STUDIES TOWARDS THE TOTAL SYNTHESIS OF LACTONAMYCIN: INVESTIGATIONS INTO GLYCOSIDATION REACTIONS

A Thesis Submitted by

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in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

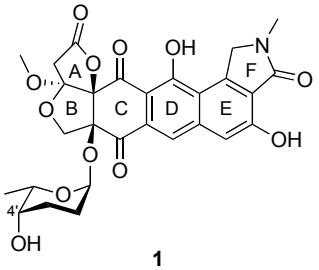
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Abstract

The total synthesis of lactonamycin (**1**), a natural product isolated from a soil sample, by Matsomoto and co-workers[1] is currently under investigation. Lactonamycin (**1**) possesses antimicrobal activity against Gram-Positive bacteria including MRSA and VRE as well as appreciable levels of cytotoxicity against tumor cell lines.[2]

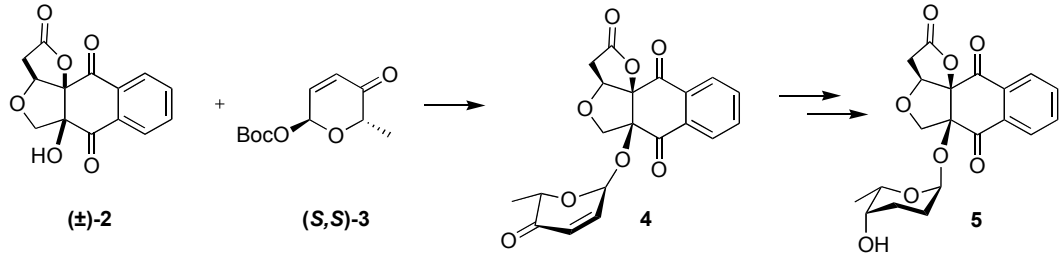


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A highly oxygenated fused perhydrofuran-furanone structural motif and a naphtha[*e*]isoindole ring system make up the hexacylcic core of lactonamycin (**1**). Adding to the structural complexity, a 2,3,6-trideoxy sugar unit is connected to the core structure *via* a highly hindered tertiary glycosidic linkage.

Various strategies for glycosidation, using the known ABCD alcohol **(±)-2** as a model for the tertiary alcohol of lactonamycin (**1**) are discussed. Of these include, the use of classical glycosidation approaches and more novel strategies that employ open chain glycosyl donors.

In particular, the synthesis of glycoside **4** and subsequent investigations towards target compound **5** are described.



(±)-2 **(*S,S*)-3** **4** **5**

Acknowledgements

I thank Professor Tony Barrett for providing me with a challenging project and for his help and advice throughout the course of my PhD.

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And finally, my loving thanks to Gregg.



"*You got to be careful if you don't know where you're going, because you might not get there*." Yogi Berra

Abbreviations

Å	angstrom
Ac	acetate
AD	asymmetric dihydroxylation
Anal.	analysis
app.	apparent
aq.	aqueous
Ar	aryl or aromatic
9-BBN	9-borabicyclo(3.3.1)nonane
Bn	benzyl
Boc	*tert*-butyl carbonate
BOM	benzyloxymethyl
br.	broad
Bu	butyl
Bz	benzoate
°C	degrees Celcius
CAN	ceric ammonium nitrate
cat.	catalytic
CI	chemical ionisation
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
dba	dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec	decomposition
DIAD	di*iso*propyl azodicarboxylate

DIBAl-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DMTST	dimethyl(methylthio)sulfonium triflate
DNP	dinitro phenyl
dppf	*bis*-(diphenylphosphino)ferrocene
dt	doublet of triplets
DTBMP	2,6-di-*tert*-butyl-4-methyl pyridine
dq	doublet of quartets
E	electrophile
Et	ethyl
Equiv./eq	equivalents
FAMSO	methyl methylsulfinylmethyl sulfide
g	gram(s)
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
i.e.	*id est*
imid.	imidazole
IR	infrared spectroscopy
J	coupling constant
L	litre
LDA	lithium di*iso*propylamide
lit	literature
m	multiplet
M	molar
m	*meta*

m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
MRSA	methicillin-resistant *Staphylococcus aureus*
Ms	mesyl
MS	mass spectrometry
m/z	mass/charge
n	normal
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
o	*ortho*
p	*para*
Ph	phenyl
PIFA	phenyliodine(III) bis(trifluoroacetate)
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
Py.	pyridine
q	quartet
quin	quintet
R	general substituents
R_f	retention factor
rt	room temperature

s	singlet
sat.	saturated
t	triplet
td	triplet of doublets
Tf	triflate
TFA	trifluoroacetic acid
tt	triplet of triplets
t or *tert*	*tertiary*
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDMS or TBS	*tert*-butyldimethylsilyl
Temp. or T	temperature
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflic)
TFA	trifluoroacetic acid
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethyl silyl
THF	tetrahydrofuran
Tr	trityl
Ts	*para*-toluenesulfonyl
µL	microlitre(s)
µM	micromole(s)
VRE	vancomycin-resistant *enterococci*
VRSA	vancomycin-resistant *Staphylococcus aureus*

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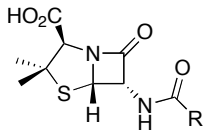
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Chapter 1: Introduction

1.1 Project Background

1.1.1 The Search For Novel Antibiotics

In 1928, bacteriologist Sir Alexander Fleming made a revolutionary, chance discovery from a discarded, contaminated Petri dish.[3] He observed that bacterial cell lysis of colonies of *Staphylococcus aureus* occurred in an area adjacent to the contaminant mold *Penicillium notatum*. On growing the mold in pure culture form, he found that it produced a substance that killed a number of disease-causing bacteria. As a result he proved that the mold contained a powerful antibiotic, now commonly known as penicillin (**6**). Over 50 natural or semi-synthetic penicillins now exist, all of which consist of a β lactam ring with a unique R group attached (Figure 1).



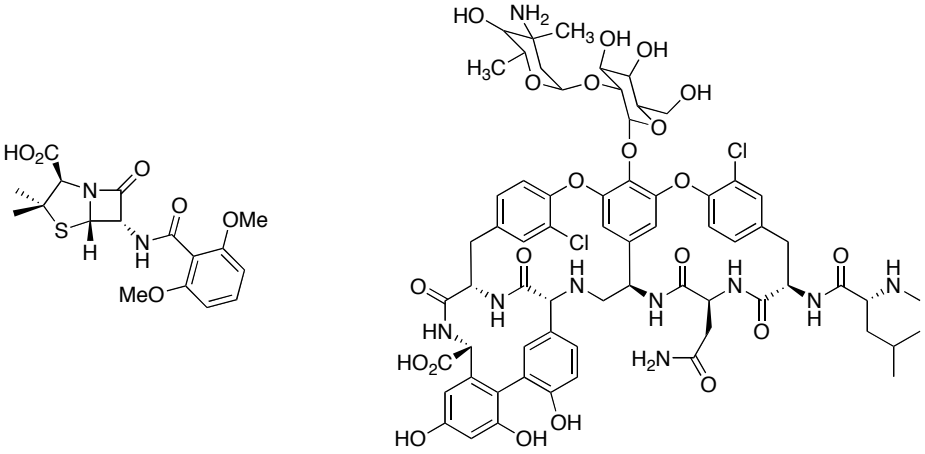
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Figure 1: Penicillin.

Though Fleming was credited for the discovery, it was over a decade before Howard Florey and Ernst Chain isolated and developed the active ingredient in powdery form.[4-6] Penicillin (**6**) became the pioneering medicine of the 20th century and was mass-produced for clinical use by 1944.[7, 8] It was a medical miracle, rapidly vanquishing many types of the world's most deadly infectious diseases such as pneumonia, wound sepsis and tuberculosis.[9] Not so soon after, penicillin (**6**) resistant microbes began surfacing and by the late 1950s, up to 85% of clinical isolates of *Staphylococci* were found to be penicillin (**6**) resistant.[10]

Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first "super bugs" to be encountered and was originally identified in the early 1960s, just one year after the introduction of methicillin (**7**) antibiotics into clinical practice (Figure 2).[11, 12] MRSA has since spread to hospitals worldwide with alarmingly high incidence. Normally a harmless passenger in the human body, it can cause illnesses, such as pneumonia or toxic shock syndrome and has become an increasingly challenging disease to defeat.

More than forty years ago, scientists introduced vancomycin (**8**) (Figure 2) as an alternative therapy in response to the new strains of *Staphylococci* that were growing resistant to penicillin (**6**) and methicillin (**7**).[13] However, in 1987 the hope that vancomycin (**8**) would be a "cure all" antibiotic came to an end when vancomycin-resistant *enterococci* (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA) were discovered in hospitals.[14-16]



7 **8**

Figure 2: Methicillin (**7**) and Vancomycin (**8**).

The rapid evolution of new bacterial strains, such as MRSA, VRE and VRSA, have raised serious concerns within the scientific and health care communities. The current pharmacological world faces a serious challenge as the spread of increasingly resistant “super bugs” still accounts for millions of premature deaths all over the world. The constant search for and development of novel antibiotics, active against MRSA, VRE and VRSA is essential in order to combat this rapid increase in cases of antibiotic resistant pathogens.

1.2 Lactonamycin (1): A Novel Antibiotic

The natural product (+)-lactonamycin (**1**) was first isolated from a culture broth of *Streptomyces rishiriensis* MJ773-88K4 obtained from a soil sample collected near Yokohama City, Japan in 1996 by Matsomoto and co-workers (Figure 3).[1] Biological assessment of lactonamycin (**1**) against Gram-positive bacteria—including MRSA and VRE—revealed significant levels of antimicrobal activity. In addition to its antimicrobal properties, lactonamycin (**1**) displayed appreciable levels of cytotoxicity against tumor cell lines.[2]

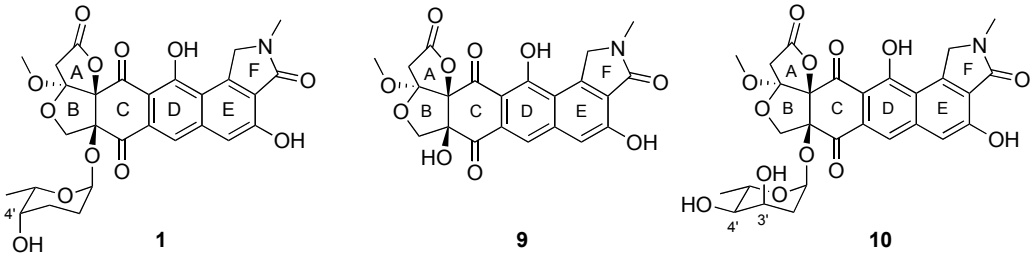


Figure 3: Structures of lactonamycin (**1**), lactonamycinone (**9**) and lactonamycin-*Z* (**10**).

The interesting biological properties combined with the intriguing molecular architecture of lactonamycin (**1**) (assigned through spectroscopic and X-ray crystallographic measurements)[17] has brought about a significant interest in the total synthesis of this complex and fascinating molecule. The hexacyclic core, known as lactonamycinone (**9**), unlike any other natural product, contains towards the western part, a highly oxygenated fused perhydrofuran-furanone ring connected to a tertiary anomeric-like methoxyl unit and towards the eastern side, a novel naphtha[*e*]isoindole ring system. Adding to the structural complexity of lactonamycin (**1**) a tertiary glycosidic linkage holds host to a 2,3,6-trideoxy sugar unit (Figure 3).

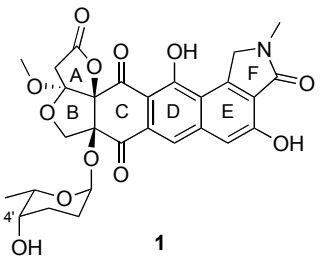
In 2003, a closely related structure to that of lactonamycin (**1**), lactonamycin-Z (**10**) (Figure 3) was isolated from a culture of *Streptomyces sanglieri* AK 623 obtained from a pine wood soil sample in County Durham, UK by Fiedler and co-workers.[18] Both structures are identical aside from differences in the sugar unit, specifically the additional presence of a hydroxyl group at C-3' and the opposite stereochemistry of the C-4' alcohol. Weak activity against Gram-positive bacteria was found during analysis of the antibacterial properties of this compound.

1.2.1 Project Objective

Lactonamycin (**1**) is a structurally remarkable antibacterial natural product and on account of its biological activities and structural novelty, is a prime candidate for total synthesis. This project was concerned with the incorporation of the 2,3,6-trideoxy sugar unit onto the core structure of lactonamycin (**1**) and this thesis will describe the work recently undertaken towards this goal.

1.3 Published Synthetic Studies

Lactonamycin (**1**) (Figure 4) has inspired several synthetic studies from three major research laboratories. Investigations have focused on the construction of the ABCD[19, 20] and CDEF[21-25] ring systems and more recently on the total synthesis of lactonamycinone (**9**) by Danishefsky and co-workers.[25, 26] In 2004 the asymmetric synthesis of the enantiopure AB ring fragment was constructed by Kelly and co-workers, and showed that the absolute stereochemistry matched that of the naturally occurring antibiotic.[27] In more recent studies, Parsons and co-workers have elegantly demonstrated the use of a cascade sequence for the simultaneous construction of the CDEF rings.[23, 24]

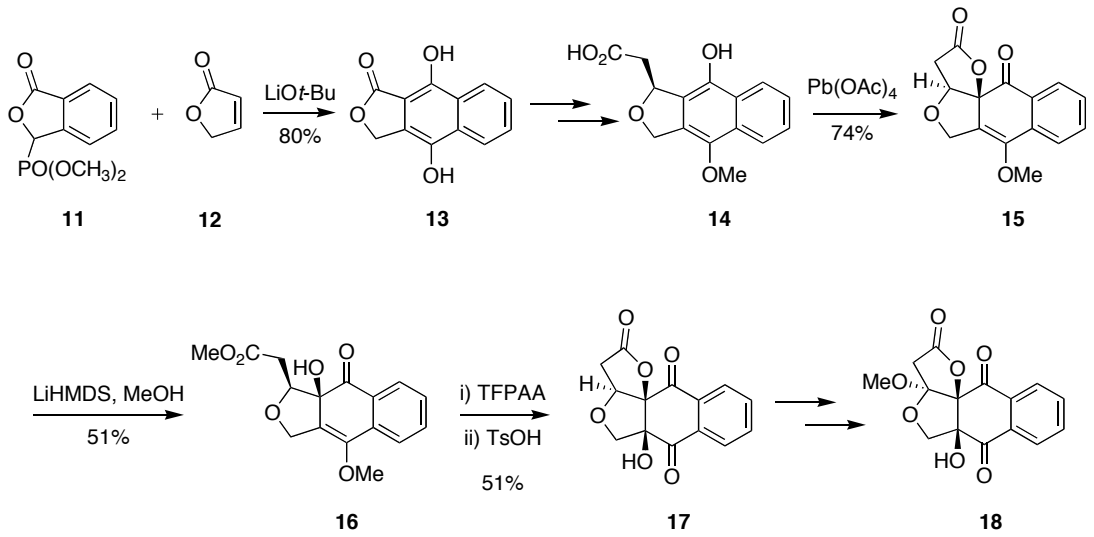


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Figure 4: Lactonamycin (**1**).

1.3.1 The ABCD Ring System

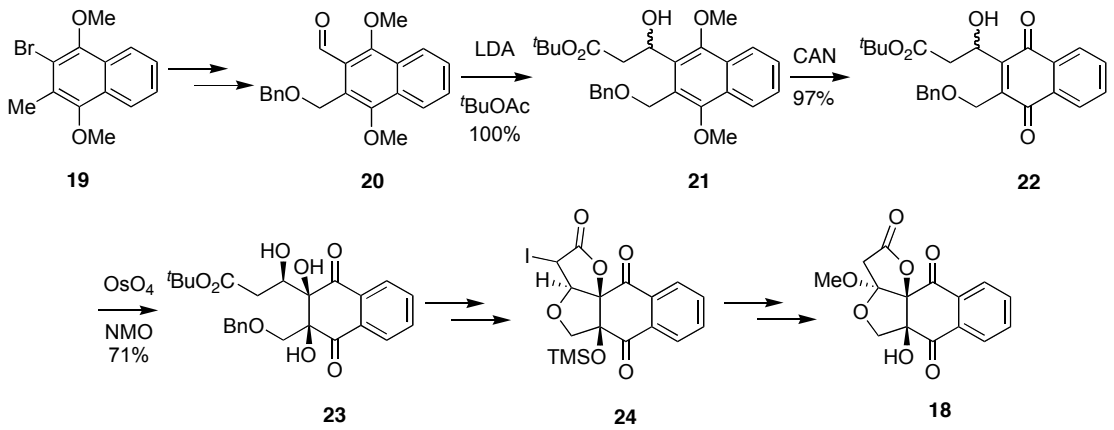
Soon after Matsomoto and co-workers revealed the structure of lactonamycin (**1**),[17] Danishefsky and Cox at Columbia University in New York published the first of two letters concerning the construction of the highly oxygenated, fused furan-furanone ring system of lactonamycin (**1**).[19, 20] Danishefsky and Cox incorporated an intramolecular Wessely oxidative lactonisation of acid **14** followed by hydroxyl-directed epoxidation of enol ether **16** as the key steps in their synthesis.[19] The Wessely precursor **16** was prepared from the known phosphonate **11** *via* a Michael addition-cyclisation sequence to give phthalide **13**, followed by several further manipulations (Scheme 1).



Scheme 1: Danishefsky and Cox's Approach to the ABCD Ring System of Lactonamycin (**1**) *via* an Intramolecular Wessely Oxidative Lactonisation.

Difficulties arose during the introduction of the angular methoxy group into alcohol **17**, but through various strategic alterations, lactone **18** was obtained in five steps to give the model ABCD ring system (Scheme 1).

Nearly one year later, Danishefsky and Cox published the second of the two letters and introduced an approach towards a highly diastereo- and enantioselective synthesis of lactonamycin (**1**).[20] The vital step featured an unprecedented, highly stereoselective dihydroxylation reaction of highly functionalised naphthoquinone **22**, to give triol **23 (**Scheme 2**)**.



Scheme 2: Danishefsky and Cox's Approach to the ABCD Ring System of Lactonamycin (**1**) *via* a Highly Stereoselective Dihydroxylation Reaction.

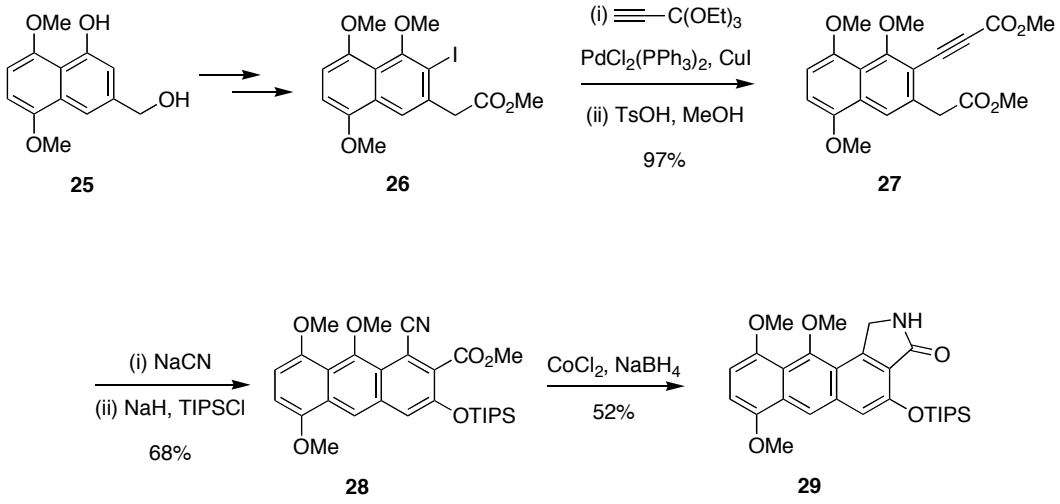
Synthesis of aldehyde **20** from readily available bromide **19**, followed by an aldol type reaction with *tert*-butyl acetate gave alcohol **21**. Oxidation using ceric ammonium nitrate (CAN) gave the highly substituted naphthoquinone precursor **22** (Scheme 2).

In order to promote the ring closure of diol **23** to iodide **24**, numerous problematic manipulations were required. In addition, introduction of the angular methoxy unit to supply lactone **18** necessitated elaborate procedures (Scheme 2).

1.3.2 The CDEF Ring System

1.3.2.1 Behar's Approach to the CDEF Ring System

In 2002, Behar and co-workers were the first of two groups to report the construction of the aromatic eastern fragment of lactonamycin (**1**).[21] The methodology behind Behar's approach involved the sophisticated, late stage, tandem cyanide conjugate addition-Dieckmann condensation of alkyne **27** to give fully functionalised anthracene **28** after tautomerisation. Further elaboration of the molecule allowed the formation of the CDEF ring system **29** of lactonamycin (**1**) (Scheme 3).

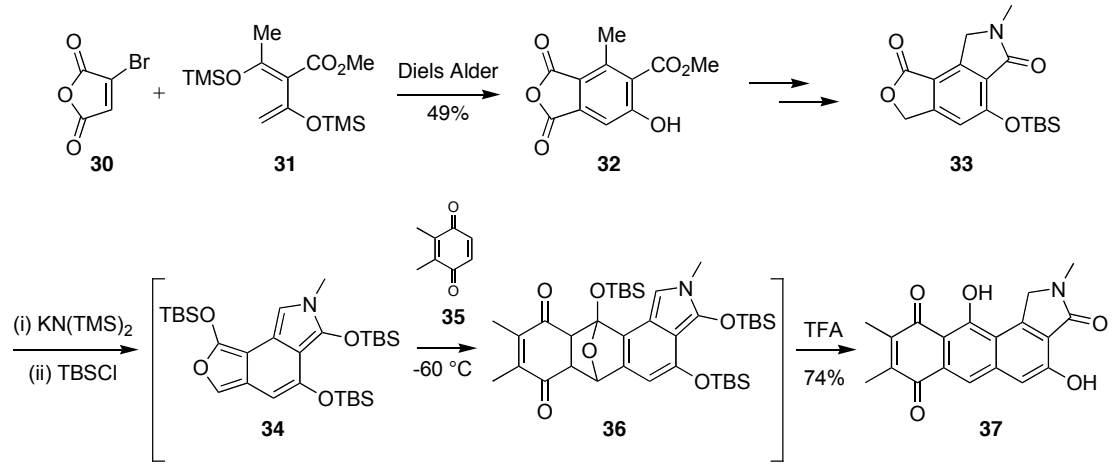


Scheme 3: Behar's Approach to the CDEF Ring System of Lactonamycin (**1**) *via* a Late Stage Tandem Cyanide Conjugate Addition-Dieckman Condensation.

Preparation of alkyne precursor **27**, for the key cyanide conjugate addition reaction was achieved starting from the known naphthalene system **25**. Naphthalene **25** was transformed through a series of steps to give iodo ester **26**, which was then coupled with 3,3,3-triethoxy propyne using a palladium catalysed Sonogashira reaction to give the cyclisation precursor **27** after *ortho* ester hydrolysis. Cyclisation of alkyne **27** followed by immediate protection to the tri-*iso*-propylsilyl ether **28** was achieved in 68% yield over the two steps. Selective reduction followed by lactam formation, gave anthracene **29** in 52% yield (Scheme 3).

