THE TOTAL SYNTHESIS OF AIGIALOMYCIN D AND ANALOGUES

by

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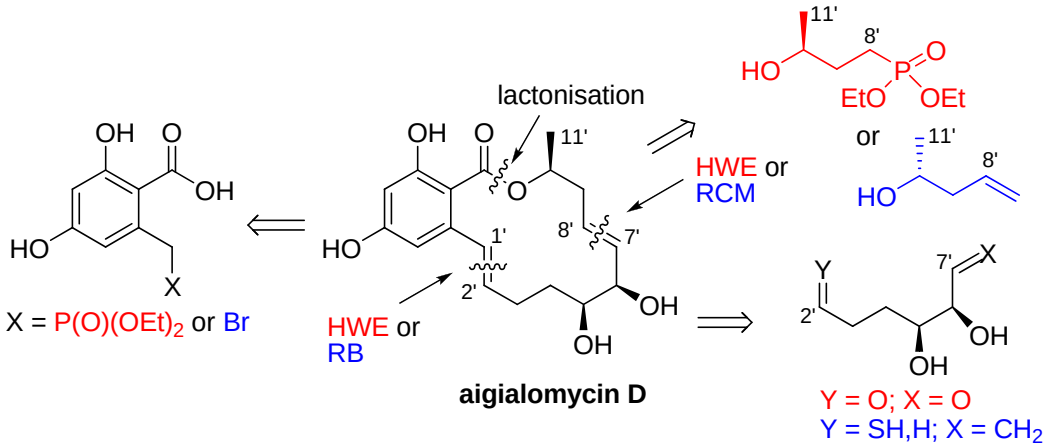
Abstract

In 2002 a new family of 14-membered resorcylic macrolides, the aigialomycins, were isolated from the mangrove fungus *Aigialus parvus* BCC 5311. Subsequent biological testing of these new natural products found aigialomycin D (Am D) to be the most biologically active member of the family, exhibiting moderate activity against malaria (*Plasmodium falciparum* K1, IC_{50} 19.7 μM) and modest cytotoxicity towards certain cancer cells (KB cells: IC_{50} 9.0 μM and BC-1 cells: 53.8 μM). More recently, Am D has been shown to inhibit the kinases CDK1/5 and GSK at low μM concentrations.

At the onset of this research project, with only one total synthesis of Am D reported in the literature, there remained a need for an efficient synthesis of Am D that would be amenable to the synthesis of a range of analogues. This thesis reports two synthetic approaches to Am D that differ primarily in the chemistry utilised to install the (*E*)-olefins at C1′–C2′ and C7′–C8′: a Horner-Wadsworth-Emmons (HWE) strategy and a Ramberg-Bäcklund (RB) strategy. The Ramberg-Bäcklund strategy ultimately proved to be successful, providing Am D in 16 steps with 9% overall yield. A retrosynthetic analysis of Am D disconnects the molecule into three major fragments: an aromatic fragment, a C2′–C7′ carbohydrate-derived fragment and a C8′–C11′ alcohol fragment.



The synthesis of the three fragments for each strategy is described and the attempts made to couple the fragments together, first with HWE methodology and then successfully with ring-closing metathesis (RCM) and RB reactions, are discussed. The synthesis of several Am D analogues and their preliminary biological testing is also described.

Acknowledgements

What is a PhD like? To what shall I compare it?

It is like a long journey; an adventure that takes you through the well trod streets, the green lush meadows and the barren wildernesses. With the vision of the end goals fixed in mind, you press on for the prize. Once you reach the end and look back, you realize that the whole process was the prize. The small successes, the frustrating failures, the sudden crystallisations, the imparted chemical wisdom, the laboratory camaraderie; are all important parts of a good PhD. But you can't succeed in this journey without the guidance and support of many people.

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To Anna, my love, thank you. You have been at my side for most of this journey, always willing to listen to my chemical frustrations and celebrations. You have had to deal with all the tears, late nights and stress. Your patience, unconditional love and smile have brought me to this place. May I grow to be the husband you deserve.

Thank you Jesus, for in You there is life, abundant life.

Table of Contents

Chapter Two:

Chapter Three:

Chapter Four:

Chapter Five:

Chapter Six:

Chapter Seven:

Chapter Eight:

List of Figures

Chapter One:

Chapter Two:

Chapter Three:

Chapter Four:

Chapter Five:

Chapter Six:

Chapter Seven:

Appendix:

List of Schemes

Chapter One:

Chapter Two:

Chapter Three:

Chapter Four:

Chapter Five:

Chapter Six:

List of Tables

Chapter One:

Chapter Two:

Chapter Three:

Chapter Five:

List of Abbreviations

Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Am	aigialomycin
aq.	aqueous
ATP	adenosine triphosphate
BAIB	[bis(acetoxy)iodo]benzene
9-BBN	9-borabicyclo[3.3.1]nonane
brs	broad singlet
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
CALB	*Candida Antarctica* lipase B
Calcd	calculated
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata
(*R*)-Me-CBS	(*R*)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole
COD	cyclooctadiene
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
dd	doublet of doublets
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
Decomp.	decomposed
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess

eq.	equivalent
ESI	electrospray ionisation
Et_2O	diethyl ether
EtOAc	ethyl acetate
FTIR	Fourier transform infrared
HL-60	human promyelocytic leukemia cells
HRMS	high-resolution mass spectrometry
Hsp90	heat shock protein 90
HSV1	Herpes Simplex Virus 1
HWE	Horner-Wadsworth-Emmons
IC_{50}	Inhibitory concentration 50%
Im	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	mol L^{-1}
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
MAP	mitogen-activated protein
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl
min	minute
MOM	methoxymethyl
Ms	mesylate
MTPA-Cl	α-methoxy-α-(trifluoromethyl)phenylacetyl chloride
MTT	dimethylthiazolyldiphenyltetrazolium salt
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NOESY	nuclear Overhauser effect spectroscopy
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
pH	negative logarithium of hydrogen ion concentration
Piv	pivaloyl

PKS	polyketide synthase
PPh_3	triphenylphosphine
ppm	parts per million
ppt	precipitate
i-Pr_2NEt	diisopropylethylamine
py	pyridine
q	quartet
Ra-Ni	Raney-Nickel
RALs	resorcylic acid lactones
RB	Ramberg-Bäcklund
RBF	round bottom flask
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium dihydride
R_f	retention factor
rt	room temperature
s	singlet
SAR	structure activity relationship
sat.	saturated
SET	single electron transfer
t	triplet
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl triflate
TEMPO	4-methoxy-2,2,6,6-tetramethyl-piperidine-1-oxyl
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl
p-TsOH	*para*-toluenesulfonic acid
TLC	thin layer chromatography
TBAF	tetra-*n*-butylammonium fluoride
UV	Ultraviolet
^{1}H NMR	proton nuclear magnetic resonance
^{13}C NMR	carbon 13 nuclear magnetic resonance
δ	chemical shift (ppm)
4Å MS	4Å molecular sieves

Chapter One:

Introduction

1.1 Synthesis of Natural Products

Friedrich Wöhler's synthesis of urea from ammonium cyanate in 1828[1] was not only the birth of organic chemistry; it also marked the dawn of natural product synthesis. This landmark event once-and-for-all closed the debate over whether the synthesis of natural products was constrained to the realm of nature. These days, the discipline of natural product synthesis is an important investigative field whose returns range from drug discovery to process development.[2,3] Natural product synthesis provides an ideal stage to demonstrate the power of organic synthesis and illustrate the scope and limitations of synthetic prowess at a given point in time. The challenge of synthesising natural products requires the development of the new synthetic tools needed to push towards higher molecular complexity, diversity and efficiency.[4]

Not only does natural product synthesis give opportunities for the discovery and development of new synthetic techniques and methodology with application stretching far beyond the discipline, it also provides an alternative source of natural products with promising biological activity. Normatively, natural products of interest are present at very low concentrations in the natural source, such that an exhaustive amount of the organism needs to be harvested and extracted to provide enough material for further extensive biological testing and/or medical application. Thus total synthesis is often necessary to provide enough material to be of use. Additionally, natural products can provide a structural platform which can be elaborated upon or simplified to achieve enhanced potency, improved selectivity, reduced toxicity, or other desirable physical and chemical properties.[5] Synthesis of such analogues enables study of the relationship between the structure of the natural compound and its activity (the structure activity relationship, SAR). Finally, the chemical synthesis of a natural product still provides the absolute proof of the configuration and connectivity assigned to its structure.[6]

1.2 Resorcylic Acid Lactones (RALs)

One subclass of natural products that exhibits promising biologically activity is the resorcylic acid lactones (RALs) (Figure 1–1).[7] RALs are macrocyclic lactones that contain a β-resorcylic acid unit (shown in blue) and feature an array of chemical functionality across both the β-resorcylic acid unit and the macrocyclic ring. The term RAL is used to denote the 14-membered β-resorcylic acid macrolactones in particular.

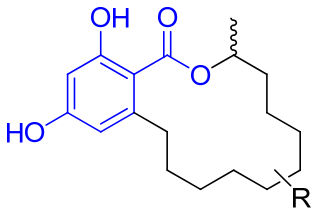
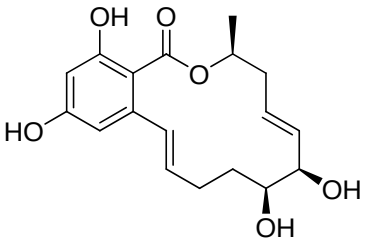


Figure 1–1. General structure of RALs.

One member of the RAL family is the fungal metabolite aigialomycin D (Am D, **1**) (Figure 1–2). This natural product was isolated in 2002 from the mangrove fungus *Aigialus parvus* BCC 5311. The relative stereochemistry and absolute configuration of Am D was proposed to be 1′*E*,5′*S*,6′*R*,7′*E*,10′*S* based on extensive NMR analysis and comparisons with related metabolites of known X-ray structure.[8] This macrolactone was initially observed to exhibit modest cytotoxicity against certain cancer cell lines and moderate antimalarial activity.[8] Several years later, Am D was shown to inhibit three protein kinases.[9]



Aigialomycin D (Am D)
1

Figure 1–2. Structure of the fungal metabolite aigialomycin D (**1**).

1.2.1 Biosynthesis of RALs

Resorcylic acid lactones (RALs) are mycotoxins produced by a variety of different fungal strains via polyketide biosynthesis. The fungal polyketide synthases (PKSs) involved in RAL biosynthesis are large multidomain enzymes that iteratively catalyse the condensation of nine units of thioacetates or malonates (Figure 1–3).[7] Different modules in the enzyme complex can further process the product of each condensation by reduction or dehydration of the resulting β-diketone. The only RAL whose biosynthesis has been studied in detail is zearalenone.[10,11] This biosynthesis is proposed to involve two PKSs, the first of which is responsible for the coupling of the first six acetate units, with further processing to arrive at the final oxidation state at each carbon. The second PKS performs the remaining three rounds of condensation without any carbonyl reduction. The unreduced ketones are highly reactive and spontaneously cyclise and aromatize, mediated by the enolisation of the ketone groups via a nonenzymatic process. After cyclisation, the macrolactone is subsequently released from the second PKS.[10] The diversity of functionality present in RAL macrocycles can be accounted for by the different combinatorial arrangements of the various β-keto processing modules involved in the first five condensations.

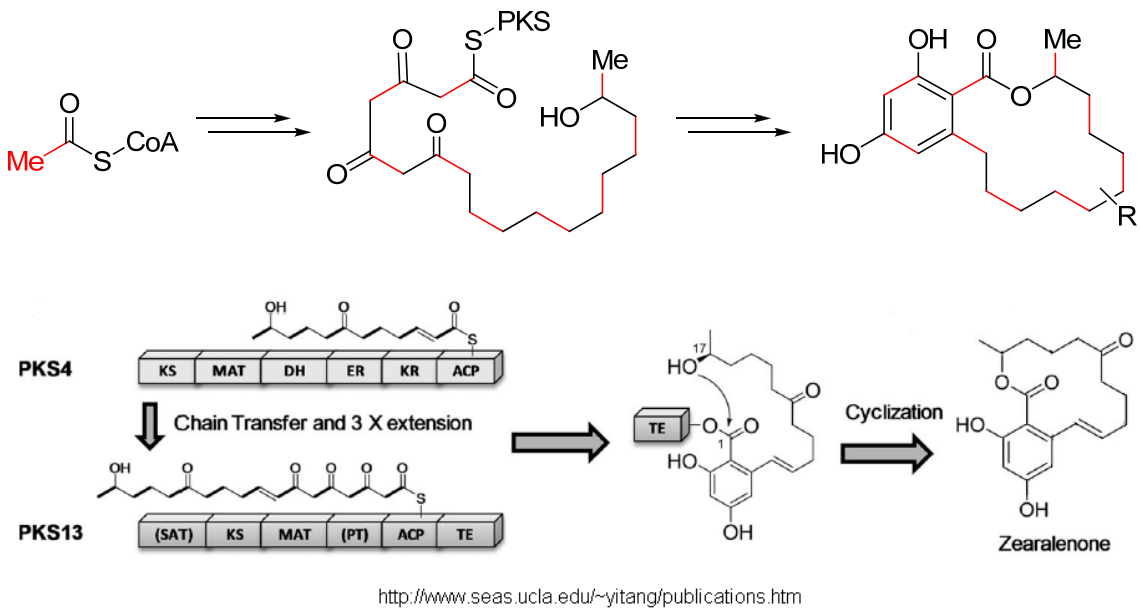


Figure 1–3. *Top*: Generalised biosynthesis of resorcylic acid lactones. The red bonds represent the two-carbon units that are added in each of the nine iterative condensations. *Bottom*: Representation of the two multidomained polyketide synthases involved in the biosynthesis of zearalenone.[11]

1.2.2 The Family of 14-Membered RALs.

The first RAL to be isolated was monorden (**2**, Figure 1–4), extracted in 1953 from the fungus *Monosporium nordinii*.[12] This same metabolite was independently isolated 10 years later from *Nectria radicicola* and renamed radicicol.[13] The structural configuration originally proposed for monorden was found to be incorrect and hence the name radicicol has prevailed. Initially reported to have mild sedative and moderate antibiotic properties,[13] the potent and selective inhibition of heat shock protein 90 (Hsp90) by this compound remained undiscovered until 1998.[14,15] The molecular chaperone Hsp90 mediates the stabilisation and folding of various client oncogenic proteins such as *Raf*1 and *Her*2.[16] Inhibition of the chaperoning activity of Hsp90 results in the degradation of its client proteins by the proteasome. This ultimately results in antitumor activity. The structurally related pochonin D (**3**) has also been shown to be a nanomolar inhibitor of Hsp90.[17]

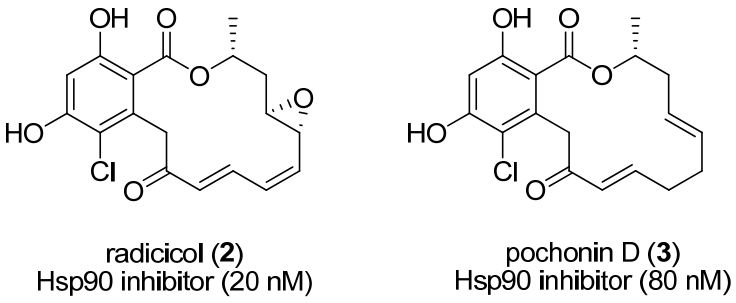


Figure 1–4. Structures, targets and inhibitory concentrations (IC_{50})[24] of Hsp90 inhibitors radicicol (**2**)[14,15] and pochonin D (**3**).[17]

Several RALs that have the *cis*-enone functionality incorporated into the macrocycle have been reported to be protein kinase inhibitors. Protein kinases are enzymes that chemically alter their protein substrates by attaching phosphate groups to them. This process, phosphorylation, usually results in functional changes to the target protein and altered enzyme activity, cellular location, or association with other proteins. The kinase reversibly transfers a phosphate group from adenosine triphosphate (ATP) to serine, threonine or tyrosine residues on their target that can be removed by protein phosphatases in a dephosphorylation step (Figure 1–5).[18] These two reactions play a crucial role in the regulation of a large number of cellular processes, including the transmission of signals within the cell along the many signal transduction pathways.

[24] The $IC_{50,}$ or inhibitory concentration for 50% inhibition, is the concentration at which growth or activity is inhibited by 50%. It is often used as a measure of the cytotoxicity of a compound.

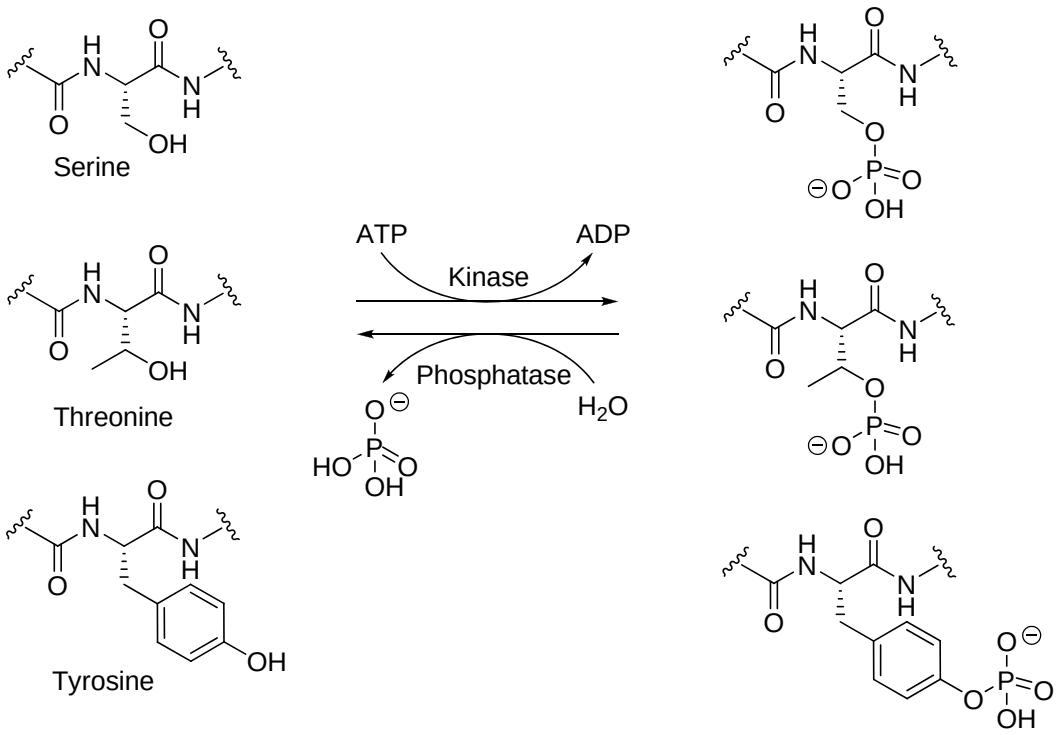


Figure 1–5. Phosphorylation and dephosphorylation mediated by kinases and phosphatases.[19]

The profound effects that protein kinases can have on cells require their strict regulation. Research over the past 40 years has shown that deregulation of kinase activity, resulting in defective signalling, is a frequent cause of cancer and many other human diseases such as diabetes, inflammation disorders and cardiovascular diseases.[20] Specific kinase inhibitors are a promising new class of therapeutics. This class includes drugs such as the tyrosine kinase inhibitors Imatinib and Gefitinib. The vast majority of these compounds compete with ATP, inhibiting the kinase at the ATP-binding site.

Kinases belonging to the MAP (mitogen-activated protein) pathway are important in regulating the cellular response to environmental stimuli by translating these cues into gene expression, cell growth or apoptosis. Consequently, MAP kinases have become primary targets in drug discovery.

cis-Enones hypothemycin (**4**), LL-Z1640-2 (**5**), radicicol A (**6**), and LL-783,277 (**7**) have all been reported to be inhibitors of various kinases (Figure 1–6). These RALs exemplify the observation that small structural differences in this family of compounds are able to change their mode of action and presumably the target of inhibition.

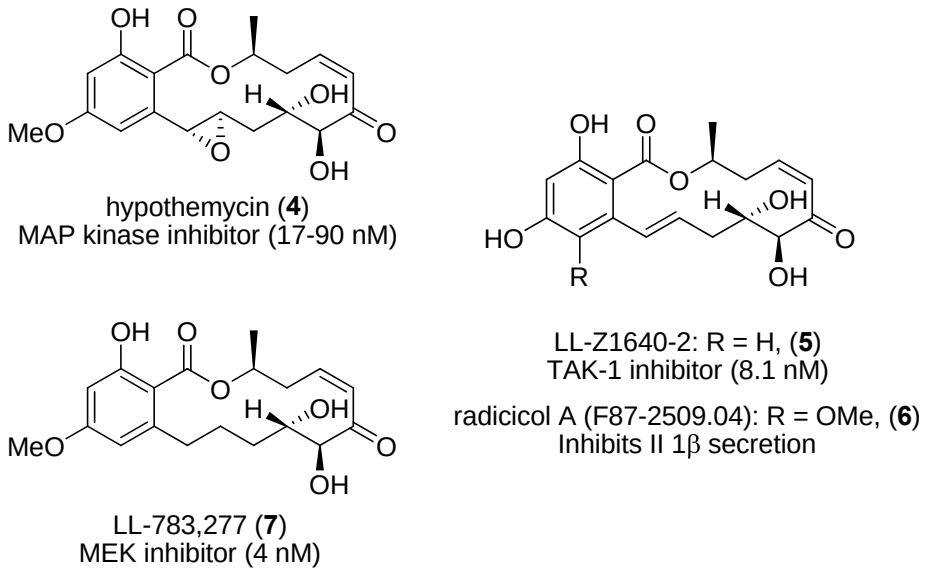


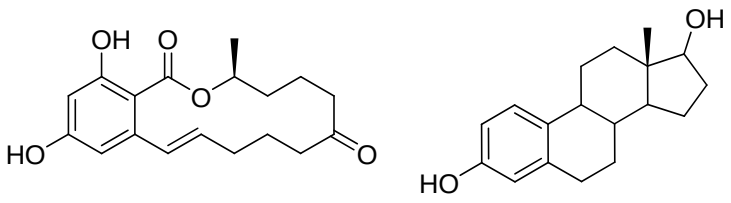
Figure 1–6. Structures, targets and IC_{50}'s of hypothemycin (**4**), LL-Z1640-2 (**5**), radicicol A (**6**), and LL-783,277 (**7**).[21-24]

The first RAL reported to inhibit a kinase was radicicol A (**6**, Figure 1–6). Radicicol A was isolated in 1987 from a strain of fungus F/87-2509.04 while screening for interleukin 1 beta (IL1β) inhibition, an important mediator of inflammation.[23] Several years later, Traber and co-workers showed that radicicol A (**6**) also inhibited tumour necrosis factor alpha (TNF-α) secretion, another major mediator of inflammation.[21] Discovered in 1980,[25] hypothemycin (**4**) was shown by researchers at Merck in 1999 to inhibit MEK[25] with an IC_{50} of 15 nM, slightly less active than LL-783,277 (**7**) which exhibited an IC_{50} of 4 nM.[24] LL-783,277 was shown to express inhibition of MEK1 through competing with ATP binding. First isolated in 1978,[26] LL-Z1640-2 (**5**) was shown in 2003 by Matsumoto et al. to irreversibly inhibit the kinase activity of TAK1[26] (IC_{50} of 8.1 nM) at the ATP-binding site.[22]

In addition to the macrolactones already mentioned, several other RALs have been characterised in the literature. Zearalenone (**8**, Figure 1–7), first isolated from *Gibberella zea* in 1962,[27] generated much interest in the organic chemistry community due to its estrogenic agonistic properties. These properties were shown to arise from the metabolite's ability to adopt a conformation that mimics that of the native steroid 17-estradiol.[28]

[25] MEK (MAP kinase kinase) is a dual-specificity kinase that phosphorylates tyrosine and threonine residues and is involved in the MAP (mitogen activated protein) kinase cascade. The MAP kinases relay, amplify and integrate signals from a variety of extracellular stimuli thereby regulating the cell's response to the environment.

[26] TAK1 is MAPKKK (MAP kinase kinase kinase) involved in the p38 signalling cascade for proinflammation signals (e.g. cytokines)



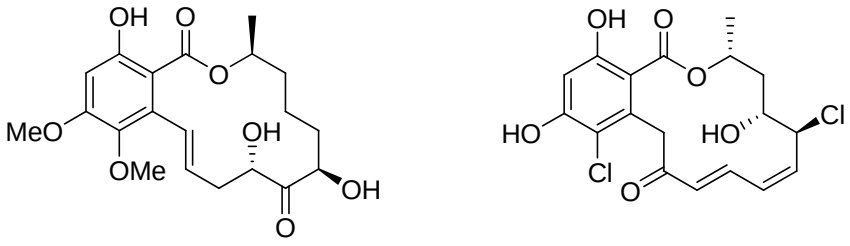
zearalenone (**8**)
estorgen agonist

17-estradiol

Figure 1–7. The structures of zearalenone (**8**) and 17-estradiol whose conformation is mimicked by **8**.

More recently isolated RALs include queenslandon (**9**, Figure 1–8), which was isolated from the fungal strain *Chrysosporium queenslandicum* IFM51121 in 2002.[29] This macrolide showed distinct anti-fungal activity but lacked antibacterial activity.

In 2003, a new family of RALs, the pochonins, were reportedly isolated from *Pochonia chlamydosporia* var. *catenulata* alongside the known metabolite, radicicol.[30] The family was identified in a Herpes Simplex Virus 1 (HSV1) replication assay. All pochonins except for pochonin D (**3**) exhibited low micromolar range activity against HSV1, for example pochonin C (**10**) exhibited an IC_{50} of 6 μM (Figure 1–8).



queenslandon (**9**)
anti-fungal activity

pochonin C (**10**)
HSV inhibitor (6 μM)

Figure 1–8. Structures and targets of queenslandon (**9**)[29] and a representative of the pochonin family, pochonin C (**10**).[30]

1.3 Aigialomycin D

1.3.1 Discovery and Isolation of Aigialomycin D

In 2002, a new family of 14-membered resorcylic macrolides, the aigialomycins (Am) A–E (Figure 1–9, **11–13**, **1**, **14**), was isolated from the mangrove fungus *Aigialus parvus* BCC 5311 (Figure 1–10).[8] They were present alongside the already known metabolite hypothemycin (**4**). Their isolation was achieved through activity guided fractionation and chromatographic separation. The structures of the natural products, including absolute configuration, were elucidated by using a variety of spectroscopic methods, chemical conversions and x-ray analyses.

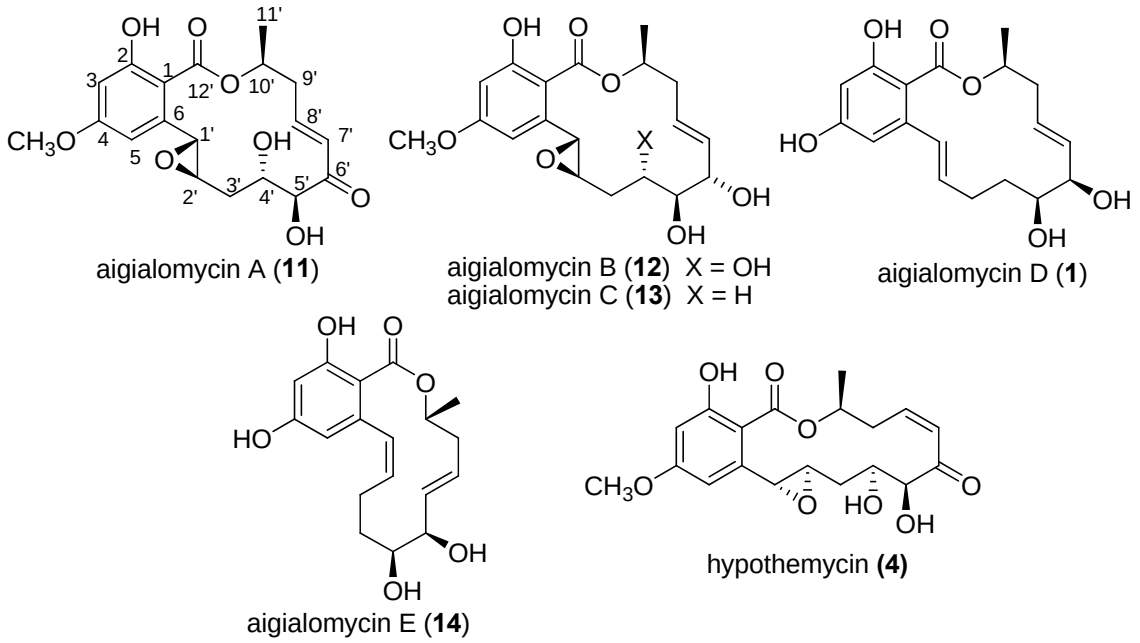


Figure 1–9. Structures of aigialomycins A–E (**11–13**, **1**, **14**) and hypothemycin (**4**) isolated from *Aigialus parvus* BCC 5311.

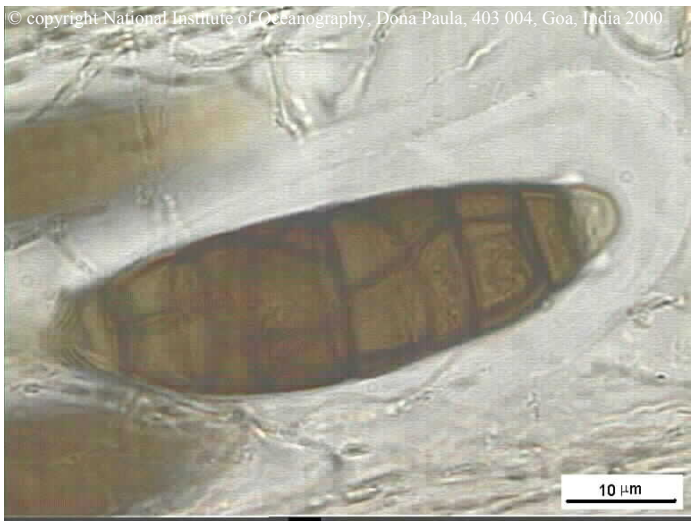


Figure 1–10. *Aigialus parvus*, a mangrove fungus.

Like other members of the RAL family, compounds **1** and **11** to **14** are characterised by the presence of a resorcylic aromatic ring fused to a 14-membered macrocycle containing a benzoate lactone functionality and a high degree of oxygenation and/or unsaturation. Am D (**1**) was found to have a second (*E*)-olefin at C1′–C2′ instead of the epoxide functionality found on compounds **11**–**13** and two free phenolic hydroxyl groups. A NOESY NMR experiment on the acetonide derivative of **1** confirmed that the two hydroxyls at C5′ and C6′ are in a *cis* relationship.[8] The structure of Am E (**14**) differs from Am D only by having a *(Z)*-configuration at C1′–C2′.

Two other metabolites, the acetal aigialone (**15**) and the spiroacetal aigialospirol (**16**) (Figure 1–11), were isolated from the same fungus in 2004.[31] Aigialospirol is structurally related to the aigialomycins and hypothemycin in having a resorcylic portion with a polyketide chain. It differs, however, in the presence of spiroketal system instead of the 14-membered macrocycle found in the aigialomycins and hypothemycin.

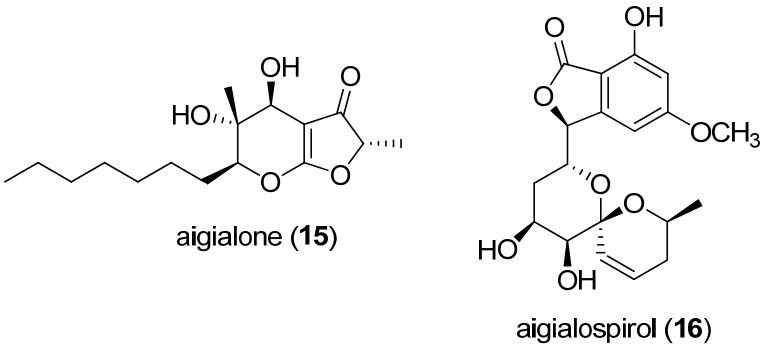


Figure 1–11. Structures of Aigialone (**15**) and aigialospirol (**16**), metabolites isolated from *Aigialus parvus* BCC 5311.

1.3.2 Biological Testing of Aigialomycin D

The natural products **1, 4** and **11**–**14** isolated from *Aigialus parvus* BCC 5311 were all screened for antimalarial activity and cytotoxicity (Table 1–1).[8] Compounds **15** and **16** were inactive in all the biological assays they were subjected to.[31]

Table 1–1. Antimalarial Activity and Cytotoxicity of Macrolides **11**–**13**, **1**, **14** and **4**

Compound	*Plasmodium falciparum* K1 (IC_{50}, μM)	Cytotoxicity (IC_{50}, μM)[b]		
		KB	*BC-1*	*Vero*
aigialomycin A (**11**)	> 50	> 50	29	11
aigialomycin B (**12**)	> 50	> 50	> 50	> 50
aigialomycin C (**13**)	> 50	> 50	> 50	> 50
aigialomycin D (**1**)	20	9.0	54	5.4
aigialomycin E (**14**)	> 50	> 50	40	> 50
hypothemycin (**4**)	5.8	45	16	17
chloroquine diphosphate[a]	0.3	31	39	39
ellipticine[b]	–	1.9	2.4	4.1

[a] standard antimalarial drug. [b] standard anticancer drug.

Am D (**1**) and hypothemycin (**4**) were the only members of this series of compounds that displayed antimalarial activity. Compounds **1** and **4** also exhibited modest cytotoxicity towards skin and breast cancer cells (KB and BC-1 cells), and Vero cells (African green monkey kidney fibroblasts). Neither of these compounds would be practical in the treatment of malaria as their average cytotoxicity is similar in magnitude to their antimalarial activity, leaving no usable therapeutic window.

Initially it was reported that Am D bound to Hsp90, albeit to a significantly lower degree than the structurally related macrolide radicicol.[32] Further investigation, however, found that Am D did not lead to degradation of *Her*2, one of the most sensitive client proteins of this chaperone, even at 10 μM, and it is therefore not likely to be an inhibitor of Hsp90.[33]

New information regarding the biological activity of Am D was reported by Winssinger and co-workers in late 2006.[9] Their tests found that Am D inhibited the kinases CDK1/cyclin B, CDK5/p25 and GSK-3 with IC_{50}'s of 5.7 μM, 5.8 μM and 14 μm respectively, suggesting that Am D's mode of cytotoxicity in human cells could be due

to the inhibition of these kinases. Interestingly, Am D was not found to inhibit the *Plasmodium* homologue of GSK-3, PfGSK-3 (IC_{50}>100 μM), suggesting Am D's antimalarial activity cannot be attributed to the inhibition of this kinase. Although the exact binding sites of Am D are yet to be determined, it is probable that Am D binds at their ATP sites as has been observed in many RAL inhibitions.

Due to its interesting biological profile, the focus of this research project was to complete the total synthesis of Am D. Before details of the synthetic methodology are discussed, a review of previous syntheses of Am D is presented.

1.3.3 Previous Total Syntheses of Aigialomycin D

To date there have been five successful total syntheses[9,32,34-36] and two partial syntheses[37,38] of Am D published in the literature. The first total synthesis, reported by Danishefsky and co-workers in 2004,[32] was the sole synthesis published when the research described in this thesis was commenced.

1.3.3.1 Danishefsky's synthesis

The first total synthesis of Am D was reported by Danishefsky et al. in 2004. Their predominantly linear synthesis was accomplished in 18 steps with an overall yield of 8%.[32]

Syntheses of RALs generally utilise an aromatic starting material.[7] Danishefsky and co-workers, however, disconnected through the aromatic ring of Am D. They chose to install the aromatic ring using a cycloaddition reaction, to take place after macrocyclisation (Figure 1–12). The macrocyclic dienophile **18** was disconnected at the olefin, which would be formed through the use of a ring-closing metathesis (RCM) reaction. Acyclic precursor **19** was further disconnected at the ester linkage and the homopropargylic alcohol to give the synthon **20**, alkyne **21**, and chiral alcohol **22**. Carbohydrate-derived **20** was built up sequentially from D-2-deoxy-D-ribose (**23**), an inexpensive, readily available starting material.

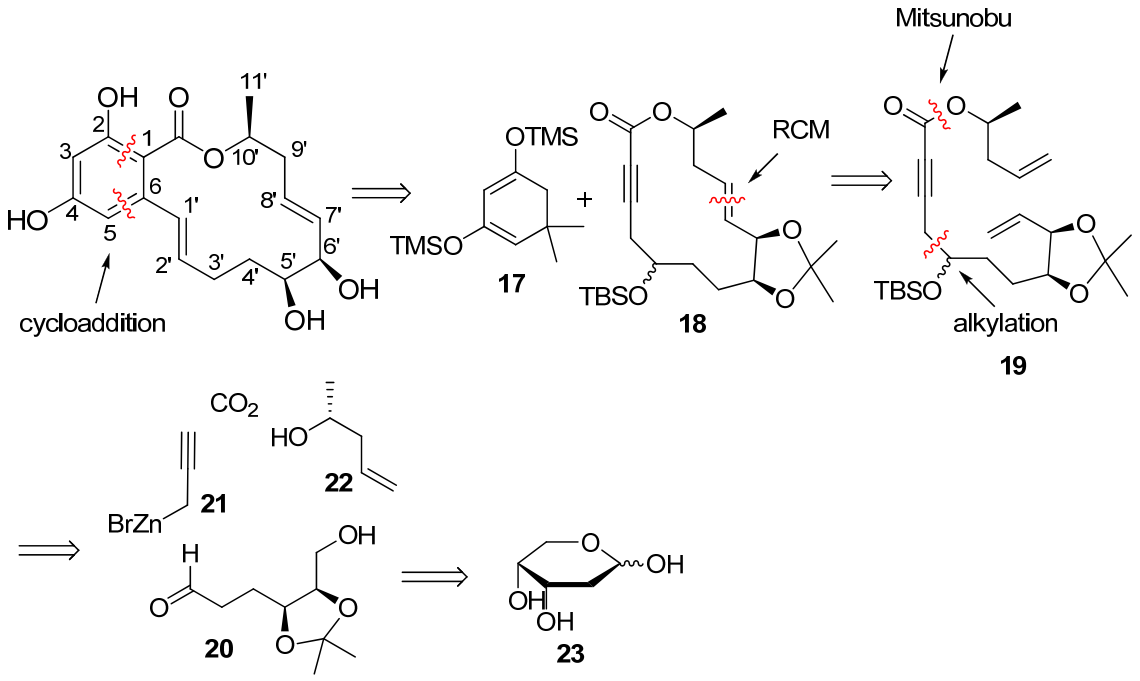
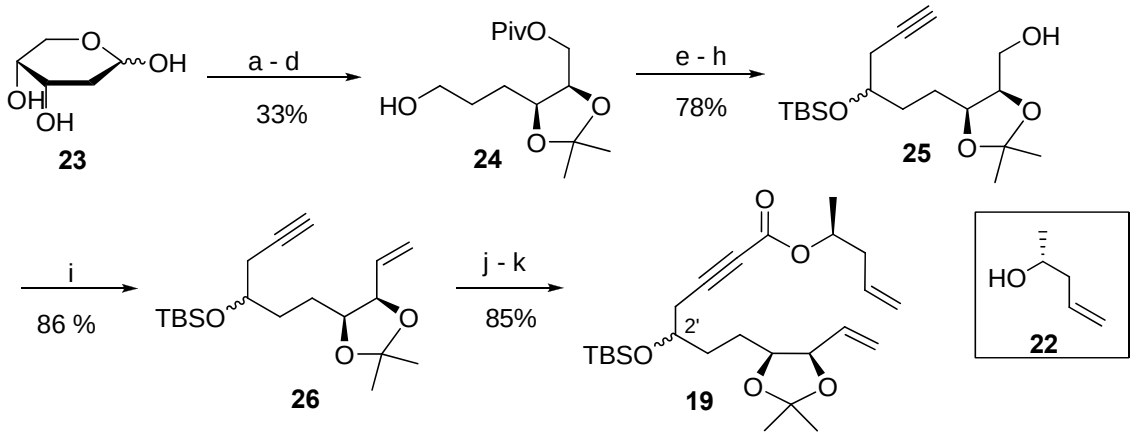


Figure 1–12. Retrosynthetic analysis of Am D conducted by Danishefsky et al.[32]

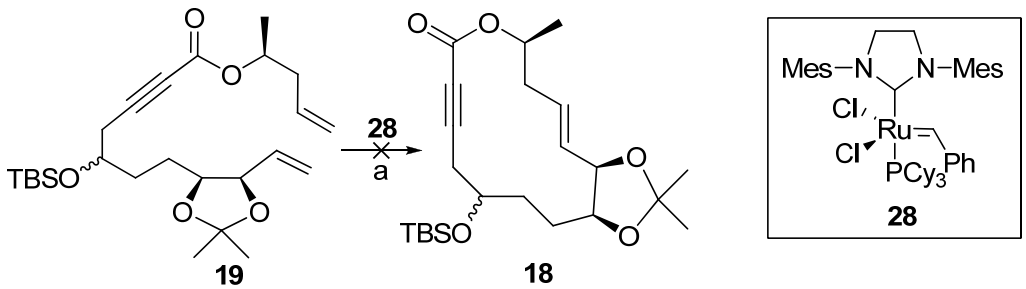
Synthesis of Am D began with a carbon chain extension of 2-deoxy-D-ribose (**23**) through a Wittig olefination reaction (Scheme 1–1). The resulting primary alcohol was protected as its pivaloyl derivative prior to hydroboration and oxidation to give alcohol **24**. Parikh-Doering oxidation[39] of alcohol **24** afforded an aldehyde before further extension of the carbon chain through nucleophilic propargylation to give a mixture of stereoisomers. These were subsequently protected as their *t*-butyldimethylsilyl (TBS) ethers before cleavage of the pivaloate group to yield alcohol **25**. A second Parikh-Doering oxidation was followed by a Wittig reaction to install the first of the vinyl groups required for the RCM reaction. After carboxylation of the alkyne **26,** esterification with the (*R*)-alcohol **22** under Mitsunobu conditions[40] gave the (*S*)-ester **19** as a mixture of epimers at the C2′ position.



Scheme 1–1. The synthetic strategy employed by Danishefsky in the synthesis of a diene precursor of Am D.

Reagents and conditions: a) 2-methoxypropene, *p*-TsOH, 62%; b) KHMDS, $Ph_3P^+CH_3I^-$, 68%; c) PivCl, Et_3N, DMAP, 90%; d) 9-BBN, then NaOH, H_2O_2, 88%; e) SO_3-Pyr, DMSO, Et_3N; f) propargyl bromide, zinc; g) TBSOTf, 2,6-lutidine, 89% (3 steps); h) NaOMe, 88%; i) SO_3-Pyr, DMSO, Et_3N, then KHMDS, $Ph_3P^+CH_3I^-$, 86% for two steps; j) *n*-BuLi, $CO_{2\,(s)}$; k) **22**, DIAD, PPh_3, 85% for two steps.

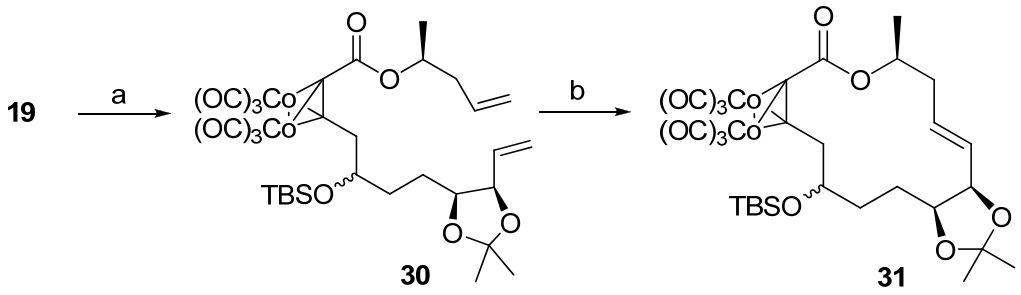
Several attempts were made to cyclise diene **19** to macrolactone **18** using Grubbs' second generation catalyst **28**[41,42] (Scheme 1–2). However, only starting material was recovered from the RCM reaction. Interestingly, there was no indication in the report that any cross-metathesis product was isolated. Danishefsky postulated that the alkyne functionality in the molecule might be the cause of the failed attempts at olefin metathesis for two reasons. Firstly, the alkyne group could unproductively coordinate to the catalyst, thus reducing the amount of free catalyst to carry out metathesis. The second important factor considered was the additional conformational rigidity of the alkyne group compared to an alkene group. It is likely that the linear geometry of the alkyne does not allow the terminal alkene groups to be close enough in space for metathesis to occur.



Scheme 1–2. Danishefsky's attempted RCM reaction on diene **19**.

Reagents and conditions: a) **28** (25 mol%), Δ, CH_2Cl_2.

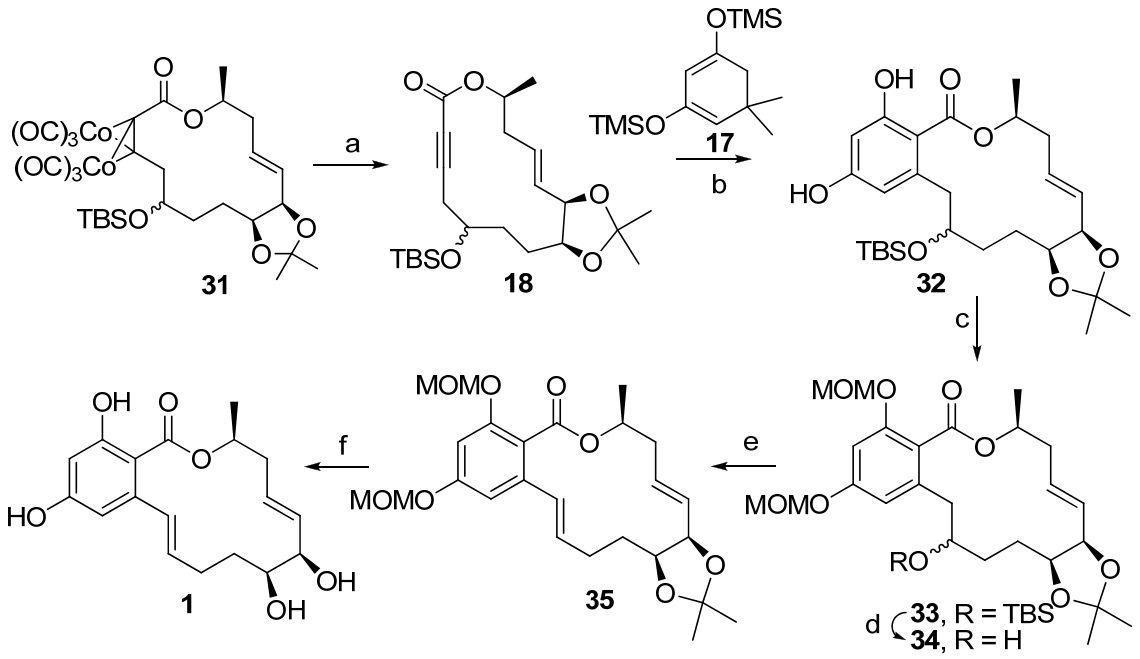
Previous work done by Danishefsky's group had shown that similar RCM precursors required further modification before ring-closing metathesis could occur.[33] Thus the alkyne group was 'protected' as its dicobalt hexacarbonyl complex (**30**) (related to intermediates formed in a Pauson-Khand reaction),[43] preventing coordination of the catalyst to the alkyne group (Scheme 1–3). Furthermore, this complexation likely causes distortion of the alkyne bond from the normal 180° to approximately 140° [44] allowing the two olefins to be in closer proximity. With this modification, metathesis occurred in excellent yield to provide compound **31** as a mixture of epimers. ^{1}H NMR spectroscopy indicated a ratio of 1:1.2 for the two isomers but their stereochemistries were not rigorously assigned, as this chiral centre would be transformed into a sp^2-hybridised carbon atom in the final steps of the synthesis. They did, however, note that for each diastereomer, only the (*E*)-alkene was generated in the RCM reaction ($J_{HH} \cong 15.2$ Hz).



Scheme 1–3. Danishefsky's synthesis of macrolactone **31**.

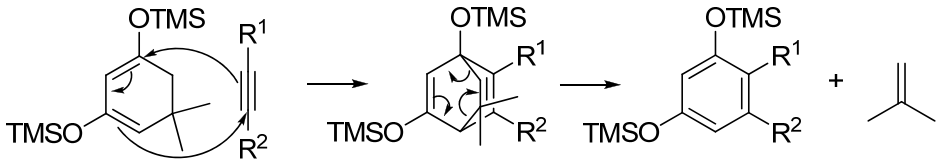
Reagents and conditions: a) $Co_2(CO)_8$, 94%; b) **28** (25 mol%), 80%.

Macrolactone **31** was then decomplexed through treatment with ceric ammonium nitrate (CAN) (Scheme 1–4). The subsequent cycloaddition reaction between alkyne **18** and disiloxydiene **17**, provided the adduct **32** in high yield (79%). This transformation involves a cycloaddition followed by a cycloreversion as the newly formed ring aromatises, extruding gaseous isobutylene (Scheme 1–5).



Scheme 1–4. Final steps in Danishefsky's total synthesis of Am D.

Reagents and conditions: a) CAN, 95%; b) **17**, Δ, 79%; c) MOMCl, DIPEA, 80%; d) HF-py, 83%; e) $[PhC(CF_3)_2O]_2SPh_2$, 87%; f) 0.5 M HCl, 69%.



Scheme 1–5. Installation of the aromatic ring through a cycloaddition/cycloreversion reaction sequence.

The cycloaddition product underwent aromatic desilylation during the course of purification by silica gel chromatography. The two phenol groups were orthogonally protected as their methoxymethyl (MOM) derivatives, before the secondary alcohol was selectively deprotected, yielding **34**. Installation of the (*E*)-olefin at C1′–C2′ was accomplished through dehydration of alcohol **34** using Martin's sulfurane reagent.[45] Both epimers of **34** led to the same product, **35**, which underwent global acidic deprotection, completing the first total synthesis of Am D. The final product was established as Am D through the very close correspondence of the ^{1}H NMR, ^{13}C NMR, mass spectral and IR data of the synthetically derived material with the data previously reported for the natural product.[8]

1.3.3.2 Pan's synthesis

The second total synthesis of Am D was published by Pan et al. in 2006.[34] Despite this synthesis being more convergent than that undertaken by Danishefsky et al., 18 steps were still required to deliver Am D in an overall yield of 2.5%.

Like the approach of Danishefsky, Pan and co-workers disconnected Am D at the two olefins (Figure 1–13). However, rather than disconnecting through the aromatic ring, their third disconnection at the lactone gave an intact resorcylic unit (**36**) and two benzothiazol-2-yl sulfone units (**37** and **38**). Pan envisioned that the olefins could be installed with two Juliá-Kocienski olefinations before formation of the macrocycle through a Yamaguchi macrolactonisation.

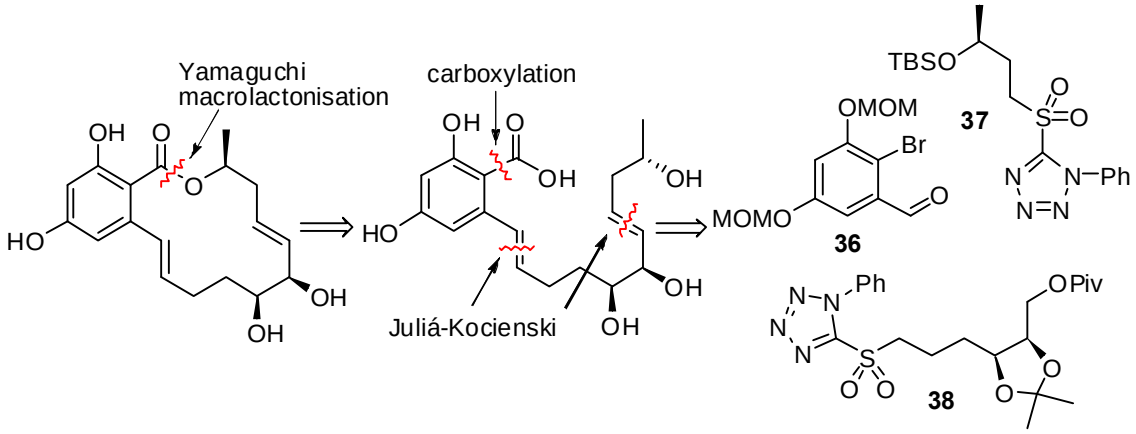
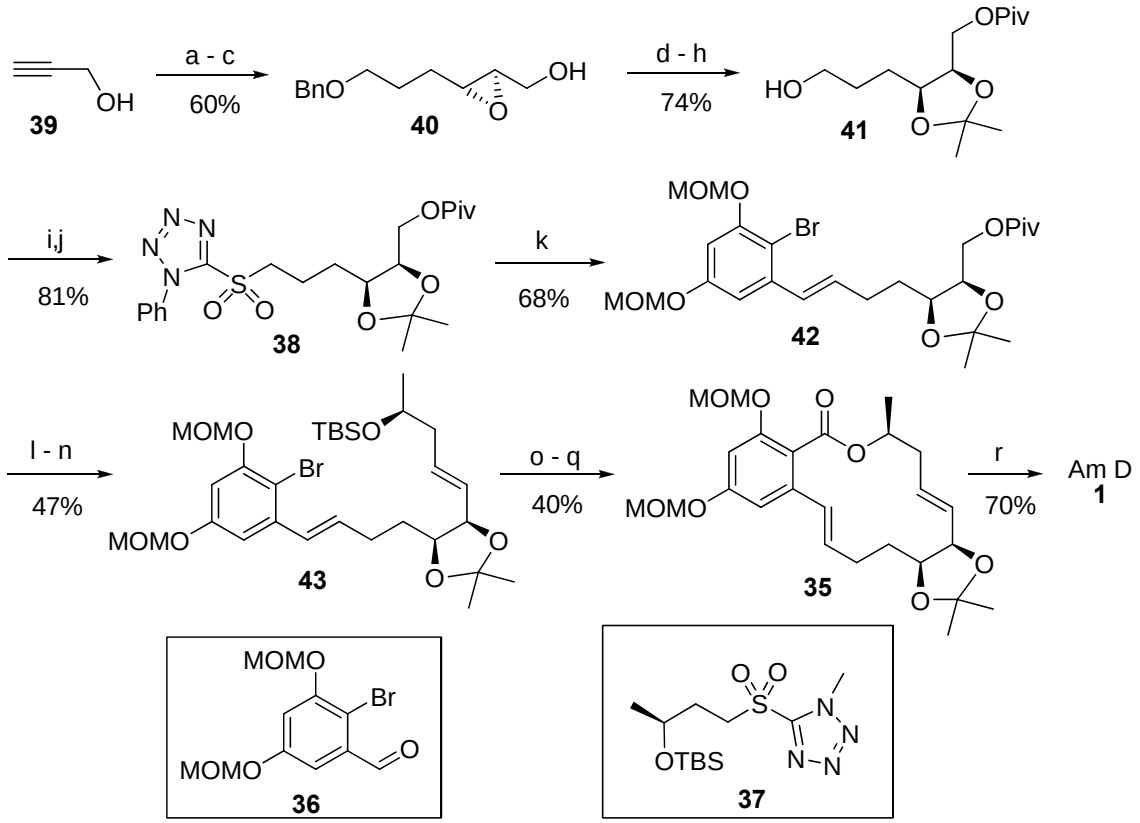


Figure 1–13. Retrosynthetic analysis of Am D conducted by Pan et al.

Synthesis of the first fragment began with commercially available propargyl alcohol (Scheme 1–6). Alkylation of **39** with 1-benzyloxy-3-iodopropane followed by reduction with lithium aluminum hydride (LAH) afforded an (*E*)-allylic alcohol. This underwent asymmetric epoxidation under Sharpless conditions[46,47] to give epoxide **40**. Regioselective opening of the epoxy alcohol with benzoic acid was mediated by Ti(*i*-PrO)$_4$,[48] which after manipulation of protecting groups gave alcohol **41**. Compound **41** was readily converted to sulfone **38** through a Mitsunobu reaction and oxidation of the resulting thioether in 81% yield over two steps. The benzylic olefin was installed through a Juliá-Kocienski[49,50] reaction by addition of aldehyde **36** to the preformed potassium salt of sulfone **38**, furnishing the (*E*)-olefin with good stereoselectivity (*E*/*Z* = 95:5). After reductive cleavage of the pivaloate and oxidation of the resulting hydroxyl group under Dess-Martin conditions,[51] the second Juliá-Kocienski reaction proceeded

with moderate stereoselectivity, affording TBS ether **43** with an *E/Z* ratio of 83:17. After cleavage of the TBS group and carboxylation with *n*-butyllithium and carbon dioxide, the macrocyclic lactone **35** was formed using a Yamaguchi macrolactonisation.[52] The macrocycle was then globally deprotected under acidic conditions to afford the target compound with identical physical and spectroscopic data to those reported for Am D.[8,32]



Scheme 1–6. Pan's synthesis of Am D.

Reagents and conditions: a) $BnOCH_2CH_2CH_2I$, *n*-BuLi, 70%; b) $LiAlH_4$, 96%; c) $Ti(O\text{-}iPr)_4$, TBHP, (–)-DIPT, cat. CaH_2, 89%; d) $Ti(O\text{-}iPr)_4$, $PhCO_2H$, 75%; e) EtMgBr, 95%; f) PivCl, Et_3N, DMAP, 88%; g) 2-methoxypropene, PPTS, 95%; h) 10% Pd/C, H_2, 4 h, 95%; i) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, PPh_3; j) *m*-CPBA, $NaHCO_3$, 81% for two steps; k) KHMDS, **36**, 68%; l) DIBAL-H, 96%; m) Dess–Martin periodinane, 85%; n) KHDMS, **37**, 58%; o) TBAF, 95%; p) *n*-BuLi, CO_2, 83%; q) 2,4,6-trichlorobenzoylchloride, Et_3N, then DMAP, 51%; r) 0.5M HCl, 70%.

Despite Pan's synthesis having the identical number of steps in the longest linear sequence as the synthesis of Danishefsky and co-workers, their yield is significantly lower. The three coupling reactions are the lowest yielding steps (51-68%), greatly diminishing the overall yield at such late stages in the synthesis.

1.3.3.3 Winssinger's Synthesis

A third total synthesis of Am D was published shortly after that of Pan. Winssinger and co-worker's efficient and highly convergent synthesis was completed in a mere 10 steps with a 21% overall yield.[9] They also developed a polymer supported synthesis of Am D.

Like Pan, Winssinger disconnected Am D at the lactone and two olefins yielding three main fragments (Figure 1–14). A key part of their strategy was the use of a benzylic thio- or selenoether which facilitated alkylation chemistry and provided a site for attachment to a polymer support. The macrocycle would be formed through a ring-closing metathesis, installing the (*E*)-olefin between C7′–C8′. Winssinger et al. followed a similar approach to that of Pan et al., generating the *cis*-diol through a stereoselective opening of the epoxide **46**. The benzylic olefin could finally be accessed through oxidation of thio- or selenoether and elimination of the resulting sulfoxide or selenoxide.

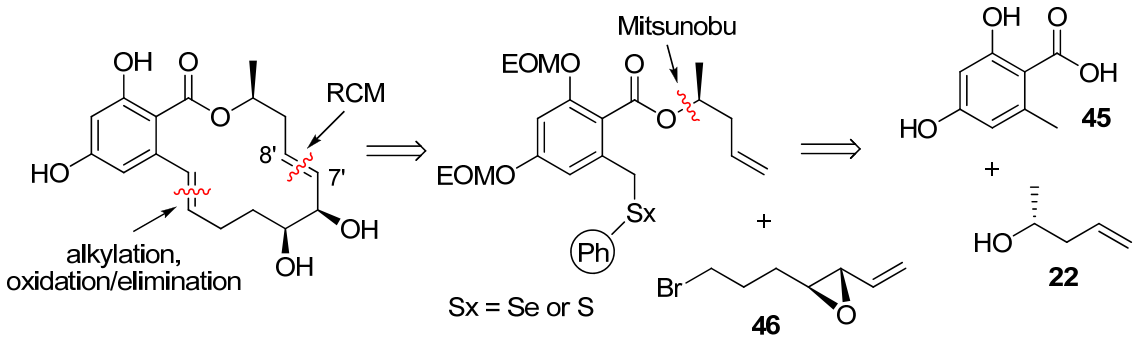
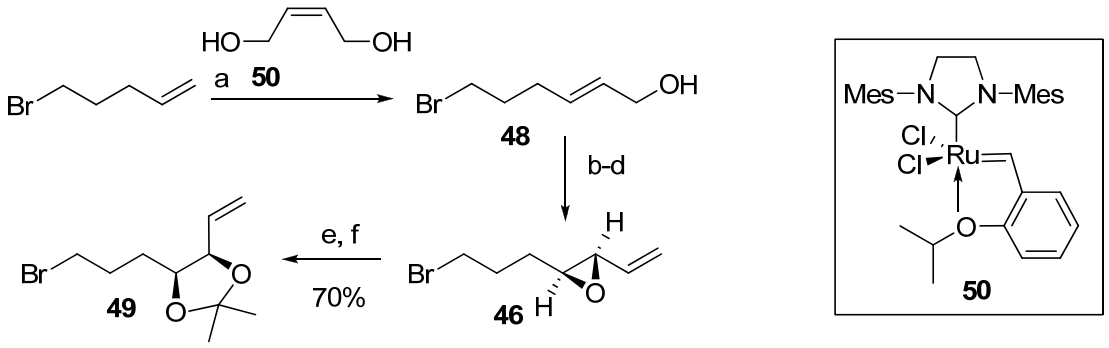


Figure 1–14. Retrosynthetic analysis of Am D conducted by Winssinger et al.

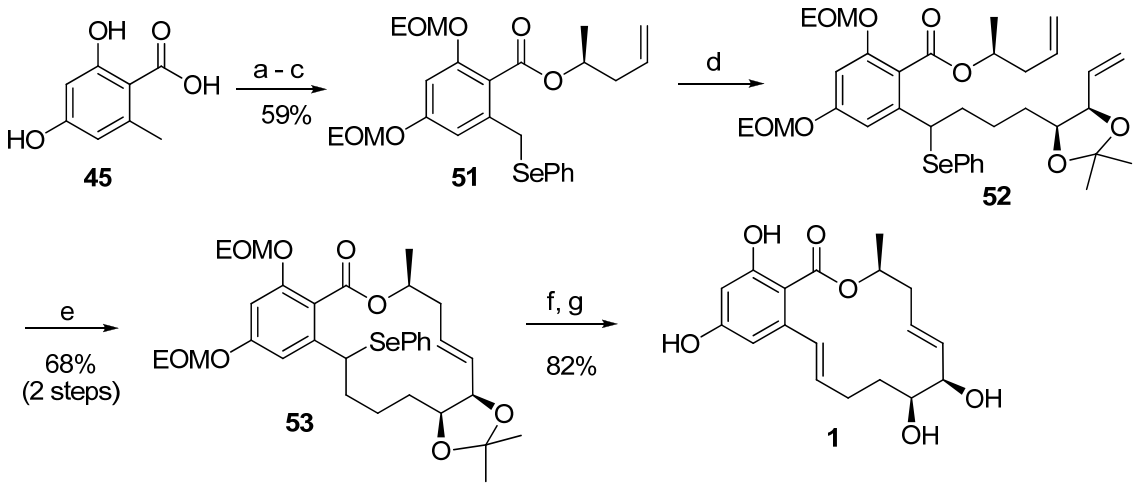
The key intermediate **46** was obtained in four steps from commercially available starting materials (Scheme 1–7). Thus, cross-metathesis of 5-bromopentene with (*Z*)-1,4-but-2-enediol, catalysed by Hoveyda–Grubbs' second generation catalyst (**50**),[53] gave alcohol **48** in excellent yield and *E/Z* ratio (>25:1). Sharpless asymmetric epoxidation of allylic alcohol **48**, followed by oxidation and Wittig olefination, lead to epoxide **46** in 62% overall yield. $Sc(OTf)_3$ mediated opening of epoxide **46** gave the desired diol, which was subsequently protected as the isopropylidene **49**.



Scheme 1–7. Synthesis of key intermediates **46** and **49**.

Reagents and conditions: a) 10% Hoveyda–Grubbs II catalyst (**50**), 97%; b) Sharpless asymmetric epoxidation, 85%; c) SO_3·py, DMSO; d) $Ph_3P{=}CH_2$, 70% over two steps; e) $Sc(OTf)_3$, 100%; f) 2,2-dimethoxypropane, *p*-TsOH·H_2O, 70%.

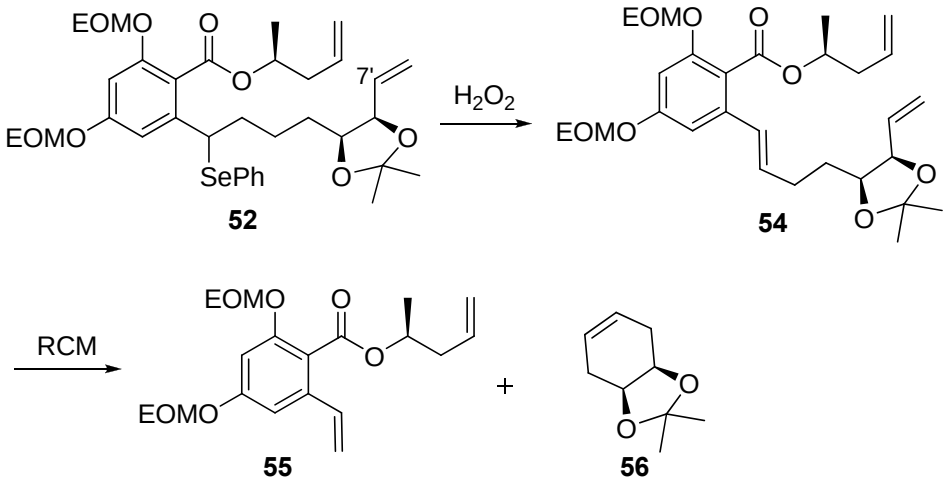
The aromatic fragment was obtained in three steps from the benzoic acid **45** (Scheme 1–8). The unprotected benzoic acid **45** was esterified through a Mitsunobu reaction with (*R*)-4-penten-2-ol (**22**). The use of tri(*meta*-chlorophenyl)phosphine in the Mitsunobu reaction was crucial in preventing the undesired coupling of aromatic units through the *para*-hydroxyl group.[54] Polymer supported diethyl azodicarboxylate (PS-DEAD) allowed for easy purification of the product. After protection of both phenolic hydroxyl groups, the selenide was introduced through deprotonation at the benzylic position followed by the addition of diphenyldiselenide, providing compound **51** in 59% yield. Selenide **51** was alkylated with bromide **49** to give the metathesis precursor **52** in good yield. Treatment of diene **52** with second generation Grubbs' catalyst (**28**) under equilibrating conditions[55] (80 °C for 12 h) gave the macrocycle **53** with a good *E/Z* ratio of 10:1. Treatment of macrocycle **53** with hydrogen peroxide led to oxidation and elimination of the selenide to give protected Am D. Global deprotection of the isopropylidene and ethoxymethyl (EOM) groups was achieved in quantitative yield by treatment with polymer supported sulfonic acid, affording Am D with identical spectral properties to that of the isolated natural product. This method of deprotection improved on the ~70% yields achieved by Danishefsky and Pan using their methanolic hydrogen chloride conditions.



Scheme 1–8. Synthesis of Am D by Winssinger.

Reagents and conditions: a) PS-DEAD, (*R*)-4-penten-2-ol (**22**), (*m*-$ClC_6H_4)_3P$, 83%; b) *i*Pr_2EtN, EOMCl, TBAI (cat.), 95%; c) LDA then $(PhSe)_2$, 75%; d) LDA, **49**, 75%; e) 5% Grubbs II catalyst (**28**), 92%; f) H_2O_2, 82%; g) PS–SO_3H, quant.

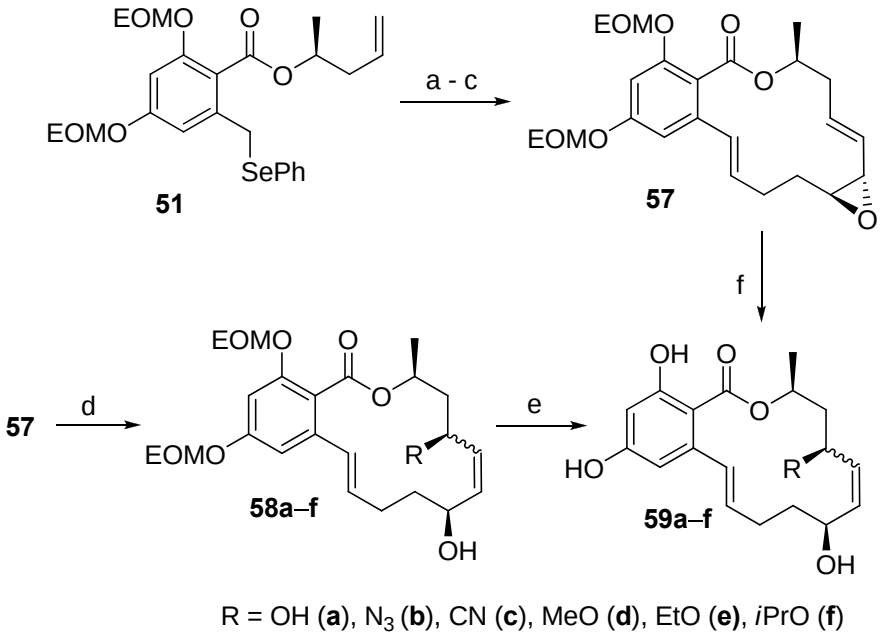
The order of the oxidation/elimination and metathesis reactions was found to be very important. If the oxidation/elimination step was carried out first, a significant amount of undesired styrene derivative **55** and six-membered ring product **56** were formed in the RCM reaction through cyclisation of the C7′ alkene with the benzylic olefin (Scheme 1–9).



Scheme 1–9. Alternative order in oxidation/elimination and RCM of advanced intermediate **52**.

Winssinger also investigated carrying forward epoxide **57** as a masked diol (Scheme 1–10). The alkylation, metathesis and oxidation/elimination steps all proceeded efficiently, however, when it came to the Lewis acid mediated opening of epoxide **57** they observed no 1,2-*cis*-diol product. Instead, the nucleophile carried out an S_N2' opening, affording a

1,4-diol (**58a**). This divergent reaction pathway was taken advantage of to synthesise aigialomycin analogues (**59a–f**) through the use of nucleophiles such as sodium azide or postassium cyanide or simultaneous epoxide opening/deprotection with different alcohols (methanol, ethanol, isopropanol), all in the presence of sulfonic acid resin.



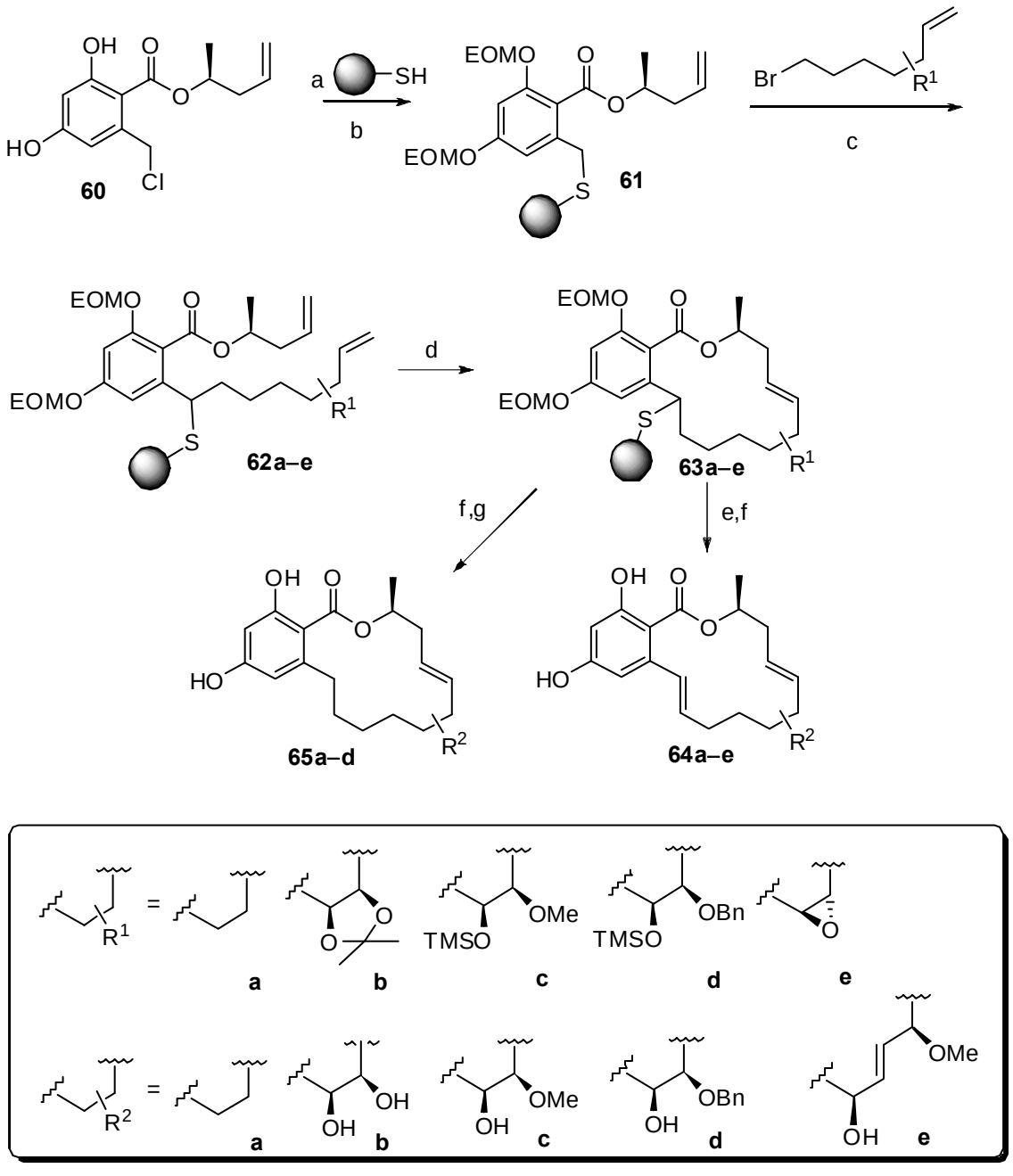
Scheme 1–10. Access to Am D analogues through S_N2' attack of various nucleophiles.

Reagents and conditions: a) LDA, **46**, 74%; b) 5% Grubbs' II catalyst (**28**), 90%; c) H_2O_2, 85%; d) THF/H_2O, PS-SO_3H, quant.; or NaN_3, PS-SO_3H, 83%; or KCN, PS-SO_3H, 89% (for R = OH, N_3, CN); e) PS-SO_3H, >90% (for R = OH, N_3, CN); f) PS-SO_3H, ROH, quant. (for R = MeO, EtO, *i*-PrO)

After a successful solution-phase synthesis of Am D, Winssinger et al. investigated the utility of solid-supported synthesis for Am D and analogues. To this end, the phenyl selenide was replaced with a polymer-bound thioether. Gratifyingly, the chemistry to Am D proved to be as efficient on solid phase as in solution.

Once coupled to the thiophenol resin and the phenol groups protected, the polymer-bound substrate was alkylated the benzylic position with a variety of alkyl bromides yielding a raft of metathesis precursors (**62a–e**) (Scheme 1–11). The RCM conditions developed for the selenide based synthesis failed to deliver any macrocyclic product. However, excellent yields of the macrocycles (**63a–e**) were achieved when microwave (MW) irradiation was used to heat the CH_2Cl_2 solution to 120 °C for 75 min. The lifetime of the second-generation Grubbs' catalyst **28** is short under such conditions, requiring the addition of the catalyst in three portions of 6 mol%. The macrocycles were

released from the resin by oxidation/elimination (H_2O_2/HFIP) or by free-radical cleavage (Bu_3SnH, AIBN), which, followed by global deprotection with sulfonic acid resin, led to aigialomycin D (**1**) and analogues thereof (**64a,c–e**), including a series of dihydro-aigialomycin analogues (**65a-d**).



Scheme 1–11. Diversity-oriented synthesis of aigialomycin D and analogues by Winssinger and co-workers.

Reagents and conditions: a) PS-SH, *i*-Pr_2EtN, 82% (by mass gain assuming 0.8 mmol g^{-1} for PS-SH); b) DBU, EOMCl, TBAI (cat.), ~96% (by mass gain assuming 0.8 mmol g^{-1} for PS-SH); 80% over two steps (by radical cleavage: AIBN (cat), *n*Bu_3SnH, MW); c) LDA, R_1Br, ~quant. (by radical cleavage; and by oxidation/elimination: H_2O_2 then Δ); d) 3 x 6% Grubbs' II catalyst (**28**), MW, 100% (by radical cleavage); e) H_2O_2, Δ, >90%; f) PS-SO_3H, >90%; g) AIBN (cat), Bu_3SnH, MW, >98%.

To increase understanding about the biological activity of Am D, Winssinger screened the natural product and several analogues (**1**-acetonide, **59a** and **59b**) against a panel of kinases.[56] Whilst Am D was found to inhibit kinases CDK1/cyclin B, CDK5/p25 and GSK-3 at micromolar levels, the isopropylidene-protected aigialomycin D and analogues with different relative arrangements of the hydroxyl groups (**59a** and **59b**) showed no notable activity.

1.3.3.4 Chen's Synthesis

Chen and co-workers completed the fourth total synthesis of Am D in 2007 with a longest linear sequence of 11 steps and in 19% overall yield.[35] Chen et al. also disconnected Am D at the lactone and two olefins giving three fragments (Figure 1–15), and envisioned assembling Am D through a Mitsunobu reaction, alkylation/elimination and RCM reaction.

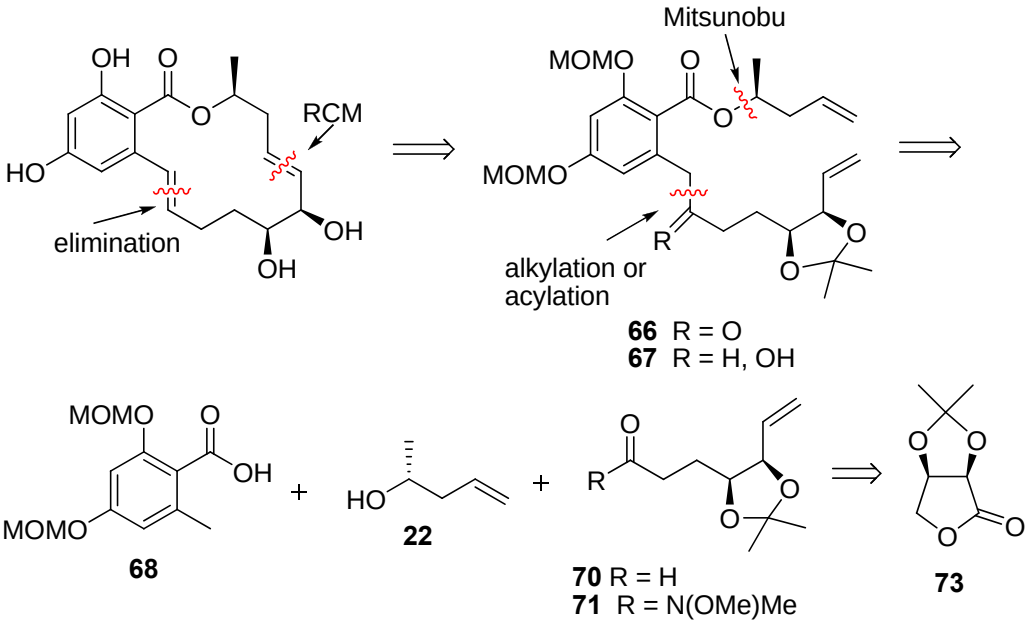
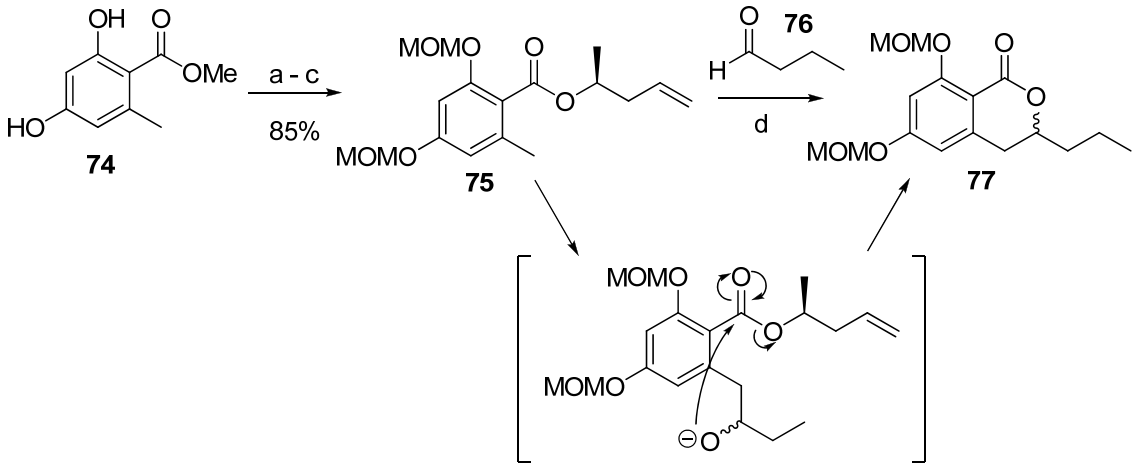


Figure 1–15. Retrosynthetic analysis of Am D conducted by Chen et al.

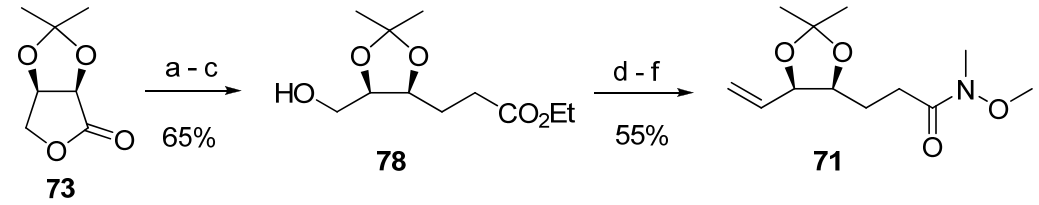
Methyl orsellinate (**74**) was MOM-protected, saponified and exposed to Mitsunobu conditions to provide aromatic segment **75** in excellent overall yield (85%) (Scheme 1–12). To investigate the proposed benzylic lithiation–addition coupling of ester **75** to aldehyde **70**, the 1′-lithiated derivative of **75** was reacted with model aldehyde butanal (**76**). Disappointingly, the product from this reaction was found to be δ-lactone **77**, proposed to have been formed by cyclisation of the hydroxy ester. Therefore, Chen et al. turned to acylation methodology to carry out the coupling with an appropriate Weinreb amide (**71**).



Scheme 1–12. Undesired formation of δ-lactone **77** from the 1′-lithiated derivative of **75**.

Reagents and conditions: a) MOMCl, NaH, quant.; b) KOH then HOAc, pH 6, 99%; c) DIAD, Ph_3P, (*R*)-4-penten-2-ol (**22**), 86%; d) LDA, **76**.

To secure the *cis*-diol functionality in Am D, Chen and co-workers initiated their synthesis with the commercially available chiral building block D-(-)-erythronolactone acetonide, **73**, from which Weinreb amide **71** was accessed in six steps (Scheme 1–13). To extend the carbon chain of the fragment, Wittig methodology was used twice. The sequence of hydrogenation and Wittig olefination reactions avoided any difficulties in the selective reduction of the α,β-unsaturated olefin in the presence of the terminal olefin.

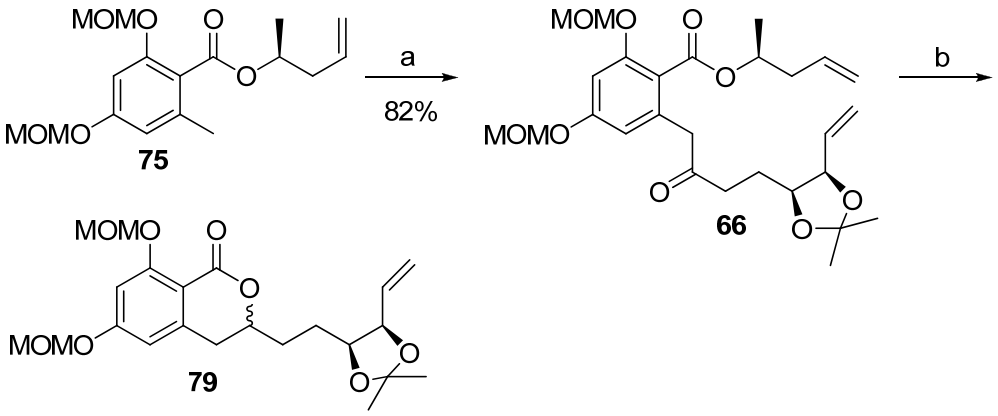


Scheme 1–13. Chen's synthesis of Weinreb amide **71**.

Reagents and conditions: a) DIBAL-H, 92%; b) $Ph_3P{=}CHCO_2Et$, $PhCO_2H$ (0.2 mol%), *E*/*Z* = 1:2, 73%; c) H_2, 10% Pd/C (cat.), 97%; d) PCC, NaOAc, 4Å mol. sieves, 80%; e) $Ph_3P^+CH_3Br^-$, *n*-BuLi, 71%; f) MeONHMe·HCl, *i*-PrMgCl, 96%.

Acylation of **75** at the benzylic position with Weinreb amide **71** afforded the desired ketone **66** in 82% yield (Scheme 1–14). As might be expected from the model reaction in Scheme 1–12, reduction of the ketone with sodium borohydride did not give the desired alcohol **67** but instead gave the δ-lactone **79** following an intramolecular

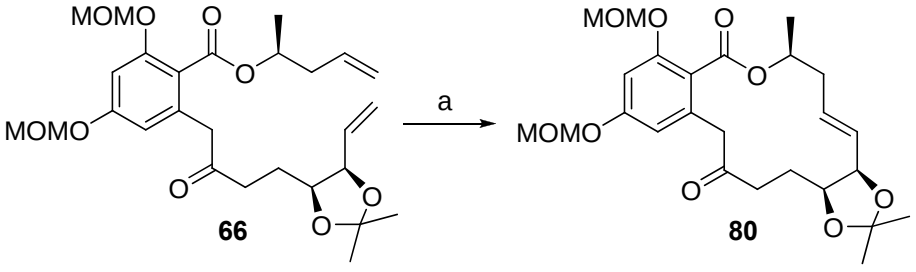
lactonisation of the 2′-alkoxide with the ester. Chen and co-workers hypothesised that if the macrocycle was formed prior to the reduction, the structural rigidity of the molecule should keep the 2′-alkoxide far enough away from the ester to avoid this attack.



