mL). The organics were combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 Et_2O : pentane) to afford nitro-ketoester **252** (560 mg, 88%) as a pale yellow oil (*mixture of diastereoisomers in a 1 : 1 ratio*):

R_f 0.70 (1 : 9 Et_2O : pentane);

IR (neat) ν_{max} 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 $C_{18}H_{31}NO_5Na$ $[M+Na]^+$: requires 364.2100, found 364.2098 (Δ –0.5 ppm);

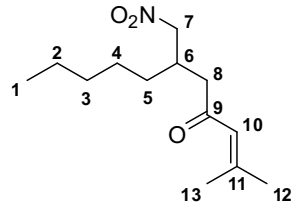
^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.17 (app. t, *J* = 1.0 Hz, 0.5H, **13**), 6.15 (app. t, *J* = 1.0 Hz, 0.5H, **13**), 4.68-4.61 (m, 0.5H, **7**), 4.55-4.51 (m, 0.5H, **7**), 3.62 (d, *J* = 5.0 Hz, 0.5H, **8**), 3.58 (d, *J* = 5.0 Hz, 0.5H, **8**), 2.87-2.81 (m, 1H, **6**), 2.17 (d, *J* = 0.5 Hz, 1.5H, **16**), 2.16 (d, *J* = 0.5

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**);

^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{31}NO_5$: 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)



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 Et_2O : pentane) to afford nitro-ketone **257** (125 mg, 72%) as a colourless oil:

R_f 0.65 (1 : 9 Et_2O : pentane);

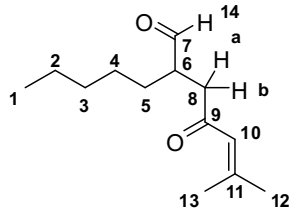
IR (neat) ν_{max} 2930 (m, **C-H**), 2860 (w, **C-H**), 1686 (sh., **C=O**), 1618 (sh., **C=C**), 1547 (s, **N-O**), 1439 (w), 1379 (m, **N-O**), 1125 (w), 1038 (w), 1100 (w) cm^{-1};

HRMS (ESI) calc. for $C_{13}H_{24}NO_3$: requires 242.1756, found 242.1766 (Δ +4.1 ppm);

^{1}H NMR ($CDCl_3$, 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**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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)



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_2O 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_2O (2 x 10 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 Et_2O : pentane) to afford aldehyde **258** (10 mg, 71%) as a clear gum:

R_f 0.55 (1 : 9 Et_2O : pentane);

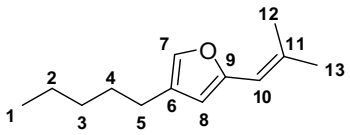
IR (neat) ν_{max} 2930 (s, **C-H**), 2858 (m, **C-H**), 1726 (w, **C=O**), 1687 (s, **C=O**), 1622 (s, **C=C**), 1445 (m), 1379 (w), 1114 (m), 1074 (m) cm^{-1};

HRMS (EI) calc. for $C_{13}H_{22}O_2$: requires 210.1620, found 210.1622 (Δ +1.0 ppm);

^{1}H NMR (500 MHz, $CDCl_3$) δ 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) δ 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)



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_4OAc (2.68 g, 35.0 mmol, 25.0 equiv.) in H_2O (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_2O (2 x 10 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 8 Et_2O : 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_2O : pentane);

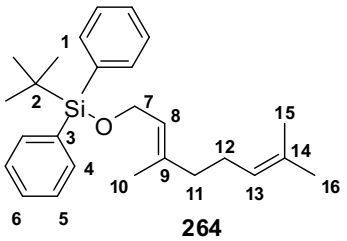
IR (neat) ν_{max} 2928 (w, **C-H**), 2858 (w, **C-H**), 1720 (s, **C=O** (furan)), 1376 (m), 1142 (m) cm^{-1};

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**).

(*E*)-*t*-Butyl(3,7-dimethylocta-2,6-dienyloxy)diphenylsilane (264)



264

Geraniol (**265**) (2.70 g, 17.3 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (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 H_2O (100 mL), extracted with CH_2Cl_2 (2 x 100 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 to 2 : 8 EtOAc : hexanes) to afford silylether **264**[202] (6.0 g, 88%) as a colourless oil:

R_f 0.8 (2 : 8 EtOAc : hexanes);

IR (neat) ν_{max} 2960 (w, **C-H**), 2930 (m, **C-H**), 2857 (m, **C-H**), 1473 (w), 1428 (sh.), 1379 (w), 1110 (s), 1056 (sh.) cm^{-1};

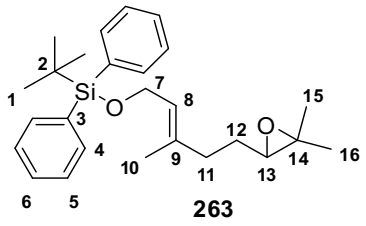
HRMS (CI) calc. for $C_{26}H_{40}NO_2Si$ $[M+NH_4]^+$: requires 426.2828, found 426.2842 (Δ +3.3 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71-7.68 (m, 4H, **5**), 7.44-7.35 (m, 6H, **4** & **6**), 5.40-5.36 (m, 1H, **8**), 5.12-5.08 (m, 1H, **13**), 4.22 (d, *J* = 8.0 Hz, 2H, **7**), 2.09-1.96 (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**);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 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**);

Anal. Calc. for $C_{26}H_{36}OSi$: C, 79.53; H, 9.24. Found: C, 74.07; H, 8.76.

(*E*)-*t*-Butyl(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enyloxy)diphenylsilane (263)



263

Based on a procedure by Tago *et al.*[153] Olefin **264** (5.20 g, 13.2 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (50 mL) at 0 °C. *m*-CPBA (3.60 g, 15.8 mmol, 1.2 equiv.) in CH_2Cl_2 (50 mL) was added dropwise and the reaction mixture stirred for 2 h. The mixture was filtered and $Ca(OH)_2$ (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_2O : pentane) to afford epoxide **263**[202] (4.0 g, 75%) as a colourless oil:

R_f 0.65 (3 : 7 Et_2O : pentane);

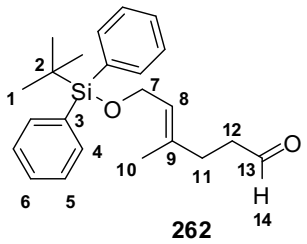
IR (neat) ν_{max} 2931 (m, **C-H**), 2959 (m, **C-H**), 2857 (m, **C-H**), 1473 (w), 1428 (sh.), 1378 (w), 1112 (s), 1057 (m) cm^{-1};

HRMS (ESI) calc. for $C_{26}H_{36}O_2NaSi$ $[M+Na]^+$: requires 431.2382, found 431.2369 (Δ –3.0 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 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**);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 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**).

(*E*)-6-(*t*-Butyldiphenylsilyloxy)-4-methylhex-4-enal (262)



262

Based on a procedure by Tago *et al.*[153] Epoxide **263** (4.0 g, 9.8 mmol, 1.0 equiv.) was stirred in THF (32 mL). H_5IO_6 (4.14 g, 19.5 mmol, 2.0 equiv.) in H_2O (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 $NaHCO_3$ (50 mL), extracted with Et_2O (2 x 200 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (3 : 7 Et_2O : pentane) to afford aldehyde **262**[202] (2.0 g, 60%) as a colourless oil:

R_f 0.60 (3 : 7 Et_2O : pentane);

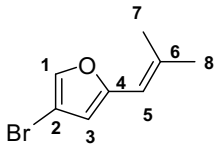
IR (neat) ν_{max} 2931 (m, **C-H**), 2857 (m, **C-H**), 1722 (w, **C=O**), 1472 (w), 1428 (sh.), 1390 (w), 1111 (s), 1069 (m) cm^{-1};

MS (CI) $[M+NH_4]^+$: requires 340, found 340; $[M+H]^+$: requires 323, found 323;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 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)



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 NH_4Cl (20 mL), extracted with Et_2O (2 x 20 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 19 Et_2O : pentane) to afford olefin **261**[107] (12 mg, 20%) as a colourless oil:

R_f 0.90 (1 : 9 Et_2O : pentane);

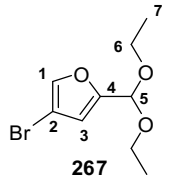
IR (neat) ν_{max} 2971 (m, **C-H**), 2870 (w, **C-H**), 1738 (m, **C-O** (furan)), 1365 (m), 1227 (m), 1143 (sh.), 1002 (sh.) cm^{-1};

HRMS (CI) calc. for $C_8H_{10}OBr$ $[M+H]^+$: requires 200.9915, found 200.9907 (Δ –4.0 ppm);

^{1}H NMR ($CDCl_3$, 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**);

^{13}C NMR ($CDCl_3$, 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**).

4-Bromo-2-(diethoxymethyl)furan (267)



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 NH_4NO_3 (3 mg, 32 μmol, 5 mol%.) and $HC(OEt_3)$ (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 Et_2O (50 mL). The organics were combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 49 Et_2O : pentane) to afford 4-bromo-2-(diethoxymethyl)furan (**267**)[107] (120 mg, 77%) as a pale yellow oil:

R_f 0.90 (1 : 9 Et_2O : pentane);

IR (neat) ν_{max} 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};

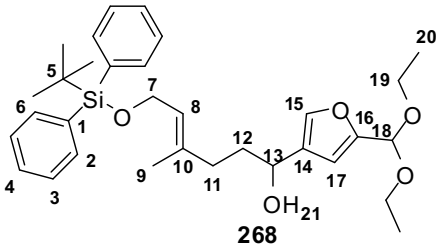
HRMS (EI) calc. for $C_9H_{13}O_3Br$ $[M+H]^+$: requires 248.0048, found 248.0041 (Δ –2.8 ppm);

^{1}H NMR ($CDCl_3$, 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**);

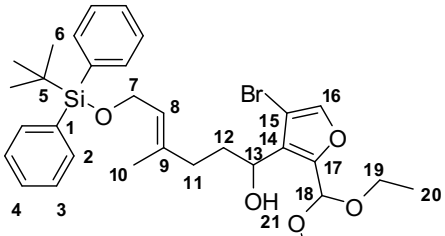
^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8 (**4**), 140.5 (**1**), 111.6 (**3**), 100.0 (**2**), 95.8 (**5**), 61.4 (2C, **6**), 15.1 (2C, **7**);

Anal. Calc. for $C_9H_{13}O_3Br$: requires C, 43.39; H, 5.26. Found, C 43.46; H, 5.18.