1.3.2.2 Kelly's Approach to the CDEF Ring System

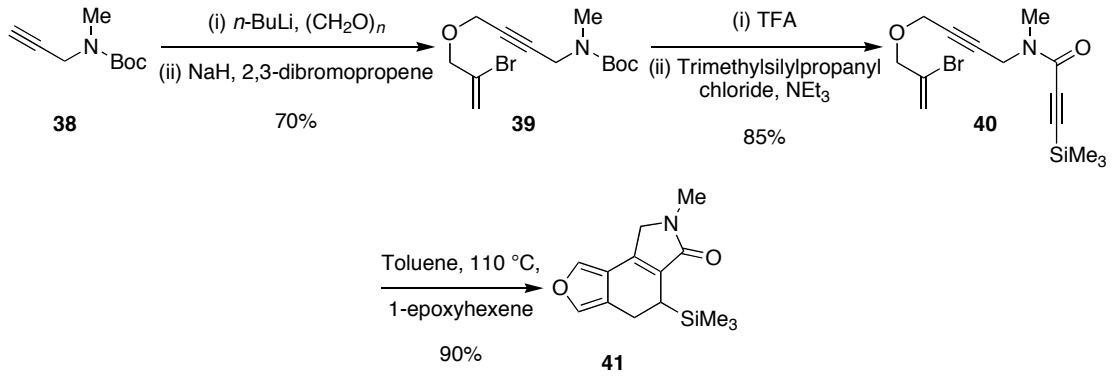
A mere two days later, Kelly revealed his synthesis of the same eastern aromatic core of lactonamycin (**1**), varying in strategy by the application of a key Diels-Alder cycloaddition reaction between tricycle **34** and 2,3-dimethylbenzoquinone (**35**) (Scheme 4).[22]



Scheme 4: Kelly's Approach to the CDEF Ring System of Lactonamycin (**1**) *via* Cycloaddition Diels-Alder Chemistry.

The intermediate lactone **33**, was prepared in eight steps from the phthalic anhydride **32**. Further elaboration gave *iso*-indole **34**, which was then taken forward in the key Diels-Alder cycloaddition reaction with quinone **35**, to give cycloadduct **36**. Direct treatment with trifluoroacetic acid (TFA) gave the eastern portion **37** of lactonamycin (**1**) (Scheme 4).

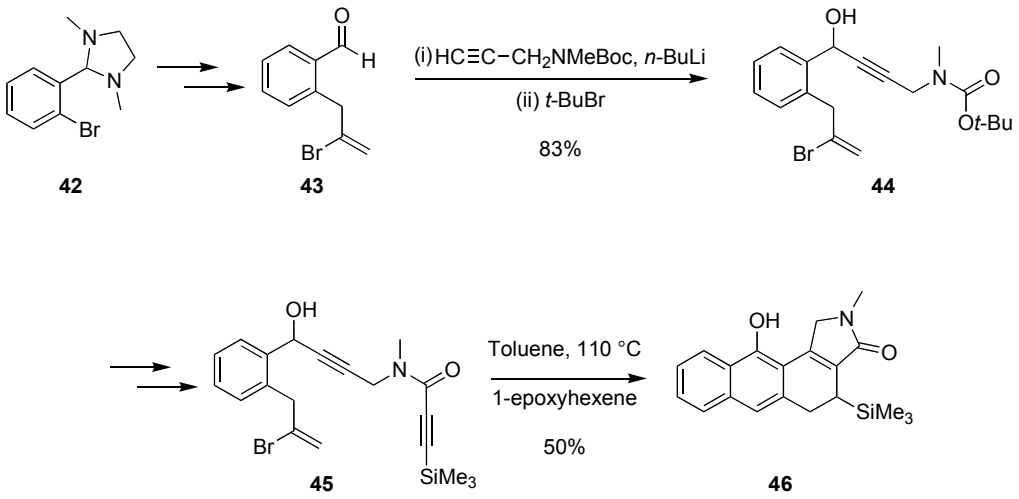
Complementary to this approach, Parsons and co-workers recently revealed a much-improved synthesis of 3,4-disubstituted furans **41** *via* a novel, metal free, thermally induced cascade reaction (Scheme 5).[23]



Scheme 5: Parsons' Improved Synthesis of 3,4-Disubstituted Furan **41**.

Ether **39** was prepared in 70% overall yield by treatment of propargyl amine **38** with *n*-butyllithium and *para*-formaldehyde, followed by reaction of the resulting alcohol with sodium hydride and 2,3-dibromopropene (Scheme 5). Upon exposure to TFA, deprotection of the *tert*-butyl carbonate protecting group was effected, which after *N*-acylation with trimethylsilylpropynoyl chloride gave the desired cyclisation precursor **40** in 85% overall yield. Refluxing in toluene for an hour with the addition of ten equivalents of epoxyhexene as an acid trap, gave the desired cyclisation product **41** in 90% yield (Scheme 5).

This approach was also applied towards the construction of the CDEF ring system of lactonamycin (**1**) and elegantly demonstrates the use of a cascade sequence for the simultaneous construction of the CDEF rings (Scheme 6).[24]

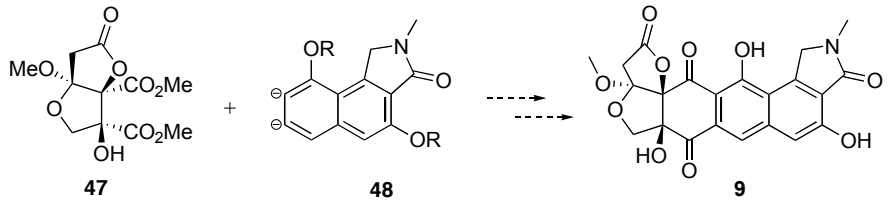


Scheme 6: Parson's Novel Cascade Reaction for the Formation of the CDEF Rings of Lactonamycin (**1**).

Once more, upon heating of alkyne **45** in toluene at reflux in the presence of the epoxyhexene acid scavenger, tetra-cycle **46** was obtained in 50% yield (Scheme 6).

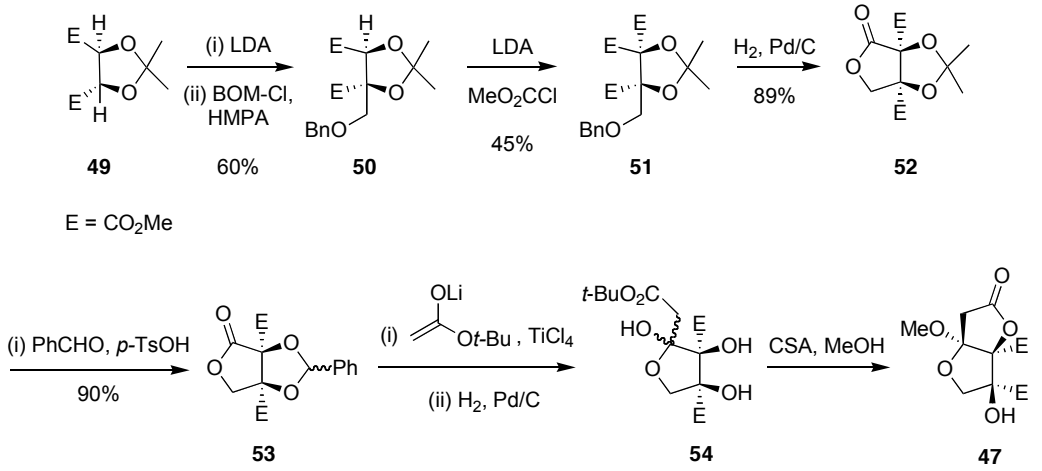
1.1.3 The AB Ring System

In 2004, Kelly featured again in the literature and this time described his work towards the asymmetric synthesis of the AB ring system of lactonamycin (**1**).[27] Kelly visualised the use of the enantiomerically pure diester **47** in a reaction with anion **48** for future application in the total synthesis of lactonamycinone (**9**) (Scheme 7).



Scheme 7: Kelly's Proposal for the Application of Enantiomerically Pure Diester **47** in the Total Synthesis of Lactonamycinone (**9**).

In eight steps, the synthesis of diester **47** was achieved from dimethyl D-tartrate. The underlying key strategic steps demanded the use of ester enolate chemistry to introduce side chains for the construction of the B ring (Scheme 8).



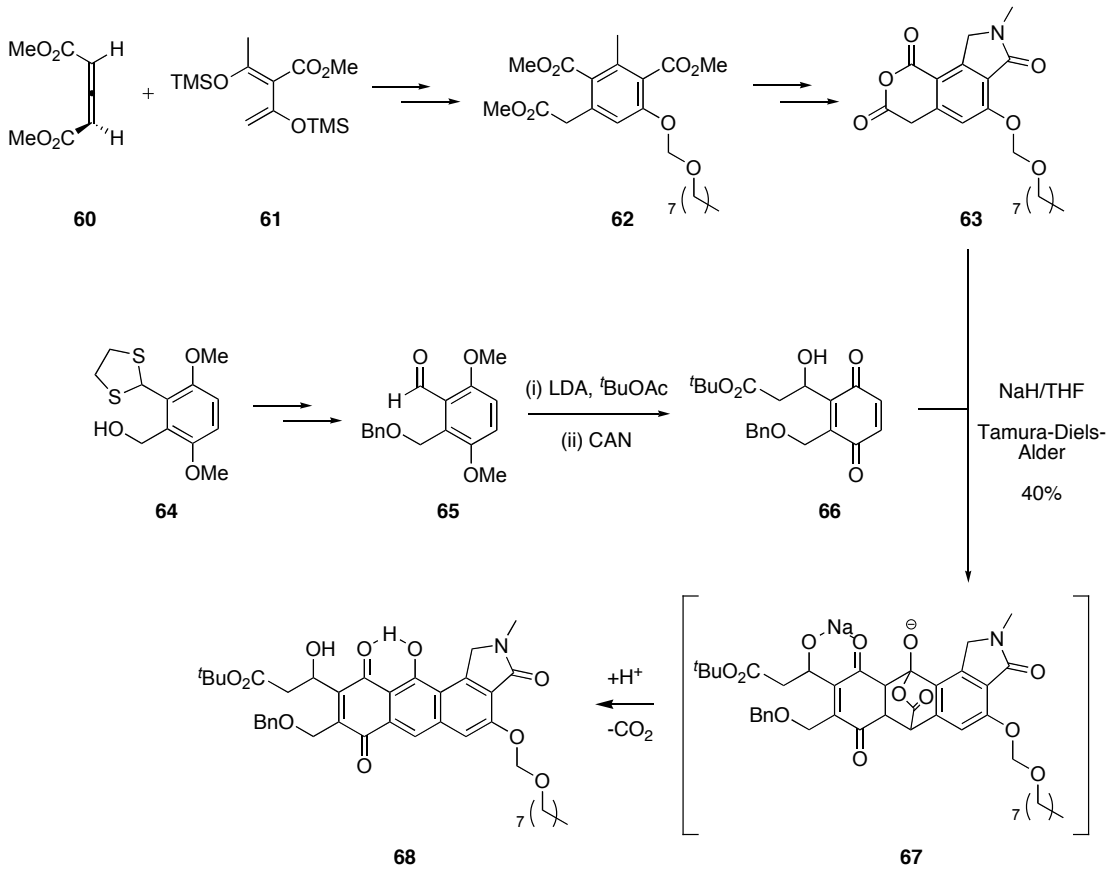
Scheme 8: Kelly's Asymmetric Synthesis of the AB Ring System of Lactonamycin (**1**) *via* Ester Enolate Chemistry.

Dimethyl D-tartrate was readily converted in two steps to acetonide **49**, which was alkylated with benzyloxymethyl chloride *via* enolate formation to give **50** as the only stereoisomer. The second alkylation was again achieved through enolate chemistry; deprotonation with lithium di-*iso*-propylamide (LDA) and reaction with methyl chloroformate gave triester **51**. Deprotection of the benzyl group initiated spontaneous cyclisation to lactone **52** (Scheme 8).

Reprotection at this stage was essential as problems were encountered later in the synthesis during the cleavage of the acetonide protecting group. Consequently acetonide **52** was cleaved with TFA and reprotected to give the benzylidene acetal **53** in a 90% yield as a mixture of diastereoisomers. Separately, both isomers were treated with $LiCH_2CO_2{}^tBu$ in the presence of titanium tetrachloride and deprotected under hydrogentative conditions to give diol **54**. Treatment of diol **54** with methanolic camphorsulfonic acid (CSA) initiated a chain of reactions; methyl acetal formation, anomerisation and ring closure providing lactone **47**.

1.3.3 Total Synthesis of Lactonamycinone (**9**)

In 2003, following up on their model studies of the ABCD and CDEF ring systems of lactonamycin (**1**), Danishefsky and co-workers published a succession of papers directed towards the total synthesis of lactonamycinone (**9**).[25, 26] Their approach was centred around the condensation of homophthalic anhydride **63** with highly functionalised quinone **66** *via* a process based on the anionically mediated Tamura-Diels-Alder reaction (Scheme 9).



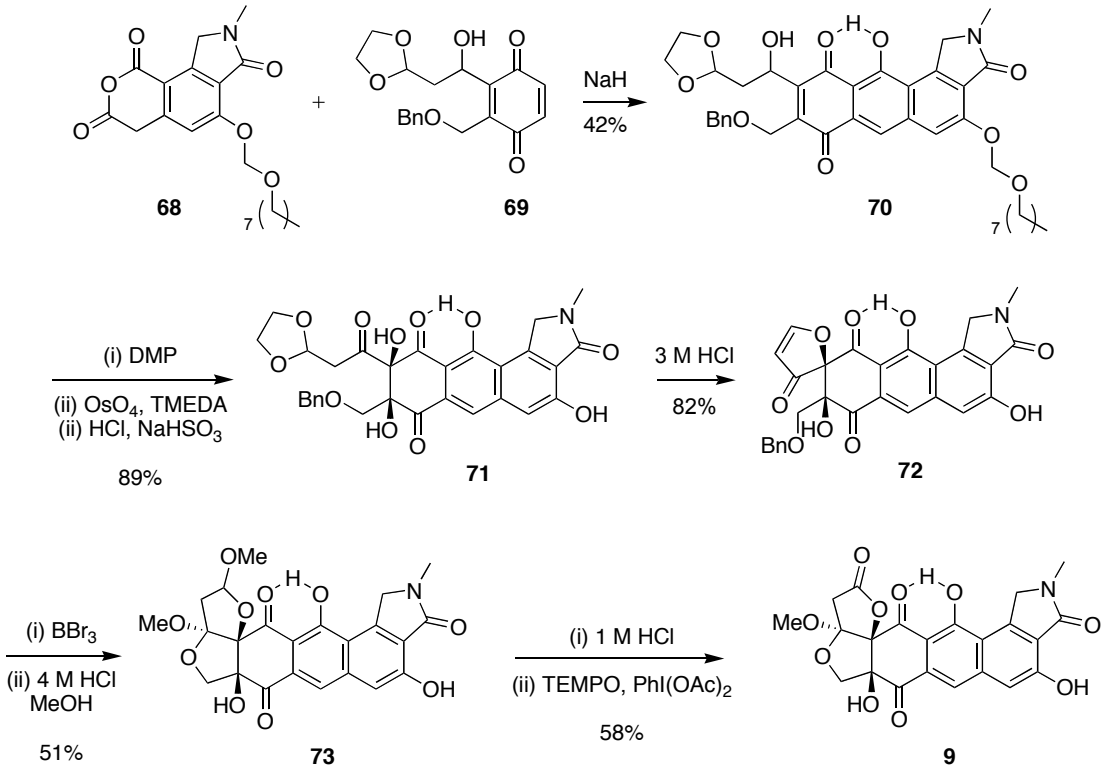
Scheme 9: The Danishefsky Tamura-Diels-Alder Approach to the Aromatic Portion of Lactonamycin (**1**).

Synthesis of the two cycloaddition partners **63** and **66** mirrored the procedures described in their previous reports.[19, 20] Formation of the pyrrolo homophthalic anhydride **63** was achieved in seven steps and began with the cycloaddition of *bis*-silyl enol ether **61** with 1,3-dicarbomethoxyallene (**60**). Protection as the octyloxymethyl ether (to avoid solubility issues), bromination and subsequent amination gave rise to the desired lactam functionality. Hydrolysis to the diacid followed by dehydration gave desired coupling partner **63** (Scheme 9).

Construction of highly substituted quinone **66** began with known thioacetal **64**, protection of the alcohol functionality and reduction of the thioacetal moiety provided benzylic aldehyde **65**. Aldol condensation with *tert*-butyl acetate followed by oxidation with CAN, gave the second coupling partner **66** (Scheme 9).

Coupling of the two Diels-Alder precursors was achieved by formation of anion **67** by treatment of lactam **63** with two equivalents of sodium hydride at –78 °C, subsequent addition of two equivalents of quinone **66** and warming to 0 °C, gave highly substituted tetracycle **68** in 40% yield after decarboxylation (Scheme 9).

All attempts at the incorporation of the AB system into this substrate were unsuccessful despite the similarities to the equivalent substrate **22** from their preceding report (Scheme 2).[20] Thus it became necessary for Danishefsky and co-workers to consider an alternative ending to their already proposed work, and various subtle modifications were performed. The Tamura-Diels-Alder reaction remained the underlying key step, however quinone **66** was replaced with quinone **69** giving tetracycle **70** upon reaction with pyrrolo homophthalic anhydride **68** in 42% yield (Scheme 10).



Scheme 10: Danishefsky's Modified Approach to the Aromatic Portion of Lactonamycin (**1**).

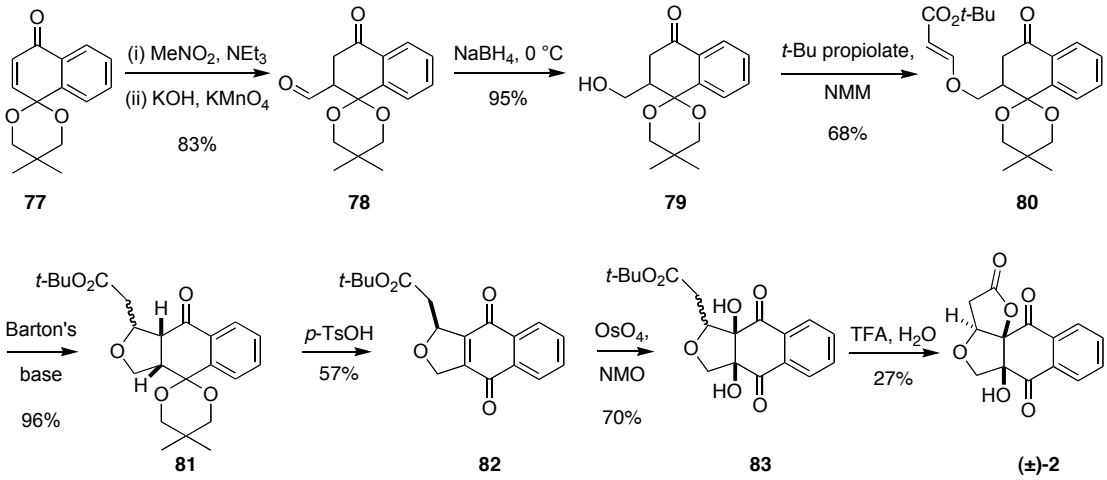
Oxidation of alcohol **70** by treatment with Dess-Martin periodinane (DMP) followed by dihydroxylation using osmium tetroxide and subsequent deprotection gave diol **71**. Deprotection with aqueous HCl (3 M) initiated spontaneous cyclisation *via* intramolecular attack of the tertiary alcohol at the proximal aldehyde to give spiro butenolide **72** in 82% yield. Deprotection of the benzyl group and subsequent treatment with methanolic HCl led to intramolecular acetalisation and addition of methanol to the resulting enol ether to give acetal **73**. Lactonamycinone (**9**) was reached by hydrolysis to the lactol followed by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) mediated oxidation in 58% yield (Scheme 10).

1.4 Work Previously Undertaken by the Barrett Group

Over the past fifteen years or so a significant amount of research into the total synthesis of lactonamycin (**1**) has been conducted within the Barrett group.[28-31] As a result of this research, a significant amount of methodology for application towards the synthesis of lactonamycin (**1**) has been developed and whilst advanced in its progress, is not yet complete. Throughout the course of this time, the originally proposed retrosynthetic route has changed considerably—as is often the case in natural product synthesis—and for the interests of concise presentation, the original retrosynthetic analyses for lactonamycin (**1**) will not be discussed.

1.4.1 Synthesis of the ABCD Ring System of Lactonamycin (**1**)

The construction of the highly oxygenated portion of lactonamycin (**1**) was initially constructed through the use of a sequence of Michael reactions (Scheme 11).[29]

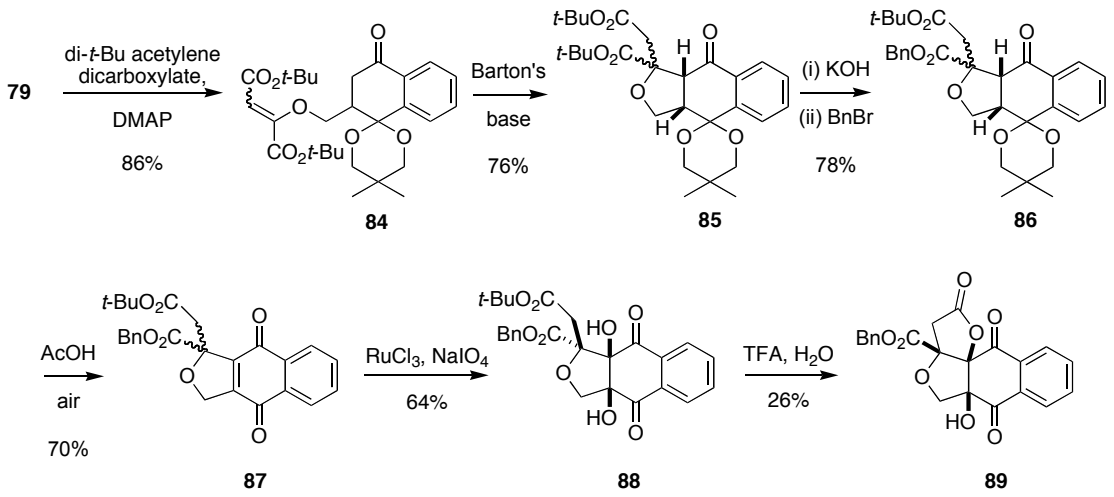


Scheme 11: Synthesis of ABCD Alcohol **(±)-2**.

In a modification of the oxidative Corey procedure,[32] quinone mono-ketal **77** was prepared from 4-methoxy-1-naphthol and 2,2-dimethyl-1,3-propanediol by treatment with phenyliodine(III) bis(trifluoroacetate) (PIFA). Subsequent triethylamine catalysed conjugate Michael addition of nitromethane nitronate, followed by an oxidative Nef reaction using potassium hydroxide and potassium permanganate in aqueous methanol gave aldehyde **78**. Reduction using sodium borohydride, followed by *N*-methyl morpholine (NMM) catalysed Michael addition of *tert*-butyl propiolate gave vinyl ether **80** as a single geometric isomer. Action of Barton's base (*N*-*tert*-butyl-*N*,*N*,*N*',*N*'-tetramethylguanidine) induced cyclisation to provide tetrahydrofuran **81** as a 1 : 1 mixture of diastereoisomers. Following this, acid mediated hydrolysis using *para*-toluenesulfonic acid in the presence of air gave naphthoquinone **82**. Following Danishefsky's precedent,[20, 25, 26] dihydroxylation of naphthoquinone **82** provided diol **83** as a 7 : 3 mixture of diastereoisomers, which was subsequently treated with TFA to give the racemic tetracyclic unit **(±)-2**.

1.4.2 Synthesis of the ABCD Ring System of Lactonamycin (**1**): Masking the Angular Methoxy Group

Unfortunately, attempts at oxidation of lactone **(±)-2** to introduce the angular methoxy group were unsuccessful and as a result, an alternative route was devised. This incorporated the use of an oxidative decarboxylation reaction for unmasking the methoxy unit *via* a carboxylic ester. Accordingly, the chemistry in Scheme 11 was modified to allow for the incorporation of the second carboxylic ester by using di-*tert*-butylacetylene dicarboxylate as the initial Michael acceptor for the reaction with alcohol **79** (Scheme 12).