Scheme 1–14. Formation of undesired δ-lactone **79**.

Reagents and conditions: a) LDA, then **71**, 82%; b) $NaBH_4$.

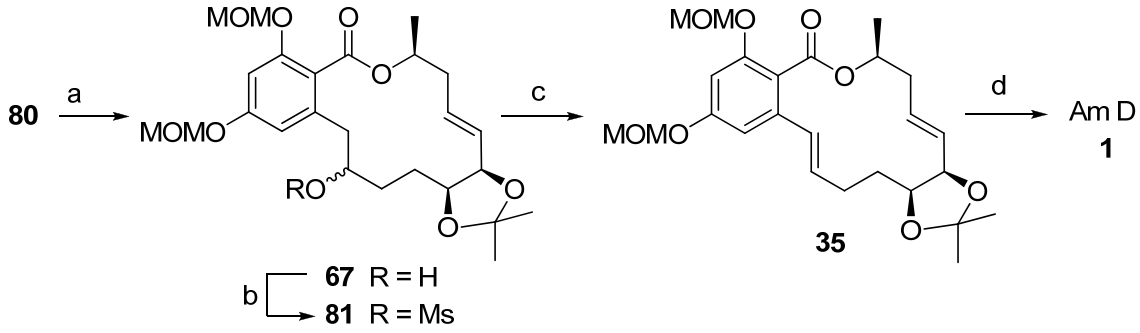
The macrocyclisation of diene **66** under the RCM conditions employed by Danishefsky and co-workers afforded an inseparable mixture of *E*/*Z* stereoisomers of **80** in 86% yield with an *E/Z* ratio of only 5.7:1, as evident from the ^{1}H NMR spectrum. Chen and co-workers sought alternative conditions to both improve the yield and increase the (*E*)-selectivity of the product. MW-irradiation of RCM reactions has been reported to both improve the yield and reaction efficiency.[57-59] It was proposed that the RCM of **66** under MW irradiation at elevated temperatures should favour the thermodynamically more stable (*E*)-isomer. Satisfyingly, cyclisation of **66** with Grubbs' second generation catalyst (**28**) at high dilution (0.005 M in CH_2Cl_2) under MW irradiation (100 °C for 30 minutes) afforded the cyclised product **80** in 98% yield with complete (*E*)-selectivity (Scheme 1–15). Only one set of olefinic peaks was observed in the ^{1}H NMR spectrum with a coupling constant of 15.0 Hz.



Scheme 1–15. MW-assisted RCM reaction of diene **66** by Chen.

Reagents and conditions: a) CH_2Cl_2 (0.005 M), Grubbs' II catalyst (**28**) (10 mol%), MW irradiation, 100 °C, 30 min, 98%, (*E*) only.

Reduction of macrocyclic ketone **80** with sodium borohydride under standard conditions did indeed give desired alcohol **67** without any δ-lactone product being observed (Scheme 1–16). With the formal total synthesis of Am D complete, Chen set about to replicate the last steps of Danishefsky's synthesis. Installation of the benzylic olefin through treatment of alcohol **67** with Martin's sulfurane dehydrating agent led to the formation of the desired product **35** mixed with decomposed sulfurane reagent, which could not be separated from the product. However, elimination of mesylate **81** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under reflux was found to cleanly give the diene **35** in 74% yield and with complete regio- and (*E*)-selectivity. Global deprotection under acidic conditions afforded Am D in 91% yield.



Scheme 1–16. Final steps in Chen's synthesis of Am D.

Reagents and conditions: a) $NaBH_4$, quant.; b) (i) MsCl, Et_3N, DMAP (10 mol%); (ii) DBU, 74% over two steps; c) 1M HCl/MeOH (1:1), 91%.

1.3.3.5 Montgomery's Synthesis

The fifth total synthesis of Am D was reported by Montgomery et al. in 2008.[36] Montgomery and co-workers envisioned that chemistry developed in their laboratory for the catalytic macrocyclisation of ynals[60] and intermolecular diastereoselective coupling of alkynyl silanes and α-silyloxy aldehydes[61] could be employed for the cyclisation of **82** (Figure 1–16). Alkynyl silane **82** could be further disconnected to give three key fragments: aryl iodide **83**, alcohol **84** and diol **85**. These three building blocks could be assembled through a Mitsunobu reaction and Suzuki coupling reaction.

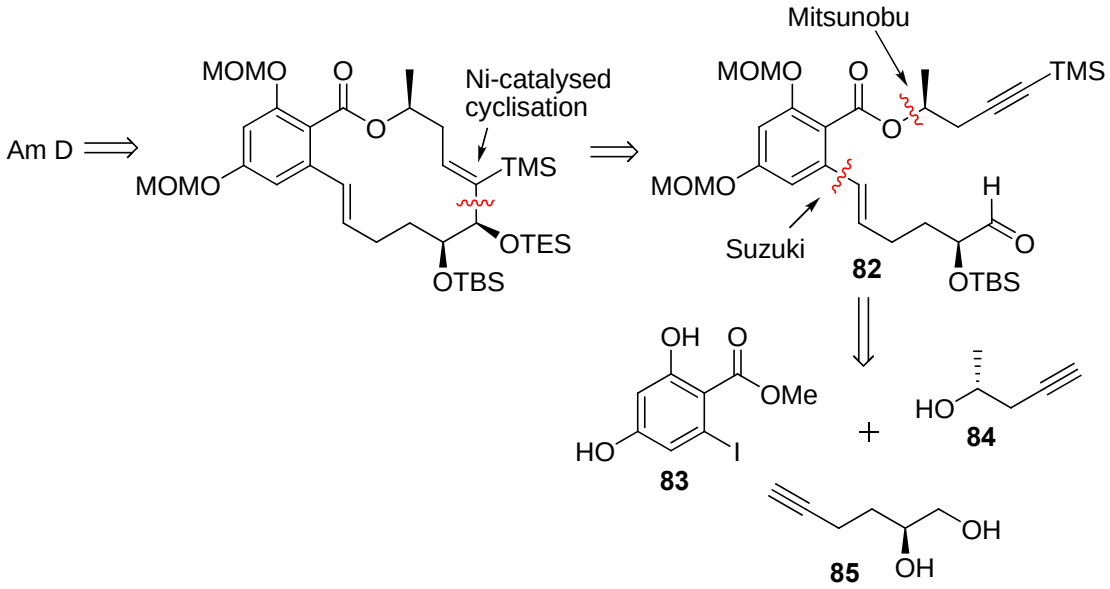
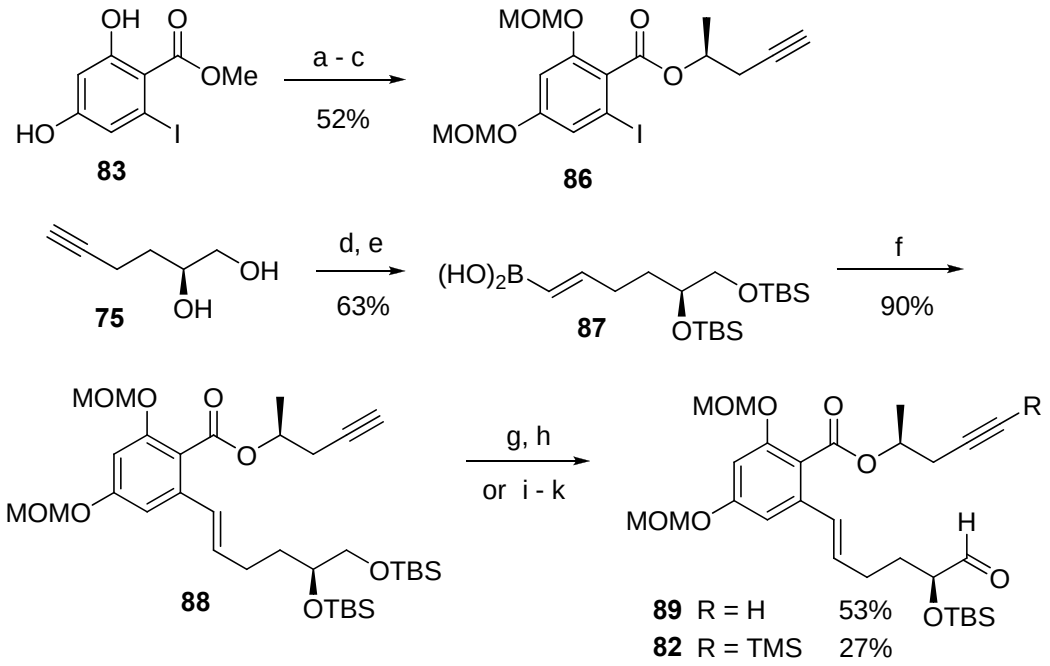


Figure 1–16. Retrosynthetic analysis of Am D by Montgomery et al.

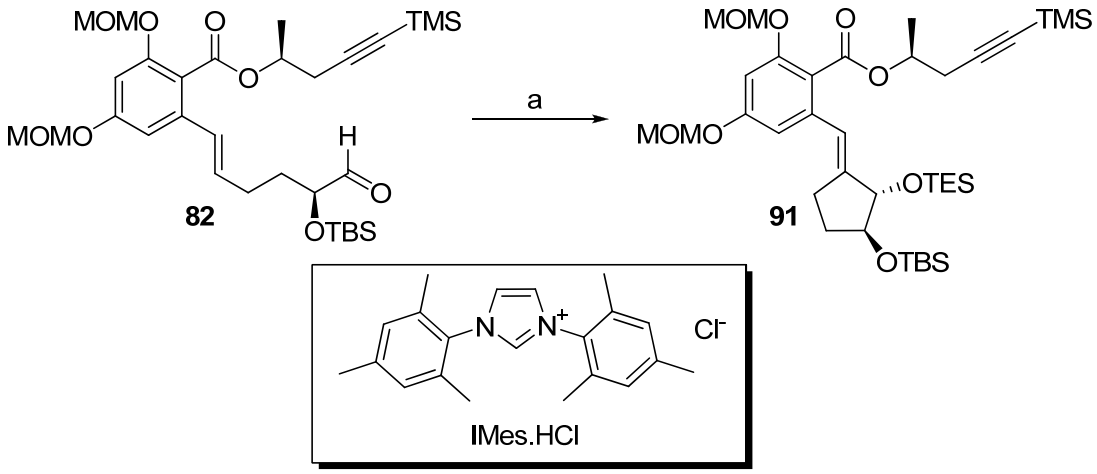
Aryl iodide **83** was protected as the bis-MOM derivative before ester hydrolysis and subsequent Mitsunobu esterification with alcohol **84** which afforded ester **86** in 52% yield (Scheme 1–17). Alkenyl boronic acid **87** was prepared from the known diol **85** by bis-silyl protection prior to treatment with catecholborane and catalytic 9-BBN. The carbon skeleton was completed through the palladium-catalysed cross-coupling of the boronic acid **87** with aryl iodide **86** providing **88** in excellent yield. Intermediate **88** was either selectively monodeprotected and oxidised to aldehyde **89** or silanated prior to selective monodeprotection and oxidation giving aldehyde **82**.



Scheme 1–17. Montgomery's synthesis of key fragments and assembly of the cyclisation precursors **82** and **89**.

Reagents and conditions: a) MOMCl, *i*-PrNEt$_2$, 87%; b) NaOTMS, 86%; c) DEAD, PPh$_3$, then **84**, 70%; d) TBSCl, Im, 97%; e) catecholborane, 9-BBN (8 mol%), then NaOH, 65%; f) **86**, TlOET, Pd(PPh$_3$)$_4$ (35 mol%), 90%; g) HF.py, 66%; h) Dess-Martin, 81%; i) LDA, TMSCl, 49%; j) HF.py; k) Dess-Martin, 56% (two steps).

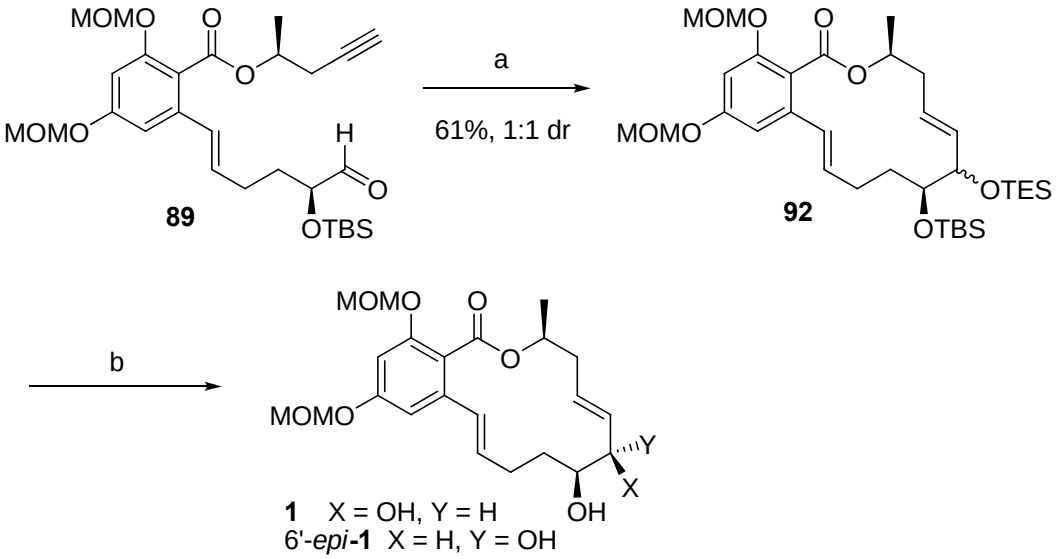
Montgomery and co-workers first investigated the macrocyclisation of the precursor **82** with Et$_3$SiH (5.0 equiv.), Ni(COD)$_2$ (25 mol%), IMes·HCl (25 mol%), and *t*-BuOK (25 mol%) (Scheme 1–18). Rather than forming the expected macrocycle, a new product that retained the alkynyl silane but had lost the aldehyde was isolated as the major product. Evaluation of the COSY, HMQC and NOE data led to the structural assignment of **91**.



Scheme 1–18. Attempted macrocyclisation of alkynyl silane **82**.

Reagents and conditions: a) Et$_3$SiH, Ni(COD)$_2$ (25 mol%), IMes·HCl (25 mol%), t-BuOK (25 mol%), 50%.

With the failure of the alkynyl silane **82** to cyclise to the desired macrocycle, Montgomery and co-workers turned to the cyclisation of alkyne **89** (Scheme 1–19). Prior studies carried out in their laboratory had shown that terminal alkynes undergo intermolecular couplings with α-silyloxy aldehydes albeit with a considerably lower diastereoselection than alkynyl silanes. Under these same cyclisation conditions desired macrocyle **92** was obtained in 61% yield as a 1:1 mixture of diastereoisomers. Global deprotection under acidic conditions afforded aigialomycin D (**1**) in 46% yield and the 6′-epimer of Am D (6′-*epi*-**1**) in 44% yield after preparative HPLC separation. Thus, Montgomery completed the synthesis of Am D in a total of 8 steps from known starting materials with a 7% overall yield.



Scheme 1–19. Montgomery's synthesis of Am D.

Reagents and conditions: a) Et_3SiH, $Ni(COD)_2$, IMes·HCl, t-BuOK (25 mol% each), 61%; b) 0.5M HCl/MeOH, then HPLC separation, 46%.

1.3.3.6 Zhang's Synthesis of the C2′–C7′ Segment of Am D

Synthesis of the C2′–C7′ segment of Am D was published by Zhang and Chen in 2007 (Figure 1–17).[37] They reported the synthesis of this segment in six steps from D-ribose (**93**) with 37% overall yield.

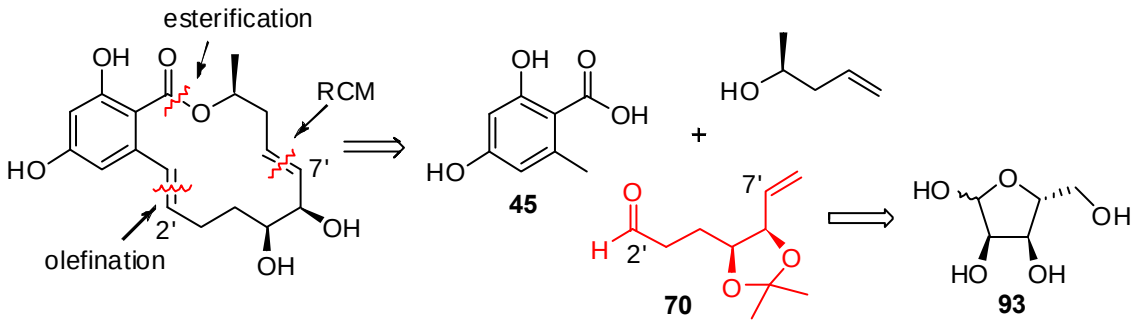
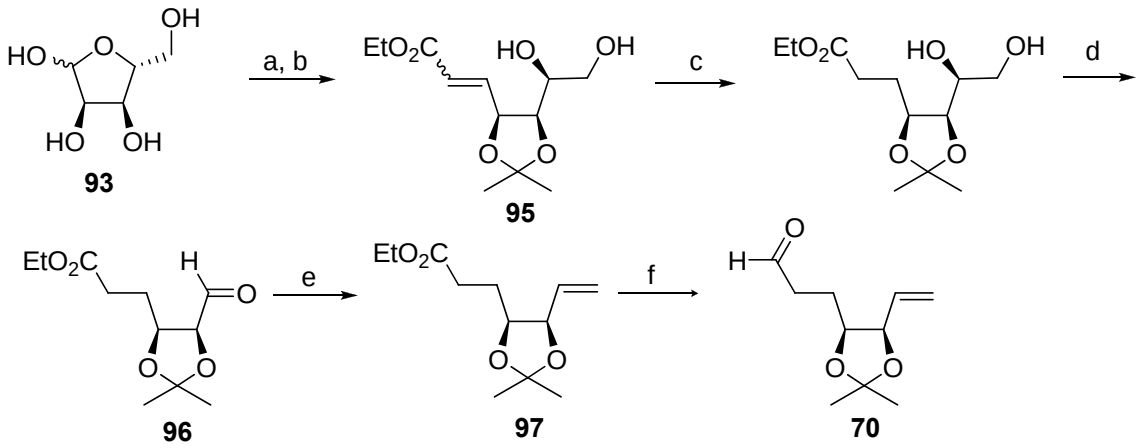


Figure 1–17. Retrosynthetic analysis of Am D by Zhang and Chen.

After acetonide protection of the *cis*-diol of D-ribose (**93**), the carbon chain was extended through a Wittig olefination (Scheme 1–20). Alkene **95** was hydrogenated prior to oxidative cleavage of the unprotected diol to give aldehyde **96**. A second Wittig reaction was used to install the terminal olefin of the desired fragment. Finally, selective reduction of ethyl ester **97** afforded aldehyde **70**, the desired C2′–C7′ segment of Am D.



Scheme 1–20. Zhang and Chen's synthesis of the C2′–C7′ segment.

Reagents and conditions: a) acetone, H_2SO_4 (cat.), 93.5%; b). CH_2Cl_2, $PPh_3{=}CHCO_2Et$, $PhCO_2H$ (cat.), 97%; c). MeOH, H_2 (101.3 kPa), 5% Pd/C (cat.), 94%; d). MeOH/H_2O (1:1), $NaIO_4$, 78%; e). THF, $Ph_3P^+CH_3Br^-$, *n*-BuLi, 80%; f). THF, DIBAL-H, -78 °C, 70%.

Zhang and Chen are likely to strike difficulties incorporating aldehyde **70** into a total synthesis of Am D, as Chen and co-workers[35] have shown that δ-lactone formation results from an alkylation of an aldehyde such as **70** with a suitable aromatic fragment. Futhermore, olefination through a Wittig, HWE or Juliá-Kocienski reaction will likely result in the formation of the undesired six-membered cycle upon subsequent RCM, as shown by Winssinger.[9]

1.3.3.7 Jennings' Synthesis of 6′-*epi*-Am D

Jennings and Bajwa reported an attempt to synthesise Am D that led to the synthesis of 6′-*epi*-aigialomycin D and *deoxy*-aigialomycin C.[38] Jennings and Bajwa utilised the common disconnections at the lactone and C1′–C2′ alkene, and a disconnection at C6′ – C7′ (Figure 1–18). A key feature of Jennings and Bajwa's approach was the utility of an alkynyl addition to obtain the diol functionality. Other important features were the esterification of the diol fragment to form the metathesis precursor and the attempted use of a RCM reaction to form the macrocyle of Am D via installation of the benzylic olefin.

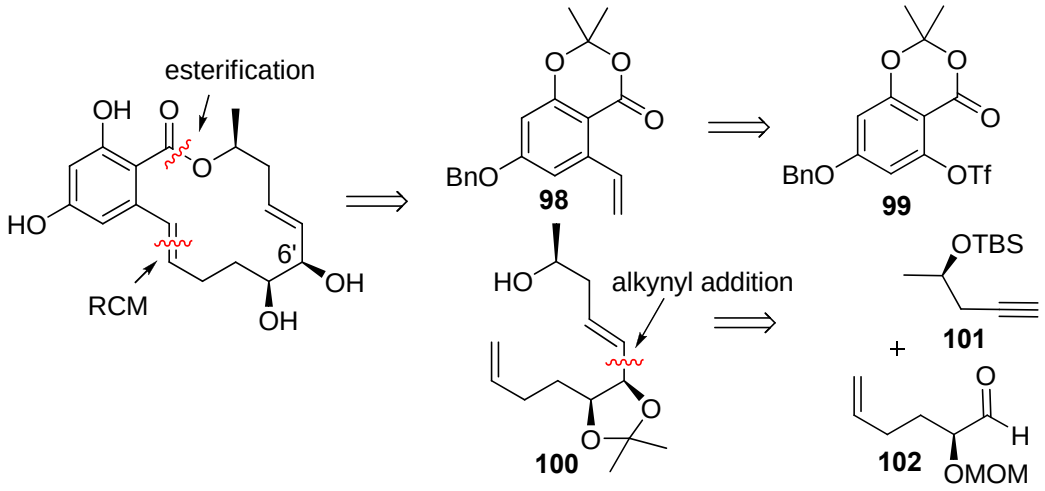
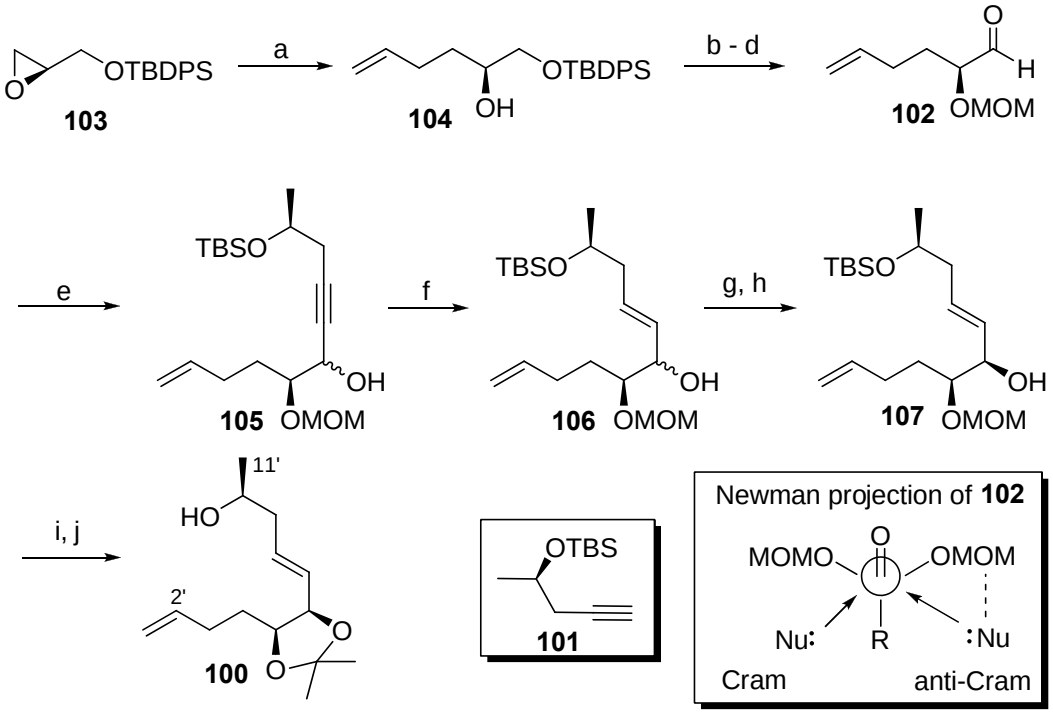


Figure 1–18. Retrosynthetic analysis of Am D by Jennings and Bajwa.

Synthesis of the diol fragment started with the treatment of known epoxide **103**[62] with allyl magnesium bromide to give alcohol **104**. Protection of the free hydroxyl group as the MOM ether before selective deprotection and oxidation of the resulting primary alcohol afforded aldehyde **102** in 57% yield over 4 steps. Addition of alkyne **101** to aldehyde **102** yielded the entire carbon skeleton of the C2′–C11′ fragment, **105**, in 71% yield. The addition of **101** to **102** gave rise to alcohol **105** with a 2:1 diastereoselective ratio (dr) favouring the desired Cram product[63] (Scheme 1–21), contrary to expectations of modest selectivity for the anti-Cram product due to the ability of the MOM group to provide chelation-control in such additions. Stereoselective reduction of alkyne **105** was achieved through chelated hydroalumination with Red-Al, affording olefin **106** with an *E/Z* ratio ≥ 15:1, whilst retaining the 2:1 dr at the C6′ hydroxyl group.

To set the required stereochemistry at C6′, alcohol **106** was oxidised with TPAP-NMO, and reduced by chelation control to afford *cis*-diol **107**. Both lithium and sodium borohydrides failed to give any selectivity in this reduction. LAH reduction provided the diol in high yield but with a selectivity that replicated the dr from the addition reaction. However, reduction with Red-Al provided the desired alcohol **107** with an acceptable dr of 6:1 (by ^{1}H NMR of crude product) in a good yield of 84%. Deprotection of alcohol **107** under acidic conditions was followed by reprotection of the *cis*-diol as isopropylidene **100** in 62% yield over two steps.

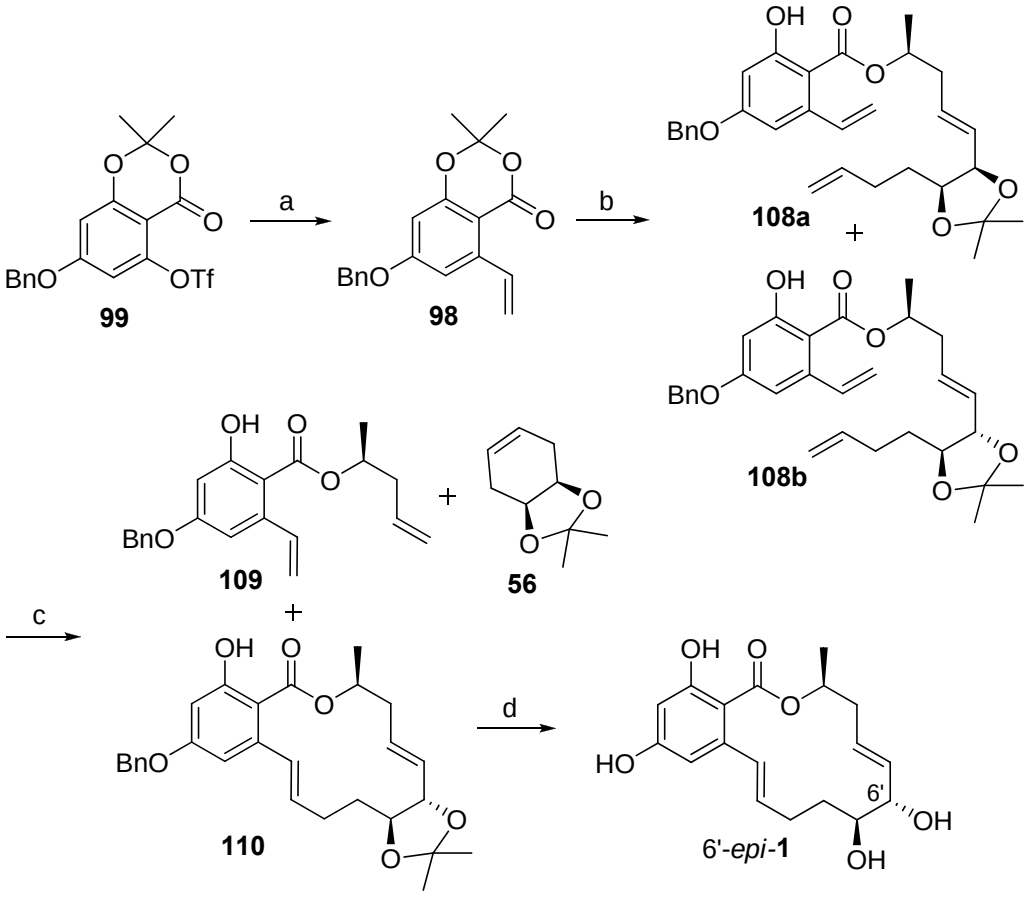


Scheme 1–21. Jennings and Bajwa's synthesis of diol intermediate **100**.

Reagents and conditions: a) Li_2CuCl_4 (2 mol%), allylMgBr; b) MOMCl, DIPEA, 93%; c) TBAF, 96%; d) TPAP (10 mol%), NMO, 74%; e) *n*-BuLi , **101**, 71%; f) Red-Al, 72%; g) TPAP (10 mol%), NMO, 92%; h) Red-Al, 84%; i) HCl (two drops concd), MeOH, 100%; j) DMP, PPTS (2 mol%), 62%.

The aromatic fragment was prepared from known aryl triflate **99** (Scheme 1–22).[64] Suzuki-Miyaura coupling of aryl triflate **99** with potassium vinyl trifluoroborate and $Pd(dppf)Cl_2$ provided styrene derivative **98** in 77% yield.[65] Treatment of **98** with the alkoxide anion of **100** afforded an inseparable mixture of esters **108a** and **108b** in a 6:1 diastereoisomeric ratio, the same as that for starting material **100**. Jennings and Bajwa relied on a chemoselective RCM reaction to provide the desired macrocycle. However, as Winssinger had earlier discovered,[9] carrying out the RCM reaction in the presence of an internal alkene resulted in the undesired formation of the six-membered ring **56**.

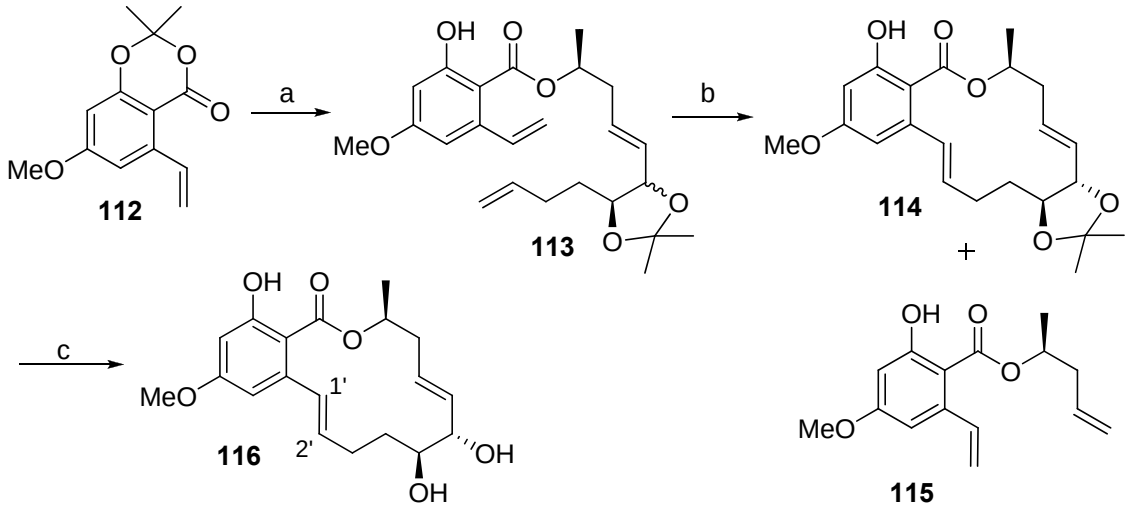
Thus, when the mixture of dienes **108a** and **108b** were submitted to RCM with second-generation Grubbs' catalyst **28** in refluxing CH_2Cl_2 (0.0002 M), macrocycle **110** and acyclic diene **109** were isolated in 14% and 84% yields (1:6), respectively. Thus it appears that the stereochemistry present at C6′ influences the result of the RCM reaction giving resolution of the two diastereoisomers. In the mechanism of the RCM reaction, the initial formation of the carbene must occur at the more accessible isolated alkene group followed by either 6- or 14-membered ring formation via RCM. Formation of the *cis*-isopropylidene protected cyclohexene diol (**56**) appeared to be favoured over macrocyclisation. Formation of the *trans*-isomer of **56** would be unfavourable due to the energy barrier in forming such a strained bicyclic system. Indeed, RCM macrocyclisation of epimer **108b** gave macrocycle **110** exclusively. Global deprotection of macrocycle **110** with boron tribromide afforded 6′-*epi* Am D (6′-***epi*-1**) in a respectable yield of 74%.



Scheme 1–22. Jennings and Bajwa's synthesis of 6′-*epi*-aigialomycin D.

Reagents and conditions: (a) potassium vinyl trifluoroborate, Et_3N, $Pd(dppf)Cl_2$ (10 mol%), 77%; b). NaH, **100**, 78% (6:1); c) Grubbs' 2nd gen. (5 mol%), 13% of **110** and 84% of **109**; d) BBr_3, 74%.

1′,2′-*deoxy*-Aigialomycin C was prepared by taking advantage of this diastereoselective RCM reaction (Scheme 1–23). Esterification of the methyl protected styrene derivative **112** with alcohol **100** (2:1 ratio at C6′) provided ester **113** in good yield. The subsequent RCM of diene **113** afforded macrocycle **114** in quantitative yield with respect to the *trans*-diol diastereomer of **113**. Deprotection of the isopropylidene moiety with HCl yielded 1′,2′-*deoxy*-aigialomycin C (**116**) in 17% yield over the 3 steps.



Scheme 1–23. Jennings and Bajwa' synthesis of 1′,2′-*deoxy*-aigialomycin C via a diastereoselective RCM reaction.

Reagents and conditions: (a) NaH, **100**, 78%. (b) Grubbs' 2nd gen. (5 mol%), 31%. (c) HCl (two drops conc.), MeOH, 69%.

1.3.3.8 Summary of Total and Partial Syntheses of Am D and Analogues

The partial and total syntheses discussed above can be summarised by considering Figure 1–19, which depicts all the disconnections made by these researchers. The most common disconnections of Am D were made at the two olefins and lactone functionality. Four of the seven routes used or envisioned use of an RCM reaction for macrocyclisation at C7′–C8′. Danishefsky, Chen, and Zhang accessed the *cis*-diol moiety from a chiral starting material, whilst Winssinger and Pan obtained this functionality through a stereoselective epoxide formation followed by ring opening. Montgomery and Jennings set the stereochemistry of the hydroxyl at C6′ through alkynyl additions with limited success.

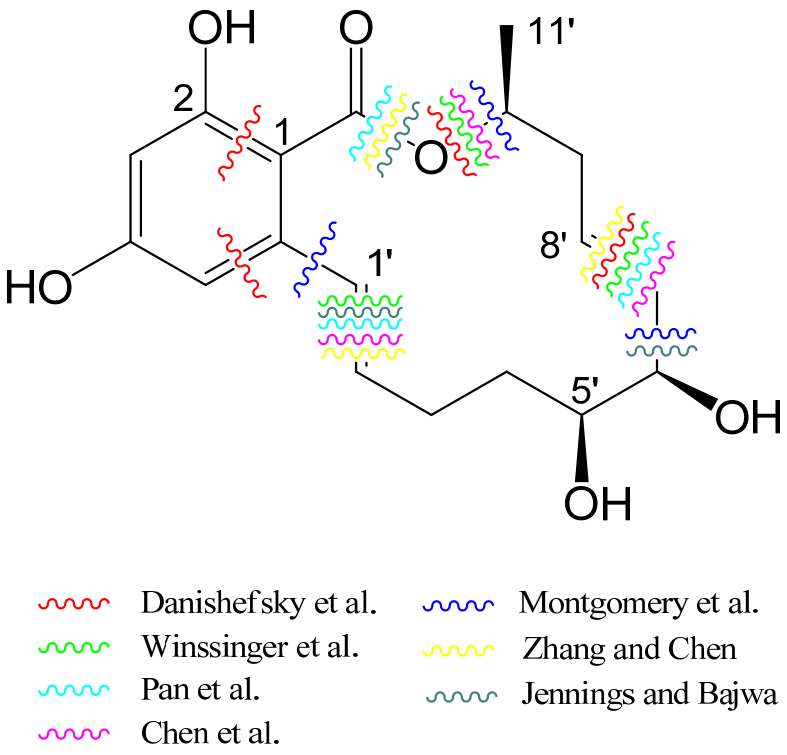


Figure 1–19. Summary of the retrosynthetic disconnects for all total and partial syntheses of Am D.

1.4 Research Objectives

Aigialomycin D (Am D) belongs to a family of important bioactive natural products whose small structural differences lead to wide ranging biological activities (from anabolic to antitumour activities) in the micromolar to nanomolar range (refer to Section 1.2.2). At the onset of this research project (2005), Danishefsky's synthesis of Am D was the only synthesis published in the literature. Therefore, there remained a need for a more efficient synthesis of Am D and analogues thereof. The aim of this research was to develop an efficient and convergent synthesis of Am D that would be amenable to the preparation of a variety of interesting analogues. With these analogues the hope was to either amplify the compound's activity into the nanomolar range or create a therapeutic window by skewing its bioactivity towards either antimalarial or cytotoxic activity whilst exploring the structure activity relationship (SAR) inherent in Am D. Thus, the following proposed routes to Am D were investigated. It became apparent during the course of the research project that a number of other research groups had devised similar synthetic strategies to those detailed below. Pan's synthesis, in particular, used similar Wittig and macrolactonisation chemistry to that which was proposed in the original synthetic approach to Am D presented here.

1.4.1 Total Synthesis of Am D and Analogues

In the two main approaches to Am D presented in this thesis, it was decided to make retrosynthetic disconnections between the lactone and the olefins at C1′ to C2′ and C7′ to C8′ (Figure 1–20). Subsequent publications revealed that these were to be commonly selected disconnections during Am D synthesis.[9,34,35,37] In all, five related strategies were designed. Three were part of the original plan, providing different options should key reactions fail. Two further options were later devised following experience from our own studies and that of recently published literature. The first strategy proposes the use of the Horner-Wadsworth-Emmons (HWE) variation of the Wittig reaction[66,67] to install the two (*E*)-olefins of Am D. The lactone functionality could be installed either before the C7′–C8′ alkene is incorporated or in a late-stage macrolactonisation. The second proposed strategy utilises a RCM reaction to connect the macrocycle at the C7′–C8′ olefin and the Ramberg-Bäcklund (RB) reaction to install the benzylic olefin. In this strategy, the ester linkage would be installed before the RCM reaction.

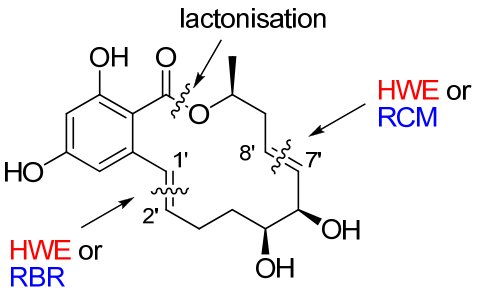


Figure 1–20. Proposed retrosynthetic disconnects for the HWE and RBR/RCM strategies to Am D.

1.4.2 HWE-Based Retrosynthetic Analysis of Am D

The HWE reaction is a well documented method for the installation of (*E*)-alkenes in the total synthesis of natural products.[68] Hence, HWE methodology seemed to be an ideal choice for the installation of the C1′–C2′ alkene, with the potential to couple arylphosphonate **121** with a carbohydrate-derived 2,3-dihydroxyaldehyde (e.g. **122** or **123**). The benzyl bromide **120** [69] and glucal-derived aldehydes **122** [70] and **123** [71] have been described previously in the literature. Similarly, the C7′–C8′ alkene could be installed through the HWE coupling of aldehyde **119** with hydroxyphosphonate **118**.

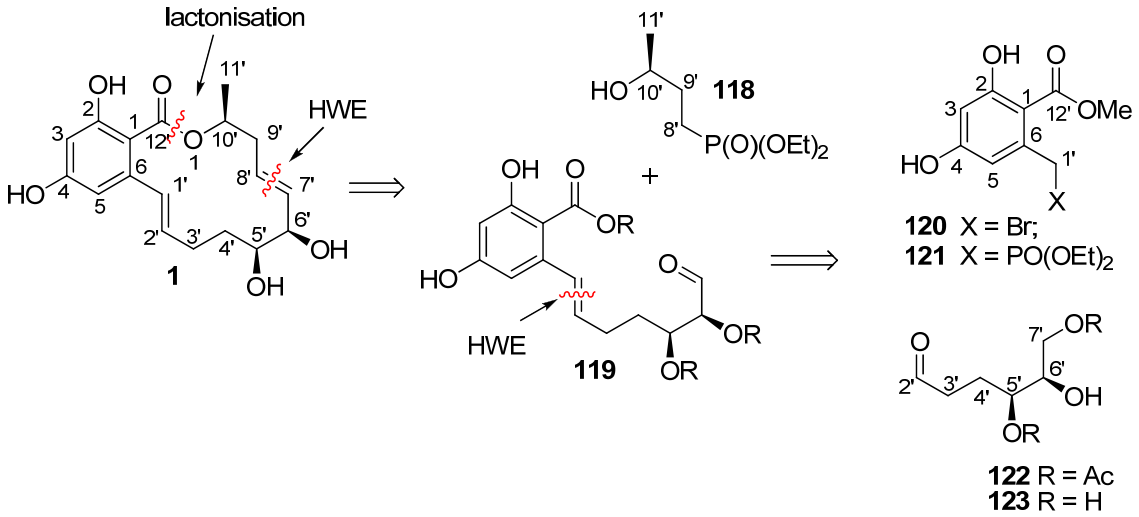


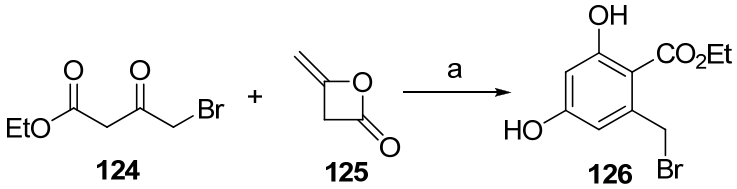
Figure 1–21. Proposed retrosynthetic analysis of Am D: the HWE route.

1.4.2.1 HWE-Based Synthetic Route

In this route, the aromatic segment, and the C2′–C7′ and C8′–C11′ segments would be prepared separately prior to their assembly. The aromatic segment could then be coupled with the C2′–C7′ chain before linking this extended moiety with the C8′–C11′ segment. Macrolactonisation would thus afford a protected derivative of Am D.

1.4.2.2 Proposed Synthetic Approaches to the Aromatic Segment

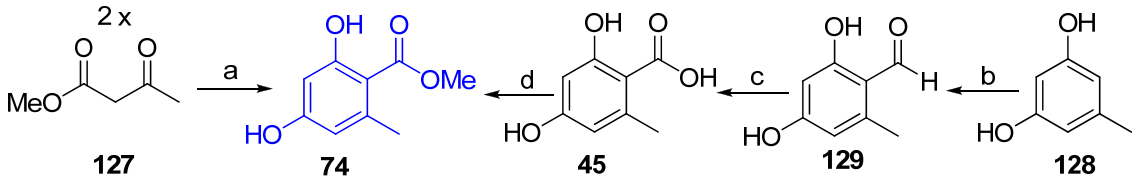
The ethyl analogue of arylmethyl bromide **126** (Scheme 1–24) has been previously prepared by a reaction of ethyl bromoacetoacetate (**124**) with diketene (**125**), albeit in low yield (8%).[69]



Scheme 1–24. Preparation of benzylic bromide **126**.[69]

Reagents and conditions: (a) NaH, 8%.

Alternatively, the non-brominated analogue **74** has been prepared in significantly better yield (46-78%) by self-condensation of methyl acetoacetate (**127**) (Scheme 1–25).[72] The resultant benzoate **74** (or a protected variant) could be brominated at the benzylic position. Another potential route to methyl orsellinate (**74**) is by formylation of 3,5-dihydroxytoluene (**128**) with DMF/$POCl_3$ to aldehyde **129**. This is then oxidised to the desired carboxylic acid (**45**) with sodium chlorite[73] prior to a Fisher esterification to compound **74** (Scheme 1–25).

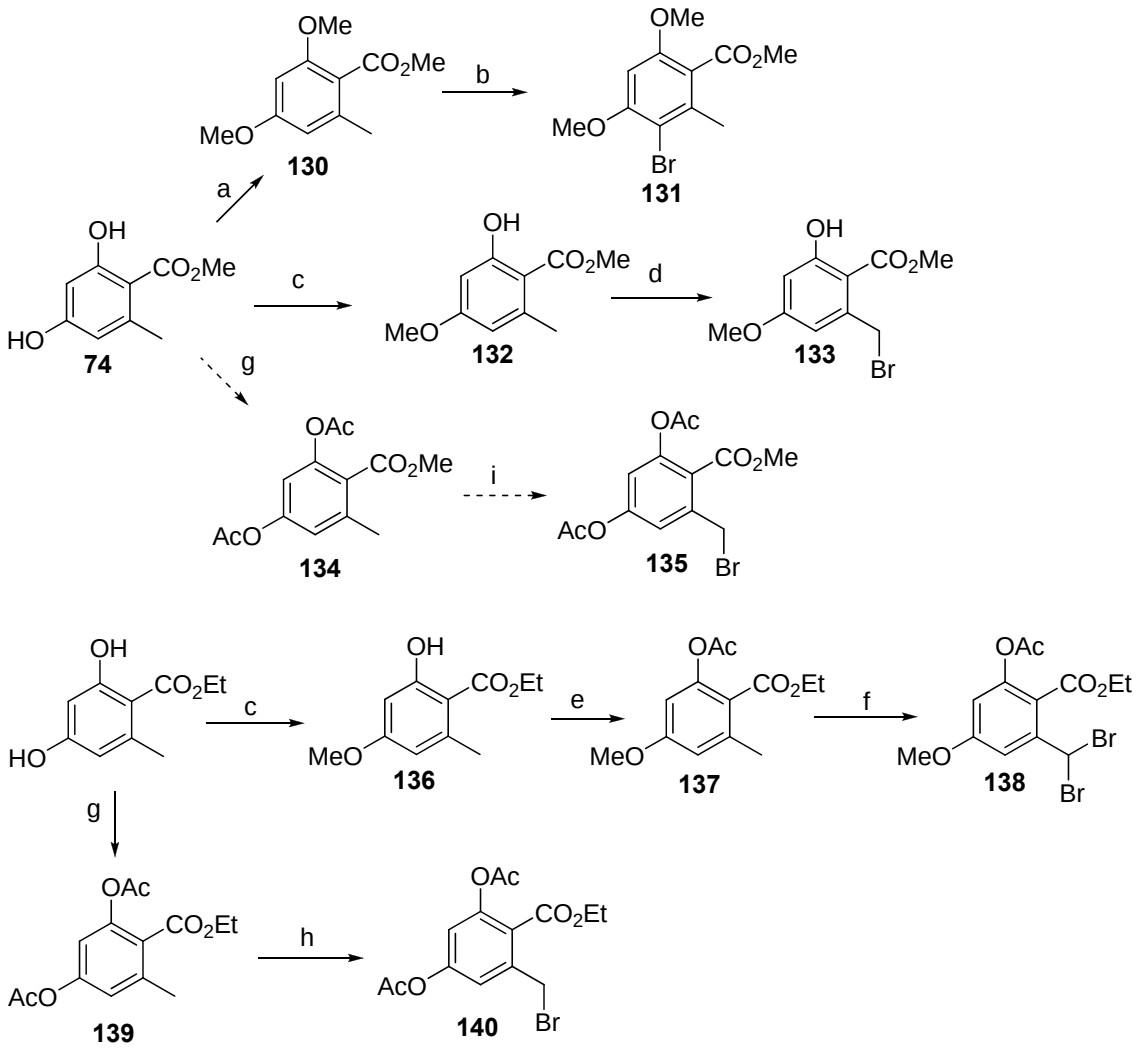


Scheme 1–25. Previous syntheses of methyl orsellinate (**74**).[72,73]

Reagents and conditions: a) NaH, *n*-BuLi, 46-78%;[72] b) DMF, $POCl_3$, then 10% NaOH; then 10% HCl; c) $NaClO_2$, NaH_2PO_4, 97% (two steps);[73] d) MeOH, H_2SO_4.

Franck and co-workers found that bromination of the 2,4-dimethoxy analogue **130**[74] with *N*-bromosuccinimide (NBS) without a radical initiator led to electrophilic aromatic substitution of a bromine atom (**131**)[75] (Scheme 1–26). However, benzylic bromination has been successfully achieved when the 4-hydoxyl group is methylated (**132**).[76] The efficient dibromination of **137**, with the 2-hydroxyl group acetylated, has also been claimed in a patent.[77] Unfortunately, the use of methyl ethers as protecting groups for phenolic hydroxyl groups has been shown to be problematic in later synthetic steps, as

deprotection requires harsh conditions that can cause decomposition of other parts of the molecule.[74] Eicher and co-workers successfully brominated diacetate **139** under UV-Vis irradiation in good yield (76%).[78] As a suitable UV-Vis irradiator was unavailable to us, Eicher's procedure required adaptation. Hence, bromination of **134** with NBS and benzoyl peroxide in carbon tetrachloride was expected to afford the desired bromide **135**. Acetate protection of the phenolic hydroxyl groups would also avoid the necessity for harsh deprotection conditions.

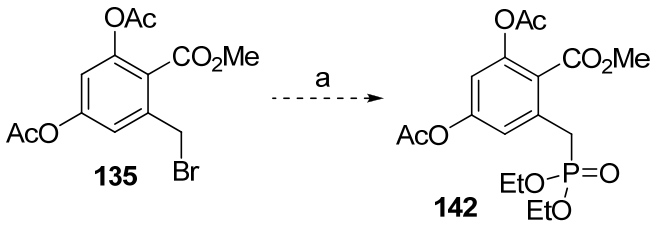


Scheme 1–26. Bromination of protected analogues of benzoate **74** and its ethyl homologue.[27] [75-78]

Reagents and conditions: (a) K_2CO_3, Me_2SO_4, 98%;[74] (b) NBS, CCl_4;[75] (c) MeI, K_2CO_3, 87%;[76] (d) Br_2, CCl_4, *hv*, 59%;[76] (e) Ac_2O, pyridine, 100%; (f) NBS, AIBN, CCl_4, 99%;[77] (g) Ac_2O, NEt_3; (h) Br_2, CCl_4, *hv*, 76%; [78](i) NBS, benzoyl peroxide, CCl_4.

[27] Solid arrows represent reactions described in the literature, whereas dotted arrows represent reactions that have not been reported.

With the arylmethyl bromide (**135**) in hand, the next step would be an Arbuzov reaction[79] with triethylphosphite to provide desired phosphonate **142** (Scheme 1–27).

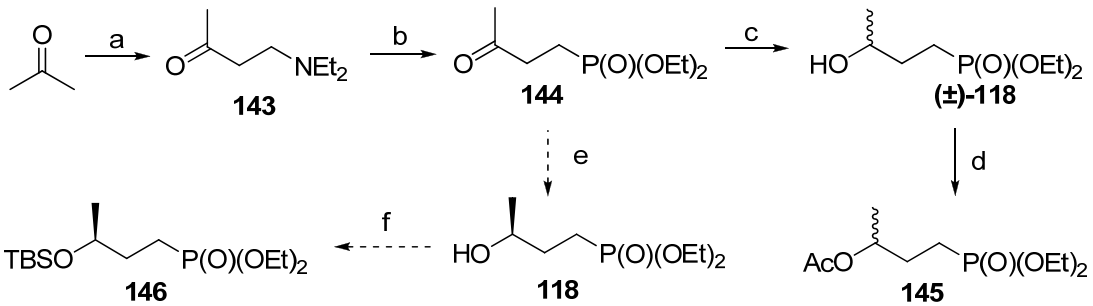


Scheme 1–27. Proposed synthesis of phosphonate **142**.

Reagents and conditions: (a) $P(OEt)_3$, 120 °C.

1.4.2.3 Proposed Synthetic Approaches to the C8′–C11′ Segment

The formation of compound **118** could be achieved via the reduction of diethyl 3-oxybutylphosphonate (**144**). The ketophosphonate **144** would be prepared from ketoamine **143**,[80] which itself could be obtained from a Mannich reaction[81] of diethyl amine hydrochloride, acetone and paraformaldehyde (Scheme 1–28). Amine **143** would then undergo an Arbuzov-like reaction with triethylphosphite upon activation with methyl iodide.[82] Diethyl 3-hydroxybutylphosphonate (**118**) has been prepared in racemic form by reduction of ketone **144**.[83] Despite successful kinetic resolution of lower homologues, treatment of this particular substrate with an acylating lipase did not lead to formation of the corresponding acetate in adequate optical purity.[83] Nonetheless, there are a number of chemical methods for stereoselective reduction of ketones,[84] so enantiopure **118** should be attainable. The hydroxyl group of the target synthon **118** may need protection prior to the HWE reaction. The TBS silyl ether (**146**) should be a suitable protecting group.

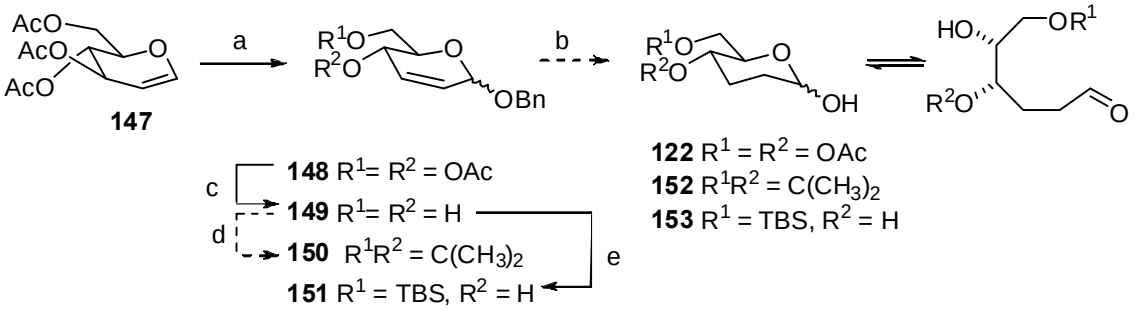


Scheme 1–28. Proposed preparation of phosphonate **118**.

Reagents and conditions: a) $HNEt_2 \cdot HCl$, CH_2O, 59%;[80] b) MeI, $P(OEt)_3$, 72%;[82] c) reduction; d) *Candida antarctica* lipase B (CALB), vinyl acetate;[83] e) (*R*)-2-methyl-CBS-oxazaborolidine, (*S*,*S*)-dimethylborolane or $RuCl_2$(*S*-BINAP); f) TBSCl, Im.

1.4.2.4 Proposed Synthetic Approaches to the C2′–C7′ Segment

The 2,3-dideoxyhexose derivatives **122**, **152** and **153** could serve as substrates for Wittig chemistry. Synthesis of these intermediates could be achieved via the Ferrier rearrangement[85] of tri-*O*-acetyl-D-glucal (**147**) with benzyl alcohol (Scheme 1–29).[86] Hydrogenation of this product (**148**) should remove the anomeric benzyl protecting group and reduce the double bond concurrently.[71] If the acetate protecting groups were to be not robust enough for the basic conditions of the HWE olefination, diacetate **148** could be converted to isopropylidene **152**. Deprotection of diacetate **148** would give diol **149**, which could then be protected as an isopropylidene acetal and undergo hydrogenation to hemiacetal **152**. Alternatively, if the acetal was found to be unsuitable for the hydrogenation conditions, **149** could be protected as silyl ether **151**[86] and then subsequently hydrogenated to give hemiacetal **153**.



Scheme 1–29. Preparation of carbohydrate-derived C2′–C7′ segments.

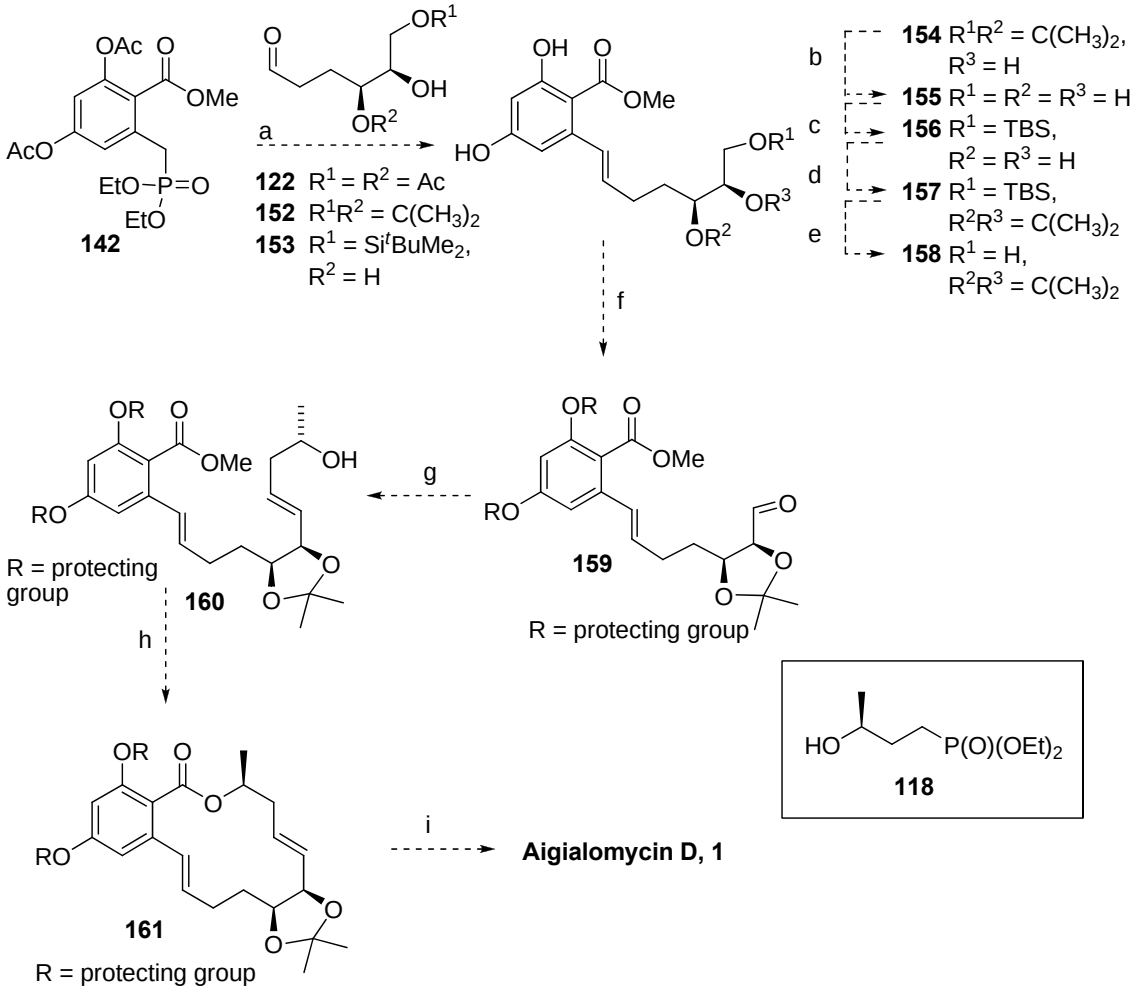
Reagents and conditions: a) BnOH, $FeCl_3$, 93%;[86] b) H_2, Pd/C; c) Na, MeOH, 95%;[86] d) 2,2-dimethoxy propane, *p*-TsOH; e) TBSCl, Im., 92%.[86]

1.4.2.5 Proposed Assembly of the Three Segments

The HWE reaction between the anion of phosphonate **142** and the open-chain form of hemiacetal **122** should afford alkene **140** (Scheme 1–30). As the base-labile acetate groups of **122** and **142** are likely to be cleaved in the HWE reaction, reprotection may be required before carrying out further chemistry. Selective protection of the primary hydroxyl as a TBS ether could be followed by formation of an isopropylidene acetal to protect the *cis*-diol moiety (**157**). Alternatively, silyl ether **153** could be suitable for use in the first HWE reaction, followed by protection of the *cis*-diol of **156** as isopropylidene **157**. If the lability of the acetate and silyl protecting groups on **122** and

153 prove to be problematic, the acetonide-protected hemiacetal **152** could alternatively be used as the HWE substrate. After deprotection of **154**, triol **155** could be transformed to isopropylidene **157** in three steps.

Removal of the silyl group and oxidation of resulting primary alcohol on **158** would provide aldehyde **159**. The HWE reaction between aldehyde **159** and phosphonate **118** should afford diene **160**, thus completing the carbon framework of Am D. Saponification of the methyl ester and then esterification, using either a carbodiimide protocol[87] or Yamaguchi macrolactonisation,[52] could provide the desired macrocycle **161**. Finally, the acetal could be hydrolysed under mildly acidic conditions, to complete the synthesis of aigialomycin D (**1**).



Scheme 1–30. Proposed final steps in the synthesis of Am D (**1**).

Reagents and conditions: a) base; b) 1M HCl; c) TBSCl, Im; d) 2,2-dimethoxypropane, *p*-TsOH; e) HF.py; f) oxidation; g) **118**, base; h) LiOH, THF/MeOH/H_2O then EDCI, HOBt, DMAP or 2,4,6-trichlorobenzoylchloride, Et_3N, then DMAP; i) 1M HCl.

1.4.3 RB-Based Retrosynthetic Analysis of Am D

An alternative approach to Am D was envisioned that utilises a combination of ring-closing metathesis (RCM) and the Ramberg-Bäcklund (RB) reaction[88] as the key steps for the generation of alkenes C7′–C8′ and C1′–C2′ respectively (Figure 1–22). Disconnections at the lactone and two alkenes give three fragments that are constitutionally related to those required for the HWE route. This approach enables coupling of the aromatic and C2′–C7′ prior to the RCM. The benzylic olefin is 'masked', initially as a thioether and later as a sulfone, with the olefin only revealed after the successful macrocyclisation. Intermediate thioether **167** could be obtained by either coupling iodide **168** with thiol **170** or by coupling thiol **169** with bromide **135**.

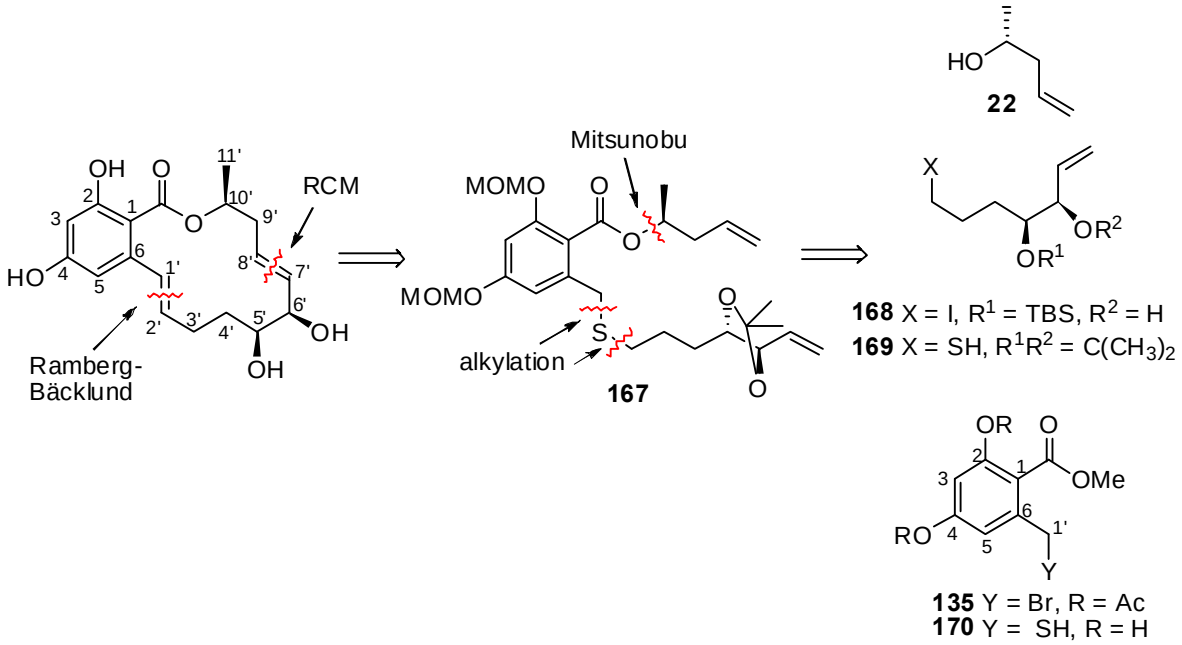
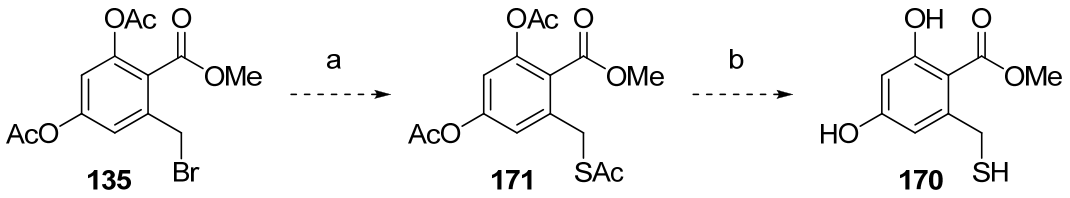


Figure 1–22. Proposed retrosythetic analysis of Am D: the RB route.

1.4.3.1 Proposed Synthetic Approaches to the Aromatic Segment

The two potential aromatic fragments required for the RB route are bromide **135** and thiol **170**. The proposed synthesis of bromide **135** was discussed earlier in Section 1.4.2.2. Thioacetate **171** could be prepared through the nucleophilic substitution of bromide **135** with potassium thioacetate (Scheme 1–31). Global deacetylation should be attainable by treatment with sodium methoxide in methanol to give thiol **170**.

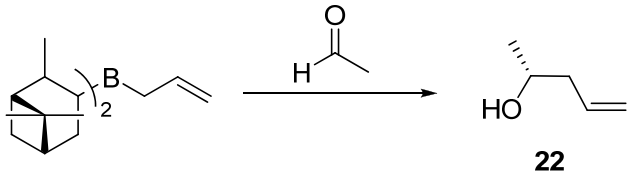


Scheme 1–31. Proposed synthesis of thiol **170**.

Reagents and conditions: a) KSAc; b) NaOMe.

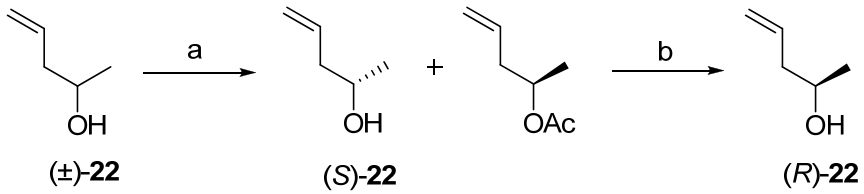
1.4.3.2. Proposed Synthetic Approaches to the C8′–C11′ Segment

The homoallylic alcohol segment, (*R*)-4-penten-2-ol (**22**), is commercially available from Sigma-Aldrich™ but could also be prepared via a boron-mediated asymmetric allylation of acetaldehyde (Scheme 1–32).[89,90] Utilisation of this methodology should provide sufficient quantities of alcohol **22**.



Scheme 1–32. The boron-mediated asymmetric allylation of acetaldehyde.

Alternatively, Banwell and Loong have described the enzymatic resolution of (±)-4-penten-2-ol [(±)-**22**] using *Candida antarctica* lipase B (CALB), leading to the isolation of homoallylic alcohols on a multigram scale with an ee > 99.9% (Scheme 1–33).[91]



Scheme 1–33. Banwell's enzymatic resolution of alcohol **22**.

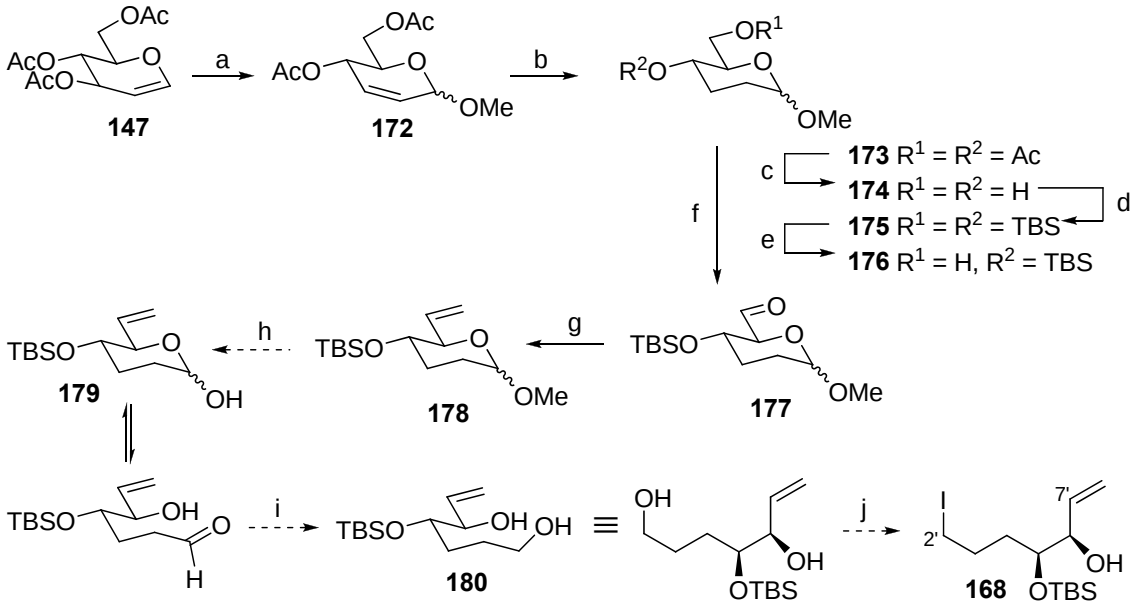
Reagents and conditions: a) vinyl acetate, CALB; b) pH 7.3 aq. phosphate buffer, CALB.

1.4.3.3 Proposed Synthetic Approaches to the C2′–C7′ Segment

In the proposed RB route to Am D, the diol segment of Am D could either be functionalised as an iodide (**168**) or thiol (**169**) depending on the functional group

present at the benzylic position of the aromatic segment (**135** or **170**). Iodide **168** could be prepared from tri-*O*-acetyl-D-glucal (**147**) (Scheme 1–34).

The synthesis of aldehyde **177** and subsequent conversion to olefin **178** has been previously reported by Nakata[92] and Saski[93], respectively. A Ferrier reaction of glucal **147** with methanol, followed by hydrogenation would give methyl glycoside **173**. Deprotection of diacetate **173**, reprotection as bis-TBS ether **175** and selective deprotection of the primary TBS ether would give access to alcohol **176**. Oxidation to aldehyde **177** would provide the substrate for a Wittig olefination to give alkene **178**. Hydrolysis of the methyl glycoside should lead to hemi-acetal **179**. Sodium borohydride[94] or lithium aluminium hydride (LAH) reduction[95] of the open-chain form of **179** should reveal a primary alcohol that could be selectively converted to iodide **168**.[96,97]

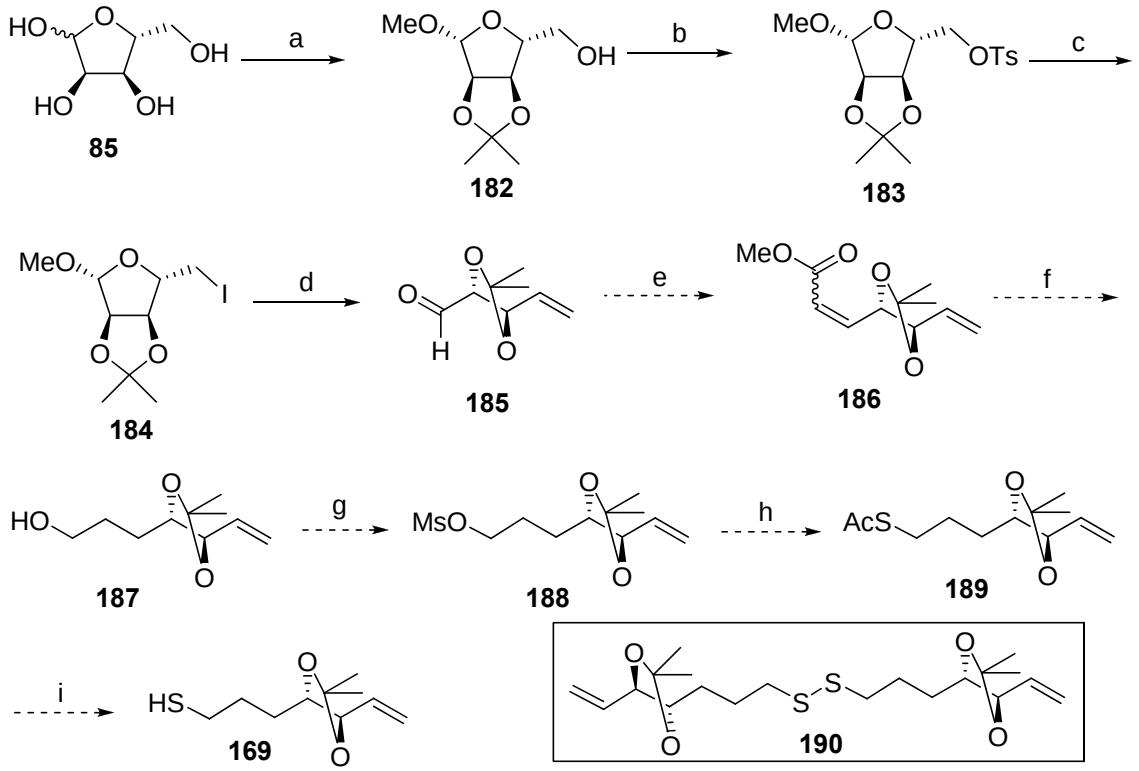


Scheme 1–34. Proposed preparation of C2′–C7′ segment **168**.

Reagents and conditions: a) MeOH, montmorillonite K-10; b) H_2, Pd/C; c) K_2CO_3, MeOH, 95% (three steps);[92] d) TBSCl, Im, 100%;[92] e) CSA, 97%;[92] f) SO_3·pyridine,[93] or $(COCl)_2$, DMSO, *i*-Pr_2NEt;[92] g) $Ph_3P^+CH_3Br^-$, base, 95%;[93] h) $AcOH/H_2O$; i) $NaBH_4$ or LAH, j) PPh_3, I_2.

Alternatively, thiol **169** could be accessed from D-ribose (**93**) via the known ω-enal **185** (Scheme 1–35).[98] It has been shown that D-ribose can be rapidly transformed to iodide **184**, via the nucleophilic displacement of tosylate **183** with potassium iodide.[98] Iodide **184** is the required substrate for a Vasella reaction[99] that should yield aldehyde **185**.[100-103] A two-carbon chain elongation of crude aldehyde **185** with methyl

triphenylphosphoranylidene acetate should give α,β-unsaturated ketone **186**. This Vasella/Wittig reaction system was used by van Boom in the synthesis of a variety of highly functionalised carbocycles.[104] These two steps might be able to be carried out in one pot, avoiding the isolation of the reactive aldehyde **185**. Selective reduction of the conjugated double bond in the presence of the terminal alkene should be achievable using a metal-catalysed conjugate reduction system: e.g. Mg metal/MeOH;[105] $NiCl_2.6H_2O/NaBH_4$;[106] $CuCl_2/NaBH_4$;[107] or $CuCl/NaBH_4$.[108] Subsequent reduction of the methyl ester with LAH should give alcohol **187**. In fact, it is possible that LAH might be a suitable reagent to carry out reduction of the conjugated alkene prior to reduction of the ester, thus affording saturated alcohol **187** in one step.[109] However, LAH reductions of such α,β-unsaturated systems have been shown in some cases to give a mixture of the unsaturated and saturated alcohols.[110] Activation of alcohol **187** by mesylation followed by nucleophilic displacement with potassium thioacetate should give thioacetate **189**. Deprotection of thioacetate **189** would afford desired thiol **169**. If the oxidation of thiol **169** to disulfide **190** is a concern, it could be generated in situ during the subsequent coupling reaction.



Scheme 1–35. Proposed synthesis of thiol **154** from D-ribose.

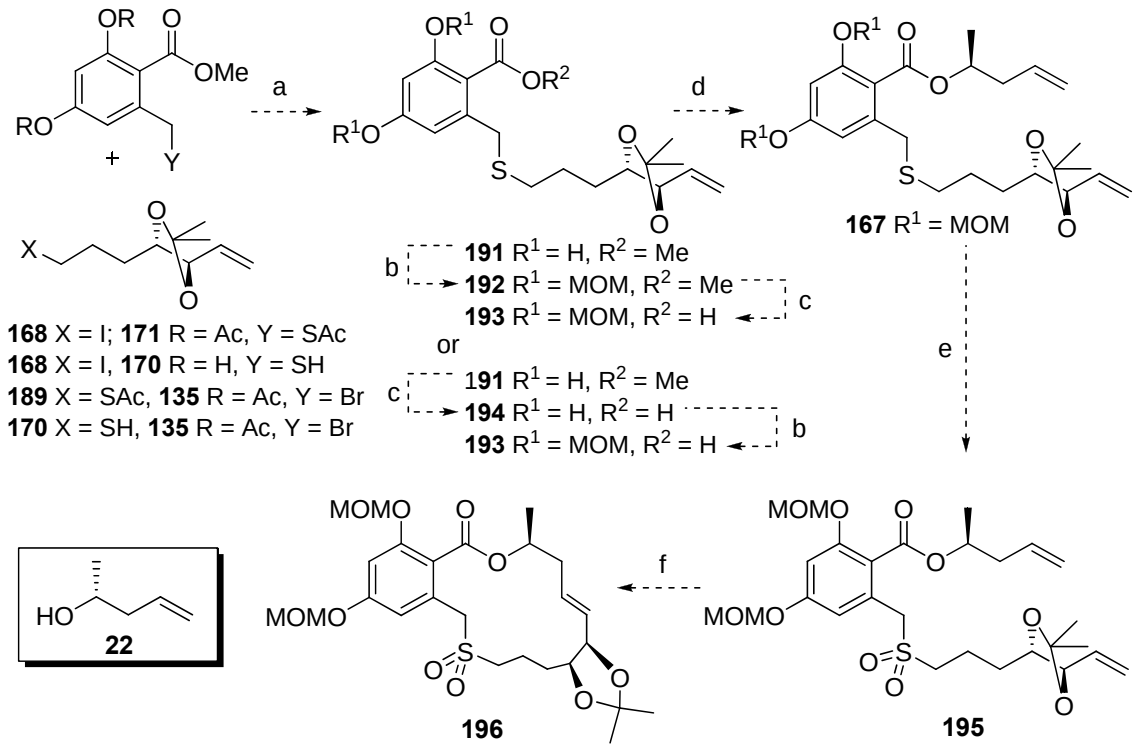
Reagents and conditions: a) Me_2CO, MeOH, HCl; b) TsCl, py., 54% (two steps);[98] c) NaI, 94%;[98] d) Zn, cat. AcOH; e) $Ph_3P{=}CHCO_2Me$; f) stepwise reduction; g) MsCl, NEt_3; h) KSAc; i) NaOMe.

1.4.3.4 Proposed Assembly of the Three Segments

It was proposed that the coupling of the aromatic and carbohydate-derived C2′-C7′ segments would involve a nucleophilic displacement of the alkyl or benzylic halide with a thiol, which would be prepared in situ or prior to the coupling reaction (Scheme 1–36). The basic conditions used in the coupling reaction should also cleave the two phenolic acetates, giving two other potential nucleophiles. However, when the "hard and soft acids and bases" (HSAB) theory[111-113] is considered, the soft organohalide should favour nucleophilic attack of the soft thiolate ion leading to the desired product **191**. The free phenolic hydroxyl groups could be protected as MOM ethers either before or after saponification of the methyl ester. Homoallylic alcohol **22** could be coupled to carboxylic acid **193** through a Mitsunobu esterification thus completing the carbon framework of Am D.

The RB reaction requires thioether **167** to be oxidised to a sulfone. Thioethers are typically oxidised with *meta*-chloroperbenzoic acid (*m*-CPBA),[114-116] $NaBO_3$/AcOH,[117] Oxone™ ,[118] or H_2O_2/AcOH;[119] reagents which also have the potential to epoxidise double bonds. The fact that terminal alkenes are generally less reactive towards epoxidation than internal alkenes[120] suggests that it would be prudent to oxidise the thioether prior to RCM. Indeed, Yao has demonstrated the chemoselective oxidation of thioethers to sulfones with *m*-CPBA in the presence of terminal alkenes.[116] Formation of the sulfone at this early stage also avoids the potential difficulties associated with RCM reactions of compounds containing low oxidation state sulfur.[121] The presence of the acid sensitive acetonide in thioether **167** suggests that *m*-CPBA and Oxone™ would be more suitable oxidising agents than the systems requiring acetic acid.

Following sulfone formation, the macrolactone will be formed by a RCM reaction. MW-assisted RCM reactions of macrocyclic systems similar to RCM precusor **195** have displayed improved yield and stereoselectivity for (*E*)-alkenes than the RCM reactions attempted under standard thermal condition.[35] Hence, treatment of diene **195** with Grubb's second generation catalyst (**28**) under MW-irridiation should provide the desired macrolactone **196**.

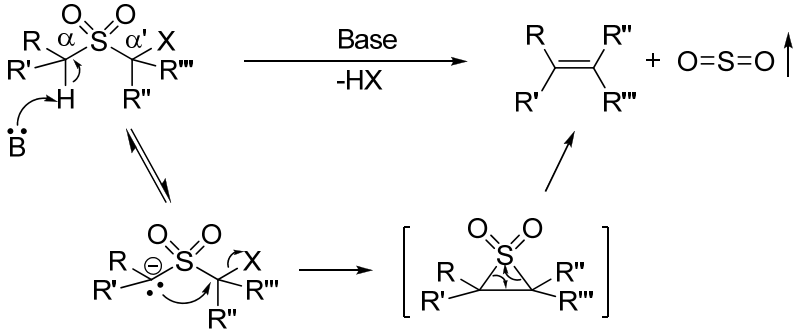


Scheme 1–36. Proposed coupling of the segments for the RB route.

Reagents and Conditions: (a) base; (b) MOMCl, NEt_3; (c) NaOH, $MeOH/H_2O$, Δ; (d) **22**, PPh_3, DIAD, THF; (e) *m*-CPBA; (f) **28**, MW

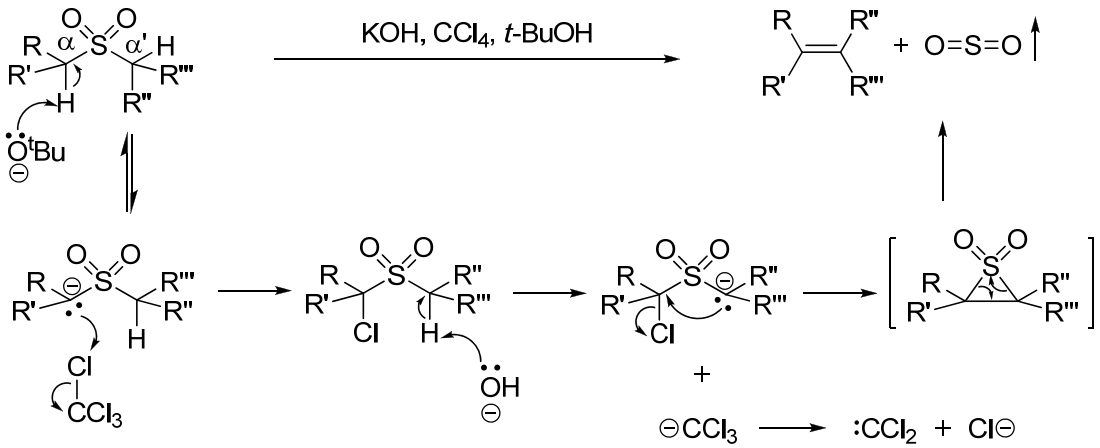
1.4.3.5 Ramberg-Bäcklund (RB) Reaction

At this stage, the benzylic olefin in Am D remains to be installed via a RB reaction. The RB reaction converts an α-halo sulfone into an alkene in the presence of a strong base, with the extrusion of sulfur dioxide (Scheme 1–37). The α-protons of a sulfone are of sufficient acidity that they can be abstracted by a strong base such as potassium *tert*-butoxide. The carbanion formed can nucleophilically displace the halide in the α′-position creating a short-lived episulfone. The unstable strained intermediate undergoes a cheletropic rearrangement, providing the desired alkene.