(*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)



268



269

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 NH_4Cl (40 mL), extracted with Et_2O (2 x 30 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 Et_2O : 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 Et_2O : pentane);

IR (neat) ν_{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) cm^{-1};

HRMS (ESI) calc. for $C_{32}H_{44}O_5NaSi$ $[M+Na]^+$: requires 559.2856, found 559.2863 (Δ +1.3 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70-7.67 (m, 4H, **3**), 7.43-7.36 (m, 6H, **2** & **4**), 6.44 (d, J = 0.5 Hz, 1H, **15**), 5.48 (d, J = 5.0 Hz, 1H, **17**), 5.41-5.39 (m, 1H, **8**), 4.76-4.72 (m, 1H, **21**),

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_2O : pentane);

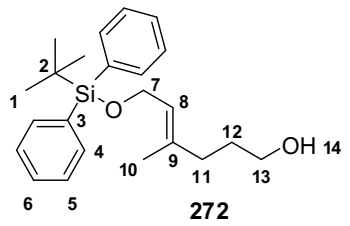
IR (neat) ν_{max} 2970 (m, **C-H**), 2930 (m, **C-H**), 2857 (w, **C-H**), 1738 (s, **C-O** (furan)), 1428 (w), 1366 (m), 1217 (sh.), 1110 (sh.), 1047 (m) cm^{-1};

HRMS (ESI) calc. for $C_{32}H_{43}O_5NaBrSi$ $[M+Na]^+$: 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**), 2.17-2.00 (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**).

(*E*)-6-(*t*-Butyldiphenylsilyloxy)-4-methylhex-4-en-1-ol (272)



272

Based on a procedure by Tago *et al.*[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_2O : pentane) to afford alcohol **272** (1.3 g, 81%) as a colourless oil:

R_f 0.55 (2 : 1 Et_2O : pentane);

IR (neat) ν_{max} 3343 (br., **O-H**), 2931 (m, **C-H**), 2857 (m, **C-H**), 1473 (sh.), 1428 (sh.), 1112 (sh.), 1052 (s) cm^{-1};

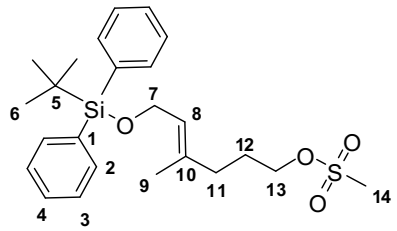
HRMS (ESI) calc. for $C_{23}H_{36}NO_2Si$ $[M+NH_4]^+$: requires 386.2515, found 386.2517 (Δ +0.5 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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 $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 74.87; H, 8.75.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-4-enyl methanesulfonate 320



320

Based on a procedure by Joullié *et al*.[107] Alcohol **272** (1.6 g, 4.3 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (25 mL) at 0 °C. Et_3N (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_4Cl (100 mL), extracted with Et_2O (2 x 100 mL), the organics combined, washed with brine (100 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 Et_2O : pentane) to afford mesylate **320** (1.5 g, 80%) as a colourless oil:

R_f 0.5 (1 : 1 Et_2O: pentane);

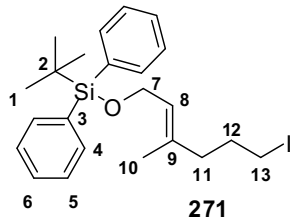
IR (neat) ν_{max} 2931 (w, **C-H**), 2857 (w, **C-H**), 1428 (w), 1355 (m), 1173 (m), 1111 (sh.), 1051 (m) cm^{-1};

HRMS (ESI) calc. for $C_{24}H_{34}O_4NaSiS$ $[M+Na]^+$: requires 469.1845, found 469.1837 (Δ –0.2 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 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**);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 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**).

(E)-*t*-Butyl(6-iodo-3-methylhex-2-enyloxy)diphenylsilane (271)



271

Based on a procedure by Joullé *et al.*[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 $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$ (100 mL), extracted with Et_2O (2 x 100 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 99 Et_2O : pentane) to afford iodide **271** (1.15 g, 70%) as a colourless oil.

R_f 0.90 (1 : 9 Et_2O : pentane);

IR (neat) ν_{max} 2930 (m, **C-H**), 2856 (m, **C-H**), 1427 (sh.), 1388 (w), 1217 (w), 1110 (s), 1051 (m) cm^{-1};

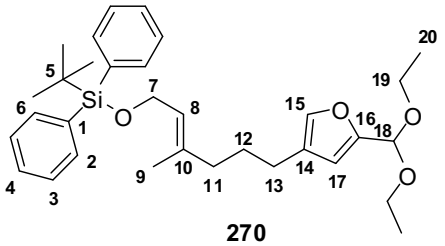
HRMS (CI) calc. for $C_{23}H_{35}NOSiI$ $[M+NH_4]^+$: requires 496.1533, found 496.1542 (Δ +1.8 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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, 2 H, **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**);

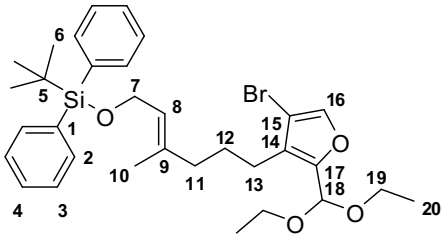
^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.6 (**9**), 134.9 (2C, **10**), 133.9 (4C, **4**), 129.5 (2C, **6**), 127.6 (4C, **5**), 125.4 (**8**), 61.0 (**7**), 39.8 (**11**), 31.3 (**12**), 26.8 (3C, **1**), 19.1 (**2**), 16.1 (**10**), 6.4 (**13**);

Anal. Calc. for $C_{23}H_{31}ISiO$: C, 57.73; H, 6.53. Found: C, 57.85; H, 6.62.

(*E*)-*t*-Butyl(6-(5-(diethoxymethyl)furan-3-yl)-3-methylhex-2-enyloxy)diphenylsilane (270) and (*E*)-(6-(4-bromo-2-(diethoxymethyl)furan-3-yl)-3-methylhex-2-enyloxy)(*t*-butyl)diphenylsilane (273)



270



273

Based on a procedure by Joullié *et al.*[107] 4-Bromo-2-(diethoxymethyl)furan (**267**) (270 mg, 1.09 mmol, 2.0 equiv.) was stirred in THF (4 mL) at –78 °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_4Cl (50 mL), extracted with Et_2O (2 x 50 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 29 to 3 : 27 Et_2O : 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 Et_2O : pentane);

IR (neat) ν_{max} 2930 (w, **C-H**), 2857 (w, **C-H**), 1683 (w), 1461 (w), 1427 (w), 1361 (w), 1109 (sh.), 1051 (sh.), 1005 (m) cm^{-1};

HRMS (ESI) calc. for $C_{32}H_{44}O_5NaSi$ $[M+Na]^+$: requires 559.2856, found 599.2856 (Δ 0.0 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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_2O : pentane);

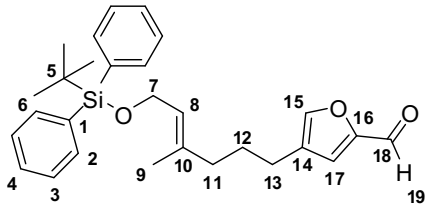
IR (neat) ν_{max} 2930 (w, **C-H**), 2856(w, **C-H**), 1684 (m, **C=O** (furan)), 1518 (w), 1427 (w), 1283 (w), 1109 (m), 1057 (m) cm^{-1};

HRMS (ESI) $C_{32}H_{43}O_4NaSiBr$ $[M+Na]^+$: requires 621.2012, found 621.2013 (Δ +0.2 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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)



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 $NaHCO_3$ (10 mL), extracted with Et_2O (2 x 10 mL), dried ($MgSO_4$) and rotary evaporated to afford aldehyde **274** (141 mg, 89%) as a colourless oil:

$\mathbf{R}_f$ 0.40 (2 : 9 Et_2O : pentane);

IR (neat) ν_{max} 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 $C_{28}H_{38}NO_3Si$ $[M+NH_4]^+$: requires 464.2621, found 464.2638 (Δ +3.7 ppm);

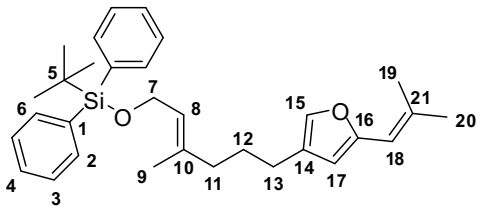
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.60 (s, 1H, **19**), 7.70-7.68 (m, 4H, **3**), 7.45 (s, 1H, **15**) 7.42-7.35 (m, 6H, **2** & **4**), 7.11 (s, 1H, **17**), 5.39-5.36 (m, 1H, **8**), 4.24 (d, *J* = 6.0 Hz, 2H, **7**), 2.42 (t, *J* = 7.0 Hz, 2H, **13**), 2.01 (t, *J* = 7.0 Hz, 2H, **11**), 1.67 (quin. *J* = 7.0 Hz, 2H, **12**), 1.44 (s, 3H, **9**), 1.05 (s, 9H, **6**);