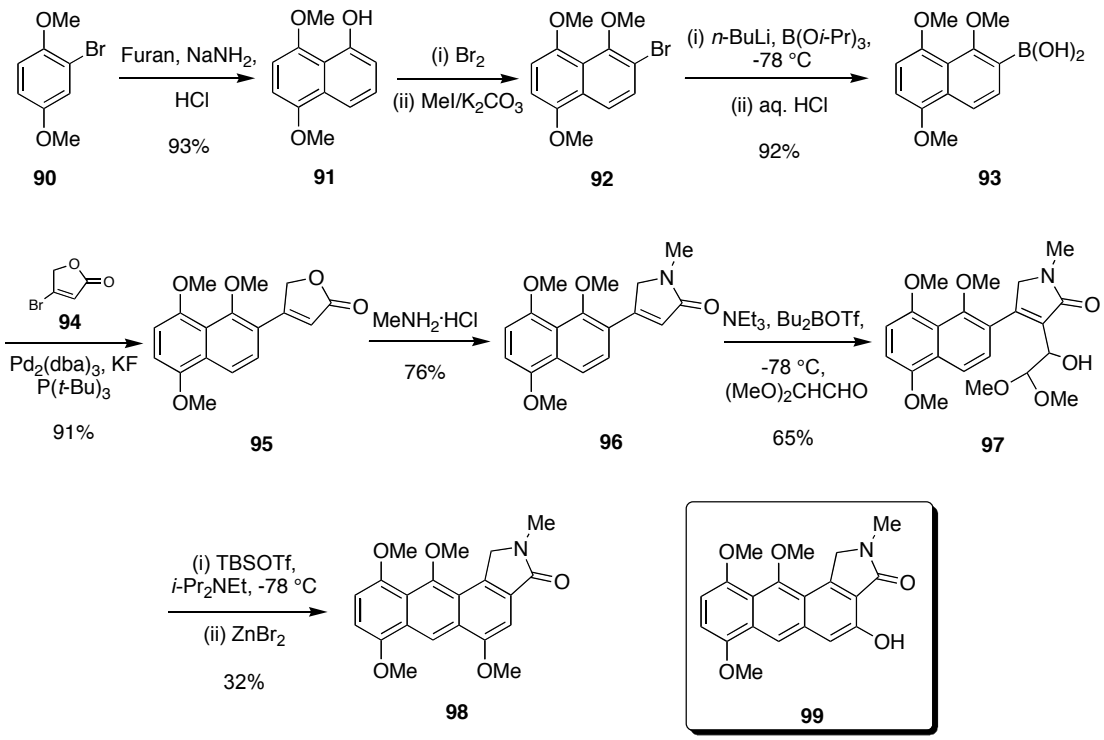


Scheme 12: Synthesis of a Model ABCD Ring System of Lactonamycin (**1**) using a Carboxylate as a Masked Methoxy Group.

As before, Michael addition of alcohol **79** to di-*tert*-butylacetylene dicarboxylate using catalytic 4-dimethylaminopyridine (DMAP) gave adduct **84**, which upon treatment with Barton's base, initiated the second Michael reaction to give tetrahydrofuran **85** as a mixture of diastereoisomers. Monohydrolysis of diester **85** and subsequent monobenzylation provided benzyl ester **86**, which was then converted to naphthoquinone **87** upon reaction with TFA. Dihydroxylation with catalytic ruthenium(III) chloride provided diol **88**, which upon treatment with TFA underwent lactonisation to provide lactone **89** (Scheme 12). Work towards unmasking the methoxy unit is currently in progress.

1.4.3 Initial Synthesis of the CDEF Ring System of Lactonamycin (**1**)

The initial approach to the eastern aromatic core of lactonamycin (**1**) utilised benzyne cycloaddition chemistry to construct the CD ring system followed by a ring closing Friedel Crafts acylation reaction (Scheme 13).[30]



Scheme 13: Initial Attempts at the Synthesis of the CDEF Ring System of Lactonamycin (**1**).

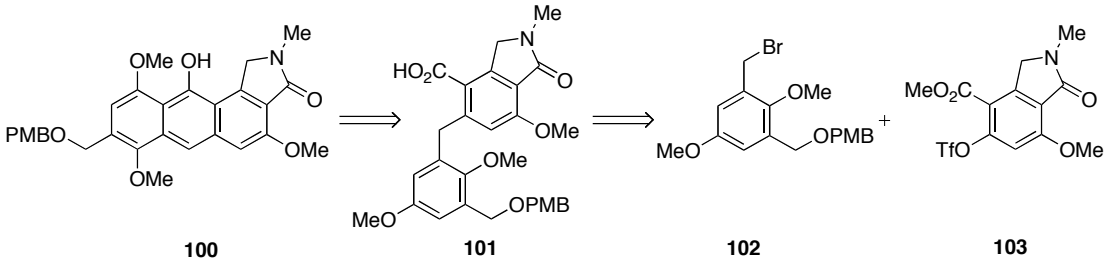
The use of a benzyne-furan cycloaddition reaction provided naphthol **91**, which after regio-selective *ortho*-bromination with bromine and phenolic methylation gave bromide **92**. Introduction of the boronic acid by bromine-lithium exchange followed by reaction with tri-*iso*-propyl borate and hydrolysis provided the Suzuki precursor **93**. Coupling under palladium catalysed Suzuki reaction conditions with 4-bromo-furan-2-one (**94**) provided the naphthyl-butenolide **95**, which was then treated with methylamine to provide *N*-methyl lactam **96**. Functionalisation of the γ-lactam to provide the aldol adduct **97** was achieved by sequential reaction with dibutylboron triflate, triethylamine and dimethoxy acetaldehyde (Scheme 13).

Unfortunately, cyclisation of aldol adduct **97** to anthracene **99** using a diverse range of Brønsted and Lewis acid catalysts or *via* oxidation to the corresponding ketone was unsuccessful and was attributed to the deactivation of the naphthalene unit by the

electron withdrawing nature of the pyrrolinone carbonyl. In only one instance was any tetracyclic product detected. Treatment of **97** with *tert*-butyldimethylsilyl triflate and Hünig's base followed by zinc bromide gave the regioisomeric anthracene **98**, arising from the loss of water or silanol *via* the pyrrole stabilised carbenium ion.

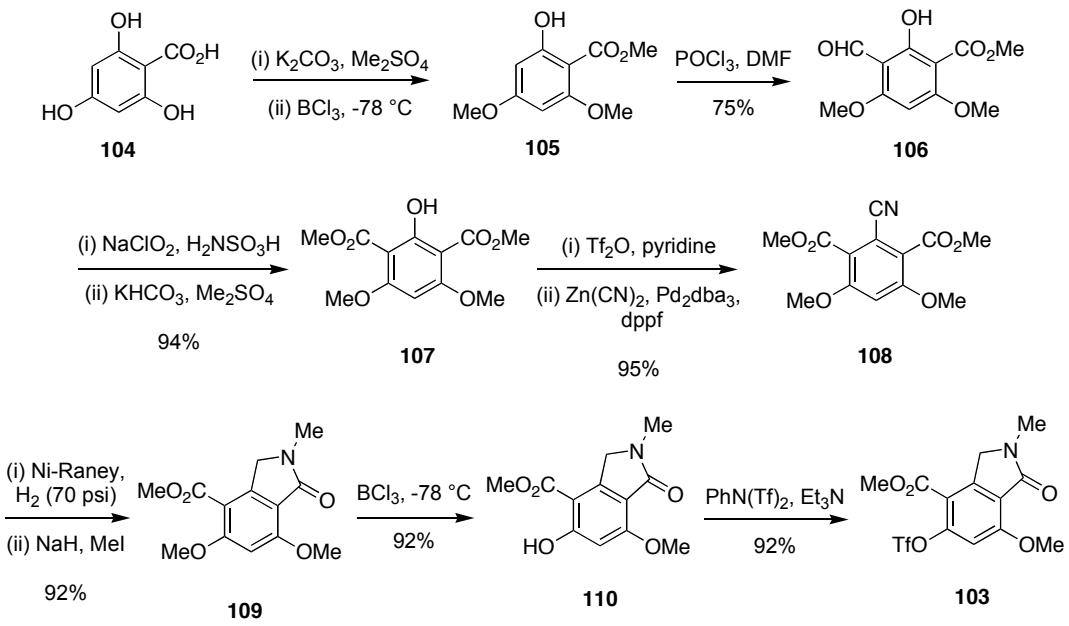
1.4.4 Improved Synthesis of the CDEF Ring System of Lactonamycin (**1**)

In an alternative approach, a Negishi cross coupling reaction between bromide **102** and triflate **103** was envisaged in order to allow for the construction of the D ring, by the use of an intramolecular Friedel Crafts acylation reaction. In addition, it was hoped that the *para*-methoxy benzyl (PMB) protected side chain would allow to elaboration of the highly oxygenated furan-furanone ring system as discussed in Sections 1.4.1 and 1.4.2 (Scheme 14).[31]



Scheme 14: Alternative Retrosynthetic Analysis of the Model CDEF Tetracylic Unit **100**.

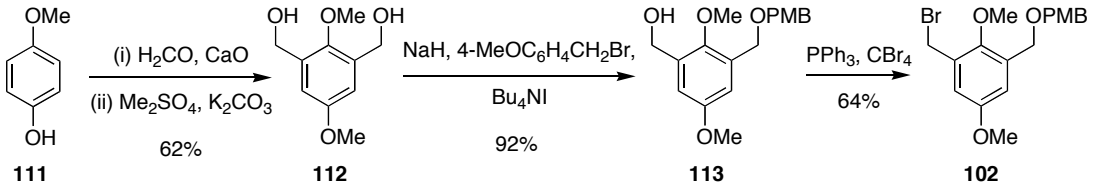
The multi-gram scale chemistry utilised in the synthesis of triflate **103** was achieved in eleven steps starting from commercially available trihydroxy acid **104** (Scheme 15).



Scheme 15: Synthesis of Triflate **103**.

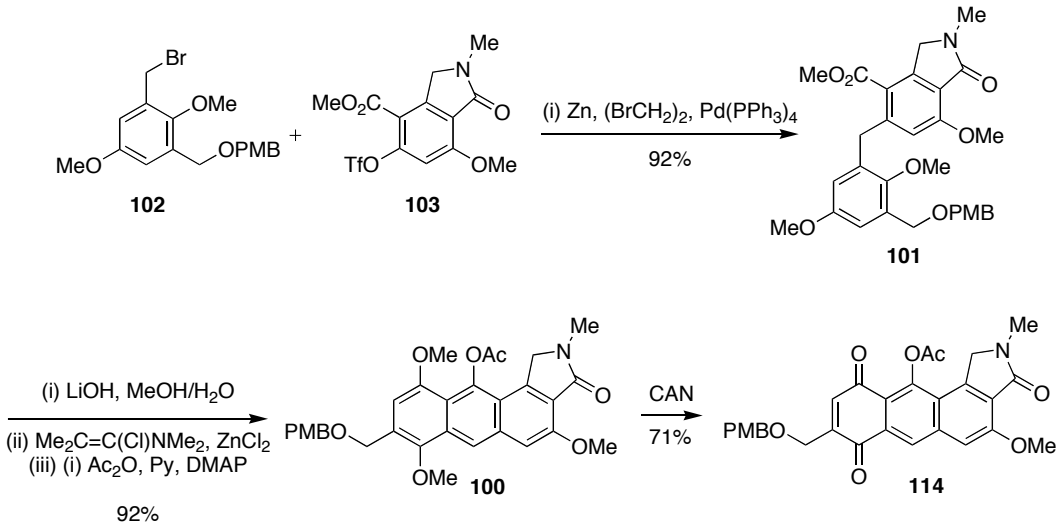
Methylation of trihydroxy acid **104** by treatment with dimethyl sulfate, followed by selective mono-deprotection with boron trichloride gave phenol **105**. This was followed by Vilsmeier-Haack formylation to provide aldehyde **106** which was subsequently oxidised—using sodium chlorite in the presence of sulfamic acid—and then methylated to give symmetric diester **107**. Conversion to the triflate and subsequent palladium catalysed Negishi cross coupling with zinc cyanide gave nitrile **108**. Hydrogenation of nitrile **108** over Raney Nickel and methylation of the resulting γ-lactam furnished **109**. Regioselective de-*O*-methylation provided phenol **110** which was then treated with *N*,*N*-ditrifylaniline and triethylamine to give triflate **103** (Scheme 15).

The second Negishi cross coupling partner, bromide **102** was prepared by successive *ortho*-formylation and selective phenolic methylation of *para*-methoxy phenol (**111**) to give diol **112**. Mono PMB protection to alcohol **113** and bromination using carbon tetrabromide and triphenylphosphine gave bromide **102** (Scheme 16).



Scheme 16: Synthesis of Bromide **102**.

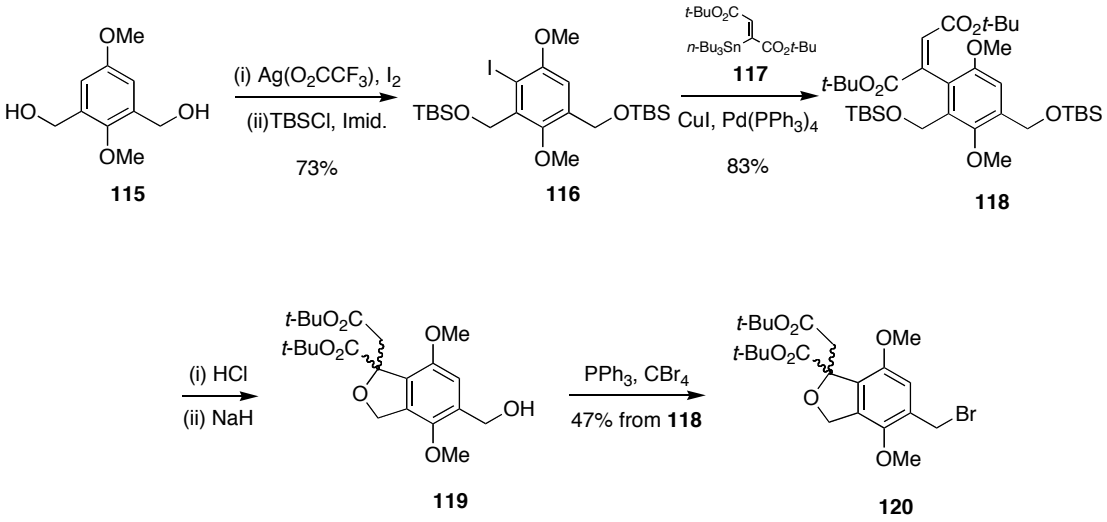
The two fragments **102** and **103** were coupled together under palladium catalysis with zinc-dust and dibromoethane to initially convert the bromide **102** into the corresponding organozinc reagent. The resulting product **101** was hydrolysed and then subjected to Friedel-Crafts acylation reaction conditions by treatment with 1-chloro-*N*,*N*,2-trimethyl-1-propylenamine and zinc chloride to bring about cyclisation. Direct treatment with acetic anhydride and DMAP in pyridine provided acetate **100** which was then converted to naphthoquinone **114** using CAN (Scheme 17).



Scheme 17: Synthesis of the CDEF Fragment of Lactonamycin (**1**).

1.4.5 Studies on the Core Lactonamycin (**1**) Coupling Reaction

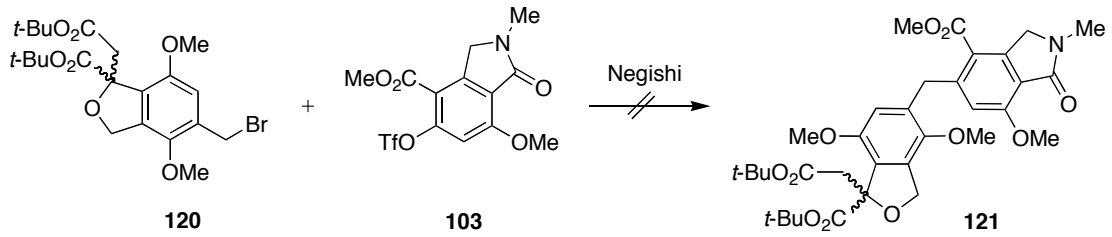
Whilst the above methodology (Scheme 12 and Scheme 17) established key routes for the synthesis of the ABCD and CDEF ring fragments **(±)-2, 89** and **114**, a more convergent approach was deemed necessary for a more elegant synthesis. With this in mind, a more elaborate coupling partner for the Negishi cross coupling reaction with triflate **103** was prepared (Scheme 18).



Scheme 18: Synthesis of Alternative Bromide **120**.

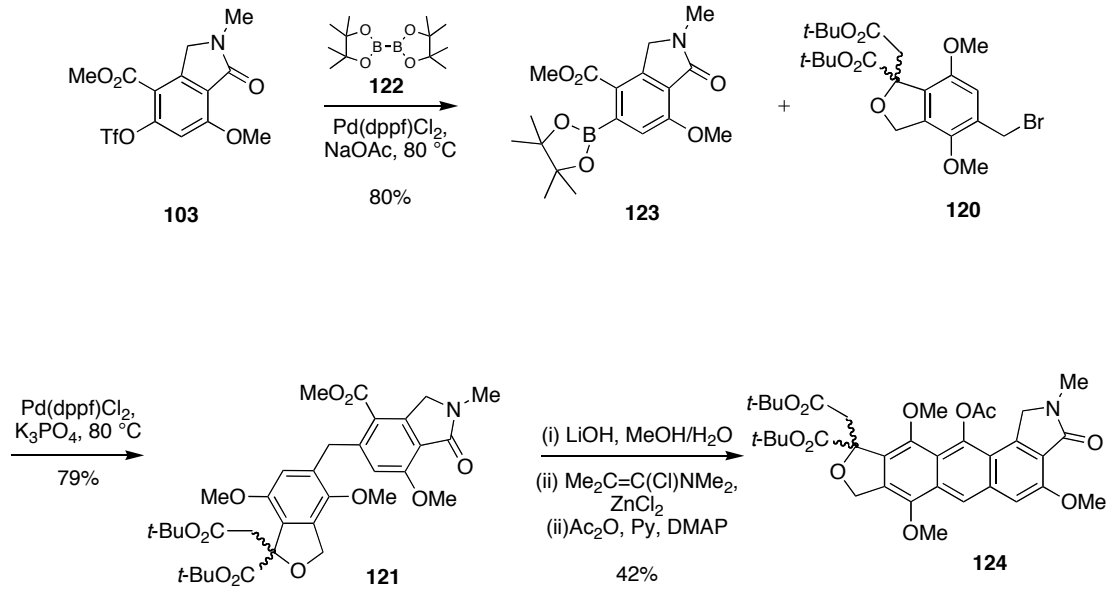
Iodide **116** was prepared from diol **115**, and converted into diester **118** by a Stille coupling reaction with stannane **117**. Global deprotection under acidic conditions and ring closure by treatment with sodium hydride provided alcohol **119**. Finally, bromination under standard conditions afforded bromide **120** (Scheme 18).

The attempted Negishi cross coupling reaction of triflate **103** with the organozinc reagent derived from bromide **120** was unsuccessful despite the range of conditions tested (Scheme 19).



Scheme 19: Unsuccessful Negishi Coupling Of Bromide **120** and Triflate **103**.

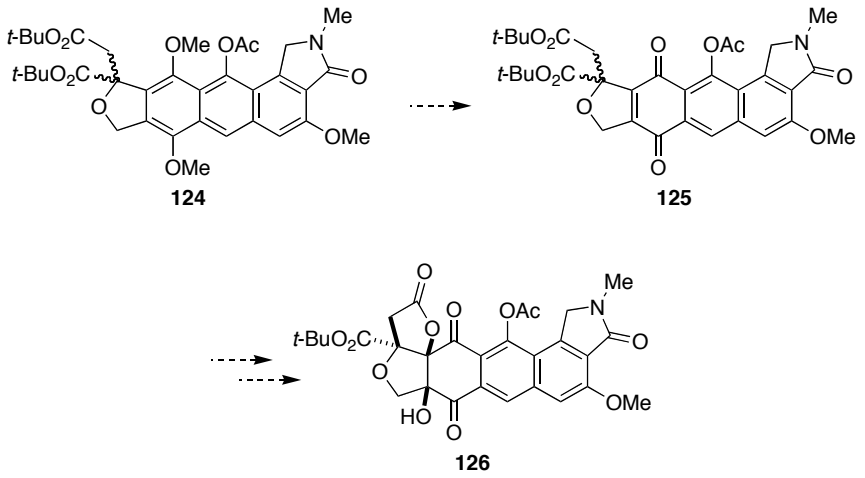
In contrast however, conversion of triflate **103** to the corresponding boronate **123** by reaction with *bis*(pinacolato)diboron (**122**) in the presence of 1,1'*bis*-(diphenylphosphino)-ferrocene)-palladium(II) chloride, allowed a successful Suzuki cross coupling reaction to yield coupled product **121** in 79% (Scheme 20).



Scheme 20: Synthesis of the BCDEF Ring System of Lactonamycin (**1**).

Selective hydrolysis of the methyl ester in the coupled product **121**, followed by Friedel-Crafts acylation using the previously employed reaction conditions in Scheme 17 and acetylation gave the cyclised product **124** in good overall yield (Scheme 20).

Further investigations are currently underway to bring about oxidation to naphthoquinone **125** and dihydroxylation followed by lactone formation to the ABCDEF hexacyclic core **126** (Scheme 21).

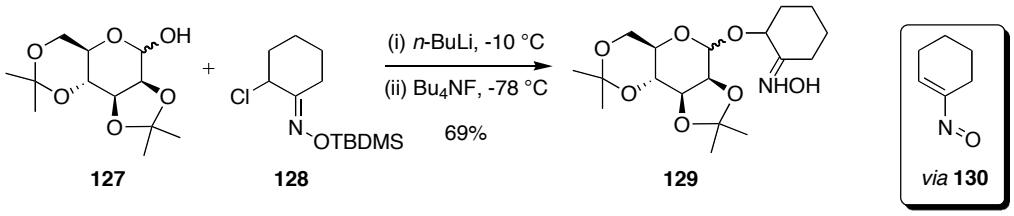


Scheme 21: Proposed Route to the ABCDEF Hexacyclic Core **126**.

1.4.6 Studies Towards Glycosidation *via* Conjugate Addition of Anomeric Alkoxides to Nitroalkenes and Nitrosoalkenes

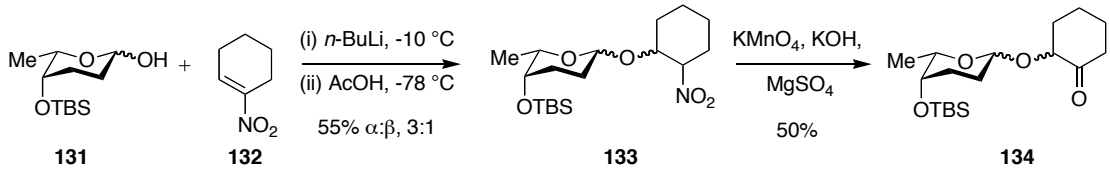
The introduction of the 2,3,6-trideoxysugar unit to the core structure of lactonamycin (**1**) was of key importance for the total synthesis programme. A non-traditional method for the construction of the glycosidic bond was explored since it was considered that direct glycosidation of the sterically hindered tertiary α-hydroxy-ketone would be problematic. Given the known potent reactivity of both nitro- and nitrosoalkenes as Michael acceptors[33-36] towards a diverse range of oxygen nucleophiles[37-40] it was envisaged that such reactions could be employed in the formation of 2-nitroalkylglycosides. In a recent

publication, studies towards the conjugate addition reactions of nitro- **132** and nitrosoalkenes **130** (derived from α-chloro-ketoximes **128**) with a range of pyranose derivatives has been conducted by Barrett and co-workers (Scheme 22 and Scheme 23Scheme 23).[28]



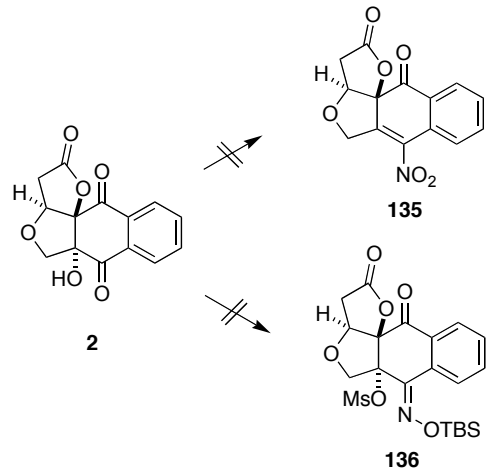
Scheme 22: Use of Nitrosoalkenes **130** for the Preparation of *O*-glycosides Through the Michael Addition of Anomeric Alkoxides.