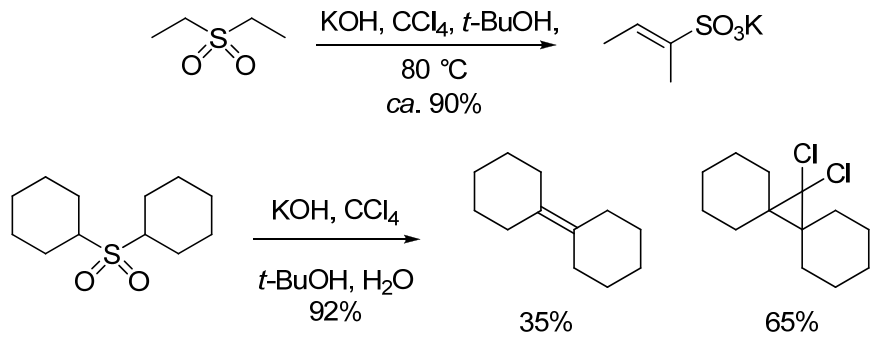
Scheme 1–37. Mechanism for the Ramberg-Bäcklund reaction.[122]

Two modifications of the RB reactions are commonly used; namely the Meyers[123] and Chan[124] modifications. The Meyers' modification of the RB reaction allows the direct conversion of unhalogenated sulfones to their corresponding alkenes via an in situ chlorination (Scheme 1–38). Meyers' protocol involves the treatment of a suitable sulfone with pulverised KOH suspended in a mixture of *t*-BuOH and CCl_4. Meyers' variant of the RB reaction further extended the synthetic utility of this olefination reaction and has been used extensively.[125,126]



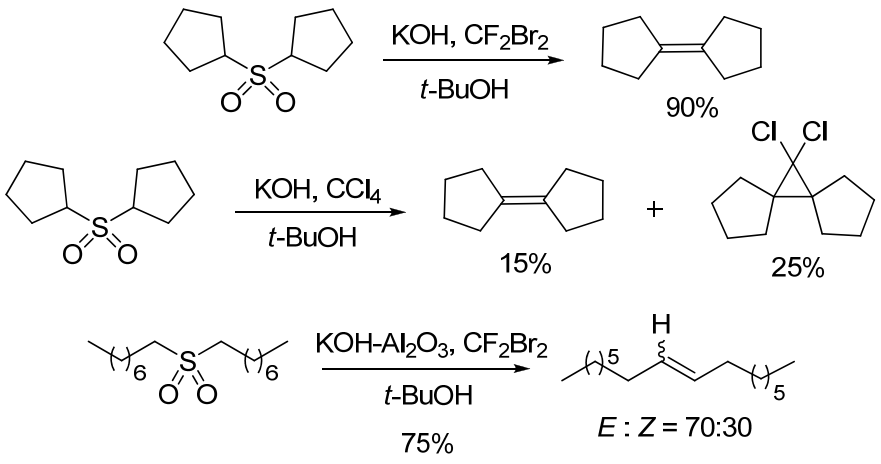
Scheme 1–38. Mechanism for Meyers' modification of the RB reaction.[127]

Whilst Meyers' protocol gives quantitative yields for the preparation of stilbenes from dibenzyl sulfones[123] and 1,1-diarylalkenes from benzhydryl sulfones,[128] sulfones of other structural types give rise to different byproducts: bis(primary alkyl) sulfones face α, α- and/or α, α′-dichlorination before the 1,3 elimination to afford predominantly the potassium salts of alkenesulfonates;[129] benzyl primary-alkyl sulfones suffer similar problems to give mixtures of the desired β-alkylstyrenes, α-chloro-β-alkylstyrenes, and potassium alkenesulfonates;[124] bis(*sec*-alkyl) sulfones give rise to largely tetraalkyl *gem*-dichlorocyclopropanes emerging from the subsequent attack of the tetrasubstituted alkenes by dichlorocarbene which is the by-product resulting from the initial chlorination (Scheme 1–39).[123]



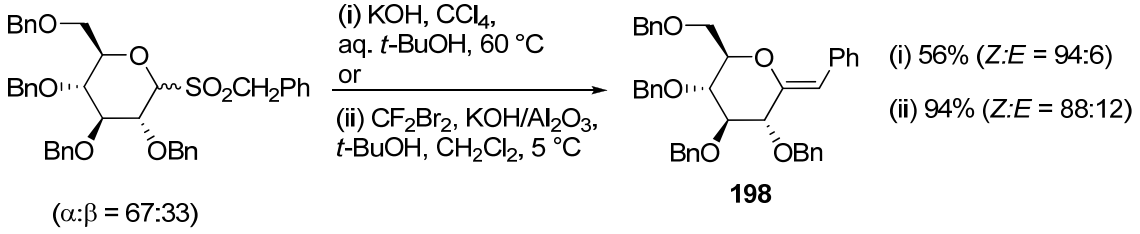
Scheme 1–39. Formation of the dichlorocyclopropanes and potassium alkenesulfonates under Meyers' protocol above.[125]

Chan and co-workers addressed these limitations by investigating alternative halogen sources for the RB reaction.[124] Chan found CF_2Br_2 to be the best substitute for CCl_4. The treatment of dicyclopentyl sulfone with pulverised KOH–CF_2Br_2–*t*-BuOH gave bicyclopentylidene as the only isolable product in 90% yield, whereas Meyers' protocol gave a mixture of products consisting of bicyclopentylidene (15%) and its dichlorocarbene adduct (25%) (Scheme 1–40).[123] Chan also found that exchanging pulverised KOH for alumina-supported KOH (KOH–Al_2O_3) subdued the dihalogenation prior to 1,3-elimination that plagued RB reactions with bis(primary alkyl) sulfones (Scheme 1–40). This change allowed to conversion to alkenes in good yields. Moreover, KOH–Al_2O_3 proved to be a superior base for all types of sulfones trialled.[124] The efficacy of the alumina-supported KOH was proposed to be a consequence of the greater surface area of the base and was perhaps also due to the activating effects of the alumina surface.[130]



Scheme 1–40. Comparison of the RB reactions of dicyclopentyl sulfone with CF_2Br_2 and CCl_4 as the halogen sources[127] and the successful RB reaction of dioctyl sulfone with Chan's protocol.[124]

The superiority of the Chan modification of the RB reaction over Meyers' modification was exemplified in Taylor's synthesis of *exo*-gycals (Scheme 1–41).[118] Despite Meyers' conditions delivering *exo*-glycal **198** in reasonable yield (56%), Chan's conditions gave exceptional conversion to the glycal **198** in 94% yield. In both cases the *Z*-product predominated.



Scheme 1–41. Synthesis of *exo*-glycal **198** via Meyers' and Chan's modifications of the RB reaction.[118]

There are a few examples in the literature of the RB reaction being used in the construction of macrocycles. MaGee and Beck attempted to use the RB reaction to install an (*Z*)-olefin in an 11-membered macrocycle (Table 1–2).[115] To their surprise, treatment of α-chlorosulfone **199** with *t*-BuOK afforded (*E*)-olefin **200** in excellent yield and stereoselectivity (97%, 98:2 *E*/*Z*) despite the expectation that the (*Z*)-isomer of **200** would dominate. Attempts to reverse the stereoselectivity of the reaction through changing the base failed to provide stereochemically pure (*Z*)-olefin. Although the levels of (*Z*)-olefin did improve, it was at the expense of the overall yield. MaGee's results support our expectation that the RBR on sulfone **196** will give the desired (*E*)-olefin **35**.

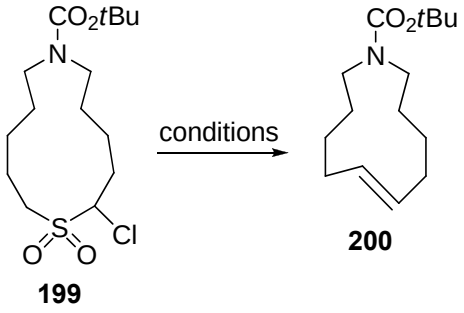
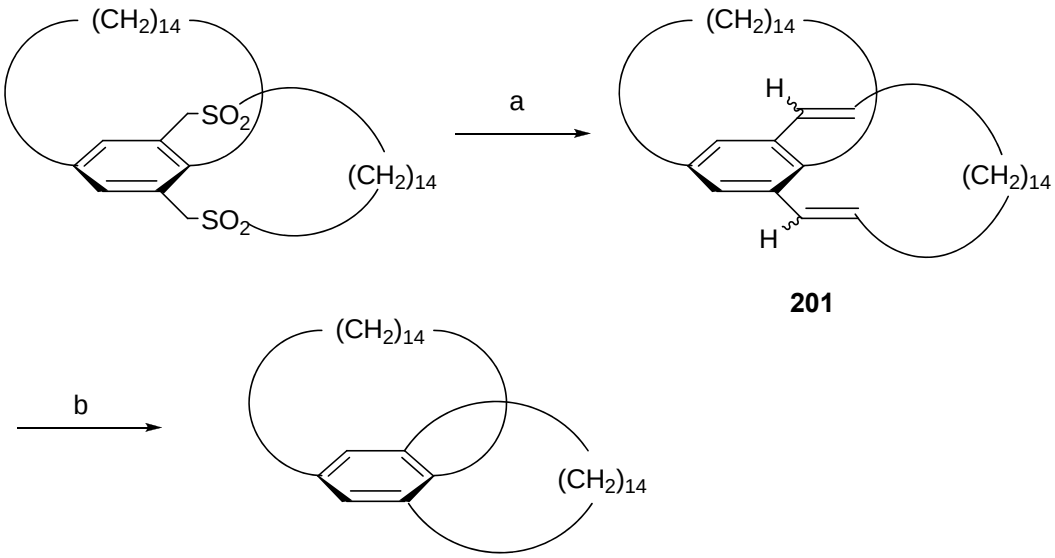


Table 1–2. RB reactions of sulfone **189** reported by MaGee and Beck.[115]

Reaction conditions	Yield (%)	% (*E*)	% (*Z*)
t-BuOK, DMSO, rt, 10 min	97	98	2
aq. KOH, H_2O, 100 °C, 1 h	57	61	39
DBU, toluene, 110 °C, 1 h	56	57	43
NEt_3, toluene, 110 °C, 1 h	NR		
Urea, H_2O, 100 °C, 1 h	NR		
NBu_3, toluene, 110 °C, 1 h	NR		

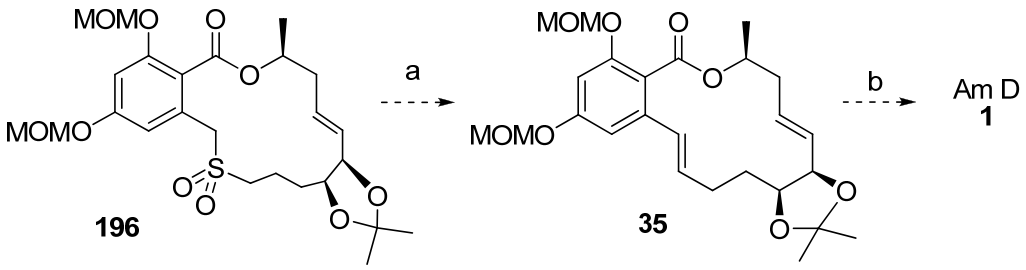
Chan et al. utilised the RB reaction to form a 17-membered macrocycle in the synthesis of [14][14] metaparacyclophane (Scheme 1–42).[131] The ^{1}H NMR spectrum of diene **201** showed a doubling of olefinic signals which indicated the presence of a mixture of stereoisomers. No ratio of these isomers was reported as this isomeric mixture was vanquished in the subsequent hydrogenation of the material.



Scheme 1–42. Chan's synthesis of [14][14] metaparacyclophane.

Reagents and Conditions: (a) CF_2Br_2, KOH–Al_2O_3, *t*-BuOH/CH_2Cl_2; (b) H_2, Pd/C, 28% (two steps).

Both Meyers' and Chan's protocols were explored during the course of this research to find the optimal conditions for the RB reaction of substrate **196**. A successful RB reaction would yield macrocycle **35** and thus complete the formal total synthesis of Am D (Scheme 1–43). Global deprotection of **35** would be achieved by treatment in acidic conditions, affording the natural product **1**.[33,35]



Scheme 1–43. Use of RB reaction to complete the synthesis of Am D, **1**.

Reagents and conditions: (a) CCl_4, *t*-BuOH, KOH, or CF_2Br_2, *t*-BuOH, KOH/Al_2O_3; (b) HCl.

1.5 Plans for Analogue Synthesis

Our devised synthetic route should be adaptable to analogue synthesis by making functional group or stereochemical changes to one or more of the three major fragments of Am D. These functional modifications could be included prior to assembly or a variation could potentially also be introduced at a later stage. For example, one could invert the stereochemistry of the hydroxyl at C5′, creating a *trans*-diol (**202**), simply by using D-galactose instead of D-glucose as the starting material for the carbohydrate fragment (Figure 1–23). Likewise, the stereochemistry of the C10′ methyl (**203**) could be inverted by either reducing the ketophosphonate to the (*S*)-alcohol, by esterifying **118** under Mitsunobu conditions or by coupling homoallylic alcohol **22** via a carbodiimide protocol (Figure 1–23). The 2,4-dideoxy Am D analogue **204** could be accessed from methyl 2-methylbenzoate derivates **205**. This simplified aryl analogue should additionally be an excellent model system on which to investigate the key reactions proposed for our strategies towards Am D.

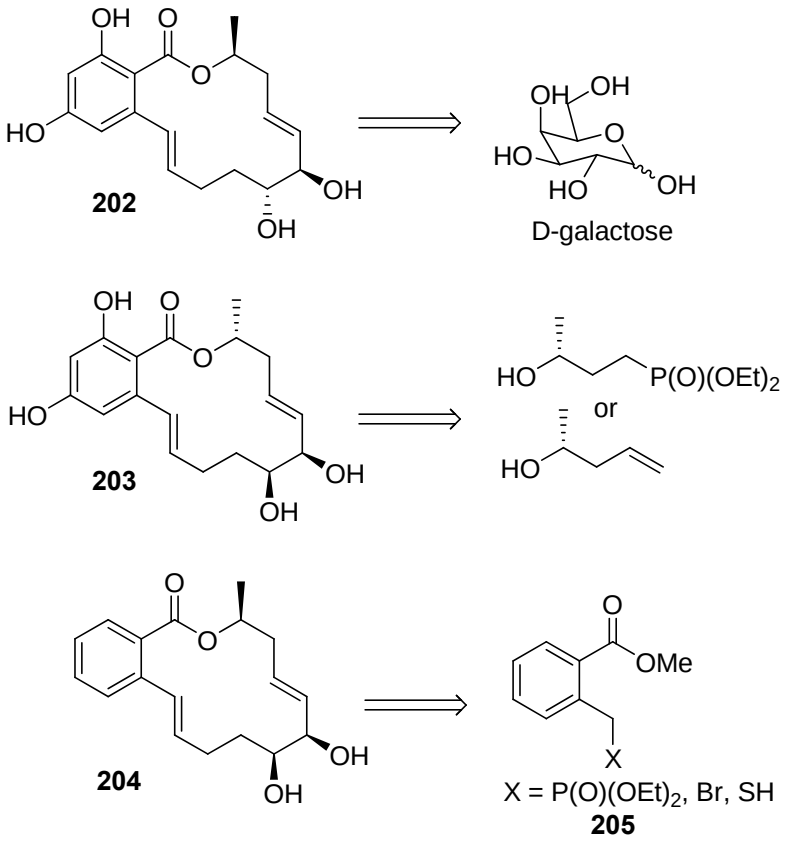


Figure 1–23. Potential analogues of Am D with different stereochemistries or aryl functionalisation.

Other simple modifications include alkyl substitution of one or both of the phenol groups (**206**) (Figure 1–24). An aryl substituent could be introduced at C5 (**207**), in a similar manner to the chlorine atom that is present in radicicol and some of the pochonins. Regioselective chlorination has been achieved with such resorcylic compounds using thionyl chloride.[33] However, this product is usually accompanied with its isomeric chlorinated product (~70:30, desired aryl chloride to isomer). Blagg used calcium hypochlorite to accomplish this transformation on a similar system in good yield (88%), without reporting isolation of the C3-isomer.[132]

An epoxide or cyclopropyl group could potentially be introduced at a late stage in the synthesis (**208**) (Figure 1–24). The epoxide of pochonin A has previously been introduced after formation of the macrolactone using methyl(trifluoromethyl)-dioxirane giving a 3:1 diastereomeric mixture.[133] Introduction of a cyclopropyl group at a similar stage using (*R,R*)- or (*S,S*)-dioxaborolane, diethyl zinc and diiodomethane could also be attempted.[134] Hydrogenation of Am D (**209**) would yield a C5′ hydroxy analogue of β-zearalanol,[135] which might exhibit some interesting anabolic properties.

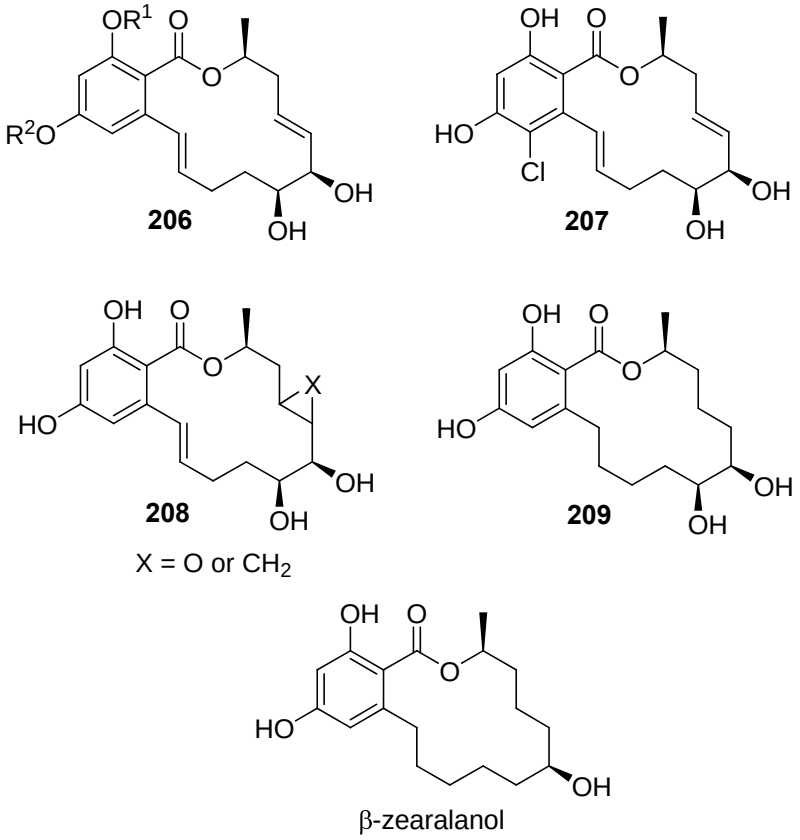


Figure 1–24. Potential analogues of Am D containing alkylation, substitution, epoxidation, cyclopropanation or hydrogenation.

1.6 Summary of Synthetic Routes

The above two sections have described several potential routes to the natural product aigialomycin D (**1**) and analogues thereof, which rely on HWE or RCM and RB methodology to install the two (*E*)-alkenes. These two main convergent strategies are amenable to the synthesis of a wide range of analogues that will enable exploration of the structure activity relationship inherent in Am D. Flexibility has also been built into the design such that, as is inevitably needed, the protecting groups may be altered and the order of the final steps may be changed. The successful development of our proposed synthetic strategies are discussed in the following chapters.

Chapter Two:

Synthesis of the Aromatic Segment

The aromatic portion of Am D comprises a benzoic acid derivative with an *ortho* methyl group and phenolic groups *ortho* and *para* to the ester functionality. It was envisaged that this portion could be accessed from methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate, **74**) (Figure 2–1). In a Horner-Wadsworth-Emmons (HWE) strategy, a protected phosphonate derivative of **74** could be prepared from the related bromide. Alternatively, a Ramberg-Bäcklund (RB) strategy would require the preparation of a protected bromide derivative of **74** or the related thiol derivative.

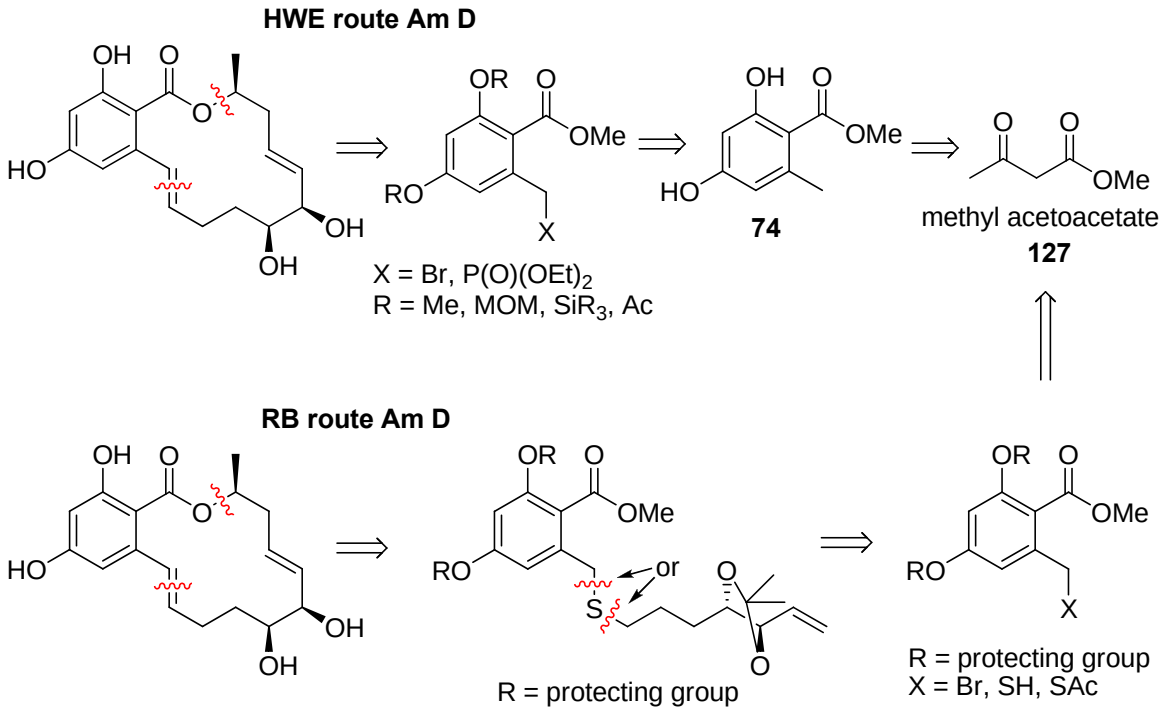


Figure 2–1. Two proposed retrosynthetic analyses of Am D with focus on the aromatic fragment.

2.1 Model Aromatic Fragment

In order to investigate the utility of the proposed HWE strategy, synthesis of the simplified 2,4-deoxy analogue of Am D (**204**) was undertaken (Figure 2–2). The absence of the two phenolic hydroxyl groups in the analogue removes their potentially problematic reactivity and the additional protection/deprotection steps required for

synthesis of the natural product. Disconnection of analogue **204** at the benzylic alkene and lactone gives benzylic phosphonates **210** or **211** as the model aromatic fragment. Thus, phosphonates **210** and **211** were prepared as model compounds to investigate the utility of the HWE reaction for installation of the benzylic (*E*)-alkene of Am D. Phosphonate **211** was synthesised to provide a model with a slightly bulkier ester group than the methyl ester of **210**.

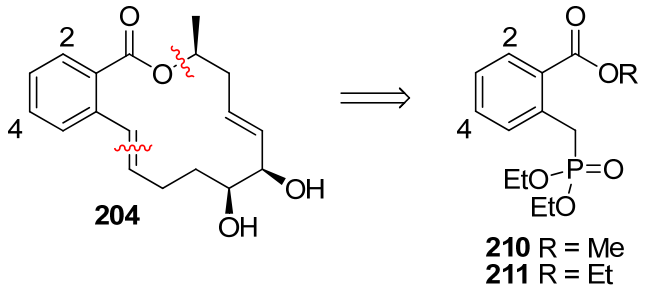
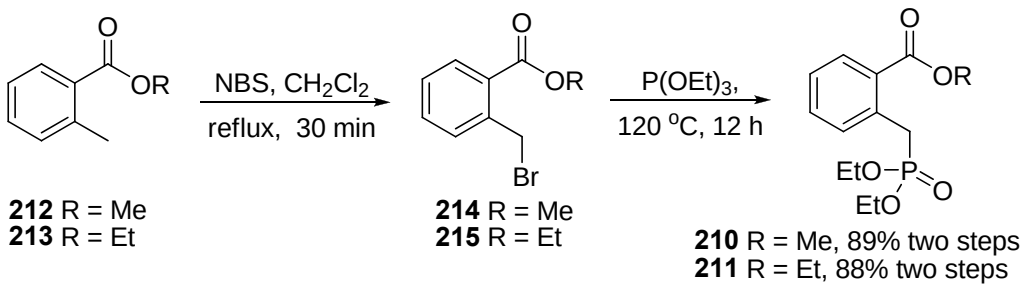


Figure 2–2. Retrosynthetic analysis for the aromatic segment of 2,4-deoxy model analogue of Am D: the HWE route.

Methyl 2-methyl benzoate **212** was purchased from Sigma-Aldrich and commercially available 2-methylbenzoic acid was subjected to a Fischer esterification[136] with ethanol to afford ethyl 2-methylbenzoate **213**. The methylbenzoates **212** and **213** were then rapidly and efficiently brominated with N-bromosuccinimide (NBS) in refluxing CH_2Cl_2 (Scheme 2–1). Trace amounts of the α,α-dibromide were visible in the ^{1}H NMR spectra of the crude reaction mixtures. Bromide **214** was initially purified by flash column chromatography, providing the pure compound in 90% yield. However, the dibromide contaminants were found to be unreactive towards triethyl phosphite in the subsequent Arbuzov reaction, and the crude reaction mixtures were thus used without further purification. The resulting phosphonates **210** and **211** were purified by a distillation followed by column chromatography to provide both phosphonates in excellent yield.[137]

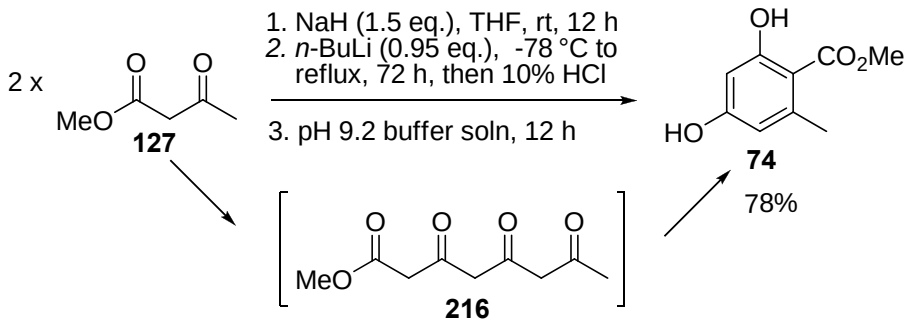


Scheme 2–1. Synthesis of model phosphonates **210** and **211**.

2.2 Synthesis of Methyl Orsellinate (74)

Methyl orsellinate (**74**) is a naturally occurring compound that was first isolated in 1940 from the lichen *Parmelia latissima*[138] and more recently from lichens *Lobaria linita*[139] and *Peltigera leucophlebia*.[140] Methyl orsellinate was used as the aromatic starting material in Chen et al.'s synthesis of Am D[35] and has been a key component in the synthesis of a range of natural products.[141-146]

A one-pot synthesis of orsellinate **74** was developed by Barrett et al.[72] inspired by the work of Harris et al.[147] Barrett's protocol[72] involved the base-promoted self-condensation of methyl acetoacetate (**127**) in the presence of sodium hydride and *n*-butyllithium (Scheme 2–2). Upon acidification, the self-condensation produced methyl 3,5,7-trioxo-octanoate (**216**). After treatment of triketo-ester **216** with a pH 9.2 buffer solution for 12 hours and re-acidification, methyl orsellinate **74** was extracted and recrystallised to give a white solid in excellent overall yield (78%).



Scheme 2–2. Barrett's synthesis methyl orsellinate (**74**).

Joullié and Chiarello subsequently reported a simplified version of Barrett's protocol, refluxing the reaction for only 24 hours before acidifying the solution to pH 1.5 – 2.0 for 12 hours.[141] When the synthesis of **74** via Joullié's modified protocol was attempted, it proved to be more challenging than anticipated. Initial attempts to self-condense methyl acetoacetate (**127**) only returned starting material (Table 2–1).

As indicated in Table 2–1, different reaction solvents and reaction temperatures were investigated for the reaction. Previous studies by Hu[148,149] had found that the optimal reaction conditions for the condensation required the slow addition of *n*-butyllithium over a period of two hours, followed by reflux for 40 hours. These conditions were implemented but failed to improve the result.

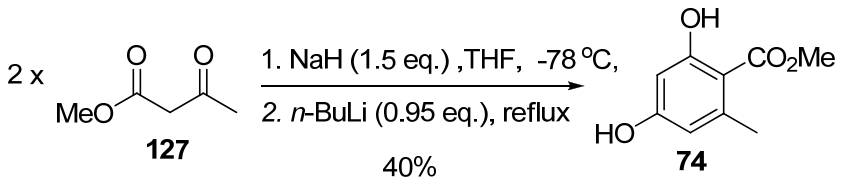


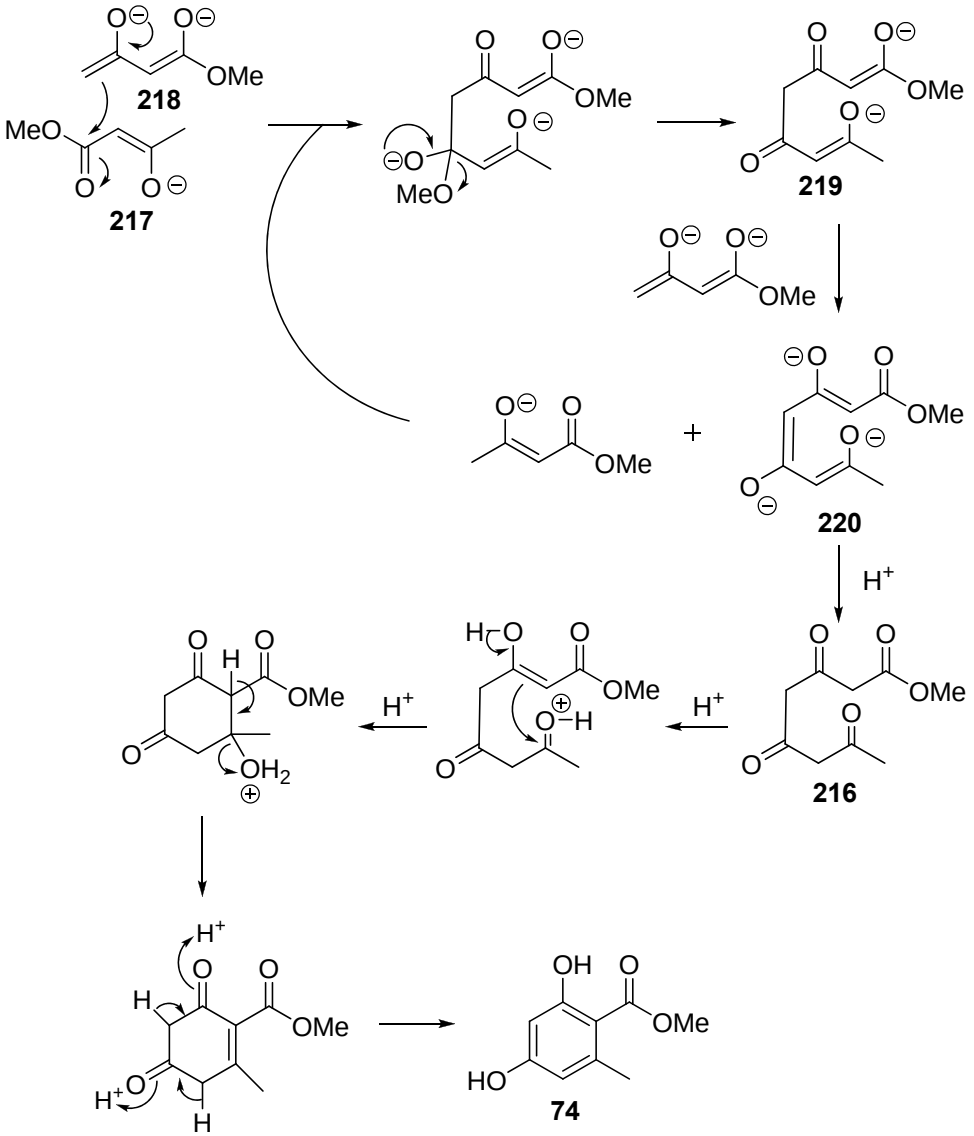
Table 2–1. Conditions used in attempts to prepare methyl orsellinate (**74**) via the self-condensation of methyl acetoacetate.[a]

Solvent	*Temperature at addition of n-BuLi (°C)*[b]	*Time for n-BuLi addition (min)*[c]	*Temperature after n-BuLi addition*[d]	*Time of heating (h)*[e]	*Yield of **74** (%)*
THF	-78	20	reflux	24	0
	-78	120	rt	24	0
	-78	120	rt	40	0
	-40	120	reflux	40	0
	0	120	reflux	40	0
	-78	120	reflux	40	40
Et_2O	-78	20	rt	24	0
	-78	20	reflux	24	0
Hexanes	-40	20	rt	24	0
	-40	120	reflux	40	0

[a] The first step of the reaction was carried out by addition of **127** to a NaH suspension in the solvent stated at 0 °C. The reaction was stirred for 1.5 h, warming to room temperature. [b,c] In the second step of the reaction, *n*-BuLi was added to the cooled reaction mixture over a set period of time. [d,e] The reaction was warmed to room temperature or heated at reflux for 24 or 40 h. The reaction was then cooled to room temperature and acidified with 10% HCl to pH 1 before being stirred at room temperature overnight and worked up.

Correspondence with Dr Y. Gimbert[150] revealed that Gimbert and co-workers had also experienced the same difficulty with this reaction,[151] occasionally only getting starting material returned. They found that the source of the sodium hydride was crucial to the success of the reaction. Macdonald et al.[152] noted that commercially available potassium hydride (KH) is often contaminated with impurities that can greatly influence the efficiency of chemical processes. Macdonald and co-workers found a great deal of variability in the quality of the KH between batches, which lead to yields ranging from 0 to 76% in studies of an anionic oxy-Cope rearrangement. Macdonald postulated that the contaminants present in the commercial reagent could be unreacted elemental potassium or its subsequent oxidation product, potassium superoxide. We proposed the same problem was occurring with the NaH used for this reaction. Thus, upon changing the source of sodium hydride used for the reaction and following the optimised conditions of Hu,[149] **74** was observed in the crude reaction mixture and obtained in a modest yield of 40%.

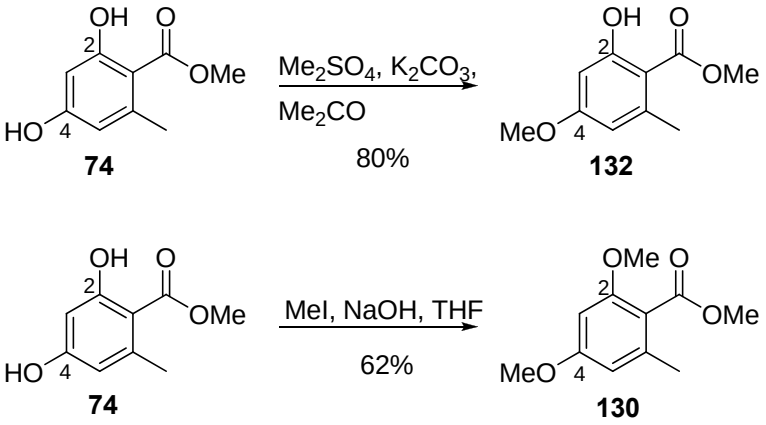
The mechanism for the base-promoted self-condensation of methyl acetoacetate (**127**) has been proposed in the literature (Scheme 2–3)[153-155] Thus, **127** is deprotonated with sodium hydride (1.5 eq) to give monoanion **217**. The majority of monoanion **217** is deprotonated again by *n*-butyllithium (0.95 eq.) to form the strongly nucleophilic dianion **218**. It is believed that the dianion undergoes a Claisen condensation reaction with the remaining monoanion, forming triketo-ester **219** with the loss of methoxide. This triketo-ester can be further deprotonated by dianion **218**, producing trianion **220** and reforming monoanion **217** which can then react with another molecule of dianion **218**. Quenching the reaction with 1N HCl protonates the triketo-ester and induces an intramolecular aldol condensation between the terminal ketone and an enol tautomer of the methyl ester **216** forming a 6-membered ring. Subsequent elimination of water and tautomerisation leads to aromatisation, providing ester **74**.



Scheme 2–3. Proposed mechanism for the self-condensation of methyl acetoacetate.

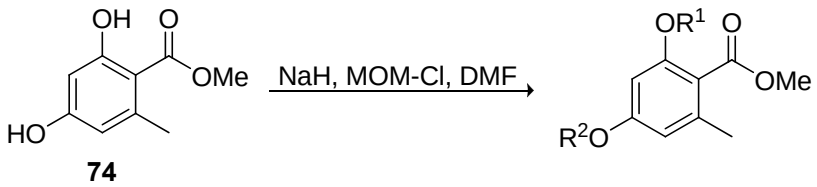
2.3 Strategies for the Protection of Orsellinate 74

The HWE strategy for synthesis of Am D requires phenolic protecting groups that are base stable. To this end, the two phenolic groups were initially protected as their methyl ethers. The 4-hydroxyl group is more reactive than the 2-hydoxyl group, which is presumably involved in a strong hydrogen bond with the neighbouring ester carbonyl group. This led to the isolation of methyl orsellinate derivatives predominately protected only at the 4-hydroxyl when standard methylating conditions [K_2CO_3 and $(MeO)_2SO_2$] were employed (Scheme 2–4). Under these conditions, mono-methylated compound **132** was formed in 80% yield. Methylation with methyl iodide and sodium hydroxide in THF at room temperature was found to be the optimal conditions for the protection of both phenolic groups. Thus, dimethylated **130** was obtained in 62% yield.



Scheme 2–4. Protection of **74** with methyl ethers.

Methyl ethers are renowned for being challenging to remove, especially in the presence of sensitive functional groups.[74] Therefore, methoxymethyl (MOM) ethers were investigated as an alternative base-stable protecting group for methyl orsellinate. The phenolic groups were first deprotonated with sodium hydride before the addition of MOM-Cl (Scheme 2–5). Small amounts of both possible mono-protected esters (**222** and **223**) were often isolated alongside the desired di-protected **221**.

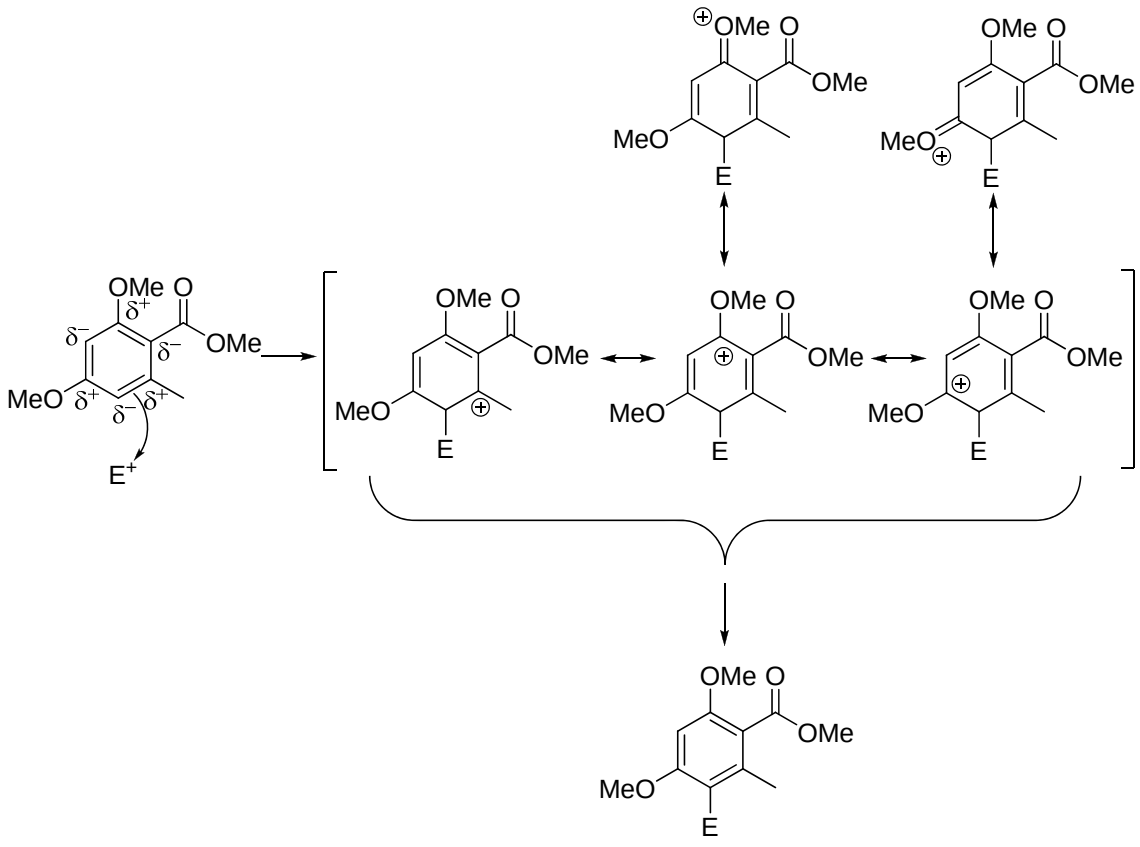


74

221 $R^1 = R^2$ = MOM 74%
222 R^1 = H, R^2 =MOM 15%
223 R^1 = MOM, R^2 = H 3%

Scheme 2–5. Protection of **74** as bis(methoxymethyl) ether **221**.

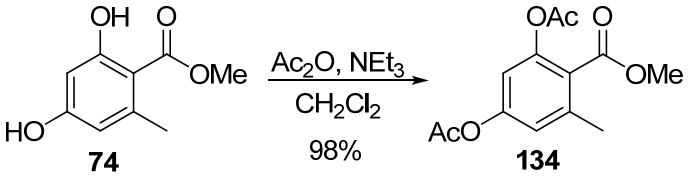
The propensity of orsellinate **74** and its derivatives to undergo electrophilic aromatic substitutions at C3 [156,157] and C5 [74,132,156] has been well documented in the literature. The ability of the methyl and MOM ethers to stabilise the positive charge created during the electrophilic substitution by resonance may activate the aromatic ring to the undesired substitution (Scheme 2–6).



Scheme 2–6. Electrophilic aromatic substitution of **130** at C5.

In contrast, acetate protecting groups should deactivate the aromatic ring towards electrophilic substitution by withdrawing electron density. However, they undergo facile cleavage by nucleophilic bases, such as methoxide, which may be required for the

HWE reaction. Despite this disadvantage, diacetate **134** was also prepared with plans to reprotect the phenolic groups at a later stage in the synthesis, if necessary. Protection of the phenolic hydroxyl groups of **74** with acetyl groups did not suffer the difficulties associated with methylation, affording at room temperature the diacetate in near quantitative yields (Scheme 2–7).

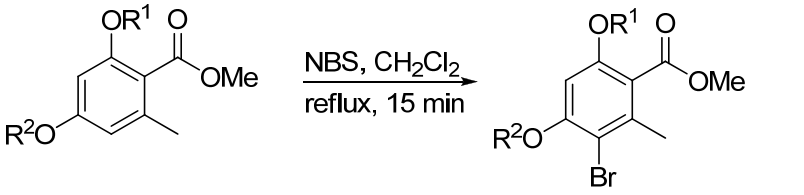


Scheme 2–7. Protection of **74** as diacetate **134**.

2.4 Benzylic Derivatisation of Aromatic Segment

2.4.1 Synthesis of Phosphonate 142

Attempts to brominate the benzylic position of **130** and **132** using the same conditions used for the successful bromination of model compound **214** (see Section 2.1), led to competing electrophilic aromatic substitution of the aromatic ring (Scheme 2–8). The bromide was assumed to be substituted at C5 as has been reported previously in the literature.[75]



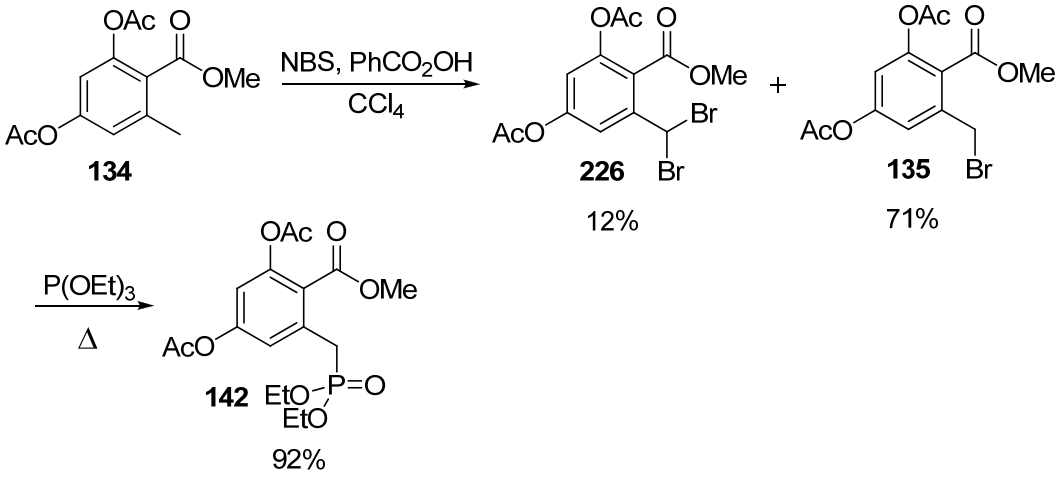
130 R^1 = H, R^2 = Me
132 R^1, R^2 = Me
224 R^1 = H, R^2 = Me 71%
225 R^1, R^2 = Me 65%

Scheme 2–8. Bromination of methyl ethers **130** and **132**.

It has been found, however, that replacement of at least one of the methyl groups by an acetate group deactivates the aromatic ring enough to favour bromination at the benzylic position.[78,158,159] Following a reported procedure[159] bromide **135** was prepared in 71% yield from diacetate **134** (Scheme 2–9). N-Bromosuccinimide (NBS) and the radical initiator benzoyl peroxide were added in portions to a solution of **134** in carbon tetrachloride (CCl_4) in an attempt to reduce the amount of dibromide **226** formed in the

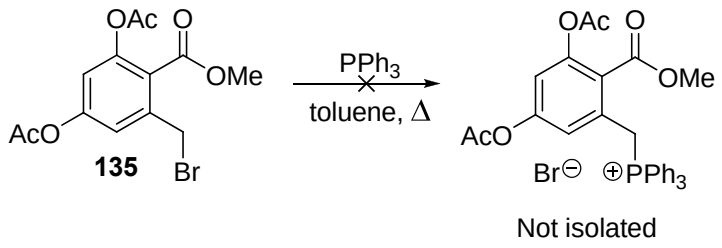
reaction. The progress of the bromination reaction was monitored via ^{1}H NMR spectroscopy. At the end of the reaction, the crude residue contained a mixture of starting material and mono- and di-bromo products. Fortunately, the desired monobromomethylbenzoate **135** could be isolated through careful column chromatography. Although the R_f vaules of these three components were almost identical in the eluent (CH_2Cl_2), they all stained a different colour when the TLC plates of the eluted fractions were developed in anisaldehyde dip: black for dibromo-, brown for monobromo- and red for starting material. This colour difference allowed the identification of the fractions that contained pure monobromomethylaryl **135**.

The benzylic bromide was converted into the arylmethylphosphonate through an Arbuzov reaction[79] with triethyl phosphate (Scheme 2–9). The first step of this reaction involves nucleophilic attack by the phosphorus on the arylmethyl bromide, followed by the bromide ion dealkylation of the resulting trialkoxyphosphonium salt, providing phosphonate **142** and bromoethane as the by-product. The excess reagent was removed by distillation to give the required aromatic fragment **142** as a pale yellow oil.



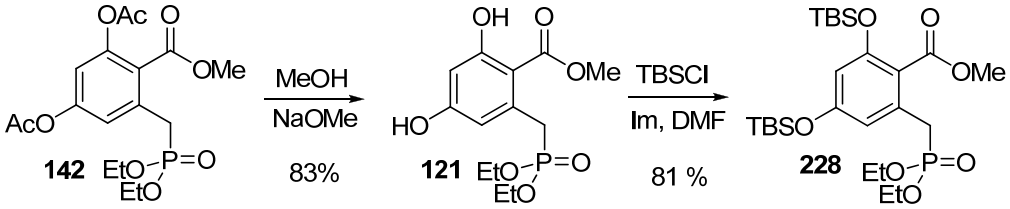
Scheme 2–9. Synthesis of the aromatic segment (**142**) for the HWE route.

Several attempts were also made to prepare the Wittig salt of the aromatic bromide **135** (Scheme 2–10). The product from the reaction of bromide **135** with triphenylphosphine would not crystallise out of solution despite trying a wide range of solvent mixtures. The ^{1}H NMR spectrum of the crude product in $CDCl_3$ was too complex to determine whether the reaction was indeed successful. This route was thus abandoned and focus returned to the phosphonate **142**, which should favour the formation of the desired (*E*)-olefin in an HWE reaction.



Scheme 2–10. Attempted Wittig salt preparation.

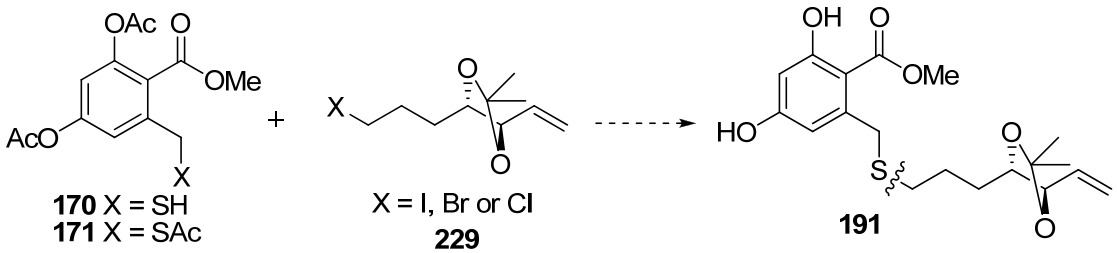
As previously discussed, the acetate protecting groups are susceptible to the nucleophilic bases that might be used in the HWE reactions. Therefore conversion of the acetate groups of the aromatic segment to TBS ethers was undertaken (Scheme 2–11). The acetates of phosphonate **142** were easily removed by treatment with sodium methoxide in methanol and reprotected with TBSCl, providing phosphonate **228** in good yield.



Scheme 2–11. Preparation of the TBS-ether protected aromatic phosphonate.

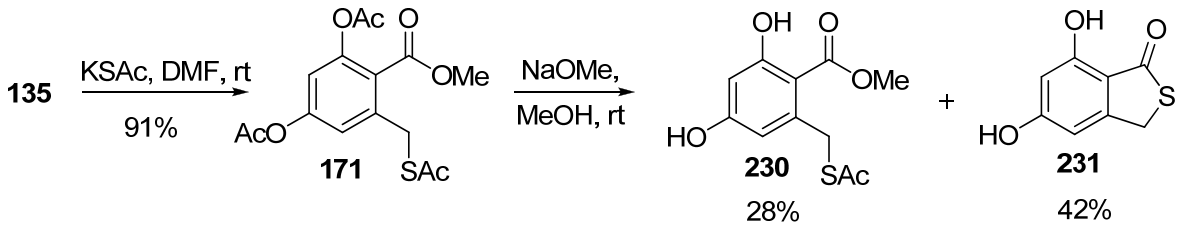
2.4.2 Attempted Synthesis of Thiol 170

Thioether **191** was required as an intermediate in the Ramberg-Bäcklund (RB) route to Am D (Scheme 2–12). One approach to compound **191** would involve the preparation of thiol **170** or thioacetate **171** to react with alkyl halide **229**.



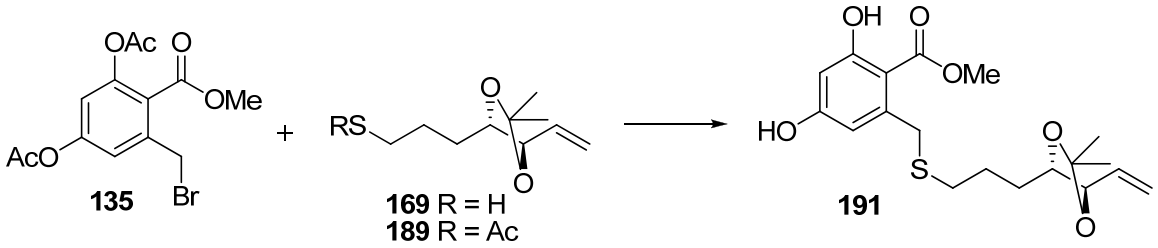
Scheme 2–12. Proposed synthesis of intermediate **191**.

Thioacetate **171** was prepared through the nucleophilic displacement of bromide **135** with potassium thioacetate (Scheme 2–13). Attempts were made to obtain the free thiol by deprotecting **171** with sodium methoxide. However, a mixture of compounds was formed in this reaction, including the major products thioacetate **230** and thiolactone **231**. The latter presumably arises via the attack of the methyl ester by the sulfide formed by methanolysis of **230**, forming a stable thiolactone. This reactivity has been exploited in the literature for the synthesis of thiolactones.[160]



Scheme 2–13. Synthesis of thioacetate **171** and its subsequent methanolysis products thioacetate **230** and thiolactone **231**.

To avoid the formation of thiolactone **231**, an alternative strategy, involving displacement of benzylic bromide **135** by a carbohydrate-derived thiol **169**, was instead investigated (Scheme 2–14). This strategy was ultimately successful in the total synthesis of Am D and is discussed in Section 5.2.

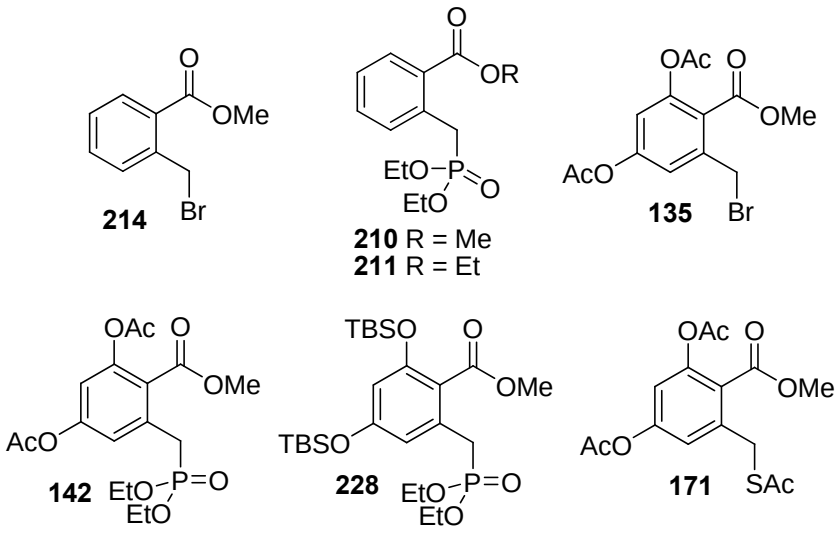


Scheme 2–14. Alternative strategy to thioether **191**.

2.5 Summary of Chapter Two

In summary, bromide **214** was obtained in 90% yield from methyl 2-methylbenzoate. The simplified model aromatic phosphonates **210** and **211** were prepared in two steps from commercially available methyl benzoates **212** and **213** in 88% and 89% yield respectively.

Three aromatic fragments relevant to the synthetic strategies for Am D have been prepared for the HWE and RB routes. Bromide **135** was synthesised in two steps from methyl orsellinate in 70% overall yield. Phosphonate **142** and thioacetate **171** were prepared in three steps from methyl orsellinate in 64% and 63% overall yield, respectively. Phosphonate **228** was obtained in five steps from methyl orsellinate in 43% overall yield



Chapter Three:

Synthesis of the C2'–C7' Segment

In both retrosynthetic analyses under consideration, disconnections at the olefins of Am D would lead to terminally functionalised six-carbon synthons containing the required diol moiety. It was envisaged that this unit could be derived from carbohydrate chiral pool reagents with the appropriate *cis*-stereochemistry at adjacent centres.

3.1 The Horner-Wadsworth-Emmons (HWE) route

The proposed HWE strategy to Am D involves disconnections at olefins C1′–C2′ and C7′–C8′ giving, *inter alia*, a dialdehyde synthon (Figure 3–1). D-Glucose (**232**) would be a suitable carbohydrate precursor for various protected derivatives of the dialdehyde synthon, in which the diol at C5′ and C6′ would be retained in the product, while the C2′ and C7′ termini would be differentially functionalised as aldehydes or masked aldehydes and oxygens at C3′ and C4′ would be removed.

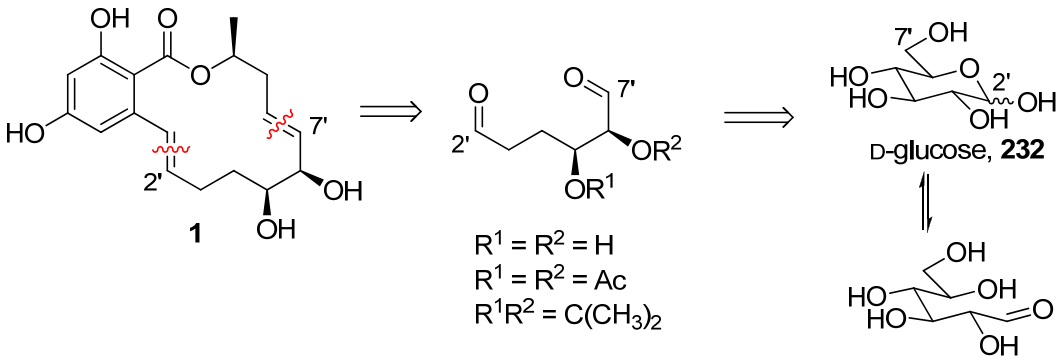
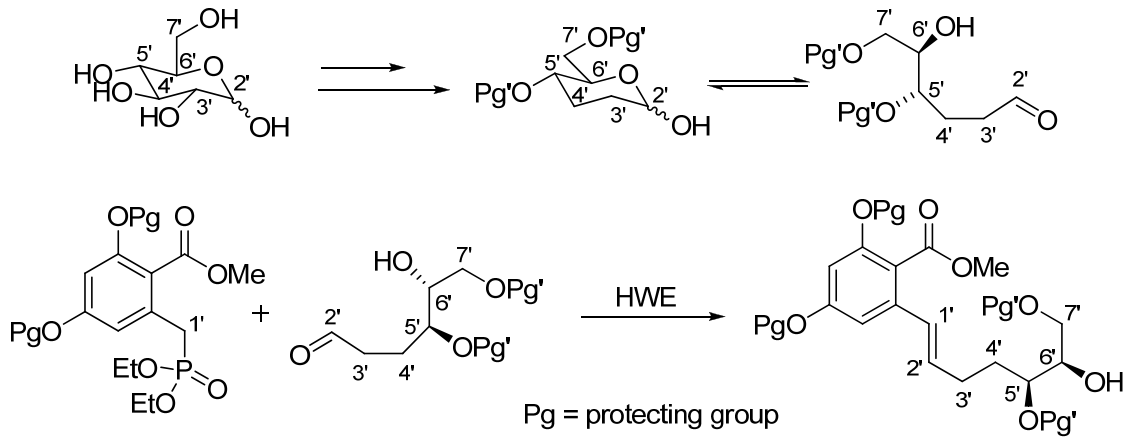


Figure 3–1. Retrosynthetic analysis of Am D with focus on the C2′–C7′ fragment.

Over a series of transformations, D-glucose could be converted to a protected hemiacetal (Scheme 3–1), with the open-chain form able to react with an appropriate phosphonate to afford the required benzylic (*E*)-alkene. Deprotection and oxidation of the primary hydroxyl of the resulting conjugate would provide the aldehyde required for the second HWE olefination, thus completing the full carbon backbone of Am D.



Scheme 3–1. Conversion of D-glucose to protected hemiacetals and their proposed use in HWE reactions to install the benzylic (*E*)-alkene. The numbering of the carbohydrate-derived segments corresponds to their numbering in Am D.

3.1.1 Synthesis of Hemiacetal Fragments

Three carbohydrate substrates were prepared for use in this strategy (Figure 3–2): the diacetate **122**, acetonide **152** and silyl ether **153**. These three targets differ in the extent, type and stability of protecting groups, thus the likelihood of finding a suitable substrate for the HWE was increased.

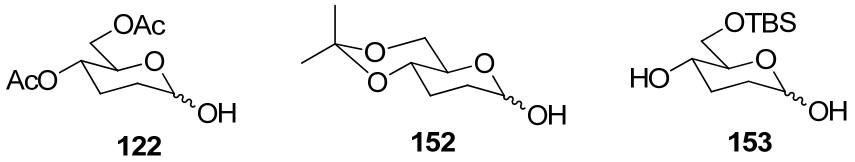
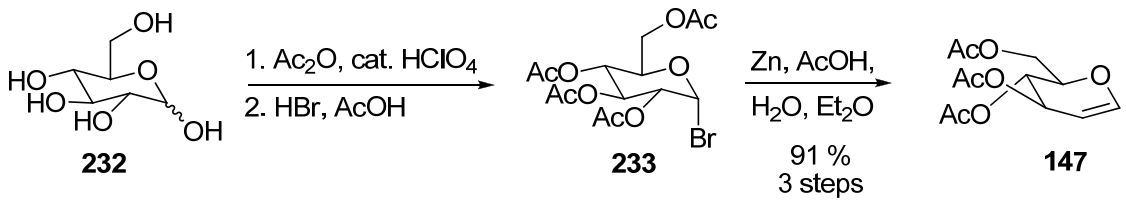


Figure 3–2. The three proposed hemiacetals (**122**, **152** and **153**) targeted for use as substrates in the HWE reaction.

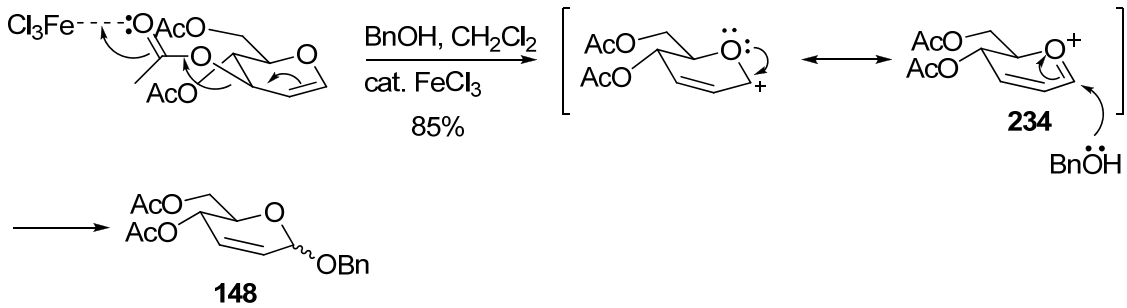
3.1.1.1 Synthesis of Diacetate 122

The synthesis of all three protected carbohydrate derivatives began with the efficient conversion of D-glucose to tri-*O*-acetyl-D-glucal on a multigram scale (Scheme 3–2). Thus, global acetylation of D-glucose with acetic anhydride and catalytic perchloric acid was performed prior to treatment with hydrogen bromide affording bromide **233**. These somewhat harsh acidic conditions led to the formation of the α-bromo anomer, which, upon elimination with zinc in 1:1 solution of acetic acid/water, gave tri-*O*-acetyl-D-glucal, **147**, in 91% yield (over 3 steps).[161,162]



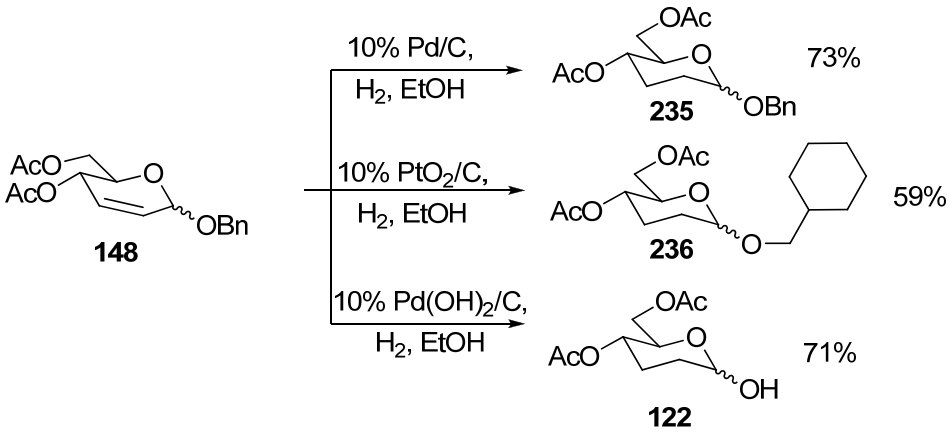
Scheme 3–2. Preparation of tri-*O*-acetyl-D-glucal (**147**).

Tri-*O*-acetyl-D-glucal readily underwent a Ferrier rearrangement[85] with benzyl alcohol catalysed by the Lewis acid iron(III) chloride ($FeCl_3$) (Scheme 3–3).[163] Benzyl glycoside **148** was afforded as an inseparable mixture of anomers with an α:β ratio of 9:1 as determined by ^{1}H NMR spectroscopy. Presumably, the α-anomer was favoured due to the anomeric effect. The mechanism involves complexation of $FeCl_3$ to the carbonyl oxygen of the allylic acetate, thereby activating it as a leaving group. A lone pair of electrons on the ring oxygen provides stabilisation of the resulting allylic cation through formation of an oxonium intermediate **234**. The short-lived oxonium ion is attacked at C2′ by a nucleophile (in this case benzyl alcohol) restoring the lone pair of electrons to the pyranose oxygen, giving benzyl glycoside **148**.



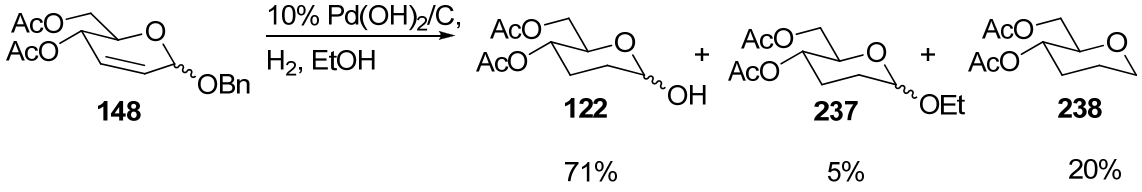
Scheme 3–3. The Ferrier rearrangement of tri-*O*-acetyl-D-glucal with benzyl alcohol.

It was envisaged that catalytic hydrogenation of the anomeric mixture of benzyl glycoside **148** would simultaneously reduce the olefin and remove the benzyl protecting group (Scheme 3–4). Initial investigations found that catalytic palladium on carbon (Pd/C) was suitable for the hydrogenation of the double bond but was ineffective in catalysing the hydrogenolysis of the benzyl group. Reaction in the presence of catalytic platinum oxide on carbon (PtO_2/C) hydrogenated the olefin and the aromatic ring of the benzyl group giving cyclohexylmethyl glycoside **236**. Finally, the catalyst palladium(II) hydroxide on carbon [$Pd(OH)_2$/C] was found to be reactive enough to hydrogenate the double bond and remove the benzyl protecting group in good yield.



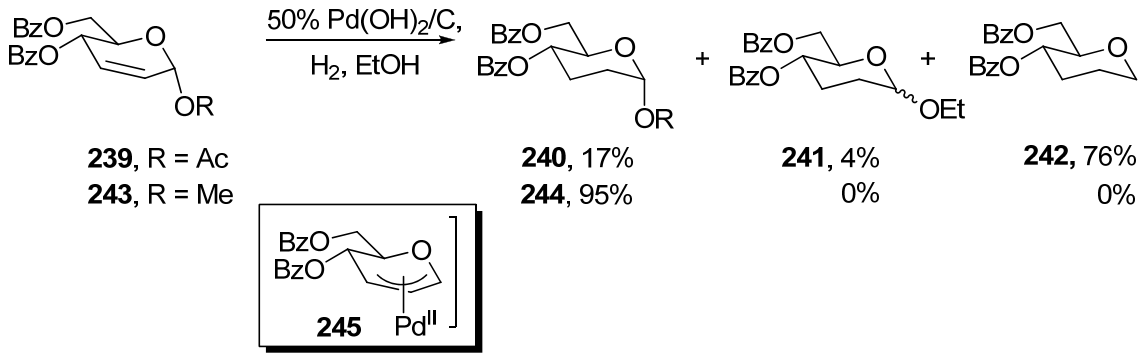
Scheme 3–4. Catalytic hydrogenation of benzyl glycoside **148**.

Alongside desired hemiacetal **122**, two other products from the hydrogenation reaction were frequently observed as minor by-products, namely ethyl glycoside **237** and tetrahydropyran **238** (Scheme 3–5). In fact, on several occasions, ethyl glycoside **237** was isolated as the major product (70–80%). There seemed to be no consistent factors that differentiated these instances from those giving the expected outcome.



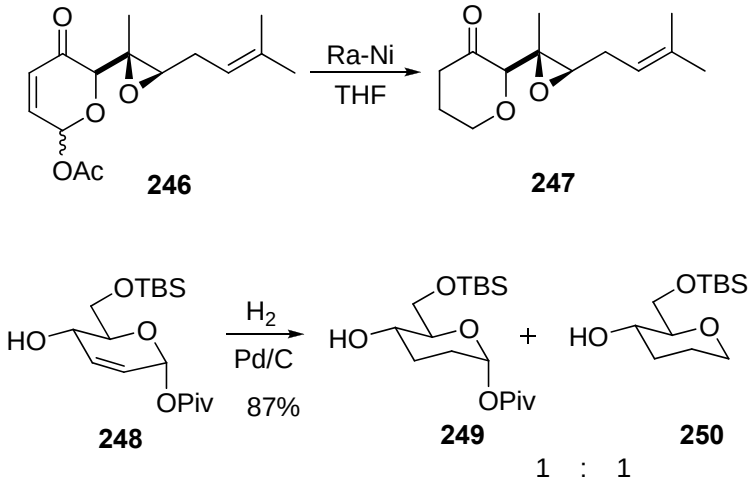
Scheme 3–5. Products from the hydrogenation reaction of benzyl glycoside **148**.

Toshima and co-workers reported the formation of related side products when attempting the hydrogenation of acetate **239** (Scheme 3–6).[164] The isolation of tetrahydropyran **242** as the major product suggested that the allylic acetate has a tendency to eliminate hydrogenolytically via a π-allyl palladium complex (**245**) under the given hydrogenation conditions. Anomeric acetate **240** was found to be unreactive when exposed to the same hydrogenation conditions. This suggested that the double bond at C2–C3 is indeed required for cleavage of the anomeric acetate and thus supported the hypothesis of a π-allyl palladium complex as an intermediate. Hydrogenation of methyl glycoside **243** gave saturated methyl glycoside **244** as the sole product, which suggested that the reduction to tetrahydropyran **242** requires an appropriate leaving group as the anomeric substituent.



Scheme 3–6. Products from the hydrogenation of acetates **239** and **243** by Toshima.[164]

This tendency of allylic acetates to eliminate hydrogenolytically was previously shown by Baldwin and co-workers when allylic acetate **246** was reduced to tetrahydropyran **247** upon treatment with Raney-Nickel (Ra-Ni) (Scheme 3–7).[165] Haukaas and O'Doherty extended this observation to allylic anomeric pivaloates having obtained a 1:1 ratio of pivaloate **249** and tetrahydropyran **250** in excellent yield from the palladium-catalysed hydrogenation of allylic pivaloate **248**.[166]

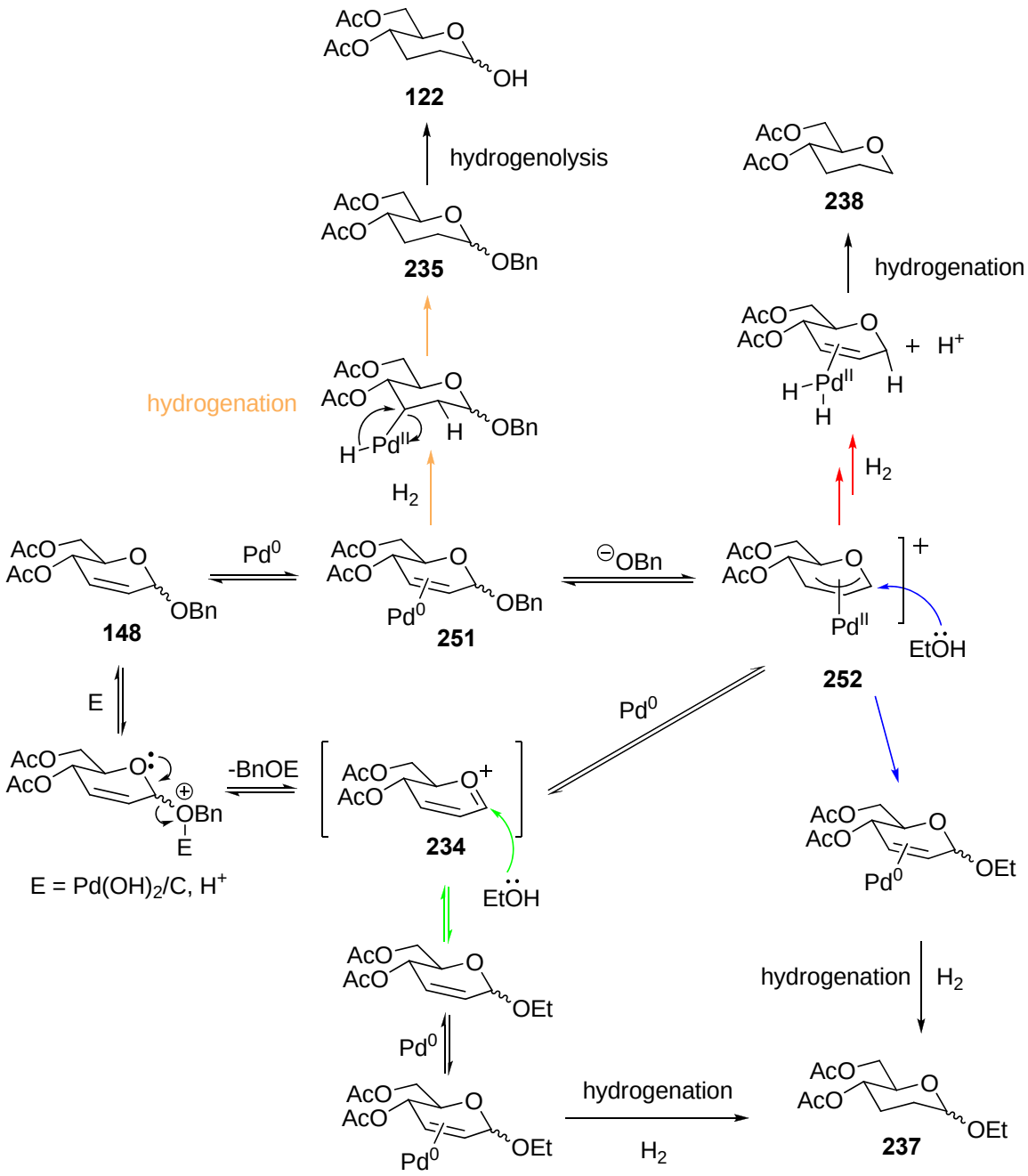


Scheme 3–7. Formation of tetrahydropyrans from the hydrogenolysis of anomeric acetates[165] and pivaloates.[166]

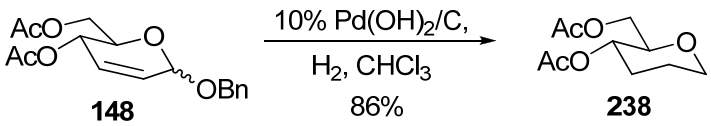
A mechanism proposed for the formation of hemiacetal **122**, ethyl glycoside **237** and tetrahydropyran **238** is presented in Scheme 3–8. Upon co-ordination of the palladium catalyst (Pd) to the olefin, complex **251** could follow the hydrogenation pathway (shown in orange) to give saturated **235** and ultimately hemiacetal **122**. Complexation could also lead to formation of a π-allyl Pd complex of type **252** via elimination of the benzyl group.[164] This π-allyl intermediate could then proceed along one of two pathways: it might be trapped by a molecule of ethanol (shown in blue) and

subsequently hydrogenated to give ethyl glycoside **237;** or a Pd-complexed hydride could attack at the anomeric centre (shown in red). Tetrahydropyran **238** could ultimately be obtained through this latter pathway, after addition of hydrogen to Pd and subsequent hydrogenation. Alternatively, ethyl glycoside **237** and π-allyl Pd complex **252** could be formed via conjugated oxonium ion **234**. This pathway requires the activation of benzyl glycoside **148** by either acid or $Pd(OH)_2/C$ acting as a Lewis acid.[164,167] Oxonium ion **234** could then either be trapped as ethyl glycoside **237** by reacting with the solvent (ethanol) prior to alkene hydrogenation (shown in green), or it could co-ordinate to Pd to give π-allyl Pd complex **252**. These mechanistic pathways would be in competition with each other, with the formation of hemiacetal **122** being the favoured process under the conditions used (10% $Pd(OH)_2/C$, H_2, EtOH).

When the reaction solvent was changed from ethanol to chloroform, tetrahydropyran **238** was obtained as the major product (Scheme 3–9) with only trace amounts of compounds **122** and **235** being observed in the ^1H NMR spectrum of the reaction mixture (≥5% combined). Under palladium-catalysed hydrogenation conditions, chloroform is known to produce small quantities of hydrogen chloride.[168] The presence of hydrogen chloride could promote the formation of oxonium ion **234** over Pd complex **251**. In the absence of a bountiful nucleophilic source (e.g. ethanol solvent), the formation of tetrahydropyran **238** via π-allyl Pd complex **252** would be the end result. Furthermore, we propose that the incidental formation of hydrogen chloride from chloroform could enhance the rate of formation of tetrahydropyran **238** over the desired product **122**, indicating that π-allyl Pd complex **252** might be formed from oxonium ion **234**, thus bypassing π-complex **251**. Hydrogenation of **148** in deuterated chloroform confirmed that the hydrogen atom from chloroform was not being incorporated into the product, as the ^1H NMR spectra of the products from both the deuterated and non-deuterated solvents were identical. Therefore it appears that tetrahydropyran **238** derives from a mechanism related to that shown in Scheme 3–8.



Scheme 3–8. Proposed mechanisms for the formation of hemiacetal **122**, ethyl glycoside **237** and tetrahydropyran **238** in the hydrogenation reactions of benzyl glycoside **148.**

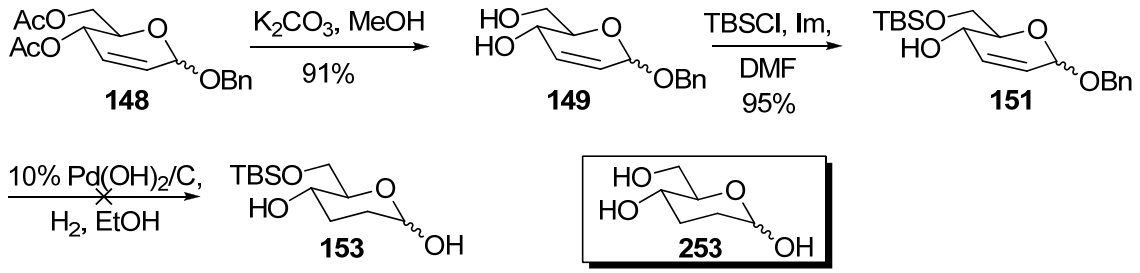


Scheme 3–9. Product from hydrogenation of benzyl glycoside **148** in $CHCl_3$.

Despite the aforementioned formation of by-products **237** and **238**, the desired HWE substrate, hemiacetal **122**, was successfully generated over 5 steps from D-glucose in an excellent yield of 55%.

3.1.1.2 Synthesis of Silyl Ether 153

Silyl ether **153**, the second desired carbohydrate substrate, was targeted to provide a substrate with superior protecting group stability to that of diacetate **122** in the basic conditions of the HWE reaction (Scheme 3–10). Diacetate **148** was deprotected with a catalytic amount of methoxide (prepared in situ from methanol and K_2CO_3) giving diol **149** as a white solid. The primary hydroxyl group of diol **149** was selectively protected as its TBS ether in excellent yield (95%). However, hydrogenation/hydrogenolysis of the benzyl glycoside **151** with catalytic $Pd(OH)_2/C$ in EtOH did not afford hemiacetal **153**. The absence of aromatic and olefinic peaks in the ^1H NMR spectrum of the crude product confirmed that the hydrogenation and hydrogenolysis reactions were successful. However, the characteristic TBS signals were missing from the spectrum, indicating that the silyl ether had also been cleaved in the reaction. Toshima and co-workers have previously reported the susceptibility of TBS ethers to undergo cleavage when exposed to $Pd(OH)_2/C$ catalysed hydrogenation conditions.[167] The product was assumed to be the corresponding triol **253**. Thus, the route was abandoned as the additional protection group manipulations required to prepare a suitable HWE substrate from **253** rendered it inefficient.

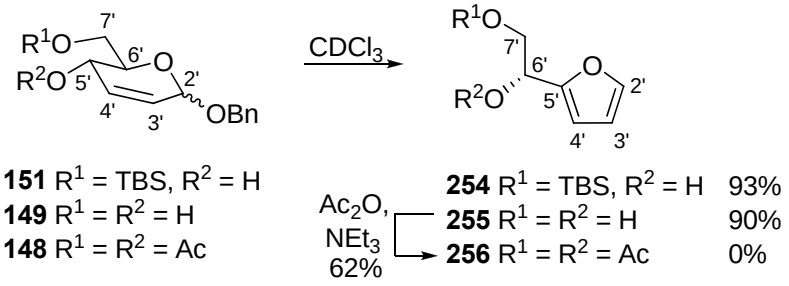


Scheme 3–10. Attempted synthesis of desired hemiacetal **153**.

3.1.1.3 Elimination/Rearrangement of Benzyl Glycosides 149 and 151

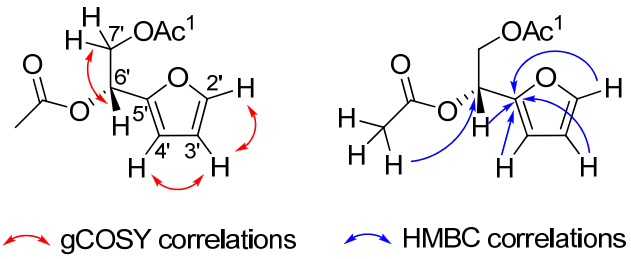
Whilst characterising samples of silyl ether **151** in $CDCl_3$ via NMR spectroscopy, it was observed that, over the course of 12 hours, the signals corresponding to the benzyl group were disappearing and a new proton signal at 7.40 ppm was concurrently appearing (Scheme 3–11). Diol **149** was found to also undergo the same transformation but at much slower rate. An NMR sample of the unprotected diol would typically be fully converted to this new compound over a period of 4 days. Diacetate **148** was,

however, found to be inert to $CDCl_3$ over a period of two weeks. This result suggested that the C5′ hydroxyl group is involved in this transformation.



Scheme 3–11. Rearrangement of benzyl glycosides **149** and **151** in $CDCl_3$.

Detailed NMR analysis of the acetylated product from the degradation of diol **149** led to elucidation of its structure. The ^{1}H NMR spectrum of the acetylated degradation product (**256)** contains seven signals representing a total of 12 protons (Figure 3–4). The ^{13}C NMR contains ten carbon signals, four of which are in the characteristic unsaturated region (~110–150 ppm).[169] The HSQC spectrum indicates that the methylene signals at 4.43 and 4.47 ppm belong to the protons on C7′, while the gCOSY spectrum exhibits a correlation between the methylene protons and the signal at 6.10 ppm (Figure 3–3). Thus the 6.10 ppm signal belongs to the proton on C6′. A weak correlation between the methyl group of the acetate at 2.10 ppm and the C6′ methine in the HMBC spectrum indicates that the hydroxyl on C6′ is acetylated (Figure 3–5). Hence, C6′ is no longer part of the ring system. The chemical shift of the C6′ methine is shifted up field from a typical –C<u>H</u>(OAc)– resonance,[170] indicating that there is further deshielding from a neighbouring group. The HMBC spectrum shows that the methine at C6′ is also adjacent to a quaternary carbon at 149.4 ppm (C5′). Carbon C5′ in turn, exhibits correlation with the methines at 6.36, 6.40 and 7.40 ppm and thus forms part of the ring. The chemical shifts of the protons (6.36, 6.40 and 7.40 ppm) and their adjoining carbons (110.4, 109.6 and 143.0 ppm) are typical of the furans.[171] Thus it became clear that the products from these transformations are substituted furans.



Carbon	C (ppm)	H (ppm)
2'	143.0	7.40
3'	110.6	6.36
4'	109.3	6.40
5'	149.2	-
6'	66.2	6.11
7'	63.3	4.47, 4.43
Ac C=O	170.6	-
Ac Me	20.9	2.09
Ac^1 C=O	170.0	-
Ac^1 Me	20.7	2.06

Figure 3–3. Assignment of chemical shift and the gCOSY and HMBC couplings exhibited by furan **256**.

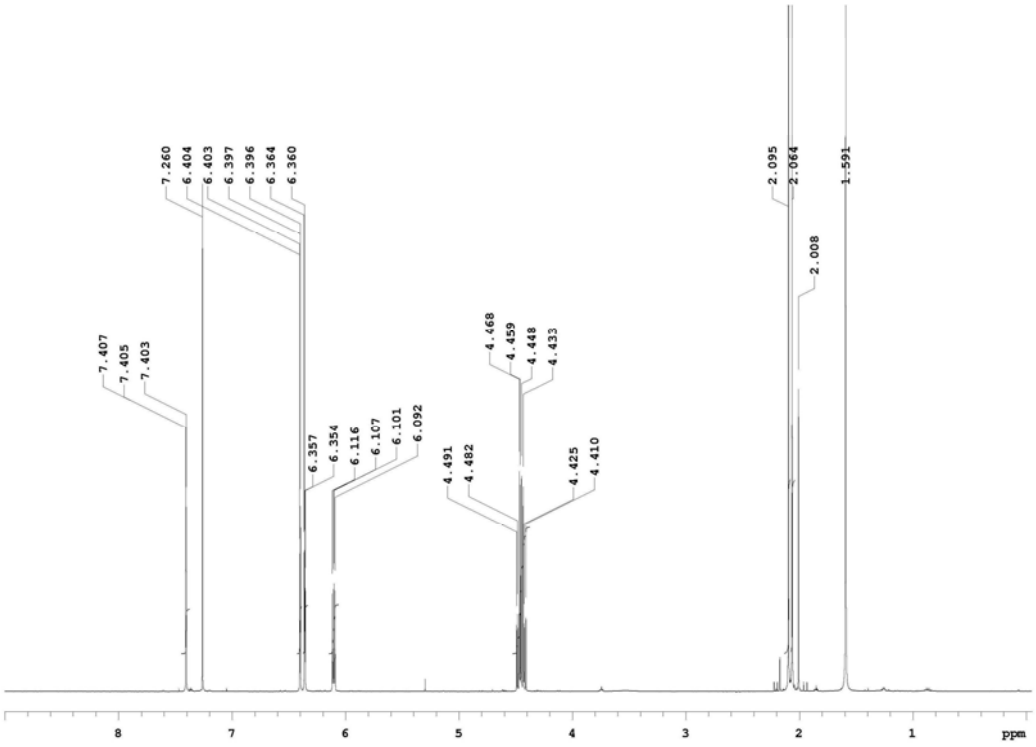


Figure 3–4. 1H NMR spectrum of diacetyl furan **256**.