^{13}C NMR ($CDCl_3$, 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 NH_4Cl (20 mL), extracted with Et_2O (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*-Butyl(3-methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-enyloxy)diphenylsilane (259)



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_4Cl (20 mL), extracted with Et_2O (2 x 40 mL), the organics combined, washed with brine (30 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 98 Et_2O : pentane) to afford olefin **259** (120 mg, 70%) as a colourless oil:

R_f 0.95 (1:9 Et_2O : pentane);

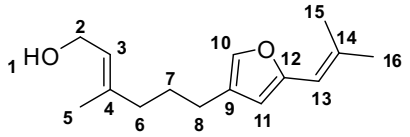
IR (neat) ν_{max} 2930 (m, **C-H**), 2856 (m, **C-H**), 1472 (w), 1428 (w), 1261 (w), 1111 (sh.), 1059 (m) $cm^{-1;}$

HRMS (CI) calc. for $C_{31}H_{41}O_2Si$ $[M+H]^+$: requires 473.2876, found 473.2874 (Δ –0.4 ppm);

^{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)



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_2O, the organics combined, washed with brine (10 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 Et_2O : pentane) to afford alcohol **275** (25 mg, 81%) as a colourless gum:

R_f 0.42 (1 : 1 Et_2O : pentane);

IR (neat) ν_{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};

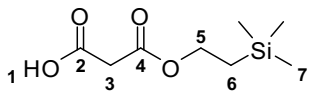
HRMS (EI) calc. for $C_{15}H_{22}O_2$ $[M+H]^+$: requires 234.1620, found 234.1635 (Δ +6.4 ppm);

^{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-

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) δ 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)



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 $NaHCO_3$ (200ml) and the resulting solution stirred for 8 h at rt. The reaction mixture was extracted with Et_2O : 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_2O : pentane);

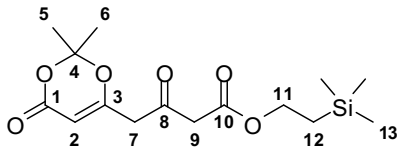
IR (neat) ν_{max} 2954 (m, **C-H**), 1736 (s, **C=O**), 1380 (w), 1322 (w), 1249 (m), 1217 (w), 1151 (m) cm^{-1};

HRMS (EI) calc. for $C_8H_{16}O_4Si$ $[M+H]^+$: requires 204.0818, found 204.0826 (Δ +3.9 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 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) δ 167.8 (**2**), 166.9 (**4**), 64.7 (**5**), 40.3 (**3**), 17.2 (**6**), –1.6 (3C, **7**).

2-(Trimethylsilyl)ethyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (278)



278

Based on a procedure by Navarro *et al.*[82] Carboxylic acid **281** (3.0 g, 14.4 mmol, 1.0 equiv.) was stirred in CH_2Cl_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_4Cl (20 mL), acidified to pH 2 using 1 M HCl, extracted with Et_2O (2 x 300 mL), the organics combined, washed with brine (200 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 8 to 1 : 1 Et_2O : pentane) to afford ketoester-dioxinone **278** (2.6 g, 55%) as a yellow oil:

R_f 0.45 (1 : 1 Et_2O : pentane);

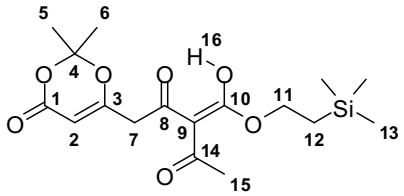
IR (neat) ν_{max} 2954 (w, **C-H**), 1719 (s, **C=O**), 1638 (m, **C=C**), 1390 (m), 1375 (m), 1319 (m), 1271 (m), 1249 (m), 1201 (m), 1176 (sh.), 1015 (sh.) cm^{-1};

HRMS (ESI) calc. for $C_{15}H_{23}O_6Si$ $[M+H]^+$: requires 327.1264, found 327.1287 (Δ +7.0 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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**).

2-(Trimethylsilyl)ethyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (276)



276

Based on a procedure by Navarro *et al.*[82] Ketoester-dioxinone **278** (470 mg, 1.41 mmol, 1.0 equiv.) in CH_2Cl_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_2Cl_2 (7 mL) at 0 °C for 20 min. Acetyl chloride (150 µL, 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_4Cl (50 mL), extracted with Et_2O (2 x 50 mL), dried ($MgSO_4$), rotary evaporated, chromatographed (1 : 1 : 4 CH_2Cl_2 : EtOAc : pentane) to afford diketo-ester-dioxinone **276** (402 mg, 77%) as a yellow oil:

R_f 0.65 (1 : 1 Et_2O : pentane);

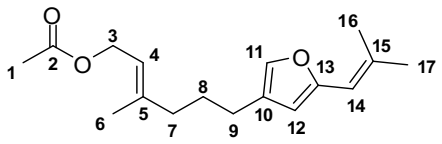
IR (neat) ν_{max} 2954 (w, **C-H**), 1730 (s, **C=O**), 1639 (m, **C=C**), 1391 (m), 1376 (m), 1272 (m), 1250 (m), 1204 (w), 1071 (w), 1016 (w) cm^{-1};

HRMS (CI) calc. for $C_{17}H_{27}O_7Si$ $[M+H]^+$: 388.1792, found 388.1798 (Δ +1.5 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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)



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_2CO_3 (36 mg, 0.26 mmol, 2.0 equiv.), 1 micro stapula head tip of DMAP and Ac_2O (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_2O : pentane) to afford acetate **277** (20 mg, 60%) as a clear gum:

R_f 0.52 (2 : 8 Et_2O : pentane);

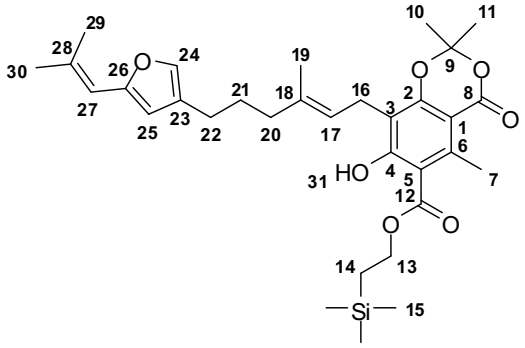
IR (neat) ν_{max} 2938 (w, **C-H**), 1736 (s, **C=O**), 1442 (w), 1382 (w), 1233 (m), 1166 (w), 1023 (m) cm^{-1};

HRMS (EI) calc. for $C_{17}H_{24}O_3$ $[M+H]^+$: requires 276.1725, found 276.1739 (Δ +5.1 ppm);

^{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-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (283)



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_4Cl (50 mL), extracted with Et_2O (2 x 50 mL), the organics combined, washed with brine (20 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 8 Et_2O : pentane) to afford furan-resorcylate **283** (89 mg, 65%) as a colourless oil:

R_f 0.70 (3 : 7 Et_2O : pentane);

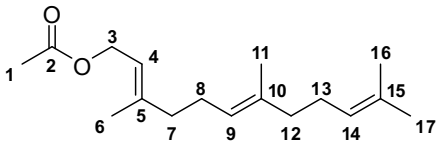
IR (neat) ν_{max} 2933 (m, **C-H**), 1733 (sh., **C=O**), 1653 (sh., **C=C**), 1584 (sh., **C-C**), 1448 (w), 1387 (w), 1265 (sh.), 1234 (sh.), 1173 (w), 1031 (w) cm^{-1};

HRMS (CI) calc. for $C_{32}H_{45}O_7Si$ $[M+H]^+$: requires 425.2328, found 425.2319 (Δ –2.1 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 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) δ 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**).

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyl acetate (284)



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_2CO_3 (1.24 g, 9.0 mmol, 2.0 equiv.), 1 micro spatula head tip of DMAP (cat.) and Ac_2O (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_2O : pentane);

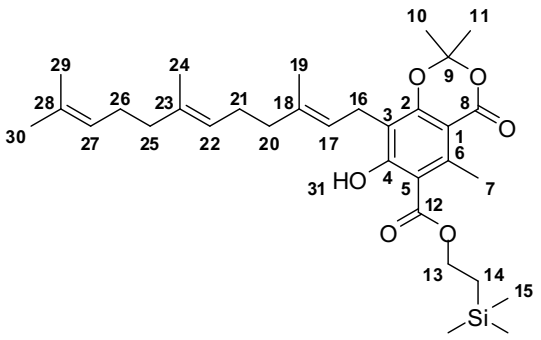
IR (neat) ν_{max} 2970 (m, **C-H**), 2924 (m, **C-H**), 1740 (s, **C=O**), 1441 (w), 1365 (m), 1228 (s), 1021 (w), 954 (w) cm^{-1};

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) δ 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) δ 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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (285)



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_4Cl (50 mL), extracted with Et_2O (2 x 50 mL), the organics combined, washed with brine (20 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 8 Et_2O : pentane) to afford silylester-farnesyl-resorcylate **285** (150 mg, 60%) as a colourless oil:

R_f 0.65 (2 : 8 Et_2O : pentane);

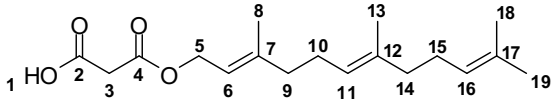
IR (neat) ν_{max} 2917 (w, **C-H**), 1731 (m, **C=O**), 1654 (sh., **C=C**), 1584 (sh., **C-C**), 1448 (w), 1387 (w), 1298 (m), 1265 (m), 1235 (m), 1172 (w), 1033 (w) cm^{-1};

HRMS (ESI) calc. for $C_{32}H_{47}O_6Si$ $[M+H]^+$: requires 555.3142, found 555.3119 (Δ –4.1 ppm);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.88 (s, 1H, **31**), 5.15 (t, *J* = 7.0 Hz, 1H, **17**), 5.08-5.05 (m, 2H, **22** & **27**), 4.49-4.45 (m, 2H, **13**), 3.31 (d, *J* = 7.0 Hz, 2H, **16**), 2.88 (s, 3H, **7**), 2.07-1.91 (m, 8H, **20**, **21**, **25**, **26**), 1.77 (s, 3H, **19**), 1.69 (s, 6H, **24** & **30**), 1.66 (s, 3H, **29**), 1.57 (s, 3H, **10** / **11**), 1.56 (s, 3H, **10** / **11**), 1.19-1.16 (m, 2H, **14**), 0.05 (s, 9H, **15**);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6 (**12**), 164.6 (**8**), 160.2 (**2**), 158.0 (**4**), 146.6 (**6**), 135.8 (**18**), 135.0 (**23**), 131.2 (**28**), 124.3 (**22**), 124.0 (**27**), 121.0 (**17**), 115.4 (**3**), 110.8 (**5**), 106.4 (**1**), 104.5 (**9**), 64.7 (**13**), 39.7 (2C, **20** & **25**), 26.6 (2C, **21** & **26**), 25.7 (3C, **10**, **11** & **30**), 21.8 (**16**), 20.2 (**29**), 17.6 (**14**), 17.5 (**7**), 16.1 (2C, **19** & **24**), -1.6 (3C, **15**).