Of particular importance to the lactonamycin (**1**) programme, was the successful construction of the glycosidic bond between the 4-*O*-*tert*-butyldimethylsilyloxy-L-rhodinopyranose sugar (**131**) and nitrocyclohexene (**132**) (Scheme 23). Relevant to the synthesis of the keto glycoside of lactonamycin (**1**); an oxidative Nef reaction[41] of the resulting glycoside **133** with potassium permanganate, potassium hydroxide and magnesium sulfate in methanol provided ketone **134**.



Scheme 23: Use of Nitroalkenes **132** for the Preparation of *O*-glycosides Through the Michael Addition of Anomeric Alkoxides.

Whilst this demonstrated a novel method for the construction of *O*-glycosides from nitro- and nitrosoalkenes, its application to lactonamycin (**1**) proved unsuccessful.[42] Specifically, elaboration of model ABCD alcohol **2** to the required oxime **135** or nitro derivative **136** was problematic (Scheme 24).



Scheme 24: Attempts at the Formation of Nitroalkene **135** and Oxime **136**.

1.5 Conclusions

The efforts made thus far towards the total synthesis of lactonamycin (**1**) reveal the intense synthetic complexity associated with the construction of this highly functionalised hexacyclic compound. Significant challenges remain to be met, not least of which involves the introduction of the key glycoside unit.

Chapter 2: Glycosidation Reactions and Their Application to Natural Product Synthesis

2.1 Introduction

Amongst the vast reservoir of known natural products exist an impressive variety of carbohydrate containing molecules that function as important biological substances, some of which have been highlighted in Figure 5.

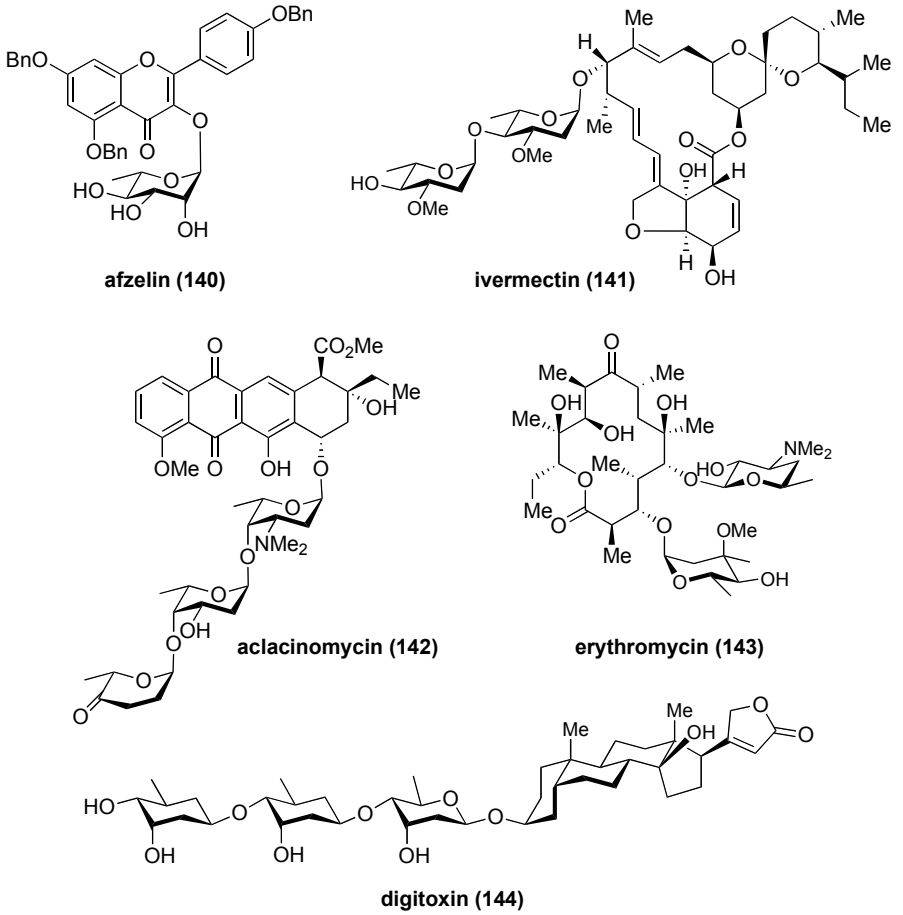


Figure 5: A Selection of Biologically Active Carbohydrate Containing Natural Products.

Within these glycomolecules are present mono/oligosaccharide units (glycons) that vary markedly in chemical structure and function. The structural diversity of the saccharide portion has been shown to be biologically important in molecular recognition.[43, 44] Carbohydrates and glycomolecules therefore play an important role in the physiological function and survival of biological systems and are consequently used widely as therapeutic agents. For example the anthracycline antitumour antibiotics such as aclacinomycin (**142**) are commonly used as extremely potent anticancer agents (Figure 5).

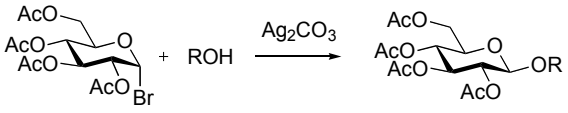
Not surprisingly, given the interesting molecular complexity and varied biological activity of carbohydrate containing natural products, significant advances have been made in the field of synthetic carbohydrate chemistry. Of significant importance are the *O*-glycosidation methods that have been developed towards the efficient and simple synthesis of *O*-glycosidic linkages under high stereocontrol. Despite this, the control of stereochemistry during the construction of glycosidic bonds continues to be a significant challenge in carbohydrate chemistry.

In this thesis, the use of a novel glycosidation method for the construction of the highly congested α-glycosidic linkage in lactonamycin (**1**) was deemed to be a crucial step in the synthetic strategy. Hence, in the forthcoming chapter, a short historical overview of the various methods of *O*-glycosidation methodology used for the synthesis of natural products will be discussed. The reader is directed towards several excellent reviews[45-49] and texts[50, 51] for a more detailed overview.

2.2 Classical O-Glycosidation Methods

2.2.1 The Koenigs and Knorr Method.

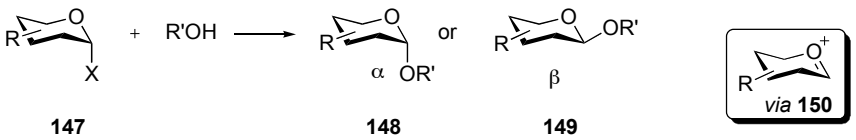
The Koenigs and Knorr method[52] and its variants still remain one of the most widely used and modified procedures for the synthesis of *O*-glycosides. At its conception, Koenigs and Knorr found that when acetobromoglucose (**145**) was treated with a halophilic promoter such as silver carbonate in the presence of an alcohol, the corresponding *O*-glycosides **146** were produced (Scheme 25).



145 **146**

Scheme 25: Koenigs' and Knorr's Original Glycosidation Method.

This method is based on a nucleophilic substitution reaction at the anomeric centre of a halo glycosyl donor such as **147** (usually X = bromide/chloride[53] with other examples where X = fluoride[54, 55]) and proceeds through the generation of an intermediate oxonium species **150** (Scheme 26). This is initiated by the treatment of the glycosyl donor **147**—bearing a leaving group at the anomeric position—with a suitable activating agent to promote the irreversible glycosyl transfer. On the whole, most glycosidation methods rely on this basic principle, and vary mostly by the nature of the leaving group (Scheme 26).



147 **148** **149**

X = leaving group

Scheme 26: General Glycosidation Strategy.

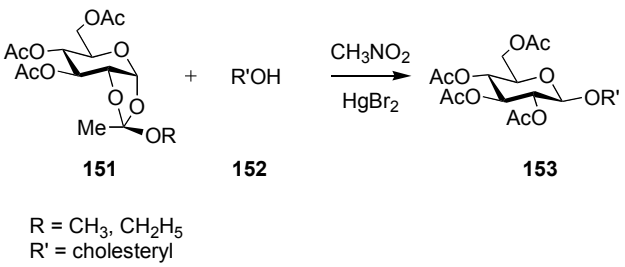
The choice of appropriate reaction conditions (*i.e.* favouring a stereo controlled S_N2-type reaction) or substrates (*i.e.* encouraging neighbouring group participating) can induce diastereoselectivity in the resulting product to give either the α or β product exclusively.[50, 56]

Whilst this procedure has proved to be a highly useful tool for various syntheses of *O*-glycoside containing natural products,[57] its associated disadvantages make it unsuitable as a general glycosidation method.[53] These include: i) the use of particularly harsh reaction conditions for the preparation of the glycosyl halide; ii) the subsequent problems associated with isolation of the glycosyl halide, due to thermal and hydrolytic instability and iii) the use of stoichiometric amounts of toxic, expensive and moisture sensitive heavy metal salts.

Since then, a myriad of leaving groups at the anomeric position have been incorporated into this methodology including the more commonly used ortho esters, imidates, thioglycosides, esters, carbonates and phosphates. With these variations have come improvements in the synthesis and storage of starting materials, reaction conditions, efficiency and α/β selectivity.

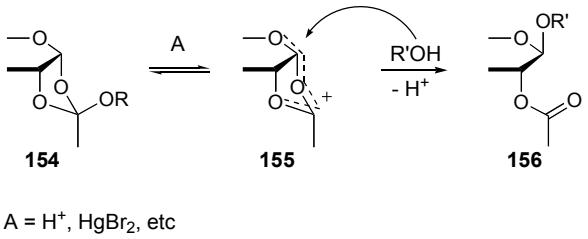
2.2.2 The Ortho Ester Method

In the mid 1960's and early 70's Kochetkov and co-workers[58-60] realised the need for a new glycosidation procedure that improved upon the often low yielding and inefficient Koenigs and Knorr method. They discovered that 1,2-*O*-alkyl orthoacetates, prepared from glycosyl halides**,** were excellent candidates for the stereospecific conversion to 1,2-*trans*-glycosides under the action of a protic or Lewis acid. The reaction between acetylated D-glucose-1,2-*O*-alkyl orthoacetates **151** and cholesterol (**152**) is one of the earliest examples (Scheme 27).[58]



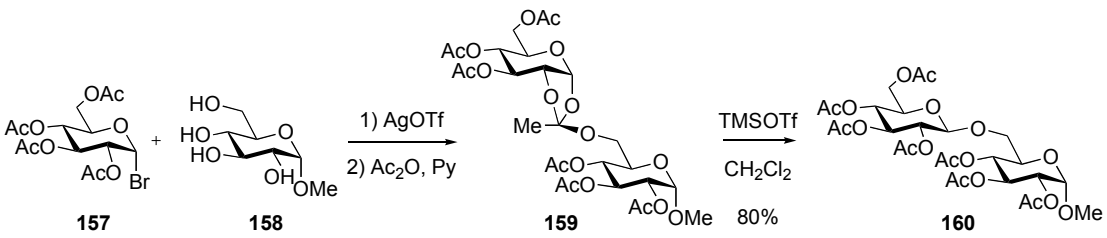
Scheme 27: Kochetkov's Ortho Ester Glycosidation Strategy.

It is thought that the mechanism proceeds *via* the dissociation of the ortho ester **154** to the 1,2-acyloxonium ion **155**, which consequently undergoes glycosidation by nucleophilic attack of the aglycon alcohol (Scheme 28).[61, 62]



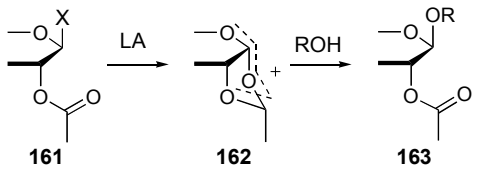
Scheme 28: Mechanism of the Ortho Ester Rearrangement.

Various modifications of this procedure have been developed since its dawn and all have been used extensively in *O*-glycoside containing natural product syntheses.[63-65] A recent example from the literature utilises this method for the regio- and stereoselective construction of 1,6-β-linked disaccharides such as **160**.[66] In this case, a modified ortho ester rearrangement is employed where the ortho esters are constructed from the aglycon alcohol **158** (Scheme 29).



Scheme 29: Construction of 1,6-β-linked Disaccharides **160** by the Modified Ortho Ester Rearrangement.

The regioselective formation of the 1,2-*trans* glycoside results from the incoming nucleophile approaching from the opposite side to that in which the 1,2-acyloxonium ion **162** resides. Indeed, the formation of the transient 1,2-acyloxonium ion **162** has been shown[67, 68] to be crucial for imparting 1,2-*trans* relationships in *O*-glycosides bearing participating functionality at C-2 and has been reported extensively in the literature.[69-72] This is commonly known as neighbouring group participation (Scheme 30). In these cases, the intermediate bridging cation **162** is formed by the intramolecular attack of the neighbouring ester group functionality at the anomeric centre. Intermolecular attack by the nucleophile results in formation of the 1,2-*trans*-glycoside **163** (Scheme 30).

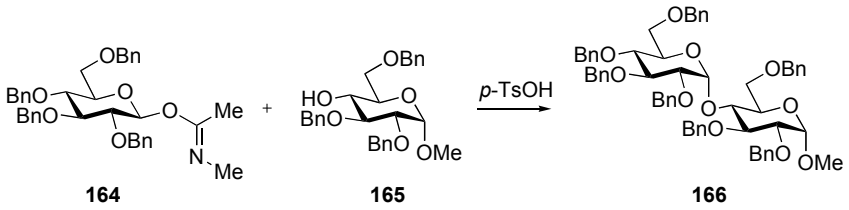


Scheme 30: Neighbouring Group Participation.

The use of the ortho ester methodology has proved to be a useful technique for the regioselective construction of 1,2-*trans* glycosides and additionally reduces the need for the use of heavy metal salts in the glycosidation step.

2.2.3 The Imidate Procedure

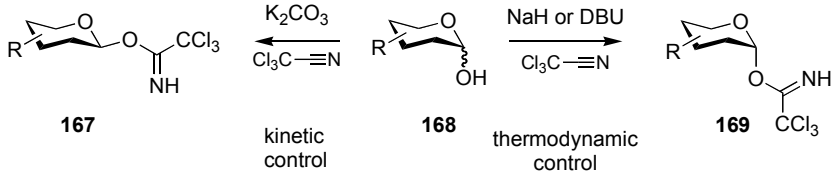
In 1978 the imidate procedure was introduced by Sinay and coworkers[73] as a novel alternative to the Koenigs and Knorr method. In this work, mild acid treatment of β-imidates **164** in the presence of glycosyl acceptors such as **165**, were shown to react stereoselectively to produce the corresponding α-disaccharides **166** in good yields. Importantly, this method avoided the use of heavy metal salts as promoters; instead the glycosidations could be carried out by the use of simple acid catalysts such as *para*-toluenesulfonic acid (Scheme 31).



Scheme 31: The Imidate Procedure for the Synthesis of disaccharides **166**.

Again however, the preparation of the imidates still depended on the use of α-haloses as starting materials and silver salts as promoters. In addition, only the β-imidates could be prepared and were relatively unreactive under the acid catalysed glycosidation conditions, with reactions taking on average six days for completion.

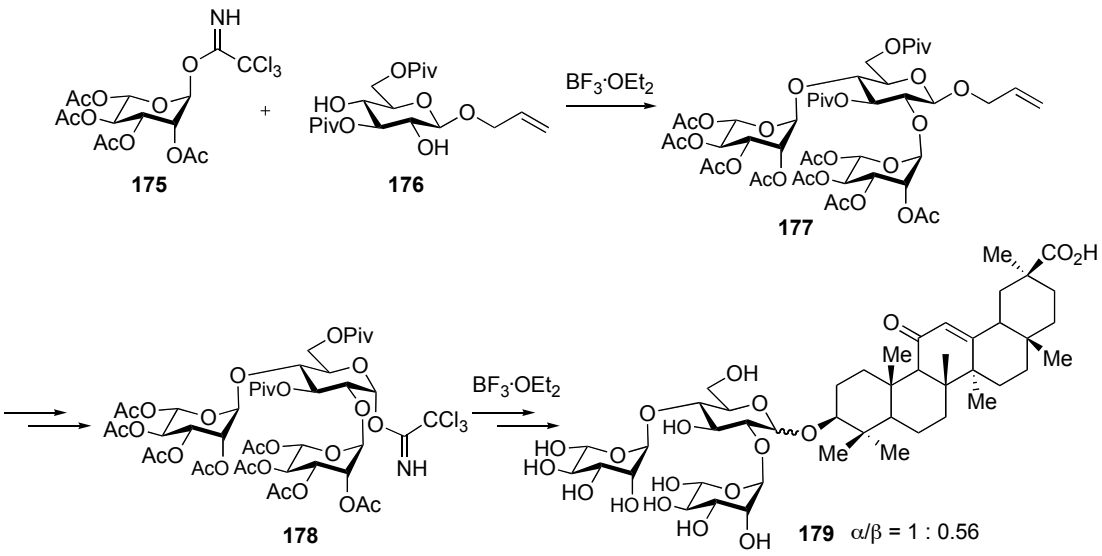
Soon after, Schmidt and co-workers[74] improved on this work by introducing the use of trichloroacetimidates **167** and **169** as more readily accessible glycosyl donors (Scheme 32). These were prepared by treatment of lactols such as **168** with base in the presence of trichloroacetonitrile or aryl-substituted ketenimines and were found to be stable under prolonged storage. Various methods have since been developed where either the α- or β-imidates can be prepared selectively depending on the reaction conditions (Scheme 32).[75, 76]



Scheme 32: Trichloroacetimidates **167** and **169** as Readily Accessible Glycosyl Donors.

O-β-Glycosyl imidates **167** can be obtained exclusively under kinetic control by the use of a weak base such as potassium carbonate. Conversley the use of a strong base, such as sodium hydride or 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), provides the thermodynamic *O*-α-glycosyl imidates **169** as the sole products. Control of the configuration at the anomeric centre of these trichloroacetimidates consequently allows for control (by careful choice of catalyst, solvent and participating groups) of stereoselectivity in the resulting glycoside.[74]

This procedure has thus proved to be an extremely useful stereoselective and efficient entry into *O*-glycosides—starting from readily available precursors—and has found widespread use for the synthesis of carbohydrate containing natural products.[77, 78] One recent example involves the use of trichloroacetimidates **175** and **178** for the synthesis of chacotriosyl containing neosaponins (Scheme 33).[79]



Scheme 33: Use of Trichloroacetimidates for the Synthesis of Chacotriosyl Containing Neosaponins **179**.

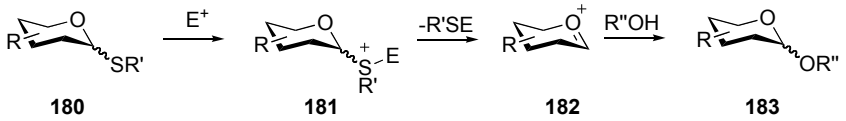
In this example, the initial glycosidation reaction proceeds with complete retention of configuration at the anomeric centre producing the 1,2-*trans*-glycoside **177** due to the participating functionality at C-2 (Scheme 33).

2.2.4 Thioglycosides as Glycosyl Donors

The use of thioglycosides as glycosyl donors have proved to be one of the most popular methods for glycosidations due to both their high reactivity towards relatively non-nucleophilic acceptors and their ability to tolerate a wide variety of diverse chemical operations. Moreover, they are inert under a variety of glycosidation conditions so can act as glycosyl acceptors in one step and donators in the next.

Their activation can be achieved through the use of a wide variety of thiophilic reagents, under very mild reaction conditions. The resulting sulfonium ion **181** is an especially

good leaving group and by facilitation through the ring oxygen lone pair or neighbouring group assistance, the glycoside **183** is formed readily *via* the oxonium species **182** (Scheme 34).



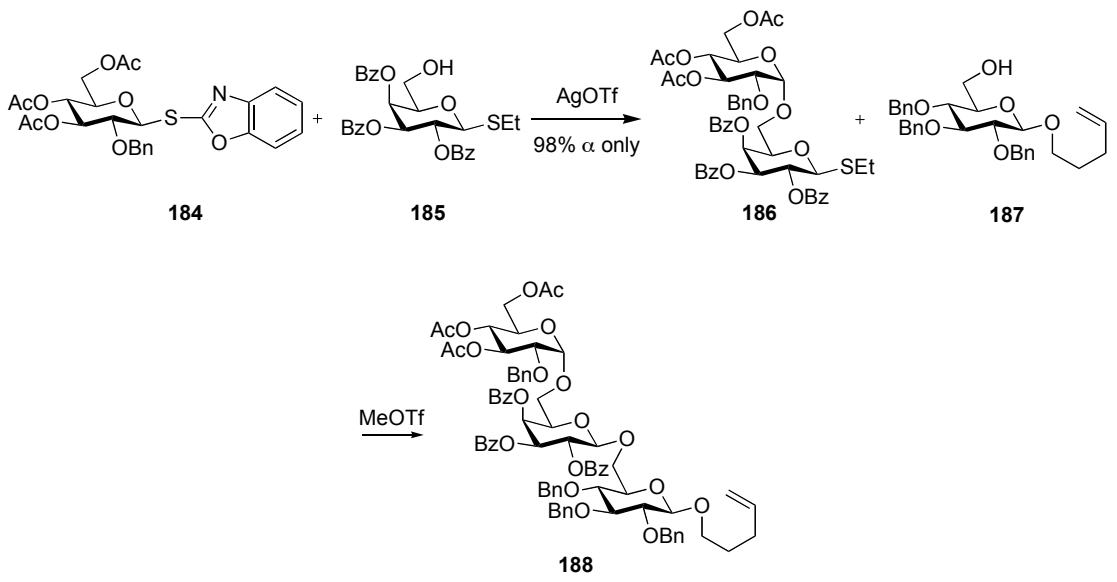
180 **181** **182** **183**

E = Electrophilic activating agent

Scheme 34: Thioglycosides **180** as Glycosyl Donors.

Of the wide variety of activators, mercury salts were amongst the first to be used in this methodology, however with limited uses.[80] At a later date, methyl triflate[81-83] and dimethyl(methylthio)sulfonium triflate (DMTST)[84-86] were successfully employed as efficient and more direct alternatives. More recently, the use of the dimethyl disulfide—triflic anhydride (Me_2S_2–Tf_2O) reagent has been used as a highly reactive, inexpensive promoter for use at low temperatures (–78 °C). Other notable promoters such as *N*-bromosuccinimide (NBS)[87, 88] and *N*-iodosuccinimide (NIS)[89-91] have also been used effectively.

Of particular interest and use is the ability to tune the reactivity of individual thioglycosides. By careful selection of sugar protecting groups and varying the steric bulk and electronics of the thioglycoside aglycon, one can chemoselectively activate the desired thioglycoside in the presence of others so as to carry out glycosidation steps sequentially. These distinguishable differences in reactivity between a pair of glycoside donors or acceptors allows for the use of thioglycosides in one-pot glycosidation strategies. The work of Demchenko and co-workers[92] demonstrates this approach for the construction of trisaccharide **188** and consequently avoids the use of protecting group manipulations in between glycosidation steps (Scheme 35).