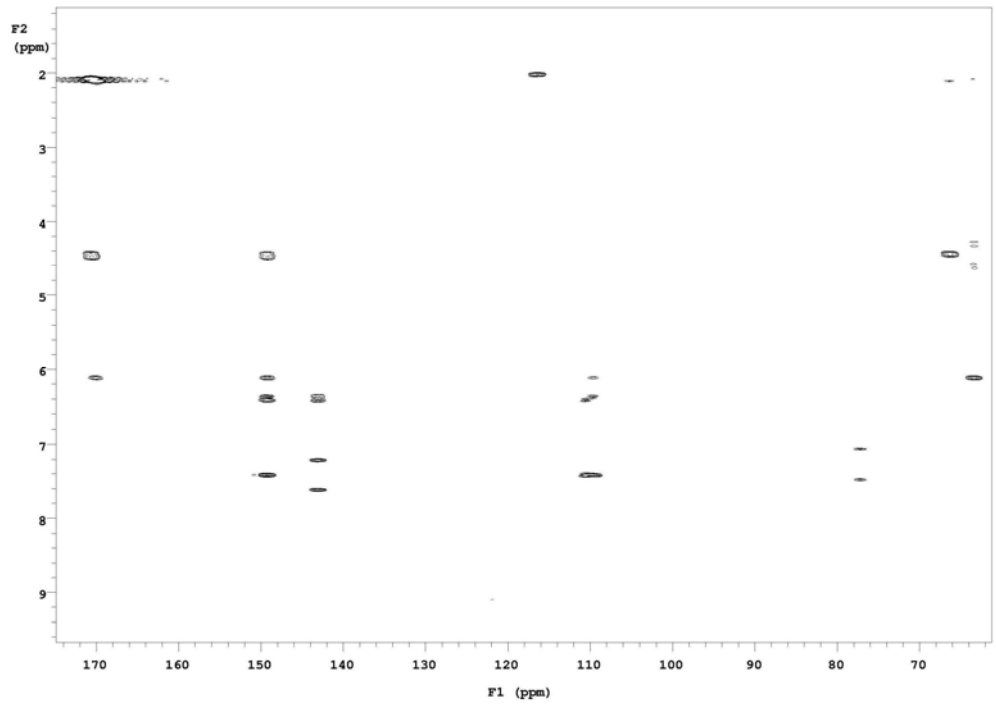
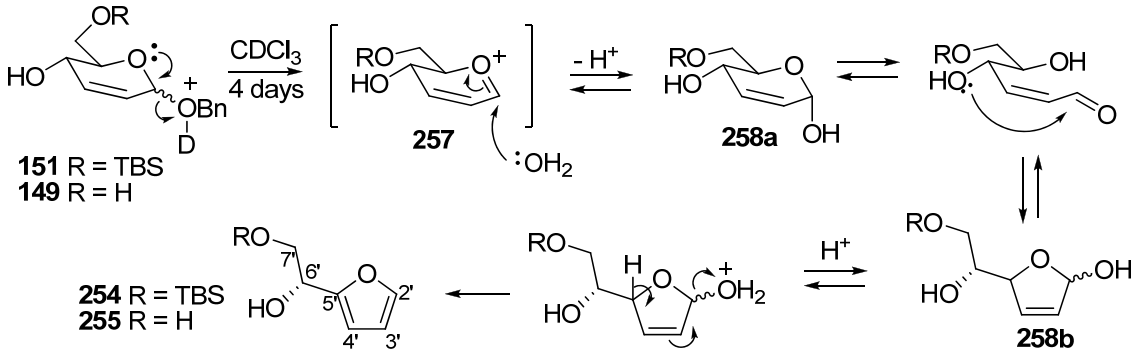


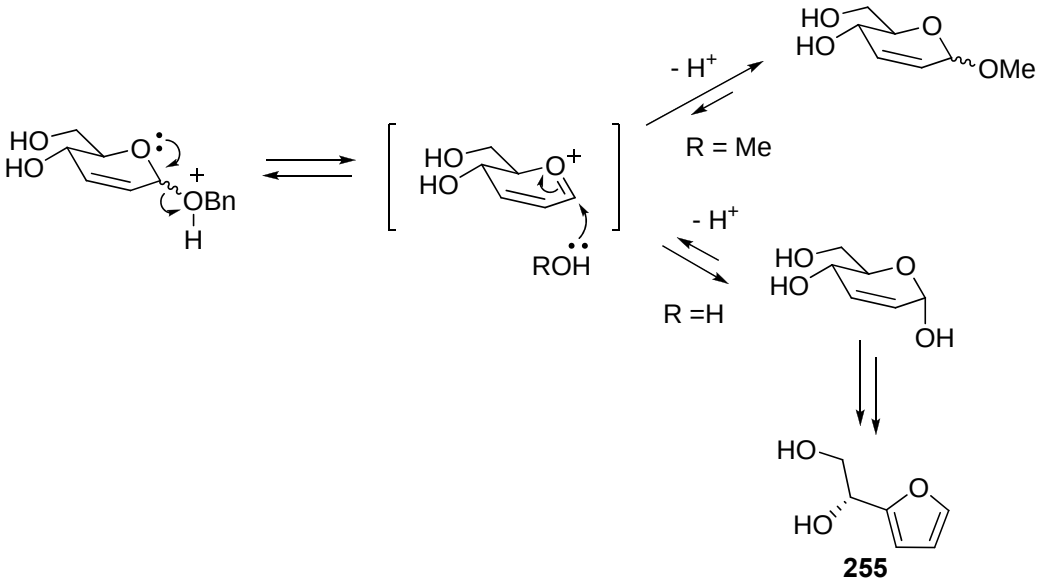
Figure 3–5. HMBC spectrum of diacetyl furan **256.**

Having noted that a free C5′ hydroxyl was required for the transformation to occur, a mechanism related to the alternative mechanism for the formation of ethyl glycoside **237** (Scheme 3–8) was proposed (Scheme 3–12). Activation and elimination of the benzyl group would generate oxonium ion **257**. Trace amounts of water could then attack at the anomeric centre to give hemi-acetal **258a**. The free C5′ hydroxyl could attack the carbonyl of the open-chain form hemi-acetal **258a** to give hemi-acetal **258b**. Protonation of the anomeric hydroxyl would activate hemi-acetal **258b** toward elimanition, giving the highly stable furan.



Scheme 3–12. A proposed mechanism for the benzyl glycoside transformation to furans **254** and **255**.

This proposed mechanism is supported by an investigation into the potential role of acid in this rearrangement. A catalytic amount of *para*-toluenesulfonic acid (*p*-TsOH) was added to a solution of benzyl glycoside **149** in MeOH. The benzyl group was found to be labile under these conditions, being completely exchanged with MeOH within ten minutes, as judged by TLC and ^{1}H NMR spectroscopy (Scheme 3–13). Over the next four hours, furan **255** gradually accumulated to become the major product. Mechanistically, the benzyl oxygen is protonated, activating it as a leaving group. The resulting oxonium intermediate is common to both pathways. This can be intercepted by the solvent methanol, the leaving group (benzyl alcohol), or by water. While the excess of solvent molecules ensures that the methyl glycoside is the kinetic product, the thermodynamic preference for furan **255** leads ultimately to this material.

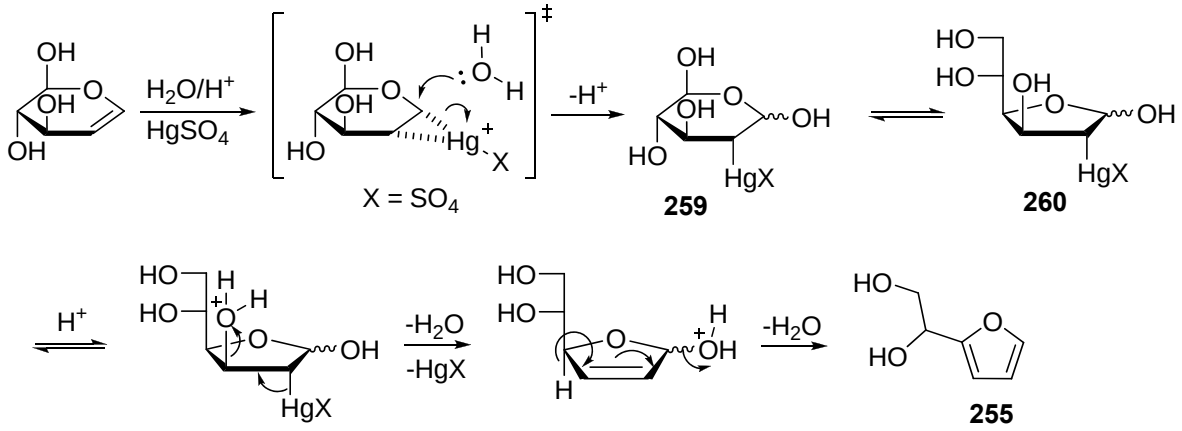


Scheme 3–13. Proposed mechanisms for the transformation of **149** in acidic methanol.

This experiment seemed to imply that the earlier instability of diol **149** and silyl ether **151** in deuterated chloroform was due to activation of the benzyl group through deuteration. These transformations did not, however, occur in non-deuterated $CHCl_3$, even when the substrates were left in the solvent for a period of several days. Lab grade $CHCl_3$ usually contains ethanol or amylenes as stabilisers, which could retard the acidity of the solvent. However, quenching the stabiliser by washing $CHCl_3$ with 10% HCl prior to its reaction with silyl ether **151** also did not lead to furan **255**. Theoretically, $CDCl_3$ should be less acidic than $CHCl_3$ since C–D bonds are stronger than C–H bonds (C–H 349.2 kJ mol^{-1}, C–D 374.5 kJ mol^{-1} for $CHCl_3$ and $CDCl_3$ respectively).[172] On the other hand, D^+ might be more stable than H^+ due to having a

larger nucleus that could better accommodate the positive charge and therefore dissociate more easily. A clear explanation for the difference in reactivity between $CDCl_3$ and $CHCl_3$ has not yet been found.

A similar rearrangement of D-glucal in the presence of acid and catalytic mercuric sulfate was observed by Perlin et al. (Scheme 3–14).[173] The reaction is thought to proceed via initial oxymercuration of the 1,2 π-bond. The product **259** is in equilibrium with its furanose form **260**. Elimination of the mercuric ion followed by a second elimination leads to the highly stable furan **255**.

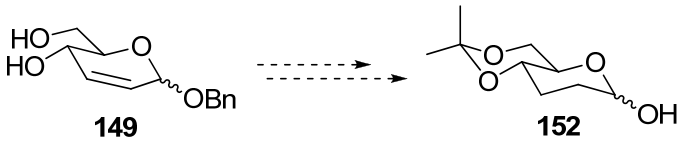


Scheme 3–14. Mechanism proposed by Perlin for the conversion of D-glucal to furan **255**.

Since this first report there have been a number of examples of furan synthesis from D-glucal catalysed by a variety of Lewis acids including: $Sm(OTf)_2$,[174] $InCl_3$,[175] $HClO_4$–SiO_2,[176] KSF Montmorillonite[177] and $FeCl_3 \cdot 6H_2O$.[178]

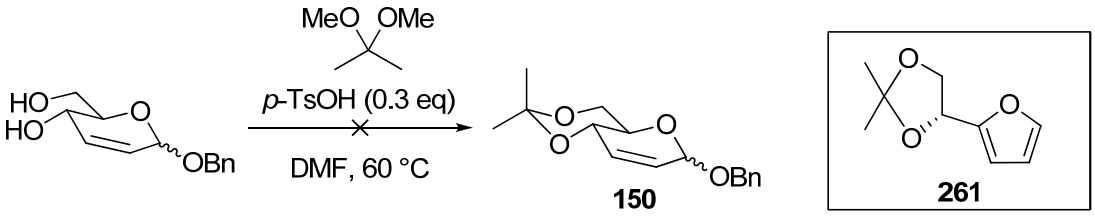
3.1.1.4 Synthesis of Acetonide 152

The third proposed substrate for the HWE reaction was synthesised by protecting the C5′ and C7′ hydroxyl groups of benzyl glycoside **149** as an isopropylidene acetal prior to hydrogenation/hydrogenolysis (Scheme 3–15). Isopropylidene acetals are stable to base treatment and additionally may favour the open form of hemiacetal **152**.



Scheme 3–15. Conversion of benzyl glycoside **149** to isopropylidene acetal **152**.

Initial attempts to install the isopropylidene group by heating a solution of diol **149**, 2,2-dimethoxypropane and 0.3 equivalents of *p*-TsOH in DMF at 60 ˚C failed to give the desired product. Instead, a significant proportion of starting material was returned alongside a side product resulting from the acid catalysed elimination/rearrangement, isopropylidene protected **261** (Scheme 3–16).

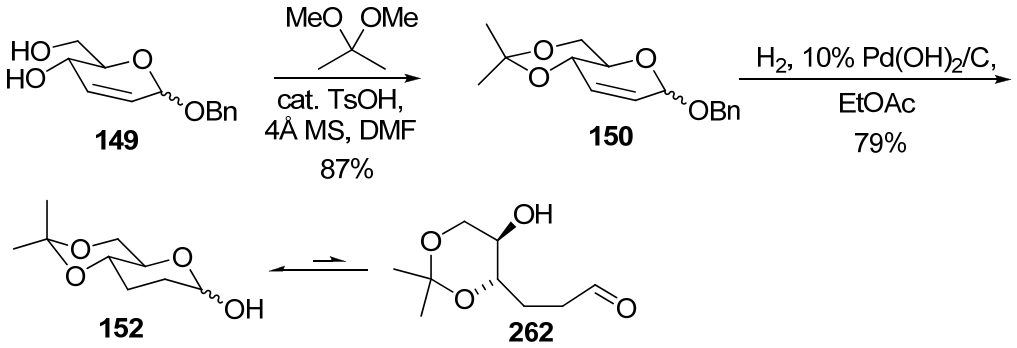


Scheme 3–16. Acid catalysed rearrangement/elimination.

The acetonide synthesis was repeated and eventually proved successful by warming a solution of 2,2-dimethoxypropane and catalytic *p*-TsOH in DMF at 50 ˚C for 12 hours in the presence of 4Å molecular sieves (4Å MS) (Scheme 3–17). A catalyst loading of 2 mol% was found to be the ideal acid concentration to avoid side-product formation.

Benzyl glycoside **150** was found to be relatively acid sensitive, with loss of the acetonide group occurring whilst sitting overnight in $CDCl_3$. To buffer hydrogenation/hydrogenolysis reactions, triethylamine has been used as a co-solvent with EtOH.[179] When triethylamine was added to the $Pd(OH)_2/C$ catalysed reaction, the reaction did not proceed past olefin hydrogenation, leaving the benzyl group intact. The catalyst poisoning property of triethylamine is known and has been exploited to selectively hydrogenate an olefin whilst preventing hydrogenolysis of *O*-benzyl groups.[180,181] The successful hydrogenolysis of *O*-benzyl anomeric groups by López et al. might be explained by the high pressures of hydrogen gas (25 psi) that were used in their work.[179]

In the event, hydrogenation of **150** in ethanol without triethylamine proceeded with little loss of the isopropylidene group. After this discovery, a range of other solvents were investigated to improve the yield. Ethyl acetate was found to be the optimal solvent, giving the highest yields without any detectable decomposition occurring.



Scheme 3–17. Preparation of hemiacetal **152** from benzyl glycoside **149**.

The ^{1}H NMR spectrum of hemiacetal **152** exhibits a small signal at ~9.77 ppm characteristic of aldehyde protons, which suggested that about 10% of this material exists in the open-chain aldehyde form **262** in solution. Hemiacetal **152** was the second HWE substrate successfully prepared from D-glucose, in a total of six steps and an overall yield of 48%.

3.2. The Ramberg-Bäcklund (RB) route

In the proposed Ramberg-Bäcklund (RB) route to Am D two approaches to the intermediate thioether **263** were considered (Figure 3–6): either bromide **135** could be coupled with thiol **169**, or thioacetate **171** could be coupled with iodide **168**. Thiol **169** and iodide **168** could ultimately be derived from D-ribose and D-glucose respectively.

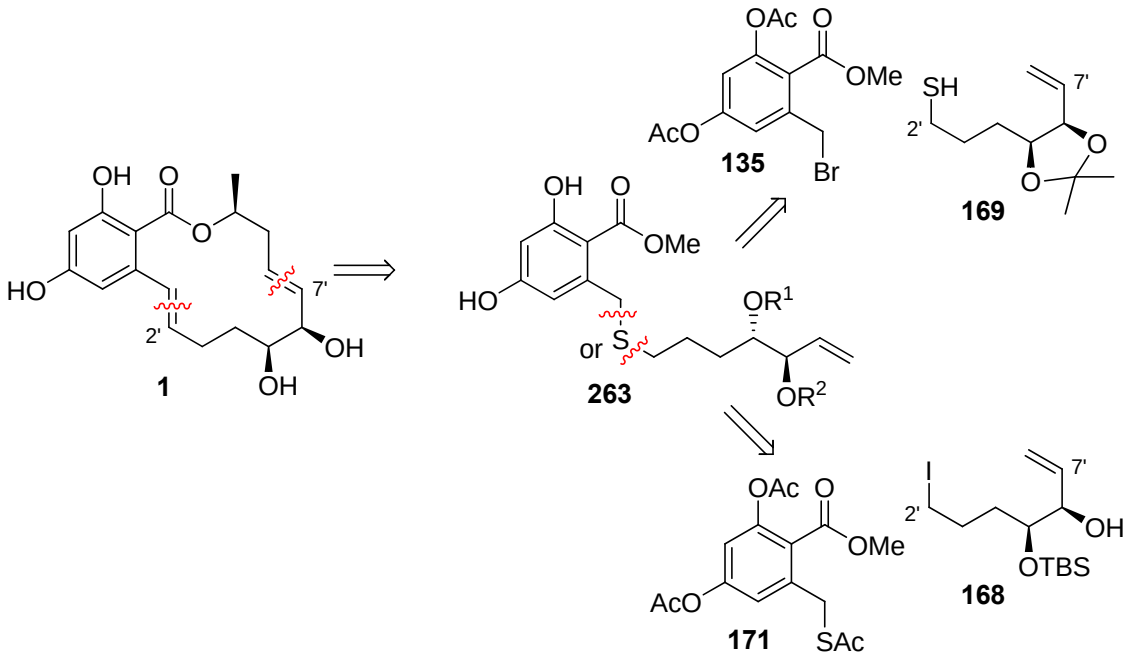
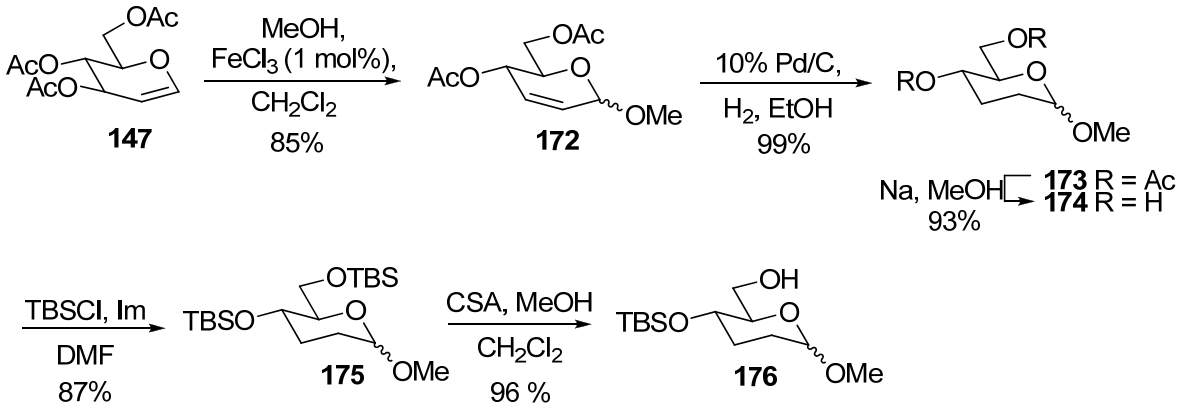


Figure 3–6. Retrosynthetic analysis for the RB route with focus on the C2′ to C7′ segment.

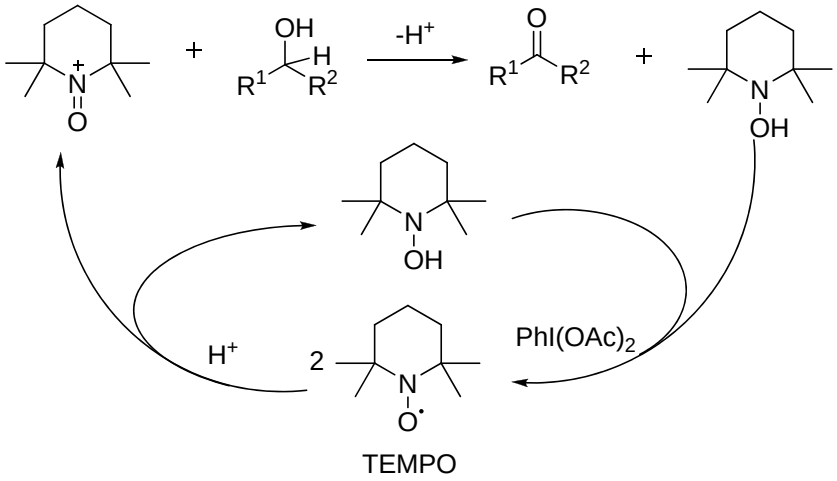
3.2.1 Attempted Synthesis of Iodide 168

The RB approach to Am D was initially focused on coupling thioacetate **171** with iodide **168**. Synthesis of iodide **168** began from tri-*O*-acetyl-D-glucal, **147** (Scheme 3–18). Nakata's procedure was followed to afford alcohol **176** in 65% yield over 5 steps.[92] Here a Ferrier reaction with methanol gave methyl glycoside **172** in good yield (85%). Hydrogenation proceeded quantitatively without the formation of undesired side products, consistent with Toshima's observations.[164] After removal of the acetate groups, the resulting hydroxyl groups were reprotected as TBS ethers. Upon treatment with (±)-camphorsulfonic acid (CSA), the primary TBS ether was selectively cleaved affording primary alcohol **176**.



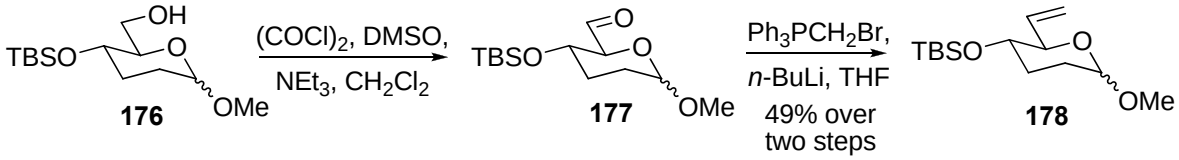
Scheme 3–18. Synthesis of alcohol **176** following Nakata's procedure.[92]

A mild method for oxidation of primary alcohol **176** to the corresponding aldehyde was sought. The *N*-oxoammoium salt based oxidation developed by Piancatelli and co-workers[182] involves the use of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO), which gives an oxoammonium salt and a hydroxylamine moiety by disproportionation, in the presence of bis(acetoxy)iodobenzene (BAIB) that regenerates TEMPO by oxidation of the hydroxylamine (Scheme 3–19).



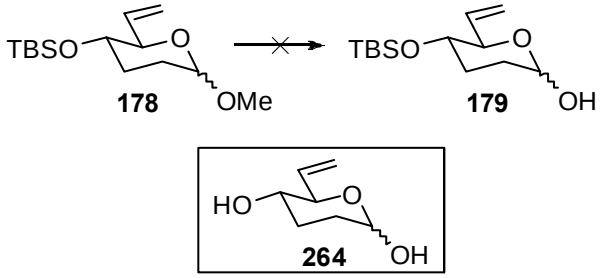
Scheme 3–19. The catalytic cycle for the TEMPO/BAIB oxidation system.[182]

This TEMPO/BAIB oxidation system has been used to oxidise the C6–OH of carbohydrate substrates similar to alcohol **176** to their corresponding aldehydes.[183] However, when this system was used on alcohol **176**, the reaction did not go to completion, returning a 1:1 mixture of starting material and desired aldehyde **177**. In contrast, Swern oxidation[184] of alcohol **176** provided the desired aldehyde in a better yield and purity (Scheme 3–20). With concerns about its stability, aldehyde **177** was immediately reacted in a Wittig olefination without purification. Alkene **178** was isolated in 49% yield from alcohol **176**.



Scheme 3–20. Oxidation and olefination of alcohol **176**.

Hydrolysis of methyl glycoside **178** was attempted several times but did not provide hemiacetal **179** (Table 3–1). It is likely that the TBS ether was unstable in the acidic reaction conditions required, presumably providing deprotected **264** as the major product. Attempted purification of the reaction mixture did not lead to the isolation of any recognisable compounds.



Reagents	Solvent	Temp	Yield of **179**
6% HCl	THF	RT	n.d.[a]
10% HCl	dioxane	reflux	n.d.
10% HCl	dioxane	50 °C	n.d.
50% AcOH	dioxane	50 °C	n.d.

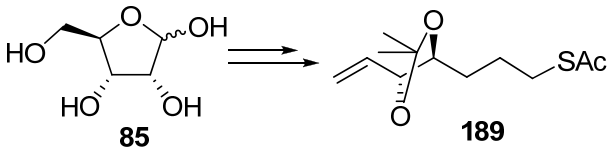
[a] n.d. = not detected

Table 3–1. Attempted hydrolysis of methyl glycoside **178** under various conditions.

Nevertheless, the crude mixture from the 50% AcOH hydrolysis reaction was carried forward in an attempted reduction with sodium borohydride. This resulted in an even more complex mixture of compounds. Due to the lack of success with the hydrolysis and reduction reactions, this approach to thioether **263** was abandoned in favour of a route to thiol **169** starting from D-ribose as described below.

3.2.2 Synthesis of Thioacetate 189

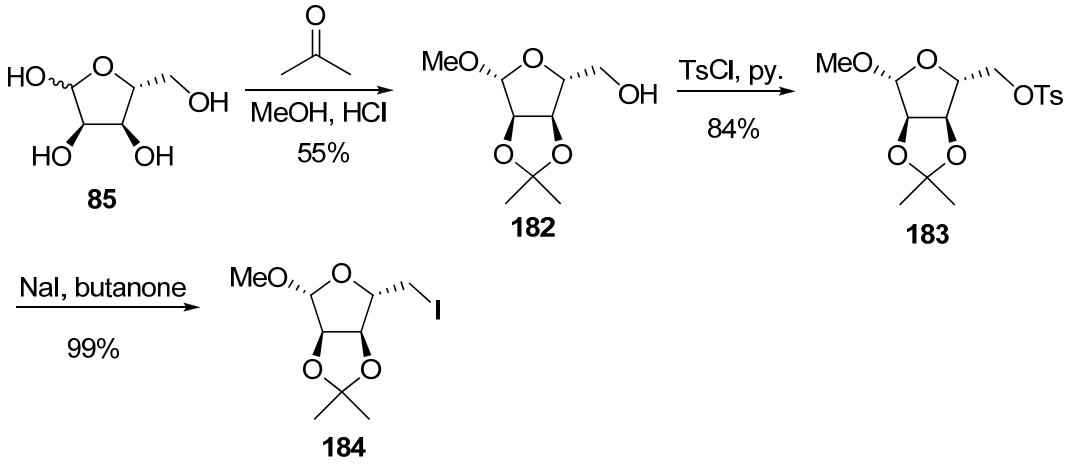
In the alternative route for the RB approach, D-ribose was converted to thiol derivative **189** over 8 steps (Scheme 3–21).



Scheme 3–21. Transformation of D-ribose to thioacetate **189**.

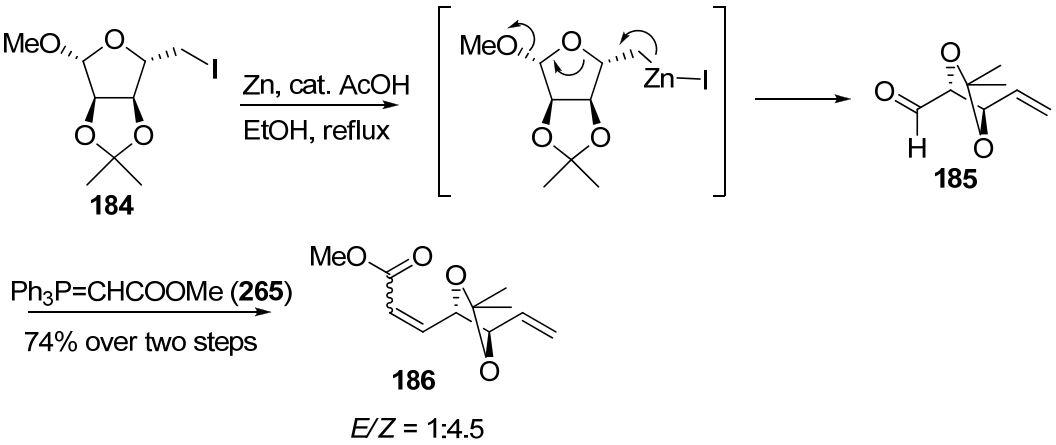
D-Ribose was transformed into the acetonide-protected β-methyl glycoside (**182**) in a one-pot reaction (Scheme 3–22).[98] The crude product was easily isolated from the starting material with a solvent extraction before activation as the tosylate **183**, which was purified by recrystallisation.

Tosylate **183** underwent nucleophilic substitution with sodium iodide to give iodide **184**.[98] The iodide had the same R_f as the starting material on silica and was UV active, requiring ^{1}H NMR analysis of the crude reaction mixture to determine if reacton was complete. No impurities were detected in the ^{1}H NMR spectrum of the crude product, so it was carried through without further purification.



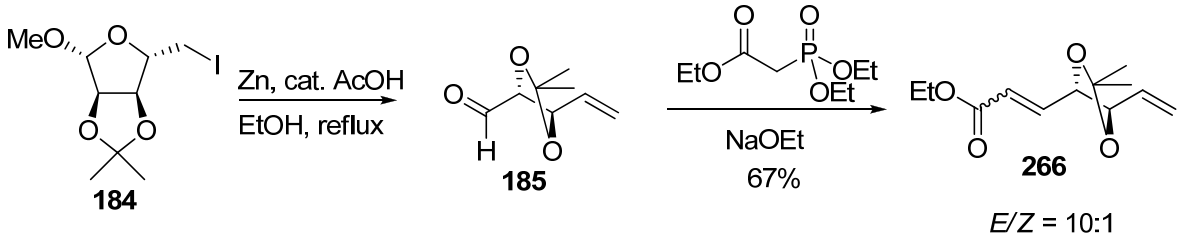
Scheme 3–22. Synthesis of iodide **184** from D-ribose.[98]

The key step in the synthesis of thiol derivative **189** was the one-pot Vasella-Wittig reaction sequence (Scheme 3–23). This sequence involves opening the sugar ring and extending the carbon chain by the two units required for Am D. The Vasella reaction (or Bernet-Vasella reaction) is a zinc-induced reductive ring opening of 6-deoxy-6-halopyranoside or 5-deoxy-5-halofuranoside derivatives.[99,185-187] This reaction produces a ω-enal, which could react in situ with a stabilised ylide such as **265**. Thus, after zinc insertion into the C–I bond of **184**, elimination of zinc iodide and loss of methoxide leads to the formation of aldehyde **185** (Scheme 3–23). The addition of acetic acid activates the zinc towards oxidative insertion in the C–I bond. Vasella has proposed that the reductive fragmentation of β-anomers is concerted since all the bonds that are breaking can become anti-periplanar (Scheme 3–23).[187] Following completion of the reaction, the excess zinc and zinc salts were removed by filtration through a wud of silica before the addition of Wittig reagent **265**. Ester **186** was isolated in a good 74% yield with an *E*/*Z* ratio of 1:4.5. Although the *E* and *Z* stereoisomers could be separated by careful silica column chromatography, methyl ester **186** could be carried forward as a mixture of stereoisomers, as the conjugated olefin was to be saturated in the subsequent reaction.



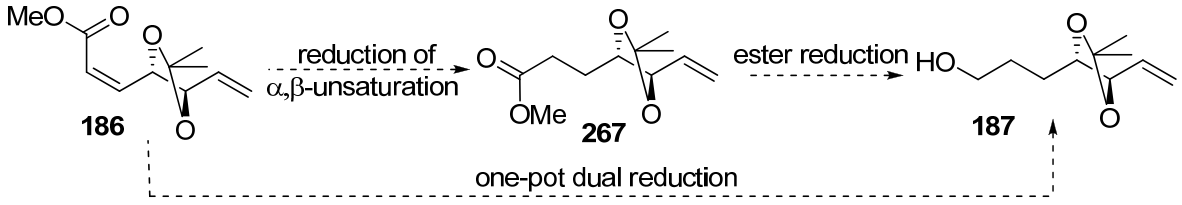
Scheme 3–23. One-pot Vasella-Wittig reaction leading to α,β-unsaturated ester **186**.

The use of a HWE reaction to obtain the ethyl analogue of methyl ester **186** was also investigated (Scheme 3–24). Sequential addition of triethyl phosphonoacetate and sodium ethoxide to the filtered solution of aldehyde **185** provided ethyl ester **266** in superior stereoselectivity but lower overall yield than when the Wittig reagent was used. Hence, the chain extension of aldehyde **185** with Wittig reagent **265** was continued.



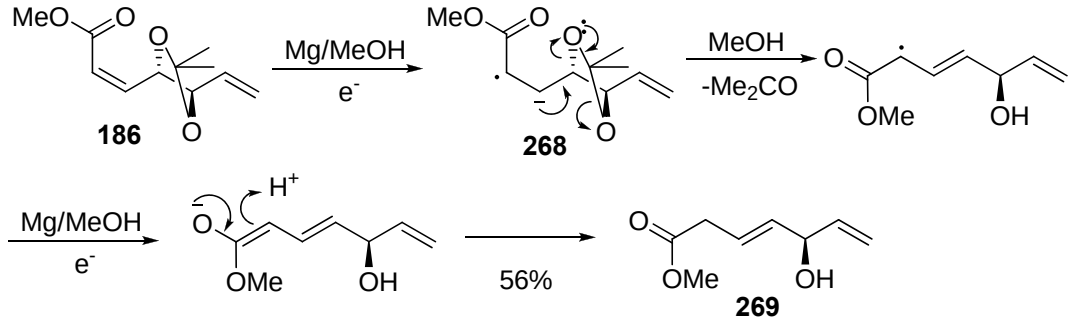
Scheme 3–24. One-pot Vasella-HWE reaction leading to α,β-unsaturated ester **266**.

With the α,β-unsaturated ester in hand, methodology was sought for the selective reduction of the α,β-unsaturated ester to a saturated primary alcohol in either a single step or over two consecutive steps (Scheme 3–25). This selective reduction proved to be quite a challenge.



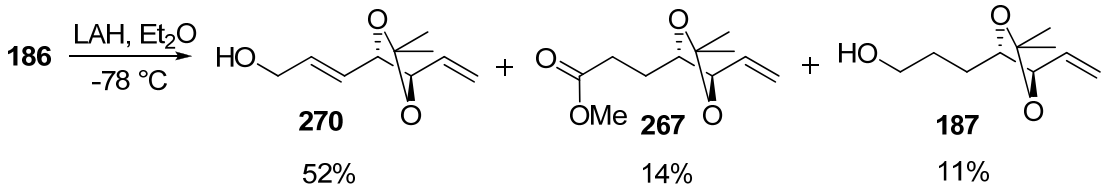
Scheme 3–25. Stepwise or one-pot reduction of α,β-unsaturated ester **186** to alcohol **187**.

An attempted reduction with magnesium metal in methanol[105] led to reductive cleavage of the γ-hydroxyl group to give allylic alcohol **269** (Scheme 3–26). The reaction mechanism is proposed to occur via stepwise single electron transfers (SETs) from the metal to the substrate.[188] The carbanion (**268**) formed in the first SET undergoes the cleavage of the dioxolanyl group which, followed with the second SET and subsequent protonation, gives allylic alcohol **269**.



Scheme 3–26. Proposed mechanism for the reductive cleavage of α,β-unsaturated ester **186**, with magnesium in methanol.[188]

Reduction of α,β-unsaturated ester **186** with lithium aluminium hydride (LAH)[109,110,189] afforded three products: the allylic alcohol **270** as the major product, along with ester **267** and desired saturated alcohol **187** as minor components (Scheme 3–27). Since **187** and **270** were chromatographically inseparable and selective hydrogenation of the major unsaturated alcohol **270** would be difficult, an alternative reduction system was sought.



Scheme 3–27. Reduction of the α,β-unsaturated olefin with LAH.

A variety of simple transition metal catalysts were trialled for the sodium borohydride reduction of the α,β-unsaturated olefin (Table 3–2). Such reduction systems have been reported to reduce the olefin of an α,β-unsaturated ester group whilst leaving the ester intact.[106-108,190] In general, when α,β-unsaturated ester **186** was subjected to these published reduction systems, the reactions rarely went to completion and the undesired reduction of the terminal olefin was difficult to prevent.

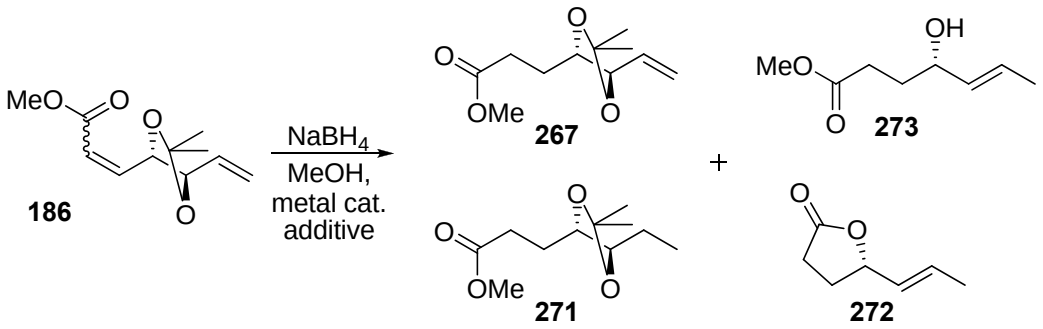


Table 3–2. Reduction of the α,β-unsaturated olefin with $NaBH_4$ and metal catalysts.

Entry	*Metal*	*Amount (equiv.)*	*Temp.*	*Additive*	*Yields* **186**	**267**[a]	**271**[a]	**272**	**273**
1	none		0 °C		100%				
2	$NiCl_2.6H_2O$	0.5	0 °C				84%		
3	$CoCl_2$	0.2	rt				67%		
4	$CuCl_2$	0.75	0 °C		18%	32%	15%	17%	
5	$CuCl_2$	0.75	0 °C		24%	45%	8%	10%	3%
6	$CuCl_2$	0.75	0 °C	THF (1 mL)	37%	47%	9%		
7	$CuCl_2$	0.75	-78 °C		24%	24%	5%	10%	10%
8	CuCl	0.75	0 °C		47%	33%	5%		
9	CuCl	0.75	-78 °C	cyclohexene (4 eq.), NaOMe (0.75 eq.)	13%	71%	6%		
10	CuCl	0.75	-78 °C	cyclohexene (4 eq.)		96%			

Typical procedure: To a cooled solution of the olefin **186** in MeOH and metal catalyst was added $NaBH_4$ over several minutes. The reaction was kept cool for 1 h before warming to rt. *Entry 5* involved addition of the metal catalyst to a solution of olefin **186** already charged with $NaBH_4$.
[a] when mixtures of **267** and **271** were obtained their yields were estimated from the ^{1}H NMR spectra.

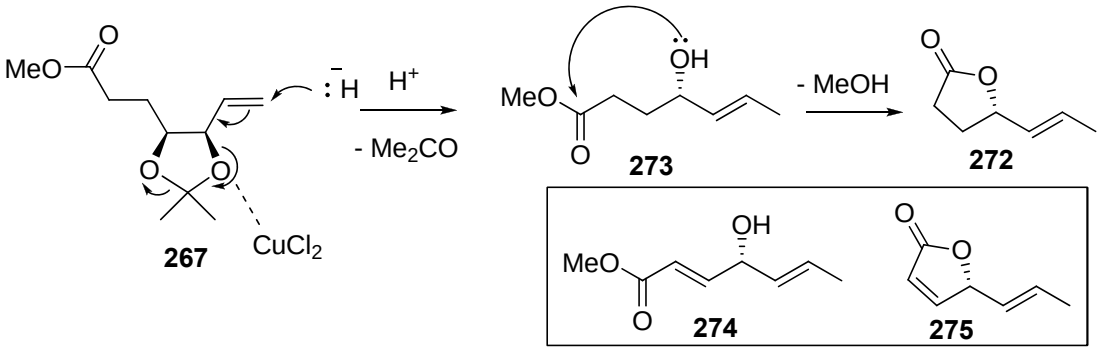
As a control, α,β-unsaturated olefin **186** was treated with sodium borohydride in the absence of a transition metal catalyst (entry 1), returning starting material after 3 h at 0 °C. The first metal catalyst trialled was nickel(II) chloride hexahydrate ($NiCl_2.6H_2O$) (entry 2).[106,191-193] Although the α,β-unsaturated olefin was successfully reduced, the terminal olefin was also hydrogenated in the process. Reduction catalysed by cobalt(II) chloride hexahydrate ($CoCl_2.6H_2O$)[190] similarly led to the sole isolation of saturated **271** (entry 3).

Focus turned to the use of catalytic anhydrous copper(II) chloride ($CuCl_2$), as this reduction system has been used to selectively reduce an α,β-unsaturated olefin in the presence of a terminal alkene (entries 4–7).[107] Conjugate reduction catalysed by $CuCl_2$ afforded some desired product but unfortunately it was chromatographically inseparable from hydrogenated **271** (entry 4). The $CuCl_2$ catalysed reductions failed to go to completion, returning significant amounts of starting material. Lactone **272** and allylic

alcohol **273** were also frequently isolated as minor products from the copper(II) catalysed reductions. Changing the order of addition of reagents (entry 5) improved the yield of desired product **267** but still returned a noteworthy amount of starting material. Use of THF as co-solvent gave a similar yield of desired product to entry 5, but without the side products **272** and **273** (entry 6).[194] Lowering the temperature improved the yield of desired product with respect to saturated **271** but not with respect to side products **272** and **273** (entry 7). When the copper catalyst was changed from copper(II) chloride to copper(I) chloride (CuCl) similar conversions were initially obtained (entry 8).[108]

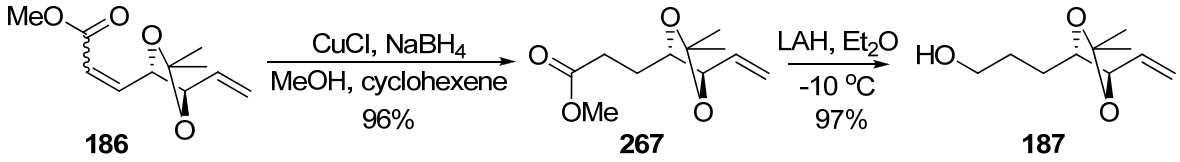
The four products from the reduction reactions all have the α,β-unsaturated olefin of **186** reduced, suggesting that this more reactive olefin was the first to react. If the reactivity of the reduction system could be lowered it might be possible to prevent the reduction of the terminal olefin. It was proposed that over-reduction could be prevented by the addition of an unsaturated compound that could compete with the terminal alkene in **187** for the undesired hydrogenation. Cyclohexene was chosen as the unsaturated additive since it contains a reactive olefin due to ring strain and because both cyclohexene and cyclohexane can be easily removed under reduced pressure at the completion of the reaction. Sodium methoxide was initially also included to counteract the Lewis acidity of the copper catalyst which presumably leads to lactone **272** and allylic alcohol **273** (Scheme 3–28). Indeed, use of these two additives afforded the highest yield of desired product yet, with a greatly reduced amount of starting material returned (entry 9). When sodium methoxide was excluded, the desired product **267** was the sole product and isolated in an excellent yield (entry 10).

Formation of allylic alcohol **273** and lactone **272** is likely to arise after the reduction of the α,β-unsaturated olefin since their conjugated equivalents **274** and **275** were not observed (Scheme 3–28). It is proposed that a hydride attacks the terminal olefin with the π-electrons flowing to eliminate acetone giving allylic alcohol **273,** which can then cyclise to give the lactone **272**. Evidence for these products can be seen in their ^{1}H NMR spectra with new methyl doublets being observed at 1.70 and 1.75 ppm respectively and the presence of only two signals characteristic of olefinic protons.



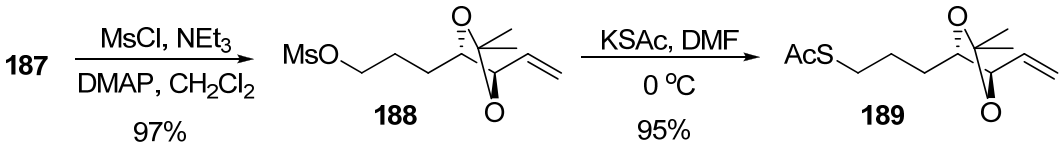
Scheme 3–28. A proposed mechanism for the synthesis of the isolated side products **272** and **273**.

After selective reduction of the α,β-unsaturated olefin using catalytic copper(I) chloride and sodium borohydride, ester **267** was reduced with LAH to give alcohol **187** in excellent yield (Scheme 3–29).



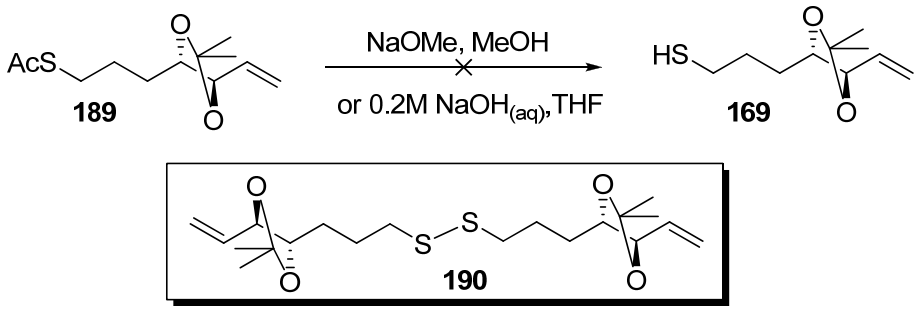
Scheme 3–29. Stepwise reduction of conjugated ester **186** to alcohol **187**.

Alcohol **187** was activated to nucleophilic attack by conversion to mesylate **188** (Scheme 3–30). Nucleophilic substitution of the mesylate with potassium thioacetate in dimethylformamide proceeded to give thioacetate **189** in 93% yield over the two steps.



Scheme 3–30. Synthesis of thioacetate **189**.

Attempts were made to deprotect thioacetate **189** to the free thiol moiety (Scheme 3–31). These attempts resulted in the synthesis of a product less polar than thioacetate **189**, with a ^{1}H NMR spectrum that was almost identical to that of the starting material but with loss of the characteristic acetate methyl peaks. This compound was confirmed to be the symmetrical disulfide **190** by HRMS. Thiol **169** was likely oxidised to disulfide **190** on work up.

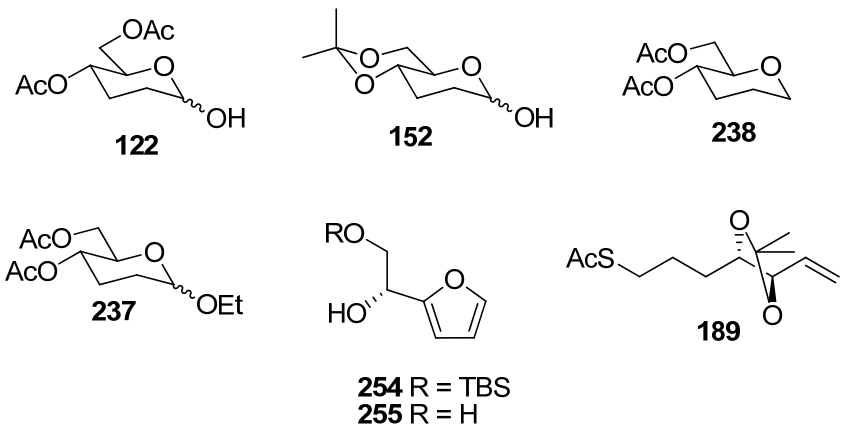


Scheme 3–31. Attempted preparation of thiol **169** that led to disulfide product **190**.

The couplings of benzylic halides and thiols formed by in situ deprotection of the corresponding thioacetate have been previously reported. In one such procedure, Yelm preformed the sulphide with pyrrolidine in acetonitrile prior to addition of a benzylic bromide and triethylamine to the reaction.[195] Han and Balakumar more simply reported that the addition of K_2CO_3 to a solution of thioacetic acid and benzyl bromide in MeOH led to an efficient coupling of the two units.[196] Therefore, thioacetate **189** was stockpiled as the masked form of the thiol **169** to be the key fragment to couple with the aromatic fragment **135**.

3.4 Summary of Chapter Three

Two substrates for the HWE reaction were successfully prepared from D-glucose. Diacetate **122** and acetonide **152** were obtained in 55% (5 steps) and 48% (7 steps) yields respectively. A mechanism for the formation of hydrogenation by-products **237** and **238** was proposed. A similar mechanism was invoked for the formation of furans **254** and **255**. The RB substrate, thioacetate **189**, was prepared from D-ribose in 39% yield over seven steps. With both aromatic and C2′–C7′ segments in hand, access to the remaining segment, the C8′–C11′ portion, was sought (Chapter 4).



Chapter Four:

Synthesis of the C8'–C11' Segment

Preparation of the C8′–C11′ segments for both synthetic strategies centred around establishing the appropriate stereochemistry at C10′ using asymmetric methodology. The HWE strategy involved the preparation of phosphonate **118** via an asymmetric reduction of the corresponding ketone, whilst the RB strategy involved the preparation of alcohol **22** via an asymmetric allylboration of acetaldehyde (Figure 4–1).

Figure 4–1. Desired C8′–C11′ segments for the HWE and RB routes, respectively.

4.1 Route to Hydroxyphosphonate 118

Our initial approach to Am D utilised a HWE reaction to install the olefin at C7′ and C8′ (Figure 4–2). This approach required the synthesis of phosphonate (*S*)-**118** or its enantiomer (*R*)-**118**, depending on the method of ester formation chosen. Compound **118** and its enantiomer comprise the C8′–C11′ fragment of Am D.

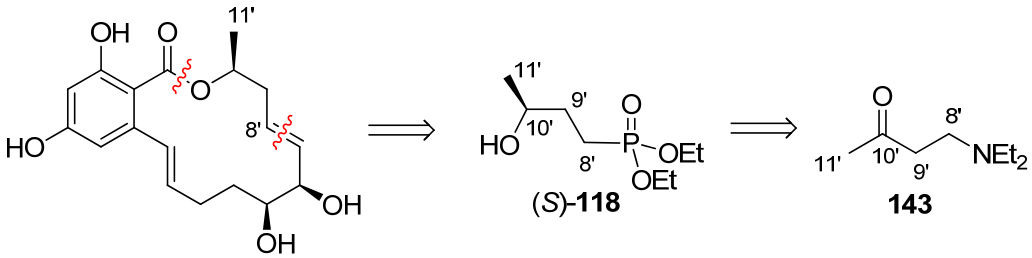
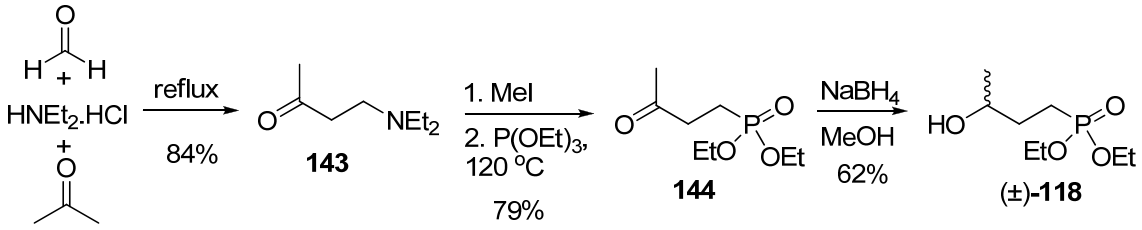


Figure 4–2. Retrosynthetic analysis of the C8′–C11′ fragment of Am D: the HWE route.

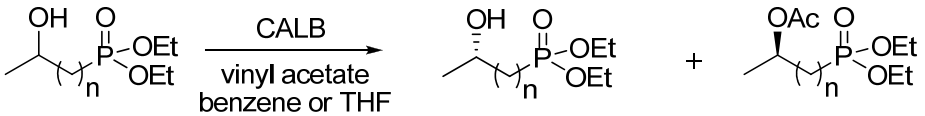
In the first instance, it was decided to synthesis racemic **118**. Following the procedure published by Wilds and Shunk,[80] the four-carbon chain of this fragment was synthesised in the form of amine **143**, using a Mannich reaction[81] between acetone, formaldehyde and diethylamine hydrochloride (Scheme 4–1). The addition of methyl iodide to amine

143 provided a quaternary ammonium salt, activating the adjacent carbon to nucleophilic attack by triethyl phosphite in an Arbuzov-like reaction, affording phosphonate **144**.[82] The sodium borohydride reduction of keto-phosphonate **144** provided the racemic form of desired hydroxyphosphonate (±)-**118** in moderate overall yield (41%).



Scheme 4–1. Synthesis of phosphonate (±)-**118**.

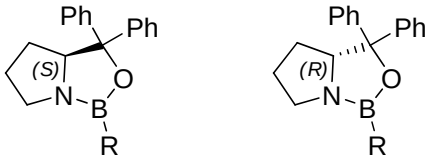
The first avenue considered for obtaining hydroxyphosphonate (*R*)- or (*S*)-**118** was the non-stereoselective reduction of ketone **144** followed by enzymatic resolution. A published investigation of the kinetic resolution of hydroxyalkanephosphonates catalysed by *Candida antarctica* lipase B[83] found that one enantiomer of diethyl 2-hydroxypropanephosphonate [(±)-**277**] was a good substrate for the enzyme, giving excellent resolution on acetylation of one enantiomer (Scheme 4–2). The acetate **278** and free alcohol **277** were both found to have enantiomeric excesses (ee) of > 95%. However, diethyl 3-hydroxybutanephosphonate [(±)-**118**] was not resolved under the same conditions, with both enantiomers being equally acetylated by the enzyme.[83] It was postulated that this was due to the enzyme–substrate binding of the enantiomers differing less in the transition states than that of the diethyl 2-hydroxypropanephosphonate isomers.[83]



n = 1 (±)-**277** n = 1 **277** 40%, >95% ee n =1 **278**, 39%, >95% ee
n = 2 (±)-**118** n = 2 (±)-**118** 0% n =2 Ac-(±)-**118**, 80%, 0% ee

Scheme 4–2. Kinetic resolution of hydroxyalkanephosphonates with *Candida antarctica* lipase B (CALB).

With enzymatic resolution of phosphonate (±)-**118** ruled out, attention was focussed instead on the use of asymmetric reduction of ketone **144** to prepare the enantiomerically pure alcohol (*S*)-**118**. A number of methods exist in the literature for such an asymmetric reduction.[84] Corey and co-workers have developed a family of compounds called the oxazaborolidines for the enantioselective reduction of ketones (Figure 4–3).[84,197,198]

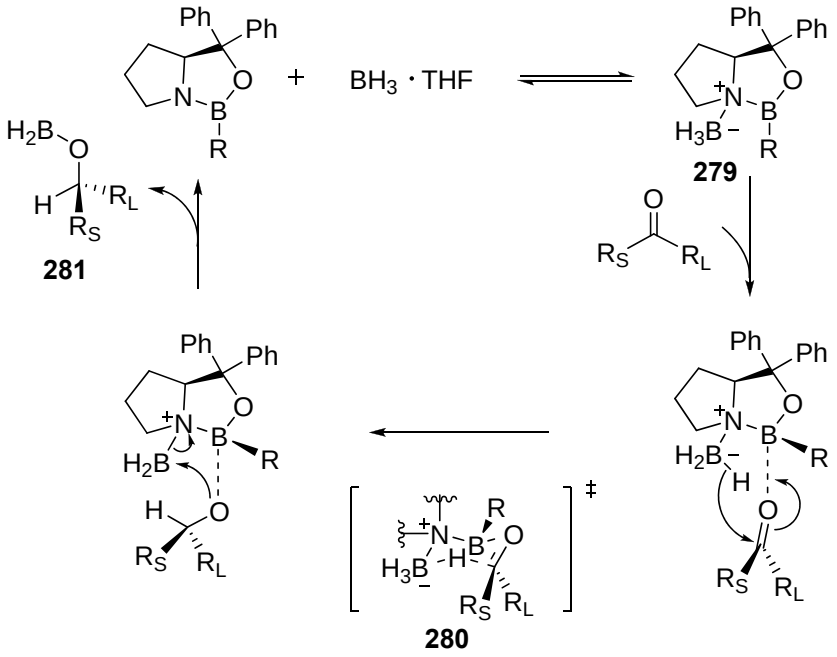


(*S*)-CBS (*R*)-CBS

R = H, Me, Bu

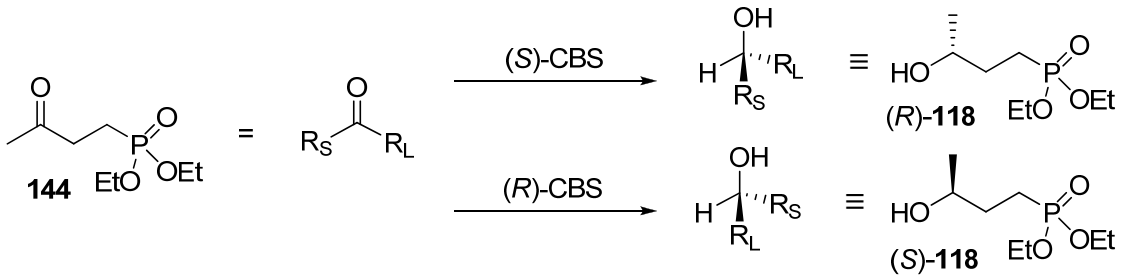
Figure 4–3. Oxazaborolidine catalysts for the asymmetric reduction of ketones developed by Corey et al.

In these Corey-Bakshi-Shibata (CBS) reductions, the oxazaborolidine catalyst behaves like an enzyme in the sense that it binds both the ketone (substrate) and borane (reducing agent), activating them both to reaction (Scheme 4–3). After the reaction is complete, the product is released, freeing the oxazaborolidine catalyst to react again. The mechanism of the CBS reduction proposed by Corey is based on early spectroscopic studies.[197] Upon addition of the borane reagent to the oxazaborolidine catalyst, coordination and activation of borane by the nitrogen gives species **279**. This activates the borane as a reducing agent. The carbonyl oxygen of the ketone substrate coordinates to the oxazaborolidine ring boron with the larger carbonyl appendage (R_L) pointing away from the boron substituent (R) and the phenyl rings on the catalyst. Hydrogen transfer from the activated borane takes place via a six-membered transition state, **280**. The enantiomerically pure alcohol is finally released as boron ether **281**, which provides the alcohol upon aqueous workup.



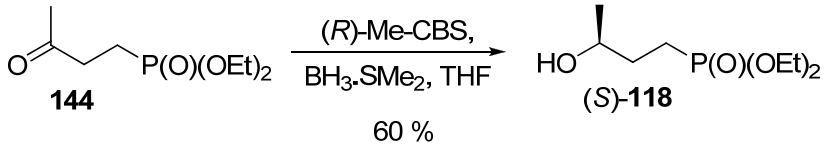
Scheme 4–3. Corey's proposed mechanism for the catalytic reduction of ketones by oxazaborolidine catalysts.

When ketophosphonate **144** is the substrate for the CBS reduction, the methyl and alkylphosphonate groups correspond to the small and large carbonyl appendages respectively (Scheme 4–4).



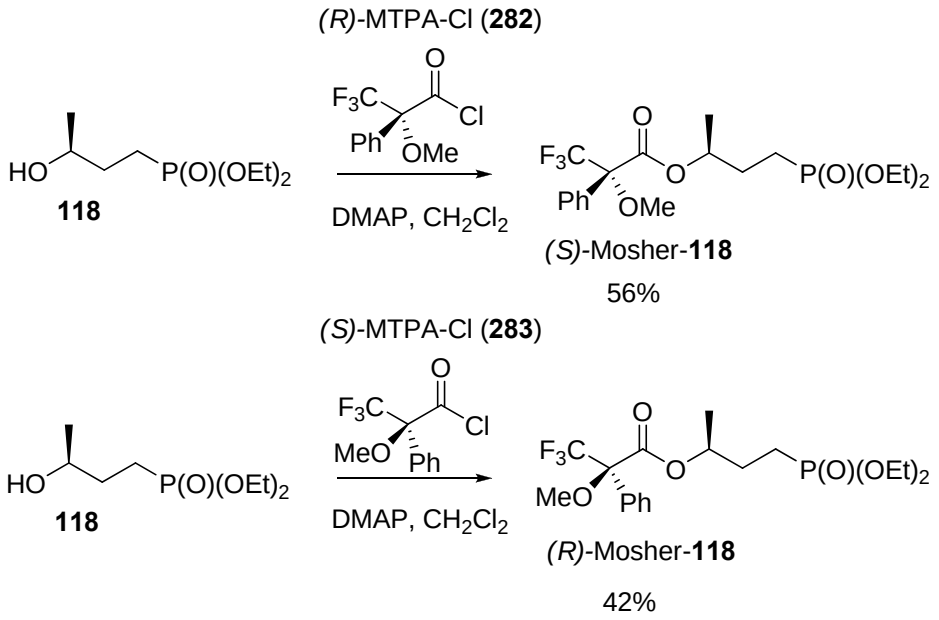
Scheme 4–4. Expected hydroxyphosphonate products from CBS-catalysed reductions.

Either alcohol (*R*)-**118** or (*S*)-**118** could be used in the total synthesis of Am D, depending on the esterification methodology to be employed. As the formation of the macrocycle by Yamaguchi macrolactonisation[52] was initially planned (Section 1.4.2.5, Scheme 1–29), (*S*)-**118** was required. Thus a solution of (*R*)-2-methyl-CBS-oxazaborolidine [(*R*)-Me-CBS] in toluene was used to catalyse the reduction of ketophosphonate **144** (Scheme 4–5).



Scheme 4–5. (*R*)-Me-CBS catalysed reduction of ketophosphonate **144** to alcohol (*S*)-**118**.

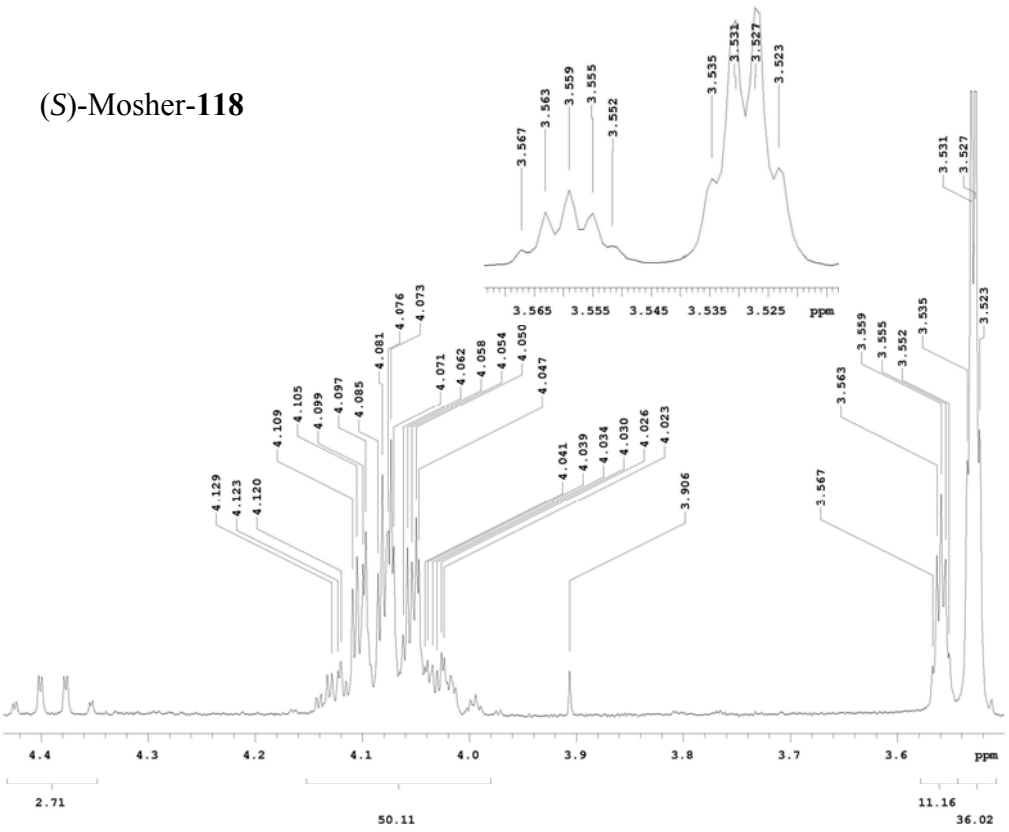
The reduction was rather low yielding (60%) compared with the yields reported with other substrates (85–99%).[84] It was, however, comparable to the yield for the non-stereoselective reduction of ketophosphonate **144** with sodium borohydride (62%). To assess the stereoselectivity of the reaction, the (*S*)- and (*R*)-Mosher esters of alcohol (*S*)-**118** were prepared and analysed using ^{1}H NMR spectroscopy.[199,200] (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) are chiral derivatising agents that are useful for determining the ee of chiral alcohol substrates and for identifying the stereochemistry of their chiral centre(s). Upon separate reaction with (*R*)- and (*S*)-MTPA-Cl the substrate in question should yield diastereomers with non-equivalent chemical shifts in their ^{1}H and ^{19}F spectra. When (*R*)- and (*S*)-MTPA-Cl were individually reacted with phosphonate **118**, the corresponding (*S*)- and (*R*)-Mosher esters were isolated in only 56% and 42% yields, respectively (Scheme 4–6). It is likely that the acid chlorides **280** and **281** had slowly hydrolysed whilst in storage, forming their carboxylic acids, which were unreactive towards the alcohols under the reaction conditions used. For accurate measurement of the ee, near quantitative yields of the Mosher esters are required so as to negate any kinetic resolution due to differential reaction rates of the substrate enantiomers.[201] Thus, it is plausible that some kinetic resolution could have occurred in this reaction. Analysis of the non-equivalent $-OCH_3$ peaks in each ^{1}H NMR spectrum suggested diastereoisomeric excesses (de's) of 47% and 73%, for the (*S*)- and (*R*)-Mosher esters respectively. The difference in these values suggests that kinetic resolution of the mixture of enantiomers may have been occurring during its reactions with the chiral acid chlorides.



Scheme 4–6. Synthesis of Mosher esters of hydroxyphosphonate **118**.

The quartet expected for the $-OCH_3$ peak at 3.56 ppm appears to be quintet in the ^1H NMR spectrum of (*S*)-Mosher-**118** (Figure 4–4). This multiplet could potentially arise from the overlap of the $-OCH_3$ quartet from (*S*)-Mosher-**118** and the $-OCH_3$ quartet from (*R*)-MTPA-OH.[202] However, the persistence of (*R*)-MTPA-OH after washing the reaction mixture with 1M sodium hydroxide solution is improbable. Further analysis of the ^1H NMR spectrum reveals the presence of a small quartet of doublets at 4.39 ppm (J_{HH} = 7.1, 0.8 Hz) that is characteristic of ethyl Mosher esters.[203] Furthermore the $-OCH_3$ peak for ethyl (±)-Mosher ester is reported to be observed as a singlet at 3.56 ppm.[203] The small quartet of doublets at 4.39 ppm is also present in the ^1H NMR spectrum of (*R*)-Mosher-**118**. However, it is impossible to detect the singlet at 3.56 ppm under the large quartet present. The contribution of this singlet to the integration of the $-OCH_3$ peaks at 3.56 ppm would have the effect of both reducing the de of (*S*)-Mosher-**118** and enhancing the de of (*R*)-Mosher-**118**. Hence, any conclusions drawn from the calculated de's (e.g. apparent kinetic resolution) can only be made tentatively. The formation of these ethyl esters could result from the hydrolysis of diethyl phosphonate **118**. This could additionally explain the why no starting material was observed in the ^1H NMR spectra despite the low yields of the reactions (confirmed by absence of the $CH_3C\underline{H}(OH)$-R methine at 3.82 ppm).

(*S*)-Mosher-**118**



(*R*)-Mosher-**118**

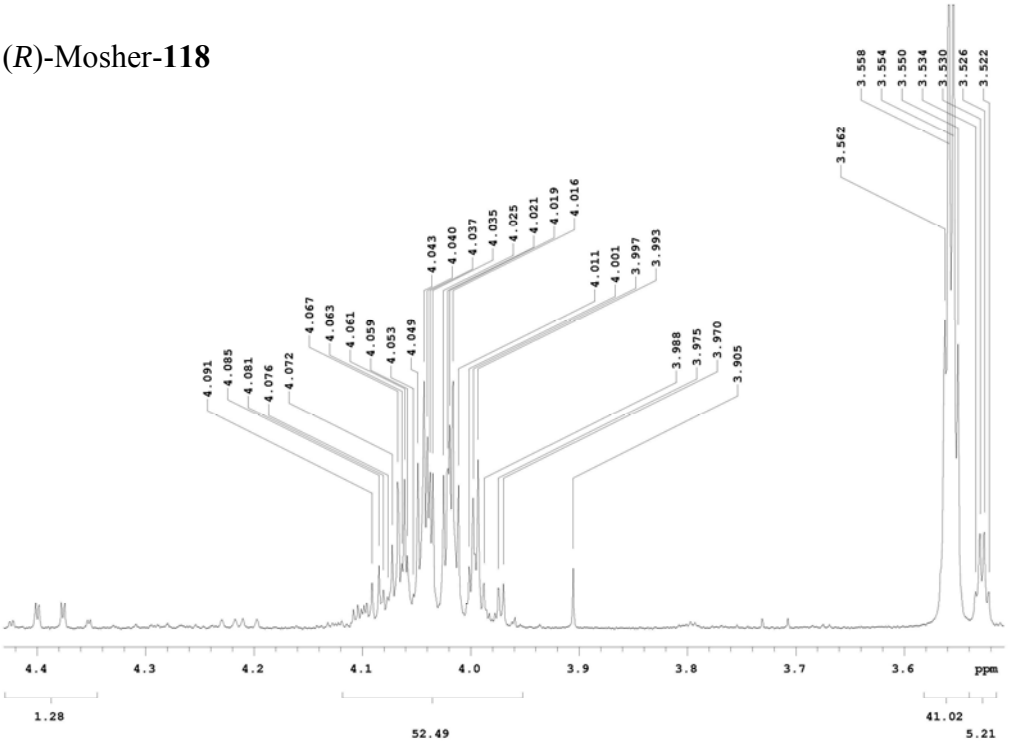


Figure 4–4. Sections from ^{1}H NMR spectra of (*S*)-Mosher-**118** (above) and (*R*)-Mosher-**118** (below).

Unfortunately, before the CBS reduction of ketophosphonate **144** could be repeated, the CBS catalyst degraded, precipitating out of solution. At this point in time, the HWE

route was being re-evaluated due to difficulties with the HWE reaction required to install the olefin at C1′ and C2′. As a result, this route to the C8′–C11′ fragment of Am D was abandoned in favour of a route utilising an asymmetric allylation reaction as described in the following section.

4.2 Route to (*R*)-4-Penten-2-ol (22)

In the Ramberg-Bäcklund (RB) route to Am D, the C8′–C11′ fragment is obtained from the homoallylic alcohol (*R*)-4-penten-2-ol (**22**) (Figure 4–5). Past syntheses of Am D have shown the Mitsunobu reaction to be an effective method for coupling the aromatic moiety with alcohol **22**.[9,32,35]

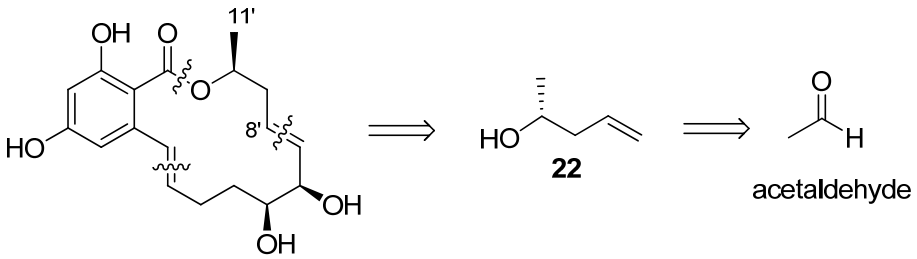
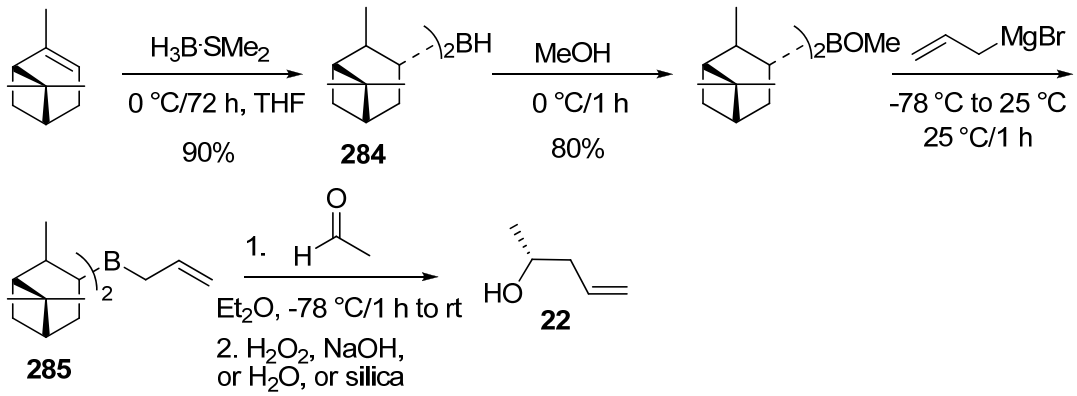


Figure 4–5. Retrosynthetic analysis of the C8′–C11′ fragment of Am D: the RB route.

Brown and co-workers have developed a route to enantiomerically-pure homoallylic alcohols through the asymmetric allylboration of aldehydes.[89,204] Preparation of (*R*)-4-penten-2-ol (**22**) via Brown's methodology began with synthesis of (-)-*B*-allyldiisopinocampheylborane by treatment of (+)-α-pinene with borane-dimethyl sulphide complex (Scheme 4–7). The hydroboration reaction is left for several days, to allow for equilibration, which results in a reagent with a 98.9% ee, from (+)-α-pinene with a 91.3% ee.[89] Methanolysis of borane **284** was directly followed by treatment with allylmagnesium bromide to give the allylating agent (-)-*B*-allyldiisopinocampheylborane, **285**. It has been shown that removal of the magnesium salts from this reagent leads to shorter reaction times and can improve the enantiomeric excess.[205] However, the increase in ee is outweighed by the time-consuming filtration required and hence the reagent **285** was used directly by cooling to -78 °C before the addition of acetaldehyde. After warming to room temperature the reaction mixture was worked up with either the addition of alkaline hydrogen peroxide, water or silica to give the desired alcohol **22**.



Scheme 4–7. Asymmetric allylboration of acetaldehyde.

The ^{1}H NMR spectrum of the crude residue exhibited the characteristic signals associated with (*R*)-4-penten-2-ol alongside those of (+)-α-pinene and its derivatives.[204] All attempts to isolate the alcohol, however, failed. Following reported procedures for purification by distillation[89,90] and column chromatography,[89] pure (*R*)-4-penten-2-ol was never isolated beyond trace quantities. Despite having a reported atmospheric boiling point of 115–116 °C, alcohol **22** seemed too volatile to be concentrated under reduced pressure (~20 mmHg). It was also found to form an azeotrope with diethyl ether at atmospheric pressure. Additionally, the distilled alcohol was often contaminated with an isopinocampheol by-product from the allylation reaction. Though separable by flash column chromatography from by-products, alcohol **22** co-evaporated with the eluant (1:4, diethyl ether–pentanes). Thus a commercial source of alcohol (*R*)-**22** was obtained.

4.3 Summary of Chapter Four

The racemate of alcohol **118** was successfully prepared in three steps from acetone with 41% overall yield. The asymmetric reduction of ketophosphonate **144** catalysed by (*R*)-methyl-CBS-oxazaborolidine provided alcohol (*S*)-**118** with an estimated ee of between 47 – 73%, based on Mosher's ester analysis. After re-evaluation of the HWE route, the synthesis of alcohol (*S*)-**118** was abandoned in favour of (*R*)-4-penten-2-ol (**22**).

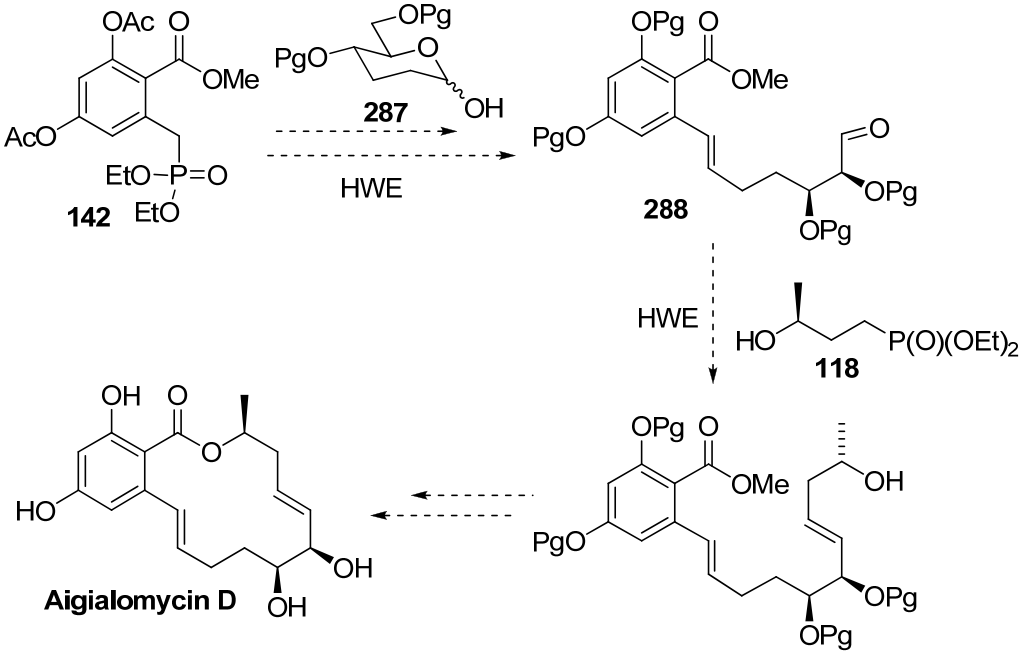
After much experimentation, the synthesis of (*R*)-4-penten-2-ol (**22**) was also abandoned in favour of purchasing it from Sigma-Aldrich. The racemate of alcohol **22** was also purchased from Merck and used whilst waiting for delivery of alcohol (*R*)-**22**. Thus, the C8′–C11′ segment of Am D was obtained from a commercially available reagent with known enantiomeric purity (95%).

Chapter Five:

Piecing Together Aigialomycin D

5.1 Investigation of a HWE Reaction for Installation of the C1′-C2′ Bond

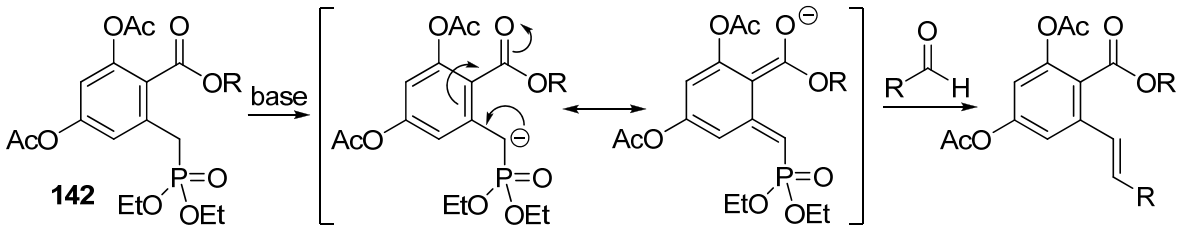
The first proposed route to Am D relied on the use of the Horner-Wadsworth-Emmons (HWE) reaction for the installation of the two (*E*)-olefins present in Am D (Scheme 5–1). The reaction of phosphonate **142** with protected hemiacetal **287** could provide the conjugated C1′–C2′ olefin of Am D. In like manner, derived aldehyde **288** could be reacted with phosphonate **118** to install the C7′–C8′ olefin. Macrolactonisation and global deprotection would ultimately deliver the natural product. It is noteworthy that Pan and co-workers[34] successfully installed the two (*E*)-alkenes utilising another variant of the Wittig reaction, the Juliá-Kocienski olefination (Section 1.3.3.2).



Scheme 5–1. Proposed HWE olefinations for the installation of the (*E*)-alkenes of Am D.

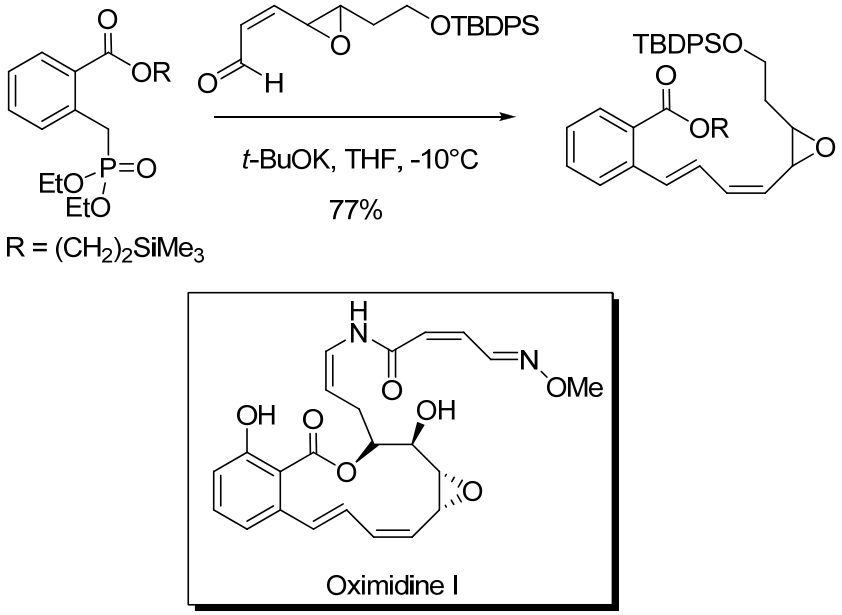
Phosphonate **142** contains an ester group in the δ-position (Scheme 5–2). Once deprotonated, the electron density from the carbanion could flow through the aromatic system to the ester, contributing an additional resonance structure for the phosphonate

carbanion. This conjugation should help stabilise the phosphonate carbanion, increasing the acidity of benzylic hydrogens.



Scheme 5–2. Generic HWE reaction of δ-keto phosphonate **142** with an aldehyde.

Similar HWE methodology was employed by Taylor and co-workers in the synthesis of the epoxide-containing macrolactone nucleus of oximidine I (Scheme 5–3).[137] In this synthesis, the aryl phosphonate involved in the HWE reaction was a derived *ortho*-toluenic acid.



Scheme 5–3. Utility of the HWE reaction in the synthesis of an oximidine I analogue by Taylor.

5.1.1 HWE Reactions With Simplified Model Phosphonates

Initial investigations into the utility of the HWE reaction for the installation of the conjugated alkene of Am D focused on the reaction between the model phosphonates **210** and **211** and the straight-chain aldehydes butanal (**76**) and octanal (**289**) (Scheme 5-3, Table 5–1). A solution (THF, Et_2O or toluene) of the phosphonate at a set temperature (-78 °C, 0 °C or rt) was first treated with a base (*t*-BuOK, NaH, LiHMDS, or K_2CO_3). After addition of the base, the solution typically turned bright orange, suggesting that deprotonation had occurred. The addition of the freshly distilled aldehyde to this solution caused fading of the colour, although a pale yellow colour would typically persist even after quenching with saturated ammonium chloride solution (sat. $NH_4Cl_{(aq)}$). These reactions produced very little of the desired substituted styrenes **290a/b** and **291a/b** (0 – 30%). The major products of the reactions (21 – 69%) were very polar compounds, which were found in the aqueous layer after washing the crude reaction mixture with 2M sodium hydroxide solution.

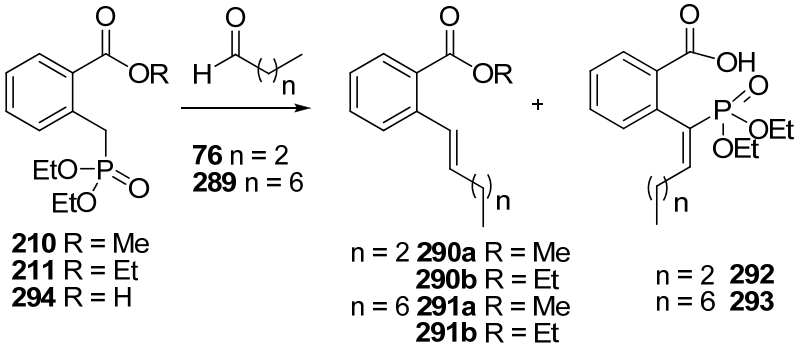


Table 5–1. HWE reactions of phosphonates **210** and **211** with butanal (**76**) and octanal (**289**).

Phosphonate	Aldehyde	Solvent	Base	Reaction Temp. (° C)[a]	Yield SM	290a/b	291a/b	292	293
210	octanal	THF	LiHMDS (1 eq)	0	15	-	30	-	28
210	octanal	ether	LiHMDS (1 eq)	-78		-	7	-	55
210	octanal	THF	LiHMDS (1 eq)	-78		-		-	69
210	octanal	toluene	LiHMDS (1 eq)	-78	22	-	9	-	33
210	octanal	THF	K_2CO_3 (2 eq)	rt	100	-		-	
210	butanal	ether	LiHMDS (1.1 eq)	-78	14		-	29	-
210	butanal	toluene	LiHMDS (1.2 eq)	-78	18	20	-	21	-
211	butanal	THF	NaH (1 eq)	-78		20	-		-
211	butanal	neat	MeONa (2 eq)	0	100		-		-
294	butanal	THF	LiHMDS (2.2 eq)	-78	100		-		-

[a] The reactions were allowed to warm to room temperature (rt) after two hours stirring at the stated reaction temperature.

A signal characteristic of an olefinic proton was visible at ~6.7 ppm in the ^{1}H NMR spectrum of these polar compounds (Figure 5–2). This one-proton doublet of triplets (J_{HX} = 23.1, 7.3 Hz) did not exhibit coupling to any peaks in the characteristic unsaturated region (4.5–7.5 ppm)[206] suggesting that the benzylic carbon has two non-hydrogen substituents. Indeed, the large coupling constant (J_{HP} = 23.1 Hz) is typical of the proton–phosphorus coupling (^{1}H–^{31}P coupling) between diethyl phosphonates in a *cis*-relationship with a hydrogen across a double bond.[207,208] Kobayashi and William utilised the characteristic coupling constants between vicinal hydrogen and phosphorous atoms to assign the stereochemistry of a series of α-arylalkenylphosphonates they had synthesised (Figure 5–1).[209] Thus it is highly probable that the by-products also contain a phosphonate group *trans* to the aliphatic chain from the aldehyde. The protons coupling to the peak at ~6.7 ppm in the gCOSY spectrum are complex signals in the aliphatic region (1.99 – 1.82 ppm). The ethyl signals from the phosphonate esters are still visible but the methyl ester peak is no longer present in the spectrum (Figure 5–2). Further detailed analysis of the NMR spectral data supported the assignment of the structures as alkenylphosphonates **292** and **293** (Figure 5–2). Assignment of this structure was further supported by the high resolution mass spectrum (HRMS) of compound **292**, which contained a peak corresponding to the sodium ion of this structure.