3-Oxo-3-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)propanoic acid (295)



295

Based on a procedure by Tararov *et al.*[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 $NaHCO_3$ (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 ($MgSO_4$) and rotary evaporated to afford carboxylic acid **295**[204] (11.0 g, 81%) as a colourless oil:

R_f 0.2 (1 : 9 MeOH : CH_2Cl_2);

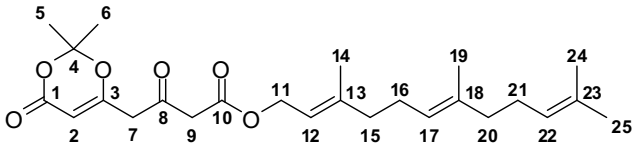
IR (neat) ν_{max} 3521 (br., **O-H**), 2922 (m, **C-H**), 1719 (s, **C=O**), 1382 (m), 1151 (s) cm^{-1};

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) δ 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) δ 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-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (293)



293

Based on a procedure by Navarro *et al*.[82] Acid **295** (4.0 g, 13 mmol, 1.0 equiv.) was stirred in CH_2Cl_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

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 NH_4Cl (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_2O) to afford keto-farnesylester-dioxinone **293** (1.09 g, 65%) as a yellow oil:

R_f 0.35 (1 : 2 hexanes : Et_2O);

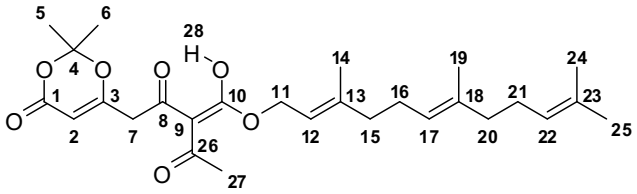
IR (neat) ν_{max} 2917 (w, **C-H**), 1722 (sh., **C=O**), 1638 (m, **C=C**), 1374 (m), 1271 (sh.), 1203 (sh.), 1015 (sh.) cm^{-1};

HRMS (EI) calc. for $C_{25}H_{36}O_6$ $[M+H]^+$: requires 432.2512, found 432.2518 (Δ +1.4 ppm);

^{1}H NMR ($CDCl_3$, 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**);

^{13}C NMR ($CDCl_3$, 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**),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**).

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (292)



292

Based on a procedure by Navarro *et al*.[82] Keto-farnesylester-dioxinone **293** (2.0 g, 4.6 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added to a solution of $MgCl_2$ (1.10 g, 11.5 mmol, 2.5 equiv.) and pyridine (1.0 mL, 12.5 mmol, 2.7 equiv.) in CH_2Cl_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_4Cl (100 mL), extracted with Et_2O (2 x 100 mL), the organics combined, dried ($MgSO_4$) and rotary evaporated to afford diketo-farnesylester-dioxinone **292** (2.1 g, 98%) as a yellow oil:

R_f 0.61 (7 : 3 Et_2O : pentane);

IR (neat) ν_{max} 3923 (w, **C-H**), 1729 (s, **C=O**), 1709 (s, **C=O**), 1638 (m, **C=C**), 1390 (m), 1374 (s), 1270 (sh.), 1203 (sh.), 1069 (m), 1014 (sh.) cm^{-1};

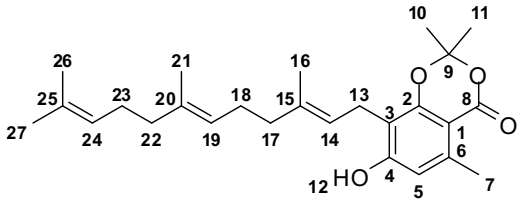
HRMS (ESI) calc. for $C_{27}H_{38}O_7Na$ $[M+Na]^+$: requires 497.2515, found 497.2516 (Δ +0.2 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 17.61 (s, 1H, **28**), 5.42 (t, 1H, *J* = 7.0 Hz, **12**), 5.36 (s, 1H, **2**), 5.11 (br. s, 2H, **17** & **22**), 4.77 (d, *J* = 7.0 Hz, 2H, **11**), 3.75 (s, 2H, **7**), 2.43 (s, 3H, **27**), 2.16-1.97 (m, 8H, **15**, **16**, **20** & **21**), 1.77 (s, 3H, **25**), 1.72 (s, 6H, **14** & **19**), 1.70 (s, 3H, **24**), 1.62 (s, 6H, **5** & **6**);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.8 (**26**), 193.5 (**8**), 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 (2C, **2** & **9**),

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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (286)



286

Diketo-farnesylester-dioxinone **292** (900 mg, 2.11 mmol, 1.0 equiv.) was stirred in THF (20 mL), $Pd(PPh_3)_4$ (244 mg, 0.21 mmol, 0.1 equiv.) and Cs_2CO_3 (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 NH_4Cl (100 mL), extracted with Et_2O (2 x 50 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (3 : 7 Et_2O : pentane) to afford farnesyl-resorcylate **286** (574 mg, 66%) as a pale yellow solid.

m.p. 180-184 °C (pentane);

R$_f$ 0.40 (1 : 1 Et_2O : pentane);

IR (neat) ν_{max} 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};

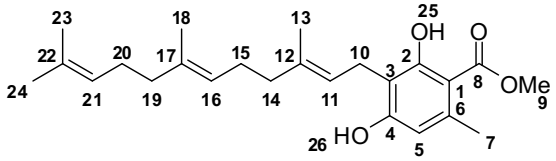
HRMS (ESI) calc. for $C_{26}H_{35}O_4$ $[M+H]^+$: requires 411.2542, found 411.2535 (Δ +1.7 ppm);

^{1}H NMR ($CDCl_3$, 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**,

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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)benzoate (300)



300

Diketo-farnesyl-resorcylate **286** (70 mg, 0.17 mmol, 1.0 equiv.) and Cs_2CO_3 (110 mg, 0.34 mmol, 2.0 equiv.) in MeOH (2 mL) were heated at 60 ^{o}C in a sealed tube for 72 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), extracted with Et_2O (2 x 10 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 1 Et_2O : pentane) to afford farnesyl-resorcylate **300** (68 mg, 94%) as a yellow oil:

R_f 0.66 (7 : 3 Et_2O : pentane);

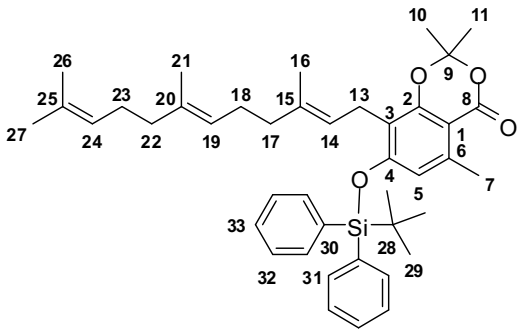
IR (neat) ν_{max} 3408 (br., **O-H**), 2916 (m, **C-H**), 2854 (m, **C-H**), 1649 (sh., **C=C**), 1618 (sh., **C=C**), 1438 (m), 1318 (m), 1270 (s), 1196 (m), 1155 (sh.) cm^{-1};

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**);

^{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*-Butyldiphenylsilyloxy)-2,2,5-trimethyl-8-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (301)



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_2Cl_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_4Cl (50 mL), extracted with Et_2O (2 x 50 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (1 : 9 Et_2O : pentane) to afford silylether **301** (360 mg, 88%) as a colourless oil:

R_f 0.70 (1 : 9 Et_2O : pentane);

IR (neat) ν_{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};

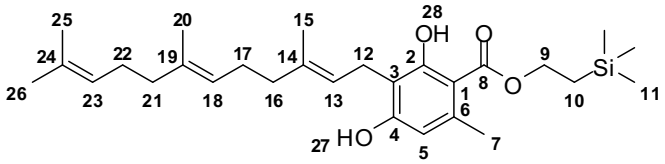
HRMS (ESI) calc. for $C_{42}H_{55}O_4Si$ $[M+H]^+$: requires 651.3870, found 651.3878 (Δ +1.2 ppm);

^{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**),

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**);

^{13}C NMR ($CDCl_3$, 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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)benzoate (303)



303

Isopropylidene protected resorcylate **286** (16 mg, 40 μmol, 1.0 equiv.) and Cs_2CO_3 (25 mg, 76 μmol, 2.0 equiv.) were heated in a sealed tube with $HOCH_2CH_2OTMS$ **280** (0.5 mL) and THF (0.25 mL) for 18 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL), extracted with Et_2O (2 x 20 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (2 : 8 Et_2O : hexanes to Et_2O) to afford resorcylate **303** (19 mg, 75%) as a colourless oil:

R_f 0.85 (2 : 8 Et_2O : hexanes);

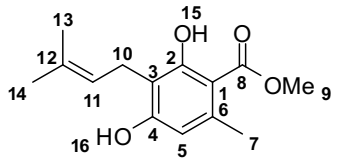
IR (neat) ν_{max} 3460 (w, **O-H**), 2970 (m, **C-H**), 2947 (m, **C-H**), 1738 (s, **C=O**), 1436 (w), 1366 (s), 1217 (s), 1206 (m) cm^{-1};

HRMS (ESI) calc. for $C_{28}H_{45}O_4Si$ $[M+H]^+$: requires 473.3087, found 473.3081 (Δ –1.3 ppm);

^{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)



308

Isopropylidene protected resorcylate **142** (50 mg, 0.17 mmol, 1.0 equiv.) and Cs_2CO_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_4Cl (20 mL), extracted with Et_2O (2 x 20 mL), the organics combined, dried ($MgSO_4$), rotary evaporated and chromatographed (3 : 7 Et_2O : hexanes) to afford methylester **308**[69] (38 mg, 90%) as a white solid:

m.p. 75 - 77 ^{o}C (pentane);

R_f 0.55 (1 : 1 Et_2O : hexanes);

IR (neat) ν_{max} 2988 (w, C-H), 1746 (m, C=O), 1372 (m), 1216 (sh.) cm^{-1};

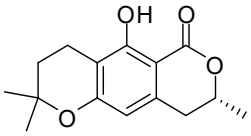
HRMS (CI) calc. for $C_{14}H_{19}O_4$ $[M+H]^+$: requires 251.1283, found 251.1287 (Δ +1.6 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 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) δ 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**).

6.3 Additional Experimental Procedures[XI]

(*R*)-5-Hydroxy-2,2,8-trimethyl-3,4,8,9-tetrahydropyrano[3,4-g]chromen-6(2*H*)-one (122)[XII]



122

H_2SiF_6 in H_2O (20% w/w; 50 µL, 80 µmol, 4.0 equiv.) was added with stirring to a solution of resorcylate **109** (10 mg, 20 µmol, 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 $NaHCO_3$ (20 mL). The mixture was extracted with Et_2O (3 x 25 mL), dried ($MgSO_4$), concentrated by rotary evaporation and chromatographed (3 : 1 hexanes : Et_2O) to afford tricyclic resorcylate **122** (3 mg, 51%) as a colourless solid:

R_f 0.49 (3 : 1 hexanes : Et_2O);

$[\alpha]_D^{25}$ = +33.00 (*c* 0.2, $CHCl_3$);

IR (neat) ν_{max} 3432 (**O-H**), 2925 (**C-H**), 1659 (**C=C**), 1634 (**C=C**), 1584 (**C-C**), 1434, 1370, 1311, 1253, 1235, 1157, 1118, 1041 cm^{-1};

HRMS (ESI) calc. for $C_{15}H_{19}O_4$ $[M + H]^+$: requires 263.1283; found 263.1294;

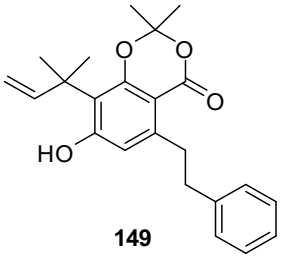
[XI]The additional experimental procedures were carried out by colleagues within the Barrett group. They have been added into this thesis for clarity and to aid the reader. Each experiment is clearly labelled with the name of the person that conducted it. These colleagues are duly thanked for their contribution to this research.

[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.

^{1}H NMR (400 MHz,CDCl3) δ 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);

^{13}C NMR (100 MHz, $CDCl_3$) δ 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-4*H*benzo[*d*][1,3]dioxin-4-one (149)[XIII]



149

Diketo-dioxinone **148** (50 mg, 0.13 mmol, 1.0 equiv.) and Cs_2CO_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_2O (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 ($MgSO_4$), 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) ν_{max} 3213 (**O-H**), 2986 (**C-H**), 1693 (**C=O**), 1684 (**C=C**), 1593 (**C-C**), 1497, 1400, 1298, 1209, 1070, 884 cm^{-1};

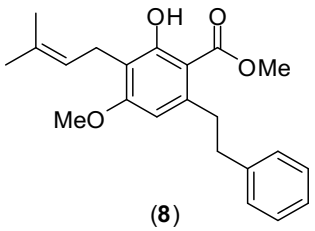
HRMS (ESI) calc. for $C_{23}H_{27}O_4$ $[M+H]^+$: requires 367.1904; found [M+H]+ 367.1896;

[XIII] This experiment was carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this research.

^{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]



(**8**)

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) ν_{max} 2867 (**C-H**), 1630 (**C=C**), 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;

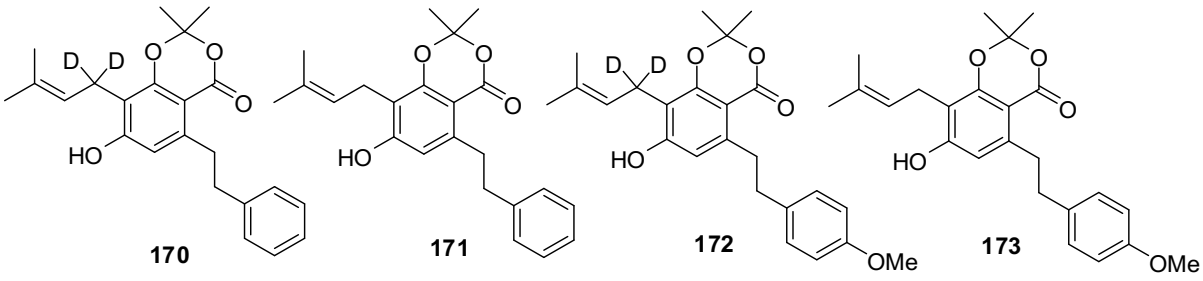
[XIV] This experiment was carried out by Dr Sylvain Laclef. He is duly thanked for his contribution to this research.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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-4*H*-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-4*H*-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)-4*H*-benzo[*d*][1,3]dioxin-4-one (172) and 7-hydroxy-5-(4-methoxyphenethyl)-2,2-dimethyl-8-(3-methylbut-2-enyl)-4*H*-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 μmol, 5 mol%) and Cs_2CO_3 (42 mg, 0.13 mmol, 3.0 equiv.) in THF (2 mL) at 0 °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_4Cl (10 mL) and extracted with Et_2O (2 x 10 mL). The organics were combined, dried ($MgSO_4$) and rotary evaporated. The crude

[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 ^{o}C (hexanes);

$\mathbf{R}_f$ 0.81 (3 : 1 EtOAc : hexanes);

IR (neat) v_{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 $C_{23}H_{24}D_2O_4$, 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);

^{1}H NMR ($CDCl_3$, 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);

^{13}C NMR ($CDCl_3$, 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 ^{o}C (pentane);

$\mathbf{R}_f$ 0.43 (2 : 8 EtOAc : hexanes);

IR (neat) v_{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};

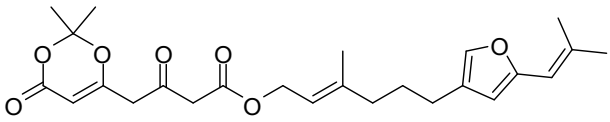
172: **HRMS** (ESI) cal. for $C_{24}H_{26}D_2O_5$, 399.2135, found 399.2131 (Δ = 1.0 ppm);

173: **HRMS** (ESI) cal. for $C_{24}H_{28}O_5$, 397.2015, found 397.1992 (Δ = 5.8 ppm);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 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): δ 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-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (195)[XVI]



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 °C. The reaction was allowed to warm to rt and stirred for 18 h. The reaction was quenched with H_2O (50 mL), extracted with Et_2O (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_2NH (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 °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 °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 °C and a solution of imidazole carboxylate **287** (280 mg, 0.85 mmol, 1.0 equiv.) in THF (3 mL) was added

[XVI] This experiment was carried out by Dr Nicolas George. He is duly thanked for his contribution to this research.

dropwise. The reaction was stirred at −78°C for 45 min and the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The solution was allowed to warm to rt, H_2O (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 Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), 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);

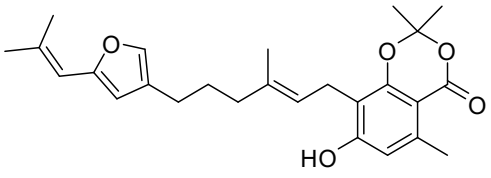
IR (neat) ν_{max} 2987 (**C-H**), 1722 (C=O), 1639 (C=C), 1390, 1375, 1272, 1253, 1203, 1016 cm^{-1};

HRMS (ES) calc. for $C_{25}H_{33}O_7$ $[M + H]^+$: requires 445.2226; found 445.2229;

^{1}H NMR ($CDCl_3$, 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);

^{13}C NMR ($CDCl_3$, 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)-4*H*-benzo[*d*][1,3]dioxin-4-one (193)[XVII]



193

To a solution of the ketoester-dioxinone **195** (192 mg, 0.43 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added $MgCl_2$ (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_4Cl (25 mL), extracted with CH_2Cl_2 (3 × 25 mL), the organics combined, washed with brine (30 mL), dried ($MgSO_4$) 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, $Pd(PPh_3)_4$ (24 mg, 22 μmol, 5 mol%) was added and the resultant solution was stirred at rt for 70 h. Cs_2CO_3 (420 mg, 1.29 mmol, 3.0 equiv.) was added and the reaction stirred for 15 h. The reaction was quenched with H_2O (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 ($MgSO_4$), 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 (7 : 3 hexanes : EtOAc);

[XVII] This experiment was carried out by Dr Nicolas George. He is duly thanked for his contribution to this research.