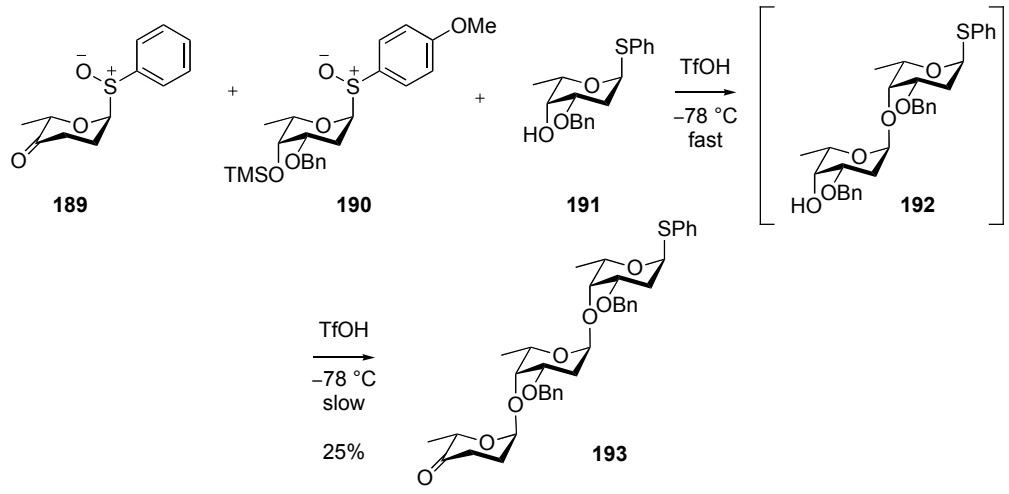


Scheme 35: Selective Activation of Thioglycosides.

Silver triflate was employed for the selective activation of the heterocyclic thioglycoside **184** over the more common alkyl thioglycoside **185**. Subsequent activation of the unaffected alkyl thioglycoside was accomplished by treatment with methyl triflate to give the trisaccharide unit **188** (Scheme 35).

Glycosyl sulfoxides have also been incorporated into this methodology and are especially good glycosyl donors for exceptionally unreactive substrates; in addition they can be easily prepared by the oxidation of thioglycosides. Various promoters can be used for their activation, however the most commonly used reagent is triflic anhydride in the presence of a base such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).[50]

An example of their application by Kahne and co-workers revealed a similar method to that of Demchenko's[92] to accomplish sequential one-pot activations of glycosyl sulfoxides **189** and **190** for the total synthesis of ciclamycin trisaccharide **193** (Scheme 36).[93] The success of this approach was based on the difference in reactivities of the two glycosyl sulfoxide donors **189** and **190** when treated with triflic acid.



Scheme 36: Sequential One-pot Synthesis of Ciclamycin Trisaccharide **193**.

2.3 Novel Glycosidation Methods: The Lactonamycin (1) Challenge

The use of these established *O*-glycosidation methods for the controlled construction of *O*-glycosidic linkages has enabled the synthetic chemist to build a wide variety of naturally occurring products. However, in certain cases, when these methods fail to provide the required degree of reactivity and/or selectivity, the use of novel approaches for the formation of *O*-glycosidic linkages is essential. With regard to the lactonamycin (**1**) program, a number of obstacles concerning the construction of the α-glycosidic bond between the sterically hindered α-oxo-*tert*-alcohol and the 2,3,6-trideoxysugar must be overcome. Specifically, these include the highly congested nature of the tertiary alcohol, the deactivation of the tertiary alcohol by hydrogen bonding to the adjacent carbonyl moiety and the low stereoselectivity and stability of the resulting glycosidic bond (Figure 6).

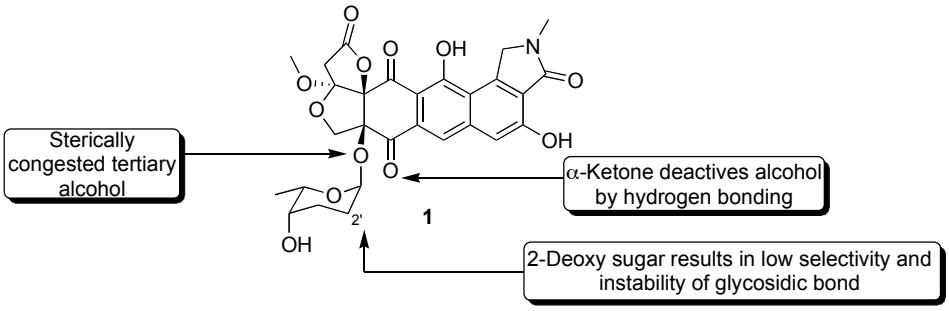


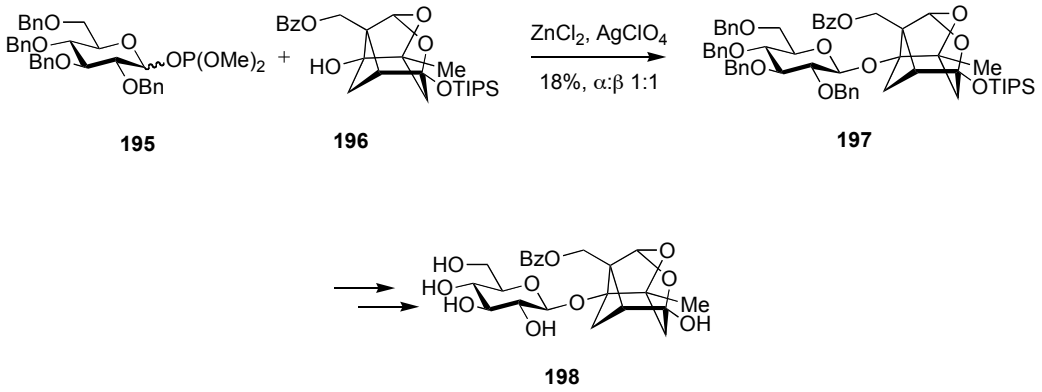
Figure 6: Difficulties Associated with the Glycosidation of Lactonamycin (**1**).

2.3.1 Glycosidation of Tertiary Alcohols

The construction of *O*-tertiary-glycosides remains a challenging feat for the synthetic chemist. The inherent low reactivity of tertiary alcohols—due to their increased steric hindrance—demands powerful methods for the synthesis of the resulting highly congested bonds. A variety of methods have been reported in the literature[94-101] and demonstrate the difficulties associated with such a demanding challenge.

2.3.1.1 The Total Synthesis of Paeoniflorin

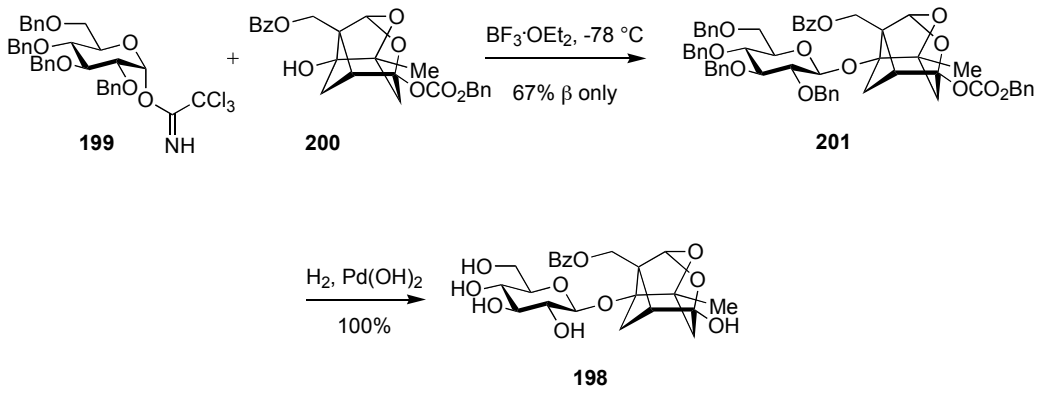
For almost three decades the total synthesis of paeoniflorin (**198**) remained elusive due to the challenging problems associated with creating the glycosidic linkage between the tertiary alcohol **196** and the glucose sugar **195**.[102] However, in the early 90's the groups of Corey[94] and Hatakeyama[95] published two total syntheses that demonstrated the construction of such a unit. The work of Corey and co-workers[94]—the first of the two syntheses—reported the use of Watanabe's procedure[99] for the construction of the congested glycosidic linkage (Scheme 37). This entailed the use of the 1-dimethylphosphite derivative of the tetrabenzyl ether of 1-glucose **195** as the glycosyl donor. Its activation, by treatment with zinc chloride and silver perchlorate, gave the corresponding glycoside **197** in 18% yield and in a 1:1 α,β-anomeric mixture (Scheme 37).



Scheme 37: Corey's Synthesis of Paeoniflorin (**198**) Using Watanabe's Dimethylphosphite Procedure.

Prior to this success, Corey and co-workers reported that up to ten different methods for the construction of the β-glycoside were ineffective.[94] Given the number of attempted glycosidation processes and the inefficiency of the successful glycosidation it was clear that the development of a new and improved methodology for the glycosidation of tertiary alcohols was essential.

Four months after Corey's report, Hatakeyama and co-workers described the glycosidation of tertiary alcohol **200** employing Schmidt's imidate methodology[75] (Scheme 38).[95]

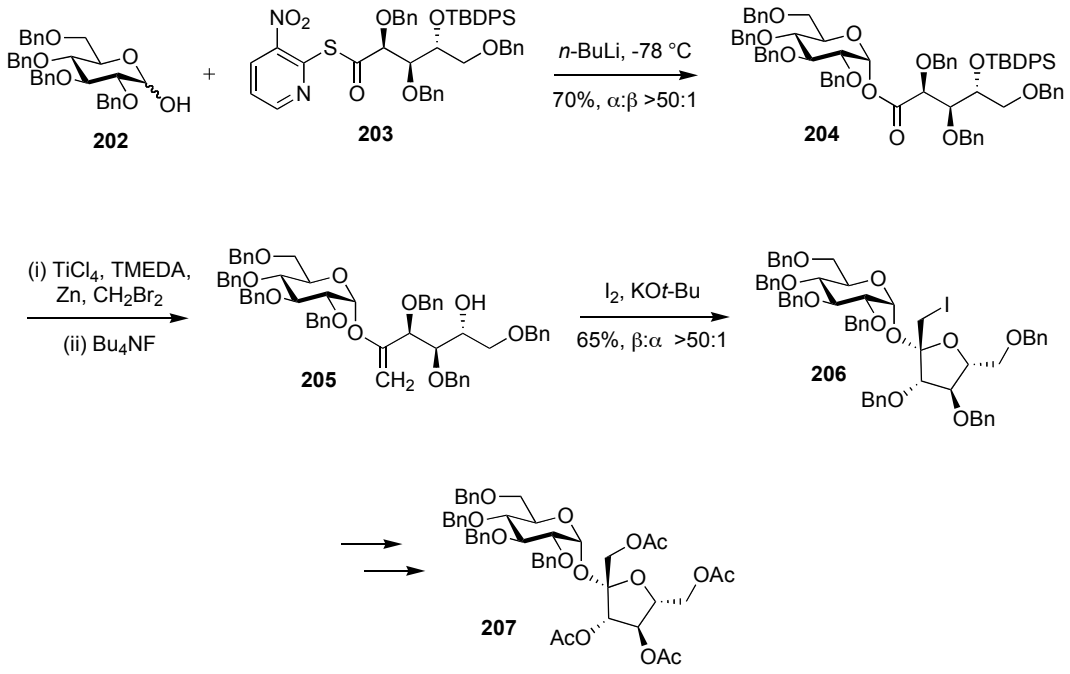


Scheme 38: Hatakeyama's Total Synthesis of Paeoniflorin (**198**) using Schmidt's Imidate Methodology.

The use of this procedure required 18 equivalents of boron trifluoride diethyl etherate as the activating agent and gave the β-glycoside **201** exclusively in 67% yield. Whilst the yield and selectivity were much improved, the use of large amounts of activating agent employed in the glycosidation step revealed the need for improvements in the formation of such hindered structures.

2.3.1.2 A Novel Glycosidation: Stereoselective Synthesis of Sucrose

In a novel approach to *O*-glycosidation, Barrett and co-workers[104] demonstrated an approach whereby the difficulties associated with tertiary-glycosidation were overcome by construction of the tertiary glycoside framework after glycosidation (Scheme 39).

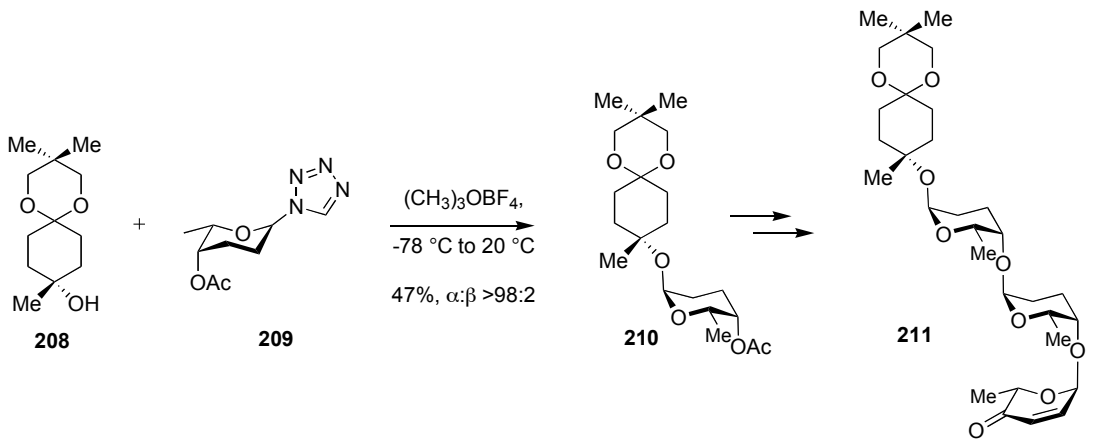


Scheme 39: Barrett's Stereoselective Synthesis of Glycoside **207** *via* a Novel Glycosidation Reaction.

Simple *trans*-esterification of pyranose **202** with thioester **203** using *n*-butyllithium provided glycoside **204** in 70% yield and good α-selectivity. After methylenylation and desilylation the resulting highly congested quarternary centre was formed using iodine induced cyclisation to provide the β-glycoside **206** in 65% yield (Scheme 39).

2.3.1.3 Glycosidation Using Glycosyl Tetrazoles

In 1996 Sulikowski and co-workers[97] successfully applied the use of glycosyl tetrazoles **209** to the α-glycosidation of tertiary alcohol **208** as a model system for the antibiotic PI-080[105] (Scheme 40).



Scheme 40: Use of Glycosyl Tetrazoles in the Glycosidation of Tertiary Alcohol **208**.

Treatment of tertiary alcohol **208** with glycosyl tetrazole **209** at low temperature provided predominantly the α-glycoside **210** in a modest yield of 47% (Scheme 40). This example is of particular relevance to the lactonamycin program and demonstrates the successful glycosidation of a tertiary alcohol with a 2,3,6-trideoxy-glycosyl donor **209**.

2.3.2 Glycosidation of 2-Deoxy Sugars

Along with the difficulties associated with the glycosidation of tertiary alcohols, come the additional problems connected with the formation of 2-deoxyglycosides (Figure 7). These structural motifs exist in numerous naturally occurring compounds and consequently, much attention has been given to their synthesis.[106, 107]

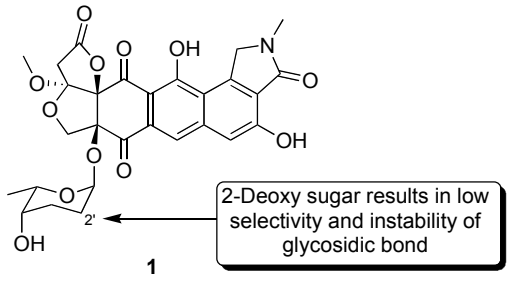


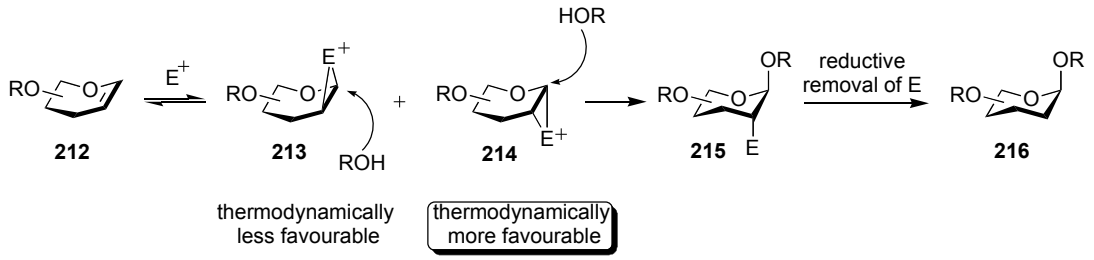
Figure 7: 2-deoxy-glycoside.

The stereocontrolled construction of such sugar linkages—in comparison to that of usual glycosides—is particularly challenging because the absence of a C-2 substituent on the 2-deoxyglycosyl donor prevents any stereodirecting effect (through anchimeric assistance) and furthermore renders the resulting glycosidic linkage unstable under acidic conditions. As a result, the anomeric effect[108, 109] dictates the predominance for the formation of α-glycosides.

The construction of 2-deoxy-β-glycopyranosyl linkages however, are more challenging and have mostly been prepared from latent 2-deoxysugars by indirect methods.[110-113] Their formation however, is not significant to the lactonamycin (**1**) programme, and will not be discussed in this thesis.

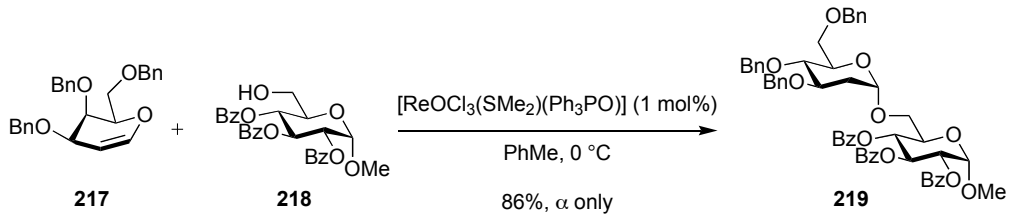
2.3.2.1 Approaches to 2-Deoxy-α-Glycosides

With regard to the stereocontrolled construction of 2-deoxy-α-glycosidic linkages, two main approaches are prominent in the literature and include the use of indirect and direct glycosidation methods. The former of the two involves the use of latent directional functionality at C-2 (glycals are often used) and has the disadvantage that it requires an additional reductive step to reveal the required oxygenation pattern of the sugar unit (Scheme 41).[114-116]



Scheme 41: Indirect Method for the Stereocontrolled Construction of 2-Deoxy-α-Glycosides **216**.

Whilst this may be a satisfactory approach in some cases, in others, the use of additional steps in the synthesis of complex natural products may be unsuitable and as a result, the use of direct methods for the construction of such linkages has found more wide spread use.[106, 107] Most examples include the use of traditional glycosidation methods,[117, 118] whilst more recently Toste and co-workers have demonstrated the use of a high-oxidation-state rhenium—oxo complex for the formation of 2-deoxy-α-glycosides **219** from glycals **217** and primary or secondary alcohols **218** (Scheme 42).[119]



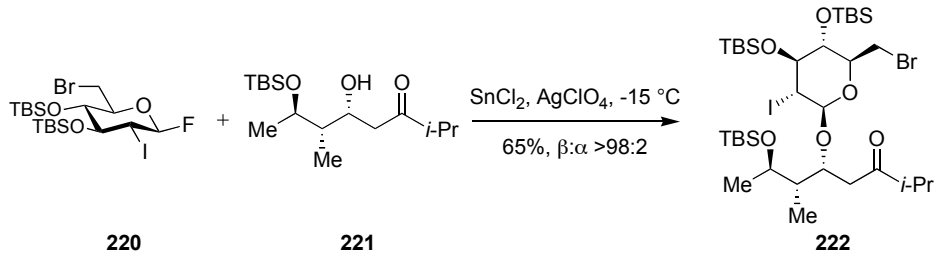
Scheme 42: Toste's Rhenium(V)-Catalysed Synthesis of 2-Deoxy-α-Glycoside **219**.

The air-and moisture-tolerant oxo complex catalyses the formation of the α-glycosides in excellent yields and selectivity (Scheme 42).

2.3.3 Glycosidation of α/β-Oxo-*tert*-alcohols

The presence of the ketone moiety alpha to the hydroxyl group in lactonamycin (**1**) also contributes to the difficulties associated with the impending glycosidation step. In particular, the reactivity of such α/β-oxo-*tert*-alcohols is particularly low due to the result of stabilisation by intramolecular hydrogen bonding of the hydroxyl hydrogen to the carbonyl moiety. Consequently, glycosidations of this nature are relatively difficult and as a result, the yields of such transformations have generally been found to be quite low (12-30%).[111, 120-122]

In a recent publication, Roush and co-workers[111] have revealed that under relatively mild activating conditions, 2-deoxy-2-iodo-β-glucopyranosyl fluoride (**220**) acts as an efficient glucopyranosyl donor for the glycosidation of a number of β-hydroxy-ketones such as **221** (Scheme 43).



220 **221** **222**

Scheme 43: Roush's Glycosidation of β-Hydroxy-Ketones using Glycosyl Fluoride **220**.

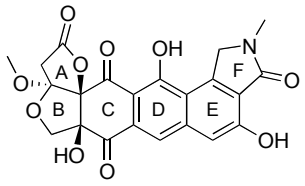
2.4 Conclusions

Despite the number of wide ranging procedures for the construction of *O*-glycosides in natural product synthesis, it is clear that the use of novel methodology will be essential for the successful introduction of the glycoside residue in lactonamycin (**1**). In particular, the glycosidation method must overcome the selectivity and reactivity issues associated with the construction of an α-glycosidic bond between a sterically hindered α-oxo-*tert*-alcohol and a 2,3,6-trideoxysugar.

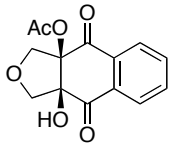
Chapter 3: Results and Discussion: Synthesis of Model Alcohols

3.1 Introduction

The successful total synthesis of lactonamycin (**1**) will require an efficient method for the stereoselective construction of an α-glycosidic bond between a 2,3,6-trideoxy sugar unit and an α-*tert*-oxo alcohol, the known difficulties of which have been highlighted in Chapters 1 and 2. With the aim of carrying out such a glycosidation, we required a model alcohol that displayed similar chemical reactivity to that of lactonamycinone (**9**). Of particular importance was the presence of the tertiary alcohol and the α-ketone functionality. It was envisaged that alcohol **230** could act as a suitable model for the glycosidation experiments (Figure 8).



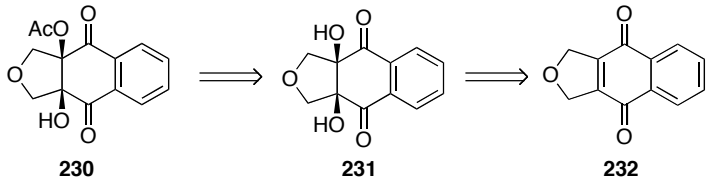
9



230

Figure 8: Lactonamycinone (**9**) and Model Alcohol **230**.

Retrosynthetically we envisaged the synthesis of alcohol **230** through the key naphthoquinone intermediate **232** (Scheme 44). Dihydroxylation of naphthoquinone **232** according to Danishefsky's precedent,[20, 25, 26] should furnish diol **231**, which under standard acetylation conditions would give the desired model alcohol **230** (Scheme 44).

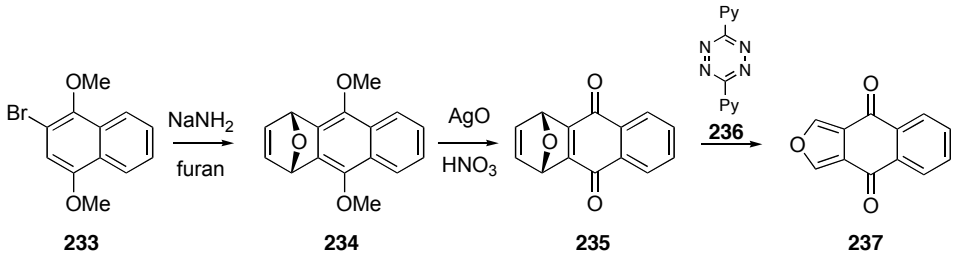


Scheme 44: Retrosynthetic Analysis of Model Alcohol **230**.