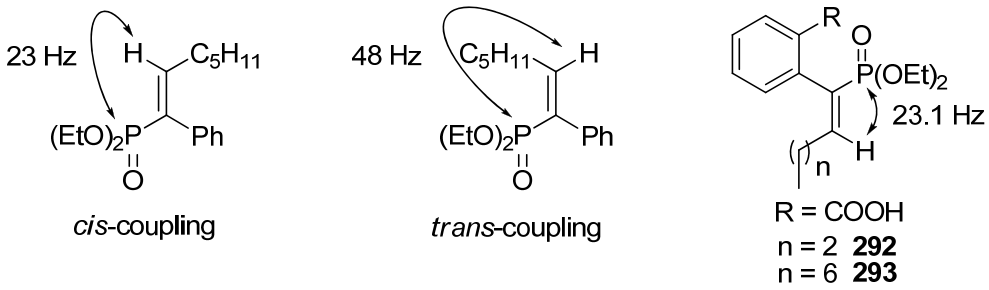


Figure 5–1. Diagnostic ^{31}P–^{1}H coupling in diethyl (*E*)-1-phenyl-1-heptenylphosphonate, diethyl (*Z*)-1-phenyl-1-heptenylphosphonate[209] and alkenylphosphonates **292** and **293**.

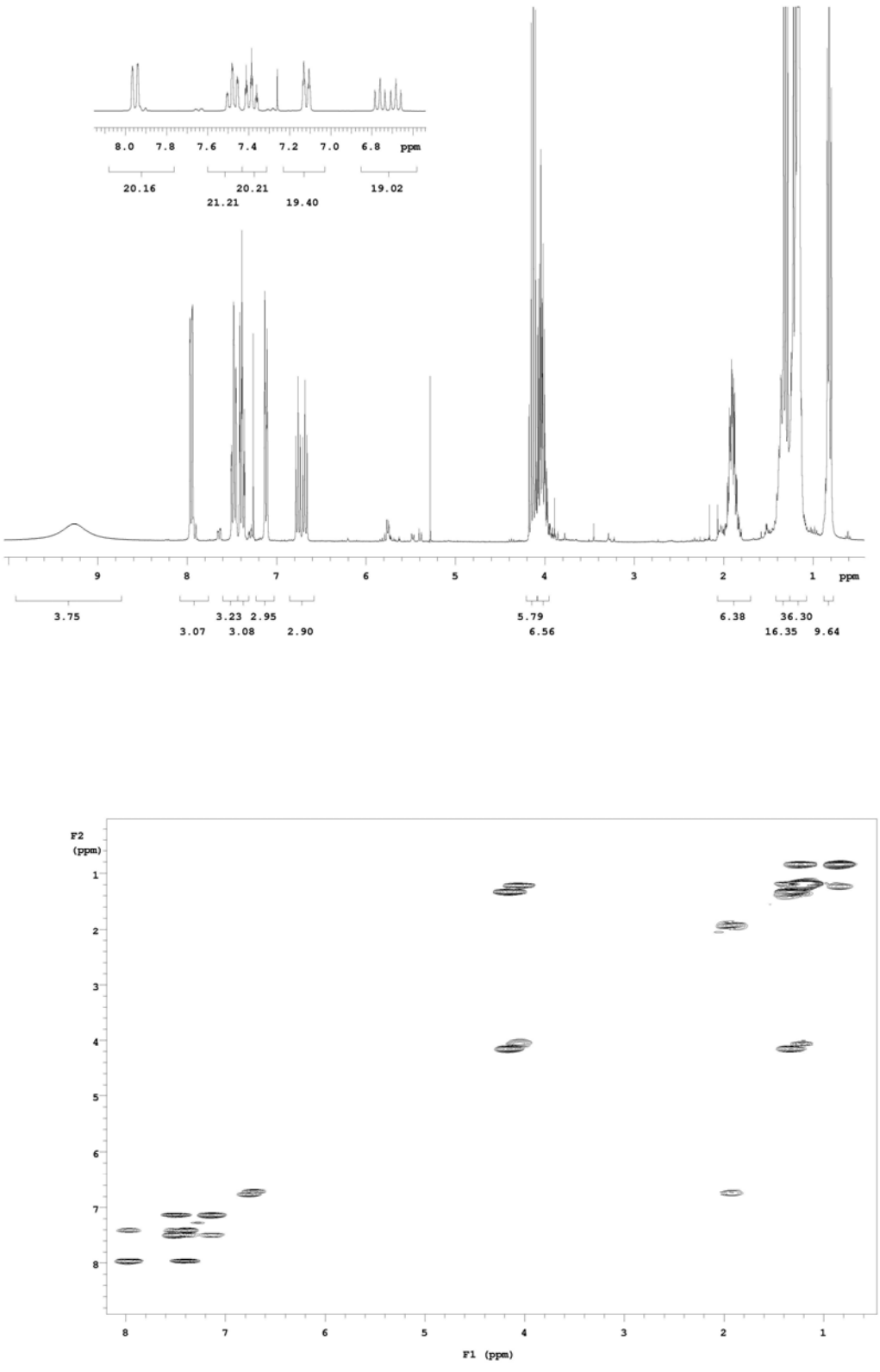
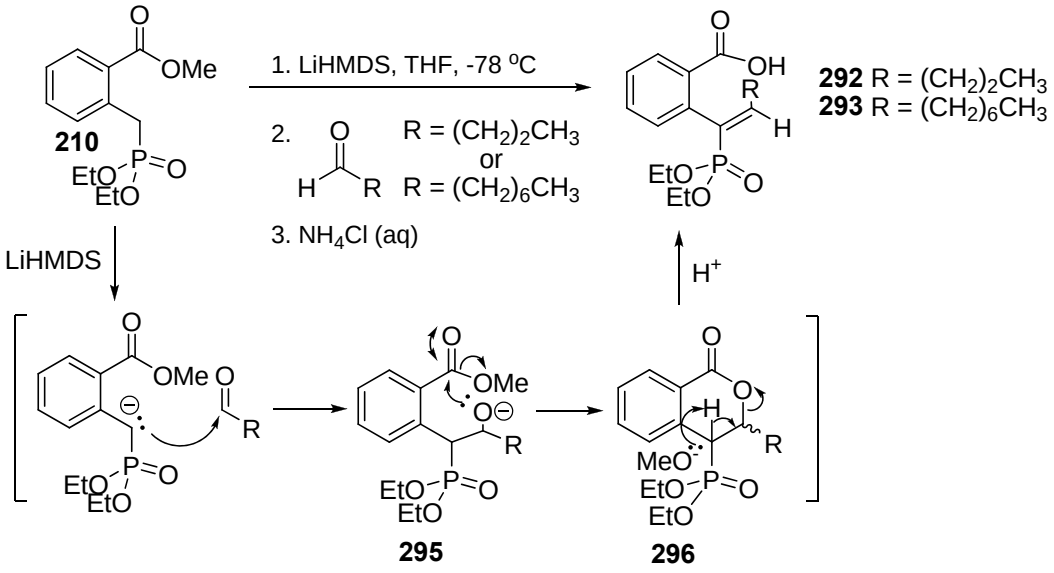


Figure 5–2. The ^{1}H and gCOSY NMR spectra of alkenylphosphonate **293**.

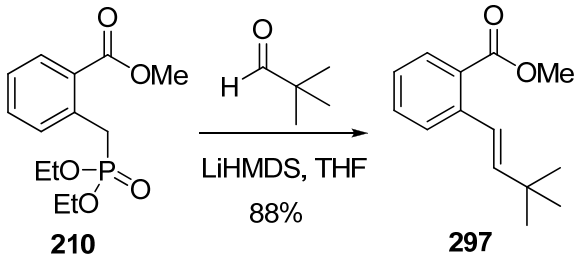
The proposed mechanism for the formation of alkenylphosphonates **292** and **293** is shown in Scheme 5–4. The deprotonated phosphonate attacks the carbonyl of the

aldehyde as in the usual HWE mechanism. The reaction then deviates from the desired mechanism with the resulting alkoxide **295** attacking the methyl ester that resides in close proximity. This forms a δ-lactone (**296**) rather than the standard oxaphosphetane intermediate. The released methoxide likely causes the elimination that forms the ring-opened carboxylate, which would be protonated upon quenching with sat. $NH_4Cl_{(aq)}$.



Scheme 5–4. Proposed mechanism for the unexpected formation of alkenylphosphonates **292** and **293**.

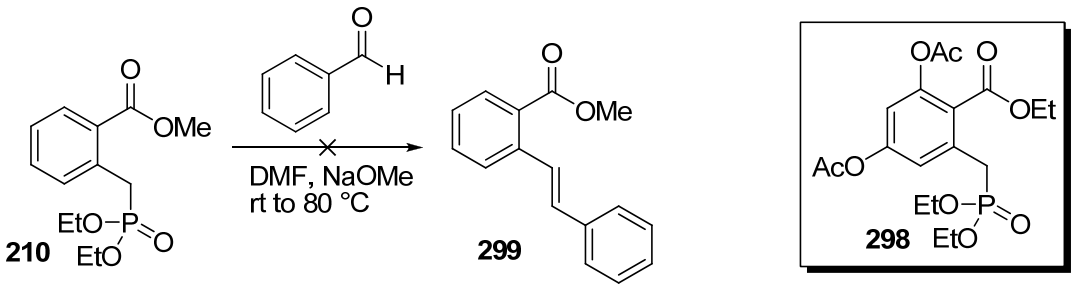
When aldehydes **76** and **289** were exchanged for pivaldehyde, the HWE reaction proceeded to give benzylic (*E*)-alkene (**297**) in excellent yield (Scheme 5–5). It is postulated that the extra steric bulk of the *tert*-butyl group does not allow the alkoxide to adopt the conformation required to form the lactone and the usual HWE product is formed. The added steric bulk might also enhance the rate of the irreversible elimination of the usual HWE mechanism to alleviate the unfavoured steric interactions.



Scheme 5–5. HWE reaction between phosphonate **210** and pivaldehyde.

Eicher et al. have reported the successful HWE olefination between the phosphonate **298** and benzaldehyde.[78] However, our adaptation of Eicher's reaction conditions to the reaction between phosphonate **210** and benzaldehyde failed to replicate their success

(Scheme 5–6). Unreacted phosponate and benzaldehyde were returned from the reaction mixture.



Scheme 5–6. Attempted synthesis of stilbene **299**.

Several attempts were made to couple hemiacetal **122** and phosphonate **210** utilising the HWE reaction (Table 5–2). The expected product of the HWE reaction would be alkene **300**, which could also undergo attack by the free hydroxyl to give tetrahydropyran **301**. However, neither of these products were observed or isolated from the reaction mixtures. Phosphonate **210** was recovered, while hemiacetal **122** was not. Hemiacetal **122** may have been lost in the aqueous workup after base induced deacetylation to a water-soluble triol.

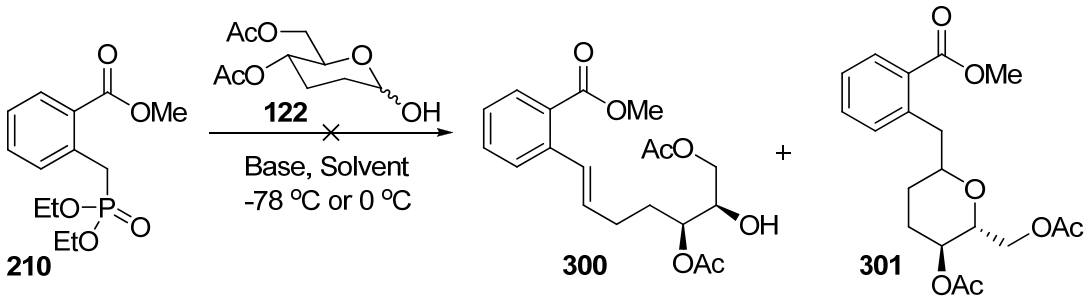


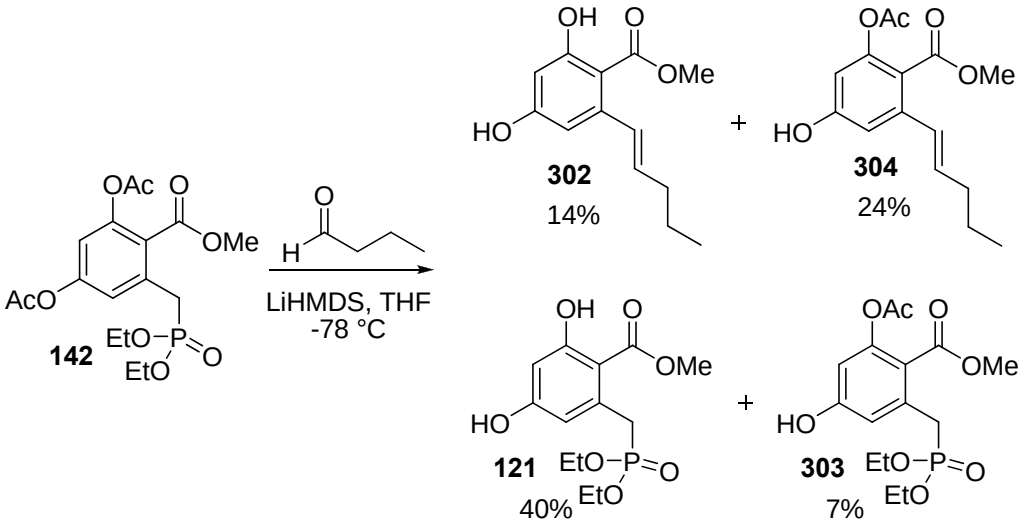
Table 5–2. Attempted HWE reactions between model phosphonate **210** and hemiacetal **122**.

Phosphonate	Aldehyde	Solvent	Base	Temperature (°C)	Results
210	**122**	THF	*t*-BuOK (1.2 eq)	0	recovered **210**
210	**122**	THF	*t*-BuOK (1.2 eq), 18Crown6 (1.2 eq)	0	recovered **210**
210	**122**	THF	NaH (2 eq)	0	recovered **210**
210	**122**	THF	LiHMDS (1 eq)	0	recovered **210**

Despite the limited success of HWE reactions of the simplified phosphonates **210** and **211** with a range of aldehydes and hemiacetals, our investigation turned to HWE reactions involving phosphonates with various protection on the phenol groups at C2 and C4 in order to determine whether these would provide more favourable results.

5.1.2 HWE Reactions with Phosphonate 142

The HWE reaction of phosphonate **142** with butanal gave four partially or fully deacetylated compounds (Scheme 5–7). Alkene **304** and phosphonate **303** both retained an acetate group, as evidenced by three-proton singlets at 2.26 ppm in their ^{1}H NMR spectra. Alkene **304** was isolated alongside alkene **302** giving a combined yield of 38% for the (*E)*-alkenes. Interestingly, no product analogous to alkenylphosphonates **292** or **293** was isolated from this reaction. The oxygens in the real system may increase the electron density on the aromatic ring sufficiently to decrease the rate of lactonisation (*viz.* Scheme 5–4), thus circumventing the production of unwanted alkenylphophonates and promoting the usual HWE mechanism.



Scheme 5–7. HWE reaction between phosphonate **142** and butanal (**76**).

The HWE reactions between phosphonates **142** and **228** and hemiacetals **122** and **152** were explored over a range of reaction conditions (Table 5–3). However, no conditions were found to provide the desired conjugated alkene **305** or its ring-closed product **306**. Deprotection of the phenolic groups of phosphonates **142** and **228** was observed and deprotection of hemiacetals **122** and **152** was inferred from the poor recovery of these starting materials after aqueous work-up.

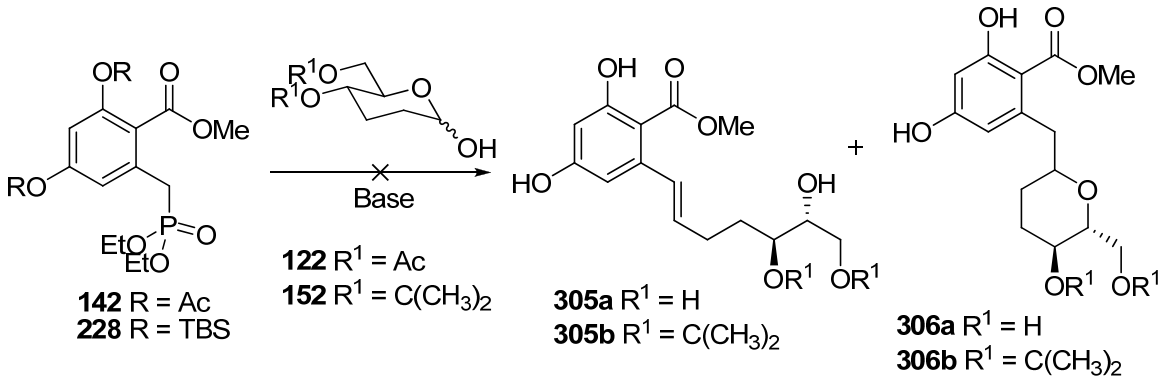
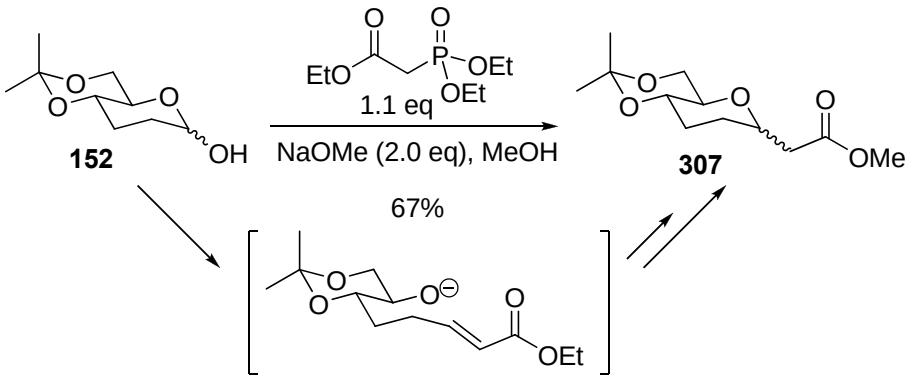


Table 5–3. Summary of HWE reactions between phosphonates **142** and **228** and hemiacetals **122** and **152**.

Phosphonate	Hemiacetal	Base	Solvent	Reaction Temperature	Results
142	**122**	LiHMDS (2 eq)	THF	0 °C	No product
142	**152**	NaOMe (3 eq)	MeOH	rt	No product
142	**152**	*t*-BuOK (2 eq)	THF	0 °C to rt	No product
142	**152**	NaOMe (3 eq)	DMF	0 °C to 80 °C	No product
228	**152**	LDA (1.2 eq)	THF	-78 °C to rt	No product
228	**152**	NaOMe (3 eq)	Toluene	rt	No product
228	**152**	NEt_3, LiBr (1.1 eq)	THF	rt	No product
228	**152**	NaOMe (2 eq)	DMF	0 °C to rt	No product

The failure of hemiacetal **122** to participate in an HWE reaction might be due to the lability of the acetate protecting groups. Base-induced cleavage of the two acetate protecting groups would give a triol which is likely to have poor solubility in most of the solvents examined. Acetonide **152**, however, should not suffer concomitant deprotection under the basic reaction conditions. Indeed, when acetonide **152** was reacted with triethyl phosphonoacetate, the homologated product **307** was isolated (Scheme 5–8). Pyran **307** presumably forms by the internal conjugate addition of the alkoxide upon the newly formed double bond. The successful coupling of hemiacetal **152** in this HWE reaction suggested that, in the above reactions, the arylmethylphosphonates **142** and **228** were the problematic substrates. Stabilisation of the deprotonated derivatives phosphonates **142** and **228** by conjugation through to the ester group (Scheme 5–2) is therefore likely to be less significant than originally postulated.



Scheme 5–8. HWE reaction between hemiacetal **152** and triethyl phosphonoacetate.

After many failed attempts to utilise the aforementioned aromatic phosphonates in HWE reactions and the predominance of by-product formation, this route was abandoned in favour of the Ramberg-Bäcklund (RB) approach to Am D. Fortuitously, some of the intermediates synthesised for the HWE approach were useful for the RB route.

5.2 Investigation of RB Reaction for Connecting the C1′-C2′ Bond

As was discussed earlier (Chapter 3, Section 3.2), the RB route was to involve the same disconnections as the HWE route; that is through the C1′-C2′ and the C7′-C8′ olefins and the lactone. Thus, Am D would be synthesised from key intermediate **263**, to which there were two possible paths (Figure 5–3). However, as described in Section 3.2.1, synthesis of iodide **168** was abandoned due to the problematic hydrolysis of the methyl glycoside, leaving the coupling between benzylic bromide **135** with thiol source **189** as the method of choice. Having observed the undesired formation of disulfide **190** when thioacetate **189** was deprotected (Section 3.2.2), focus turned to the in situ deprotection of thioacetate **189** for the coupling reaction with benzylic bromide **135**.

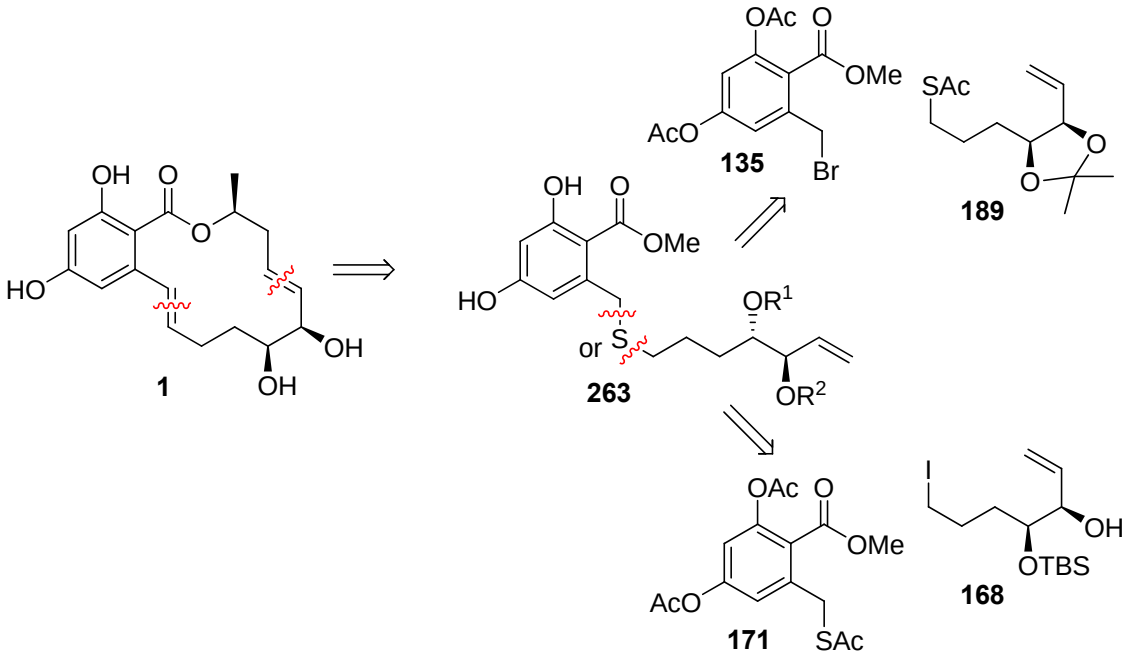
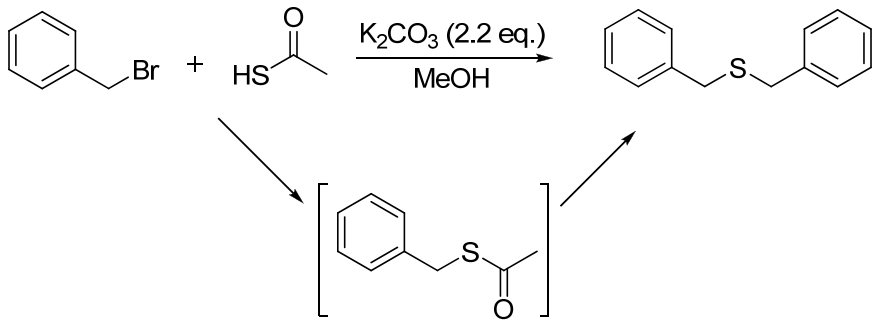


Figure 5–3. Retrosynthetic analysis of Am D with focus on the RB reaction precursors.

5.2.1 Preparation of RB Precursor 196

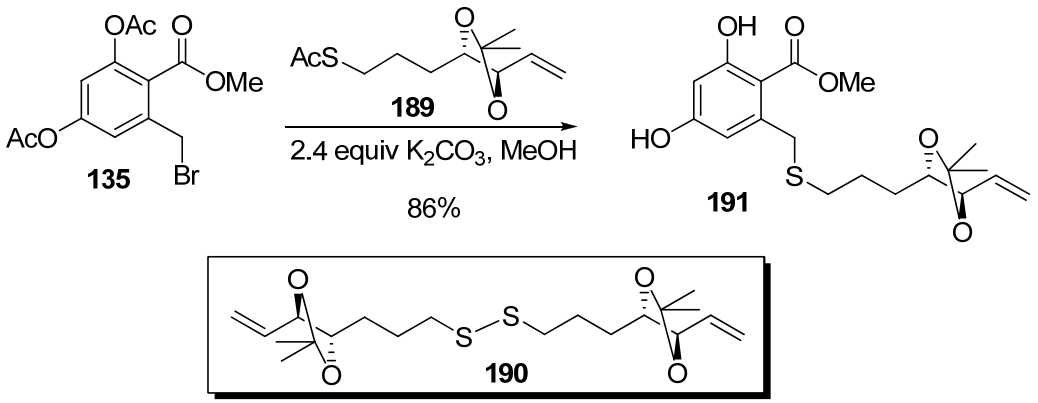
Whilst developing mild and efficient routes to benzylic thiols from benzylic bromides, Han and Balakumar found that the treatment of 1.0 equivalent of benzyl bromide and 1.2 equivalent of thioacetic acid with 2.2 equivalent of potassium carbonate in methanol afforded dibenzylsulfide as the major product (87%) (Scheme 5–9).[196] Dibenzylsulfide was presumably formed via intermediate benzyl thioacetate.



Scheme 5–9. The formation of dibenzylsulfide observed by Han and Balakumar.[196]

Adaptation of Han's method to the coupling of bromide **135** with thioacetate **189** produced thioether **191** in excellent yield (86%) (Scheme 5–10). Although, concomitant deprotection of the phenolic acetates did occur in the reaction, no undesired etherification between aromatic units was observed. It is probable that the phenolic

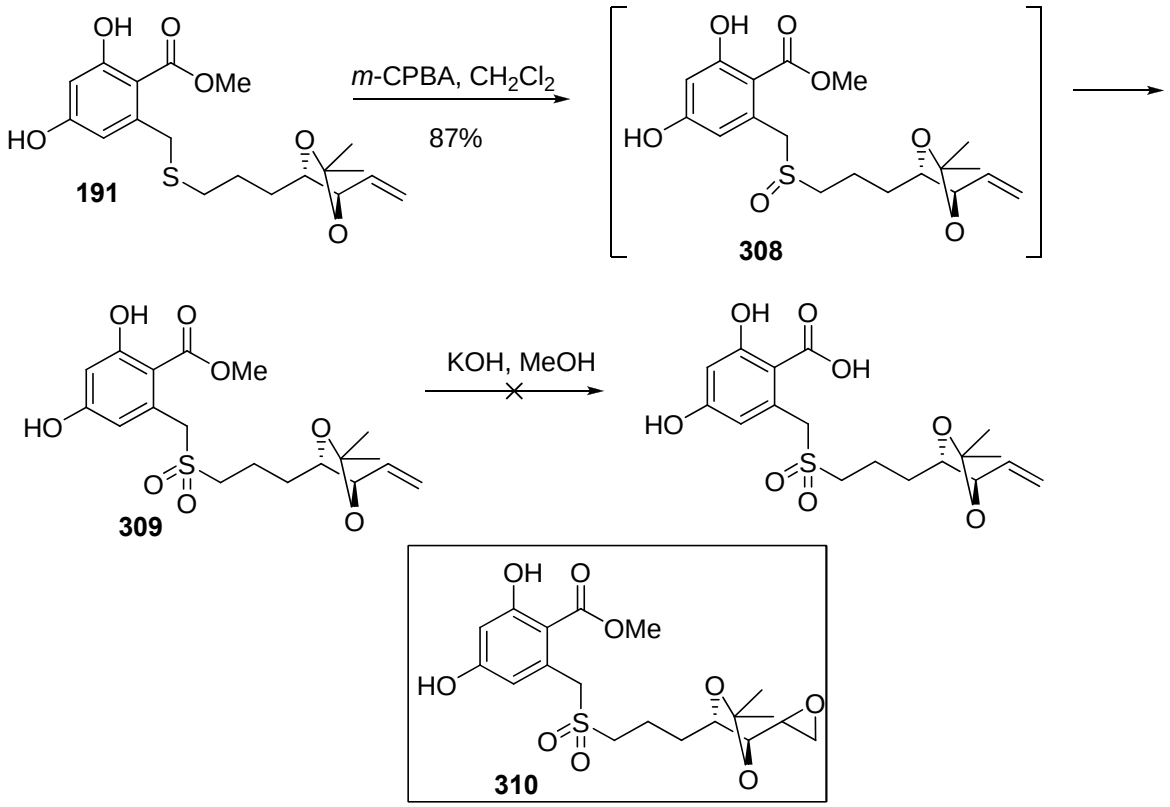
groups have a low nucleophilicity towards the benzylic bromide due to the ester group withdrawing electron density. Disulfide **190** was also isolated as a minor by-product from the reaction.



Scheme 5–10. Coupling of the aromatic and carbohydrate-derived fragments.

Thioether **191** was successfully oxidised to sulfone **309** with *meta*-chloroperbenzoic acid (*m*-CPBA) without any epoxidation of the terminal alkene being observed (**310**) (Scheme 5–11). Thin layer chromatographic (TLC) analysis suggests that the oxidation proceeds sequentially, with oxidation to sulfoxide **308** before the second oxidation to sulfone **309**. Interestingly, the sulfoxide **308** (R_f = 0.07, 2:1 hexanes/EtOAc) is more polar than the desired sulfone **309** (R_f = 0.26, 2:1 hexanes/EtOAc). This marked difference in polarity initially caused some confusion when following the reaction by TLC, resulting in the premature quenching of the reaction when the sulfoxide spot was assumed to be that of epoxide **310**.

Saponification of ester moiety **309** with KOH in methanol unfortunately led to decomposition of the material. The presence of the sulfone introduces acidic protons at the α and α′ positions. It is likely that basic conditions of the saponification could lead to deprotonation at these positions, and ultimately a variety of decomposition products.



Scheme 5–11. Oxidation and saponification of thioether **191**.

To avoid the undesirable reactivity associated with the sulfone group, the approach was modified and saponification was attempted prior to oxidation of the thioether. Treatment of thioether **191** with a hydroxide base in aqueous methanol or aqueous THF unexpectedly yielded a product with a R_f higher than the starting material (R_f = 0.21 vs. 0.09, 2:1 hexanes/EtOAc) (Table 5–4, entries 1–3). The methyl ester signal in the ^{1}H NMR spectrum of the product was notably absent. The aromatic signals had also changed to a two proton doublet and one proton triplet at 6.37 and 6.23 ppm respectively. The presence of three aromatic protons in the ^{1}H NMR spectrum and absence of a carbonyl signal in the ^{13}C NMR implied that thioether **191** had undergone a decarboxylative saponification to form compound **311**. Different conditions were thus sought. Ester hydrolysis with ethanthiolate returned starting material when used with *n*-butyllithium (entry 4) and a mixture of starting material and decarboxylated product when the base was sodium hydride (entry 5). Decarboxylation in the latter case might result from the traces of sodium hydroxide often present in sodium hydride. Attempted saponification of methyl ester **191** with ethanolic barium hydroxide resulted in the decomposition of the starting material (enty 6).

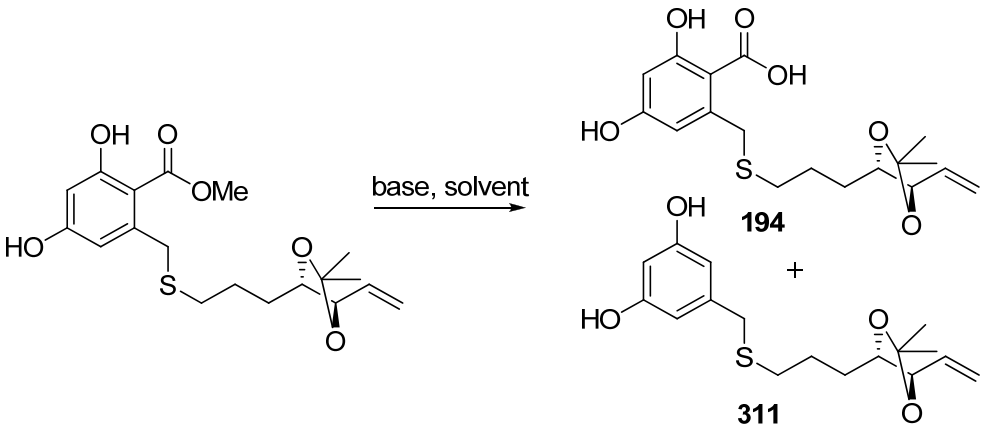
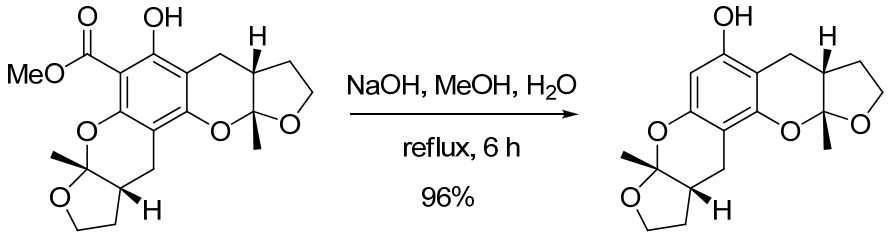


Table 5–4. Summary of attempted hydrolyses of methyl ester **191**.

Entry	Reagent	Solvent	Reaction temperature	Reaction time (h)	Yield SM	Yield 194	Yield 311
1	LiOH (4 eq)	1:1 THF/H_2O	50 °C	12	5 [a]	0	23 [a]
2	LiOH (4 eq)	2:1 MeOH/H_2O	50 °C	6	64 [b]	0	36 [b]
3	NaOH (4 eq)	2:1 MeOH/H_2O	50 °C	6	37 [b]	0	63 [b]
4	EtSH (5 eq), *n*-BuLi (4.5 eq)	THF	-10 °C to rt	2	100 [b]	0	0 [b]
5	EtSH (5 eq), NaH (4.5 eq)	DMF	-10 °C to rt	12	20 [b]	0	80 [b]
6	$Ba(OH)_2$ (3 eq)	EtOH	rt	18	decomposed		

[a] Isolated yield. [b] Relative yields are based on ratios in the ^{1}H NMR spectrum of the crude product mixture.

Aromatic esters with phenol groups located in positions *ortho* to the ester are known to undergo decarboxylation upon saponification.[73,210,211] Pettigrew and Wilson exploited this property of alkyl *ortho*-hydroxybenzoates in their synthesis of xyloketal B analogues (Scheme 5–12).[212]



Scheme 5–12. An example of decarboxylative saponification utilised in the synthesis of analogues of xyloketal B by Pettigrew and Wilson.[212]

To avoid the unproductive expending of valuable intermediate **191** in the quest for suitable ester hydrolysis conditions, the ester hydrolysis of methyl orsellinate (**74**) was studied. Not unexpectedly, orsellinate **74** was found to also undergo decarboxylative saponification when treated with a hydroxide base in aqueous methanol (Table 5–5,

entries 1 and 2). The literature was then further examined for saponification procedures suitable for benzoic esters with *ortho* phenolic groups. Despite implementing the saponification and hydrolysis conditions that have been used successfully in the cleavage of other aromatic esters *ortho* to a phenol group, no conditions were found to be suitable for this particular system. All procedures returned varied ratios of starting material and the decarboxylated product, orcinol (**312**) (Table 5–5). Coutts and co-workers described the mild ester hydrolysis benzoic esters with *ortho* amine and hydroxyl groups with pyridine hydrochloride (py.HCl) in refluxing pyridine.[213] Refluxing methyl benzoate **74** in either neat pyridine or pyridine hydrochloride in pyridine both returned mixtures of the starting material **74** and orcinol (**312**) (entry 7).

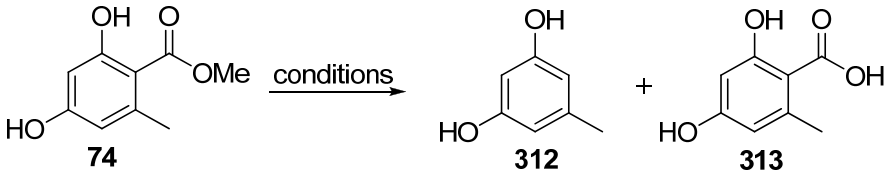
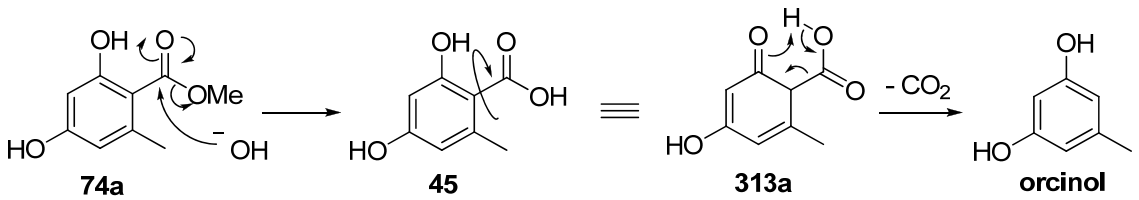


Table 5–5. Summary of attempts to hydrolyse methyl orsellinate, **74**.

Entry	Reagent	Solvent	Temperature	Reaction time	Yield (%) SM	312	313
1	KOH (5 eq)	1:1 MeOH/H_2O	reflux	12 h	0 [a]	82 [a]	0 [a]
2	KOH (11 eq)	2:1 MeOH/H_2O	rt	4 days	68 [b]	32 [b]	0 [b]
3	KOH (7 eq)	3:1 DMSO/H_2O	80 °C	12 h	decomposed		
4	NaOH (6 eq)[214]	1:1 dioxane/H_2O	rt	12 h	100 [b]	0 [b]	0 [b]
5	*t*-BuOK (6 eq)[215]	THF	rt	6 days	74 [b]	26 [b]	0 [b]
6	py.HCl[213]	pyridine (py)[213]	reflux	18 h	68 [b]	32 [b]	0 [b]
7		py	reflux	12 h	43 [b]	57 [b]	0 [b]
8		5:1 10% $H_2SO_{4(aq)}$/THF	50 °C	4 h	100 [b]	0 [b]	0 [b]

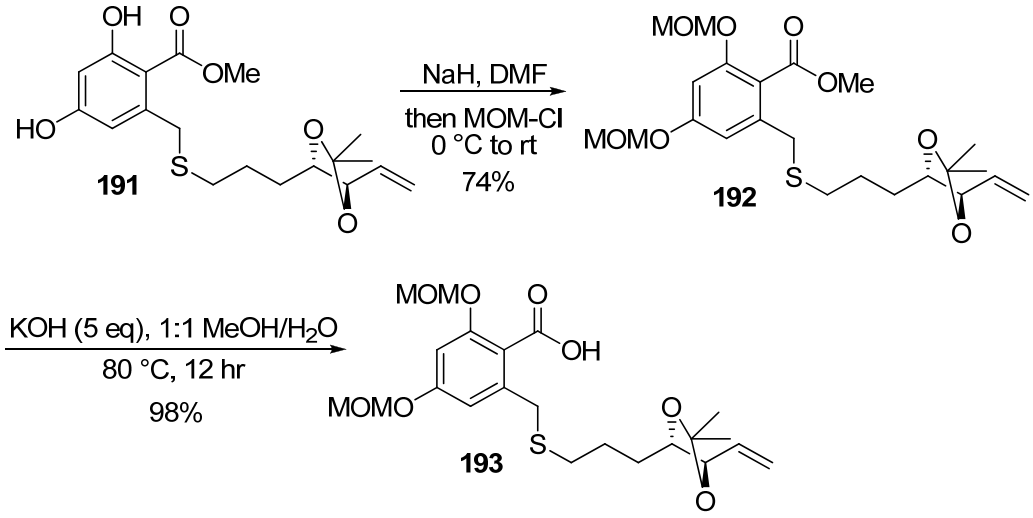
[a] Isolated yield; [b] relative yield based on ^{1}H NMR spectrum of crude product mixture.

The proposed mechanism for this decomposition is shown in Scheme 5–13. The deprotonated orsellinate **74a** is attacked by a hydroxide ion, forming a carboxylic acid. The other tautomer of carboxylic acid **45** is diene **313a**. Upon rotation of the carboxylic acid moiety, the compound would readily lose carbon dioxide and re-aromatise to give orcinol.This mechanism is supported by the fact that this type of decarboxylative saponification has only been observed in benzoates with *ortho* amine or hydroxyl groups.



Scheme 5–13. Proposed mechanism for the decarboxylative saponification of methyl orsellinate, **74**.

Chen and co-workers have shown that MOM protection of the phenolic hydroxyl groups on benzoate **74** (Scheme 1–11, Section 1.3.3.4) allows for the facile saponification of the methyl ester, providing the desired benzoic acid in quantitative yields.[35] Consequently, ester **191** was protected as the bis-MOM ether **192** in good yield (Scheme 5–14). Subjection of this compound to saponification with potassium hydroxide in 1:1 MeOH/H_2O, gratifyingly afforded desired benzoic acid **193** in near quantitative yield. The workup procedure for this reaction involved acidifying the reaction mixture to pH 6 with 50% $AcOH_{(aq)}$ prior to extraction with EtOAc. Washing the crude organic extract with enough water to remove excess AcOH was found to be extremely important. If AcOH remained in organic phase when the solvent was concentrated, the acid cleaved the MOM-groups from **193**.

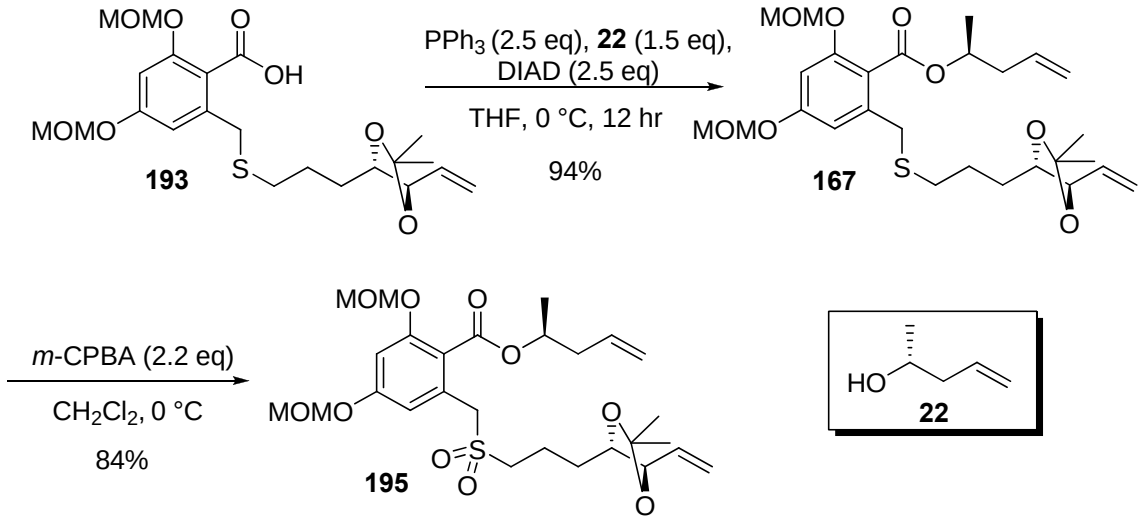


Scheme 5–14. Preparation of benzoic acid **193**.

The sequence of reactions that are described below were all first carried out with racemic alcohol (±)-**22** whilst waiting for delivery of (*R*)-**22** from the supplier. To avoid redundancy, only discussion of the enantiopure synthesis of Am D is included below.

The procedure that Chen and co-workers used for the Mitsunobu reaction in their synthesis of Am D involved the addition of diisopropyl azodicarboxylate (DIAD) to a

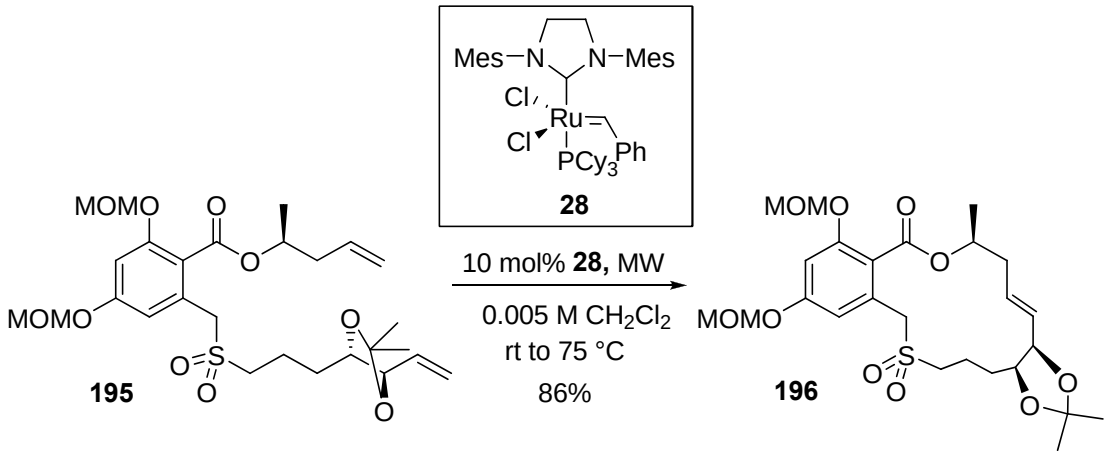
THF solution of the benzoic acid, (*R*)-4-penten-2-ol (**22**) and triphenylphosphine at 0 °C.[35] Adaption of Chen's procedure to the coupling of the benzoic acid derivative **193** and alcohol (*R*)-**22** provided diene **167**, albeit in a low 34% yield. However, when a THF solution of acid **193** was added to a premixed solution of triphenylphosphine, DIAD and alcohol (*R*)-**22**, the reaction proceeded to give the desired diene **167** in 94% yield (Scheme 5–15). Diene **167** contains the complete carbon framework of Am D, requiring a ring-closing metathesis (RCM) cyclisation and RB reaction to produce the 14-membered ring of Am D. Oxidation of the thioether in **167** proceeded selectively without observable production of any epoxide by-product, affording the metathesis precursor, sulfone **195**, in excellent yield.



Scheme 5–15. Synthesis of sulfone **195**.

Following recent reports on the utility of microwave-assisted (MW-assisted) RCM reactions to obtain products with high yield[57-59] and stereoselectivity,[35] a 0.005 M solution of diene **195** and 10 mol% of catalyst **28** in CH_2Cl_2 was subjected to MW irradiation, heating the solution to 75 °C for 30 minutes (Scheme 5–16). The (*E*)-alkene of macrocycle **196** was the sole product in 86% yield, as evidenced by the 15 Hz coupling constant present in the two olefinic signals at 5.71 ppm and 5.55 ppm respectively. In an attempt to compare the MW-assisted RCM reaction with standard thermal RCM reactions, 0.005 M solutions of diene **195** in CH_2Cl_2 or toluene with 10 mol% of catalyst **28** were heated to reflux and 80 °C respectively, for 12 hours. Surprisingly, no product was observed for either reaction. The RCM reaction in toluene was expected to yield macrocycle **196** as this procedure has been successfully used by

Chen[35] and Winssinger[9] in their syntheses of Am D. However, since the MW-assisted RCM procedure was working well, the thermal RCM reactions were not repeated.

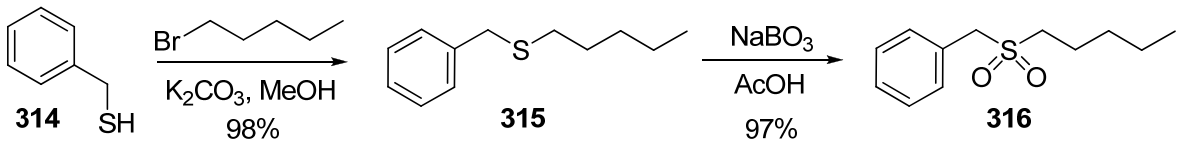


Scheme 5–16. The MW-assisted RCM reaction of diene **195**, yielding RB reaction precursor **196**.

The macrocycle of Am D was now complete, and work could begin on the RB reaction to produce the C1′–C2′ olefin.

5.2.2 Preliminary Trials of the RB Reaction

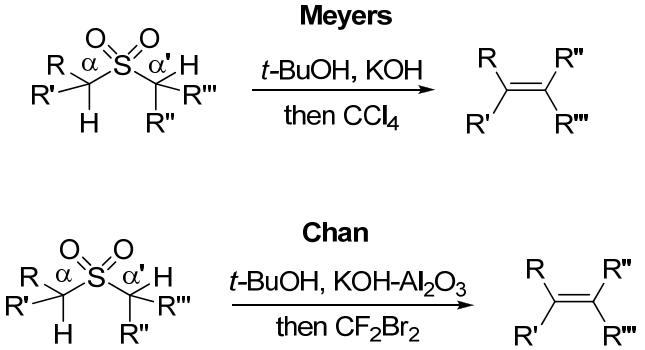
To identify suitable RB reaction conditions for the installation of the C1′–C2′ (*E*)-olefin in Am D, sulfone **316** was studied as a simplified model of sulfone **196**. Sulfone **316** was prepared from benzyl mercaptan (**314**) in two steps with excellent yield (Scheme 5–18). Thus, thioether **315**, itself obtained from the coupling of 1-bromopetane and benzyl mercaptan, was oxidised to sulfone **316** by treatment with sodium perborate in acetic acid.[117]



Scheme 5–17. Preparation of model sulfone **316**.

There are two general approaches reported in the literature to utilising the RB reaction in synthesis (see Section 1.4.3.5). In one approach, the α-halogenated sulfone intermediate can be isolated and subsequently treated with a base to form the desired alkene over two discrete steps using classical methodology.[115] Alternatively one-pot

methods have been developed that involve in situ α-halogenation immediately prior to the RB reaction. The two common examples of such one-pot systems are the Meyers[123] and Chan[124] modifications of the RB reaction (Scheme 5–18).



Scheme 5–18. The two common one-pot modifications of the RB reaction.

In the first instance, the classical two-step methodology was employed. Attempts to prepare and isolate α-chloro or α-bromo derivatives of sulfone **316** using succinimide reagents were unsuccessful (Table 5–6, entries 1 and 2). Starting material was returned in both instances. Focus therefore turned to the one-pot systems. Chan's modification of the RB reaction replaced carbon tetrachloride (CCl_4), which was used as the halogen source for the in situ halogenation in Meyers' modification, for dibromodifluoromethane (CF_2Br_2), as the latter was shown to avoid formation of by-products commonly produced in Meyers' method.[124] Unfortunately, the import of CF_2Br_2 into New Zealand is banned due to its potential as an ozone depleter. Chan's other modification to Meyers' method was changing the form of the base from powdered potassium hydroxide (KOH) to alumina-loaded KOH (KOH–Al_2O_3). This was suggested to improve the reaction by increasing the surface area of the base.[124] KOH–Al_2O_3 was easily prepared and substituted as the base in Meyers' modification of the RB reaction (entries 3 and 4). This modification to Meyers' method gave a 51% conversion of the sulfone (entry 3). Unfortunately alkene **318** was inseparable from other by-products. The yields could be estimated by analysis of the integration of the olefinic protons in the ^{1}H NMR spectra. Alkene **318** could be differentiated from the other products in the ^{1}H NMR spectra as it was the only compound that contained two olefinic protons. Thus, alkene **318** was produced in 20% yield (estimated by ^{1}H NMR) along with a mix of the other unidentified by-products. Increasing the temperature of the reaction failed to improve the conversion of the starting material, although the relative yield of alkene **318** improved (entry 4). An attempt was next made to use the more environmentally friendly NBS as the halogen source (entry 5). However, the conversion

was significantly lower, returning 78% starting sulfone. Completely changing the system to the use of an organic base (DBU) in DMF resulted in no reaction (entry 6). Meyers' original method, in fact, gave the best result, with a 75% conversion, including 45% yield of the desired alkene **318** (entry 7).

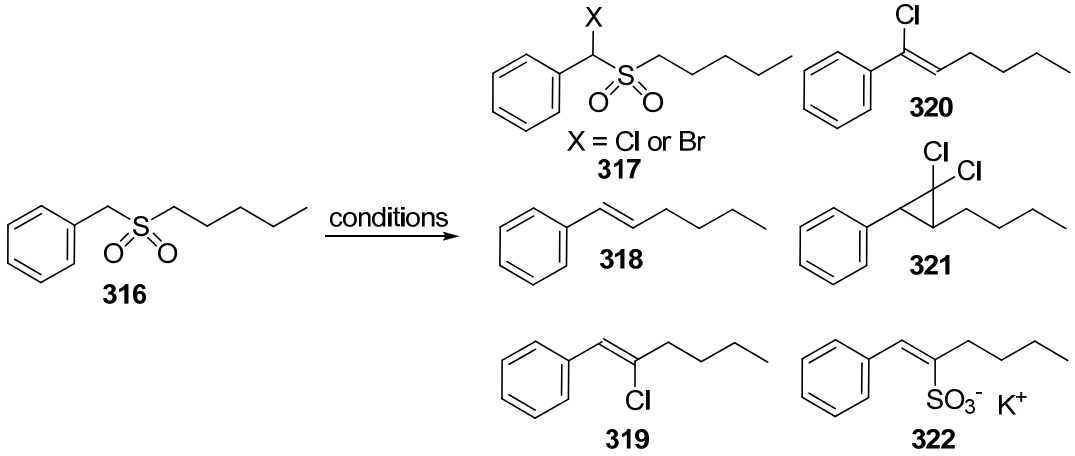


Table 5–6. Investigation into the RB reactions of sulfone **316**.[a]

Entry	Reagent(s)	Solvent(s)	Yield[b] 318	319, 321 320, 322	SM
1	NCS	CCl_4			100
2	NBS	CH_2Cl_2			100
3	CCl_4, KOH–Al_2O_3	*t*-BuOH	20	31	49
4[c]	CCl_4, KOH–Al_2O_3	*t*-BuOH	30	20	49
5	NBS, KOH–Al_2O_3	*t*-BuOH/CH_2Cl_2	16	6	78
6	NBS, DBU	DMF			100
7	CCl_4, KOH, H_2O	*t*-BuOH	45	30	25

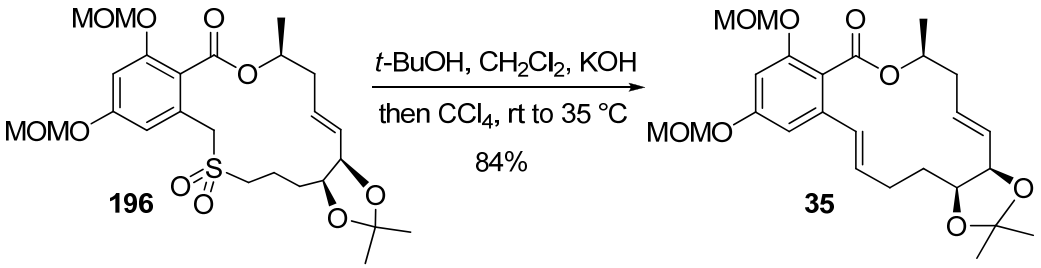
[a] reactions were stirred at rt for 2 h unless otherwise noted. [b] estimated from ^{1}H NMR of crude products. [c] reaction heated to 40 °C.

5.2.3 Use of RB Reaction in the Synthesis of Am D.

Although the problems with incomplete conversion and side reactions were not fully overcome, Meyers' method was implemented in the RB reaction of macrocyclic sulfone **196**. The constrained cyclic structure of sulfone **196** is likely to influence the reactivity in ways unexamined in the simple straight-chain model, **316**.

Sulfone **196** was found to be only sparingly soluble in *tert*-butanol (*t*-BuOH) and required the addition of dichloromethane to dissolve the material (Scheme 5–19). Addition of freshly powdered KOH resulted in the formation of a pale yellow solution. The immediate addition of CCl_4 to the suspension was followed with visible evolution of sulfur dioxide. The reaction was warmed to 35 °C and was deemed complete by TLC

analysis after 30 minutes. The ^{1}H NMR spectrum provided evidence that only one stereoisomer was formed in this reaction, with the two sets of olefinic signals present in the spectrum all containing coupling constants of ~15 Hz. Gratifyingly, the ^{1}H NMR spectrum was found to be identical to those reported by Danishefsky[33] and Chen.[35]



Scheme 5–19. The use of Meyers' modification of the Ramberg-Bäcklund reaction in the preparation of protected Am D **35**.

The stereoselectivity of the RB reaction in cyclic systems can be justified by an investigation by MaGee and Beck who carried out RB reactions and recorded the stereoselectivities on a series of sulfonated azacycles. The RB reaction under Chan's conditions (i., Table 5–7) gave the *cis*-7 and 8-membered rings as the sole products (i. entries 1 and 2). However, as the ring size increased, the formation of the *trans*-cycles predominated with a *Z/E* ratio ranging from 40:60 for the 10-membered azacycle (i. entry 4) to 15:85 for the 12-membered azacycle (i. entry 6). The *trans*-stereoselectivity in the larger rings is much more pronounced in the classical RB reactions of the corresponding pre-formed α-chlorosulfones (ii., Table 5–7). As with Chan's modification, *cis*-7 and 8-membered rings were the sole products of the reaction between *t*-BuOK and the corresponding α-chlorosulfones (ii. entries 1 and 2). Beyond these first two cases, the RB reaction produced the azacycles with *Z/E* ratios of at least 6:94 for ring sizes of 9 to 13 members (ii. entries 3 – 7). Cyclic systems were thus found to behave differently to comparable acyclic systems for which the *cis*-olefin predominates in most cases.[122,125,126] In attempt to explain this observed stereoselectivity, MaGee suggested that significantly greater transannular interactions are encountered when α-chlorosulfones attempt to adopt the conformation required for the formation of *cis*-episulfones than those experienced in the formation of *trans*-episulfones. The enhanced Z/E selectivity observed in the classic RB versus Chan's modification is also likely to be influenced by the differences in reactivity between α-chloro and α-bromo sulfones. The stereoselective formation of the C1′–C2′ olefin of bis-MOM **35** is consistent with MaGee's findings.

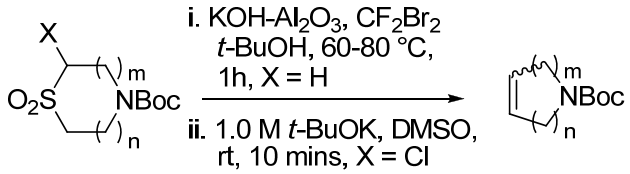
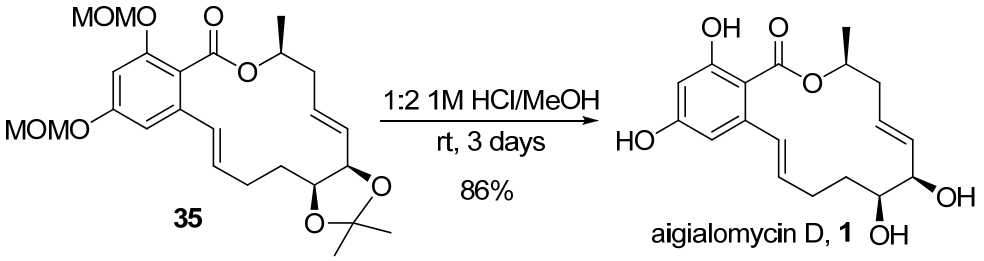


Table 5–7. Use of the RB reaction in the stereoselective synthesis of Boc-protected azacycles by MaGee and Beck.[216]

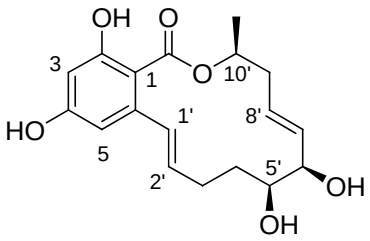
			Z:E (Yield)	
Entry	m	n	i. [a]	ii.
1	2	2	100:0 (63)	100:0 (66)
2	3	2	100:0 (33)	100:0 (41)
3	3	3	35:65 (59)	6:94 (100)
4	4	3	40:60 (67)	5:95 (54)
5	4	4	27:73 (68)	2:98 (97)
6	5	4	15:85 (62)	1:99 (76)
7	5	5	39:61 (53)	6:94 (93)

[a] over 2 steps from the sulfide

The formal total synthesis of Am D was thus complete. Global deprotection of bis-MOM **35** was achieved by stirring in methanolic hydrochloric acid for 3 days, providing the natural product in good yield (Scheme 5–20). The total synthesis of Am D was completed in 16 steps from D-ribose in 9% overall yield. The ^{1}H and ^{13}C NMR data of this synthetic Am D matched those of the natural product (Table 5–8, 5–9).[8,9,33,35]



Scheme 5–20. The acidic global deprotection of protected **35** to reveal the natural product Am D (**1**).



Aigialomycin D (**1**)

Table 5–8. ^{1}H NMR Data of Aigialomycin D.

Position	Isolated Am D	Danishefsky's Synthetic Am D	RB-route
3	6.27 (d, 2.4)	6.28 (d, 2.3)	6.28 (d, 2.0)
5	6.52 (d, 2.4)	6.53 (d, 2.3)	6.53 (d, 2.0)
1'	7.14 (d, 15.9)	7.16 (d, 15.9)	7.15 (d, 15.9)
2'	6.09 (ddd, 15.9, 5.6, 5.4)	6.10 (ddd, 15.9, 5.7, 5.5)	6.09 (ddd, 15.9, 5.7, 5.5)
3'	2.31-2.34 (m)	2.32-2.36 (m)	2.32-2.36 (m)
	2.31-2.34 (m)	2.32-2.36 (m)	2.32-2.36 (m)
4'	2.14 (m)	2.14 (m)	2.14 (m)
	1.58 (m)	1.58-1.61 (m)	1.59 (m)
5'	3.62 (m)	3.64 (m)	3.63 (m)
6'	4.35 (brd 4.3)	4.35 (brd 4.1)	4.35 (brd, 4.1)
7'	5.68 (dd, 15.7, 5.0)	5.69 (dd, 15.6, 5.1)	5.69 (ddt, 15.6, 5.2, 1.2)
8'	5.87 (tdd, 15.7, 7.3, 1.2)	5.87 (tdd, 15.6, 7.4, 1.4)	5.88 (tdd, 15.6, 7.4, 1.6)
9'	2.55 (ddd, 14.6, 7.5, 3.2)	2.55 (ddd, 14.5, 7.3, 3.1)	2.57 (ddd, 14.6, 7.4, 3.1)
	2.42 (m)	2.43-2.46 (m)	2.43 (m)
10'	5.42 (m)	5.41-5.47 (m)	5.44 (m)
10'-CH3	1.38 (d, 6.4)	1.39 (d, 6.4)	1.37 (d, 6.4)
2-OH	11.65 (s)	11.7 (s)	11.66 (s)
4-OH	9.5 (brs)	9.1 (brs)	9.25 (brs)
5'-OH	not detected	3.56 (brs)	3.20 (brs)
6'-OH	not detected	3.76 (brs)	3.82 (brs)

Table 5–9. ^{13}C NMR Data of Aigialomycin D.

Position	Isolated Am D	Danishefsky's synthetic Am D	RB-route
1	104.3	104.3	104.4
2	165.5	166.0	165.8
3	102.4	102.6	102.5
4	163.1	163.2	163.1
5	107.7	107.9	107.8
6	144.2	144.5	144.3
1'	130.6	130.8	130.6
2'	133.6	133.8	133.6
3'	27.9	28.1	28.0
4'	28.5	28.8	28.5
5'	73.1	73.1	73.0
6'	76.4	76.7	76.5
7'	135.6	135.9	135.7
8'	125.4	125.6	125.4
9'	37.9	38.1	37.9
10'	72.9	73.1	73.0
-COO-	172.1	172.3	172.2
10'-**C**H3	19.1	19.2	19.1

5.3 Summary of Chapter Five

Aigialomycin D was successfully synthesised from D-ribose in 16 steps with 9% overall yield. Our route proved to be more efficient than the original total synthesis by Danishefsky (18 steps, 8% yield), Pan's synthesis (18 steps, 2.5% yield), and Montgomery's synthesis (8 steps, 7% yield).

Many unsuccessful attempts were made to couple the various aromatic phosphonate and carbohydrate-derived hemiacetal substrates utilising the HWE reaction. Success in coupling phosphonates and simple aldehydes was limited, affording the benzylic olefins in low yields (0–38%). The HWE reaction between simplified phosphonate **210** and pivaldehyde was the sole exception, giving the desired product in 88% yield.

The aromatic and C2′–C7′ segments were readily coupled via a thioether linkage. Saponification of the unprotected thioether **191** resulted in undesired decarboxylation. Protecting the phenolic hydroxyls as MOM ethers allowed the saponifcation to proceed with near quantitative yields. The Mitsunobu reaction of acid **193** with alcohol (*R*)-**22** completed the carbon backbone of Am D. Oxidation to sulfone **195** prior to the stereoselective MW-assisted RCM of the diene precursor facilitated the successful installation of the C7′–C8′ (*E*)-olefin present in Am D. The Ramberg-Bäcklund reaction provided the bis-MOM protected **35** in excellent yield and stereoselectivity. Global deprotection under acidic conditions provided the natural product from D-ribose in 16 steps and 9% overall yield.

Chapter Six:

Synthesis of Am D Analogues and Biological Evaluation

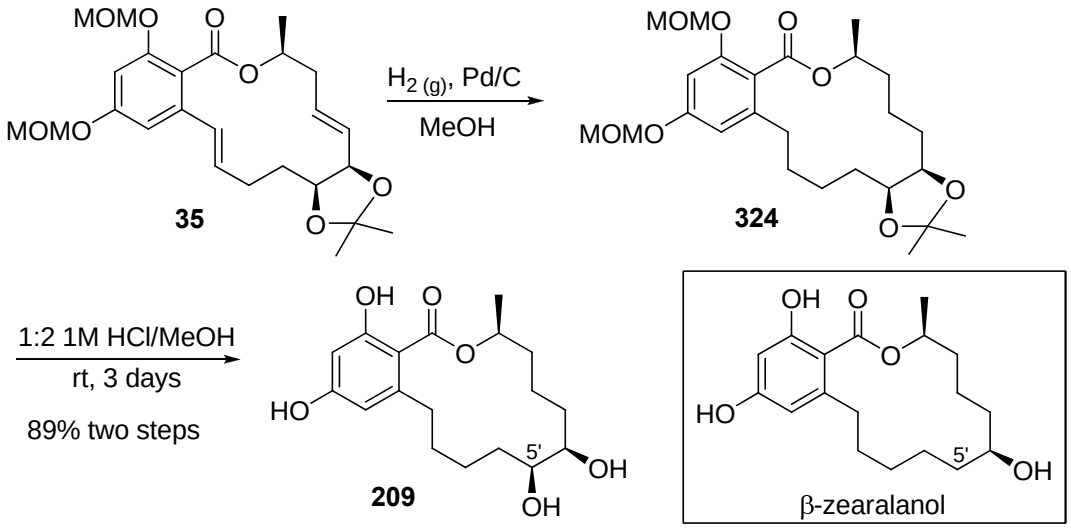
6.1 Synthesis of Am D Analogues

After the successful synthesis of Am D via the Ramberg-Bäcklund route (Chapter 5, Section 5.2), focus turned to the synthesis of Am D analogues. Analogues of bioactive compounds are commonly used to help probe the molecular source of the observed biological activity through examination of their structure-activity relationships. Modification of functional groups that results in a significant change of the particular activity of interest highlights the biologically important regions or groups. Likewise, changes that result in no observable change in activity highlight areas that are most likely not involved in eliciting the biological response. Analogues that simplify the required synthetic chemistry whilst retaining or improving the natural product's level of bioactivity are the prized end goals of analogue synthesis.

Three considerations guided the design of Am D analogues that would be synthesised in this project. Firstly, the proposed analogues should explore modifications to the key functional groups of Am D, i.e. the (*E*)-alkenes, *cis*-diol, aromatic ring and phenolic groups. These groups are the parts of the molecule that are most likely to be interacting with the biological target. Modifications that generate products which interpolate between Am D and other resorcylic acid lactones are also of interest. Such modifications include the epoxidation of the (*E*)-alkene(s), methylation of the 4-hydroxyl group, oxidation of the C6′-hydroxyl group, and inversion of the C11′ methyl group. Finally, the ability to access analogues from existing synthetic intermediates is desirable, avoiding the arduous task of engineering new routes.

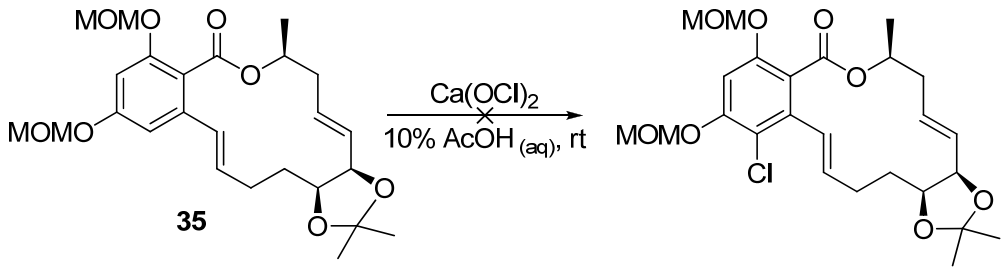
Thus, to investigate the importance of the two (*E*)-alkenes in Am D, tetrahydro-aigialomycin D (**209**) was prepared in two steps from the protected form of Am D **35** (Scheme 6-1). Palladium-catalysed hydrogenation reduced the olefins to give the saturated macrocycle **324**. Global deprotection under acidic conditions afforded saturated diol **209** in 89% yield over two steps. Saturation of the two alkene bonds should greatly increase the conformational freedom of the macrocycle, which in turn

may impart a different mode of biological activity than that exhibited by the natural product. Tetrahydro-aigialomycin D (**209**) is a C5′ hydroxy analogue of the fungal metabolite β-zearalanol[135] and therefore might exhibit similar anabolic properties.



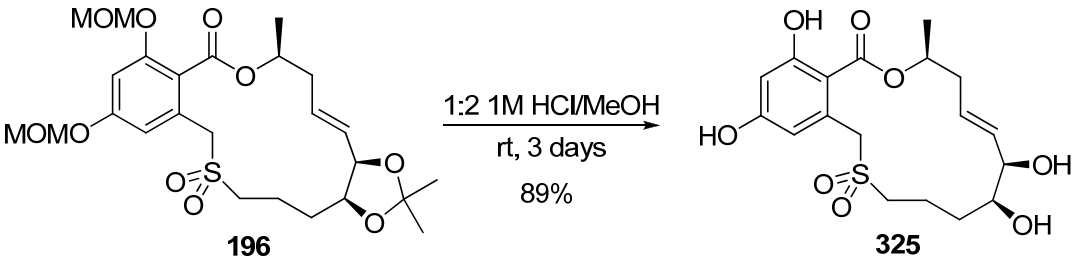
Scheme 6–1. Synthesis of the saturated analogue **209** of Am D.

The potent Hsp90 inhibitors radicicol and pochonin D both contain a chlorine atom substituted at C5 on their aromatic rings. An attempt was made to chlorinate the C5 position of protected Am D **35** (Scheme 6–2) following the procedure Blagg and co-workers developed for the chlorination of related compounds.[132] However, no reaction occurred and the starting material was recovered.



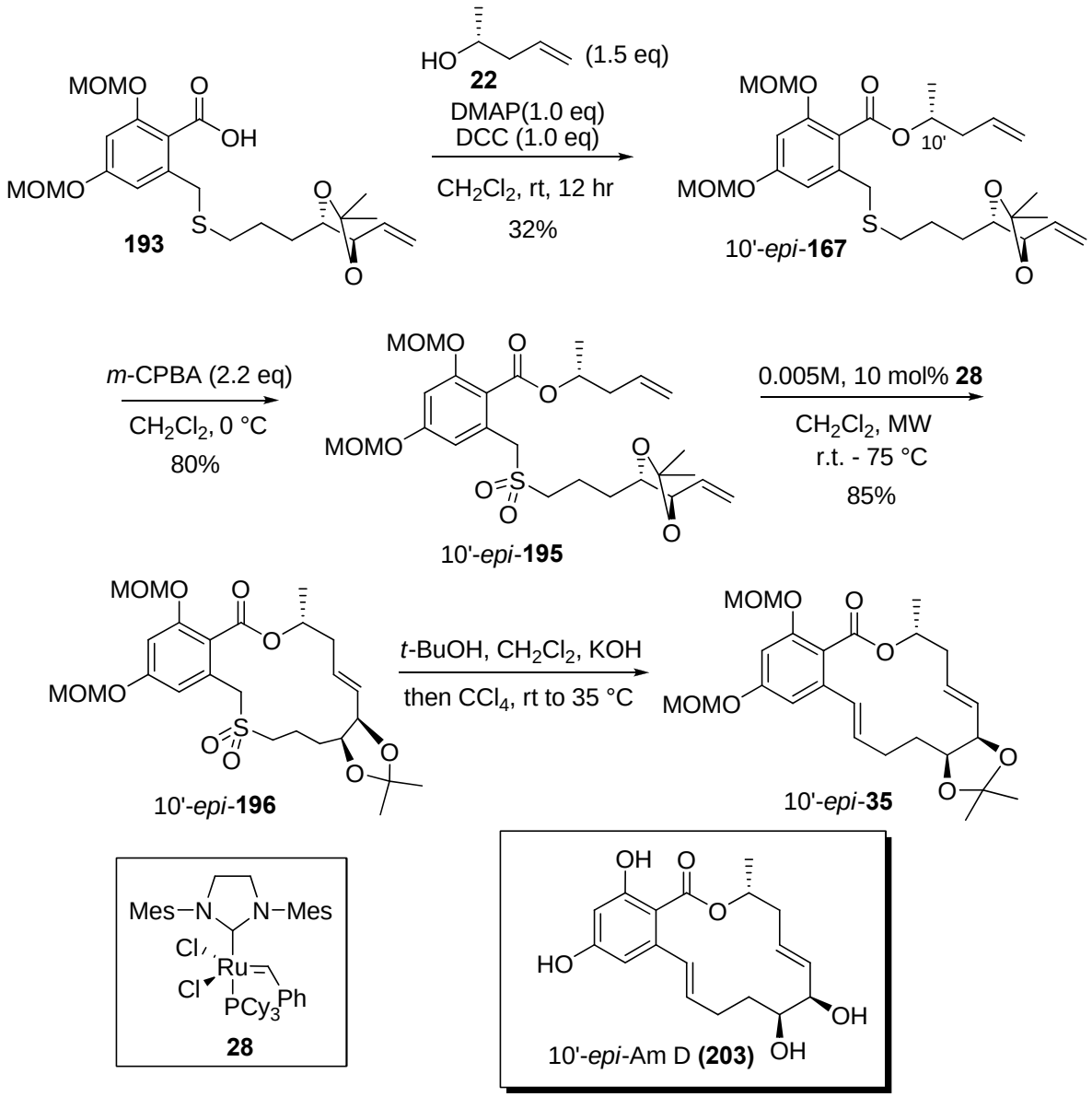
Scheme 6–2. Attempted synthesis of the 5-chloro analogue of Am D.

The sulfone-containing 15-membered macrolactone **325** (Scheme 6–3), derived from the RB precursor **196**, is an interesting analogue of Am D, containing the C7′–C8′ olefin present in Am D but with a sulfone moiety instead of the C1′–C2′ olefin. Sulfone **325** was readily prepared by deprotecting the RB precursor **196** under acidic conditions. It too may have a different mode of activity to Am D, due to the larger ring size enabling the compound to adopt different conformations than those of the natural product.



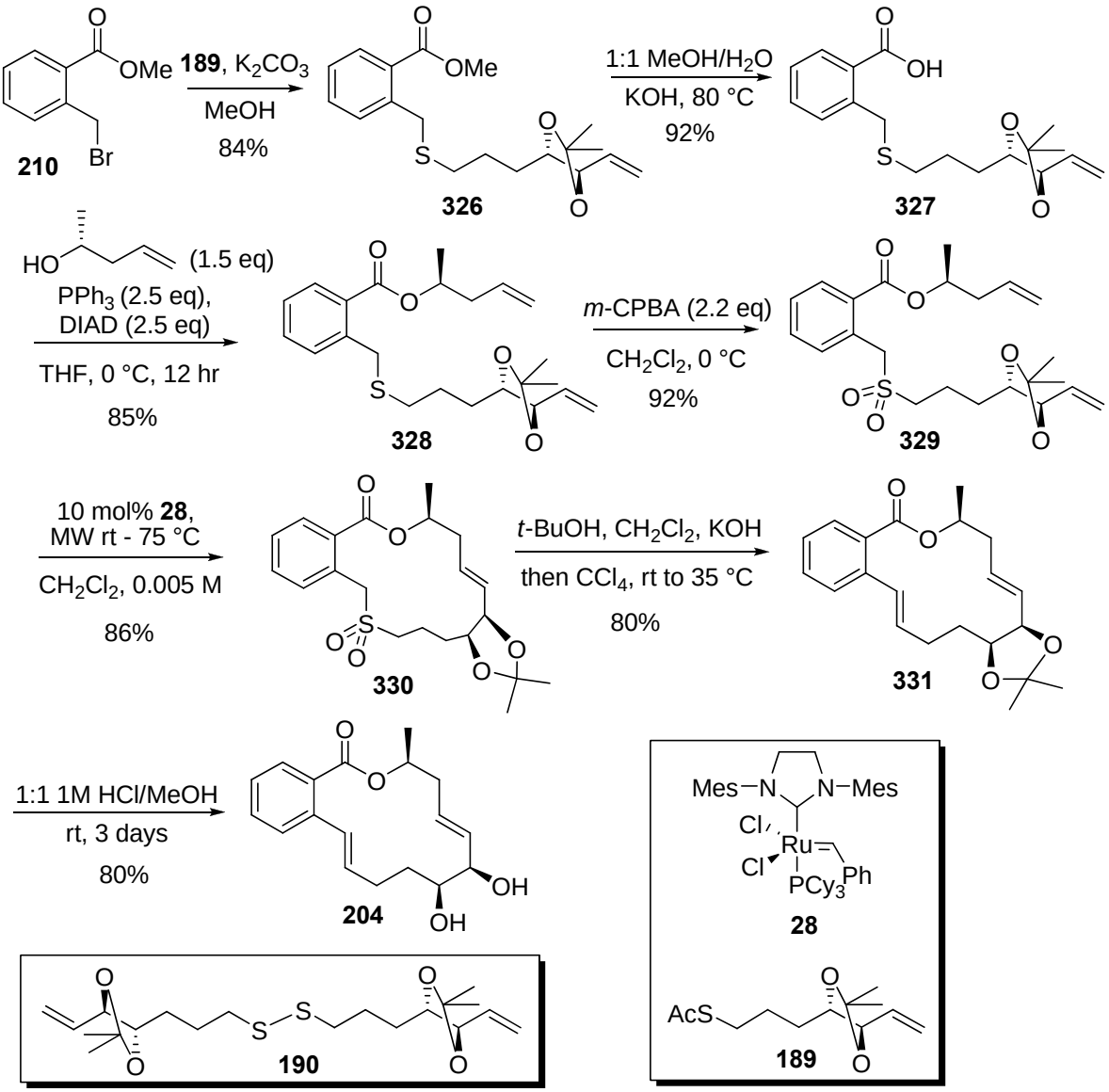
Scheme 6–3. Synthesis of the sulfone 15-membered macrolactone **325** analogue of Am D.

Significant progress was made towards the synthesis of the C10′-epimer of Am D (**203**) (Scheme 6–4). To access the non-natural C10′ configuration in compound **167**, an esterification protocol with *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) was used to couple acid **193** and alcohol (*R*)-**22**. Ester 10'-*epi*-**167** was obtained in relatively low yield (32%) compared to the esterification achieved under the Mitsunobu conditions utilised in the synthesis of the natural product (90 – 94%). The subsequent oxidation and RCM steps proceeded efficiently to give RB precursor 10'-*epi*-**196**. The RB reaction provided protected 10'-*epi*-**35** alongside small amounts of impurities. Initial attempts to purify the product by flash column chromatography failed to afford pure 10'-*epi*-**35**. Due to time constraints the synthesis of 10'-*epi*-Am D (**203**) was not completed. Once purified, the deprotection of protected 10'-*epi*-**35** should pose few difficulties.



Scheme 6–4. Progress towards the synthesis of 10'-*epi*-Am D (**203**).

The 2,4-dideoxy analogue of Am D, **204**, was synthesised in order to investigate the importance of the phenolic hydroxyl groups to the activity of Am D. These groups are likely to be involved in important hydrogen bonds to amino acid residues inside the binding site of Am D's molecular target.[132] Macrocycle **204** was readily prepared following the chemistry previously developed for the synthesis of Am D as discussed in the previous chapter (Scheme 6–5). Thus, bromide **210** was synthesised as described in Section 2.1. This was reacted with thioacetate **189** to produce thioether **326**. Complete separation of thioether **326** from the by-product disulfide **190** with flash column chromatography was not easily achieved. However, this by-product was easily removed after saponification by extraction with Et_2O prior to acidification. The remaining steps proceeded with similar yields to those obtained for the natural product, affording the 2,4-dideoxy analogue **204** in 7 steps from bromide **210** with an overall yield of 33%.



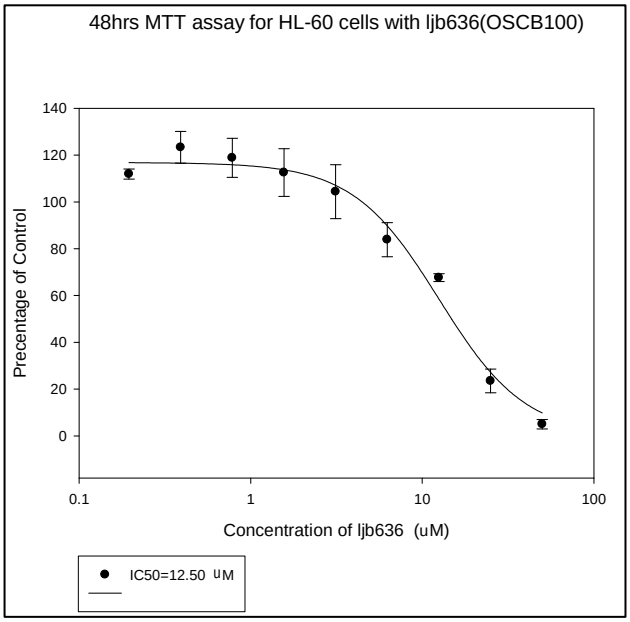
Scheme 6–5. Synthesis of the 2,4-dideoxy analogue **204** of Am D.

6.2 Biological Testing of Am D (1), Tetrahydro-Am D 209 and Sulfone 325

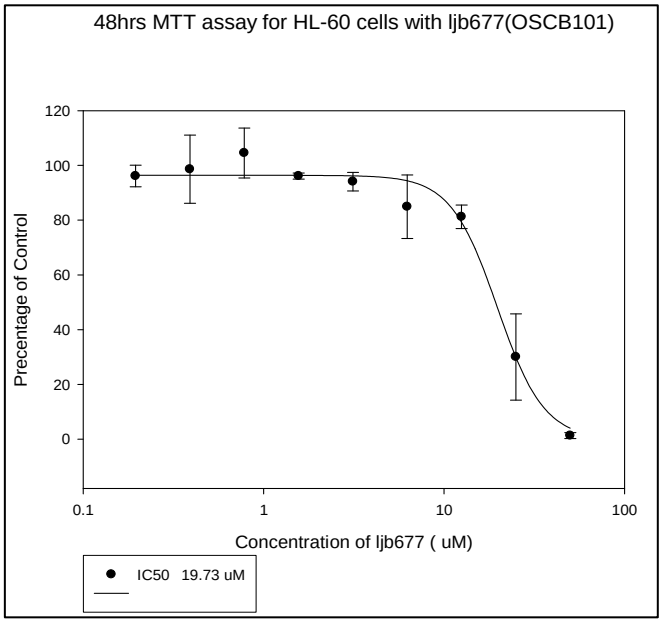
Am D (**1**) and analogues **209** and **325** were tested for cytotoxicity against the cell line HL-60 (*Human promyelocytic leukemia cells*) with 48 hour MTT assays[217] at the Centre for Biodiscovery laboratories in the School of Biological Sciences by Reem Hanna (Figure 6–1). Unfortunately, 2,4-dideoxy analogue **204** had degraded to a complex mixture of unidentified compounds before samples were submitted for biological testing. Am D was the most active compound, exhibiting an IC_{50} of 12.5 μM. Thus, the cytotoxicity of Am D for HL-60 cells was the same order of magnitude to that reported

for KB and Vero cells. Sulfone **325** and tetrahydro-aigialomycin D (**209**) exhibited similar magnitudes of activity, with an IC_{50} of 14.3 and 19.7 μM respectively. Sulfone **325** and tetrahydro-Am D **209** are likely to exist in a wider range of conformations than Am D due to the removal of sp^2 centres that reduce the flexibility of compounds. The fact that these three compounds have similar levels of cytotoxicity suggests that either they are able to exist in the same conformation as target-bound Am D or that these compounds are interacting with different targets to give their observed activity.