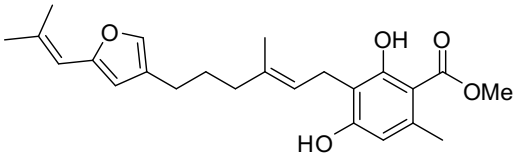
IR (neat) ν_{max} 2768 (**C-H**), 1692 (**C=O**), 1607 (**C=C**), 1592 (**C-C**), 1294, 1276, 1208, 1166, 1107, 1042, 908, 730 cm^{-1};

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) δ 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) δ 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.

Cristatic Acid Methyl Ester: (*E*)-Methyl 2,4-dihydroxy-6-methyl-3-(3-methyl-6-(5-(2-methylprop-1-enyl)furan-3-yl)hex-2-enyl)benzoate (183)[XVIII]



183

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 ($MgSO_4$), concentrated by rotary evaporation and chromatographed (6 : 1 hexanes : EtOAc) affording Cristatic cid methyl ester **183**[6] (7 mg, 64%) as a colourless oil:

R_f 0.42 (4 : 1 hexanes : EtOAc);

IR (neat) v_{max} 2865 (**C-H**), 1651 (**C=C**), 1620 (**C=C**), 1455, 1419, 1378, 1272, 1195, 808 cm^{-1};

HRMS (ES) calc. for $C_{24}H_{31}O_5[M+H]^+$: requires 399.2171; found: 399.2186 ;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 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}C NMR ($CDCl_3$, 100 MHz) δ 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.

6.4 X-Ray Date

*6.4.1 Triclyle **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

Published: Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. B. *Org. Lett.* **2011**, *13*, 5748-5750.

Table 22. Crystal data and structure refinement for 130

Identification code	**130**	
Formula	$C_{14}H_{14}O_6$	
Formula weight	278.25	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, P2(1)	
Unit cell dimensions	a = 7.72443(17) Å	α = 90°
	b = 8.2531(3) Å	β = 96.121(3)°
	c = 19.2848(7) Å	γ = 90°
Volume, Z	1222.41(7) $Å^3$, 4	
Density (calculated)	1.512 Mg/m^3	
Absorption coefficient	1.012 mm^{-1}	
F(000)	584	
Crystal colour / morphology	Colourless plates	
Crystal size	0.13 x 0.04 x 0.01 mm^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□(F)]	2902	
Absorption correction	Analytical	

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>4σ(F)]	R1 = 0.0531, wR2 = 0.0933
	R1+ = 0.0531, wR2+ = 0.0933
	R1- = 0.0532, wR2- = 0.0935
R indices (all data)	R1 = 0.1073, wR2 = 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

C(1A)-O(1A)	1.202(4)	C(11A)-C(12A)	1.504(4)
C(1A)-O(2A)	1.371(4)	C(11A)-C(18A)	1.519(5)
C(1A)-C(14A)	1.477(5)	C(12A)-C(13A)	1.501(5)
O(2A)-C(3A)	1.435(5)	C(13A)-C(14A)	1.401(5)
C(3A)-O(4A)	1.438(5)	C(1B)-O(1B)	1.214(4)
C(3A)-C(16A)	1.507(5)	C(1B)-O(2B)	1.361(4)
C(3A)-C(15A)	1.509(4)	C(1B)-C(14B)	1.464(5)
O(4A)-C(5A)	1.372(4)	O(2B)-C(3B)	1.447(4)
C(5A)-C(6A)	1.370(5)	C(3B)-O(4B)	1.436(4)
C(5A)-C(14A)	1.414(5)	C(3B)-C(16B)	1.508(5)
C(6A)-C(7A)	1.389(5)	C(3B)-C(15B)	1.513(4)
C(7A)-O(17A)	1.346(5)	O(4B)-C(5B)	1.363(4)
C(7A)-C(8A)	1.415(5)	C(5B)-C(6B)	1.388(6)
C(8A)-C(13A)	1.407(6)	C(5B)-C(14B)	1.409(5)
C(8A)-C(9A)	1.468(5)	C(6B)-C(7B)	1.376(5)
C(9A)-O(9A)	1.234(4)	C(7B)-O(17B)	1.351(5)
C(9A)-O(10A)	1.337(5)	C(7B)-C(8B)	1.416(5)
O(10A)-C(11A)	1.471(4)	C(8B)-C(13B)	1.395(5)

C(8B)-C(9B)	1.467(5)	C(9A)-O(10A)-C(11A)	117.7(3)
C(9B)-O(9B)	1.232(5)	O(10A)-C(11A)-C(12A)	111.1(3)
C(9B)-O(10B)	1.332(5)	O(10A)-C(11A)-C(18A)	105.6(3)
O(10B)-C(11B)	1.471(4)	C(12A)-C(11A)-C(18A)	112.8(3)
C(11B)-C(12B)	1.498(5)	C(13A)-C(12A)-C(11A)	111.9(3)
C(11B)-C(18B)	1.515(5)	C(14A)-C(13A)-C(8A)	118.9(4)
C(12B)-C(13B)	1.504(5)	C(14A)-C(13A)-C(12A)	123.9(4)
C(13B)-C(14B)	1.404(5)	C(8A)-C(13A)-C(12A)	117.0(3)
		C(13A)-C(14A)-C(5A)	118.7(4)
O(1A)-C(1A)-O(2A)	117.4(4)	C(13A)-C(14A)-C(1A)	122.4(4)
O(1A)-C(1A)-C(14A)	127.4(4)	C(5A)-C(14A)-C(1A)	118.8(3)
O(2A)-C(1A)-C(14A)	115.2(4)	O(1B)-C(1B)-O(2B)	116.7(4)
C(1A)-O(2A)-C(3A)	119.8(3)	O(1B)-C(1B)-C(14B)	126.9(3)
O(2A)-C(3A)-O(4A)	109.6(3)	O(2B)-C(1B)-C(14B)	116.3(4)
O(2A)-C(3A)-C(16A)	105.9(3)	C(1B)-O(2B)-C(3B)	118.7(3)
O(4A)-C(3A)-C(16A)	106.1(3)	O(4B)-C(3B)-O(2B)	109.3(3)
O(2A)-C(3A)-C(15A)	111.0(3)	O(4B)-C(3B)-C(16B)	107.2(3)
O(4A)-C(3A)-C(15A)	110.0(3)	O(2B)-C(3B)-C(16B)	105.8(3)
C(16A)-C(3A)-C(15A)	114.0(3)	O(4B)-C(3B)-C(15B)	110.9(3)
C(5A)-O(4A)-C(3A)	114.9(3)	O(2B)-C(3B)-C(15B)	110.4(3)
C(6A)-C(5A)-O(4A)	117.1(4)	C(16B)-C(3B)-C(15B)	113.0(3)
C(6A)-C(5A)-C(14A)	123.0(3)	C(5B)-O(4B)-C(3B)	115.4(3)
O(4A)-C(5A)-C(14A)	119.9(4)	O(4B)-C(5B)-C(6B)	116.2(4)
C(5A)-C(6A)-C(7A)	118.4(4)	O(4B)-C(5B)-C(14B)	121.3(4)
O(17A)-C(7A)-C(6A)	118.2(4)	C(6B)-C(5B)-C(14B)	122.4(3)
O(17A)-C(7A)-C(8A)	121.2(4)	C(7B)-C(6B)-C(5B)	118.7(4)
C(6A)-C(7A)-C(8A)	120.6(4)	O(17B)-C(7B)-C(6B)	117.9(4)
C(13A)-C(8A)-C(7A)	120.3(3)	O(17B)-C(7B)-C(8B)	121.5(4)
C(13A)-C(8A)-C(9A)	120.9(4)	C(6B)-C(7B)-C(8B)	120.6(4)
C(7A)-C(8A)-C(9A)	118.6(4)	C(13B)-C(8B)-C(7B)	120.2(4)
O(9A)-C(9A)-O(10A)	117.3(4)	C(13B)-C(8B)-C(9B)	121.5(4)
O(9A)-C(9A)-C(8A)	122.7(4)	C(7B)-C(8B)-C(9B)	118.3(4)
O(10A)-C(9A)-C(8A)	120.0(4)	O(9B)-C(9B)-O(10B)	117.3(4)