3.2 Towards the Synthesis of Model Alcohol 230

3.2.1 Approach to Naphthoquinone **232** *via* Benzyne Cycloaddition Chemistry

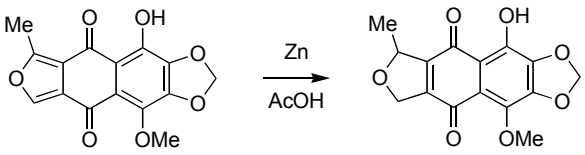
The initial approach to naphthoquinone **232** was inspired by the chemistry carried out by Karichiappan and co-workers[123] towards the synthesis of a model ring system **237** of ventilone A (Scheme 45).



Scheme 45: Karichiappan's Methodology Towards the Synthesis of a Model Ring System **237** of Ventilone A.

In Karichiappan's synthesis, the key strategic step entailed the use of a benzyne-furan-cycloaddition reaction of bromide **233**, to provide cycloadduct **234**, which was subsequently oxidised to naphthoquinone cycloadduct **235**. To reveal the final ring system, extrusion of the ethylene bridge *via* Warrener's cycloaddition-cycloreversion protocol[124-126] was realised using 2,6-di(pyridin-2-yl)-*s*-tetrazine **236** (Scheme 45).

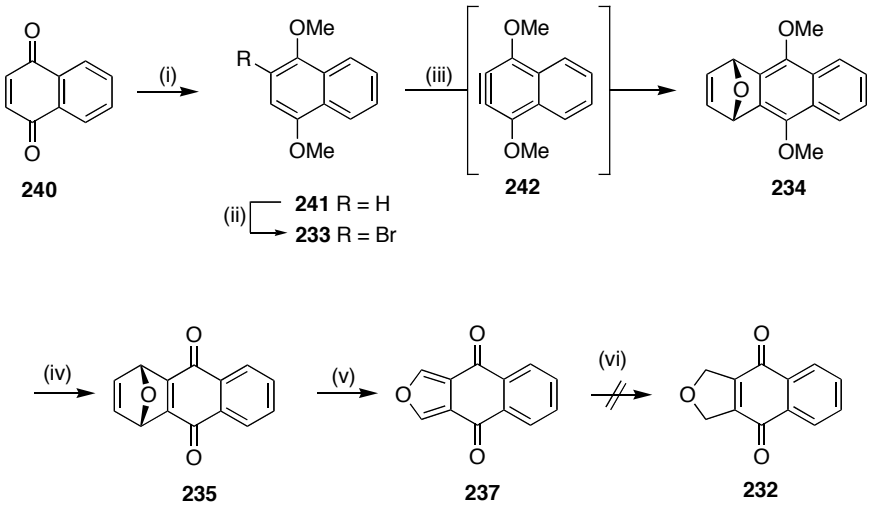
It was possible that conversion of furan **237** to our key naphthoquinone intermediate **232** could be achieved according to the procedure previously described by Hanumaiah and co-workers[127] where a zinc/acetic acid mediated reduction was used to convert ventilone B (**238**) to ventilone C (**239**) (Scheme 46).



238 **239**

Scheme 46: Hanumaiah's Zinc/Acetic Acid Mediated Reduction of Ventilone B (**238**) to Ventilone C (**239**).

Accordingly, investigations into the synthesis of the key naphthoquinone intermediate **232** were conducted starting from comercially available 1,4-naphthoquinone (**240**) (Scheme 47).



Reagents and Conditions: (i) $SnCl_2$, $HCl_{(g)}$, MeOH, 65 °C, 18 h, 78%; (ii) Fe(0), Br_2, CH_2Cl_2, 12 h, 95%; (iii) $NaNH_2$, furan, THF, 55 °C, 20 h, 81%; (iv) AgO, HNO_3, CH_3CN/H_2O, 18 h, 5%; (v) 3,6-di(pyridin-2-yl)-*s*-tetrazine, $CHCl_3$, 60 °C, 12 h , 82%; (vi) Zn(0), AcOH, CH_2Cl_2, 10 h.

Scheme 47: Attempted Synthesis of Naphthoquinone **232** using Karichiappan's Methodology.

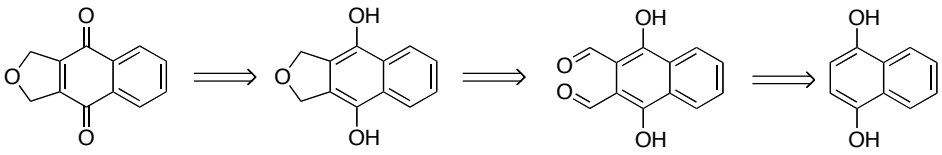
Reductive methylation of 1,4-naphthoquinone (**240**) by treatment with stannous chloride and hydrogen chloride gas in methanol provided 1,4-dimethoxynaphthol (**241**) which under exposure to bromine and iron powder gave bromide **233** in 95% yield. Treatment of bromide **233** with sodium amide in tetrahydrofuran (THF) at reflux generated benzyne **242** *in situ*, which, in the presence of freshly distilled furan, underwent [4+2] cycloaddition to give cycloadduct **234** in 81% yield. Oxidative demethylation of cycloadduct **234** by treatment with silver(II) oxide and nitric acid yielded naphthoquinone **235** in a significantly lower yield (5%) than the 42% previously reported by Karichiappan and co-workers.[123] Changing the oxidant to PIFA or CAN, proved unsuccessful and gave only starting material. However, it was decided to validate the remaining synthetic steps before considerable efforts towards the optimisation of this oxidation were conducted. Extrusion of the ethyne bridge of naphthoquinone cycloadduct **235** by reaction with 3,6-di(pyridin-2-yl)-5-tetrazine **236** in refluxing THF gave furan **237** in 82% yield (Scheme 47).

It was hoped that treatment of furan **237** with the zinc/acetic acid conditions previously reported by Hanumaiah and co-workers[127] would result in the reduction to naphthoquinone **232** in the final step of the sequence. Unfortunately, exposure of furan **237** to zinc in acetic acid gave only a complex mixture of products and none of the desired naphthoquinone **232** could be detected by ^{1}H NMR spectroscopy (Scheme 47).

Given the difficulties associated with the last step in this sequence, as well as the problematic oxidative demethylation of adduct **234**, this route was deemed unsuitable for a scale up synthesis of model alcohol **232** and consequently was abandoned.

3.2.2 Approach to Naphthoquinone **232** *via ortho*-Formylation

An alternative retrosynthetic approach to naphthoquinone **232** was therefore necessary. The *ortho*-formylation of phenols and related substrates has proved an invaluable approach for the assembly of multi-functionalised aromatic compounds in organic synthesis. This chemistry formed the basis for a new retrosynthetic route to naphthoquinone **232** and is outlined in Scheme 48.

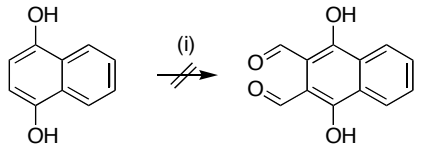


232 **245** **246** **247**

Scheme 48: Proposed Route to Naphthoquinone **232** *via ortho*-Formylation.

The use of a double *ortho*-formylation reaction of 1,4-dihydroxynaphthalene (**247**) would allow for the installation of the necessary carbon fragments for the future construction of the tetrahydrofuran ring in model alcohol **230**. Further manipulation of dialdehyde **246** through reduction and cyclisation followed by oxidation of the resulting hydronaphthoquinone **245** would provide naphthoquinone **232** (Scheme 48).

Our initial approaches to dialdehyde **246** were unsuccessful. Firstly, a modified version of the Reimer-Tiemann reaction[128] using titanium tetrachloride and dichloromethyl methyl ether as the carbene source was attempted, as too was the Vilsmeier-Haak reaction[129, 130] (Scheme 49).

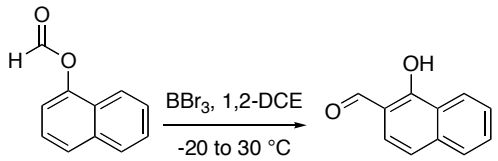


247 **246**

Reagents and Conditions: (i) $TiCl_4$, Cl_2CHOMe, CH_2Cl_2, 0 °C or $POCl_3$, DMF, CH_3CN, 0 °C.

Scheme 49: Attempted Formylation to Dialdehyde **246**.

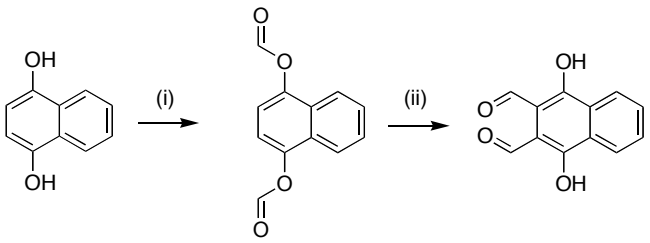
At this time, our attention was drawn to a strategy developed by Kantlehner and co-workers[131] in which a Lewis acid promoted Fries rearrangement was employed as a quick and efficient means to *ortho*-formyl phenols such as **249** (Scheme 50).



248 **249**

Scheme 50: Kantlehner's Fries Rearrangement of Aryl Formates.

Subsequently, diformate **250** was prepared by reaction of 1,4-dihydroxynaphthalene (**245**) with formic acid in the presence of dicyclohexylcarbodiimide (DCC), according to the procedure described by Hall and co-workers (Scheme 51).[132]



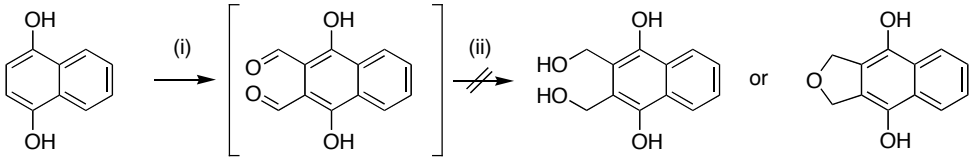
245 **250** **246**

Reagents and conditions: (i) DCC, HCO_2H, acetone, 30 °C, 45 min, 90%; (ii) BBr_3, 1,2-DCE, –20 to 25 °C, 21 h, 60% mass recovery.

Scheme 51: Synthesis of Dialdehyde **246**.

Complete conversion to diformate **250** was observed by crude ^{1}H NMR spectroscopy. However, after purification by silica gel column chromatography and prolonged storage, a significant amount of decomposition was observed. By immediately taking forward the crude reaction mixture however, the Fries rearrangement could be effected by reaction with boron tribromide in 1,2-dichloroethane at –20 °C. Issues surrounding the stability of dialdehyde **246** were also encountered and as a result only small quantities of impure product were isolated.

Given the sensitive nature of diformate **250** it was hoped that the corresponding one-pot procedure—also developed by Kantlehner and co-workers[131]—would be more efficient and subsequently increase the yield of the reaction. Towards this aim, treatment of 1,4-dihydroxynaphthalene (**245**) with formic acid and boron tribromide at –40 °C gave dihydroxy dialdehyde **246** as the major product of the reaction, identified by the appearance of the phenolic and aldehyde protons at 9.70 ppm and 12.19 ppm respectively in the ^{1}H NMR spectrum (Scheme 52).



245 **246** **251** **252**

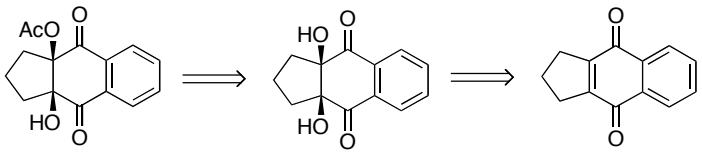
Reagents and conditions: (i) BBr_3, HCO_2H, $(CH_2)_2Cl_2$, –40 °C, 12 h; (ii) $NaBH_4$, MeOH, 0 °C, 30 min.

Scheme 52: Synthesis of Dialdehyde **246** using a One-Pot Fries Rearrangement.

Immediate reduction of the crude dialdehyde **246** was carried out by treatment with sodium borohydride at 0 °C in methanol. Complete consumption of starting material **246** was observed by thin layer chromatography, however all attempts to isolate the tetraol **251** or indeed the cyclised product **252** failed and was attributed to the sensitivity of these highly oxygenated systems. The instability issues associated with the formation of all intermediates in this reaction sequence posed problems for the future scale-up of this chemistry and as a result this route was abandoned.

3.3 Approach to Model Precursor 253 *via* Polar Cycloadditions

At this point, the successful formation of naphthoquinone **232** was proving to be more problematic than had previously been envisaged and as a result, our attention turned to the synthesis of the alternative alcohol **253** (Scheme 53). Whilst this model displayed less similarity to lactonamycinone (**9**), it was thought that the reactivity of the tertiary alcohol would show appreciable likenesses to the real system. As before, the naphthoquinone **255** was seen as the key intermediate essential for the formation of model alcohol **253** (Scheme 53).

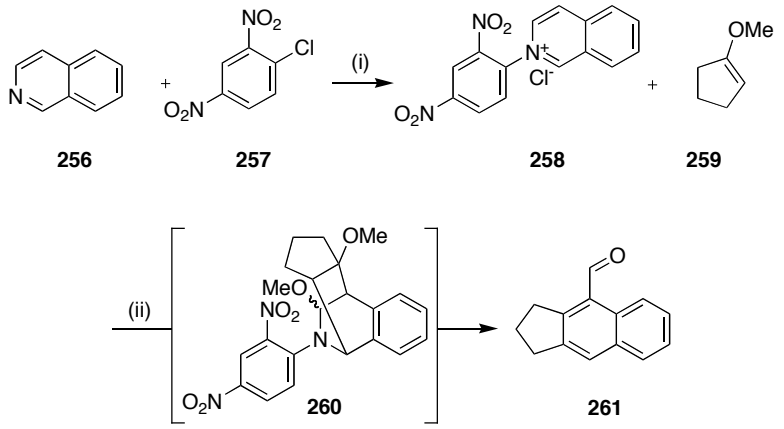


253 **254** **255**

Scheme 53: Retrosynthetic Analysis of Model Alcohol **253**.

The construction of the cyclopenta[*b*]naphthalene core unit had been formerly conducted by Mana and co-workers and necessitated the use of a polar cycloaddition reaction of an isoquinoline salt with an electron-rich alkene.[133] In a separate account, Franck and co-workers had further manipulated the cyclopenta[*b*]naphthalene core to provide naphthoquinone **255**.[134]

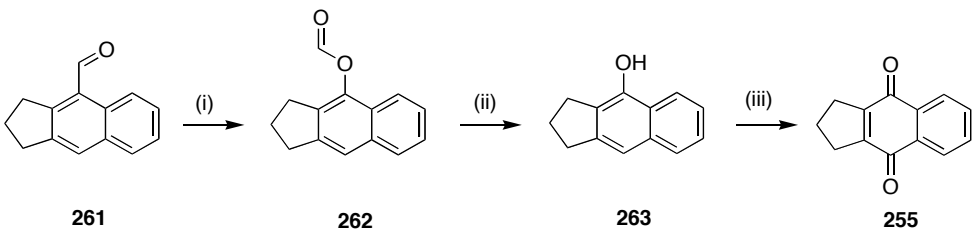
Initial attempts at this route on a small scale proved to be moderately successful. The preparation of the dinitrophenyl (DNP) salt **258** from the known reaction[135] between isoquinoline (**256**) and 1-chloro-2,4-dinitrobenzene (**257**) proceeded in 66% yield and when treated with excess 1-methoxy cyclopentene **259** (prepared by the procedure described by Wohl and co-workers[136]) underwent a [4+2] polar cycloaddition reaction to provide the cyclo-adduct intermediate **260** (Scheme 54). Direct hydrolysis in THF/water with Amberlyst-15 resin followed by heating under reflux for 5 min in aqueous sodium hydroxide furnished naphthaldehyde **261** in 43% yield. Experimentation of this step on a larger scale however, was not as effective and produced only yields between 25-35% (Scheme 54).



Reagents and conditions: (i) Acetone, reflux, 2 h, 66%; (ii) a) $CaCO_3$, MeOH, 24 h; b) Amberlyst-15 resin, THF, H_2O, 40 °C, 21 h; c) NaOH, H_2O, MeOH/THF, reflux, 5 min, 43%.

Scheme 54: Synthesis of Naphthaldehyde **261**.

From the small amount of naphthaldehyde **261** synthesised, naphthoquinone **255** was prepared by the route developed by Franck and co-workers (Scheme 55).[134] Baeyer-Villiger reaction of naphthaldehyde **261** with *meta*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane gave naphthylformate ester **262** in 99% yield. Hydrolysis using basic aluminium oxide effected the transformation to naphthol **263**, which was subsequently oxidised to naphthoquinone **255** under a stream of oxygen gas in the presence of *bis*(salicylidene) ethylenediiminocobalt(II) (salcomine), in 78% yield (Scheme 55).

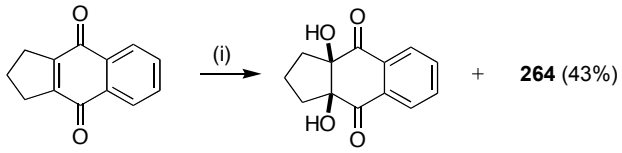


261 **262** **263** **255**

Reagents and conditions: (i) a) *m*-CPBA, CH_2Cl_2, 24 h; b) KF, 5 h, 99%; (ii) Al_2O_3, CH_2Cl_2, 24 h, 69%; (iii) Salcomine, O_2, THF, 3 h, 78%.

Scheme 55: Synthesis of Naphthoquinone **255**.

The dihydroxylation of the key naphthoquinone intermediate **255** using catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) in acetone/water proved problematic. In addition to the 35% yield of the expected diol **254**, were isolated significant amounts (43%) of a second product **264** (Scheme 56).



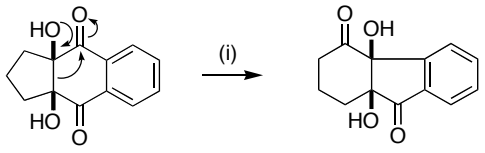
255 **254**

Reagents and conditions: (i) O_sO_4, NMO, acetone/water, 18 h, 35%.

Scheme 56: Dihydroxylation of Naphthoquinone **255**.

Analysis of the ^1H and ^{13}C NMR spectrum of the unknown compound suggested a structure that was not dissimilar to the desired diol **254**. Specifically, an extra set of signals were observed and indicated that the structure was no longer symmetrical. Moreover, following analysis by mass spectroscopy the unknown product was found to be isomeric with diol **254**.

We postulated that rearrangement of diol **254** was occurring by way of a retro-aldol ring opening ring closing reaction to give the isomeric diol **264** and may have been caused by the presence of NMM—a by-product during the dihydroxylation reaction. This was confirmed in an independent reaction, by treatment of diol **254** with NMM in acetone/water (Scheme 57).



254 **264**

Reagents and conditions: (i) NMM, acetone/H_2O,
18 h (100% conversion by ^1H NMR).

Scheme 57: Retro-Aldol Rearrangement of Diol **254** Under Basic Conditions.

Recrystallisation from ethyl acetate/petroleum ether gave crystals suitable for X-ray crystallography and confirmed the identity of the unknown compound to be that of diol **264** (Figure 9).

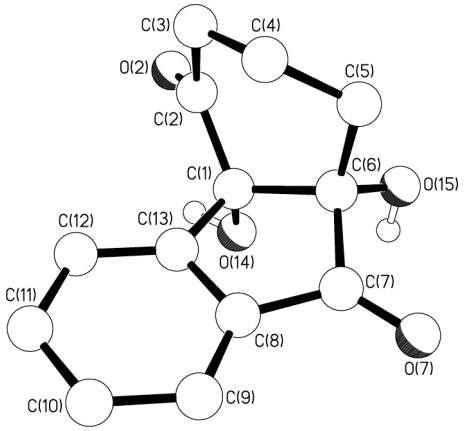
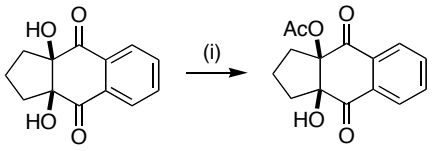


Figure 9: X-ray Crystal Structure of Compound **264**.

In order to validate the remaining chemistry for the synthesis of model alcohol **253**, the mono-protection was carried out employing acetic anhydride and pyridine and gave the desired product **253** in 91% yield (Scheme 58).



254 **253**

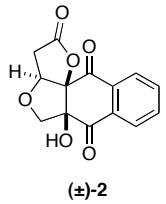
Reagents and conditions: (i) Ac_2O, pyridine, DMAP, CH_2Cl_2, 20 h, 91%.

Scheme 58: Synthesis of Model Alcohol **253**.

Overall, due to the low yields obtained during the scale up of aldehyde **261** and the problems associated with the dihydroxylation of naphthoquinone **255**, this route was not a reliable method for obtaining large quantities of model alcohol **253**. Given that the purpose of synthesising model alcohols **230** and **253** was to save on time and resources, the difficulties encountered thus far in their preparation suggested that continuation on such a theme would not be beneficial.

3.4 Synthesis of Model Precursor (±)-2

The synthesis of ABCD alcohol **(±)-2** had previously been conducted within the Barrett group in order to develop chemistry for the construction of the ABCD ring system of lactonamycin (**1**) (Figure 10).



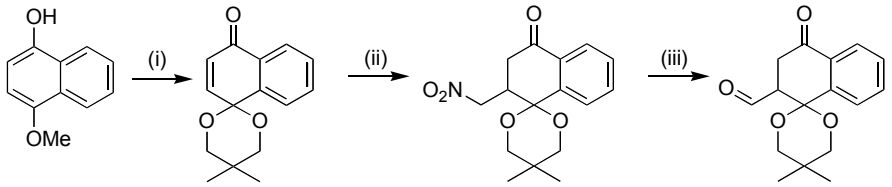
(±)-2

Figure 10: Model Compound **(±)-2**.

Following Henderson's procedure,[42] significant quantities (up to 5 g) of the model ABCD alcohol **(±)-2** were successfully prepared (Scheme 59 and Scheme 61).

Naphthoquinone mono-ketal **271** was prepared starting from four 25 g batches of 4-methoxy-1-naphthol (**270**) (Scheme 59). On conducting these large scale experiments, we found that careful control of the reaction temperature—by drop-wise addition of 4-methoxy-1-naphthol (**270**) to the solution of PIFA and *neo*-pentyl glycol—was necessary for the success of the reaction. After crystallisation, reaction of naphthoquinone mono-ketal **271** with nitromethane and triethylamine afforded the nitro product **272** in 83% yield (Scheme 59) as previously described.[42]

In the subsequent Nef reaction, following Henderson's protocol,[42] treatment with potassium hydroxide gave the corresponding nitronate, which after addition of a solution of potassium permanganate and magnesium sulfate in water gave the resulting aldehyde **273**. We found the yield of this reaction to be highly sensitive to the rate of addition of the potassium permanganate solution to the intermediate nitronate. Again, careful monitoring of the reaction temperature so as not to exceed 5 °C, was crucial to obtain an optimal yield of 62% (Scheme 59).

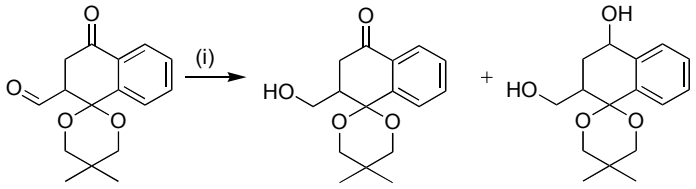


270 **271** **272** **273**

Reagents and conditions: (i) PIFA, *neo*-pentyl glycol, CH_2Cl_2/THF, 0 °C, 3 h, 66%; (ii) $MeNO_2$, Et_3N, MeOH, 3.5 h, 83%; (iii) a) 2M KOH/MeOH, 0 °C, 1 h; b) $KMnO_4$, $MgSO_4$, H_2O, 0 °C, 2 h, 62%.

Scheme 59: Synthesis of Aldehyde **273**.

Reduction of aldehyde **273** to alcohol **274** using one equivalent of sodium borohydride at –5 °C according to the procedure described by Henderson[42] gave an unsurprisingly low yield of 20% with the major product of the reaction being that of diol **275** (Scheme 60). In an attempt to increase the yield of the desired alcohol **274**, sodium borohydride was added to the reaction mixture in sequential amounts at –5 °C until aldehyde **273** was undetectable by thin layer chromatography. A total of 0.25 equivalents of reducing agent were added to aldehyde **273**, significantly increasing the yield of alcohol **274** to 95% (Scheme 60).