Am D (1)



Tetrahydro-aigialomycin D (209)



Sulfone 325

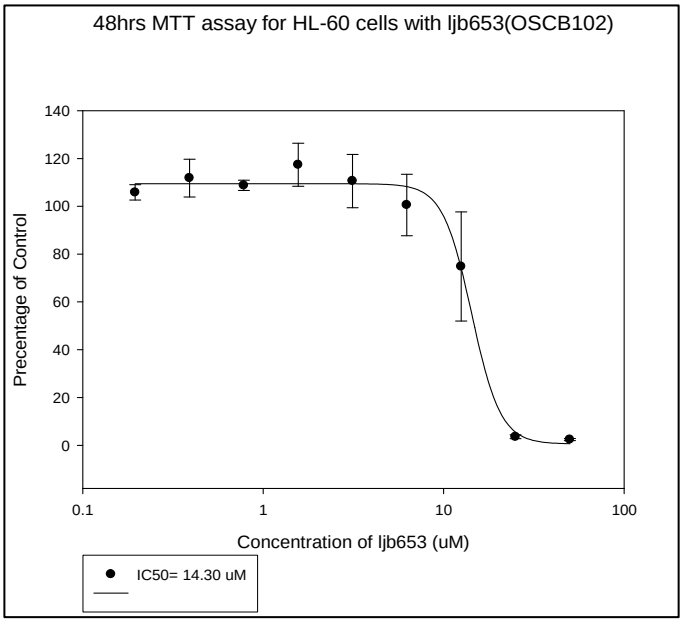


Figure 6–1. Graphs showing inhibition of cell growth as a function of concentration of Am D (**1**), tetrahydro-Am D (**209**) and sulfone analogue (**325**).

6.2 Summary of Chapter Six

Three analogues of Am D have been synthesised to investigate the importance of the double bonds and phenolic hydroxyl groups in the activity of Am D. Both sulfone **325** and tetrahydro-Am D (**209**) exhibited a similar degree of cytotoxicity towards HL-60 cells to that of Am D (12.5 μM), with IC_{50}'s 14.3 and 19.7 μM. Unfortunately, the 2,4-dideoxy analogue **204** had decomposed before a sample was submitted for biological testing. Attempts were made to prepare the 5-chloro analogue of Am D and 10′-*epi*-Am D, but due to time constraints these syntheses were not completed.

Chapter Seven:

Future Work and Conclusions

7.1 Future Work

One goal of this research project was to synthesise a range of Am D analogues to gain further insight into the structure activity relationship inherent to Am D. While the synthesis of three analogues was described in this work, there is plenty of scope to develop other interesting analogues. These may include analogues with epoxide functionality in place of one or both of the alkenes, as present in radicicol (**2**)[13] and some members of the pochonin family,[30] such as epoxide **332** (Figure 7–1). Selective oxidation of the allylic alcohol at C6′ would introduce enone functionality that is present in several other resorcylic acid lactones (RALs), for example hypothemycin (**4**) (Figure 7–1). These RALs contain C8′ to C6′ *cis*-enones whereas Am D analogue **333** would contain a *trans*-enone.

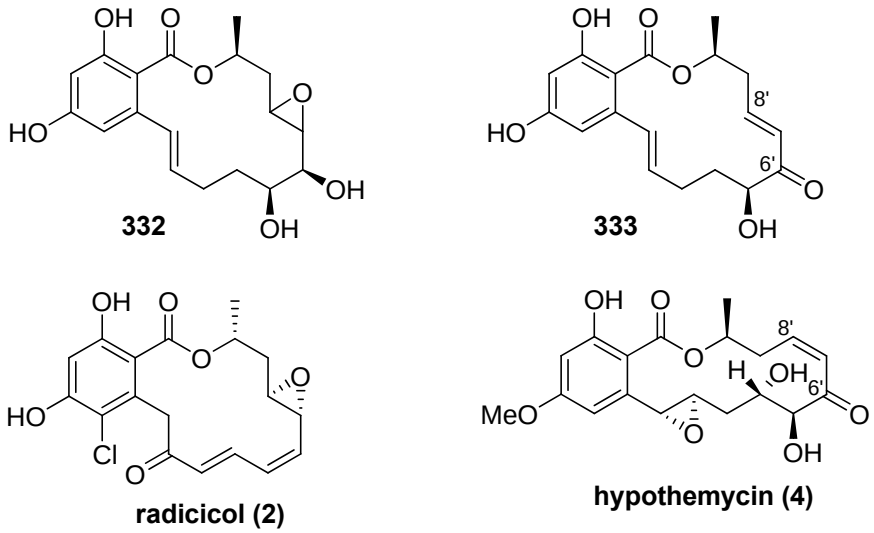


Figure 7–1. Proposed Am D analogues **332** and **333** that contain functional groups present in radicicol and hypothemycin.

The complete set of stereochemical arrangements possible for the diol at C5′ and C6′ could be accessed by starting with different sugars as such D-xylose, D-arabinose or D-lyxose (Figure 7–2). Montgomery[36] and Jennings[38] have both synthesised the 6′-epimer of Am D, which could also be prepared from D-xylose using the methodology described in this work. However, the 5′- and 5′,6′-epimers of Am D are yet to be synthesised.

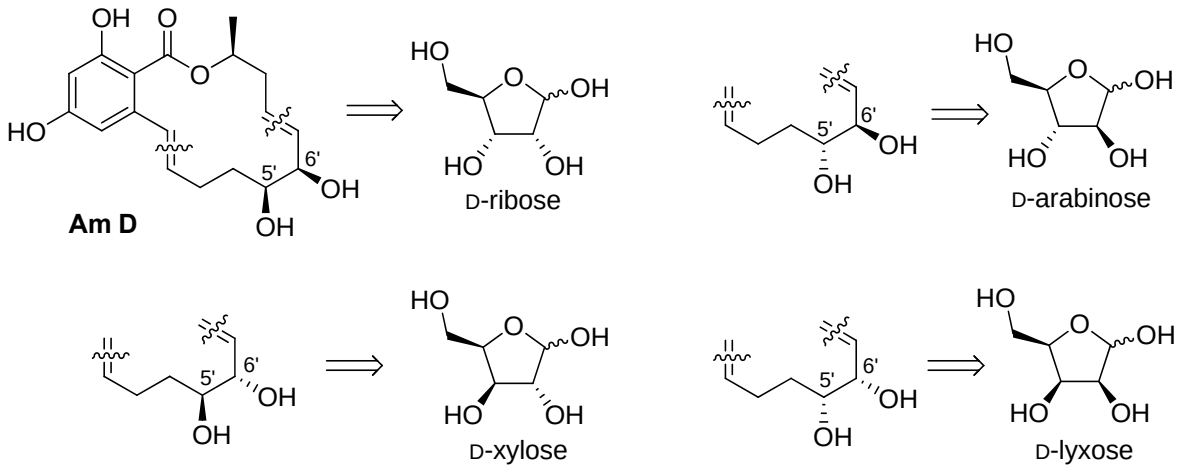


Figure 7–2. The range of stereochemistries accessible for the C5′–C6′ diol of Am D when starting from D-ribose, D-arabinose, D-xylose or D-lyxose.

Finishing the synthesis of 10′-*epi*-Am D **203** should be rather straightforward. 10′-*epi*-Am D **203** should also be amenable to the late stage modifications that have been undertaken or proposed on Am D, such as hydrogenation and epoxidation.

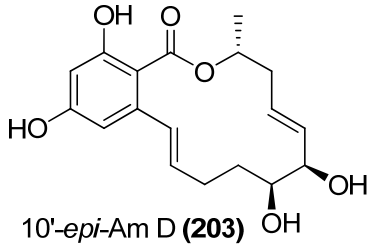


Figure 7–3. Structure of 10′-*epi*-Am D **203.**

After expanding the library of Am D analogues, these compounds will need to be tested alongside Am D in a variety of biological assays, similar to those reported in Chapter 6. The data collected from this testing will help to determine the parts of the molecule that are required to elicit the desired activity. These studies would also determine whether any of the modifications to Am D have tuned the bioactivity towards one particular activity, e.g. anti-cancer vs. anti-malarial activity, or even altered the biochemical target.

Furthermore, a chemical genetics study[218] could be undertaken to confirm whether the inhibition of kinases identified by Winssinger[9] is the cause of the Am D's cytotoxicty, and to identify other potential molecular targets of Am D. This study will be undertaken at the School of Biological Sciences at Victoria University of Wellington.

7.2 Concluding Remarks

The isolation and identification of aigialomycin D and its promising biology have resulted in a flurry of synthetic activity,[7] culminating so far in several reported total syntheses of this intriguing target[7,9,33-36] and a number of synthetic analogues.[9,36,38]

Two synthetic strategies to Am D were investigated in this research project: a HWE strategy and a RB strategy. The three major segments were successfully synthesised for both approaches. However, the coupling between the aromatic and C2′–C7′ fragments through HWE reactions proved to be more challenging than anticipated. All attempts to couple arylmethyl phosphonates with protected hemiacetals failed to provide any olefin product. Studies of the HWE reactions between model aromatic phosphonates and simple aldehydes found that the model alkenes could be synthesised, albeit in low yields, but often accompanied by formation of alkenylphosphonate by-products.

In contrast, the RB approach, which involved a combination of Mitsunobu, RCM and RB reactions allowed the assembly of the natural product with high yield and stereoselectivity. The RB reaction proved to be an excellent approach to 'masking' the benzylic olefin until late in the synthesis, thus avoiding any complications with the RCM reaction. Aigialomycin D was successfully synthesised from D-ribose in 16 steps with 9% overall yield. Our route proved to be more efficient than the original total synthesis by Danishefsky (18 steps, 8% yield), and the subsequent syntheses by Pan (18 steps, 2.5% yield) and Montgomery (8 steps, 7% yield). This RB route was also shown to be flexible towards the synthesis of several new Am D analogues.

The analogues sulfone **325** and tetrahydro-Am D **209** were successfully prepared from late-stage Am D intermediates. The RB route was shown to be flexible, resulting in the syntheses of 2,4-dideoxy analogue **204** and 10′-*epi*-**35**, the penultimate intermediate en route to analogue10′-*epi*-Am D **203**. Preliminary biological testing revealed that sulfone **325** and tetrahydro-Am D (**209**) exhibited a similar magnitude of cytotoxicity towards HL-60 cells with IC_{50}'s of 14.3 and 19.7 μM, compared to that of Am D (12.5 μM).

Thus, the major goals of this research project have been met. The RB route led to the successful total synthesis of natural product Am D and proved adaptable to synthesis of several new analogues. This project has laid the groundwork for the synthesis of many new Am D analogues.

Chapter Eight:

Experimental

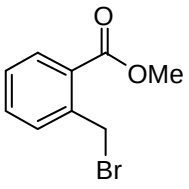
8.1 General

Unless otherwise stated, the following conditions apply. All reactions were performed under argon in oven-dried or flame-dried glassware using dry solvents and standard syringe techniques. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from the sodium benzophenone ketyl radical ion. Dichloromethane (CH_2Cl_2), triethylamine (NEt_3), and acetonitrile (MeCN) were distilled from calcium hydride. Toluene, hexanes and methanol (MeOH) were distilled from sodium. Diisopropylethylamine ($^iPr_2NEt$) and pyridine were distilled from sodium hydroxide. Acetone was distilled from potassium carbonate. Anhydrous dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were purchased from Aldrich Chemical Company and were used without further purification. Sodium hydride (NaH) was obtained as a 60% suspension in mineral oil, washed three times with dry hexanes and dried under vacuum immediately prior to use. All other reagents were of commercial quality and distilled prior to use if necessary.

Reaction progress was monitored using aluminium backed thin layer chromatography (TLC) plates pre-coated with silica UV254 and visualised by either UV radiation (254 nm), anisaldehyde dip. Retention factors (R_f) are reported for development of TLC plates in 2:1 heanes/EtOAc unless stated otherwise. Purification of products via flash chromatography was conducted using a column filled with silica gel 60 (220-240 mesh) with solvent systems as indicated. MW-assisted reactions were carried out in a Milestone Microsynth reactor, monitored by a fibre optic temperature and pressure probe. ^1H and ^{13}C NMR spectra were recorded on either a Varian Unity Inova 300 (300 MHz for ^1H and 75 MHz for ^{13}C), or a Varian Unity Inova 500 (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer. All chemical shifts (δ) were referenced to solvent peaks ($CDCl_3$: ^1H - 7.26 ppm, ^{13}C - 77.0 ppm; d_6-acetone: ^1H - 2.05 ppm, ^{13}C - 29.84 ppm; d^4-MeOH: ^1H - 3.31 ppm, ^{13}C - 49.00 ppm). Optical rotation was measured on a Perkin-Elmer Polarimeter (sodium lamp). Infrared spectra were obtained on either a Biorad FTS-7 spectrometer or a Bruker Tensor 27 FTIR spectrometer. High-resolution mass

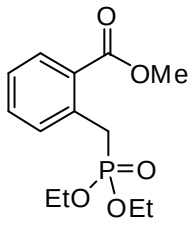
spectrometry (HRMS) was recorded on a Mariner 5158 time of flight spectrometer or a Waters Q-TOF Premier™ Tandem Mass Spectrometer. The structure of each compound is presented with its method of preparation.

8.2 Experimental for Chapter Two



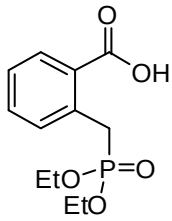
Methyl 2-(bromomethyl)benzoate (214)

A solution of methyl 2-methylbenzoate (**212**) (1.0 g, 6.67 mmol) and NBS (1.31 g, 7.35 mmol) in CH_2Cl_2 (20 mL) was heated to reflux with a heat lamp (200 W) for 30 min. The reaction mixture was cooled and filtered to remove the solid succinimide before concentrating under reduced pressure to give a pale yellow oil. The crude residue was purified by flash column chromatography (silica, 20:1 hexanes/EtOAc) to give a colourless oil (1.37 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.4 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.37 (m, 1H), 4.96 (s, 2H), 3.95 (s, 3H). Spectral data matched those reported in the literature.[219]



Methyl 2-[(diethoxyphosphoryl)methyl]benzoate (210)

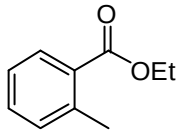
A solution of methyl 2-methylbenzoate (**212**) (2.0 g, 13.3 mmol) and NBS (2.61g, 14.7 mmol) in CH_2Cl_2 (20 mL) was heated to reflux with a heat lamp (200 W) for 30 min. The reaction mixture was cooled and filtered to remove the solid succinimide before concentrating under reduced pressure to give a pale yellow oil (~3.05 g, ~13.3 mmol). To the crude bromomethyl 2-methylbenzoate (**214**) was added triethyl phosphite (6.91 mL, 39.7 mmol) and the reaction mixture was heated to 150 °C for 12 h. The unreacted triethyl phosphite was distilled from the product to yield a yellow oil. The crude product was purified by flash column chromatography (silica, gradient elution 2:1 hexanes/EtOAc to EtOAc), yielding a pale yellow oil (3.38 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 8.5, 15.3 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 3.99 (p, *J* = 7.2 Hz, 4H), 3.91 (s, 3H), 3.80 (d, *J* = 22.8 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H).



2-[(Diethoxyphosphoryl)methyl]benzoic acid (294)

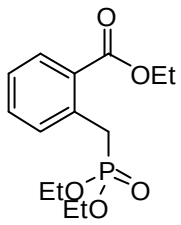
To a solution of phosphonate **210** (250 mg, 0.87 mmol) in EtOH (3 mL) was added KOH (147 mg, 2.62 mmol). The solution was stirred for 8 h

at rt before heating to reflux for 12 h. The cooled solution was acidified to pH 1 with 10% HCl and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a white solid (194 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.33 (td, *J* = 7.5, 2.0 Hz, 2H), 4.12 – 4.01 (m, 4H), 3.81 (d, *J* = 22.7 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 6H).



Ethyl 2-methylbenzoate (213)

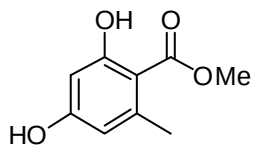
To a solution of 2-methylbenzoic acid (2.03 g, 14.9 mmol) in EtOH (25 mL) was added H_2SO_4 (0.95 mL) dropwise. The reaction mixture was heated to reflux for 12 h. The solvent was removed from the cooled reaction mixture and the crude oil was dissolved in Et_2O before being washed with 1M $NaOH_{(aq)}$ (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and reduced to give a colourless oil (2.27 g, 93%). ^{1}H NMR (300 MHz, cdcl3) δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.20 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). Spectral data matched those reported in the literature.[220]



Ethyl 2-[(diethoxyphosphoryl)methyl]benzoate (211)

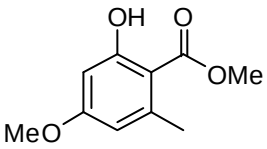
A solution of methyl 2-methylbenzoate (**213**) (2.27 g, 13.8 mmol) and NBS (2.71 g, 15.2 mmol) in CH_2Cl_2 (25 mL) was heated to reflux with a heat lamp (200 W) for 30 min. The reaction mixture was cooled and filtered to remove the solid succinimide before concentrating under reduced pressure to give a pale yellow oil. A solution of the crude bromomethyl 2-methylbenzoate (3.31 g, 13.6 mmol) in triethyl phosphite (5.9 mL, 34.1 mmol) was heated at 150 ^{o}C for 12 h. The unreacted triethyl phosphite was removed by distillation to yield the product as a yellow oil. The crude product was purified with flash column chromatography (silica, gradient elution 2:1 hexanes/EtOAc to EtOAc), affording a pale yellow oil (3.66 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.99 (q, *J* = 7.8 Hz, 4H), 3.81 (d, *J* = 22.9 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 6H). Spectral data matched those reported in the literature.[221]

Methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate, 74)[141]



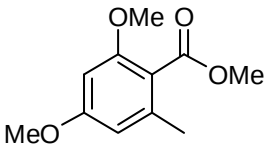
To a suspension of 60% NaH (2.56 g, 64 mmol, washed three times with dry hexanes) in THF (100 mL) at 0 °C was added

methyl acetoacetate (5.0 g, 43 mmol) dropwise. The mixture was stirred for 1 h, warming to rt. The reaction was cooled down to -78 °C and a 1.6 M solution of *n*-butyllithium in hexanes (25.6 mL, 41 mmol) was added dropwise over 2 h. The reaction was then stirred at rt for 12 h. The reaction mixture was then refluxed for a further 24 h. The cooled orange solution was acidified with 10% HCl to pH 1 and stirred at rt for 12 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 75 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified using flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) to provide methyl orsellinate **74** as a white solid (1.56 g, 40%). R_f (silica, 2:1) = 0.44. mp 141 – 142 °C. [lit.[222] mp 139 – 140 °C] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 6.23 (d, *J* = 2.5 Hz, 1H), 5.52 (s, 1H), 3.92 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 165.2, 160.3, 144.0, 111.4, 105.6, 101.2, 51.9, 24.3. Spectral data matched those reported in the literature.[141]



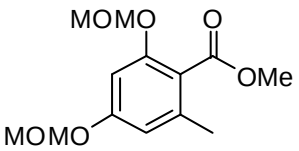
Methyl 2-hydroxy,4-methoxy-6-methylbenzoate (132)

To a solution of orsellinate **74** (50 mg, 0.27 mmol) and K_2CO_3 (152 mg, 1.10 mmol) in acetone (2 mL) was added Me_2SO_4 (105 μL, 1.10 mmol) dropwise. The reaction was heated to 50 °C for 48 h. The reaction mixture was filtered and reduced to dryness. The crude product was purified using flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) giving a white solid (43 mg, 80%). mp 68 – 69 °C. [lit.[223] mp 70 – 71 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.27 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 2.48 (s, 3H). Spectral data matched those reported in the literature.[223]



Methyl 4,6-dimethoxy-2-methylbenzoate (130)

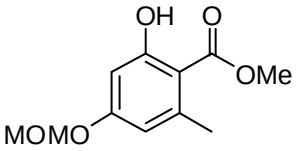
A suspension of KOH (38 mg, 0.95 mmol) and orsellinate **74** (52 mg, 0.286 mmol) in THF (2 mL) was stirred at rt for 20 min over which time a white precipitate (ppt) formed. To the reaction was added MeI (100 μL, 0.309 mmol) and it was stirred for 12 h at rt. The reaction was quenched with 10% HCl (5 mL) and extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, filtered and reduced to give a white solid. The crude product was purified using flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) giving a white solid (38 mg, 62%). mp 42 – 44 °C. [lit.[224] mp 42 – 44 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 2.28 (s, 3H). Spectral data matched those reported in the literature.[146] HRMS (ESI) calcd. for $C_{11}H_{15}O_4^+$ [M + H^+] 211.0965, found 211.1198.



Methyl 2,4-bis(methoxymethoxy)-6-methylbenzoate (221)

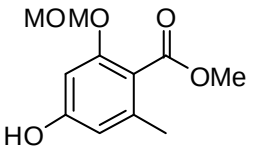
To solution of orsellinate **74** (100 mg, 0.55 mmol) in DMF cooled to 0 °C was added a 60% dispersion of NaH in mineral oil (44 mg, 1.10 mmol). The reaction was warmed to rt for 15 min before cooling back down to 0 °C. MOM-Cl was added dropwise to reaction mixture and it was left to warm up to rt over 12 h. The reaction mixture was diluted with Et_2O (15 mL) and washed with H_2O (20 mL). The organic phase was washed with sat. $NaHCO_{3(aq)}$ (3 x 10 mL), washed with brine (10 mL), dried with $MgSO_4$, filtered and reduced giving a colourless oil. The crude product purified by flash column chromatography (silica, 5:1 hexanes/EtOAc) yielding bis-MOM **221** (110 mg, 74%), 4-MOM **222** (19 mg, 15%) and 2-MOM **223** (4.5 mg, 3%). **221**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 2.1 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 5.15 (s, 4H), 3.89 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 158.7, 155.4, 138.0, 118.5, 110.7, 101.3, 94.8, 94.2, 56.2, 56.1, 52.1, 19.8. Spectral data matched those reported in the literature.[225]

Methyl 2-hydroxy-4-methoxymethoxy-6-methylbenzoate (222)

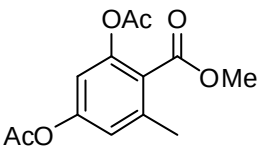


^{1}H NMR (500 MHz, $CDCl_3$) δ 11.67 (s, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.17 (s, 2H), 3.93 (s, 3H), 3.46 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 165.1, 161.4, 143.3, 111.8, 106.2, 101.4, 93.8, 56.3, 51.9, 24.4. IR: 2956, 2906, 1655, 1618, 1578, 1442, 1323, 1258, 1212, 1149, 1021, 942, 911, 735 cm^{-1}.

Methyl 2-methoxymethoxy-4-hydroxy -6-methylbenzoate (223)



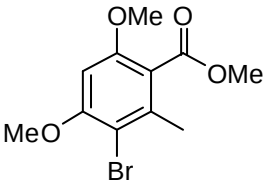
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (d, *J* = 2.2 Hz, 1H), 6.32 (d, *J* = 2.2 Hz, 1H), 5.42 (brs, 1H), 5.13 (s, 2H), 3.89 (s, 3H), 3.46 (s, 3H), 2.24 (s, 3H).



Methyl 2,4-bis(acetyloxy)-6-methylbenzoate (134)

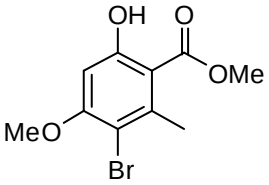
To a solution of orsellinate **74** (1.26 g, 6.90 mmol) in CH_2Cl_2 (17.5 mL) at rt was added NEt_3 (5.76 mL, 41.4 mmol) and acetic anhydride (Ac_2O) (2.56 mol, 27.6 mmol). The reaction was stirred for 12 h at rt before being quenched with sat. $NaHCO_{3(aq)}$ (30 mL). The organic layer was separated, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified through a short silica column (gradient elution 5:1 to 2:1 hexanes/EtOAc) with a few drops of AcOH, yielding the title compound as a white solid (1.82 g, 98%). R_f (silica, 2:1) = 0.31. mp 53 – 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 2.2 Hz,

1H), 6.80 (d, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 168.9, 168.6, 166.3, 151.7, 149.3, 139.8, 121.3, 114.2, 77.2, 52.2, 21.1, 20.8, 20.5. IR (neat): 3086, 2959, 1781, 1732, 1616, 1587, 1446, 1370, 1280, 1174, 1137, 1098, 1054, 1018, 953, 911 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{14}O_6Na^+$ [M + Na]$^+$ 289.0683, found 289.0685.



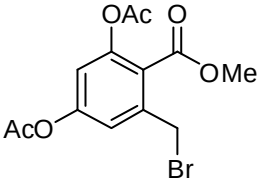
Methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate (225)

To a solution of arylmethyl **130** (35 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added NBS (30 mg, 0.17 mmol) and AIBN (10 mg) and the solution was heated to reflux for 30 min under irradiation with a heat lamp (200 W). The reaction mixture was cooled to rt, filtered and reduced to give a white solid (32 mg, 65%). mp 132 – 134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 2.31 (s, 3H). Spectral data matched those reported in the literature.[75]



(Methyl 3-bromo-6-hydroxy,4-methoxy-2-methylbenzoate (224)

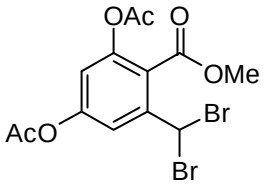
To a solution of arylmethyl **132** (15 mg, 77 μmol) in CH_2Cl_2 (2 mL) was added NBS (15 mg, 77 μmol) and AIBN (10 mg) and the solution was heated to reflux for 30 min under irradiation with a heat lamp (200 W). The reaction mixture was cooled to rt, filtered and reduced to give a white solid (15 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.55 (s, 1H), 6.41 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.77 (s, 3H), 2.68 (s, 3H).



Methyl 2,4-bis(acetyloxy)-6-(bromomethyl)benzoate (135)

To a solution of arylmethyl **134** (440 mg, 1.64 mmol) in CCl_4 (15 mL) were added NBS (180 mg, 1.01 mmol) and benzoyl peroxide (20 mg) and the reaction mixture was heated to reflux. After 3 h, another portion of NBS (180 mg, 1.01 mmol) and benzoyl peroxide (20 mg) was added to mixture and the reaction was heated to reflux for a further 3 h. After this time the reaction was cooled to rt and the solid succinimide filtered off and solvent removed under reduced pressure. The resulting orange oil was purified using careful flash column chromatography (silica, CH_2Cl_2) to yield the title compound **135** as a white solid (400 mg, 71%), and the corresponding dibromide **226** as white solid (81 mg, 12%). R_f (silica, CH_2Cl_2) = 0.46. mp 62 – 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d,

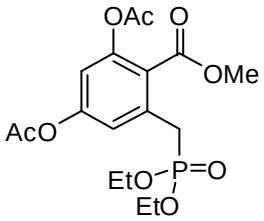
J = 2.2, 1H), 6.95 (d, J = 2.2, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 168.3, 165.2, 152.0, 149.8, 139.3, 123.0, 121.3, 117.0, 52.7, 29.7, 21.1, 20.7. IR (KBr): 3082, 2950, 1770, 1731, 1613, 1434, 1370, 1282, 1187, 1138, 1094, 1033, 1017, 907 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{13}O_6BrNa^+$ $[M + Na]^+$ 366.9793, found 366.9798.



Methyl 2,4-bis(acetyloxy)-6-(dibromomethyl)benzoate (226)

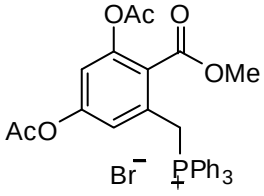
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 2.2 Hz, 1H), 7.38 (s, 1H), 7.12 (d, J = 2.2 Hz, 1H), 4.05 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 168.0, 164.6, 152.5, 148.6, 142.7, 121.2, 119.2, 118.1, 52.9, 35.8, 21.0, 20.6.

Methyl 2,4-bis(acetyloxy)-6-[(diethoxyphosphoryl)methyl]benzoate (142)



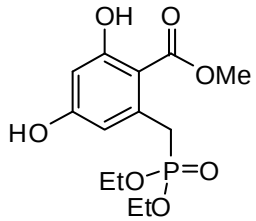
Bromide **135** was heated to 120 ˚C in neat $P(OEt)_3$ for 12 h. After TLC confirmed that all the starting bromide had reacted, the excess $P(OEt)_3$ was distilled off under reduced pressure (20 mmHg) yielding the phosphonate as a pale yellow liquid (264 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, J = 2.5 Hz, 1H), 6.90 (t, J = 2.2 Hz, 1H), 4.04 – 3.96 (m, 4H), 3.89 (s, 3H), 3.48 (d, J = 22.4 Hz, 2H), 2.28 (s, 3H), 2.26 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 168.3, 165.7, 151.9 (d, J = 3.7 Hz), 149.8 (d, J = 3.4 Hz), 134.1 (d, J = 9.4 Hz), 123.6 (d, J = 6.5 Hz), 122.1 (d, J = 5.8 Hz), 115.6 (d, J = 3.5 Hz), 62.4 (d, J = 6.8 Hz), 52.4, 31.3 (d, J = 137.5 Hz), 21.1, 20.8, 16.3 (d, J = 5.9 Hz). IR (neat): 2986, 1772, 1727, 1612, 1433, 1370, 1282, 1191, 1136, 1094, 1028, 961, 911, 787, 730 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{23}O_9PNa^+$ $[M + Na]^+$ 425.0972, found 425.1207.

[3,5-Bis(acetyloxy)-2-(methoxycarbonyl)benzyl](phenyl)phosphonium bromide

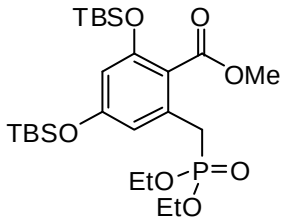


A solution of bromide **135** (113 mg, 0.328 mmol) and triphenyl phosphine (103 mg, 0.393 mmol) was heated to reflux in toluene (2.5 mL) for 12 h. The solution was cooled but the phosphorane ylid failed to precipitate out of solution. Many attempts were made to crystallise the product from toluene, toluene/THF, THF/hexanes, EtOH/hexanes, and EtOAc/hexanes. The product persistently oiled out of solution rather than crystallised.

Methyl 2-[(diethoxyphosphoryl)methyl]-4,6-dihydroxybenzoate (121)

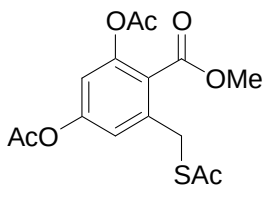


To a solution of phosphonate **142** (264 mg, 0.657 mmol) in MeOH (5 mL) was added K_2CO_3 (363 mg, 2.63 mmol) and stirred at rt for 4 h. The reaction mixture was filtered and reduced. The residue was dissolved in EtOAc before acidifying to pH 1 with 10% $HCl_{(aq)}$. The organic layer was separated and the aqueous layer further extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give a colourless oil (172 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.41 (s, 1H), 6.50 (t, *J* = 2.5 Hz, 1H), 6.34 (t, *J* = 2.5 Hz, 1H), 4.07 – 3.93 (m, 4H), 3.92 (s, 3H), 3.68 (d, *J* = 23.1 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 171.3, 165.2, 165.1, 162.5, 162.4, 134.8, 134.8, 112.9, 112.9, 104.6, 104.6, 103.0, 103.0, 62.7, 62.7, 51.8, 34.3, 33.2, 16.3, 16.3. IR: 3131, 2988, 1656, 1621, 1589, 1439, 1324, 1265, 1205, 1167, 1024 cm^{-1}.



Methyl 2,4-bis(*tert*-butyldimethylsiloxy)-6-[(diethoxyphosphoryl)methyl]benzoate (228)

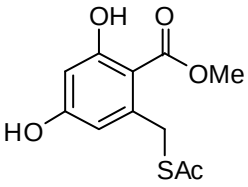
To a solution of phosphonate **227** (49 mg, 0.154 mmol) in DMF (1 mL) at 0 °C, was added TBSCl (58 mg, 0.385 mmol) and imidazole (42 mg, 0.616 mmol). The reaction was left to warm to rt whilst stirring for 12 h. The reaction was diluted with EtOAc (10 mL) before being washed with H_2O (10 mL) and sat. $NaHCO_{3(aq)}$ (3 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and reduced to give a colourless oil. The product was purified with flash column chromatography (silica, 2:1 hexanes/EtOAc) giving a colourless oil (68 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.23 (s, 1H), 4.05 – 3.95 (m, 4H), 3.84 (s, 3H), 3.25 (d, *J* = 22.3 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 18H), 0.20 (s, 12H), 0.19 (6s, H). ^{13}C NMR (125 MHz, cdcl3) δ 168.3, 157.2 (d, *J* = 3.5 Hz), 154.6 (d, *J* = 2.9 Hz), 132.4 (d, *J* = 9.0 Hz), 119.9 (d, *J* = 7.2 Hz), 115.9 (d, *J* = 5.5 Hz), 110.1 (d, *J* = 3.2 Hz), 62.1 (d, *J* = 6.8 Hz), 51.9, 31.3 (d, *J* = 137.5 Hz), 25.6, 25.5, 18.2, 18.1, 16.3 (d, *J* = 6.0 Hz), -4.4, -4.4.

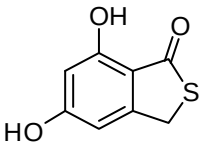


Methyl 2,4-bis(acetyloxy)-6-[(acetylthio)methyl]benzoate (171)

To a solution of the bromide **135** (148 mg, 0.43 mmol) at 0 °C in DMF (3 mL) was added KSAc (60 mg, 0.53 mmol). The reaction was allowed to warm to rt whilst stirring for 4 h. The reaction mix was diluted with

EtOAc (10 ml) and washed with sat. $NaHCO_{3(aq)}$ (3 x 10 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$, filtered and reduced to give a white solid. The white solid was purified by flash column chromatography (silica, 5:1 hexanes/EtOAc) giving a white solid (133 mg, 91%). mp 100 – 101 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 2.2 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 4.23 (s, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 194.9, 168.7, 168.4, 165.5, 152.1, 149.8, 149.8, 140.3, 122.6, 121.5, 116.1, 52.5, 31.4, 30.2, 21.1, 20.8. IR (film): 2954, 1772, 1727, 1692, 1611, 1282, 1189, 1135, 1032 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{16}O_7SNa^+$ $[M + Na]^+$ 363.0509, found 363.0460.



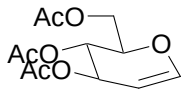


Methyl 2-[(acetylthio)methyl]-4,6-dihydroxybenzoate (230) and 5,7-dihydroxy-2-benzothiophen-1(3H)-one (231).

To a solution of thioacetate **171** (164 mg, 0.488 mmol) in MeOH (10 mL) at rt was added K_2CO_3 (4.5 mg, 33 μmol). The reaction was stirred at rt for 12 h before being filtered through a silica plug. The crude brown solid was purified by flash column chromatography (silica, gradient elution 10:1 to 5:1 hexanes/EtOAc) giving thiolactone **231** as a white solid (37 mg, 42%) and thioacetate **230** as a white solid (35 mg, 28%). **230**: mp 200 – 202 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.61 (s, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 4.35 (s, 2H), 3.94 (s, 3H), 2.32 (s, 3H). **231**: mp 204 – 206 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (brs, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 6.33 (d, *J* = 1.9 Hz, 1H), 4.36 (s, 2H).

8.3 Experimental for Chapter Three

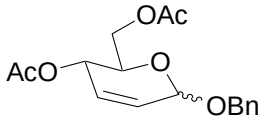
8.3.1 The HWE route



3,4,6-Tri-*O*-acetyl-D-glucal (147)[161,162]

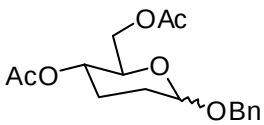
To a solution of D-glucose (0.125g, 0.694 mmol) in acetic anhydride (75 mL, 0.795 mol) was added perchloric acid (450 μL) dropwise while the temperature was kept at 40 °C. To the solution was added D-glucose (18.75 g, 104 mmol) in portions over 30 min before cooling to rt. To the cooled solution was added 45% HBr in AcOH (75 mL) and the reaction mixture was stirred for 90 min at rt. The reaction mixture was diluted with CH_2Cl_2 (175 mL) and washed with ice cold water (2 x 50 mL) and cold sat. $NaHCO_{3(aq)}$ until the solution was neutral. The organic layer was separated, dried over $MgSO_4$ and concentrated, giving 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (41.9 g, 0.102 mol).

Water (150 mL) was poured into a one litre three-necked round bottom flask and stirred with an overhead stirrer at 0 °C. Zinc powder (50 g, 0.765 mol) was added to the water followed by AcOH (150 mL). A solution of crude 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (41.9 g, 0.102 mol) in Et_2O (250 mL) was added dropwise over a period of 1 h. The reaction was allowed to warm to rt and stirred overnight (~14 h). The reaction mixture was filtered and the zinc dust was repeatedly washed with Et_2O. The aqueous layer was extracted with ether (6 x 50 mL). The combined organic fractions were washed with sat. $NaHCO_{3\,(aq)}$ solution until evolution of CO_2 ceased. The combined aqueous fractions were further extracted with ether (4 x 50 mL). The ether layers were again combined and washed with H_2O (2 x 100 mL) and brine (1 x 100 mL). These aqueous layers were extracted with ether (4 x 50 mL). Finally the ether solution was dried over $MgSO_4$ and concentrated under reduced pressure to give a white solid. The crude product was purified by recrystallising from Et_2O (25.6 g, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, *J* = 7.5 Hz, 1H), 5.32 (dd, *J* = 5.9, 3.0 Hz, 1H), 5.21 (dd, *J* = 7.5, 5.7 Hz, 1H), 4.83 (dd, *J* = 6.2, 3.2 Hz, 1H), 4.39 (dd, *J* = 11.8, 5.5 Hz, 1H), 4.28 – 4.13 (m, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H). Spectral data matched those reported in the literature.[226]



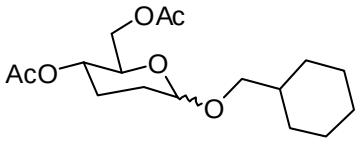
Benzyl 4,6-di-*O*-acetyl-2,3-deoxy-α-D-*erythro*-hex-2-enopyranoside (148)[86]

To a solution of 3,4,6-tri-*O*-acetyl-D-glucal (5.0 g, 18 mmol) and benzyl alcohol (1.9 mL, 18 mmol) in CH_2Cl_2 (100 mL) was added a 0.1 M solution of $FeCl_3$ in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt for 1 h before being quenched with sat. $NaHCO_{3(aq)}$ (50 mL). The layers were separated and aqueous layer was further extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (silica, 5:1 hexanes/EtOAc) giving title compound as a mixture of anomers (5.01 g, 85%, α/β = 9:1). $[\alpha]_D^{22}$ = +77.3 (*c* 1.00, $CHCl_3$) [lit.[86] +75.3 (*c* 1.04, MeOH)]. ^{1}H NMR (500 MHz, $CDCl_3$, α-anomer) δ 7.38 – 7.28 (m, 5H), 5.90 (d, *J* = 10.2 Hz, 1H), 5.85 (ddd, *J* = 10.2, 2.6, 1.8 Hz, 1H), 5.33 (ddd, *J* = 9.5, 3.1, 1.6 Hz, 1H), 5.14 (s, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.25 (dd, *J* = 11.8, 5.1 Hz, 1H), 4.18 – 4.10 (m, 2H), 2.10 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, $CHCl_3$) δ 170.8, 170.3, 137.6, 129.3, 128.5, 128.0, 127.9, 127.7, 93.6, 70.3, 67.1, 65.3, 62.9, 21.0, 20.8. IR (neat): 3033, 2906, 1742, 1455, 1370, 1227, 1100, 1037, 965, 911, 731 cm^{-1}. Spectral data matched those reported in the literature.[86]



Benzyl 4,6-di-*O*-acetyl-2,3-deoxy-α-D-*erythro*-hexopyranoside (235)

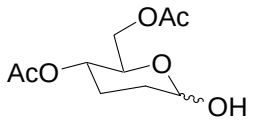
To a solution of benzyl glycoside **148** (100 mg, 0.31 mmol) in EtOH (4 mL) under an atmosphere of argon was added 10% Pd/C (10 mg). Into the reaction vessel was attached a balloon of $H_{2(g)}$ and the vessel briefly flushed with $H_{2(g)}$. The reaction was stirred at rt for 3 h. The solution was filtered through Celite® and reduced to give a colourless oil (73 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 4.96 (s, 1H), 4.77 (m, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.30 (dd, *J* = 12.0, 5.1 Hz, 1H), 4.10 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.99 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.01 – 1.83 (m, 3H), 1.72 (m, 1H).



Cyclohexylmethyl 4,6-di-*O*-acetyl-2,3-deoxy-α-D-*erythro*-hexopyranoside (237)

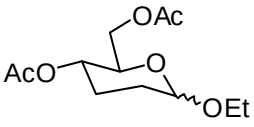
To a solution of benzyl glycoside **148** (30 mg, 0.13 mmol) in EtOH (1 mL) under an atmosphere of argon was added 10% PtO_2/C (3 mg). The reaction vessel was flushed with $H_{2(g)}$ before a attaching a balloon of $H_{2(g)}$ into the vessel. The reaction was stirred at rt for 3 h. The solution was filtered through Celite®

and reduced to give a colourless oil. The crude product was purified using flash column chromatography (silica, 2:1 hexanes/EtOAc) giving a colourless oil (18 mg, 59%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, *J* = 2.7 Hz, 1H), 3.81 (d, *J* = 4.1 Hz, 2H), 3.67 – 3.52 (m, 2H), 3.43 (dd, *J* = 9.5, 7.1 Hz, 1H), 3.17 (dd, *J* = 9.3, 5.9 Hz, 1H), 1.85 – 1.55 (m, 10H), 1.32 – 1.11 (m, 2H), 1.01 – 0.86 (m, 2H).



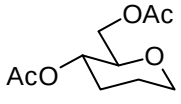
4,6-di-*O*-Acetyl-2,3-deoxy-α-D-*erythro*-hexose (122)

To a solution of benzyl glycoside **148** (550 mg, 1.72 mmol) in EtOH (10 mL) under an atmosphere of argon was added 10% $Pd(OH)_2/C$ (52 mg). The reaction vessel was briefly evacuated before attaching a balloon of $H_{2(g)}$ into the vessel. The reaction was stirred at rt for 3 h. The solution was filtered through Celite® and reduced to give a colourless oil. The crude product was purified using flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) giving the title compound as a white solid (284 mg, 71%), ethyl glycoside **237** as a colourless oil (22 mg, 5%) and tetrahydropyran **238** as a colourless oil (74 mg, 20%).**122:** mp 78 – 79 °C. $[\alpha]_D^{17}$ = +93.5 (*c* 1.05, $CHCl_3$). [lit.[70] +75.7 (*c* 0.7, CH_2Cl_2)]. ^{1}H NMR (300 MHz, $CDCl_3$, α-anomer) δ 5.32 (s, 1H), 4.80 – 4.64 (m, 1H), 4.26 – 4.10 (m, 3H), 2.56 (br s, 1H), 2.27 – 2.18 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.03 – 1.78 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, α-anomer) δ 171.0, 170.1, 90.6, 68.3, 67.8, 63.2, 28.7, 23.0, 20.9, 20.7. IR (neat): 2952, 2858, 1737, 1440, 1372, 1228, 1105, 1069, 1038, 915, 729 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{16}O_6Na^+$ $[M + Na]^+$ 255.0845, found 255.0840. Spectral data matched those reported in the literature.[70]



Methyl 4,6-di-*O*-acetyl-2,3-deoxy-α-D-*erytho*-hexopyranoside (237)

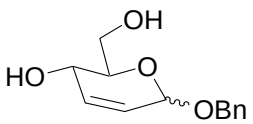
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (s, 1H), 4.73 (td, *J* = 10.1, 4.8 Hz, 1H), 4.25 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.08 (dd, *J* = 12.0, 2.2 Hz, 1H), 3.92 (ddd, *J* = 10.0, 5.2, 2.2 Hz, 1H), 3.71 (dq, *J* = 9.8, 7.1 Hz 1H), 3.47 (dq, *J* = 9.8, 7.1 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 – 1.94 (m, 1H), 1.89 – 1.78 (m, 3H), 1.22 (t, *J* = 7.1, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.0, 96.1, 68.5, 67.8, 63.2, 62.7, 28.8, 23.9, 21.1, 20.8, 15.0.



1-Anhydro-2,3-dideoxy-4,6-diacetate-D-erythro-hexopyranose (238)

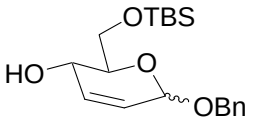
To a solution of benzyl glycoside **148** (105 mg, 0.33 mmol) in $CHCl_3$ (5 mL) under an atmosphere of argon was added 10% $Pd(OH)_2/C$ (10 mg). The reaction

vessel was briefly evacuated before attaching a balloon of $H_{2(g)}$ into the vessel. The reaction was stirred at rt for 2 h. The solution was filtered through Celite® and reduced to give a colourless oil. The crude product was purified using flash column chromatography (silica, gradient elution 5:1 to 2:1 hexanes/EtOAc) giving a colourless oil (50 mg, 86%). $[\alpha]_D^{17}$ = +38.2 (*c* 1.0, $CHCl_3$) [lit.[227] +37.5 (*c* 1.7, ethanol)] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (ddd, *J* = 10.7, 9.9, 4.8 Hz, 1H), 4.18 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.13 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.97 (ddt, *J* = 11.4, 4.4, 1.5 Hz, 1H), 3.46 (ddd, *J* = 9.7, 5.4, 2.4 Hz, 1H), 3.39 (td, *J* = 11.8, 2.6 Hz, 1H), 2.21 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.76 (tdd, *J* = 16.8, 8.5, 4.3 Hz, 1H), 1.68 (m, 1H), 1.45 (tdd, *J* = 12.9, 11.0, 4.5 Hz, 1H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 171,0 169.9, 77.5, 68.0, 67.9, 63.5, 29.2, 24.8, 21.1, 20.8.IR(neat): 2954, 2857, 1738, 1441, 1230, 1106, 1070, 1039 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{16}O_5Na^+$ $[M + Na]^+$ 239.0895, found 239.0898.



Benzyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranoside (149)[86]

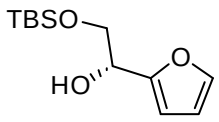
To a solution of benzyl glycoside **148** (3.28 g, 10.3 mmol) in MeOH (30 mL) at rt was added Na (15 mg, 64 μmol). The reaction was stirred at rt for 2 h. To the solution was added AcOH dropwise until the reaction was neutral. The solvent was removed yielding a colourless oil. The crude product was purified by flash column chromatography (silica, gradient elution 2:1 to 1:2 hexanes/EtOAc) to give a white solid (2.18 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 5.93 (d, *J* = 10.2 Hz, 1H), 5.75 (dt, *J* = 10.2, 2.3 Hz, 1H), 5.07 (s, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.18 (d, *J* = 8.9 Hz, 1H), 3.78 (d, *J* = 4.0 Hz, 2H), 3.72 (dd, *J* = 8.9, 4.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 133.6, 128.5, 128.1, 127.9, 126.0, 93.6, 71.5, 70.3, 64.0, 62.4. Spectral data matched those reported in the literature.[228]



Benzyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranoside (151)[86]

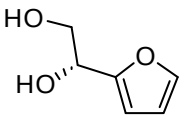
To a solution of diol **149** (2.18 g, 9.24 mmol) and imidazole (1.36 g, 20 mmol) in dry DMF (15 mL) at 0 °C was added a solution of TBSCl (1.67 g, 11.1 mmol) in DMF (5 mL). The reaction was warmed to rt and stirred for 12 h. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried with $MgSO_4$ and reduced to dryness. The crude oil was purified using flash column chromatography (silica, gradient elution 3:1 to 2:1 hexanes/EtOAc) to give a colourless oil (3.06 g, 95%). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.40 – 7.26 (m, 5H), 5.95 (dt, *J* = 10.2, 1.4 Hz, 1H), 5.76 (ddd, *J* = 10.2, 2.8, 2.3 Hz, 1H), 5.05 (dt, *J* = 2.6, 1.3 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.19 (m, 1H), 3.88 – 3.65 (m, 3H), 2.85 (brs, 1H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 133.0, 128.4, 127.9, 127.6, 125.8, 93.5, 70.2, 70.1, 67.0, 65.3, 25.9, 18.2, -5.5, -5.5. Spectral data matched those reported in the literature.[228]



***(1R)*-(2-Furyl)-2-*tert*-butyldimethylsilanyloxyethan-1-ol (254)**

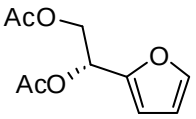
TBS ether **151** (503 mg, 1.43 mmol) was dissolved in $CDCl_3$ (5 mL) and left at rt for 48 h. The solvent was removed and the crude residue purified by flash column chromatography (silica, 5:1 hexanes/EtOAc) returning starting material (140 mg) and yielding a colourless oil (226 mg, 65% [93% based on recovered starting material]). $[\alpha]_D^{17}$ = +15.2 (*c* 1.0, $CHCl_3$) [lit.[229] +15.9 (*c* 1.37, CH_2Cl_2)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.31 (dt, *J* = 3.2, 0.9 Hz, 1H), 4.76 (dd, *J* = 7.0, 4.2 Hz, 1H), 3.86 (dd, *J* = 10.1, 4.2 Hz, 1H), 3.83 (dd, *J* = 10.1, 7.0 Hz, 1), 0.90 (s, 9), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 142.0, 110.2, 107.0, 68.4, 65.7, 25.8, 18.3, -5.4, -5.5. Spectral data matched those reported in the literature.[229] IR: 3436, 2929, 2858, 1256, 1148, 1119, 1007, 838, 778, 735. HRMS (ESI) calcd. for $C_{12}H_{22}O_3SiNa^+$ $[M + Na]^+$ 255.1236, found 239.1238.



(1*R*)-(2-Furyl)ethane-1,2-diol (255)

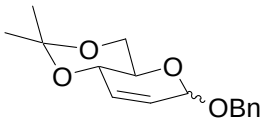
A. To a solution of diol **140** (195 mg, 0.823 mmol) in MeCN at 0 °C was added *p*-TsOH (1.6 mg, 82 μmol). The reaction mixture was warmed to rt for 3 h. The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica, 3:1 hexanes/EtOAc) yielding a colourless oil (70 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.33 (dt, *J* = 3.3, 0.7 Hz, 1H), 4.82 (t, *J* = 5.7 Hz, 1H), 3.88 (d, *J* = 5.7 Hz, 2H). Spectral data matched those reported in the literature.[229]

B. A solution of diol **140** (233 mg, 0.987 mmol) in $CDCl_3$ (5 mL) was stirred at rt for 4 days. The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica, gradient elution 3:1 to 1:3 hexanes/EtOAc) yielding a colourless oil (114 mg, 90%).



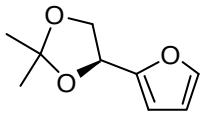
(1*R*)-(2-Furyl)ethane-1,2-diol diacetate (256)

To a solution of diol **255** (40 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) were added Ac_2O (118 μL, 1.25 mmol) and NEt_3 (261 μL, 1.88 mmol) and the mixture was stirred at rt for 72 h. The reaction was diluted with CH_2Cl_2 (5 mL) and washed with 10% $HCl_{(aq)}$ (5 mL) and sat. $NaHCO_{3(aq)}$ (2 x 5 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, 5:1 hexanes/EtOAc) to give a colourless oil (41 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 1H), 6.40 (dd, *J* = 3.3, 0.5 Hz, 1H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.10 (dd, *J* = 4.5, 7.7 Hz, 1H), 4.47 (dd, *J* = 11.8, 4.5 Hz, 1H), 4.43 (dd, *J* = 11.8, 7.7 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.0, 149.2, 143.0, 110.4, 109.6, 66.2, 63.3, 20.9, 20.7. Spectral data matched those reported in the literature.[230]



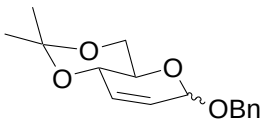
Attempted Synthesis of benzyl 2,3-dideoxy-4,6-*O*-(1-methylethylidene)-α-D-*erythro*-hex-2-enopyranoside (150)

To a solution of diol **149** (150 mg, 0.64 mmol) and 2,2-dimethoxypropane (156 μL, 1.27 mmol) in DMF (3 mL) was added *p*-TsOH (24 mg, 0.13 mmol). The reaction mixture was stirred at rt for 2 h before being heated to 60 °C for 12 h. The reaction was quenched with sat. $NaHCO_{3(aq)}$ and extracted with EtOAc (3 x 10 mL). The organic phase was washed with sat. $NH_4Cl_{(aq)}$ (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and reduced. The residue was purified by flash column chromatography (silica, gradient elution 5:1 to 1:1 hexanes/EtOAc) to return starting material (100 mg) and acetonide **255** (32 mg).



255

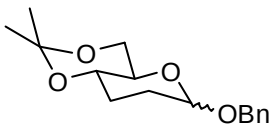
255: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 1H), 6.37 – 6.33 (m, 2H), 5.09 (dd, *J* = 7.4, 6.5 Hz, 1H), 4.22 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.10 (dd, *J* = 8.1, 7.7 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 151.6, 143.0, 110.3, 109.9, 108.4, 71.2, 67.8, 26.3, 25.9.



Benzyl 2,3-dideoxy-4,6-*O*-(1-methylethylidene)-α-D-*erythro*-hex-2-enopyranoside (150)

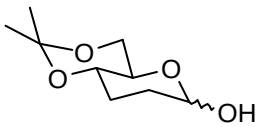
To a solution of diol **149** (255 mg, 1.08 mmol) and 2,2-dimethoxypropane (397 μL, 3.24 mmol) in DMF (3 mL) was added 4Å molecular sieves (1g) and a 0.158 M solution of *p*-TsOH in DMF (137 μL, 22 μmol). The reaction was heated for 12 h at 50 ˚C. The cooled reaction was quenched with water (10 mL) and organics were extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. $NaHCO_{3\ (aq)}$ (3 x 10 mL) and dried over $MgSO_4$ before filtering and

reducing to give a colourless oil. The crude product was purified by flash column chromatography (silica, 10:1 hexanes/EtOAc) yielding a white solid (258 mg, 87%). mp 110 – 112 °C. $[\alpha]_D^{22}$ = +46.8 (*c* 1.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 6.00 (d, *J* = 10.2 Hz, 1H), 5.71 (dt, *J* = 10.2, 2.5 Hz, 1H), 5.06 (dt, *J* = 2.5, 1.3 Hz, 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.20 (m, 1H), 3.84 – 3.72 (m, 3H), 1.51 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 131.7, 128.4, 127.9, 127.7, 126.5, 99.9, 94.3, 70.1, 67.7, 65.1, 63.0, 29.2, 19.0. IR (neat): 2995, 2913, 1494, 1455, 1376, 1267, 1199, 1100, 1045, 950, 862, 742, 720 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.44; H, 7.21.



Benzyl 2,3-dideoxy-4,6-*O*-(1-methylethylidene)-α-D-*erythro*-hexopyranoside (264)

To a solution of acetonide **150** (21 mg, 76 μmol) in 5% NEt_3 v/v EtOH (1 mL) was added $Pd(OH)_2/C$ (6.5 mg) and the flask was evacuated briefly. A H_2 balloon was attached into the sealed flask and the reaction stirred at rt for 12 h. The reaction mixture was filtered through Celite® and reduced to give a colourless oil. The crude product was purified by flash column chromatography (silica, 5:1 hexanes/EtOAc) to give a colourless oil (16 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.86 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 3.85 – 3.58 (m, 4H), 1.99 – 1.71 (m, 4H), 1.52 (s, 3H), 1.42 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 137.8, 128.4, 127.8, 127.7, 99.4, 95.9, 70.5, 68.7, 66.1, 62.9, 29.6, 29.3, 24.4, 19.2. IR (neat): 2995, 2933, 1456, 1382, 1201, 1093, 1045, 909, 732 cm^{-1}.

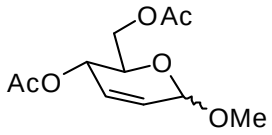


2,3-Dideoxy-4,6-*O*-(1-methylethylidene)-D-*erythro*-hexose (152)

To a solution of acetonide **150** (128 mg, 0.46 mmol) in EtOAc (7.5 mL) was added $Pd(OH)_2/C$ (14 mg) and the flask was evacuated briefly. A H_2 balloon was attached into the sealed flask and the reaction stirred at rt with monitoring by TLC. The reaction was completed after 12 h and was filtered through Celite® before reducing to give a pale brown solid. The crude product was purified by flash column chromatography (silica, gradient elution 5:1 to 2:1 hexanes/EtOAc) to give a white solid (69 mg, 79%). $[\alpha]_D^{22}$ = +55.0 (*c* 0.20, $CHCl_3$). ^{1}H NMR (500 MHz, CDCl3) δ 9.77 (d, *J* = 2.6 Hz, 0.1H), 5.22 (s, 1Hα), 4.84 (d, *J* = 4.0 Hz, 1Hβ), 3.87 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.83 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.79 – 3.73 (m, 3H), 3.68 (t, *J* = 10.6 Hz, 1H), 3.60 – 3.55 (m, 2H), 3.28 (td, *J* = 9.8, 5.3 Hz, 1H), 3.17 (s, 1H), 2.03 (m, 1H), 1.97 – 1.76 (m, 4H), 1.72 (m, 1H), 1.62 – 1.54 (m, 2H),

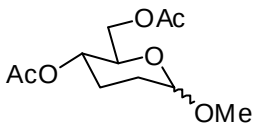
1.50 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 99.5, 99.5, 96.0, 91.3, 71.7, 70.6, 69.6, 65.9, 62.9, 62.5, 32.1, 29.6, 29.2, 29.2, 27.8, 23.6, 19.1, 19.1. IR: 3422, 2949, 2878, 1378, 1270, 1085, 1044, 970, 874 cm^{-1}. HRMS (ESI) calcd. for $C_9H_{16}O_4Na^+$ $[M + Na]^+$ 211.0946, found 211.0947.

8.3.2 The RB route



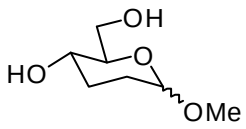
Methyl 4,6-di-*O*-acetyl-2,3-deoxy-α-D-*erythro*-hex-2-enopyranoside (172)[231]

To a solution of glucal **147** (2.00 g, 7.38 mmol) in CH_2Cl_2 (40 mL) and MeOH (0.360 mL, 8.86 mmol) at rt was added a 0.1 M solution $FeCl_3$ in CH_2Cl_2 (0.738 mL, 73.8 μmol) and the reaction stirred for 1 h. The reaction was quenched with the addition of sat. $NaHCO_{3\,(aq)}$ (40 mL) and stirred for 30 min at rt. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a pale brown oil. The crude product was purified via flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc), yielding a colourless oil (1.51 g, 84%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (d, *J* = 10.4 Hz, 1H), 5.86 – 5.79 (m, 1H), 5.32 (dd, *J* = 9.7, 1.3 Hz, 1H), 4.93 (s, 1H), 4.26 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.18 (dd, *J* = 12.1, 2.4 Hz, 1H), 4.08 (ddd, *J* = 9.6, 5.3, 2.4 Hz, 1H), 3.45 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H). Spectral data matched those reported in the literature.[231] HRMS (ESI) calcd. for $C_{11}H_{20}NO_6^+$ $[M + NH_4^+]$ 262.12851, found 262.12650.



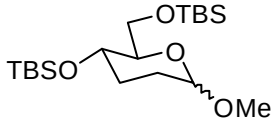
Methyl 4,6-di-*O*-acetyl-2,3-deoxy-α-D-*erythro*-hexopyranoside (173)[92]

To a solution of methyl glycoside **172** (1.51 g, 6.19 mmol) in EtOAc (40 mL) was added 10% Pd/C (150 mg). The flask was briefly evacuated before creation of a $H_{2(g)}$ atmosphere with the attachment of a balloon full of $H_{2(g)}$. The reaction was left stirring under the $H_{2(g)}$ atmosphere for 12 h. The mixture was filtered through Celite® and reduced giving a colourless oil (1.51 g, 99%) that was determined to be pure by the ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 – 4.67 (m, 2H), 4.26 (dd, *J* = 12.0, 5.3 Hz, 1H), 4.11 (dd, *J* = 12.0, 1.8 Hz, 1H), 3.90 (ddd, *J* = 9.5, 4.9, 1.8 Hz, 1H), 3.37 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.02 – 1.70 (m, 4H). Spectral data matched those reported in the literature.[232]



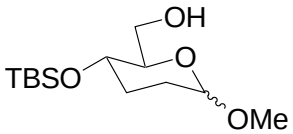
Methyl 2,3-deoxy-α-D-*erythro*-hexopyranoside (174)[92]

To a solution of diacetate **173** (6.17g, 25.1 mmol) in MeOH (125 mL) was added K_2CO_3 (231 mg, 1.67 mmol). The reaction was left to stir at rt for 3 h, after which it was filtered and reduced to dryness. The crude white solid was dissolved in 1:1 hexanes/EtOAc (20 mL) with 10 drops of AcOH and MeOH and purified by flash column chromatography (silica, gradient elution 1:1 hexanes/EtOAc to EtOAc) yielding a white solid (3.78, 93%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 1H), 3.83 (d, *J* = 3.9 Hz, 2H), 3.67-3.49 (m, 2H), 3.35 (s, 3H), 1.92-1.70 (m, 4H). Spectral data matched those reported in the literature.[233]



Methyl 4,6-di-*O*-bis(*tert*-butyldimethylsilyl)-2,3-deoxy-α-D-*erythro*-hexopyranoside (175)[92]

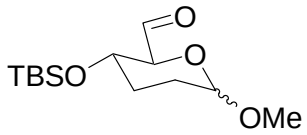
To a solution of diol **174** (3.78, 23.3 mmol) in DMF (45 mL) were added TBSCl (8.45 g, 55.9 mmol) and imidazole (3.17 g, 46.6) at 0 ˚C. The reaction was allowed to warm to rt as it stirred for 12 h. The reaction was diluted with EtOAc (100 mL), washed with water (100 mL), sat. $NaHCO_{3(aq)}$ (5 x 50 mL) and brine (50 mL) before drying over $MgSO_4$ and reducing to dryness. The crude oil was loaded neat on a silica column and eluted with 10:1 hexanes/EtOAc to afford a colourless oil (7.92 g, 87%). R_f = 0.79. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (d, *J* = 3.3 Hz, 1H), 3.88 (d, *J* = 10.9 Hz, 1H), 3.65 (dd, *J* = 11.3, 5.7 Hz, 1H), 3.55 – 3.43 (m, 2H), 3.35 (s, 3H), 1.84 – 1.72 (m, 3H), 1.72 – 1.65 (m, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.0, 74.5, 67.0, 63.3, 54.1, 29.1, 28.0, 26.0, 25.7, 18.4, 17.9, -4.1, -4.9, -5.1, -5.3. Spectral data matched those reported in the literature.[234]



Methyl 4-*O*-(*tert*-butyldimethylsilyl)-2,3-deoxy-α-D-*erythro*-hexopyranoside (176)[92]

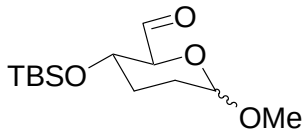
To a solution of bis-TBS ether **175** (7.92 g, 20.2 mmol) in 1:1 MeOH/CH_2Cl_2 (200 ml) at 0 ˚C was added (±)-CSA (469 mg, 2.02 mmol). The reaction was stirred at 0 ˚C for 2.5 h. The reaction was quenched with the addition of NEt_3 (280 μL, 2.02 mmol) and the solvent removed. The crude product was purified using flash column chromatography (silica, gradient elution 10:1 to 1:1 hexanes/EtOAc) returning starting material (477 mg) and yielding a colourless oil (5.01 g, 96% recovered). R_f = 0.42. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, *J* = 2.7 Hz, 1H), 3.78 (d, *J* = 11.1 Hz, 1H), 3.66 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.61 – 3.46 (m, 2H), 3.34 (s, 3H), 1.99 (s, 1H), 1.95 –

1.48 (m, 4H), 0.86 (s, 9H), 0.06 (s, 6H). Spectral data matched those reported in the literature.[92]



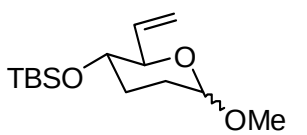
Methyl 4-*O*-(*tert*-butyldimethylsilyl)-2,3-deoxy-α-D-hexodialdo-1,5-pyranoside (177)

To a solution of the alcohol **176** (34 mg, 0.123 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added TEMPO (2.0 mg, 12.3 μmol) and BAIB (46 mg, 0.142 mmol). The reaction was left to warm to rt and stirred for 12 h. The reaction was quenched with the addition of sat. $Na_2S_2O_{3\ (aq)}$ (2.5 mL) and extracted with CH_2Cl_2 (3 x 2.5 mL). The combined organic fractions were washed with $NaHCO_{3\ (aq)}$ (10 mL), dried over $MgSO_4$, filtered and reduced to give a pale orange oil (31 mg). The ^{1}H NMR of the crude product indicated there was a 1:1 ratio of starting material to product (15.5 mg, 46%).



Methyl 4-*O*-(*tert*-butyldimethylsilyl)-2,3-deoxy-α-D-hexodialdo-1,5-pyranoside (177)[92]

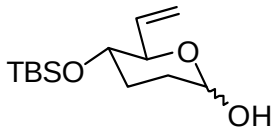
To a solution of oxalyl chloride (0.47 mL, 5.4 mmol) in CH_2Cl_2 (7.5 mL) was added DMSO (0.52 mL, 7.3 mmol) at -78 ˚C under an argon atmosphere. After stirring for 15 min, a solution of alcohol **176** (1.00 g, 3.62 mmol) in CH_2Cl_2 (2 mL) was added at -78 ˚C and the mixture stirred for 1 h. After this time Et_3N (2.5 mL, 18 mmol) was added at -78 ˚C and the mixture was stirred at rt for 1 h. The reaction was quenched with $NaHSO_{3\ (aq)}$ (20 mL) and washed with $NaHCO_{3\ (aq)}$ (2 x 20 mL). The organics were dried over $MgSO_4$, filtered and reduced to give an orange oil. The oil was purified by flash column chromatography (silica, 5:1 hexanes/EtOAc) give a colourless oil (685 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 5.30 (s, 1H), 4.76 (d, *J* = 2.3 Hz, 1H), 4.11 (d, *J* = 9.7 Hz, 1H), 3.75 (ddd, *J* = 10.5, 9.8, 4.8 Hz, 1H), 3.35 (s, 3H), 1.93 (m, 1H), 1.87 – 1.80 (m, 2H), 1.72 (tdd, *J* = 13.7, 4.6, 3.5 Hz, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 97.5, 77.3, 67.8, 55.0, 28.4, 28.4, 25.6, 17.9, -4.0, -5.0.



Methyl 4-*O*-(*tert*-butyldimethylsilyl)-2,3-deoxy-α-D-*erythro*-hept-6-enose (178)[93]

To a suspension of the $Ph_3P^+CH_3Br^-$ (820 mg, 2.23 mmol) in THF (10 mL) at -78 ˚C was added dropwise a 1.6M solution of *n*-BuLi in hexanes (1.44 mL, 2.23 mmol). To the resulting yellow solution was added aldehyde **177** (574 mg,

2.09 mmol) dissolved in THF (10 mL). The reaction was allowed to warm to rt slowly whilst stirring for 2 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (20 mL) and extracted with EtOAc (3 x 20 mL). The crude product was purified via flash column chromatography (silica, gradient elution 10:1 to 5:1 hexanes/EtOAc), yielding a colourless oil (405 mg, 72%). R_f = 0.67. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.3, 10.6, 6.3 Hz, 1H), 5.33 (ddd, *J* = 17.3, 2.0, 1.4 Hz, 1H), 5.19 (ddd, *J* = 10.5, 2.0, 1.4 Hz, 1H), 4.68 (d, *J* = 3.1 Hz, 1H), 3.91 (dd, *J* = 9.1, 6.3 Hz, 1H), 3.35 (m, 1H), 3.34 (s, 3H), 1.89 – 1.71 (m, 4H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 136.7, 116.8, 97.3, 74.1, 70.9, 54.4, 29.2, 28.2, 25.8, 18.0, -4.2, -4.6. Spectral data matched those reported in the literature.[235]



Attempted synthesis of 4-*O*-(*tert*-Butyldimethylsilyl)-2,3-deoxy-D-*erythro*-hept-6-enose (179)

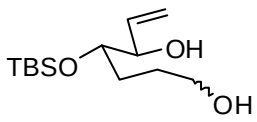
A. A solution of methyl glycoside **178** (103 mg, 0.38 mmol) in THF (5 mL) and 6% $HCl_{(aq)}$ (1.25 mL) was stirred for 18 h. The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic fraction were dried over $MgSO_4$, filtered and reduced. The crude residue contained a complex mixture of products as visualised by TLC and ^{1}H NMR spectroscopy.

B. To a solution of methyl glycoside **178** (118 mg, 0.432 mmol) in 1,4-dioxane (3 mL) was added 10% HCl (1 mL). The reaction was stirred at rt for 30 min before refluxing for 2 h. The cooled reaction was extracted with EtOAc (3 x 10 mL). The combined organic fraction were dried over $MgSO_4$, filtered and reduced. The purification of the crude product was attempted by flash column chromatography (silica, eluent gradient 3:1 to 1:2 hexanes/EtOAc). No compounds from the reaction were isolated in suitable quantity and purity to be characterised by standard NMR techniques.

C. To a solution of methyl glycoside **178** (103 mg, 0.38 mmol) in 1,4-dioxane (3 mL) was added 50% AcOH (2 mL). The reaction was heated to 50 °C for 2h. The cooled reaction was extracted with EtOAc (3 x 10 mL). The combined organic fraction were dried over $MgSO_4$, filtered and reduced. The crude residue contained a complex mixture of products as visualised by TLC and ^{1}H NMR spectroscopy.

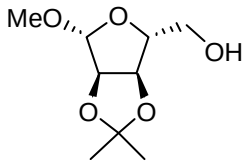
D. To a solution of methyl glycoside **178** (127 mg, 0.468 mmol) in 1,4-dioxane (3 mL) was added 10% HCl (1 mL). The reaction was heated to 50 °C for 2h. The cooled reaction was extracted with EtOAc (3 x 10 mL). The combined organic fraction were dried over $MgSO_4$, filtered and reduced. The crude residue contained a complex mixture of products as visualised by TLC and ^{1}H NMR spectroscopy.

Reduction of the crude residue from hydrolysis attempt *C* (above).



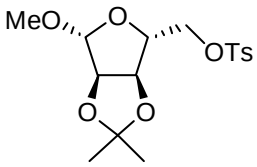
To a solution of the crude product **179** (attempt C) (44 mg, ~0.306 mmol) in MeOH (1 mL) at 0 °C was added $NaBH_4$ (23 mg, 0.612 mmol). Stirred at rt for 12 h. The reaction was quenched with the addition of water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue contained a complex mixture of products as visualised by TLC and ^{1}H NMR spectroscopy.

Methyl 2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (182)[98]



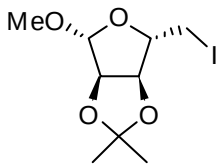
A solution of D-ribose (**85**) (25 g, 167 mmol) in Me_2CO (95 mL), MeOH (95 mL) and conc. HCl (2.5 mL) was heated under reflux for 8 h. The reaction was poured into 200 mL of water and the organic solvents were removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$, filtered and reduced, giving the title compound as a colourless oil (18.7 g, 55%), which was immediately reacted on without further purification. R_f = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.84 (d, *J* = 5.9 Hz, 1H), 4.59 (d, *J* = 5.9 Hz, 1H), 4.44 (t, *J* = 2.6 Hz, 1H), 3.70 (dt, *J* = 12.6, 2.4 Hz, 1H), 3.62 (ddd, *J* = 12.6, 10.7, 3.4 Hz, 1H), 3.44 (s, 3H), 3.23 (dd, *J* = 10.7, 2.6 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H). Spectral data matched those reported in the literature.[236]

The aqueous layer was reduced to half its volume and extracted again with Et_2O (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and reduced giving methyl-β-D-ribofuranoside as a pale brown oil (1.88 g, 7%). The aqueous layer was finally reduced to dryness returning the unreacted D-ribose (8.1 g, 32%).



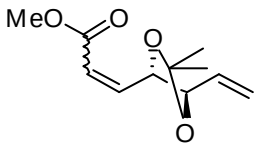
Methyl 5-(4-methylbenzenesulfonate)-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (183)[98]

Crude methyl 2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (18.7 g, 97 mmol) was dissolved in dry pyridine (40 mL) and cooled to 0 °C. To this was added tosyl chloride (23.2 g, 122 mmol) and the reaction was allowed to warm to rt as it stirred for 15 h. The reaction mixture was cooled to 0 °C and was quenched by the addition of H_2O (100 mL), then extracted with Et_2O (2 x 100 mL). The organic layer was washed with 5% H_2SO_4 (2 x 50 mL), 0.2 M KOH (3 x 50 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed under reduced pressure. The crude solid was recrystallised from EtOH, yielding a white solid, collected over three crops (29.2 g, 84%). mp 80 – 81 °C (lit.[237] mp 80 – 84). R_f = 0.67. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.93 (s, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.53 (d, *J* = 5.9 Hz, 1H), 4.31 (t, *J* = 7.5 Hz, 1H), 4.01 (dd, *J* = 7.2, 1.5 Hz, 2H), 3.23 (s, 3H), 2.45 (s, 3H), 1.44 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 132.7, 129.9, 128.0, 112.7, 109.4, 84.8, 83.5, 81.3, 69.1, 55.0, 26.3, 24.8, 21.6. Spectral data matched those reported in the literature.[238]



Methyl 5-deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (184)[98]

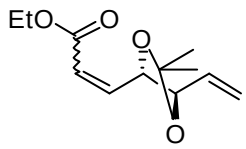
To a solution of tosylate **183** (21.9 g, 61.2 mmol) in methyl ethyl ketone (200 mL) was added NaI (18.4 g, 122 mmol). The reaction was refluxed for 24 h before it was cooled to rt and the solvent removed. The crude yellow oil was dissolved in EtOAc and washed with H_2O (2 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and reduced to give the iodide as a yellow oil (19.0 g, 99%). R_f = 0.67. The ^{1}H NMR spectrum of the crude product confirmed its purity and it was used without further purification. $[\alpha]_D^{22}$ = -68.3 (*c* 1.00, $CHCl_3$) [lit.[98] -69.7 (*c* 2.55, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 4.44 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.37 (s, 3H), 3.29 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.16 (t, *J* = 10.0 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H). Spectral data matched those reported in the literature.[239]



Methyl (2*Z*,4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hepta-2,6-dienoate [(*Z*)-186] and Methyl (2*E*,4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hepta-2,6-dienoate [(*E*)-186]

To iodide **184** (2.05 g, 6.52 mmol) in MeOH (30 mL) was added activated zinc (3.00 g, 45.9 mmol) and AcOH (100 μL) before the mixture was refluxed for 4 h. After this time another portion of zinc (1.50 g, 23.0 mmol) was added and the reaction refluxed for a further 4 h. Once TLC had confirmed the consumption of starting material, the reaction mixture was cooled and filtered through a wad of silica to remove the excess zinc and zinc salts.

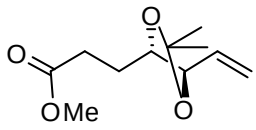
The filtrate was cooled to 0 °C and methyl (triphenylphosphoranylidene)acetate (2.62 g, 7.83 mmol) was added to the solution. The reaction was left to warm up over 12 h. The solvent was removed and the crude product partitioned between EtOAc (100 mL) and $NH_4Cl_{(aq)}$ (100 mL). The aqueous layer was extracted a further with EtOAc (2 x 50 mL). The combined organic fractions where dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting pale yellow oil was purified using flash column chromatography (silica,10:1 hexanes/EtOAc), yielding the α,β-unsaturated ester **186** as a colourless oil [1.06 g, 74% (*E*/*Z* = 1:4.7)]. R_f (*E*/*Z*) = 0.59/0.51. A portion was subjected to careful flash column chromatography for the purposes of characterization to yield separated samples of (*Z*)-**186** and (*E*)- **186**. [(*Z*)-**186**]: $[\alpha]_D^{22}$ = +216.8 (*c* 1.00, $CHCl_3$). R_f = 0.59. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 11.6, 7.5 Hz, 1H), 5.90 (dd, *J* = 11.6, 1.6 Hz, 1H), 5.68 (td, *J* = 7.3, 1.5 Hz, 1H), 5.66 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.28 (ddd, *J* = 17.1, 1.7, 1.3 Hz, 1H), 5.15 (ddd, *J* = 10.3, 7.2, 1.1 Hz, 1H), 4.87 (tt, *J* = 7.1, 0.9 Hz, 1H), 3.72 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 146.8, 134.0, 121.0, 117.9, 109.2, 79.7, 75.6, 51.5, 27.7, 25.1. IR (KBr): 2985, 2945, 1722, 1648, 1439, 1406, 1381, 1224, 1198, 1179, 1046, 1001, 927, 876, 825 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{16}O_4Na^+$ $[M + Na]^+$ 235.0946, found 235.0942. [(*E*)-**186**]: R_f = 0.51. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 15.6 5.5 Hz, 1H), 6.08 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.69 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.37 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.27 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.78 (ddd, *J* = 7.0, 5.6, 1.6 Hz, 1H), 4.71 (tt, *J* = 7.0, 0.9 Hz, 1H), 3.75 (s, 3H), 1.56 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 143.9, 133.4, 122.2, 119.3, 109.6, 79.8, 77.5, 51.7, 27.7, 25.4.



Ethyl (2Z)-3-[(4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]acrylate (266)

To iodide **184** (1.05 g, 3.34 mmol) in EtOH (15 mL) was added activated zinc (1.60 g, 24.4 mmol) and the mixture was refluxed for 4 h. After this time another portion of Zinc (0.80 g, 12.2 mmol) was added and the reaction refluxed for a further 4 h. Once TLC had confirmed the consumption of starting material, the reaction mixture was cooled and filtered through a wad of silica to remove the excess zinc and zinc salts.

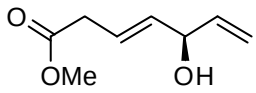
To the cooled filtrate (0 °C) was added phosphonate (803 μL, 4.01 mmol) and a solution of freshly prepared NaOEt (547 mg, 8.02 mmol) in EtOH (2 mL). The reaction was left warm to rt while stirring for 12 h. The organic solvent was removed and the crude residue partitioned between EtOAc (50 mL) and sat. $NH_4Cl_{(aq)}$ (50 mL). The aqueous layer was extracted a further with EtOAc (2 x 25 mL). The pale orange oil was purified using flash column chromatography (silica, 10:1 hexanes/EtOAc) yielding the α,β-unsaturated ester as a colourless oil (462 mg, 65% (E/Z = 10:1)). (***E***): R_f = 0.63. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (dd, *J* = 11.6, 7.5 Hz, 1H), 5.89 (dd, *J* = 11.6, 1.6 Hz, 1H), 5.69 (td, *J* = 7.3, 1.6 Hz, 1H), 5.66 (dd, *J* = 16.8, 10.4, 7.1 Hz, 1H), 5.28 (ddd, *J* = 17.0, 1.7, 1.2 Hz, 1H), 5.16 (ddd, *J* = 10.3, 1.7, 1.1 Hz, 1H), 4.87 (tt, *J* = 7.1, 1.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.55 (s, 3H), 1.42 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). (***Z***): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.12 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.83 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.41 (dt, *J* = 17.1, 1.1 Hz, 1H), 5.32 (ddd, *J* = 10.3, 1.3, 0.9 Hz, 1H), 4.25 (ddd, *J* = 7.8, 5.0, 1.0 Hz, 1H) 4.21 (q, *J* = 7.1 Hz, 2H), 4.14 (m, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).



Methyl (4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hept-6-enoate (267)

To a solution of α,β-unsaturated ester **186** (519 mg, 2.45 mmol), CuCl (186 mg, 1.88 mmol) and cyclohexene (960 μL, 9.43 mmol) in MeOH (40 mL) at -78 °C was added $NaBH_4$ (446 mg, 11.8 mmol). The reaction was left at -78 °C for 1 h, during which time it turned from green to brown. While still cold, the solvent was removed on the rotavap. The products were partitioned between sat. $NH_4Cl_{(aq)}$ (50 mL) and Et_2O (50 mL). The organic phase was separated and the aqueous layer was extracted with more Et_2O (4 x 20 mL). The organic layers were combined, dried with MgSO4, filtered and reduced to give a colourless oil (520 mg, 96%). The product was

deemed sufficiently pure by ^{1}H NMR for use without further purification. R_f = 0.46. $[\alpha]_D^{22}$ = -31.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 1H), 5.34 (ddd, *J* = 17.1, 1.7, 1.1 Hz, 1H), 5.26 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.54 (dd, *J* = 7.5, 6.4 Hz, 1H), 4.16 (ddd, *J* = 8.8, 6.2, 5.4 Hz, 1H), 3.67 (s, 3H), 2.49 (ddd, *J* = 16.3, 8.3, 6.4 Hz, 1H), 2.40 (ddd, *J* = 16.4, 8.5, 7.4 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 133.7, 118.6, 108.4, 79.5, 77.2, 51.7, 30.7, 28.2, 26.2, 25.7. IR (KBr): 2987, 2935, 1736, 1645, 1440, 1371, 1255, 1217, 1162, 1067, 1011, 931, 871 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{18}O_4Na^+$ $[M + Na]^+$ 237.1103, found 237.1100.



Attempted reduction of the α,β-unsaturated ester 186 with Mg/MeOH yielding methyl (3*E*,5*R*)-5-hydroxyhepta-3,6-dienoate (269)[105]

To a solution of α,β-unsaturated ester **186** (44 mg, 0.206 mmol) in MeOH (8 mL) was added Mg turnings (50 mg, 2.06 mmol). After ~15 min of stirring the reaction mixture began to evolve gas and over 4 h a white emulsion formed. The reaction was quenched with the addition of water (10 mL). The organics were extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The crude oil was purified by flash column chromatography (silica, 3:1 hexanes/EtOAc) to give heptadienoate **269** as a colourless oil (18 mg, 56%). R_f = 0.26. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.7, 7.4 Hz, 1H), 5.93 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.89 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.29 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.18 (dt, *J* = 10.4, 1.0 Hz, 1H), 4.29 (dd, *J* = 12.1, 6.2 Hz, 1H), 3.74 (s, 3H), 2.52 – 2.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 144.5, 139.6, 123.6, 115.6, 71.6, 51.6, 39.8.

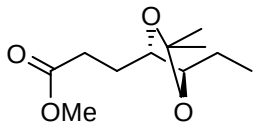
Attempted reduction of the α,β-unsaturated ester 186 with LAH

To a suspension of LAH (27 mg, 0.701 mmol) in Et_2O (5 mL) cooled to -78 °C was added α,β-unsaturated **186** (50 mg, 0.234 mmol) in Et_2O (2 mL). The reaction was stirred at -78 °C for 1.5 h before slowly warming to rt over 1.5 h. The reaction was quenched with wet Na_2SO_4. The aluminium salts were filtered through Celite®, washing the solid with Et_2O. The filtrate was reduced to give a colourless oil which was purified by flash column chromatography (silica, 5:1 hexanes:EtOAc) yielding saturated ester **267** (7 mg, 14%) and an inseparable mixture of alcohols **270** (major) and **187** (minor) (~4.5:1, 28 mg, 63%). **267**: R_f = 0.56. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.1, 10.2, 7.7 Hz, 1H), 5.34 (dd, *J* = 17.2, 2.7 Hz, 1H), 5.27 (dd, *J* = 10.3, 2.5 Hz, 1H),

4.54 (t, *J* = 7.3 Hz, 1H), 4.15 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.68 (s, 3H), 2.58 – 2.24 (m, 2H), 1.74 (dd, *J* = 14.5, 8.1 Hz, 2H), 1.47 (s, 3H), 1.36 (s, 3H). **270**: R_f = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 – 5.80 (m, 3H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.63 (m, 2H), 4.17 (d, *J* = 5.1 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H).

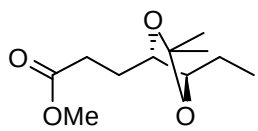
Attempted reduction of the α,β-unsaturated ester 186 with $NaBH_4$

To a solution of α,β-unsaturated ester **186** (20 mg, 93 μmol) in MeOH (1 mL) at 0 °C was added $NaBH_4$ (18 mg, 0.467 mmol). The reaction was left to warm to rt with stirring over 3 h. The reaction was quenched with the addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give a colourless oil (19 mg). ^{1}H NMR spectroscopy confirmed that starting material was recovered.



Attempted reduction of the α,β-unsaturated ester 186 with $NiCl_2/NaBH_4$ that yielded methyl 3-[(4S,5R)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate (271)[106]

A solution of α,β-unsaturated ester **186** (55 mg, 0.257 mmol) and $NiCl_2.6H_2O$ (30.5 mg, 0.129) in MeOH (4 mL) was cooled down to -40 °C. To this solution was added $NaBH_4$ (49 mg, 1.29 mmol) in portions over 10 min. The solution slowly turned black. The reaction was stirred at -40 °C for a further 30 min before filtering the cold solution through Celite®. The filtrate was reduced to dryness before redissolving in CH_2Cl_2 (10 mL) and washing with sat. $NaHCO_{3(aq)}$ (20 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give propanoate **271** a colourless oil (46 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (m, 2H), 3.67 (s, 3H), 2.54 (ddd, *J* = 16.4, 8.5, 7.0 Hz, 1H), 2.40 (ddd, *J* = 16.6, 8.4, 7.4 Hz, 1H), 1.73 (dd, *J* = 13.9, 7.4 Hz, 2H), 1.58 (dt, *J* = 13.7, 7.2 Hz, 1H), 1.48 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 107.6, 79.3, 76.8, 51.6, 30.6, 28.6, 26.0, 25.3, 22.5, 10.8. HRMS (ESI) calcd. for $C_{11}H_{20}O_4Na^+$ $[M + Na]^+$ 239.1259, found 239.1260.



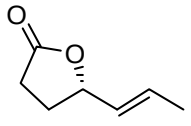
Attempted reduction of the α,β-unsaturated ester 186 with $CoCl_2/NaBH_4$ yielding methyl 3-[(4S,5R)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate (271)[190]

A solution of α,β-unsaturated ester **186** (55 mg, 0.257 mmol) and $CoCl_2.6H_2O$ (12 mg, 51 μmol) in MeOH (4 mL) was stirred at rt for 15 min. To this solution was added

$NaBH_4$ (39 mg, 1.03 mmol). The reaction was stirred at rt for 30 min before quenching with water (5 mL) and extraction with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) to give a colourless oil (37 mg, 67%). H NMR (500 MHz, $CDCl_3$) δ 4.01 (m, 2H), 3.67 (s, 3H), 2.53 (ddd, J = 16.6, 8.6, 7.5 Hz, 1H), 2.40 (ddd, J = 16.6, 8.4, 7.2 Hz, 1H), 1.73 (dd, *J* = 14.7, 7.8 Hz, 2H), 1.58 (m, 1H), 1.47 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H). The 1H NMR data was a close match with that of the $NiCl_2$ reduction and the product was taken as being **271**.