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

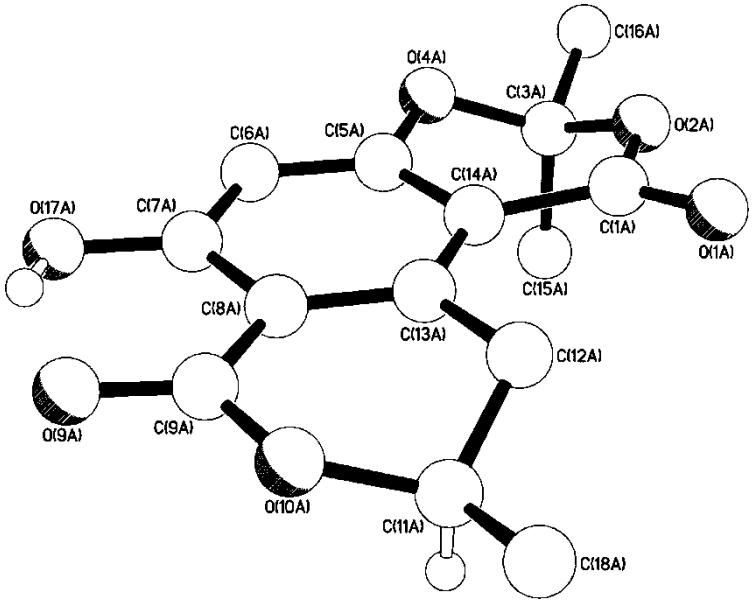
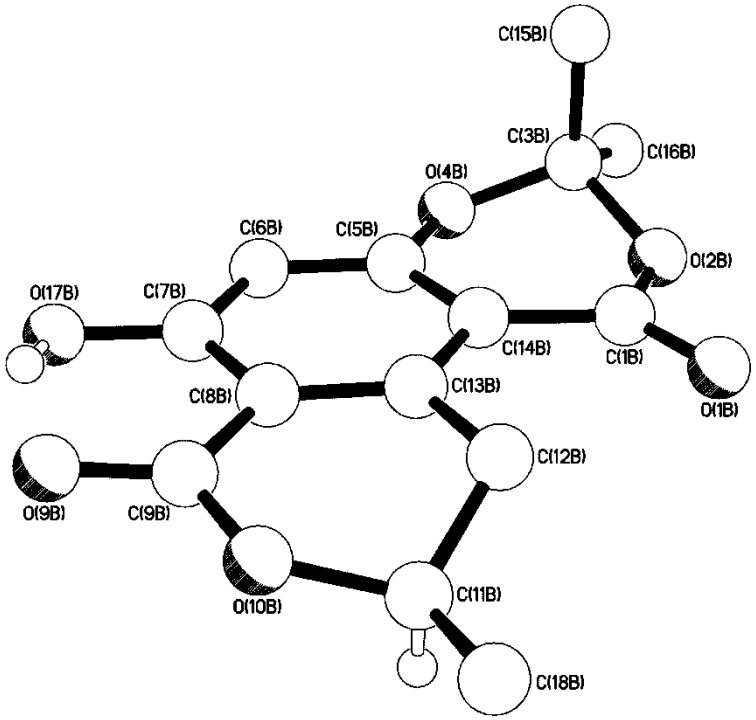


Figure 22: X-ray Crystal Structure Two of Tricycle 130



*6.4.2 Angelicoin A (**6**)*

((*R*)-6,8-Dihydroxy-3-methyl-7-(3-methylbut-2-enyl)isochroman-1-one) (**6**)

Cambridge CCDC code*:* SANSEH

Published: Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. B. *Org. Lett.* **2011**, *13*, 5748-5750.

Table 24. Crystal Data and Structure Refinement for 6

Identification code	**6**	
Formula	$C_{15}H_{18}O_4$	
Formula weight	262.29	
Temperature	173 K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, C2	
Unit cell dimensions	a = 10.00787(16) Å	α = 90°
	b = 26.3372(5) Å	β = 99.8553(16)°

	c = 10.8051(2) Å	γ = 90°
Volume, Z	2805.97(9) $Å^3$, 8	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.735 mm^{-1}	
F(000)	1120	
Crystal colour / morphology	Colourless tablets	
Crystal size	0.18 x 0.09 x 0.04 mm^3	
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 F^2	
Data / restraints / parameters	5262 / 5 / 364	
Goodness-of-fit on F^2	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	

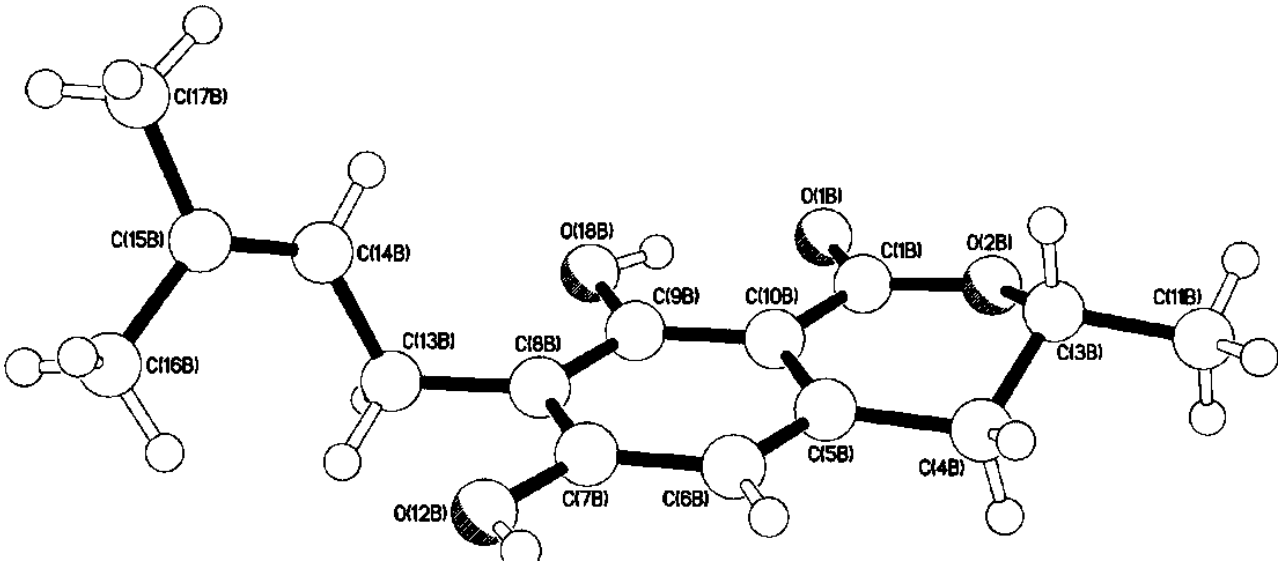
Table 25. Bond Lengths [Å] and Angles [°] for 6

O(1A)-C(1A)	1.241(2)	C(3A)-C(11A)	1.504(3)
C(1A)-O(2A)	1.337(2)	C(3A)-C(4A)	1.511(2)
C(1A)-C(10A)	1.441(3)	C(4A)-C(5A)	1.504(3)
O(2A)-C(3A)	1.465(2)	C(5A)-C(6A)	1.372(3)

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(11A)-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)

O(2B)-C(3B)-C(11B)	104.93(15)	C(7B)-C(8B)-C(13B)	121.41(17)
C(4B)-C(3B)-C(11B)	113.63(17)	O(18B)-C(9B)-C(8B)	117.26(17)
C(5B)-C(4B)-C(3B)	111.41(15)	O(18B)-C(9B)-C(10B)	121.22(16)
C(6B)-C(5B)-C(10B)	119.81(18)	C(8B)-C(9B)-C(10B)	121.51(16)
C(6B)-C(5B)-C(4B)	122.42(16)	C(5B)-C(10B)-C(9B)	119.19(16)
C(10B)-C(5B)-C(4B)	117.71(16)	C(5B)-C(10B)-C(1B)	120.45(17)
C(5B)-C(6B)-C(7B)	120.10(17)	C(9B)-C(10B)-C(1B)	120.31(16)
O(12B)-C(7B)-C(8B)	116.69(17)	C(14B)-C(13B)-C(8B)	112.22(15)
O(12B)-C(7B)-C(6B)	121.51(16)	C(15B)-C(14B)-C(13B)	126.96(18)
C(8B)-C(7B)-C(6B)	121.80(16)	C(14B)-C(15B)-C(16B)	124.20(18)
C(9B)-C(8B)-C(7B)	117.47(18)	C(14B)-C(15B)-C(17B)	120.67(19)
C(9B)-C(8B)-C(13B)	121.12(17)	C(16B)-C(15B)-C(17B)	115.12(19)

Figure 23: X-ray Crystal Structure of Angelicoin A (6)



*6.4.3 Resorcylate **155***

7-Hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**155**)

Table 26. Crystal Data and Structure Refinement for 155

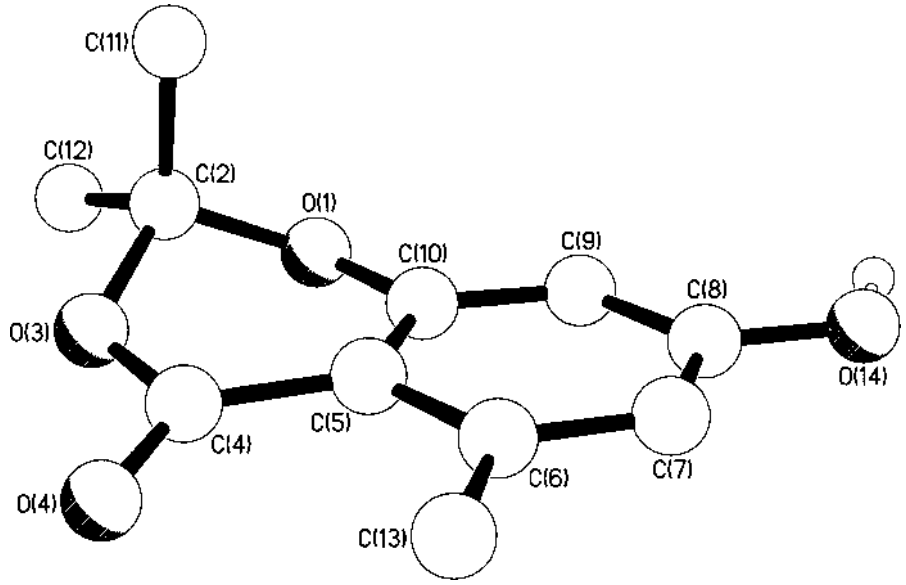
Identification code	**155**	
Formula	$C_{11}H_{12}O_4$	
Formula weight	208.21	
Temperature	173 K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 8.1052(2) Å	α = 90°
	b = 10.0123(2) Å	β = 90.567(2)°
	c = 11.9529(3) Å	γ = 90°
Volume, Z	969.95(4) $Å^3$, 4	
Density (calculated)	1.426 Mg/m^3	
Absorption coefficient	0.913 mm^{-1}	
F(000)	440	
Crystal colour / morphology	Colourless platy needles	
Crystal size	0.11 x 0.03 x 0.01 mm^3	
θ range for data collection	5.46 to 72.19°	
Index ranges	-9<=h<=9, -9<=k<=12, -11<=l<=14	
Reflns collected / unique	6427 / 1869 [R(int) = 0.0302]	
Reflns observed [F>4σ(F)]	1599	
Absorption correction	Analytical	
Max. and min. transmission	0.997 and 0.943	
Refinement method	Full-matrix least-squares on F^2	