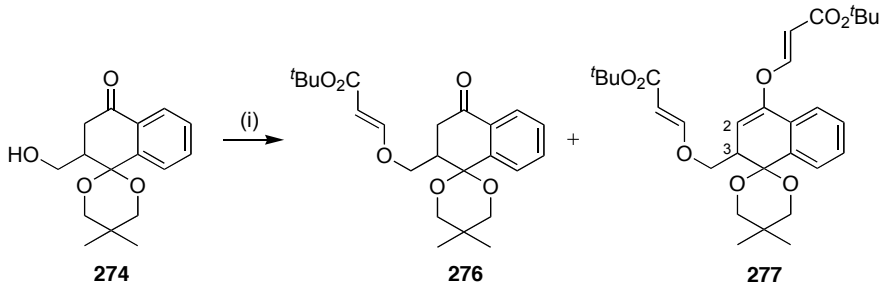


273 **274** **275**

Reagents and conditions: (i) a) $NaBH_4$ (1 eq), MeOH, –5 °C, 1 h, **274** = 20% and **275** = 72% or b) $NaBH_4$ (0.25 eq), MeOH, –5 °C, 2 h, **274** = 95%.

Scheme 60: Synthesis of Alcohol **274**.

Continuation of Henderson's route[42] to model compound **(±)-2** was realised by Michael addition of alcohol **274** to *tert*-butyl propiolate upon action of NMM and afforded the resulting ester **276** in 81% isolated yield and predominantly as a single geometric isomer (>95:5, *E*:*Z* by ^{1}H NMR spectroscopy). A second, unexpected product **277**, was also isolated in 19% yield (Scheme 61). The presence of three additional alkene signals and an extra *tert*-butyl signal in the ^{1}H and ^{13}C NMR spectra, as well as a strong correlation between the H-2 alkene and H-3 protons in the COSY NMR spectrum indicated that the unknown product **277** was a result of a second *O*-alkylation of ester **276**. Mass spectroscopy also supported the assignment of this structure.

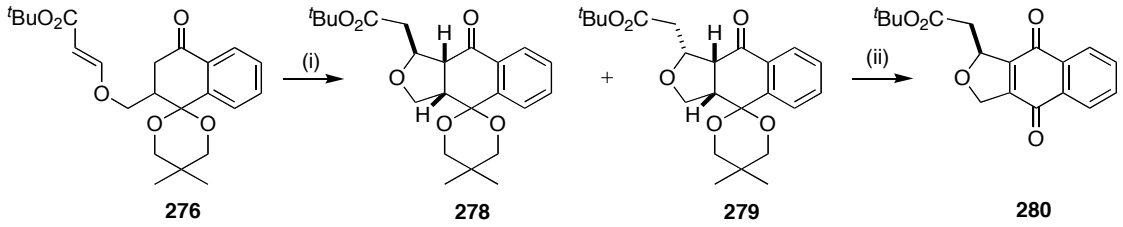


Reagents and conditions: (i) a) *tert*-butyl propiolate, NMM, Et_2O, 12 h, **276** = 81% **277** = 19% or b) *tert*-butyl propiolate, DMAP, CH_2Cl_2, 18 h, **276** = 92%.

Scheme 61: Coupling of Alcohol **274** to *tert*-Butyl Propiolate.

Altering Henderson's original procedure by using the less basic amine, DMAP avoided the formation of diester **277** and resulted in an increase in yield of the desired product **276** to 92% (Scheme 61).

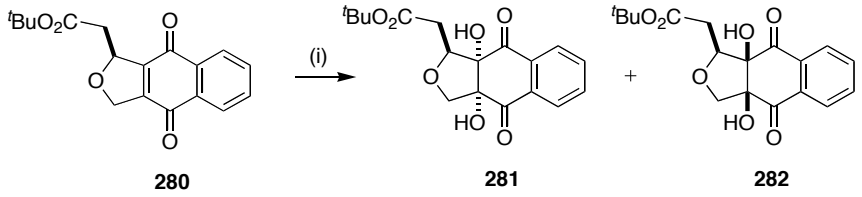
Subsequent treatment of this compound **276** with Barton's base brought about the construction of the B ring of lactonamycin (**1**) to provide tetrahydrofurans **278** and **279** as an inseparable mixture of diastereoisomers in comparable yield to Henderson's original report[42] (Scheme 62). Removal of the ketal protecting group with *para*-toluenesulfonic acid using Henderson's previous conditions[42] gave naphthoquinone **280** in 96% yield (Scheme 62).



Reagents and conditions: (i) Barton's base, CH_2Cl_2, 8 h, 100%; (ii) *p*-TsOH, acetone, air, 24 h, 96%.

Scheme 62: Synthesis of Naphthoquinone **280**.

Naphthoquinone **280** subsequently underwent complete conversion to diols **281** and **282** upon exposure to osmium tetroxide and NMO in acetone/water. In accordance with Henderson's findings[42], analysis of the crude ^{1}H NMR spectrum indicated two sets of signals for diastereoisomers **281** and **282** in a 1 : 1 ratio (Scheme 63).

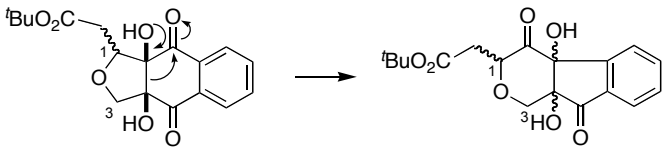


Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O, 4 h, 89%, **281** : **282** = 1 : 1.

Scheme 63: Dihydroxylation of Naphthoquinone **280**.

Unexpectedly, upon standing of the crude reaction mixture for several hours, complete decomposition of diols **281** and **282** was observed by thin layer chromatography. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed a shifting of all the proton signals and in addition, mass spectroscopy revealed an identical mass to that of diols **281** and **282**. This evidence suggested that a similar rearrangement to that

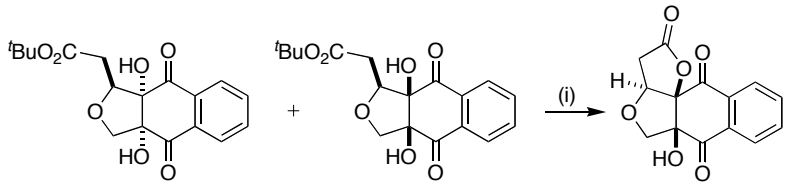
observed during the dihydroxylation of naphthoquinone **255** (Scheme 56) was occurring to provide a diastereoisomer mixture of diol **283** (Scheme 64).



281 and **282** **283**

Scheme 64: Rearrangement of Diols **281** and **282** to Diol **283**.

We postulated that residual NMM from the dihydroxylation reaction, was catalysing the rearrangement process and this prompted the search for an alternative work-up procedure. A number of acidic work-ups were evaluated including potassium hydrogen sulfate and hydrochloric acid but gave only complicated TLC profiles. Finally, citric acid was used and completely prevented the retro-aldol-rearrangement of diols **281** and **282** after standing overnight. With a suitable protocol for the dihydroxylation reaction in place, the conversion of 2.6 g of naphthoquinone **280** to diols **281** and **282** was achieved without further decomposition. Finally, Henderson's protocol for the formation of the A ring, to complete the sequence, was conducted by reaction of diols **281** and **282** with TFA and water to furnish racemic model alcohol **(±)-2** in 52% yield (Scheme 65).



281 **282** **(±)-2**

Reagents and conditions: (i) TFA/H_2O, 12 h, 52%.

Scheme 65: Synthesis of Model Alcohol **(±)-2**.

3.5 Conclusions

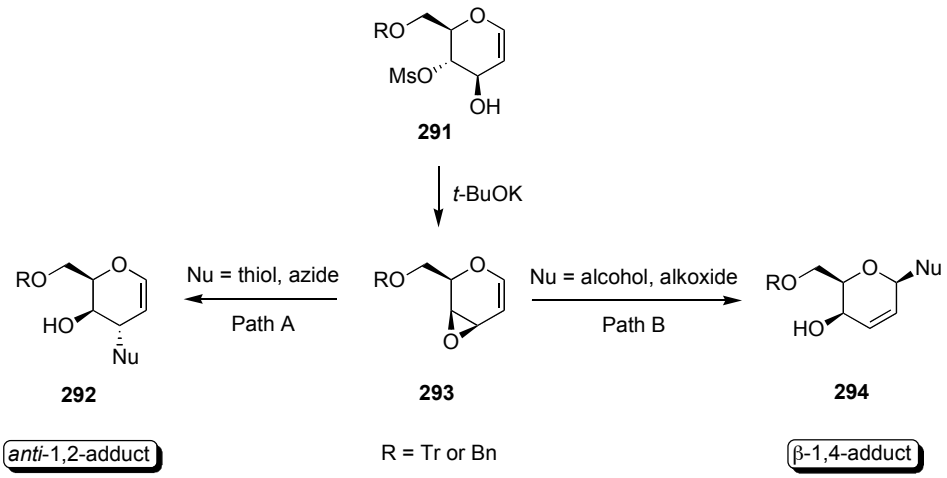
Experiments towards the synthesis of model alcohols **230** and **253** have been carried out. Whilst the synthesis of model alcohol **230** proved to be ineffective, that of model alcohol **253** was achieved on a small scale employing the known methods of Mana[133] and Franck[134]. However, due to problems associated with the scale-up of certain reactions and the formation of undesired by-products during the dihydroxylation reaction, enough material in order to thoroughly test the key glycosidation procedure was not accessible.

The preparation of gram scale quantities of the previously prepared[42] model alcohol **(±)-2** of lactonamycinone (**9**) was consequently achieved in a 9 step linear sequence starting from 100 g of 1,4-methoxy-naphthol (**270**). Several modifications to Henderson's original route[42] were performed in order to improve the yields of a number of the individual steps and were published along with the original work as a paper in the Journal of Organic Chemistry.[29]

Chapter 4: Results and Discussion: Investigations into the Crotti and Ferrier Glycosidation

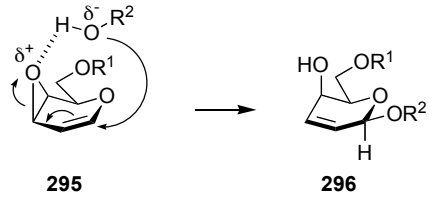
4.1 Introduction

To bring about the successful glycosidation of lactonamycinone (**9**) a powerful and stereoselective method for the construction of the sterically congested *O*-glycosidic linkage was required. One particularly attractive route for this glycosidation was the recent methodology developed by Crotti and co-workers.[137-140] In this program of research, the attack of carbon, sulfur, nitrogen and most importantly in our case, oxygen nucleophiles towards D-glucal derived β-alkenyl oxiranes such as **293** proceeded with excellent regio- and stereoselectivities. The preference between an *anti* 1,2-addition pathway (Path A) versus a β-stereoselective 1,4-addition pathway (Path B) was dependent on the ability of the incoming nucleophile to coordinate with the oxirane ring oxygen (Scheme 66).



Scheme 66: Crotti's Regio- and Stereoselective Addition of *O*-, *S*-, *N*- and *C*- Nucleophiles to D-Glucal Derived β Vinyl Oxiranes **293**.

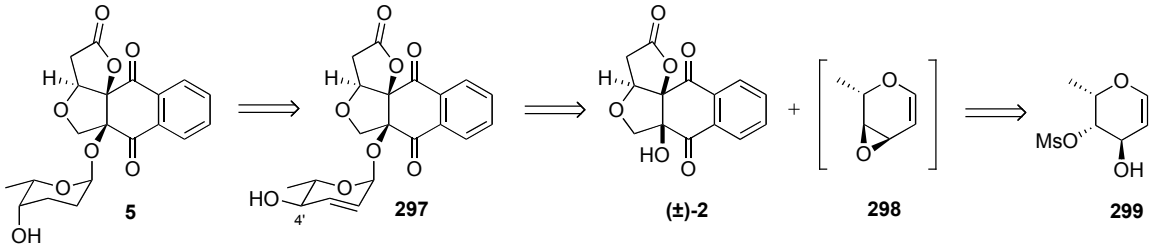
Of particular interest to us was the observation that the addition of alcohols proceeded to attack exclusively *via* the 1,4-addition pathway (Path B) to generate the corresponding unsaturated glycosides **294**. In addition, whilst relatively unhindered alcohols such as methanol gave a 1:1 mixture of anomeric 2-unsaturated methyl α- and β-glycosides, the use of more hindered alcohols such as *tert*-butanol afforded the corresponding β-glycosides exclusively. Crotti postulated that the complete stereo- and regioselective outcome of the addition reaction of *O*-nucleophiles to β-alkenyl oxiranes such as **295** was a result of the delivery of the nucleophile to the β-face of the epoxide, facilitated through hydrogen bonding between the alcohol and epoxide ring oxygen (Scheme 57).[137]



295 **296**

Scheme 67: Crotti's Rationale for the Stereo- and Regioselective Outcome of *O*-Nucleophilic Addition to Glycal Derived Oxiranes **295**.

Not only did this methodology allow for the highly β-stereoselective glycosidation of hindered alcohols, it also allowed for further manipulation of the resulting 2-unsaturated sugar into the 2,3,6-trideoxy glycoside found in lactonamycin (**1**). As a result, we proposed the following retrosynthetic route to glycoside **5** (Scheme 68).

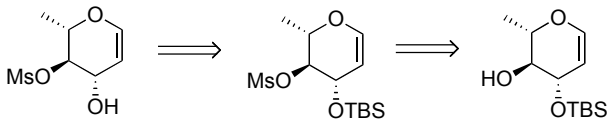


5 **297** **(±)-2** **298** **299**

Scheme 68: Retrosynthetic Analysis of Glycoside **5** Employing Crotti's Glycosidation Strategy.

In keeping with Crotti's precedent, the reaction between ABCD alcohol **(±)-2** and the reactive β-alkenyl oxirane intermediate **298**—derived from mesylate **299**—would provide glycoside **297**, which after hydrogenation and inversion of the stereochemistry at C-4' would ultimately supply target compound **5** (Scheme 68).

To verify this chemistry, we proposed to carry this sequence through with the readily accessible mesylate derivative **300** which has recently been reported[141] using the methodology described by Crotti and co-workers (Scheme 69).[138] If this chemistry proved to be successful, investigations would be made into the synthesis of the desired stereoisomer **299** (Scheme 69).

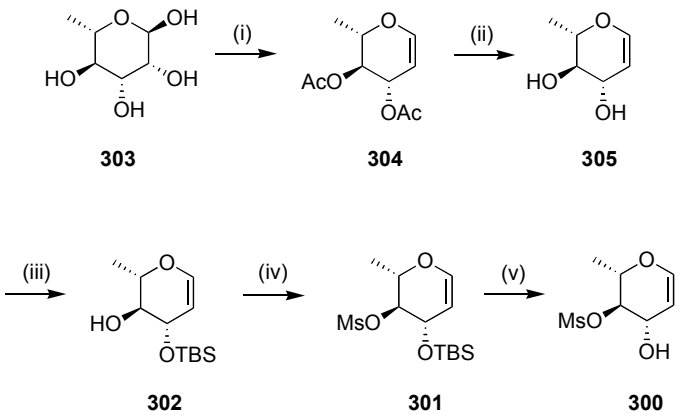


300 **301** **302**

Scheme 69: Retrosynthetic Analysis of Mesylate **300**.

4.2 Synthesis of Mesylate 300 and Subsequent Glycosidation Experiments

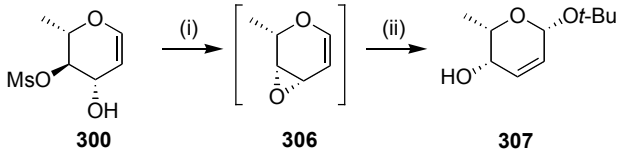
The synthesis of mesylate **300** was carried out in five steps according to the procedure described by Lunniss (Scheme 70).[141] Starting from readily available L-rhamnose **303**, conversion to di-*O*-acetyl-L-rhamnal **304** was achieved in 39% yield by acetylation, bromination and reduction in a one-pot procedure. Acetate hydrolysis using potassium carbonate in methanol gave L-rhamnal **305** and subsequent mono-protection as the *tert*-butyldimethylsilyl ether gave alcohol **302** in 100% overall yield. Mesylation and deprotection with tetra-*n*-butylammonium fluoride (TBAF) afforded mesylate **300** in 82% overall yield (Scheme 70).



Reagents and Conditions: (i) a) Ac_2O, ClO_4H, 30 to 40 °C, 2h; b) PBr_3, H_2O, 10 to 25 °C, 2 h; c) NaOAc, AcOH, Zn, $CuSO_4$, H_2O, 0 °C, 18 h, 39% over 3 steps; (ii) K_2CO_3, MeOH, 2 h, 100%; (iii) TBSCl, imid., DMAP, DMF, 2.5 h, 100%; (iv) MsCl, pyridine, 0 to 25 °C, 18 h, 82%; (v) TBAF, THF, 0 °C, 20 min, 100%.

Scheme 70: Synthesis of Mesylate **300**.

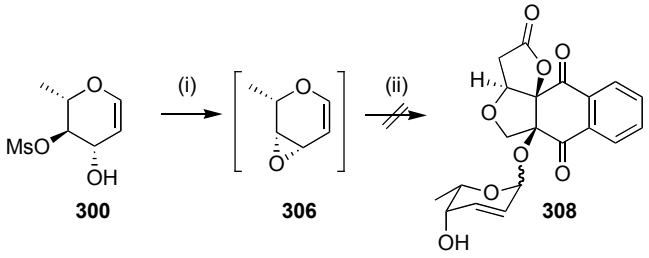
Transformation of mesylate **300** into β-vinyl oxirane **306** was effected by exposure to potassium *tert*-butoxide in diethyl ether. To test the reaction, 6 equivalents of *tert*-butanol was added to the reaction mixture and consequently provided the 2-unsaturated *tert*-butyl *O*-glycoside **307** in 62% yield as a single diastereoisomer determined by ^{1}H NMR spectroscopy (Scheme 71).



Reagents and Conditions: (i) *t*-BuOK, Et_2O, 15 min (ii) *t*-BuOH, 0 °C, 2 h, 62%.

Scheme 71: Synthesis of β-*O*-Glycoside **307**.

Unfortunately however, application of this methodology to the model ABCD alcohol **(±)-2** proved unsuccessful and resulted in complete recovery of starting material **(±)-2** (Scheme 72).



300 **306** **308**

Reagents and Conditions: (i) *t*-BuOK, Et_2O, 15 min (ii) **(±)-2**, 0 to 25 °C.

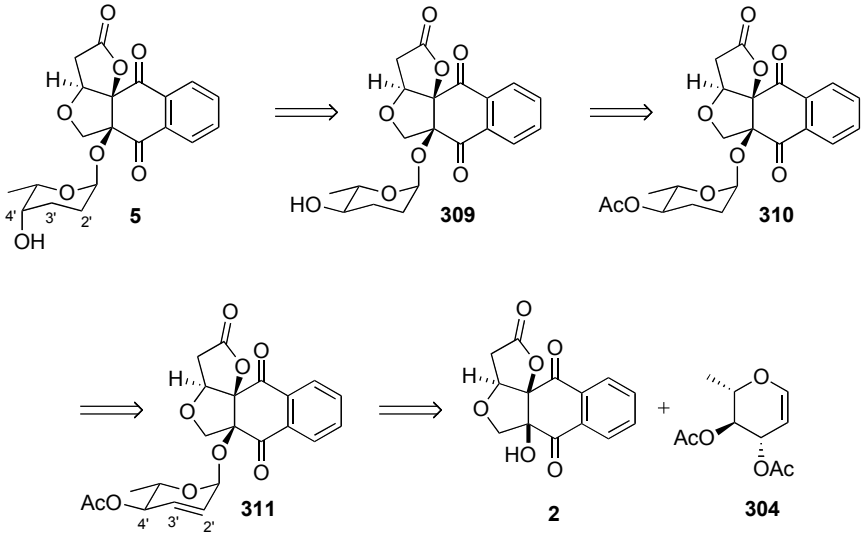
Scheme 72: Attempted Synthesis of *O*-Glycoside **308**.

It was assumed that this disappointing result was due to the poor reactivity of ABCD model alcohol **(±)-2**. In order to increase the nucleophilicity, prior deprotonation using sodium hydride and potassium *tert*-butoxide was conducted, however, under these new conditions, rapid decomposition was observed by the immediate formation of a black solution. This was perhaps not surprising given the previously observed instability of diols **281** and **282** under basic conditions (Chapter 3).

Given the results of the above experiments, it was clear that the use of β-vinyl oxirane **306** was not a viable strategy for the glycosidation of ABCD alcohol **(±)-2**. This was a possible consequence of the combination of steric hindrance and limited nucleophilicity of the tertiary alcohol **(±)-2** due to intramolecular hydrogen bonding to the α-ketone moiety.

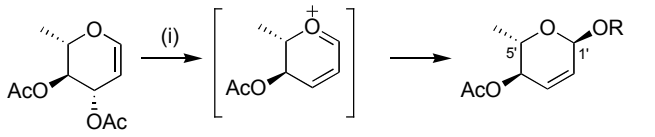
4.3 Use of Glycal 304 in a Ferrier Rearrangement

Whilst this result was disappointing, we postulated that di-*O*-acetyl-L-rhamnal **304**—prepared as an intermediate in the construction of mesylate **300**—could be used as the glycosyl donor in a Ferrier rearrangement[142, 143] with alcohol **(±)-2** for the construction of the glycosidic linkage (Scheme 73). Further manipulation of the resulting glycoside unit in **311** would be required in order to achieve both the desired stereochemistry at C-4' and the subsequent 2,3,6-trideoxygenation pattern of the sugar unit. This could be achieved by hydrogenation followed by a Mitsunobu reaction (Scheme 73).[144, 145]



Scheme 73: Retrosynthetic Analysis of Glycoside **5** Employing a Ferrier rearrangement.

A wide variety of Lewis acids have been employed for the activation of Ferrier rearrangement precursors.[146-154] In this case however, boron trifluoride diethyl etherate was found to be the most successful activating agent for the reactions between di-*O*-acetyl-L-rhamnal **304** and the alcohols; *tert*-butanol and adamantan-1-ol (Scheme 74).



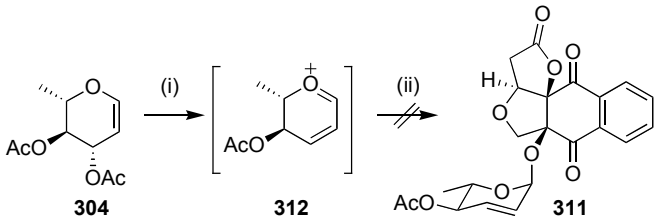
304 **312** **313** R = *t*-Bu
314 R = adamantane

Reagents and Conditions: (i) ROH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C, 2 h, **313** = 63%, $\alpha : \beta$ = 5 : 1 and **314** = 66%, $\alpha : \beta$ = 5 : 1.

Scheme 74: Synthesis of *O*-Glycosides **313** and **314** *via* a Ferrier Rearrangement.

Glycosides **313** and **314** were obtained in good yields and as a 5 : 1 mixture of diastereoisomers, detected by the presence of two sets of signals in the ^1H NMR spectrum (Scheme 74).

However, the use of ABCD alcohol **(±)-2** under the same reaction conditions did not mirror the success of the above reactions and returned only starting material **(±)-2**. The use of zinc(II) chloride and tin(IV) chloride as alternative Lewis acids was also met with failure (Scheme 75).



304 **312** **311**

Reagents and Conditions: (i) **(±)-2**, $BF_3 \cdot OEt_2$ or $ZnCl_2$ or $SnCl_4$, CH_2Cl_2, 0 °C.

Scheme 75: Attempted Synthesis of α-*O*-Glycoside **311** *via* a Ferrier Rearrangement.