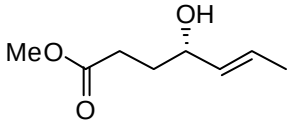
Attempted reductions of the α,β-unsaturated ester 186 with $CuCl_2/NaBH_4$[108]

A. To a solution of α,β-unsaturated ester **186** (50 mg, 0.234 mmol) in MeOH (4 mL) at 0 °C was added $CuCl_2$ (24 mg, 0.175 mmol). At this point, $NaBH_4$ (44 mg, 1.17 mmol) was added in portions over 5 min and the reaction allowed to warm to rt and stir 12 h. The reaction was quenched with the addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The crude product was purified using flash column chromatography (silica, 10:1 hexanes/EtOAc) returning **186** (9 mg, 38%) and affording an inseparable mixture of desire product **267** and compound **271** as a colourless oil (~2:1, 23 mg, 56%). R_f = 0.54. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.34 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.26 (ddd, *J* = 10.3,1.6, 0.9 Hz, 1H), 4.54 (dd, *J* = 7.4, 6.4 Hz, 1H), 4.15 (ddd, *J* = 8.8, 6.2, 5.5 Hz, 1H), 4.02 (ddt, *J* = 10.6, 8.5, 5.6 Hz, 1H, minor), 3.67 (s, 3H), 2.58 – 2.45 (m, 1H), 2.40 (dtd, *J* = 14.1, 7.9, 6.3 Hz, 1H), 1.78 – 1.71 (m, 2H), 1.62 – 1.54 (m, 0.5H, minor), 1.54 – 1.46 (m, 0.5H, minor), 1.47 (s, 3H), 1.43 (s, 1.5H, minor), 1.36 (s, 3H), 1.33 (s, 1.5H, minor), 1.00 (t, *J* = 7.4 Hz, 1.5H, minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (minor), 173.6, 133.7, 118.6, 108.4, 107.6, (minor) 79.5, 79.4 (minor), 77.2, 76.9 (minor), 51.6, 51.6 (minor), 30.7, 30.6 (minor), 28.6 (minor), 28.2, 26.2, 26.0 (minor), 25.7, 25.4 (minor), 22.6 (minor), 10.8 (minor).



γ-*trans*-1-Propenyl-γ-butyrolactone (272): Lactone **272** was also isolated (5 mg, 17%). R_f = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.52 (dddd, *J* = 15.3, 7.0, 3.1, 1.5 Hz, 1H), 4.89 (q, *J* = 7.2 Hz, 1H), 2.54 (m, 2H), 2.36 (dt, *J* = 13.6, 6.5 Hz, 1H), 1.98 (m, 1H), 1.78 – 1.72 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 130.1, 128.2, 80.7, 28.4, 28.4, 17.4. Spectral data matched those reported in the literature.[240]

B. To a solution of α,β-unsaturated ester **186** (88.5 mg, 0.411 mmol) in MeOH (5 mL) was added $NaBH_4$ (78 mg, 2.06 mmol) in portions over 5 min at 0 °C. To this was added $CuCl_2$ (41.5 mg, 0.308 mmol) slowly over 5 min. The reaction was warmed to rt and stirred for 1 h. The solvent was removed and the residue partitioned between NH_4Cl (aq) (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were combined dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) returning **186** (21 mg, 24%), a mixture of compounds **267** and **271** (~5.6:1, 47 mg, 53%), lactone **272** (5 mg, 10%) and alcohol **273** (2 mg, 3%).



Methyl (4*S*,5*E*)-4-hydroxyhept-5-enoate (273): R_f = 0.28. ^1H NMR (500 MHz, $CDCl_3$) δ 5.69 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.48 (dd, *J* = 15.3, 7.0 Hz, 1H), 4.10 (q, *J* = 6.3 Hz, 1H), 3.68 (s, 3H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.85 (dd, *J* = 13.5 , 7.2 Hz, 2H), 1.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.91, 130.52, 128.61, 81.10, 28.84, 28.82, 17.77.

C. To a solution of α,β-unsaturated ester **186** (60 mg, 0.280 mmol) in 3:1 MeOH/THF (4 mL) at 0 °C was added $CuCl_2$ (28 mg, 0.210 mmol). At this point, $NaBH_4$ (53 mg, 1.40 mmol) was added in portions over 5 min and the reaction allowed to warm to rt and stirred for 12 h. The reaction was quenched with the addition of sat. NH_4Cl (aq) (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The crude product was purified using flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) returning **186** (22 mg, 37%) and a mixture of compounds **267** and **271** (~5.2:1, 34 mg, 56%).

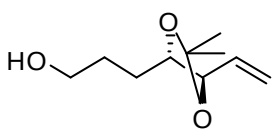
D. To a solution of α,β-unsaturated ester **186** (65.5 mg, 0.306) and $CuCl_2$ (41 mg, 0.306 mmol) in MeOH (5 mL) at -78 °C was added $NaBH_4$ (58 mg, 1.53 mmol) in portions over 10 min. The solution turned from pale green to brown and a black precipitate (ppt) began to form. The reaction was left at -78 °C for 15 min before warming to rt for 45 min. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 2:1 hexanes/EtOAc) returning **186** (16 mg, 24%), a

mixture of compounds **267** and **271** (~4.8:1, 19 mg, 29%) lactone **272** (4 mg, 10%) and alcohol **273** (5 mg, 10%).

Attempted reduction of the α,β-unsaturated ester 186 with CuCl/$NaBH_4$[108]

A. To a solution of α,β-unsaturated ester **186** (58 mg, 0.271 mmol) and CuCl (20 mg, 0.203 mmol) in MeOH (4 mL) at 0 °C was added $NaBH_4$ (51 mg, 1.35 mmol) over 10 min. A black ppt slowly formed over the course of the reaction. The reaction was warmed to rt and stirred for 4 h. The solvent was removed and the residue partitioned between NH_4Cl (aq) (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were combined dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 2:1 hexanes/EtOAc) returning **186** (27 mg, 47%) and affording a mixture of compounds **267** and **271** (~6.6:1, 22 mg, 38%).

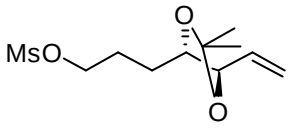
B. To the α,β-unsaturated ester **186** (70 mg, 0.330 mmol), CuCl (24.5 mg, 0.248 mmol), cyclohexene (124 μL, 1.32 mmol) in MeOH (5 mL) was added NaOMe (13 mg, 0.25 mmol). The solution went from green to brown. TLC showed new products forming. The reaction mixture was cooled down to -78 °C and $NaBH_4$ (62.4 mg, 1.65 mmol) and left to slowly warm to rt. The solvent was removed and the residue partitioned between sat. $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were combined dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 2:1 hexanes/EtOAc) returning **186** (9 mg, 13%) and affording a mixture of compounds **267** and **271** (~11.8:1, 54 mg, 38%).



(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)-hept-6-en-1-ol (187)

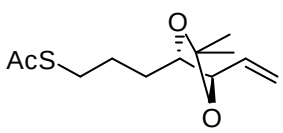
To suspension of LAH (115 mg, 3.03 mmol) in Et_2O (30 mL) at -10 °C was added methyl ester **267** (540 mg, 2.52 mmol) in Et_2O (15 mL). After 10 min, TLC analysis confirmed that all the starting material had been consumed. The reaction was quenched with wet Na_2SO_4, filtered through Celite® and reduced to dryness to yield alcohol **187** as a colourless oil (458 mg, 97%). R_f = 0.20. $[\alpha]_D^{22}$ = -6.1 (*c* 1.00, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.31 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.24 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H),

4.52 (dd, *J* = 7.4, 6.7 Hz, 1H), 4.18 (ddd, *J* = 8.5, 6.2, 5.0 Hz, 1H), 3.68 (t, *J* = 5.8 Hz, 2H), 1.91 (s, 1H), 1.75 – 1.65 (complex m, 2H), 1.55 (ddd, *J* = 16.1, 8.6, 4.5 Hz, 2H), 1.50 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 118.4, 108.3, 79.9, 78.2, 62.7, 29.8, 28.3, 27.5, 25.7. IR (KBr): 3435, 2934, 2874, 1644, 1429, 1380, 1248, 1217, 1165, 1047, 1018, 926, 872 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{18}O_3Na^+$ $[M + Na]^+$ 209.1154, found 209.1152.



(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)-hept-6-en-1-methanesulfonate (188)

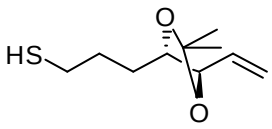
To solution of alcohol **187** (213 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added NEt_3 (320 μL, 2.30 mmol), DMAP (14 mg, 0.115 mmol), and MsCl (134 μL, 1.70 mmol). The reaction was left to warm to rt and stir for 12 h. After this time, the reaction was deemed complete by TLC (colour change from purple to black with anisaldyde dip). The solvent was removed and the crude product dissolved in EtOAc (20 mL), before being washed with water (10 mL) and sat. $NaHCO_3$ (10 mL). The organic layer was dried with $MgSO_4$, filtered and reduced to give a crude oil which was purified using flash column chromatography (silica, gradient elution 3:1 to 1:1 hexanes/EtOAc) yielding the title compound as a colourless oil (294 mg, 97%). R_f = 0.26. $[\alpha]_D^{22}$ = -14.3 (*c* 1.09, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.33 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.30 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.57 (dd, *J* = 7.5, 6.4 Hz, 1H), 4.30 (dt, *J* = 9.9, 6.3 Hz, 1H), 4.25 (ddd, *J* = 9.8, 7.0, 6.0 Hz, 1H), 4.19 (ddd, *J* = 9.0, 6.2, 4.7 Hz, 1H), 3.05 (s, 3H), 1.99 (tdd, *J* = 12.3, 9.2, 6.2 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.62 – 1.54 (complex m, 2H), 1.52 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 118.5, 108.3, 79.7, 77.7, 30.6, 29.6, 28.9, 28.2, 26.3, 25.6. IR (film): 2994, 2939, 1353, 1248, 1212, 1174, 926, 908, 733 cm^{-1}.



(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)-hept-6-en-1-thio acetate (189)

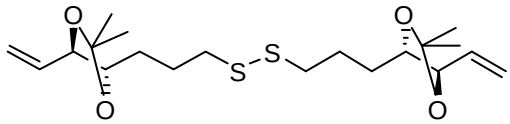
To a solution of the mesylate (1.59 g, 6.02 mmol) in DMF (50 mL) at 0° C was added KSAc (824 mg, 7.23 mmol). The reaction was left to warm and stir at rt for 12 h. The reaction was diluted with Et_2O (100 mL) and H_2O (100 mL). The organic layer was further washed with sat. $NaHCO_3$ (3 x 50 mL) before drying with $MgSO_4$, filtering and reducing to give a crude oil which was purified using flash column chromatography (silica, gradient elution 20:1 to 10:1 hexanes/EtOAc) yielding thioacetate **189** as a colourless oil (1.32 g, 90%). R_f = 0.56. $[\alpha]_D^{22}$ = -9.5 (*c* 1.05,

$CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.1, 9.7, 7.8 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.24 (d, *J* = 10.3 Hz, 1H), 4.49 (t, *J* = 6.9 Hz, 1H), 4.13 (dt, *J* = 8.6, 5.5 Hz, 1H), 2.95 – 2.83 (m, 2H), 2.32 (s, 3H), 1.80 – 1.68 (m, 1H), 1.66 – 1.50 (m, 2H), 1.49 – 1.41 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.8, 134.2, 118.5, 108.3, 79.7, 77.7, 30.6, 29.6, 28.9, 28.2, 26.3, 25.6. IR (film): 2986, 2916, 1692, 1455, 1428, 1379, 1369, 1244, 1216, 1134, 1134, 1048, 1012, 929, 871, 625 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{20}O_3SNa^+$ $[M + Na]^+$ 267.1031, found 267.1028.



Attempted synthesis of 3-[(4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]propane-1-thiol (169)

A. To a solution of thioactetate **189** (64 mg, 0.26 mmol) in MeOH (2.5 mL) was added MeONa (14 mg, 0.26 mmol). The reaction was stirred at rt for 12 h. Solvent was removed and the residue partitioned between 10% HCl (10 mL) and Et_2O (10 mL). The aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and reduced to give a colourless oil (46 mg, 87%). The colourless oil was determined to be disulfide **190** by mass spectrometric analysis.

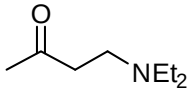


190: $[\alpha]_D^{22}$ = +5.2 (*c* 1.00, $CHCl_3$). R_f = 0.59. ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.31 (ddd, *J* = 17.1, 1.6, 1.0 Hz, 1H), 5.24 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.50 (dd, *J* = 7.7, 6.3 Hz, 1H), 4.14 (ddd, *J* = 9.0, 6.2, 4.6 Hz, 1H), 2.70 (m, 2H), 1.86 (m, 1H), 1.72 (m, 1H), 1.60 – 1.49 (m, 2H), 1.48 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 118.4, 108.2, 79.7, 77.8, 38.7, 29.2, 28.2, 25.8, 25.6. IR(neat): 2986, 2937, 1379, 1370, 1244, 1216, 1047, 914, 733 cm^{-1}. HRMS (ESI) calcd. for $C_{20}H_{34}O_4S_2Na^+$ $[M + Na]^+$ 425.1796, found 425.1790.

B. To a solution of thioactetate **189** (38 mg, 0.16 mmol) in THF (2 mL) was added 0.2 M NaOH (4 mL, 0.80 mmol). The reaction was stirred at rt for 12 h. The reaction was acidified to pH 1 with 10% HCl and extracted with EtOAc (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and reduced to give a colourless oil (28 mg, 89%). The ^1H NMR spectrum was identical to that of attempt **A**.

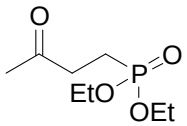
8.4 Experimental for Chapter Four

8.4.1 The HWE route



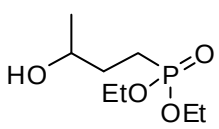
4-(Diethylamino)butan-2-one (143)[80]

A solution of acetone (12.7 mL, 174 mmol), paraformaldehyde (3.90 g, 130 mmol) and diethylamine hydrochloride (8.00 g, 74 mmol) was refluxed in isopropanol (20 mL) for 6 h. The mixture was cooled to rt and reduced in volume before a solution of 50% KOH $_{(aq)}$ was added to adjust the pH to 14. The organics were extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$ before filtering and reducing to give a dark orange oil. The crude product was purified by distillation (73 ˚C, 20 mmHg) yielding a pale orange liquid (4.78 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (t, *J* = 7.1 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.51 (q, *J* = 7.1 Hz, 4H), 2.17 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 6H).



Diethyl 3-oxobutylphosphonate (144)[82]

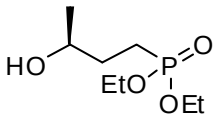
To amine **143** (4.25 g, 30.0 mmol) was added methyl iodide (2.00 mL, 32.1 mmol) and the mixture stirred for 10 min at rt. After this time triethyl phosphite (28.3 mL, 162 mmol) was added and the reaction mixture heated to 130 ˚C for 1 h. The reaction mixture was cooled to rt and the white precipitate was filtered. The solid was washed with Et_2O. The filtrate was concentrated under reduced pressure to yield a yellow liquid. The yellow phosphonate was purified by distillation (96–98 ˚C, 0.2 mmHg) followed by flash column chromatography (silica, 10% MeOH/CH_2Cl_2) to give a pale yellow oil (4.90 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (m, 4H), 2.69 (m, 2H), 2.21 (s, 3H), 2.02 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 6H). IR (neat): 2985, 2909, 1719, 1416, 1366, 1228, 1027, 964, 802, 787, 732 cm^{-1}. Spectral data matched those reported in the literature.[241]



Diethyl 3-hydroxybutanephosphonate [(±)-118]

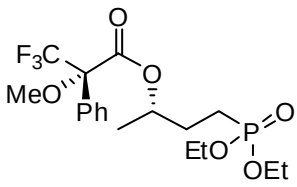
To a solution of phosphonate **144** (130 mg, 0.625 mmol) in EtOH (1 mL) at -10 °C was slowly added $NaBH_4$ (28 mg, 0.740 mmol) in portions to the reaction solution. The reaction was left to warm to rt and stirred for another 12 h. The reaction was quenched with H_2O (1 mL) and extracted with EtOAc (3 x 5 mL). The organic fractions were dried with $MgSO_4$, filtered and reduced to dryness

giving pale yellow oil. The crude oil was purified using flash column chromatography (silica, EtOAc) yielding a colourless oil (81 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (m, 4H), 3.81 (m, 1H), 2.01-1.61 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 6H), 1.15 (d, *J* = 6.1 Hz, 3H). Spectral data matched those reported in the literature.[83]



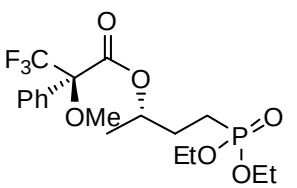
Diethyl (3*S*)-3-hydroxybutylphosphonate (118)

A solution of phosphonate **144** (97 mg, 0.47 mmol) in THF (1.6 mL) was added dropwise to a 1M THF solution of (*R*)-Me-CBS (100 µL, 0.100 mmol) and $BH_3.SMe_2$ (54 µL, 0.56 mmol) at 0 ˚C. The reaction mixture was stirred for 40 min at 0 ˚C before being quenched by the slow addition of MeOH (2 mL). The mixture was stirred for a further 20 min at rt and concentrated. The crude product was purified using flash column chromatography (silica, EtOAc) yielding a pale yellow oil (59 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (m, 4H), 3.82 (m, 1H), 1.92 – 1.53 (m, 5H), 1.29 (td, *J* = 0.9, 7.1 Hz, 6H), 1.17 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.4 (d, *J* = 14.3 Hz), 61.7 (t, *J* = 6.2 Hz), 31.6 (d, *J* = 4.9 Hz), 23.2, 22.5, 21.4, 16.4 (d, *J* = 6.2 Hz). Spectral data matched those reported in the literature.[83]



(*S*)-Mosher's ester of diethyl (3*S*)-3-hydroxybutylphosphonate [(*S*)-Mosher-118][242]

To a solution of DMAP (6.5 mg, 53 µmol) and phosphonate **118** (5.6 mg, 27 µmol) in CH_2Cl_2 (0.5 mL) was added (*R*)-MTPA-Cl (6.5 µL, 35 µmol). This was stirred at rt for 1 h before being quenched with Et_2O (1 mL) and H_2O (3 mL). This was then washed with 1 M HCl (5 mL), 1M NaOH (5 mL) and brine (5 mL) before drying with $MgSO_4$, filtering and reducing to give a colourless oil (6.4 mg, 56%). ^{1}H NMR analysis was undertaken without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H), 7.44 – 7.38 (m, 3H), 5.17 (qd, *J* = 6.1, 12.4 Hz, 1H), 4.15 – 4.00 (m, 4H), 3.56 (app.quin, *J* = 1.2 Hz, 0.8H), 3.53 (q, *J* = 1.2 Hz, 2.2H), 1.99 – 1.84 (m, 2H), 1.83 – 1.66 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.28 (d, *J* = 6.3 Hz, 3H).



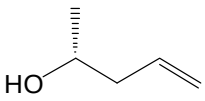
(*R*)-Mosher's ester of diethyl (3*S*)-3-hydroxybutylphosphonate [(*R*)-Mosher-118][242]

To a solution of DMAP (9.3 mg, 76 µL) and phosphonate **118** (8.0 mg, 38 µmol) in CH_2Cl_2 (0.5 mL) was added (*S*)-MTPA-Cl (9.3 µL, 50 µmol). This was stirred at rt for an hour before being quenched with Et_2O

(1 mL) and H_2O (3 mL). This was then washed with 1 M HCl (5 mL), 1M NaOH (5 mL) and brine (5 mL) before drying with $MgSO_4$, filtering and reducing to give a colourless oil (6.8 mg, 42%). ^{1}H NMR analysis was undertaken without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 2H), 7.46 – 7.36 (m, 3H), 5.17 (qd, *J* = 6.2, 12.4 Hz, 1H), 4.09 – 3.96 (m, 4H), 3.56 (q, *J* = 1.2 Hz, 2.6H), 3.53 (q, *J* = 1.2 Hz, 0.4H), 1.95 – 1.79 (m, 2H), 1.68 – 1.52 (m, 2H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.29 (td, *J* = 2.6, 7.1 Hz, 6H).

8.4.2 The RB route

Attempted syntheses of (*R*)-4-penten-2-ol (22)[242]



To a cooled (0 °C) solution of (+)-α-pinene (10 mL, 62.9 mmol) in anhydrous THF (8 mL) was added $BH_3.SMe_2$ (2.5 mL, 26.2 mmol) dropwise. After stirring for 15 min at 0 °C, the resulting mixture was cooled to -17 °C for 72 h, during which time a white precipitate formed. The suspension was warmed to rt and the supernatant removed using a syringe whilst maintaining an argon atmosphere. The white solid was washed with anhydrous Et_2O (3 x 20 mL) and the remaining solvent was removed under reduced pressure (0.2 mm Hg, 2 h) giving (-)-$(IPC)_2BH$ as a white solid (8.06 g, 90%). The white solid was resuspended in anhydrous Et_2O (22 mL) and cooled to 0 °C. Ice-cold MeOH (2.25 mL, 56.3 mmol) was slowly added to the reaction mixture over a period of 30 min. The reaction was warmed to rt and stirred for 1 h until no solid remained. The solvent was removed under reduced pressure (0.2 mmHg, 2 h) to give a colourless oil (7.11 g, 80%). The oil was redissolved in anhydrous Et_2O (18 ml) and cooled to -78 °C. To the cooled solution was added dropwise a 1.0M Et_2O solution of allylmagnesium bromide (22.5 mL, 22.5 mmol). After stirring for 1 h at -78 °C, the reaction was warmed to rt for 1 h. Over this time, white magnesium salts precipitated out of solution.

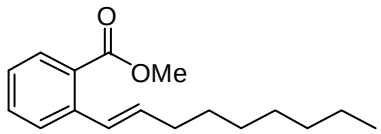
The reaction mixture was once more cooled to -78 °C and acetaldehyde (1.26 mL, 22.5 mmol) was added dropwise. The reaction was stirred at -78 °C for 1 h before warming to rt for 1 h. The reaction was quenched by a variety of reagents: addition of 1 M NaOH (15 mL) and 30% H_2O_2 (15 mL), H_2O (20 mL) or silica gel (20 g). Attempts to purify the title compound by distillation and/or column chromatography (silica, eluent gradient petane to 4:1 petane/Et_2O) failed to provide the pure alcohol.

8.5 Experimental for Chapter Five

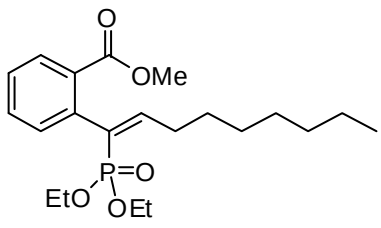
8.5.1 The HWE route

HWE reactions of phosphonates 210, 211, and 294 with octanal or butanal:

A. To a solution of phosphonate **210** (72 mg, 0.25 mmol) in THF (1 mL) at 0 °C was added a 1M solution of LiHMDS in THF (250 μL, 0.25 mmol) dropwise. Deprotonation was observed with the rapid formation of a bright orange solution. To this orange solution was added octanal (43 μL, 0.28 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) giving the alkene **291a** as a colourless oil (20 mg, 30%), phosphonate **210** (11 mg, 15%) and enephosphonate **293** (28 mg, 28%).



291a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.43 (td, *J* = 7.6, 1.4 Hz, 1H), 7.25 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.12 (d, *J* = 15.7 Hz, 1H), 6.14 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.90 (s, 3H), 2.25 (ddd, *J* = 14.8, 7.2, 1.5 Hz, 2H), 1.53 – 1.44 (m, 2H), 1.40 – 1.24 (m, 9H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 139.7, 134.2, 131.9, 130.2, 128.3, 128.1, 127.2, 126.4, 52.0, 33.2, 31.9, 29.3, 29.2, 29.2, 22.7, 14.1. IR (neat): 2928, 2850, 1723, 1434, 1254, 1121, 1078, 729 cm^{-1}.



293: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.48 (tdd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.39 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.12 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.72 (dt, *J* = 23.1, 7.3 Hz, 1H), 4.14 (p, *J* = 7.3 Hz, 2H), 4.09 – 3.97 (m, 2H), 1.99 – 1.82 (m, 2H), 1.43 – 1.26 (m, 2H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H), 1.23 – 1.17 (m, 8H), 0.82 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 148.5 (d, *J* = 8.1 Hz), 134.9 (d, *J* = 10.4 Hz), 132.1 (d, *J* = 4.6 Hz), 131.2 (d, *J* = 49.2 Hz), 131.3, 130.6 (d, *J* = 4.6 Hz), 128.8 (d, *J* = 2.3 Hz), 127.9, 62.7 (d, *J* = 6.3 Hz), 62.5 (d, *J* = 6.0), 31.6, 29.9 (d, *J* = 17.7 Hz), 29.2, 28.9, 28.2 (d, *J* = 1.4 Hz), 22.5, 16.2 (d, *J* = 4.4 Hz), 16.1 (d, *J* = 4.3 Hz), 14.0.

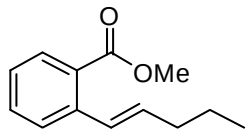
B. To a solution of phosphonate **210** (103 mg, 0.360 mmol) in Et_2O (2 mL) at -78 °C was added a 1M solution of LiHMDS in THF (360 μL, 0.36 mmol) dropwise. To this orange solution was added octanal (62 μL, 0.396 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with EtOAC (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) giving the alkene **291a** as a colourless oil (6 mg, 7%) and enephosphonate **293** (78 mg, 55%).

C. To a solution of phosphonate **210** (105 mg, 0.367 mmol) in THF (2 mL) at -78 °C was added a 1M solution of LiHMDS in THF (370 μL, 0.37 mmol) dropwise. To this orange solution was added octanal (63 μL, 0.404 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with EtOAC (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) affording enephosphonate **293** as pale yellow solid (100 mg, 69%).

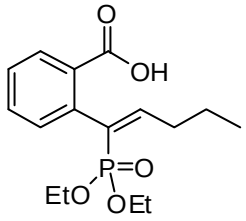
D. To a solution of phosphonate **210** (103 mg, 0.360 mmol) in toluene (2 mL) at -78 °C was added a 1M solution of LiHMDS in THF (360 μL, 0.36 mmol) dropwise. To this orange solution was added octanal (62 μL, 0.396 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with EtOAC (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) providing alkene **291a** as a colourless oil (8.4 mg, 9%), phosphonate **210** (23 mg, 22%) and enephosphonate **293** (47 mg, 33%).

E. To a solution of phosphonate **210** (40 mg, 0.14 mmol) and octanal (22 μL, 0.14 mmol) in THF (3 mL) was added K_2CO_3 (44 mg, 0.28 mmol). The reaction was stirred at rt for 12 h before being heated to reflux for 12 h. The cooled reaction mixture was quenched with the H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The residue was confirmed to be phosphonate **210** by ^1H NMR spectroscopy.

F. To a solution of phosphonate **210** (55 mg, 0.192 mmol) in Et_2O (0.5 mL) at -78 °C was added a 1M solution of LiHMDS in THF (212 μL, 0.212 mmol) dropwise. To this orange solution was added butanal (19 μL, 0.212 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAC (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) giving phosphonate **290a** (8 mg, 14%) and enephosphonate **292** (19 mg, 29%).



290a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 15.7 Hz, 1H), 6.14 (dt, *J* = 15.6, 6.9 Hz, 1H), 3.89 (s, 3H), 2.23 (q, *J* = 7.4 Hz, 2H), 1.52 (q, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

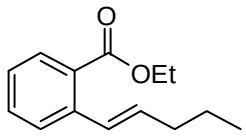


292: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.70 (dt, *J* = 23.1, 7.3 Hz, 1H), 4.16 (m, 2H), 4.09 – 3.97 (m, 2H), 2.00 – 1.82 (m, 2H), 1.39 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.24 (m, 1H), 1.20 (t, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 148.3 (d, *J* = 8.1 Hz), 134.4 (d, *J* = 9.5 Hz), 132.5 (d, *J* = 5.0 Hz), 131.2 (d, *J* = 81.2 Hz), 130.8 (d, *J* = 2.0 Hz), 130.6 (d, *J* = 4.6 Hz), 129.3, 128.0 (d, *J* = 2.3 Hz), 62.9 (appt, *J* = 6.2 Hz), 31.9 (d, *J* = 17.5 Hz) 21.5 (d, *J* = 1.7 Hz), 16.3 (d, *J* = 6.4 Hz), 16.2 (d, *J* = 6.4 Hz), 13.8. IR (neat): 3418, 2960, 2932, 2872, 1717, 1209, 1138, 1052, 1024, 978. HRMS (ESI) calcd. for $C_{16}H_{23}O_5PNa^+$ $[M + Na]^+$ 349.1181, found 349.1184

G. To a solution of phosphonate **210** (34 mg, 0.118 mmol) in toluene (0.5 mL) at -78 °C was added a 1M solution of LiHMDS in THF (142 μL, 0.142 mmol) dropwise. To this orange solution was added butanal (10 μL, 0.142 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAC (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) providing alkene **290a** as a colourless oil (5 mg, 20%), phosphonate **210** (6 mg, 18%) and enephosphonate **292** (8 mg, 21%).

H. To a solution of phosphonate **294** (50 mg, 0.184 mmol) in THF (0.5 mL) at -78 °C was added a 1M solution of LiHMDS in THF (404 μL, 0.404 mmol) dropwise. To this orange solution was added butanal (18 μL, 0.202 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAC (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The residue was confirmed to be phosphonate **294** by ^{1}H NMR spectroscopy.

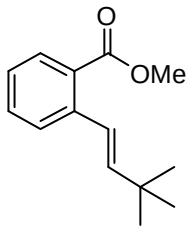
I. To a solution of phosphonate **211** (57 mg, 0.190 mmol) in THF (1.0 mL) at -78 °C was added 60% dispersion of NaH in paraffin oil (7.6 mg, 0.190 mmol). To this orange solution was added butanal (10 μL, 0.142 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAC (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude residue was purified through flash column chromatography (silica, gradient elution 20:1 hexanes/Et_2O to EtOAc) giving providing alkene **290b** as a colourless oil (8 mg, 20%).



ethyl 2-[(1*E*)-pent-1-enyl]benzoate (290b)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 15.7 Hz, 1H), 6.14 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.23 (q, *J* = 7.1 Hz, 2H), 1.52 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H).

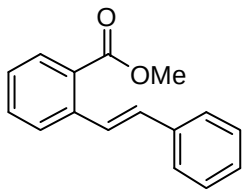
J. To phosphonate **211** (191 mg, 0.637 mmol) was added NaOMe (69 mg, 1.27 mmol). To the orange suspension was added butanal (55 μL, 0.764 mmol). The reaction was stirred at rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAC (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The residue was confirmed to be phosphonate **211** by ^{1}H NMR spectroscopy.



Methyl 2-[(1E)-3,3-dimethylbut-1-enyl]benzoate (297)

To a solution of phosphonate **210** (83 mg, 0.290 mmol) in THF (0.5 mL) at -78 ˚C was added a 1M solution of LiHMDS in THF (320 μL, 0.320 mmol). The solution immediately turned bright yellow. After 2 min, pivaldehyde (38 μL, 0.348 mmol) was added to the reaction

mixture. The reaction was stirred at -78 °C for 1.5 h before warming up to rt for a further 12 h. The reaction was quenched with the addition of sat $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The oil was purified using flash column chromatography (silica, 20:1 hexanes/EtOAc), yielding the title compound as a colourless oil (56 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.44 (td, *J* = 7.9, 1.3 Hz, 1H), 7.25 (td, *J* = 7.9, 1.3 Hz, 1H), 7.09 (d, *J* = 16.1 Hz, 1H), 6.13 (d, *J* = 16.1 Hz, 1H), 3.90 (s, 3H), 1.14 (s, 9H). NMR (125 MHz, $CDCl_3$) δ 168.1, 144.5, 140.0, 131.9, 130.3, 128.3, 127.2, 126.4, 123.7, 52.0, 33.7, 29.6. IR: 2954, 2866, 1720, 1476, 1434, 1246, 1130, 1078, 735 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{18}O_2Na^+$ $[M + Na]^+$ 241.1204, found 241.1203.



Attempted synthesis of methyl 2-[(*E*)-2-phenylvinyl]benzoate

To a solution of phosphonate (100 mg, 0.350 mmol) in DMF (1 mL) at 0 °C was added NaOMe (38 mg, 0.700 mmol). The solution immediately turned orange indicating deprotonation. To this orange solution was benzaldehyde (35 μL, 0.350 mmol) before heating to 80 °C for 30 min. The cooled solution was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAC (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. ^{1}H NMR spectroscopy showed that both starting materials were returned unreacted.

Attempted HWE reactions between phosphonate 210 and hemiacetal 122:

A. To a suspension of *t*-BuOK (60 mg, 0.54 mmol) in THF (2 mL) was added a solution of phosphonate **210** (129 mh, 0.45 mmol) in THF (2 mL) dropwise at 0 °C. After stirring for 10 min the colour changed to orange. To the orange solution was added a solution of hemiacetal **122** (93 mg, 0.45 mmol) in THF (2 mL). The reaction was allowed to warm to rt stirring for 12 h. The reaction was quenched with 10% HCl (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The residue was confirmed to be phosphonate **210** by ^{1}H NMR spectroscopy.

B. To a suspension of *t*-BuOK (25 mg, 0.220 mmol) and 18-crown-6 (59 mg, 0.220 mmol) in THF (2 mL) was added a THF (1 mL) solution of phosphonate **210** (53 mg, 0.185 mmol) at 0 °C. To the resultant orange solution was added a THF (1 mL) solution

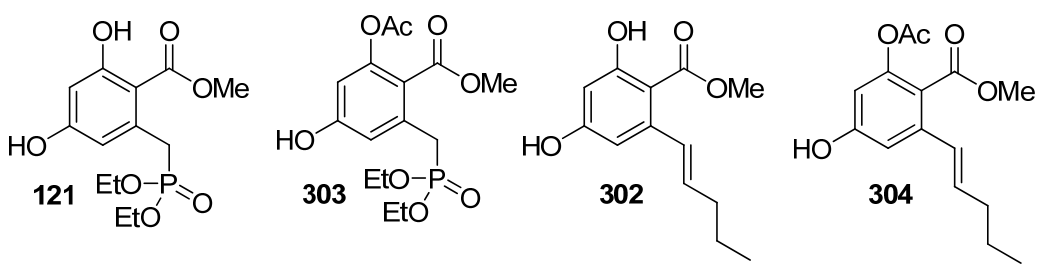
of hemiacetal **122** (37 mg, 0.185 mmol) dropwise at 0 °C. The reaction was allowed to warm to rt and stirred for 16 h. The reaction was quenched with 10% HCl (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The residue was confirmed to be phosphonate **210** by ^1H NMR spectroscopy.

C. To a suspension of a 60% dispersion of NaH in paraffin oil (10 mg, 0.250 mmol) in THF (2 mL) at 0 °C was added a THF solution (1 mL) of phosphonate **210** (41.5 mg, 0.145 mmol) and hemiacetal **122** (30 mg, 0.129 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with AcOH (4 drops) and reduced to dryness. The ^1H NMR spectrum of the crude mixture exhibited the presence of the phosphonate **210** and hemiacetal **122**.

D. To a solution of the phosphonate **210** (67 mg, 0.234 mmol) in THF (2 mL) at 0 °C was added a 1M solution of LiHMDS in THF (210 μL, 0.210 mmol). To the bright orange solution was added a solution of the hemiacetal **122** (63 mg, 0.271 mmol) in THF (1 mL). The reaction was allowed to warm to rt overnight. The mixture was filtered through a silica gel pad and concentrated under reduced pressure. The ^1H NMR spectrum confirmed that no reaction had occurred.

Attempted HWE reactions between phosphonate 142 and butanal:

To a solution of phosphonate **142** (48 mg, 0.119 mmol) in THF (1 mL) at -78 °C were added a 1M solution of LiHMDS in THF (131 μL, 0.131 mmol) followed by butanal (12 μL, 0.131 mmol). The reaction mixture was left to warm to rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The crude products were purified using flash column chromatography (silica, gradient elution 10:1 hexanes/EtOAc to EtOAc) to give alkene **302** (4 mg, 14%), alkene **304** (8 mg, 24%), and phosphonate **303** (3 mg, 7%) phosphonate **121** (15 mg, 40%) as colourless oils.



302: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.59 (s, 1H), 6.90 (d, *J* = 15.4 Hz, 2H), 6.41 (d, *J* = 2.5 Hz, 2H), 6.32 (d, *J* = 2.6 Hz, 2H), 5.91 (dt, *J* = 15.4, 6.9 Hz, 3H), 5.32 (s, 1H), 3.91 (s, 3H), 2.18 (q, *J* = 7.2 Hz, 2H), 1.50 (q, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H).
303: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, *J* = 2.5 Hz, 1H), 6.47 (t, *J* = 2.5 Hz, 1H), 4.04 – 3.94 (m, 4H), 3.84 (s, 3H), 3.55 (d, *J* = 23.1 Hz, 2H), 2.26 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 6H)
304: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 2.4 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.12 (dt, *J* = 15.6 7.0 Hz, 1H), 5.32 (s, 1H), 3.86 (s, 3H), 2.26 (s, 3H), 2.17 (q, *J* = 7.3 Hz, 2H), 1.47 (q, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

Attempted HWE reactions between phosphonate 142 and hemiactels 122 or 152:

A. To solution of phosphonate **142** (50 mg, 0.124 mmol) in THF (0.5 mL) at 0 °C was added a 1M solution of LiHMDS in THF (190 μL, 0.190 mmol). To this orange solution was added a THF solution (0.5 mL) of hemiacetal **122** (32 mg, 0.133 mmol). The reaction was left to warm to rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The ^{1}H NMR spectrum of the residue indicated that no reaction had occurred.

B. To a solution of phosphonate **142** (173 mg, 0.430 mmol) in MeOH (1 mL) was added NaOMe (70 mg, 1.29 mmol) at rt. To the reaction was added a THF solution (0.5 mL) of acetonide **152** (37 mg, 197 mmol). The reaction stirred at rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The ^{1}H NMR spectrum of the residue indicated that no reaction had occurred.

C. To a solution of phosphonate **142** (10 mg, 25 μmol) in THF (0.5 mL) was added *t*-BuOK (5.5 mg, 49 μmol) at 0 °C. To the reaction was added a THF solution (0.2 mL) of hemiacetal **152** (5.5 mg, 29 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The ^{1}H NMR spectrum of the residue indicated that no reaction had occurred.

D. To a solution of phosphonate **142** (27 mg, 67 μmol) and hemiacetal **152** (13.5 mg, 67 μmol) in DMF (0.5 mL) was added NaOMe (11 mg, 0.204 mmol) at 0 °C. The reaction was then heated to 80 °C for 30 min. The cooled reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were washed with sat. $NaHCO_{3(aq)}$, dried over $MgSO_4$, filtered and reduced. The ^1H NMR spectrum of the residue confirmed that no reaction had occurred. The main component of the reaction was deprotected phosphonate **142**.

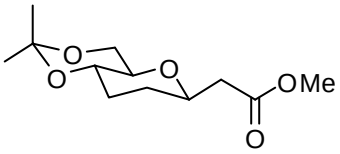
E. To a solution of phosphonate **142** (14 mg, 26 μmol) in THF (0.5 mL) was added LDA (26 μL, 4 μL) at -78 °C. To the reaction mixture was then added a THF solution (0.25 mL) of hemiacetal **152** (4 mg, 21 mmol). The reaction was allowed to warm to rt whilst stirring for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The ^1H NMR spectrum of the residue indicated that no reaction had occurred.

F. To a solution of phosphonate **142** (14 mg, 26 μmol) in toluene (0.5 mL) was added NaOMe (5 mg, 93 μmol) at rt. To the reaction was added a THF solution (0.25 mL) of hemiacetal **152** (5 mg, 27 mmol). The reaction was stirred at rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The ^1H NMR spectrum of the residue indicated that no reaction had occurred.

G. To a solution of phosphonate **142** (24 mg, 44 μmol) in THF (0.5 mL) was added Et_3N (7 μL, 51 μmol) and LiBr (4.5 mg, 52 μmol) at rt. To the reaction was added a THF solution (0.25 mL) of hemiacetal **152** (8 mg, 43 μmol). The reaction was stirred at rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced. The ^1H NMR spectrum of the residue confirmed that no reaction had occurred.

H. To a solution of phosphonate **142** (33 mg, 60 μmol) in DMF (200 μL) was added NaOMe (6.5 mg, 0.120 mmol) at 0 °C. The reaction mixture was left to warm to rt for 5 min. To this reaction mixture was added the hemiacetal **152** (11 mg, 57 μmol). Additional DMF (100 μL) was used to wash down the sides of the flask. The reaction was stirred at rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and

extracted with EtOAc (3 x 5 mL). The combined organic fractions were washed with sat. $NaHCO_{3(aq)}$, dried over $MgSO_4$, filtered and reduced. The ^1H NMR spectrum of the crude residue showed evidence of the starting materials and the deprotected phosphonate **142**.

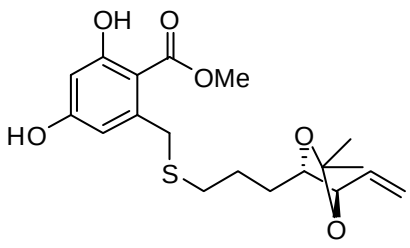


2,4,5-deoxy-6,8-*O*-(1-methylethylidene)-D-glycero-D-gulo-octonic methyl ester (307)

To a solution of sugar **122** (30 mg, 0.16 mmol) and triethyl phosphonoacetate (35 μL, 0.176 mmol) in MeOH (1.0 mL) at 0 °C was added MeONa (17 mg, 0.319 mmol). The reaction was stirred as it warmed to rt for 12 h. The solvent was removed and the crude residue was re-dissolved in EtOAc (10 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and reduced. The crude product was purified by flash column chromatography (silica, gradient elution 3:1 to 1:1 hexanes/EtOAc) yielding a colourless oil (26 mg, 67%). ^1H NMR (500 MHz, $CDCl_3$) δ 3.89 (m, 1H), 3.83 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.69 (s, 3H), 3.68 (m, 1H), 3.56 (dt, *J* = 10.5, 4.6 Hz, 1H), 3.24 (dt, *J* = 9.2, 5.3 Hz, 1H) 2.54 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.40 (dd, *J* = 15.4, 5.6 Hz, 1H), 1.94 (m, 1H), 1.86 (m, 1H) 1.62 – 1.44 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 99.3, 74.2, 70.0, 51.6, 40.5, 30.7, 29.3, 29.2, 28.9, 19.2, 19.0.

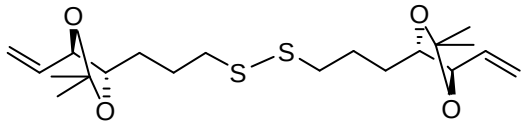
8.5.2 The RB route

Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-dihydroxybenzoate (191)

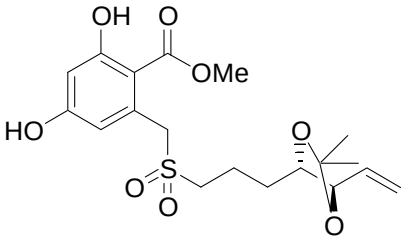


A solution of thioacetate **189** (340 mg, 1.39 mmol) and bromide **135** (485 mg, 1.41 mmol) in dry MeOH (25 mL) was degassed by bubbling dry argon through the solution for 10 min. After this time, K_2CO_3 (466 mg, 3.37 mmol) was added and the reaction was stirred at rt for 12 h. After TLC analysis confirmed the consumption of bromide **135**, the solvent was removed to dryness. The residue was dissolved in EtOAc (50 mL) and sat. $NH_4Cl_{(aq)}$ (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were combined, washed with brine (50 mL), dried with $MgSO_4$, filtered and reduced to dryness. The crude residue was purified

using column chromatography (silica, gradient column, 5:1 to 3:1 hexanes/EtOAc) to yield coupled product **191** as a colourless oil (447 mg, 86%). R_f = 0.33. $[\alpha]_D^{18}$ = -21.5 (*c* 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.67 (s, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.31 (s, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.31 (ddd, *J* = 17.1, 1.7, 1.1 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.50 (dd, *J* = 6.4, 7.7 Hz, 1H), 4.10 (ddd, *J* = 4.3, 6.1, 9.1 Hz, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.93 (s, 3H), 3.87 (d, *J* = 13.6 Hz, 1H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.76 – 1.66 (m, 1H), 1.65 – 1.50 (m, 2H), 1.49 (s, 3H), 1.50 – 1.40 (m, 1H), 1.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 165.7, 160.2, 143.9, 133.8, 118.7, 111.1, 108.4, 104.4, 102.5, 79.8, 77.7, 52.2, 37.0, 31.1, 29.5, 28.2, 25.8, 25.7. IR (KBr): 3272, 2988, 2951, 1655, 1621, 1588, 1441, 1381, 1326, 1259, 1210, 1162, 1109, 1031, 1003, 951, 851 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{26}O_6SNa^+$ $[M + Na]^+$ 405.1348, found 405.1345.



Disulfide **190** was isolated as a minor by-product. R_f = 0.59. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 17.2, 10.6, 7.8, 3.0 Hz, 2H), 5.31 (d, *J* = 17.1 Hz, 2H), 5.24 (dd, *J* = 10.3, 0.8 Hz, 2H), 4.50 (dd, *J* = 6.9, 7.8 Hz, 2H), 4.14 (ddt, *J* = 8.7, 6.1, 4.3 Hz, 2H), 2.70 (m, 2H), 2.56 (ddd, *J* = 14.4, 7.5, 3.7 Hz, 2H), 1.92 – 1.49 (m, 8H), 1.49 (s, 6H), 1.36 (s, 6H). HRMS (ESI) calcd. for $C_{20}H_{34}O_4S_2Na^+$ $[M + Na]^+$ 425.1796, found 425.1792.



Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-dihydroxybenzoate 2′,2′-dioxide (309)

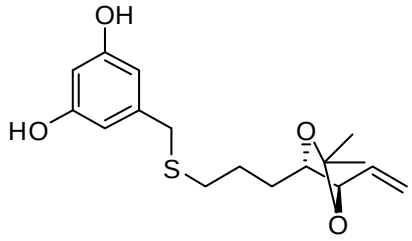
To a solution of thioether **191** (38 mg, 99 μmol) in CH_2Cl_2 (2.5 mL) was added 75% *m*-CPBA (55 mg, 0.224 mmol) at 0 °C. The solution was left to warm to rt stirring for 18 h. The solvent was removed and the crude product was purified using flash column chromatography (silica, 1:1 hexanes/EtOAc) to give a white solid (36 mg, 87%). $[\alpha]_D^{22}$ = -21.5 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.38 (s, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 1H), 5.33 (ddd, *J* = 17.1, 1.7, 1.2 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.77 (d, *J* = 13.9 Hz, 1H), 4.70 (d, *J* = 13.9 Hz, 1H), 4.53 (dd, *J* = 7.4, 6.5 Hz, 1H), 4.11 (ddd, *J* = 9.8, 6.8, 3.7 Hz, 1H), 3.97 (s, 3H), 2.93 (qdd, *J* = 13.9, 10.2, 5.8 Hz, 2H), 2.05 – 1.85 (m, 2H), 1.61 – 1.49 (m, 2H), 1.48 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 165.2, 160.6, 141.1,

133.5, 118.9, 113.4, 108.7, 105.0, 104.7, 79.5, 77.5, 58.5, 52.4, 51.4, 29.2, 28.2, 25.6, 19.0. IR: 3352, 2990, 2955, 1661, 1621, 1591, 1440, 1381, 1328, 1262, 1213, 1165, 1118, 750 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{26}O_8SNa^+$ $[M + Na]^+$ 437.1246, found 437.1241.

Attempted saponification of sulfone 309:

A solution of sulfone **309** (23 mg, 57 μmol) and LiOH (7 mg, 1.56 mmol) in 3:1 MeOH/H_2O (900 μL) was heated to 50 °C for 12 h. The cooled solution was acidified to pH 1 with 10% HCl and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the crude residue indicated that the compound had decomposed.

Saponification of ester 191 leading to 5-[({3-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]propyl}thio)methyl]benzene-1,3-diol (311)



A solution of thioether **191** (101 mg, 0.264 mmol) and LiOH (46 mg, 1.09 mmol) in 1:1 THF/H_2O (4 mL) was heated to 50 °C for 12 h. The cooled solution was extracted with Et_2O (2 x 10 mL) and the organic fractions discarded. The aqueous layer was acidified to pH 1 with 10% HCl and further extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and reduced to dryness. The crude residue was purified by flash column chromatography (silica, gradient chromatography, 10:1 to 1:1 hexanes/EtOAc), returning thioether 191 (5 mg, 5%) and affording diol **311** a colourless oil (22 mg, 26%). **311**: $[\alpha]_D^{22}$ = -22.8 (*c* 0.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, *J* = 2.2 Hz, 2H), 6.23 (t, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.33 (s, 1H), 5.31 (ddd, *J* = 17.2, 1.7, 1.2 Hz, 1H), 5.24 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.49 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.10 (ddd, *J* = 8.7, 6.1, 4.5 Hz, 1H), 3.56 (s, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.78 – 1.65 (m, 1H), 1.64-1.50 (m, 2H), 1.49 (s, 3H), 1.48 – 1.42 (m, 1H), 1.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 141.4, 134.0, 118.7, 108.4, 108.4, 101.5, 79.8, 77.8, 35.8, 31.0, 29.5, 28.2, 25.7, 25.7. IR: 3339, 2987, 2930, 1603, 1454, 1373, 1340, 1218, 1156, 1003, 735 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{24}O_4SNa^+$ $[M + Na]^+$ 347.1293, found 347.1288.

Attempted hydrolyses of methyl ester 191:

A. A solution of thioether **191** (23 mg, 60.2 mmol) and LiOH (10 mg, 0.24 mmol) in 2:1 MeOH/H_2O (1.5 mL) was stirred at rt for 1 h. The reaction mixture was then heated at 50 °C for 8 h. The cooled solution reduced to dryness. The residue was partitioned between 10% HCl (10 mL) and EtOAc (10 mL). The aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~1.78:1 ratio of ester **191** to diol **311.**

B. A solution of thioether **191** (23 mg, 60.2 mmol) and NaOH (13.5 mg, 0.24 mmol) in 2:1 MeOH/H_2O (1.5 mL) was stirred at rt for 1 h. The reaction mixture was then heated at 50 °C for 8 h. The cooled solution reduced to dryness. The residue was partitioned between 10% HCl (10 mL) and EtOAc (10 mL). The aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~1:1.70 ratio of ester **191** to diol **311**.

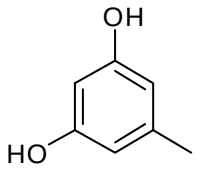
C. To a solution of thioether **191** (41 mg, 0.11 mmol) in EtOH (3.5 mL) was added $Ba(OH)_2$ (105 mg, 0.33 mmol) and the reaction mixture stirred at rt for 18 h. The solution turned a deep red colour. The reaction mixture was diluted with Et_2O (15 mL) and acidified with 10% HCl (15 mL). The organic phase was separated and the aqueous further extracted with Et_2O (10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that the material had degraded.

D. To a solution of ethanethiol (49 μL, 0.65 mmol) in THF (2 mL) was added *n*-BuLi (370μL, 0.59 mmol) at -10 °C. The solution instantly went cloudy. The solution was warmed to rt for 5 min. The reaction mixture was cooled to -10 °C and a THF solution (2 mL) of methyl ester **191** (57 mg, 0.15 mmol) was added dropwise. After stirring at -10 °C for 30 min, the reaction mixture was warmed to rt for 2 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that starting material had been recovered.

E. To a solution of ethanethiol (56 μL, 0.75 mmol) in DMF (2 mL) was added a 60% dispersion of NaH in mineral oil (27 mg, 0.67 mmol) at -10 °C. The solution was warmed to rt for 5 min. The reaction mixture was cooled to -10 °C and a DMF solution (2 mL) of methyl ester **191** (57 mg, 0.15 mmol) was added dropwise. After stirring at -10 °C for 30 min, the reaction mixture was warmed to rt for 12 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated the presence of a ~1:4 ratio of ester **191** to diol **311**.

Attempted hydrolyses of orsellinate 74:

A. To a solution of orsellinate **74** (305 mg, 1.68 mmol) in 1:1 MeOH/H_2O (10 mL) was added KOH (506 mg, 9.02 mmol) and the reaction heated to reflux for 18 h. The cooled solution was acidified to pH 1 with conc. HCl and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The crude residue was recystallised from EtOAc to give a white solid (236 mg, 82%). The product was identified as **5-methylbenzene-1,3-diol** (**orcinol**, **312**): ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (d, *J* = 2.3 Hz, 2H), 6.16 (t, *J* = 2.3 Hz, 1H), 2.24 (s, 3H). Spectral data matched those reported in the literature.[243]



B. To a solution of orsellinate **74** (125 mg, 0.69 mmol) in 2:1 MeOH/H_2O (4.5 mL) was added KOH (415 mg, 7.48 mmol) and the reaction stirred at rt for 4 days. The reaction mixture was reduced to dryness, resuspended in EtOAc (15 mL), acidified to pH 1 with conc. HCl and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated the presence of a ~2.13:1 ratio of ester **74** to diol **312**.

C. To a solution of orsellinate **74** (100 mg, 0.55 mmol) in 3:1 DMSO/H_2O (4 mL) was added KOH (220 mg, 3.78 mmol) and the reaction heated at 80 °C for 12 h. The reaction mixture was diluted with H_2O (2 mL) and extracted with Et_2O (5 mL). The aqueous phase was acidified to pH 2 with conc. HCl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with H_2O (2 x 15 mL), brine (15 mL), dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated that the material had degraded.

D. To a solution of orsellinate **74** (100 mg, 0.55 mmol) in 1:1 1,4-dioxane/H_2O (16 mL) was added NaOH (79 mg, 3.30 mmol) and the reaction stirred at rt for 12 h. The reaction mixture was reduced to dryness, resuspended in EtOAc (15 mL) and acidified to pH 1 with conc. HCl and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that starting material had been recovered.

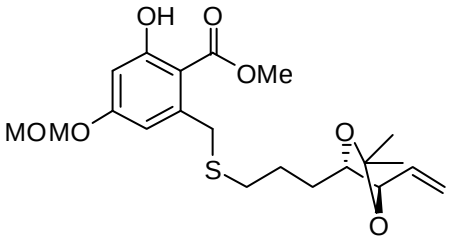
E. To a solution of orsellinate **74** (100 mg, 0.55 mmol) in THF (10 mL) was added *t*-BuOK (370 mg, 3.30 mmol) and the reaction stirred at rt for 6 days. The reaction mixture was reduced to dryness, resuspended in Et_2O (15 mL) and acidified to pH 1 with conc. HCl and separated. The aqueous phase was further extracted with Et_2O (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~2.85:1 ratio of ester **74** to diol **312**.

F. A solution of orsellinate **74** (102 mg, 0.56 mmol) in pyridine (2 mL) was refluxed 18 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 10% HCl (4 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~2.13:1 ratio of ester **74** to diol **312**.

G. A solution of orsellinate **74** (182 mg, 1.0 mmol) and pyridine hydrochloride (116 mg, 1.0 mmol) in pyridine (3 mL) was heated to reflux for 12 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 10% HCl (4 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~1:1.33 ratio of ester **74** to diol **312**.

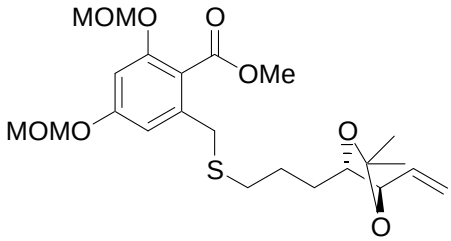
H. A solution of orsellinate **74** (169 mg, 0.93 mmol) in 5:1 THF/10% $H_2SO_{4(aq)}$ (6 mL) was heated to 50 °C for 4h. The cooled solution was extracted with Et_2O (3 x 10 mL). The combined organic fractions was dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that starting material had been recovered.

Methyl (6′*S*,7′*R*)-6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)-2-hydroxy,4-methoxymethoxybenzoate



To a solution of compound **191** (50 mg, 0.131 mmol) in THF (5 mL) at 0°C was added a 60% dispersion of NaH in mineral oil (11 mg, 0.275 mmol). The NaH was allowed to react for 10 min at 0 °C and 20 min at rt. The reaction mixture was then cooled to 0 °C before the addition of MOMCl (30 μL, 0.393 mmol). The reaction was stirred for 12 h, warming to rt. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic fractions were combined, dried over $MgSO_4$ and reduced to dryness to give a colourless oil. The crude oil was purified using flash column chromatography (silica, 20:1 to 10:1 hexanes/EtOAc) giving the mono-protected derivative of **191** (18 mg, 32%) and bis-MOM **192** (22 mg, 36%). mono-MOM: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.54 (s, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 5.79 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.30 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.23 (ddd, *J* = 10.3, 1.6, 0.8 Hz, 1H), 5.18 (s, 2H), 4.47 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.09 (ddd, *J* = 8.7, 6.1, 4.6 Hz, 1H), 3.94 (s, 3H), 3.91 (d, *J* = 1.4, 2H), 3.46 (s, 3H), 2.49 – 2.40 (m, 2H), 1.79 – 1.69 (m, 1H), 1.61 – 1.48 (m, 2H), 1.47 (s, 3H), 1.48 – 1.39 (m, 1H), 1.35 (s, 3H).

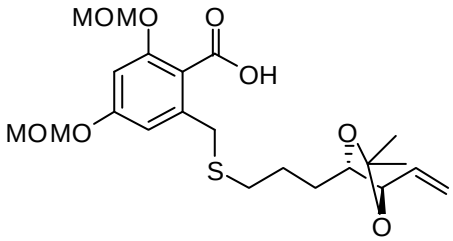
Methyl (6′*S*,7′*R*)-6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)-2,4-bis(methoxymethoxy)benzoate (192)



To a solution of compound **191** (621 mg, 1.62 mmol) in DMF (6 mL) at 0 °C was added a 60% dispersion of NaH in mineral oil (163 mg, 4.06 mmol). The reaction was stirred at 0 °C for 20 min before the addition of MOMCl (370 μL, 4.89 mmol). The reaction mixture was left to warm to rt stirring for 2 h. The reaction mixture was diluted with Et_2O (30 mL) and washed with saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer further extracted with Et_2O (2 x 15 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered and reduced to give a colourless oil. The crude oil was purified using flash column chromatography (silica, gradient chromatography, 10:1 to 5:1 hexanes/EtOAc) affording the desired bis-MOM ether as a colourless oil (562 mg, 74%). R_f = 0.30. $[\alpha]_D^{18}$ = -30.3 (*c* 0.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 2.2 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.29

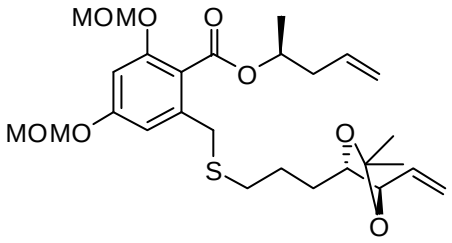
(ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.22 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 5.16 (s, 2H), 5.16 (s, 2H), 4.47 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.09 (ddd, *J* = 8.6, 4.7, 6.1 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 2.48 – 2.40 (m, 2H), 1.77 – 1.67 (m, 1H), 1.60 – 1.43 (m, 3H), 1.47 (s, 3H), 1.35 (s, H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 158.8, 156.0, 139.4, 134.3, 118.3, 110.6, 108.2, 102.5, 95.0, 94.3, 79.7, 77.8, 77.2 56.3, 56.2, 52.2, 34.0, 31.4, 29.5, 28.2, 25.8, 25.6. IR (neat): 2949, 2906, 1727, 1605, 1434, 1277, 1215, 1144, 1038, 1017, 928, 870 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{34}O_8SNa^+$ [M + Na]$^+$ 493.1872, found 493.1867.

(6′*S*,7′*R*)-6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)-2,4-(bismethoxymethoxy)benzoic acid (193)



To a solution of ester **192** (455 mg, 0.968 mmol) in 2:1 MeOH/H_2O (15 mL) was added KOH (271 mg, 4.84 mmol) and the reaction mixture heated to 90 °C for 48 h. After cooling to rt, the mixture was extracted with Et_2O (20 ml) and the organic layer discarded. The aqueous layer was acidified to pH 6 with an aqueous acetic acid solution (50%; v/v, 0.78 mL, 6.8 mmol) and extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with H_2O (4 x 20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the acid as a colourless oil (434 mg, 98%). $[\alpha]_D^{20}$ = -32.1 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 2.3 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.2, 7.8 Hz, 1H), 5.28 (ddd, *J* = 17.1, 1.6, 1.0 Hz, 1H), 5.22 (s, 2H), 5.22 (dd, *J* = 10.3, 1.6, 0.8 Hz, 1H), 5.18 (s, 2H), 4.47 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.12 (ddd, *J* = 8.4, 6.1, 4.6 Hz, 1H), 3.90 (d, *J* = 2.0 Hz, 2H), 3.50 (s, 3H), 3.47 (s, 3H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.74 (m, 1H), 1.64 – 1.38 (m, 3H), 1.47 (s, 3H), 1.35 (s, 3H). IR (neat): 2908, 2845, 1604, 1586, 1462, 1377, 1277, 1216, 1151, 1028, 1020, 927, 744 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{32}O_8SNa^+$ [M + Na]$^+$ 479.1716, found 479.1720.

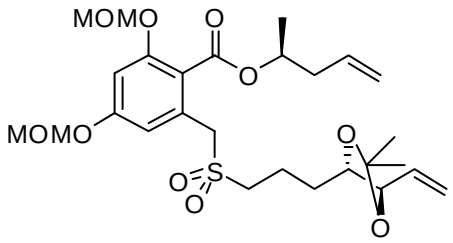
(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)-2,4-(bismethoxymethoxy)benzoate (167)



To a solution of alcohol **22** (147 μL, 1.43 mmol) and PPh_3 (624 mg, 2.38 mmol) in THF (20 mL) at 0 °C was added DIAD (463 μL, 2.38 mmol). The solution was stirred at 0 °C for 20 min during

which time a white precipitate formed. After this time a solution of the acid **194** (434 mg, 0.952 mmol) in THF (15 mL) was added dropwise and the reaction was left to stir at rt for 2 days. To the crude reaction mixture was added a small amount of silica gel before removal of solvent. The silica gel was dry loaded onto a column and eluted (gradient elution 20:1 to 5:1 hexanes/EtOAc) to yield title compound **167** as a colourless oil (468 mg, 94%). R_f = 0.60. $[\alpha]_D^{18}$ = -34.9 (*c* 0.18, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.78 (ddd, *J* = 17.9, 10.3, 7.8 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.15 (s, 2H), 5.14 (d, *J* = 1.7 Hz, 2H), 5.13 – 5.07 (m, 2H), 4.46 (dd, *J* = 7.3, 6.6 Hz, 1H), 4.09 (ddd, *J* = 8.5, 6.0, 4.8 Hz, 1H), 3.71 (q, *J* = 13.7 Hz, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 2.46 (qt, *J* = 12.9, 6.6 Hz, 3H), 2.40 – 2.33 (m, 1H), 1.72 (m, 1H), 1.60 – 1.40 (m, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 158.6, 155.8, 139.0, 134.3, 133.8, 118.4, 118.3, 117.7, 110.4, 108.2, 102.3, 94.7, 94.3, 79.7, 77.8, 71.2, 56.2, 56.1, 40.2, 33.8, 31.6, 29.5, 28.2, 25.8, 25.6, 19.4. IR (neat): 2984, 2906, 2845, 1715, 1604, 1584, 1434, 1380, 1272, 1216, 1149, 1039, 1019, 926 cm^{-1}. HRMS (ESI) calcd. for $C_{27}H_{40}O_8SNa^+$ $[M + Na]^+$ 547.2342, found 547.2342.

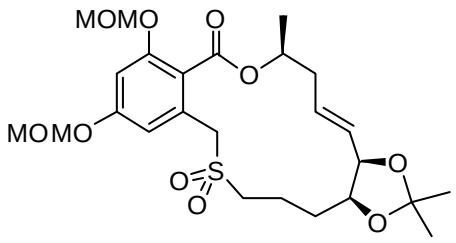
(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoate 2′,2′-dioxide (195)



To a solution of thioether **167** (122 mg, 0.230 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 75% *m*-CPBA (115 mg, 0.501 mmol). The reaction was left to warm to rt whilst stirring for 2 h. The reaction was quenched with the addition of 20% aqueous Na_2SO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with sat. $NaHCO_{3(aq)}$ (20 mL), dried over $MgSO_4$, filtered and reduced *in vacuo* to give a colourless oil. The product was purified by flash column chromatography (silica, gradient elution 3:1 to 2:1 hexanes/EtOAc) yielding the title compound as a colourless oil (109 mg, 84%). R_f = 0.31. $[\alpha]_D^{22}$ = -11.0 (*c* 1.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.5, 1.1 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.18 (s, 2H), 5.17 – 5.14 (m, 3H), 5.11 (ddt, *J* = 9.0, 2.0, 1.1 Hz, 1H), 4.48 (dd, *J* = 7.5, 6.5 Hz, 1H), 4.38 (d, *J* = 14.1 Hz, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.02

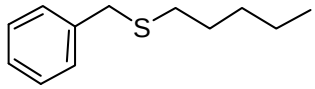
(ddd, *J* = 13.9, 10.2, 5.7 Hz, 1H), 2.94 (ddd, *J* = 13.9, 10.1, 5.7 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.42 – 2.35 (m, 1H), 2.02 – 1.91 (m, 1H), 1.89 – 1.80 (m, 1H), 1.52 (tdd, *J* = 11.2, 7.0, 3.9 Hz, 2H), 1.45 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 159.0, 156.4, 134.0, 133.7, 128.5, 119.3, 118.6, 117.9, 112.2, 108.4, 104.2, 94.8, 94.3, 79.6, 77.6, 71.7, 56.7, 56.4, 56.3, 51.5, 40.2, 29.3, 28.1, 25.5, 19.5, 18.7. IR (neat): 1708, 1605, 1586, 1285, 1214, 1150, 1122, 1039, 1018, 914, 734. HRMS (ESI) calcd. for $C_{27}H_{40}O_{10}SNa^+$ $[M + Na]^+$ 579.2246, found 579.2240.

(5*S*,7*E*,9*R*,10*S*)-1,2-(3′,5′-Di-*O*-methoxymethyl)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)-pentadec-7-ene 14,14-dioxide (196)



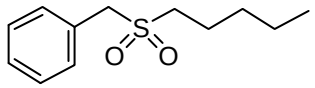
To a solution of the diene **195** (55 mg, 99 μmol) in CH_2Cl_2 (20 mL) in a 100 mL MW Teflon™ reactor vessel was added a catalytic amount of Grubbs' second generation catalyst **28** (8.4 mg, 9.9 μmol). The vessel was flushed with argon before sealing with the cap. The vessel was placed in the MW carousel and the temperature/pressure probe inserted into the reaction vessel. The vessel was irradiated for 30 min and heated to 75 °C. Once the reaction vessel had cooled to rt the cap was removed and the solution transferred to a round-bottom flask. The solvent was removed to yield a brown oil. The crude product was purified on a silica column (gradient chromatography, 5:1 to 2:1 hexanes/EtOAc) yielding compound **196** as a colourless oil (45 mg, 86%). R_f = 0.14. $[\alpha]_D^{22}$ = -28.5 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 2.2 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 5.71 (ddd, *J* = 15.2, 9.3, 4.3 Hz, 1H), 5.55 (ddd, *J* = 15.4, 9.4, 1.4 Hz, 1H), 5.29 (m, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.16 (t, *J* = 3.4 Hz, 1H), 5.16 (s, 2H), 4.47 (d, *J* = 15.3 Hz, 1H), 4.43 (dd, *J* = 9.3, 5.8 Hz, 1H), 4.13 (d, *J* = 15.1 Hz, 1H), 4.11 (m, 1H), 3.47 (s, 3H), 3.47 (s, 3H), 2.83 (ddd, *J* = 14.6, 11.1, 5.3 Hz, 1H), 2.65 (m, 1H), .47 (m, 1H), 2.41 (dd, *J* = 15.5, 9.8 Hz, 1H), 1.75 (m, 1H), 1.67 (m, 1H), 1.62 – 1.53 (m, 2H), 1.43 (s, 3H), 1.40 (d, *J* = 6.2 Hz, 3H), 1.32 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.1, 159.3, 156.6, 132.4, 129.0 (2), 118.6, 110.9, 107.9, 103.6, 94.6, 94.4, 76.3, 77.6, 72.3, 56.4, 56.4, 55.4, 51.1, 39.5, 28.3, 27.6, 25.5, 20.8, 18.5. IR (neat): 2982, 2903, 2829, 1708, 1604, 1585, 1277, 1215, 1149, 1122, 1017, 926, 737 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{36}O_{10}SNa^+$ $[M + Na]^+$ 551.1928, found 551.1927.

Benzyl pentyl sulfide (315)



To a solution of mercaptan benzyl (0.97 ml, 8.06 mmol) and 1-bromopentane (1.0 mL, 8.06 mmol) in MeOH (40 mL) was added K_2CO_3 (2.23 g, 16.1 mmol). The reaction was stirred overnight at rt. The solvent was removed and the residue dissolved in Et_2O (100 mL), washed with H_2O (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and reduced to give a yellow oil. The thioether was deemed to be pure by ^{1}H NMR and was carried forward without further purification (1.54 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 3.73 (s, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.60 – 1.50 (m, 2H), 1.38 – 1.24 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). Spectral data matched those reported in the literature.[244]

Benzyl pentyl sulfone (316)[117]



To a solution of thioether **315** (1.32g, 6.80 mmol) in AcOH (40 mL) was added $NaBO_3.4H_2O$ (3.35 g, 21.8 mmol) in portions over 30 min. The reaction mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure and the crude white solid partitioned between EtOAc (50 mL) and H_2O (50 mL) and separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic factions were washed with sat. $NaHCO_3$ aq (3 x 30 mL) and brine (30 mL) before drying over $MgSO_4$, filtering and reducing to give a white solid (1.95 g, 97%). The sulfone was deemed to be pure by ^{1}H NMR spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 5H), 4.21 (s, 2H), 2.80 (m, 2H), 1.84 – 1.78 (m, 2H), 1.40 – 1.30 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H).

Preparation of alumina-loaded KOH (KOH–Al_2O_3)[124]

Alumina (30 g) was suspended in a methanolic solution of KOH (10 g, 50 mL) in a 250 mL round bottom flask. The solvent was removed under reduced pressure at 50 °C until the powder was free flowing with a constant weight. When stored in a sealed container, the KOH–Al_2O_3 has a shelf-life of several months.

Attempted synthesis of benzyl 1-chloropentyl sulfone (317a)

A solution of sulfone **316** (52 mg, 0.24 mmol) and NCS (34 mg, 0.25 mmol) in CCl_4 (2 mL) was stirred at rt for 15 h. The reaction mixture was reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that no reaction had occurred.

Attempted synthesis of benzyl 1-bromopentyl sulfone (317b)

A solution of sulfone **316** (98 mg, 0.45 mmol) and NBS (95 mg, 0.54 mmol) in CCl_4 (5 mL) was refluxed under a heat lamp (200 W) for 15 min. The cooled reaction mixture was reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that no reaction had occurred.

Attempted Ramberg-Backlund reactions with sulfone 316

A. To a solution of sulfone **316** (100 mg, 0.45 mmol) in *t*-BuOH (1.8 mL) and CCl_4 (1.8 mL) was added KOH–Al_2O_3 (900 mg). The reaction mixture was stirred at rt for 2 h before filtering and reducing to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of sulfone **316** (49%), alkene **318** (20%) and complex mixture of other products (31%).

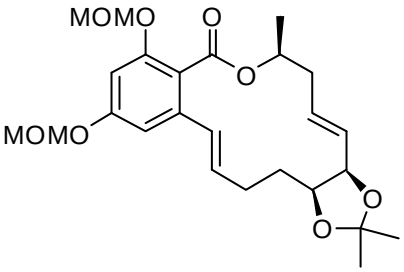
B. To a solution of sulfone **316** (64 mg, 0.29 mmol) in *t*-BuOH (1.15 mL) and CCl_4 (1.15 mL) was added KOH–Al_2O_3 (580 mg). The reaction mixture was heated to 40 °C for 2 h. The cooled solution was filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of sulfone **316** (49%), alkene **318** (31%) and complex mixture of other products (20%).

C. To a solution of sulfone **316** (32 mg, 0.15 mmol) and NBS (31 mg, 0.18 mmol) in *t*-BuOH (0.75 mL) and CH_2Cl_2 (1 mL) was added KOH–Al_2O_3 (400 mg). The reaction mixture was stirred at rt for 2 h, before filtering and reducing to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of sulfone **316** (78%), alkene **318** (16%) and complex mixture of other products (6%).

D. To a solution of sulfone **316** (95 mg, 0.43 mmol) and NBS (77 mg, 0.43 mmol) in DMF (1 mL) was added DBU (129 μL, 0.86 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (10 ml) and washed with sat. $NaHCO_{3(aq)}$ (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated that sulfone **316** was recovered.

E. To a solution of sulfone **316** (53 mg, 0.24 mmol) in *t*-BuOH (1 mL), CCl_4 (1 mL), CH_2Cl_2 (500 μL) and H_2O (50 μL) was added powdered KOH (270 mg, 4.81 mmol). After the reaction mixture was stirred at rt for 2 h, the solvent was removed to dryness

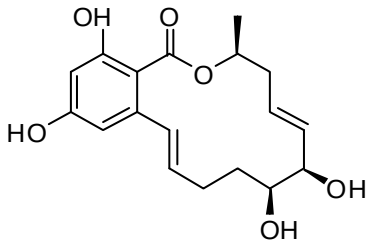
and the residue partitioned between sat. $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (5 mL). The aqueous layer was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated the presence of sulfone **316** (25%), alkene **318** (45%) and complex mixture of other products (30%).



(5′*S*,6′*R*,10′*S*)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)-aigialomycin D (35)

To a solution of sulfone **196** (34 mg, 64.4 μmol) in ^{t}BuOH (250 μl) and CH_2Cl_2 (100 μL) was added powdered KOH (72 mg, 1.29 mmol) at rt. To the resulting suspension was added CCl_4 (250 μmol) dropwise over 2 min. The reaction was then heated to 35 °C for 30 min. After cooling to rt the solvent was removed to dryness and the residue partitioned between sat. $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (5 mL). The aqueous layer was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced. The crude product was purified by flash column chromatography (silica, gradient elution 20:1 to 5:1 hexanes/EtOAc) to give the title compound **35** as a white solid (25 mg, 84%). R_f = 0.40. $[\alpha]_D^{19}$ = -118.6 (*c* 0.15, $CHCl_3$) [lit.[35] -116.5 (*c* 0.13, $CHCl_3$) and lit.[32] -120 (*c* 0.08, $CHCl_3$)] ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 6.14 (ddd, *J* = 15.3, 9.6, 4.2 Hz, 1H), 5.74 (ddd, *J* = 15.3, 9.4, 3.5 Hz, 1H), 5.60 (ddd, *J* = 15.4, 9.7, 1.7 Hz, 1H), 5.34 (m, 1H), 5.20 (d, *J* = 6.7 Hz, 1H), 5.16 (s, 2H), 5.12 (d, *J* = 6.8 Hz, 1H), 4.57 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.19 (ddd, *J* = 11.6, 5.4, 3.1 Hz, 1H), 3.46 (s, 3H), 3.46 (s, 3H), 2.58 – 2.44 (m, 2H), 2.31 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H), 1.49 (m, 1H), 1.47 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 158.9, 155.1, 136.8, 132.3, 131.9, 129.3, 128.4, 117.9, 108.3, 104.8, 102.5, 94.5, 94.3, 80.1, 77.2, 71.6, 56.2, 56.1, 39.5, 29.0, 28.7, 28.6, 25.8, 21.1. IR (neat): 2984, 2897, 1722, 1601, 1579, 1263, 1218, 1148, 1052, 1018, 925 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{34}O_8Na^+$ $[M + Na]^+$ 485.2151, found 485.2147.

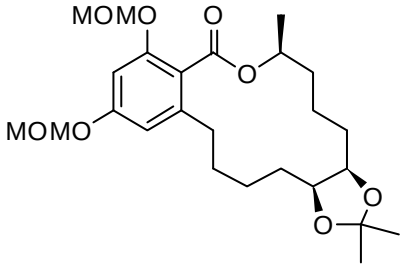
Aigialomycin D (1)



A solution of compound **15** (45 mg, 97.3 μmol) in 1:1 MeOH/1M HCl (10 mL) was stirred at rt for 3 days. The reaction mixture was extracted with EtOAc (3 x 10 mL), washed with brine (5 ml), dried over $MgSO_4$, filtered and reduced to give aigialomycin D as a white solid (28 mg, 86%). R_f (5% MeOH/CH_2Cl_2) = 0.21. $[\alpha]_D^{19}$ = -25.1 (*c* 0.78, MeOH) [lit.[35] -21.9 (*c* 0.35, MeOH)]. ^{1}H NMR (500 MHz, d_6-acetone) δ 11.66 (s, 1H), 9.25 (brs, 1H), 7.15 (d, *J* = 15.9 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.09 (ddd, *J* = 15.9, 5.7, 5.5 Hz, 1H), 5.88 (ddd, *J* = 15.6, 7.4, 1.6 Hz, 1H), 5.69 (ddd, *J* = 15.6, 5.2, 1.2 Hz, 1H), 5.44 (m, 1H), 4.35 (brd, *J* = 4.1 Hz, 1H), 3.82 (brs, 1H), 3.63 (m, 1H), 3.20 (brs, 1H), 2.57 (ddd, *J* = 14.6, 7.4, 3.1 Hz, 1H), 2.43 (m, 1H), 2.36 – 2.32 (m, 2H), 2.14 (m, 1H), 1.59 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 172.2, 165.8, 163.1, 144.3, 135.7, 133.6, 130.6, 125.4, 107.8, 104.4, 102.5, 76.5, 73.0, 73.0, 37.9, 28.5, 28.0, 19.1. IR (neat): 3338, 2979, 1644, 1608, 1448, 1312, 1259, 1167, 1110, 1018, 972 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{22}O_6Na^+$ $[M + Na]^+$ 357.1308, found 357.1314.

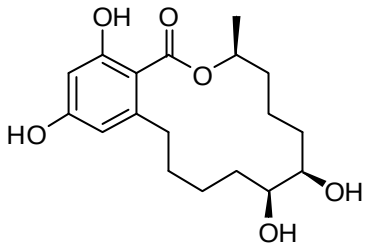
8.6 Experimental for Chapter Six

(5′*S*,6′*R*,10′*S*)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)-tetrahydro-aigialomycin D (15) (324)



To a solution of unsaturated **35** (16 mg, 34.5 μmol) in EtOH (1 mL) was added 10% Pd/C (1.5 mg). The flask was briefly evacuated before creation of a $H_{2(g)}$ atmosphere with the installation of a $H_{2(g)}$ balloon. The reaction was left stirring under the $H_{2(g)}$ atmosphere for 2 h. The mixture was filtered through Celite® and reduced, giving a colourless oil (14 mg, 88%). The crude product was carried forward without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 2.2 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 5.25 (m, 1H), 5.18 – 5.10 (m, 4H), 4.11 – 4.06 (m, 2H), 3.45 (s, 6H), 2.63 (ddd, *J* = 13.6, 11.0, 5.8 Hz, 1H), 2.49 (ddd, *J* = 13.7, 10.6, 5.2 Hz, 1H), 1.88 – 1.66 (m, 4H), 1.66 – 1.50 (m, 4H), 1.40 (s, 3H), 1.50 – 1.30 (m, 2H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.31 (s, 3H), 1.30 – 1.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 158.6, 155.1, 141.5, 119.1, 109.2, 107.1, 101.0, 94.6, 94.3, 77.7, 77.0, 72.4, 56.2, 56.1, 36.5, 33.2, 31.3, 31.3, 28.4, 27.6, 25.9, 24.7, 23.0, 21.0.

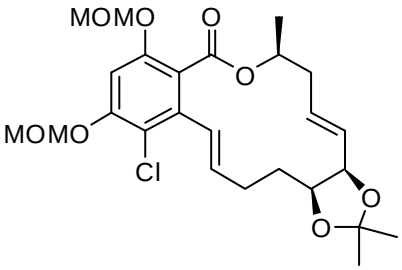
Tetrahydro-aigialomycin D (209)



To a solution of protected **324** (14 mg, 29.9 μmol) in MeOH (1.5 mL) was added 10% HCl (1.5 mL) and the mixture was stirred at rt for 3 days. The reaction was extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with H_2O (4 x 10 mL) until the aqueous layer was pH 7, dried over $MgSO_4$, filtered and reduced to dryness. The crude oil was purified by flash column chromatography (silica, gradient elution 1:1 hexanes/EtOAc to EtOAc) to give a colourless oil (6.5 mg, 89% over two steps). $[\alpha]_D^{19}$ = -8.2 (*c* 0.11, MeOH). ^{1}H NMR (500 MHz, d_6-acetone) δ 11.77 (s, 1H), 9.09 (s, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 5.10 (m, 1H), 3.83 – 3.76 (m, 2H), 3.53 (td, *J* = 12.3, 4.0 Hz, 1H), 2.36 (td, *J* = 12.1, 4.6 Hz, 1H), 2.21 (m, 1H), 1.92 – 1.79 (m, 4H), 1.77 – 1.67 (m, 2H), 1.61 (m, 1H), 1.55 – 1.35 (m, 4H), 1.33 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 172.7, 166.2, 163.1, 149.4, 111.8, 105.2, 101.8, 74.6, 73.9, 69.3, 37.2, 36.5, 34.6, 32.9, 28.3, 26.6, 21.6, 21.0. IR (neat): 3410, 3063, 2943 2869, 1643, 1607, 1489,

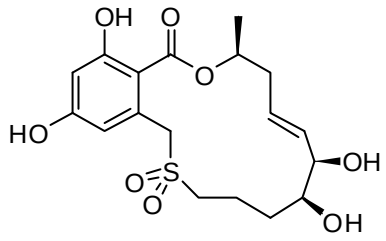
1443, 1312, 1258, 1161, 1009, 759, 698, 638 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H2_6O6Na^+$ $[M + Na]^+$ 361.1627, found 361.1627.

Attempted synthesis of (5′*S*,6′*R*,10′*S*)-2,4-Di-*O*-(methoxymethyl)-5-chloro-5′,6′-*O*-(1-methylethylidene)-aigialomycin D[30]



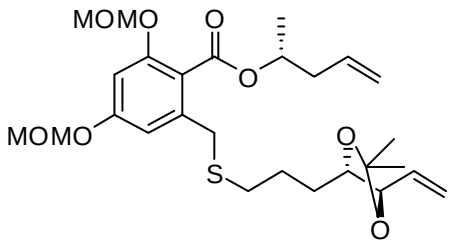
Calcium hypochlorite (6 mg, 41 μmol, 30% in Cl) dissolved in 10% AcOH/H_2O (1 mL) was slowly added to a solution of bisMOM **35** (8 mg, 17 μmol) in acetone (1 mL) at rt. After stirring for 2 h at rt, additional calcium hypochlorite (2.5 mg, 17 μmol) was added and the mixture stirred for a further 2.5 h. H_2O (2 mL) and EtOAc (5 mL) were added to the mixture and the aqueous layer removed. The organic layer was washed with H_2O (2 x 2 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered and concentrated. The ^1H NMR of the crude residue indicated that no reaction had taken place.

(5*S*,7*E*,9*R*,10*S*)-1,2-(3′,5′-Di-*O*-hydroxy)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-dihydroxypentadec-7-ene 14,14-dioxide (325)



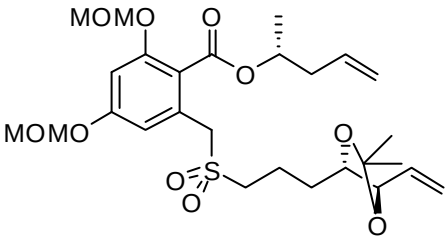
To a solution of protected **35** in MeOH (2 mL) was added 1M HCl (2 mL). The reaction was left stirring at rt for three days. The reaction mixture was extracted with EtOAc (3 x 10 mL), washed with brine (5 ml), dried over $MgSO_4$, filtered and reduced to give a colourless oil (6.4 mg, 89%). $[\alpha]_D^{19}$ = -7.2 (*c* 0.69, MeOH). ^1H NMR (500 MHz, d_6-acetone) δ 11.28 (s, 1H), 6.63 (s, 1H), 6.41 (s, 1H), 5.79 (ddd, J = 15.9, 8.5, 4.7 Hz, 1H), 5.72 (dd, J = 15.9, 6.7 Hz, 1H), 5.46 (m, 1H), 4.88 (d, J = 13.3 Hz, 1H), 4.76 (d, J = 13.4 Hz, 1H), 4.20 (d, J = 6.6 Hz, 1H), 3.94 (s, 1H), 3.74 (s, 1H), 3.66 (brs, 1H), 3.16 (dt, *J* = 14.5, 6.9 Hz, 1H), 2.87 (m, 1H), 2.67 (td, J = 15.0, 3.4 Hz, 1H), 2.41 (ddd, J = 15.0, 7.6, 7.1 Hz, 1H), 2.12 – 2.02 (m, 2H), 1.92 – 1.79 (m, 2H), 1.57 (m, 1H), 1.43 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 171.0, 170.9, 165.7, 165.4, 162.8, 135.3, 132.8, 127.4, 114.9, 106.8, 104.3, 104.3, 74.0, 57.8, 53.8, 38.3, 31.8, 19.8, 19.1. IR(neat): 3396, 2927, 1711, 1650, 1620, 1597, 1453, 1357, 1304, 1299, 1264, 1173, 1115 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{24}O_8SNa^+$ $[M + Na]^+$ 423.1090, found 423.1082.