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 27. Bond Lengths [Å] and Angles [°] for 155

O(1)-C(10)	1.371(3)	O(3)-C(2)-C(11)	109.73(19)
O(1)-C(2)	1.427(3)	C(12)-C(2)-C(11)	113.3(2)
C(2)-O(3)	1.446(3)	C(4)-O(3)-C(2)	118.98(17)
C(2)-C(12)	1.509(3)	O(4)-C(4)-O(3)	116.0(2)
C(2)-C(11)	1.519(3)	O(4)-C(4)-C(5)	127.0(2)
O(3)-C(4)	1.359(3)	O(3)-C(4)-C(5)	116.83(19)
O(4)-C(4)	1.217(3)	C(10)-C(5)-C(6)	118.4(2)
C(4)-C(5)	1.455(3)	C(10)-C(5)-C(4)	118.0(2)
C(5)-C(10)	1.398(3)	C(6)-C(5)-C(4)	123.5(2)
C(5)-C(6)	1.422(3)	C(7)-C(6)-C(5)	118.5(2)
C(6)-C(7)	1.378(3)	C(7)-C(6)-C(13)	118.9(2)
C(6)-C(13)	1.501(3)	C(5)-C(6)-C(13)	122.6(2)
C(7)-C(8)	1.399(3)	C(6)-C(7)-C(8)	121.8(2)
C(8)-O(14)	1.354(3)	O(14)-C(8)-C(9)	122.3(2)
C(8)-C(9)	1.388(3)	O(14)-C(8)-C(7)	117.5(2)
C(9)-C(10)	1.381(3)	C(9)-C(8)-C(7)	120.3(2)
C(10)-O(1)-C(2)	115.08(17)	C(10)-C(9)-C(8)	118.1(2)
O(1)-C(2)-O(3)	109.41(17)	O(1)-C(10)-C(9)	116.8(2)
O(1)-C(2)-C(12)	106.47(18)	O(1)-C(10)-C(5)	120.4(2)
O(3)-C(2)-C(12)	106.24(19)	C(9)-C(10)-C(5)	122.8(2)
O(1)-C(2)-C(11)	111.44(19)		

Figure 24: Crystal Structure of Resorcylate 155



*6.4.4 Branched Isomer Crystal Structure (**149**)*

7-Hydroxy-2,2-dimethyl-8-(2-methylbut-3-en-2-yl)-5-phenethyl-4*H*benzo[

d][1,3]dioxin-4-one (**149**)

Cambridge CCDC code: NAQBOY

Published: Laclef, S.; Anderson, K.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Letters* **2012**, *53*, 225–227.

Table 28. Crystal data and structure refinement for 149

Identification code	**149**	
Formula	$C_{23}H_{26}O_4$	
Formula weight	366.44	
Temperature	173 K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 15.26657(8) Å	α = 90°
	b = 11.06990(8) Å	β = 94.2348(5)°

	c = 23.94085(15) Å	γ = 90°
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 x 0.09 x 0.04 mm^3	
θ range for data collection	2.90 to 72.47°	
Index ranges	-18<=h<=18, -13<=k<=13, -29<=l<=19	
Reflns collected / unique	32362 / 7923 [R(int) = 0.0206]	
Reflns observed [F>4 σ (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 σ (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	0.000 and 0.001	

Table 29. Bond Lengths [Å] and Angles [°] for 149

O(1A)-C(1A)	1.221(2)	O(4A)-C(5A)	1.3678(19)
C(1A)-O(2A)	1.350(2)	C(5A)-C(6A)	1.397(2)
C(1A)-C(10A)	1.462(2)	C(5A)-C(10A)	1.410(2)
O(2A)-C(3A)	1.450(2)	C(6A)-C(7A)	1.408(2)
C(3A)-O(4A)	1.4118(19)	C(6A)-C(13')	1.540(10)
C(3A)-C(12A)	1.506(2)	C(6A)-C(13A)	1.566(5)
C(3A)-C(11A)	1.508(2)	C(7A)-O(18A)	1.3506(19)

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)

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)

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(14")-C(13")-C(6B)	109.8(9)		

Figure 25: X-ray Crystal Structure One of Branched Isomer 149

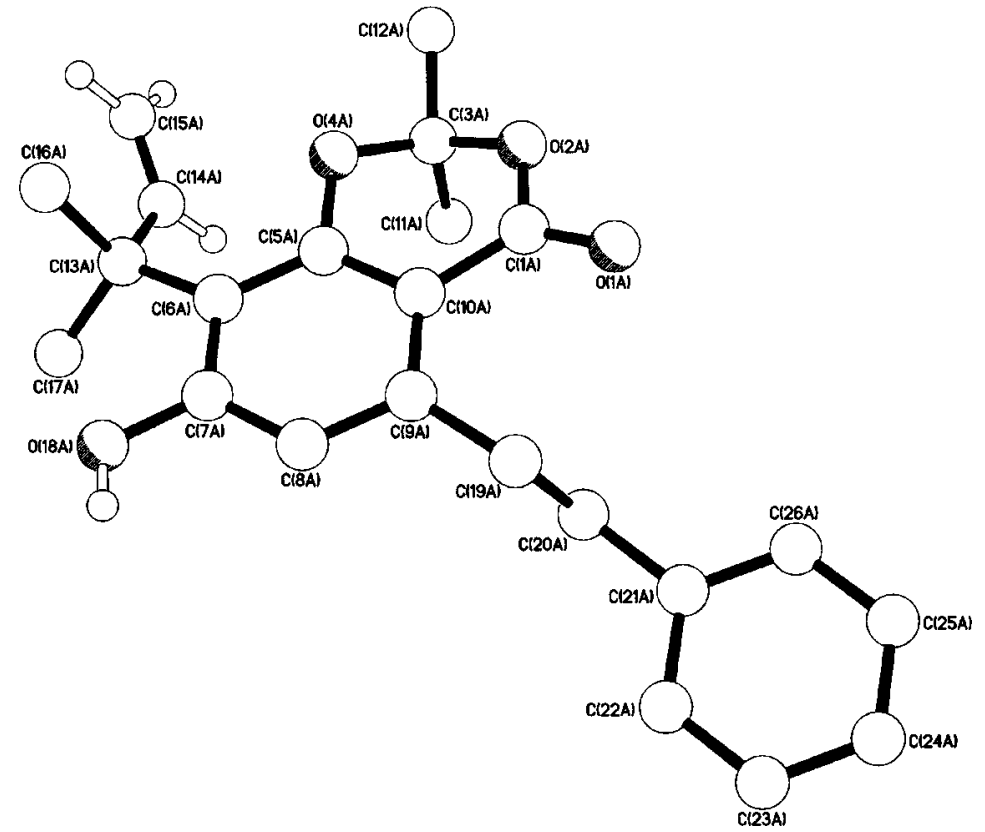
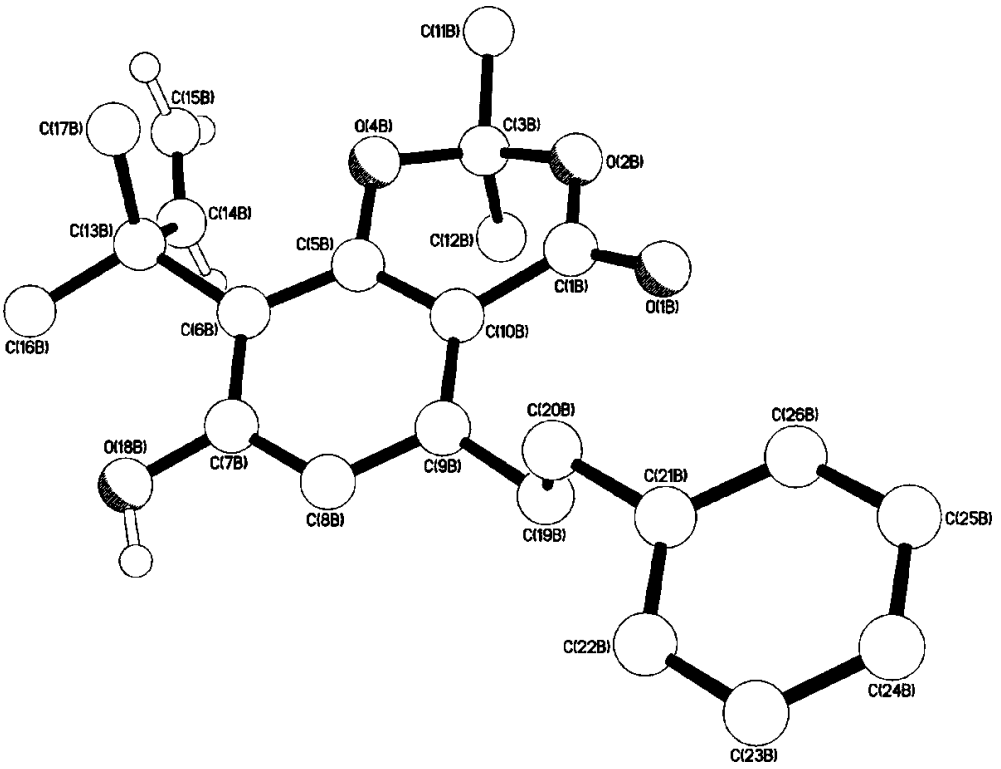


Figure 26: X-ray Crystal Structure Two of Branched Isomer 149



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