(4*R*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)-2,4-(bismethoxymethoxy)benzoate (10′-*epi*-**167)**



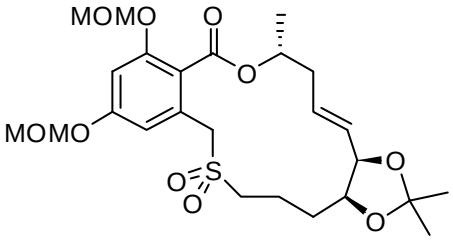
To solution of acid **193** (102 mg, 0.22 mmol) and alcohol **22** (34 μL, 0.33 mmol) in CH_2Cl_2 (2 mL) were added DMAP (27 mg, 0.22 mmol) and DCC (46 mg, 0.22 mmol). The reaction was stirred at rt for 12 h. The reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The crude oil was dissolved in CH_2Cl_2, absorbed on silica gel, dry-loaded on a silica gel column and eluted (gradient elution 20:1 to 10:1 hexanes/EtOAc) to afford a colourless oil (37 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.78 (ddd, *J* = 17.9, 10.3, 7.8 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.15 (s, 2H), 5.14 (d, *J* = 1.7 Hz, 2H), 5.13 – 5.07 (m, 2H), 4.46 (dd, *J* = 7.3, 6.6 Hz, 1H), 4.09 (ddd, *J* = 8.5, 6.0, 4.8 Hz, 1H), 3.73 (d, *J* = 13.7 Hz, 1H), 3.69 (d, *J* = 13.7 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.51 – 2.43 (m, 2H), 2.37 (m, 1H), 1.72 (m, 1H), 1.60 – 1.40 (m, 4H), 1.46 (s, 3H), 1.34 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 158.6, 155.8, 139.0, 134.3, 133.8, 118.4, 118.3, 117.7, 110.4, 108.2, 102.3, 94.7, 94.3, 79.7, 77.8, 71.2, 56.2, 56.1, 40.2, 33.8, 31.6, 29.5, 28.2, 25.8, 25.6, 19.4.

(4*R*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoate 2′,2′-dioxide (10′-*epi*-**195)**



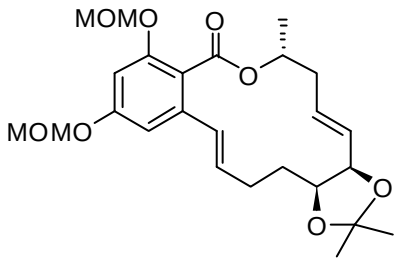
To a solution of thioether 10′-*epi*-**167** (27 mg, 52 μmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added 75% *m*-CPBA (26 mg, 0.112 mmol). The reaction was left to warm to rt whilst stirring for 2 h. The reaction was quenched with the addition of 20% aqueous Na_2SO_3 solution (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with sat. $NaHCO_{3(aq)}$ solution (20 mL), dried over $MgSO_4$, filtered and reduced *in vacuo* to give a colourless oil. The product was purified by flash column chromatography (silica, gradient elution 3:1 to 2:1 hexanes/EtOAc) yielding the title compound as a colourless oil (23 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 2.2 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.5, 1.1 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.18 (s, 2H), 5.17 – 5.14 (m, 3H), 5.11 (ddt, *J* = 9.0, 2.0, 1.1 Hz, 1H), 4.48 (dd, *J* = 7.5, 6.5 Hz, 1H), 4.38 (d, *J* = 14.1 Hz, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.02 (ddd, *J* = 13.9, 10.2, 5.7 Hz, 1H), 2.94 (ddd, *J* = 13.9, 10.1, 5.7 Hz, 1H), 2.47 (m, 1H), 2.40 (m, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.52 (m, 1H), 1.45 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H).

(5*R*,7*E*,9*R*,10*S*)-1,2-(3′,5′-Di-*O*-methoxymethyl)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)-pentadec-7-ene 14,14-dioxide (10′-*epi*-**196)**



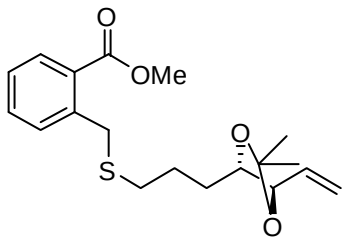
To a solution of the diene 10′-*epi*-**195** (23 mg, 41 μmol) in CH_2Cl_2 (8.5 mL) in a 100 mL MW Teflon™ reactor vessel was added a catalytic amount of Grubbs' second generation catalyst (3.5 mg, 4.1 μmol). The vessel was flushed with argon before sealing with the cap. The vessel was placed in the MW carousel and the probe inserted into the reaction vessel. The vessel was irradiated for 30 min and heated to 75 °C. Once the reaction vessel had cooled to rt the cap was removed and the solution transferred to a round-bottom flask. The solvent was removed to yield a brown oil. The crude product was purified on a silica column (gradient chromatography, 5:1 to 2:1 hexanes/EtOAc) returning diene 10′-*epi*-**195** (2.5 mg) and yielding compound 10′-*epi*-**196** as a colourless oil (18.5 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 5.86 (ddd, *J* =

15.7, 7.4, 6.2 Hz, 1H), 5.68 (dd, *J* = 15.7, 8.5 Hz, 1H), 5.40 (m, 1H), 5.19 (m, 1H), 5.19 (d, *J* = 5.3 Hz, 1H), 5.18 (s, 2H), 5.16 (d, *J* = 6.9 Hz, 1H), 4.53 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.42 (d, *J* = 14.5 Hz, 1H), 4.15 (m, 1H), 4.14 (d, *J* = 14.4 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 3.08 (ddd, *J* = 14.7, 9.8, 6.1 Hz, 1H), 2.85 (ddd, *J* = 14.7, 8.5, 5.0 Hz, 1H), 2.50 – 2.39 (m, 2H), 1.81 (m, 1H), 1.76 – 1.62 (m, 3H), 1.47 (s, 3H), 1.42 (d, *J* = 6.3 Hz, 3H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 159.1, 156.2, 130.2, 129.4, 128.0, 119.0, 111.7, 108.2, 104.0, 94.7, 94.4, 79.2, 77.0, 72.5, 56.4, 56.4, 56.1, 51.9, 37.7, 28.1, 27.7, 25.4, 20.1, 18.5. HRMS (ESI) calcd. for $C_{25}H_{36}O_{10}SNa^+$ $[M + Na]^+$ 551.1927, found 551.1923.



(5′*S*,6′*R*,10′R)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)-aigialomycin D (10′-*epi*-**35)**

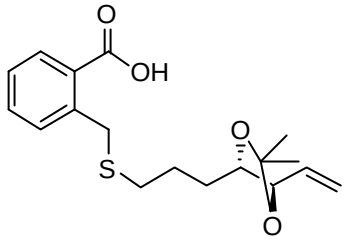
To a solution of sulfone 10′-*epi*-**196** (12 mg, 23 μmol) in *t*-BuOH (250 μl) and CH_2Cl_2 (100 μL) was added powdered KOH (25 mg, 0.46 mmol) at rt. To the resulting suspension was added CCl_4 (250 μmol) dropwise over 2 min. The reaction was then heated to 35 °C for 30 min. After cooling to rt the solvent was removed to dryness and the residue partitioned between sat. $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (5 mL). The aqueous layer was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced to dryness. Purification was attempted by flash column chromatography (silica, gradient elution 10:1 to 5:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.4 Hz, 1H), 5.86 (ddd, *J* = 15.6, 7.6, 6.0 Hz, 1H), 5.67 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.18 (d, *J* = 6.7 Hz, 1H), 5.17 (m, 1H), 5.16 (s, 2H), 5.14 (d, *J* = 6.8 Hz, 1H), 4.57 (dd, *J* = 7.8, 6.0, Hz, 1H), 4.16 (m, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 2.64 (ddd, *J* = 10.7, 8.1, 3.3 Hz, 1H), 2.43 (m, 1H), 2.34 (m, 1H), 2.11 – 2.01 (m, 1H), 1.88 – 1.80 (m, 2H), 1.49 (s, 3H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 158.8, 155.4, 137.6, 132.8, 130.3, 128.8, 128.2, 107.8, 106.4, 102.5, 94.8, 94.3, 79.6, 78.1, 72.2, 56.2, 56.1, 37.5, 28.3, 28.2, 28.1, 25.6, 20.2.



Methyl (6′*S*,7′*R*)-6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)benzoate (326)

To solution of bromide **210** (531 mg, 2.32 mmol) and thioactate **189** (566 mg, 2.32 mmol) in MeOH (10 mL) was

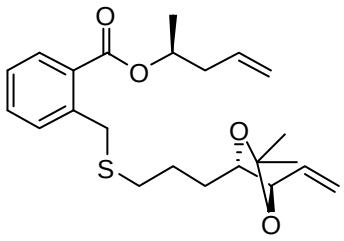
degassed with bubbling argon for 10 min. To this solution was added K_2CO_3 (641 mg, 4.64 mmol) and the reaction stirred for 18 h at rt. The solvent was removed and the crude residue partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organics fractions were washed with sat. $NH_4Cl_{(aq)}$ (10 mL), dried over $MgSO_4$, filtered and reduced to give a colourless oil. The product was purified using flash column chromatography (silica, gradient elution 20:1 to 5:1 hexanes/EtOAc) affording the title compound as a colourless oil (683 mg, 84%). $[\alpha]_D^{22}$ = -14.6 (*c* 0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.43 (td, *J* = 7.6, 1.4 Hz, 1H), 7.33 – 7.28 (m, 2H), 5.78 (ddd, *J* = 17.3, 10.3, 7.8 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.46 (dd, *J* = 7.9, 6.9 Hz, 1H), 4.12 – 4.05 (m, 3H), 3.90 (s, 3H), 2.45 (t, *J* = 5.9 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.58 – 1.45 (m, 2H), 1.46 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 140.6, 134.3, 131.7, 131.1, 130.9, 129.5, 127.0, 118.3, 108.2, 79.7, 77.8, 52.1, 34.5, 31.6, 29.5, 28.2, 25.9, 25.6. IR (KBr): 2986, 2938, 1723, 1434, 1379, 1262, 1216, 1123, 1077, 1046, 1011, 928, 872, 769, 716. HRMS (ESI) calcd. for $C_{19}H_{26}O_4SNa^+$ $[M + Na]^+$ 373.1450, found 373.1444; $C_{19}H_{26}O_4SK^+$ $[M + K^+]$ 389.1189, found 389.1189.



(6′*S*,7′*R*)-6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)benzoic acid (327)

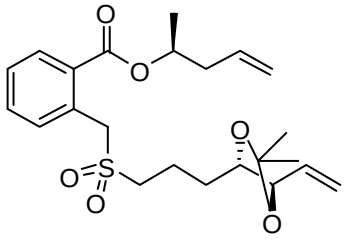
To a solution of solution of ester **326** (252 mg, 0.72 mmol) in MeOH (5 mL) was added a solution of KOH (202 mg, 3.61 mmol) in H_2O (5 mL). The reaction was warmed to 80 °C for 4 h. The reaction was cooled to rt and extracted with Et_2O (2 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The residue was identified as disulfide **190**. The aqueous layer was acidified to pH 1 with 10% HCl and extracted with Et_2O (3 x 10 mL). The second organic layer was dried over $MgSO_4$, filtered and reduced to give the acid as a colourless oil (212 mg, 92%). The product was deemed pure by ^{1}H NMR and was not purified further. $[\alpha]_D^{20}$ = -26.5 (*c* 0.12, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 – 7.32 (m, 2H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.28 (ddd, *J* = 17.1, 1.7, 1.3 Hz, 1H), 5.22 (ddd, *J* = 10.3, 1.5, 0.8 Hz, 1H), 4.47 (dd, 7.9, 6.9 Hz, 1H), 4.18 (d, *J* = 13.3 Hz, 1H), 4.14 (d, *J* = 14.1 Hz, 1H), 4.10 (ddd, *J* = 8.9, 6.2, 4.5 Hz, 1H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.75 (m, 1H), 1.66 – 1.49 (m, 2H), 1.47 (s, 3H), 1.45 (m, 1H), 1.35 (s, 3H). IR (neat): 1692, 1372, 1298,

1267, 1242, 1218, 1046, 913, 873, 733 cm^{-1}.HRMS (ESI) calcd. for $C_{18}H_{24}O_4SNa^+$ [M + Na]$^+$ 359.1293, found 359.1288.



(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6,7-*O*-(1-methylethylidene)-2-thianon-8-enyl)benzoate (328)

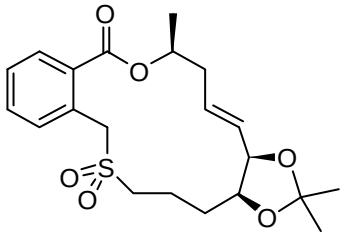
To a solution of alcohol **22** (46 μL, 0.446 mmol) and PPh_3 (195 mg, 0.744 mmol) in THF (5 mL) at 0 ˚C was added DIAD (145 μL, 0.744 mmol). The solution was stirred at 0 ˚C for 20 min during which time a white precipitate formed. After this time a solution of the acid **327** (100 mg, 0.298 mmol) in THF (2 mL) was added dropwise and the reaction mixture was left to stir at rt for 16 h. To the crude reaction mixture was added silica gel before removal of solvent. The silica gel was dry loaded onto a silica column and eluted (20:1 hexanes/EtOAc) yielding a colourless oil (103 mg, 85%). $[\alpha]_D^{22}$ = -21.9 (*c* 0.75, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.41 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 – 7.27 (m, 2H), 5.85 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.78 (ddd, *J* = 17.1, 9.8, 7.8 Hz, 1H), 5.29 (d, *J* = 17.1, 1H), 5.22 (d, *J* = 12.1, 1H), 5.21 (m, 1H), 5.15 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.11 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.46 (dd, *J* = 7.8, 6.8 Hz, 1H), 4.14 – 4.04 (m, 3H), 2.55 – 2.38 (m, 4H), 1.72 (m, 1H), 1.61 – 1.41 (m, 3H), 1.46 (s 3H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 140.4, 134.3, 133.7, 131.5, 130.9, 130.8, 130.3, 126.9, 118.4, 117.9, 108.2, 79.7, 77.8, 70.9, 40.3, 34.4, 31.6, 29.5, 28.2, 25.9, 25.6, 19.5. IR(neat): 2983, 2934, 1713, 1379, 1260, 1216, 1118, 1072, 1047, 994, 922 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{32}O_4SNa^+$ [M + Na]$^+$ 427.1919, found 427.1914.



(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)benzoate 2′,2′-dioxide (329)

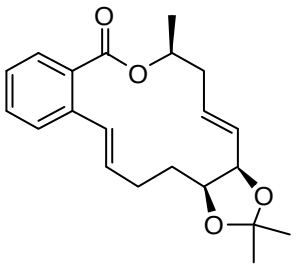
To a solution of thioether **328** (125 mg, 0.309 mmol) in CH_2Cl_2 (7 mL) at 0˚C was added ~75% *m*-CPBA (157 mg, 0.681 mmol). The solution was strirred at rt for 2 h. The reaction was quenched with addition of 20% Na_2SO_3 (10 mL). The solution was stirred for 20 min before the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with sat. $NaHCO_{3(aq)}$ (10 mL), dried over $MgSO_4$ and filtered. The crude product was purified using flash column chromatography (silica, gradient elution 3:1 to 1:1 hexanes/EtOAc) affording the title

compound as a colourless oil (124 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.49 – 7.41 (m, 1H), 5.84 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.78 (m, 1H), 5.78 (ddd, *J* = 7.7, 9.8, 17.2 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 8.9 Hz, 1H), 5.18 (dd, *J* = 2.1, 3.8 Hz, 1H), 5.11 (d, *J* = 8.3 Hz, 1H), 4.94 (d, *J* = 13.5 Hz, 1H), 4.84 (d, *J* = 13.5 Hz, 1H), 4.49 (dd, *J* = 6.8, 7.8 Hz, 1H), 4.09 (dd, *J* = 6.5, 13.2, 1H), 3.09 – 2.85 (m, 2H), 2.57 – 2.35 (m, 2H), 2.07 – 1.79 (m, 2H), 1.56 – 1.51 (m, 2H), 1.44 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H). IR(neat): 2980, 2928, 1711, 1299, 1268, 1116, 1076, 911, 733 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{32}O_6SNa^+$ [M + Na]$^+$ 459.1817, found 459.1817.



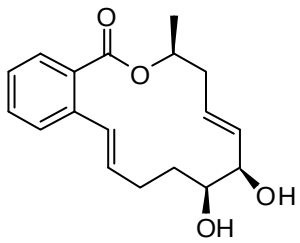
(5*S*,7*E*,9*R*,10*S*)-1,2-benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)-pentadec-7-ene 14,14-dioxide (330)

To a solution of diene **329** (120 mg, 28 μmol) in CH_2Cl_2 (55 mL) in a 50 mL MW Teflon™ reactor vessel was added a catalytic amount of Grubbs' 2nd generation catalyst (23 mg, 28 μmol). The vessel was flushed with argon before sealing with the cap. The vessel was placed in the MW carousel and probe inserted into the reaction vessel. The vessel was irradiated for 30 min and heated to 75 ˚C. Once the reaction vessel had cooled to rt the cap was removed and the solution transferred to a round bottom flask. The solvent was removed to yield a brown oil. The crude oil was dissolved up in CH_2Cl_2 and silica added to form a slurry. The solvent was removed to form a free flowing powder. The silica was loaded onto a silica column and eluted (10:1 hexanes/EtOAc) to give the macrocyle as a white solid (97 mg, 86%). mp 180 – 181 °C. $[\alpha]_D^{22}$ = -11.3 (*c* 0.54, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.6, 1.5 Hz, 1H), 7.45 (td, *J* = 7.7, 1.3 Hz, 1H), 5.94 (d, *J* = 14.8 Hz, 1H), 5.83 (ddd, *J* = 15.1, 10.2, 3.6 Hz, 1H), 5.49 (ddd, *J* = 15.3, 9.6, 1.8 Hz, 1H), 5.40 (m, 1H), 4.42 (dd, *J* = 9.6, 5.7 Hz, 1H), 4.07 (ddd, *J* = 9.8, 5.6, 3.6 Hz, 1H), 2.57 – 2.49 (m, 3H), 2.42 (dt, *J* = 15.6, 10.4 Hz, 1H), 1.72 – 1.64 (m, 2H), 1.60 – 1.49 (m, 2H), 1.42 (m, 1H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.41 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 133.2, 132.9, 132.8, 131.6, 130.6, 129.4, 128.9, 127.7, 107.8, 79.6, 77.3, 71.2, 54.4, 50.9, 40.6, 28.3, 27.9, 25.6, 21.4, 19.0. IR (neat): 2932, 2879, 1706, 1448, 1295, 1244, 1223, 1109, 1072, 1033, 973, 915, 731 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{28}O_6SNa^+$ [M + Na]$^+$ 431.1504, found 431.1502.



(5′*S*,6′*R*,10′*S*)-2,4-Dideoxy-5′,6′-*O*-(1-methylethylidene)-aigialomycin D (331)

To a solution of sulfone **330** (70 mg, 0.172 mmol) in $^{t}BuOH/CH_2Cl_2$ (750 μL/300 μL) was added powdered KOH (214 mg, 3.82 mmol) at rt. To the resulting suspension was added CCl_4 (750 μL) dropwise over 2 min. The reaction was then heated to 35 ˚C for 30 min. After cooling to rt the solvent was removed to dryness and the residue partitioned between sat. $NH_4Cl_{(aq)}$ (10 mL) and EtOAc (10 mL). The aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced to give a white solid. The product was purified using silica column chromatography (silica, 10:1 hexanes/EtOAc) yielding a white solid (47 mg, 80%). $[\alpha]_D^{22}$ = -34.8 (*c* 0.59, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 (td, *J* = 7.4, 1.0 Hz, 1H), 7.25 (td, *J* = 7.5, 1.2 Hz, 1H), 6.67 (d, *J* = 15.5 Hz, 1H), 6.12 (ddd, *J* = 15.3, 9.3, 5.2 Hz, 1H), 5.80 (m, 1H), 5.66 (ddt, *J* = 15.3, 8.9, 1.4 Hz, 1H), 5.24 (dq, *J* = 12.2, 6.1 Hz, 1H), 4.60 (dd, *J* = 8.9, 5.5 Hz, 1H), 4.19 (ddd, *J* = 11.5, 5.5, 2.9 Hz, 1H), 2.55 (dd, *J* = 7.3, 5.9 Hz, 2H), 2.31 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.64 (m, 1H), 1.48 (s, 3H), 1.40 (d, *J* = 6.1 Hz, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 136.2, 131.3, 131.1, 130.9, 130.4, 130.1, 129.6, 129.1, 126.9, 125.8, 108.2, 79.7, 77.3, 72.4, 39.5, 29.2, 29.1, 28.5, 25.8, 20.3. IR(neat): 2984, 2936, 1703, 1450, 1379, 1291, 1257, 1216, 1121, 1043, 971 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{26}O_4Na^+$ $[M + Na]^+$ 365.1729, found 365.1722.



2,4-Dideoxy-aigialomycin D (204)

To a solution of macrolide **331** (34 mg, 99 μmol) in MeOH (1.5 mL) was added 1M HCl (1.5 mL). The reaction was stirred for 2 days at rt. The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced to dryness. The crude was purified by flash column chromatography (diol silica, gradient elution CH_2Cl_2 to 5% $MeOH/CH_2Cl_2$) yielding a white solid (26 mg, 80%). $[\alpha]_D^{23}$ = -117.0 (*c* 0.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 6.97 (d, *J* = 16.2 Hz, 1H), 6.23 (dt, *J* = 16.1, 5.4 Hz, 1H), 5.88 (m, 1H), 5.67 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.35 (m, 1H), 4.41 (d, *J* = 5.5 Hz, 1H), 3.75 (brs, 1H), 2.60 (m, 1H), 2.44 (dd, *J* = 15.3, 7.6 Hz, 1H), 2.38 (dd, *J* = 11.8, 6.1 Hz, 2H), 2.18 (brs, 1H), 2.09 (m, 1H), 2.04 (s, 1H), 1.65 (m, 1H), 1.39 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 169.0, 137.3, 132.5, 132.0, 131.5, 130.5, 130.2, 127.9, 127.8, 126.7, 126.2, 76.0, 73.0, 71.8, 38.0, 27.4, 26.9, 19.7. IR (neat): 3435, 2976, 2932, 1710, 1448, 1357, 1263, 1123, 1076, 977, 756 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{22}O_4Na^+$ $[M + Na]^+$ 325.1416, found 325.1412.

Appendix

Selected ^{1}H NMR and ^{13}C NMR spectra of key compounds

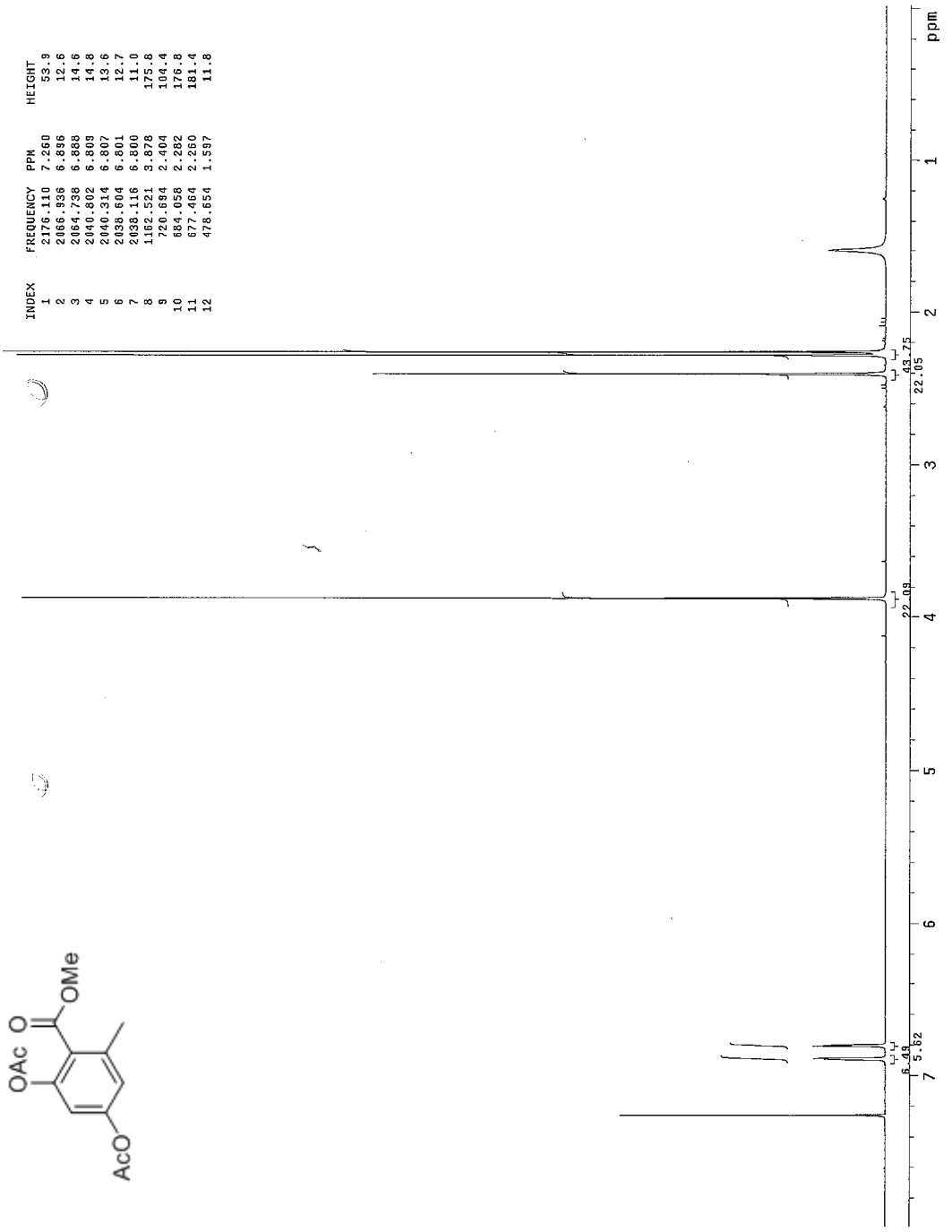


Figure A–1. ^{1}H NMR spectrum of arylmethyl **134** (300 MHz, $CDCl_3$).

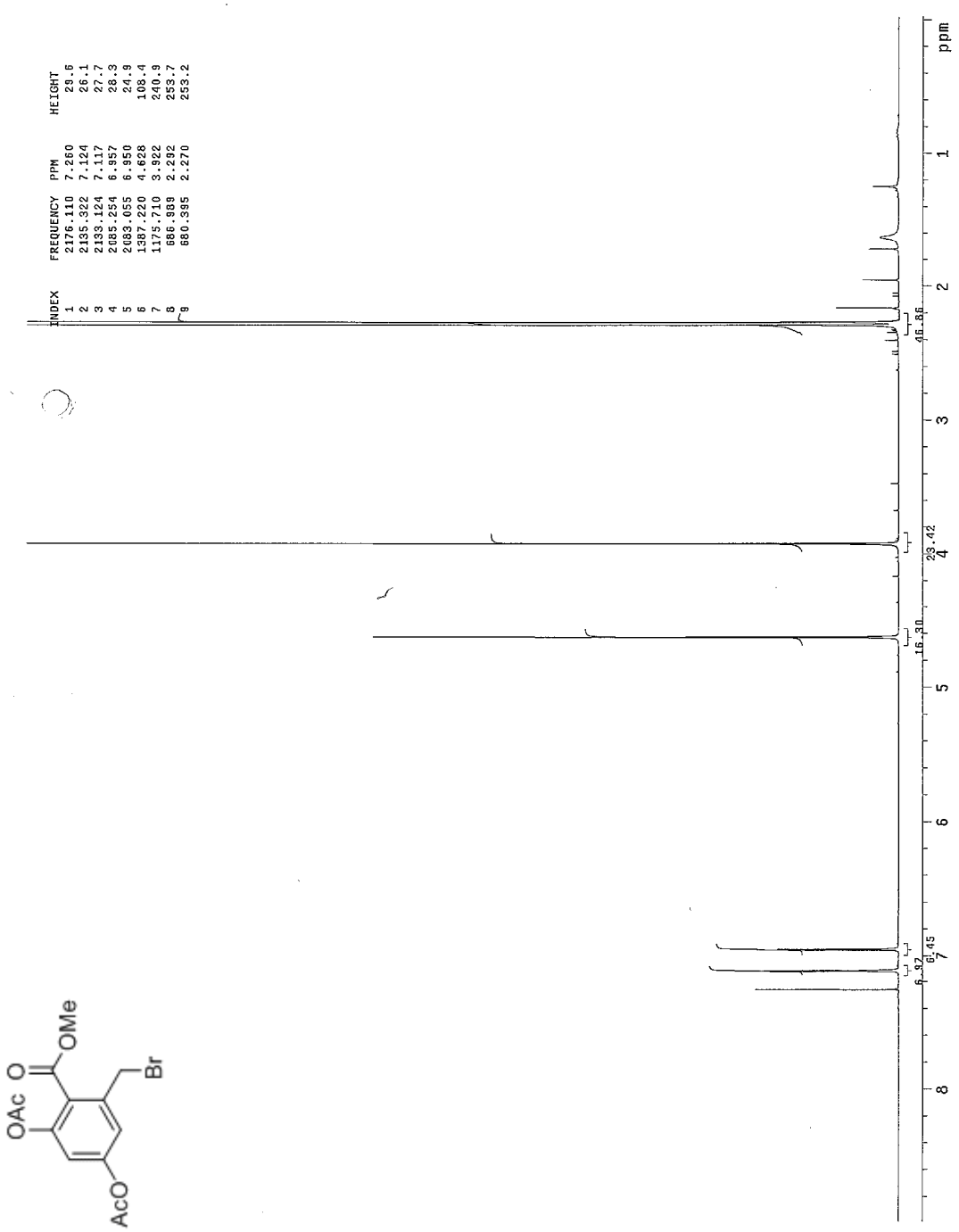


Figure A–2. ^{1}H NMR spectrum of bromide **135** (300 MHz, $CDCl_3$).

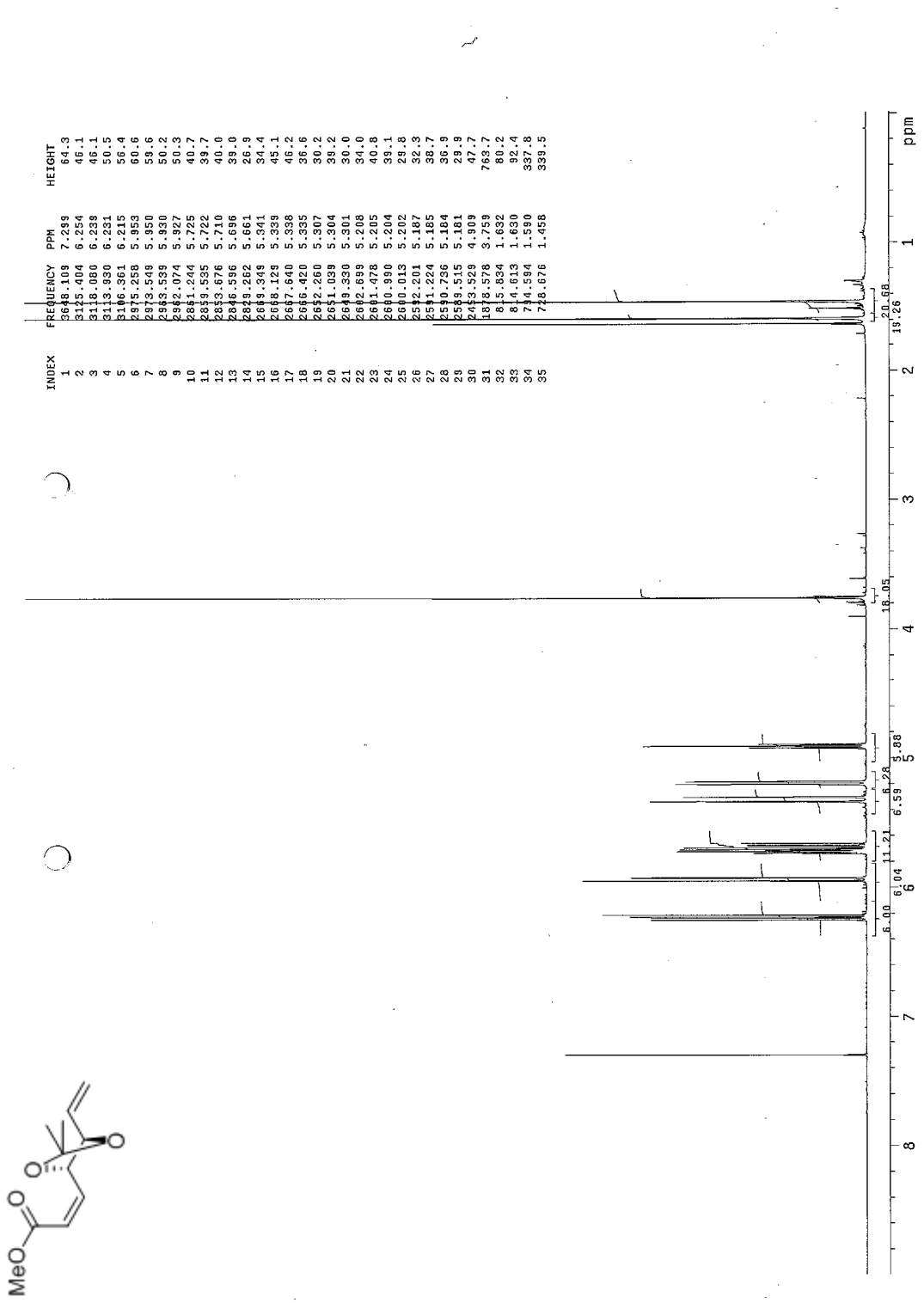


Figure A–3. ^{1}H NMR spectrum of α,β-unsaturated ester (*Z*)-**186** (500 MHz, $CDCl_3$).

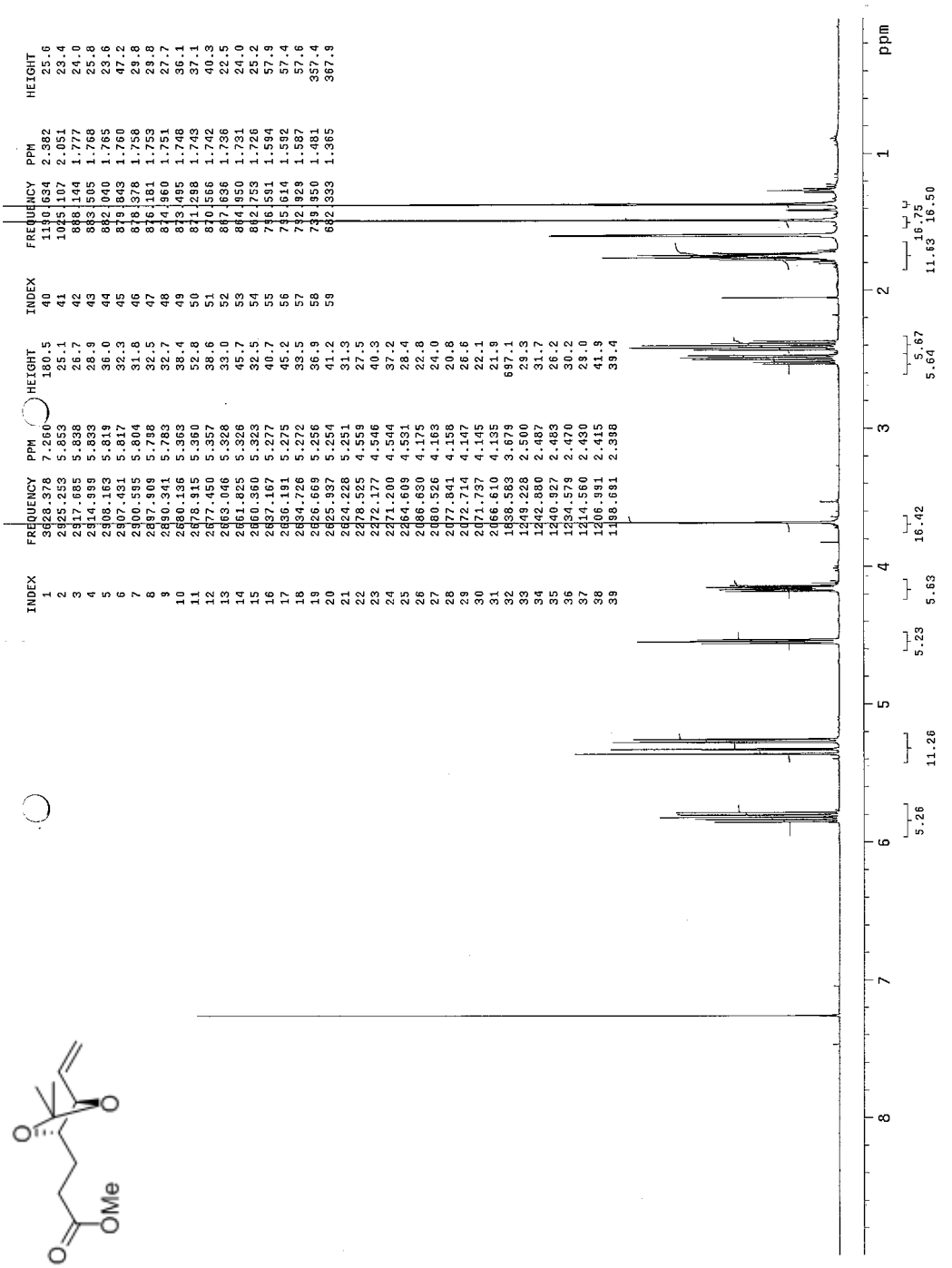


Figure A–4. ^{1}H NMR spectrum of methyl ester **267** (500 MHz, $CDCl_3$).

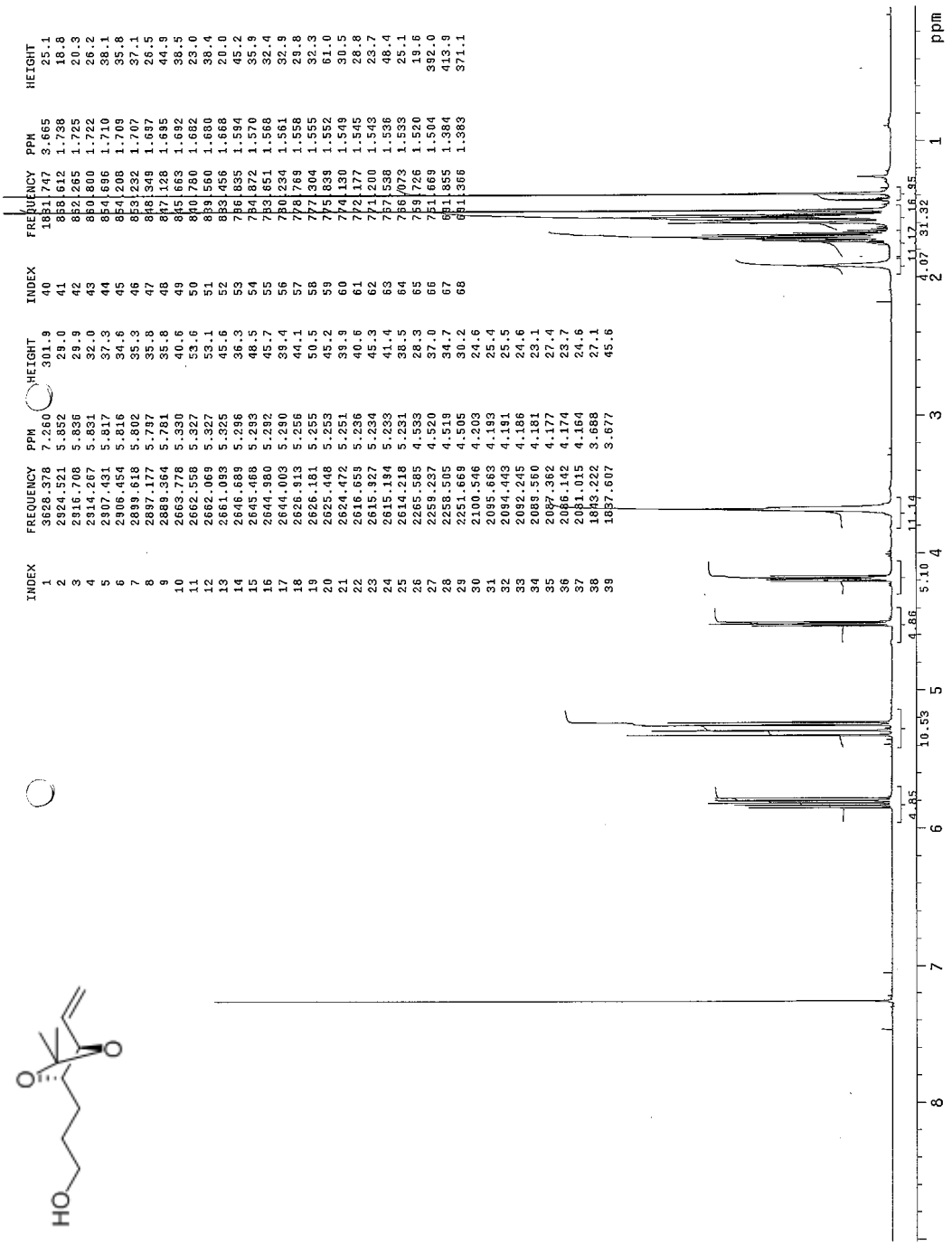


Figure A–5. ^{1}H NMR spectrum of alcohol **187** (500 MHz, $CDCl_3$).

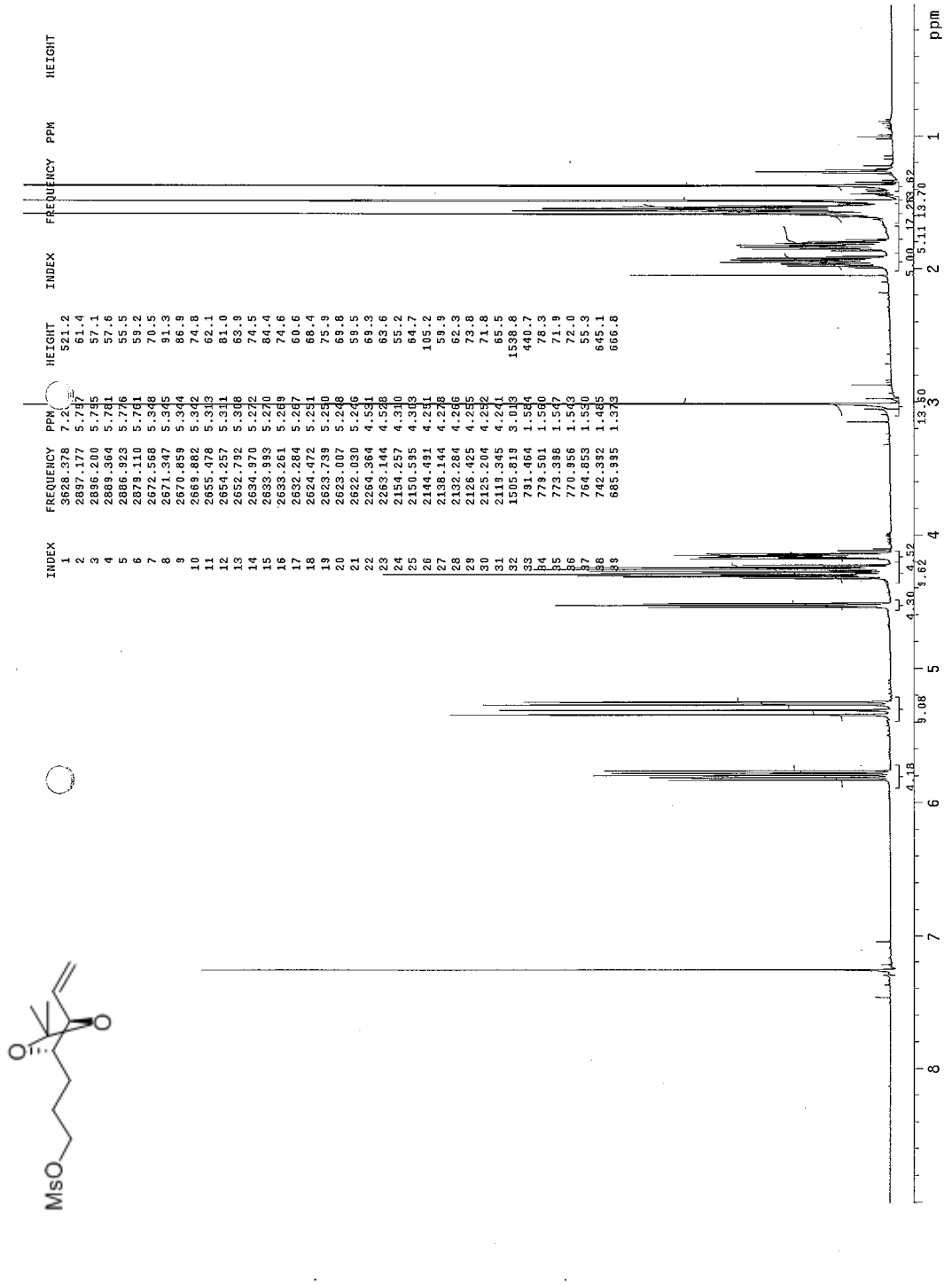


Figure A–6. ^{1}H NMR spectrum of mesylate **188** (500 MHz, $CDCl_3$).

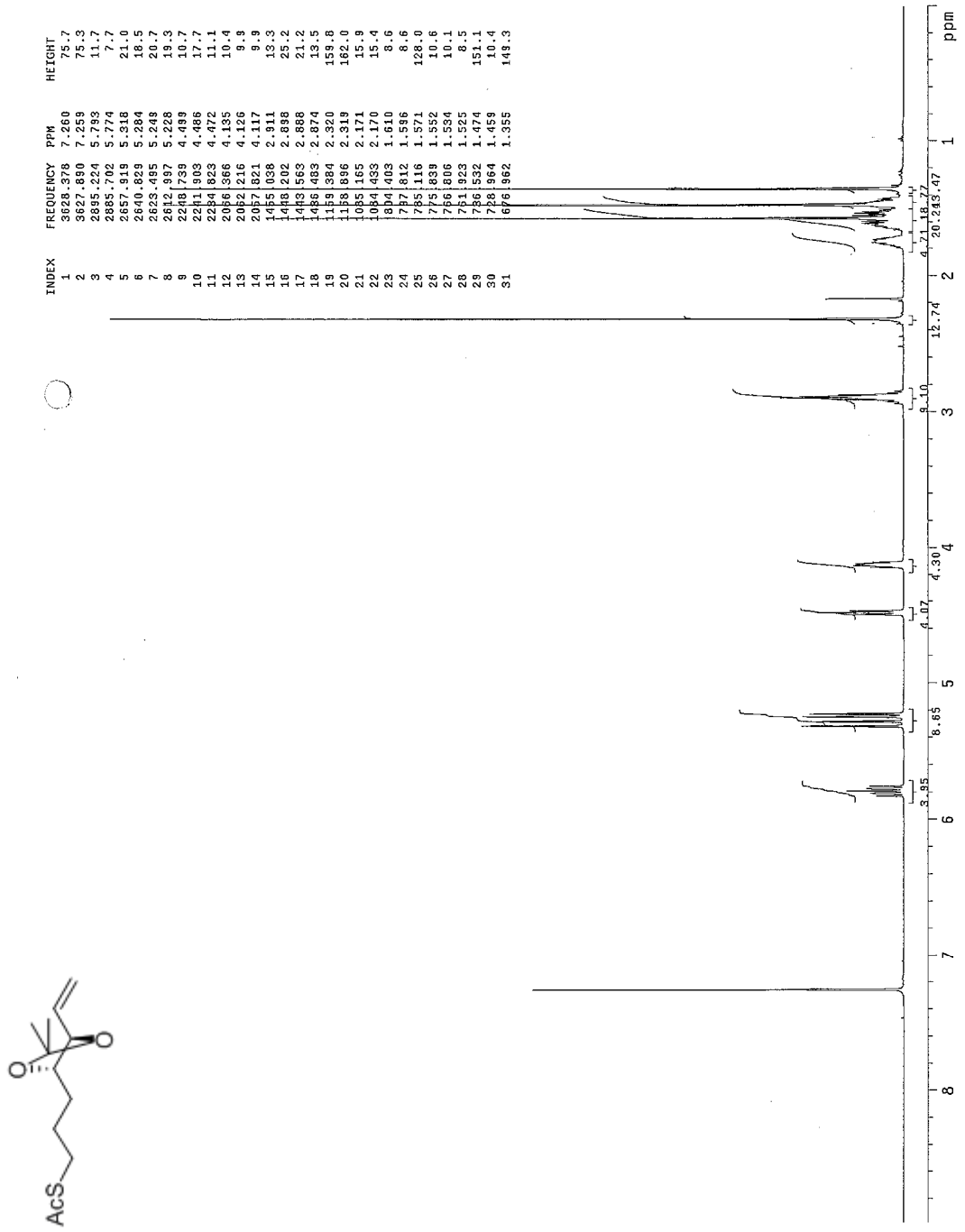


Figure A–7. ^{1}H NMR spectrum of thioacetate **189** (500 MHz, $CDCl_3$).

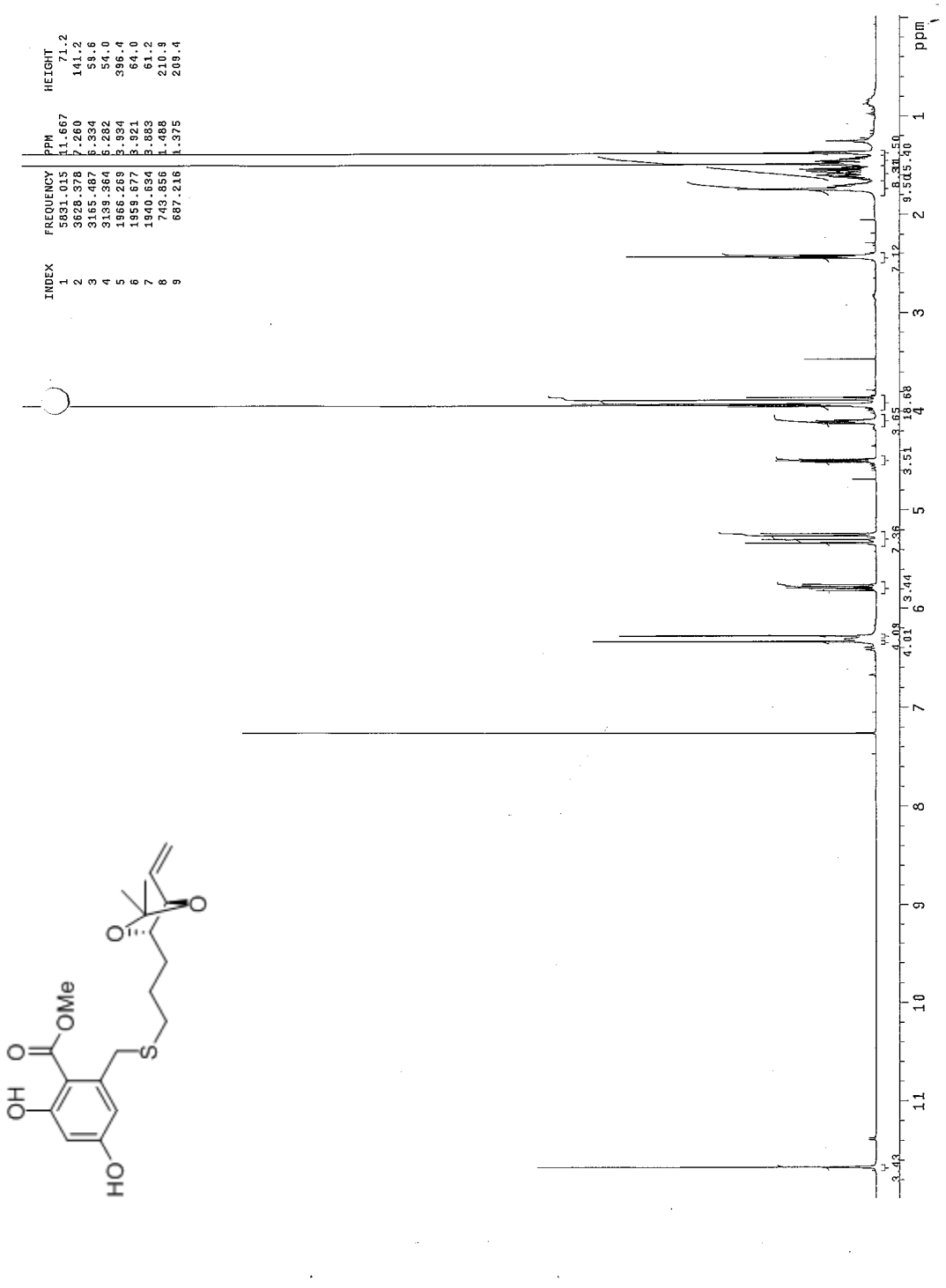


Figure A–8. ^{1}H NMR spectrum of conjugate **191** (500 MHz, $CDCl_3$).

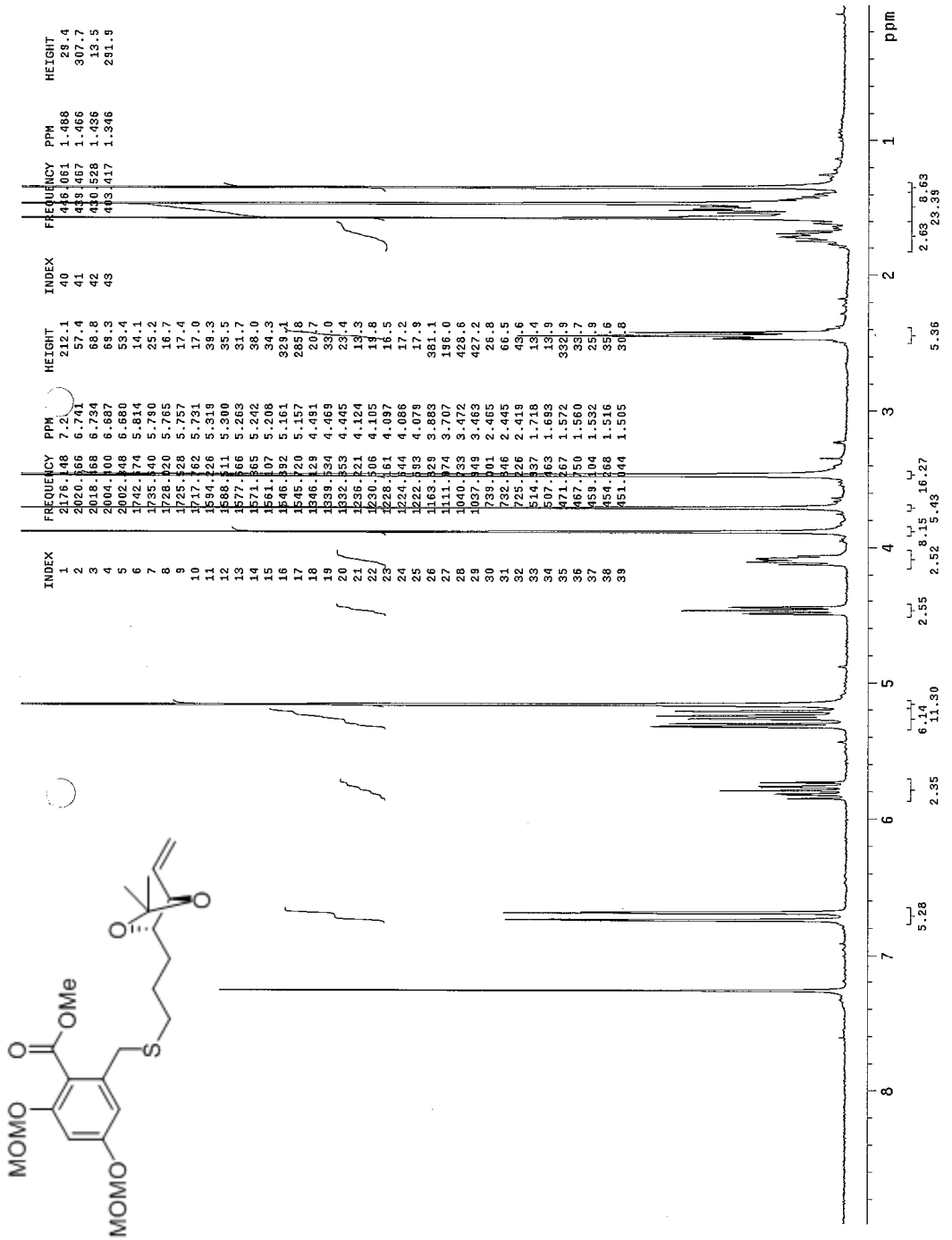


Figure A–9. ^{1}H NMR spectrum of bis-MOM protected **192** (500 MHz, $CDCl_3$).

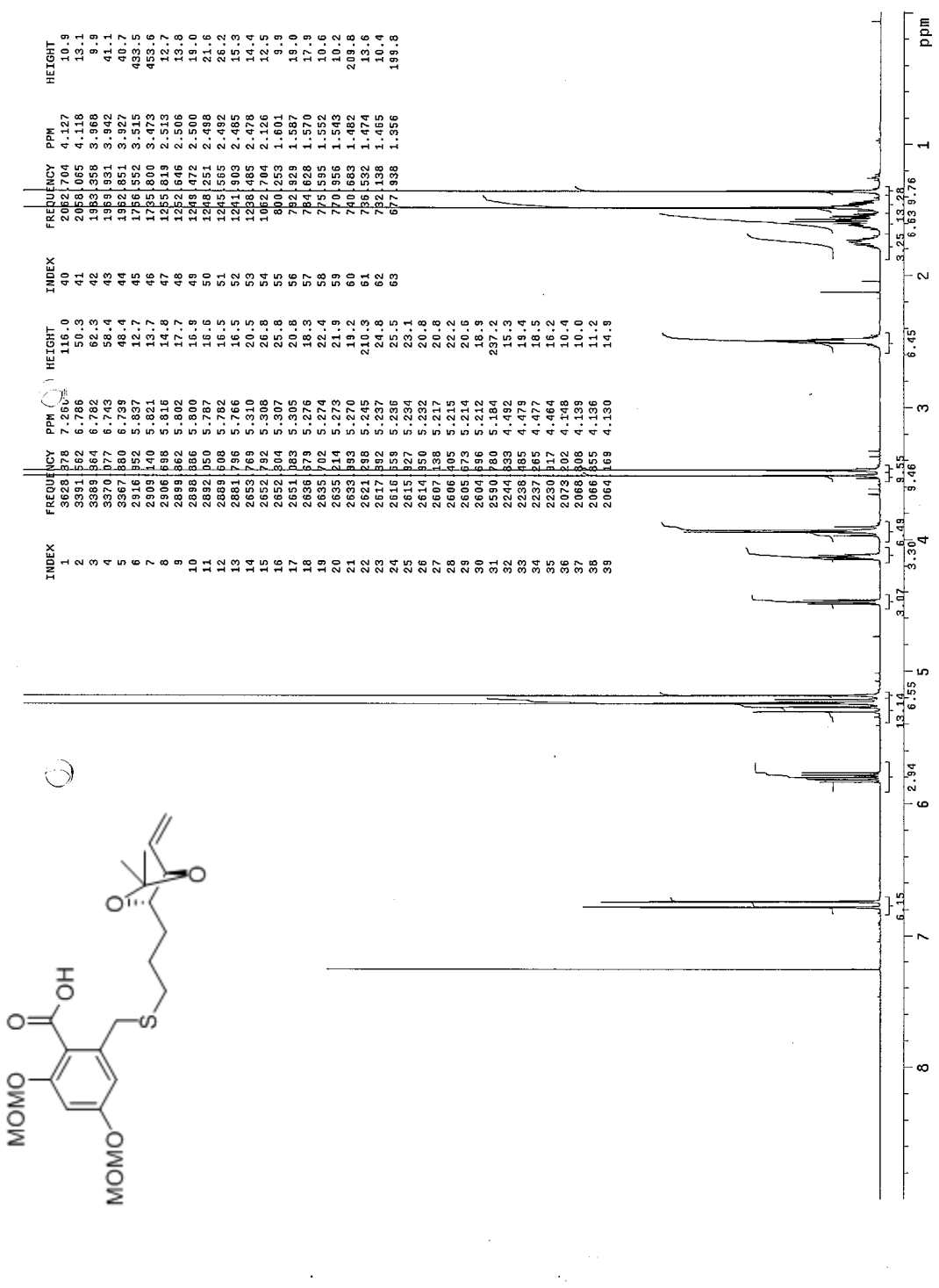


Figure A–10. ^{1}H NMR spectrum of benzoic acid derivative **193** (500 MHz, $CDCl_3$).

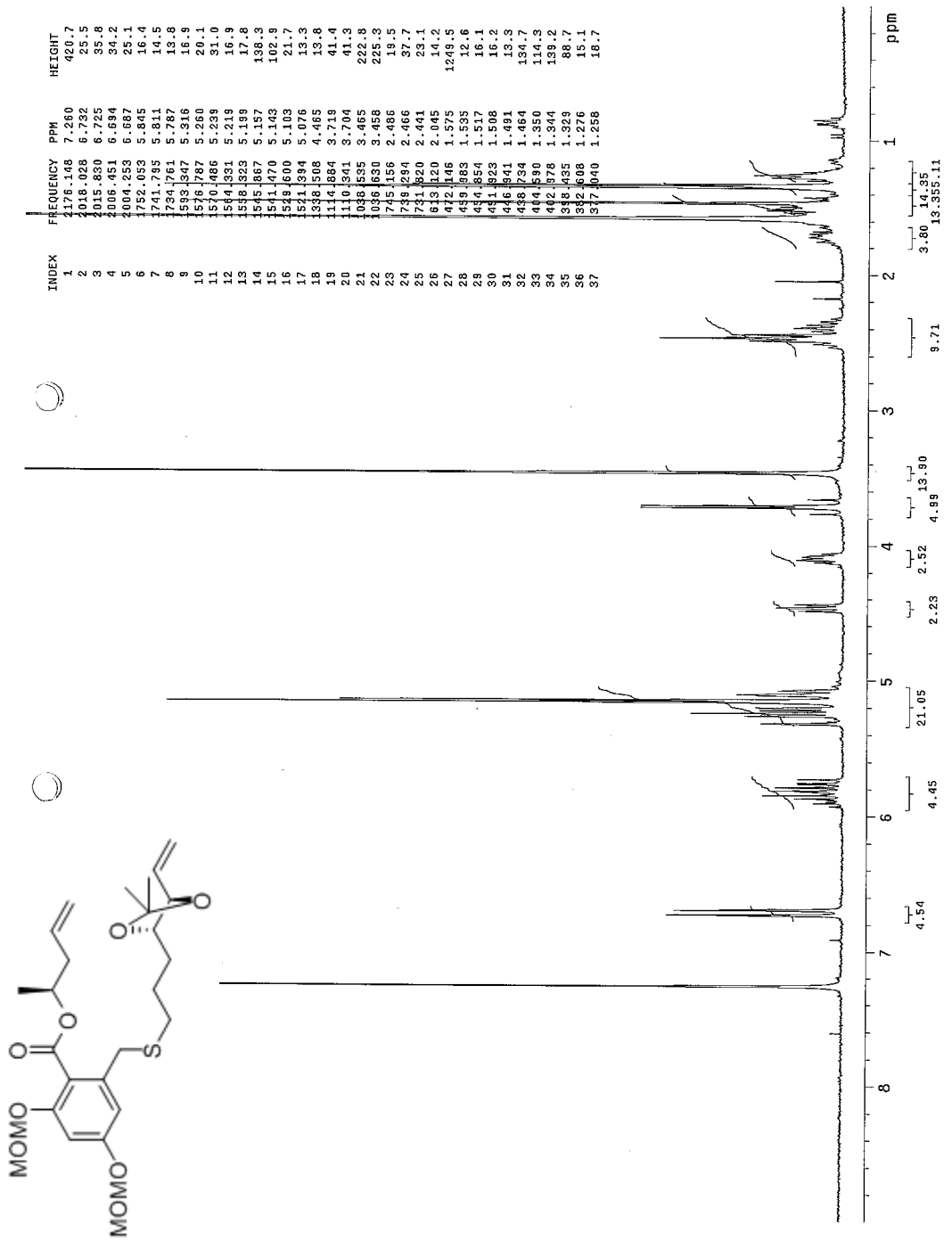


Figure A–11. ^{1}H NMR spectrum of ester **167** (500 MHz, $CDCl_3$).

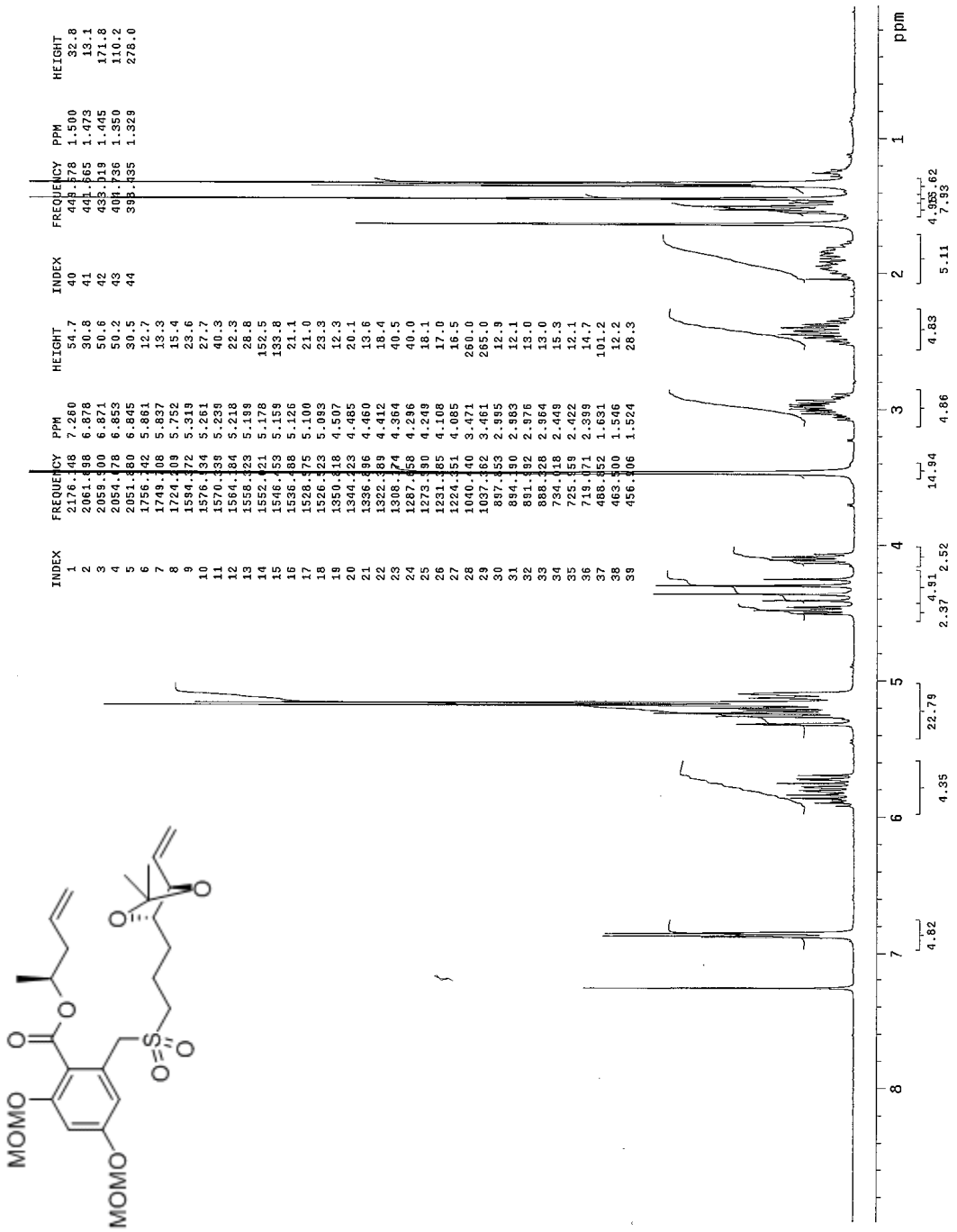


Figure A–12. ^{1}H NMR spectrum of sulfone **195** (500 MHz, $CDCl_3$).

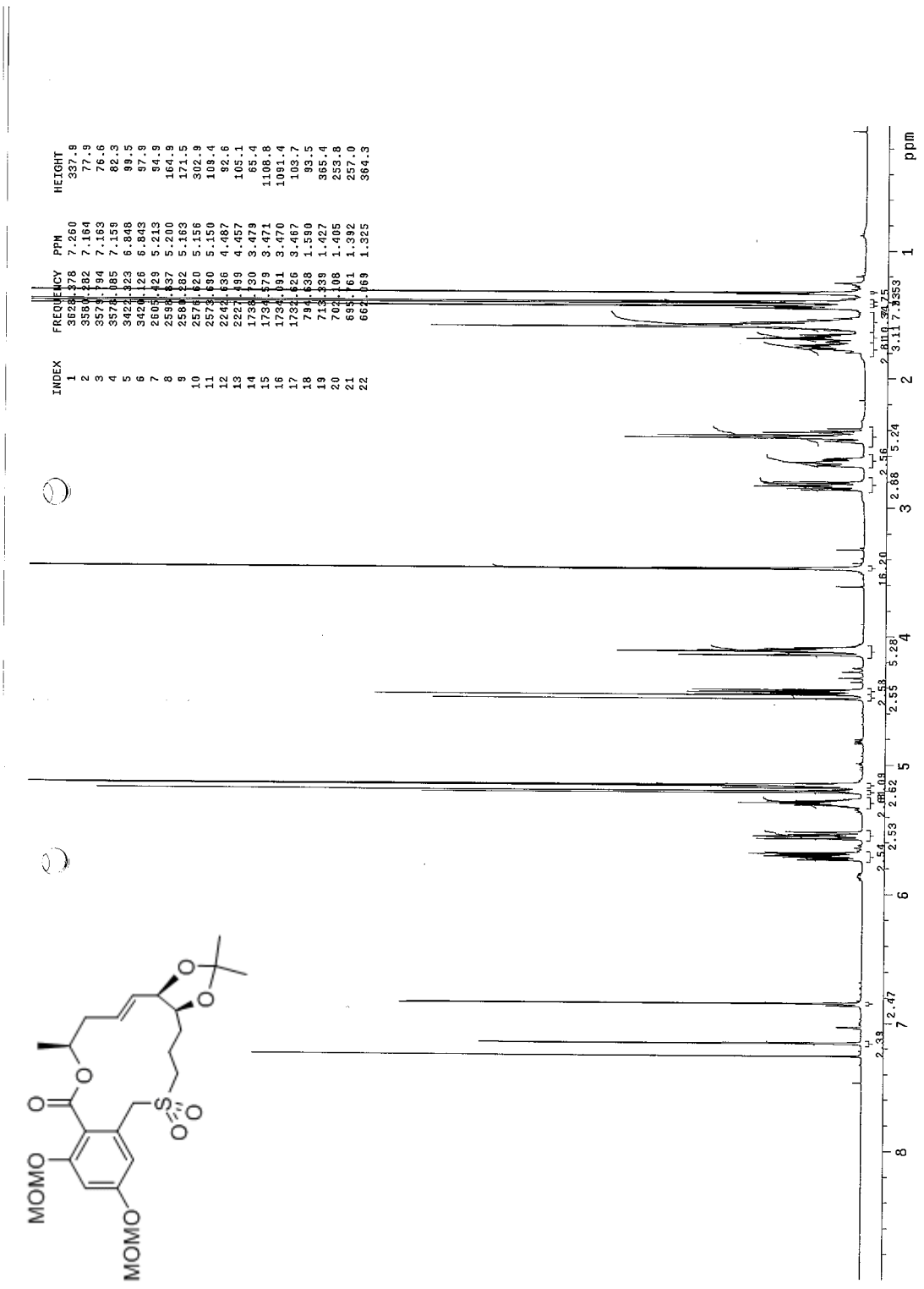


Figure A–13. ^{1}H NMR spectrum of RB precursor **196** (500 MHz, $CDCl_3$).

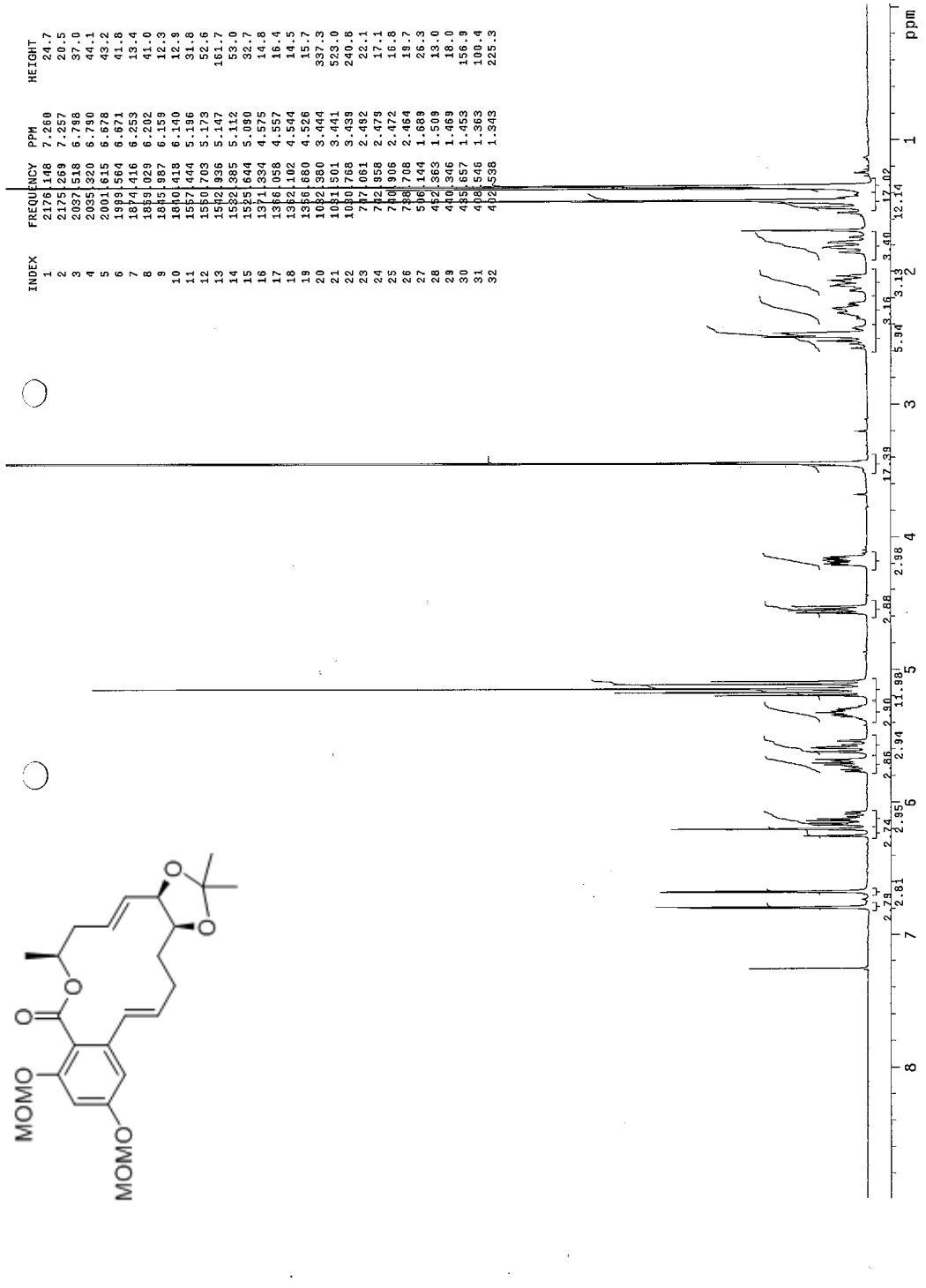


Figure A–14. ^{1}H NMR spectrum of protected Am D **35** (500 MHz, $CDCl_3$).

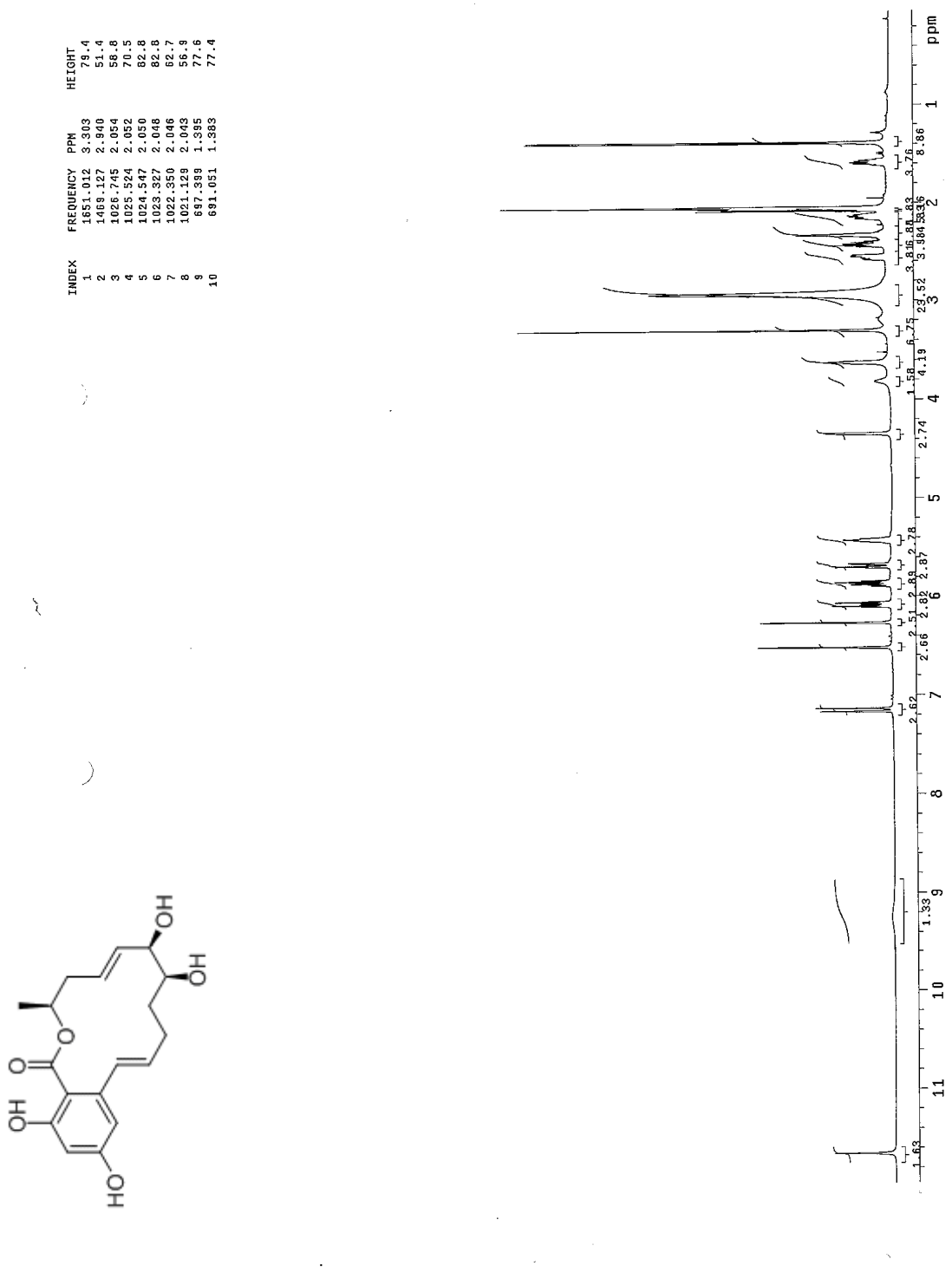


Figure A–15. ^{1}H NMR spectrum of aigialomycin D, **1** (500 MHz, acetone-d_6).

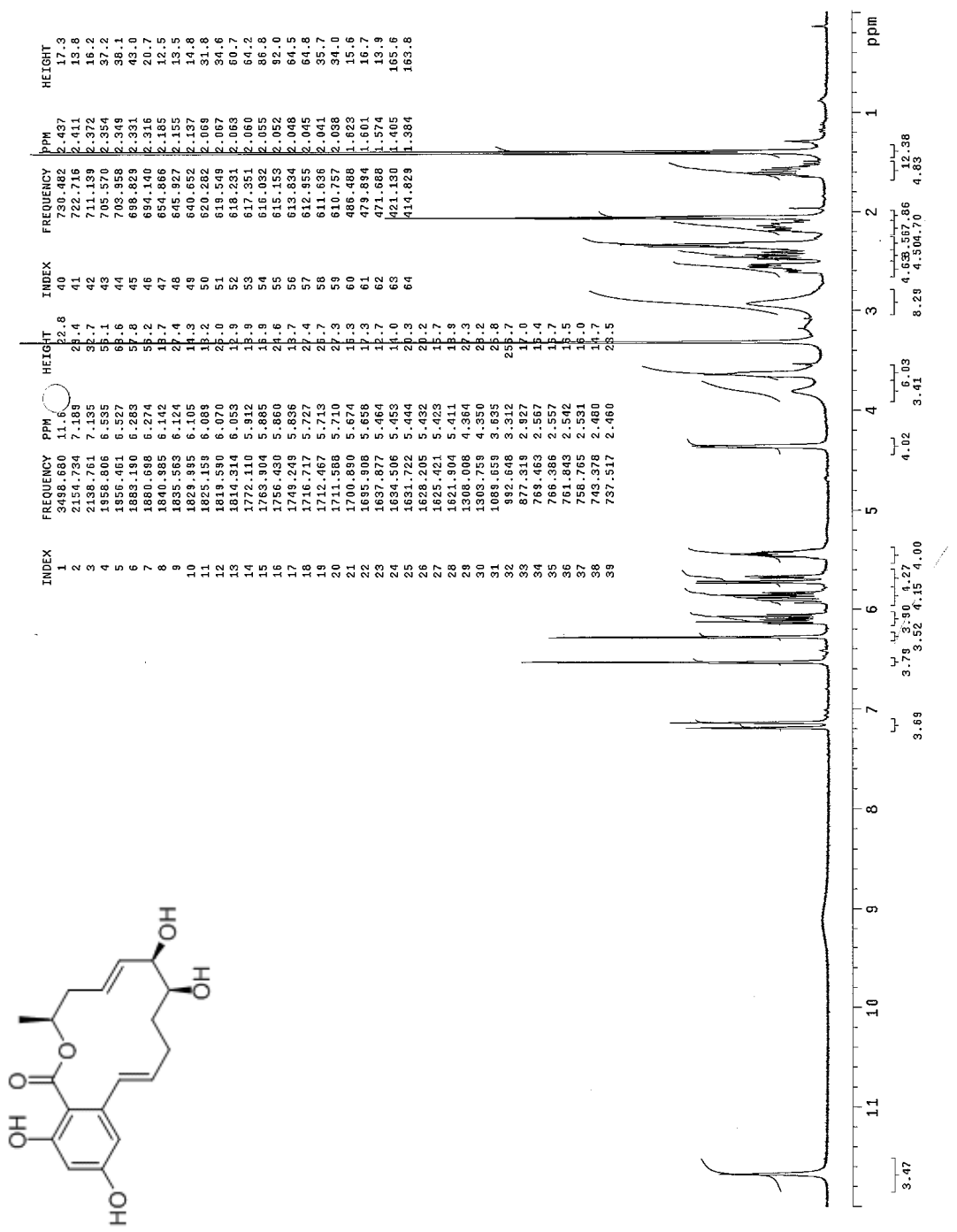


Figure A–16. ^{1}H NMR spectrum of aigialomycin D, **1** (500 MHz, acetone-d_6).

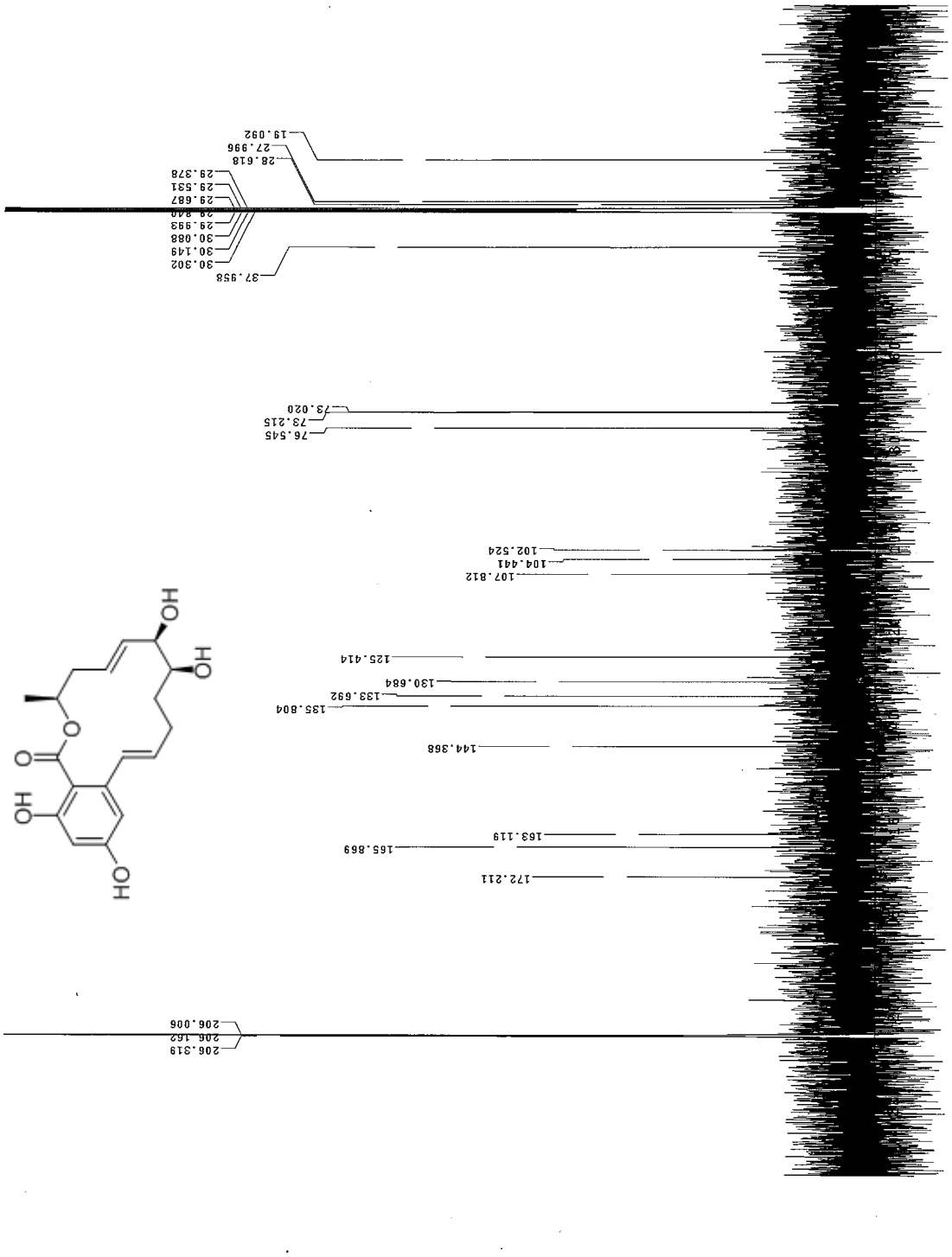


Figure A–17. ^{13}C NMR spectrum of aigialomycin D, **1** (500 MHz, acetone-d_6).

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