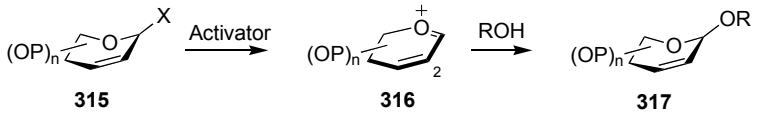
It was clear that another strategy was required for the successful glycosidation of ABCD model alcohol **(±)-2**.

4.4 Conclusions and Future Work

The use of Crotti's glycosidation methodology[137-140] for the construction of the glycosidic linkage in ABCD model alcohol **(±)-2** has been evaluated. Whilst the simple alcohol *tert*-butanol was shown to react with the β-vinyl oxirane intermediate **306**, extension of this methodology to the ABCD model alcohol **(±)-2** proved ineffective. The reactivity of the ABCD model alcohol **(±)-2** proved to be too low for the successful reaction with β-vinyl oxirane intermediate **306** and attempts to increase its reactivity by prior deprotonation with base resulted in decomposition of the highly functionalised molecule.

The use of di-*O*-acetyl-L-rhamnal **304**—prepared as an intermediate in the construction of mesylate **300**—was employed successfully in a Ferrier rearrangement with *tert*-butanol and adamantan-1-ol, again however the reactivity of ABCD alcohol **(±)-2** proved to be the limiting factor during these experiments and did not undergo a reaction. It is clear that a highly activated glycosyl donor is essential for the glycosidation of ABCD alcohol **(±)-2** to be successful.

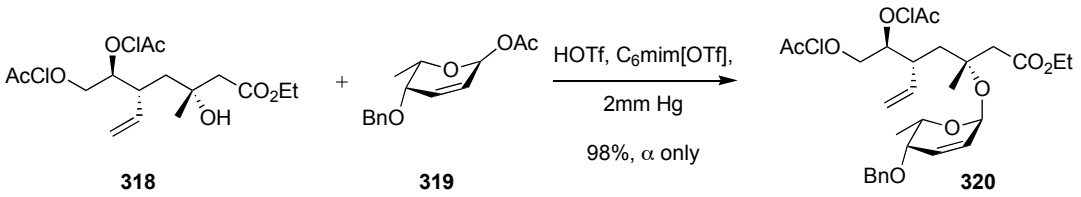
Some time after this work was conducted, Toshima and co-workers[98] reported the use of 2,3-unsaturated sugars **315** as highly activated glycosyl donors for the glycosidation of tertiary alcohols to 2,3,6-trideoxy glycosides **317** under mild Lewis acidic conditions. With the aid of the alkene functionality at the C-2 position, the oxocarbenium intermediate **316** is readily stabilised and consequently allows the use of mild glycosidation conditions (Scheme 76).



315 **316** **317**

Scheme 76: Concept Behind Toshima's Glycosidation.

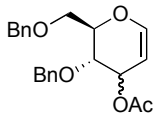
This methodology was later successfully applied to the synthesis of vineomycin B_2 building blocks such as **320** and demonstrated the successful glycosidation of the sterically hindered β-oxo-*tert*-alcohol **318** in excellent stereoselectivity (Scheme 77).[155]



318 **319** **320**

Scheme 77: Toshima's use of 2,3-Unsaturated Sugars **319** in the Synthesis of a Vineomycin Building Block **320**.

One point to note, was the additional need for the use of the ionic liquid 1-hexyl-3-methylimidazolium trifluoromethane sulfonate (C_6mim[OTf]) at reduced pressure in order to achieve the required activity for the difficult glycosidation. In addition, when glycal **321** (the synthetic equivalent of the 2,3-unsaturated glycosyl donor **319**) was subjected to the same reaction conditions the reaction did not proceed (Figure 11). This confirmed the heightened reactivity of these specific substrates towards glycosidation.



321

Figure 11: Glycal **321**.

This methodology, owing to the high reactivity of glycosyl donor **319**, could be used in the future as an effective method for the construction of the α-glycosidic linkage in lactonamycin (**1**).

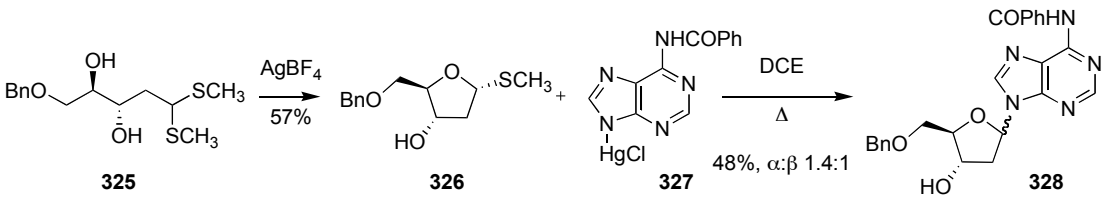
Chapter 5: Results and Discussion: Investigations into Glycosidation *via* Sulfonium Ions

5.1 Introduction

Having explored the use of Crotti's methodology and the use of a Ferrier rearrangement precursor for the glycosidation of ABCD alcohol **(±)-2** without success, our attention next turned to glycosidation via sulfonium species.

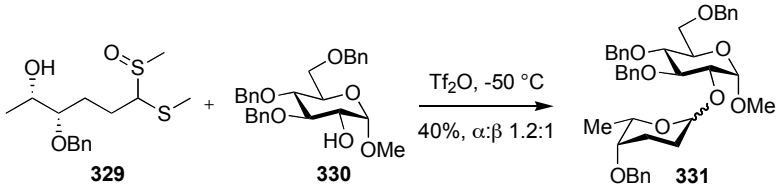
Amongst the many types of glycosyl donors available to the synthetic chemist, thioglycosides have proved to be the most advantageous and frequently used for the construction of glycosides. A brief introduction to their uses has been outlined in Chapter 2. The powerful ability to activate such groups at reasonably low temperatures using organosulfur compounds such as DMTST has proved to be a particularly attractive feature of their use.[85, 156]

The use of a dithio-acetal species is especially useful, as the sulfanyl groups can be employed in both a cyclisation step for construction of the glycoside species and the glycosidation experiment itself. Hanessian[157] and Trost[158] have used such methods for the construction of various nucleosides. In Trost's example, the open chain form of a 2-deoxy sugar such as **325**, is cyclised by the use of a thiophilic activator such as silver tetrafluoroborate, to give the thio-glycoside **326** in 57% yield (Scheme 78).[158] *N*-Glycosidation is achieved by further activation of the remaining sulfanyl group with the chloromercury salt of *N*-benzoyladenine **327** to give the *N*-glycoside **328** as a 1.4 : 1 mixture of α : β isomers (Scheme 78).



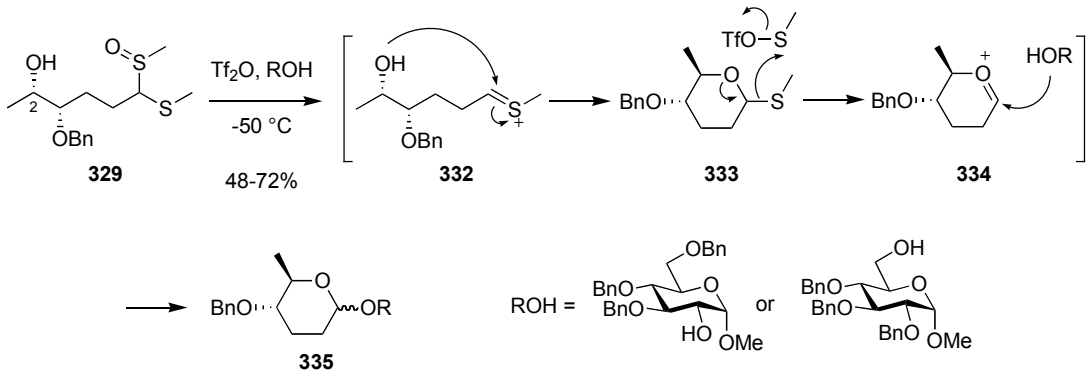
Scheme 78: Trost's Approach to 2-Deoxynucleoside **328** via Dithio-acetal **325**.

In a similar strategy, Takahashi and co-workers[159] have recently employed sulfanyl sulfoxides **329** in a one pot cyclisation/glycosidation reaction for the synthesis of 2,3,6-trideoxysugar containing disaccharides **331** from unreactive substrates under mild reaction conditions (Scheme 79).



Scheme 79: Takahashi's One-Pot Cyclisation/Glycosidation Strategy by Sequential Activation of Sulfanyl Sulfoxide **329**.

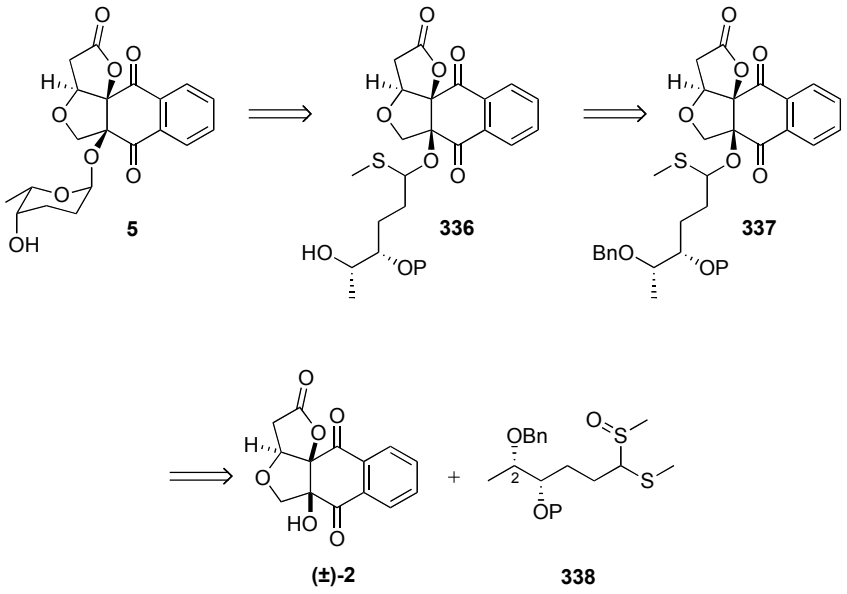
During the course of the reaction, cyclisation *via* intramolecular attack of the C-2 alcohol occurs first, by the generation of a sulfonium species **332**, through selective activation of the sulfoxide group with trifluoromethanesulfonic anhydride (Tf_2O). In the process, methane sulfanyl triflate is formed which initiates glycosidation in the second step via formation of the cyclic oxonium species **334** to provide disaccharide **335** (Scheme 80).



Scheme 80: Mechanism for the Formation of Glycosides **335** via Sulfanyl Sulfoxide **329**.

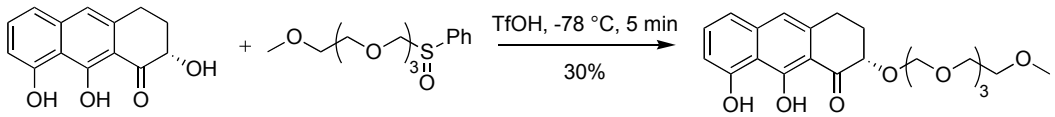
5.2 Experiments Towards Glycosidation *via* Sulfanyl Sulfoxide 338

This methodology was particularly attractive to us due to the extremely mild reaction conditions used and thus formed the basis for a new glycosidation route. However, due to the highly hindered nature of our model ABCD tertiary alcohol **(±)-2**, an alternative strategy was envisaged. In order to minimise the unfavourable steric interactions associated with such a process, we proposed to bring about the glycosidation step with an open chain form of the 2,3,6-trideoxy sugar unit **338**. After deprotection of the C-2 alcohol, the remaining mono-thio-acetal **337**, upon activation, would provide leverage for cyclisation to occur *via* the oxonium ion to provide glycoside **5** after deprotection (Scheme 81).



Scheme 81: Retrosynthetic Analysis of *O*-Glycoside **5** *via* Sulfanyl Sulfoxide **338**.

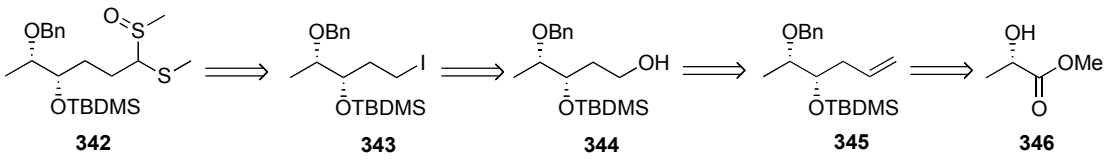
A related intermolecular process had been previously reported by Kanhe and co-workers[160] where α-oxo secondary alcohol **339** was shown to react with sulfoxide **340** after activation with trifluoromethanesulfonic acid at –78 °C and provided a certain degree of precedent for our methodology (Scheme 82).



Scheme 82: Kane's Coupling of α-Oxo Secondary Alcohol **339** with Sulfoxide **340**.

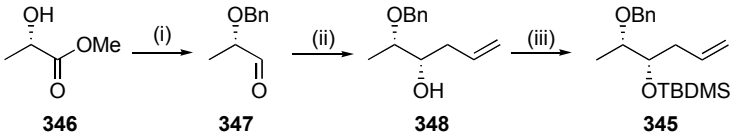
5.2.1 Synthesis of Sulfanyl Sulfoxide **342**

In a similar approach to Takahashi and co-workers,[159] sulfanyl sulfoxide **342** could be prepared by alkylation of iodide **343** with methyl (methylsulfanyl)methyl sulfoxide (FAMSO). Iodide **343**, in turn could be prepared from alkene **345** by reductive ozonolysis to alcohol **344** followed by iodination. The known alkene **345**, has been previously prepared from commercially available (*S*)-methyl lactate (**346**) (Scheme 83).[161]



Scheme 83: Retrosynthetic Analysis of Sulfanyl Sulfoxide **342**.

The alkene intermediate **345** was prepared following the procedure of Trewartha.[161] (*S*)-methyl lactate (**346**) was protected as the benzyl ether and converted to aldehyde **347** by treatment with diisobutylaluminium hydride at –78 °C in 61% yield. Subsequent treatment with allyl magnesium bromide in the presence of the chelating agent; magnesium bromide diethyl etherate, afforded alcohol **348** in 87% yield and essentially as a single diastereoisomer (95:5 by ^{1}H NMR spectroscopy analysis). Protection of the alcohol by treatment with *tert*-butyldimethylsilyl chloride, imidazole and DMAP delivered alkene **345** in 93% yield (Scheme 84).

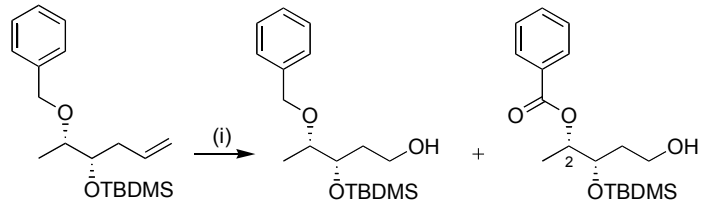


346 **347** **348** **345**

Reagents and Conditions: (i) a) NaH, BnBr, THF, 0 to 25 °C, 24 h, 86%; b) DIBAl-H, CH_2Cl_2, –78 °C, 6 h, 61%; (ii) allylmagnesium bromide, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, –78 °C, 6 h, 87%; (iii) TBDMSCl, imidazole, DMAP, DMF, 16 h, 93%.

Scheme 84: Synthesis of Alkene **345**.

Conversion of alkene **345** to alcohol **344** was attempted in a one pot procedure by reaction with ozone in methanol at –78 °C, followed by the addition of sodium borohydride (Scheme 85). ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated the formation of two compounds. The first was identified as alcohol **344** and the second product—obtained in approximately equal quantities (**344** : **349**, 5 : 4)—was shown to be that of benzoate ester **349** and resulted from the additional oxidation of the benzyl ether protecting group at C-2 (Scheme 85).



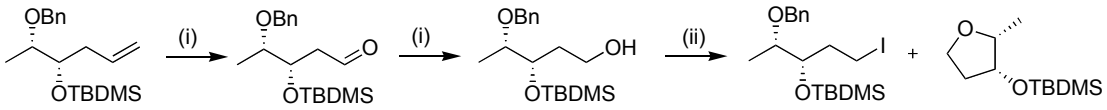
345 **344** **349**

Reagents and Conditions: (i) a) O_3, MeOH, –78 °C, 1.5 h; b) $NaBH_4$, 0 °C, 0.5 h, (**344** : **349**, 5 : 4), 66% mass recovery.

Scheme 85: Ozonolysis of Alkene **345** in Methanol.

This was proposed by the disappearance of the CH_2 protons of the benzyl protecting group, the downfield shift of the H-2 signal from 3.57 ppm to 5.22 ppm and the additional shifting and splitting of the aromatic hydrogen signals of the benzoate phenyl ring in the ^1H NMR spectrum. The observation of these unwanted oxidation by-products **349** has previously been noted[162, 163] and in certain cases their formation has been found to be suppressed in dichloromethane.[164, 165]

Our approach was modified accordingly and by isolation of aldehyde **350** after treatment with ozone and triphenylphosphine in dichloromethane, alcohol **344** could be obtained in 99% yield by a separate reduction with sodium borohydride in methanol (Scheme 86).



345 **350** **344** **343** **351**

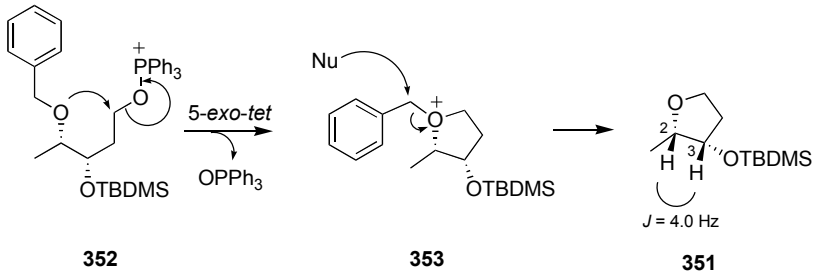
Reagents and Conditions: (i) a) O_3, CH_2Cl_2, –78 °C, 1.5 h; b) PPh_3, –78 °C, 1.5 h, 94%; b) $NaBH_4$, MeOH, 0 °C, 0.5 h, 99%; (ii) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 4 h, **343** = 39% and **351** = 59%.

Scheme 86: Synthesis of Iodide **343**.

Treatment of the resulting alcohol **344** under standard iodination conditions[166] gave iodide **343** in a surprisingly low yield of 39%. Under the reaction conditions, the formation of tetrahydrofuran **351** occurred readily and as a consequence was isolated as the major product in 59% yield (Scheme 86).

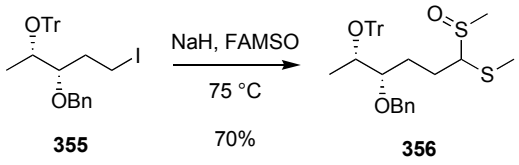
Similar ring-forming reactions have been recorded by others[167-169] and occur by intramolecular attack of the benzyl ether oxygen onto the alkoxy triphenylphosphonium ion **352** (formed during the reaction) *via* the highly favoured 5-*exo*-*tet* process (Scheme 87).[170] Dealkylation of the resulting benzyloxonium ion **353** to tetrahydrofuran **351** takes place by transfer of the benzyl group to a nucleophile present in the reaction medium, in this case either imidazole, triphenylphosphine or iodide. The vicinal coupling

constant ($^3J_{H\text{-}2,H\text{-}3}$ = 4.0 Hz) confirmed the *cis* orientation between the H-2 and H-3 hydrogen atoms (Scheme 87).



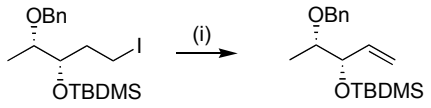
Scheme 87: Mechanism for the Formation of Tetrahydrofuran **351**.

At this stage, it was decided to carry out the remaining step of the sequence by alkylation of iodide **343** with FAMSO. Takahashi and co-workers have demonstrated the substitution reaction of iodide **355** with FAMSO in the presence of sodium hydride at elevated temperatures (Scheme 88).[159]



Scheme 88: Takahashi's Substitution Reaction Between Halide **355** and FAMSO.

This methodology was applied to iodide **343** and furnished a single product after purification by silica gel chromatography. Unexpectedly, this product was not a result of substitution, but rather elimination, and was identified through ^{1}H NMR analysis as alkene **357** (Scheme 89).

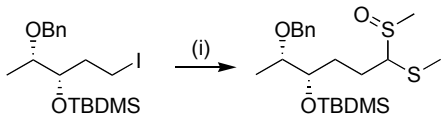


343 **357**

Reagents and Conditions: (i) FAMSO, NaH, THF, 75 °C, 12 h, 91%.

Scheme 89: Unexpected Synthesis of Alkene **357**.

The extra steric bulk of the trityl group in Takahshi's[159] iodide **355** may be accountable for the inhibition of the elimination pathway in their synthesis, thus providing the substitution product **356** exclusively. In our case, the considerably smaller benzyl protecting group did not prevent the undesired elimination pathway at elevated temperatures. Pleasingly, by lowering the temperature to –30 °C and changing the base to *n*-butyllithium the substitution product **342** was obtained exclusively in 85% yield (Scheme 90).

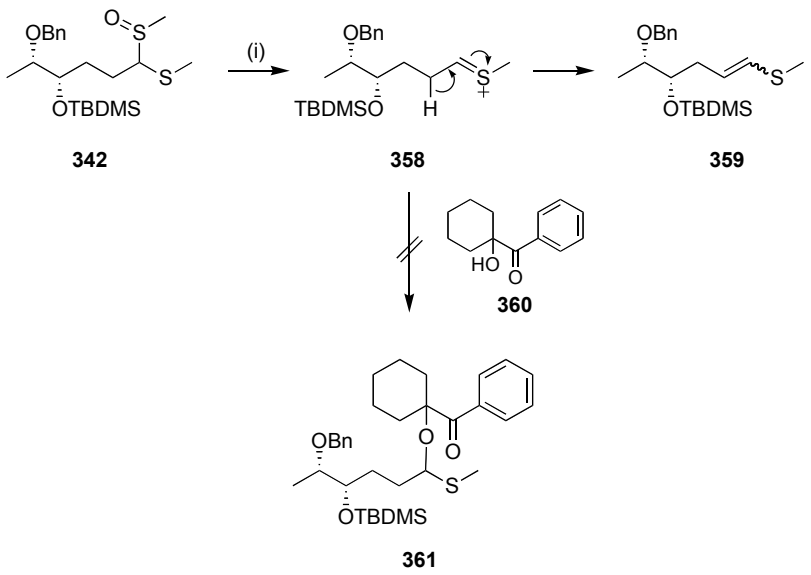


343 **342**

Reagents and Conditions: (i) FAMSO, *n*-BuLi, THF, –30 °C to 25 °C, 45 min, 85%.

Scheme 90: Synthesis of Sulfanyl Sulfoxide **342**.

With significant quantities of sulfanyl sulfoxide **342** in hand, attention turned to the glycosidation reaction (Scheme 91). The use of α-oxo-*tert*-alcohol **360** was employed as a crude model to ABCD alcohol **(±)-2**, the results of which are summarised in Table 1.



342 **358** **359** **360** **361**

Reagents and Conditions: (i) see Table 1.

Scheme 91: Attempted Glycosidation with Sulfanyl Sulfoxide **342**.

Table 1: Investigations into the Glycosidation with Sulfanyl Sulfoxide **342**.

Entry[a]	**360** (Eq)	**342** (Eq)	Tf_2O (Eq)	Order of Addition	T (°C)	Result
1	1.0	2.0	3.0	**342** to **360** and Tf_2O	–42 to 23	75% **359** + 15% **342**
2	1.0	2.0	3.0	**342** to **360** and Tf_2O	–42	41% **359** + 56% **342**
3	10.0	1.0	1.5	Tf_2O to **342** and **360**	–42 to 23	62% **359** + 19% **342**
4	10.0	1,0	1.5	**360** to **342** and Tf_2O	–42 to –5	46% **359** + 23% **342**

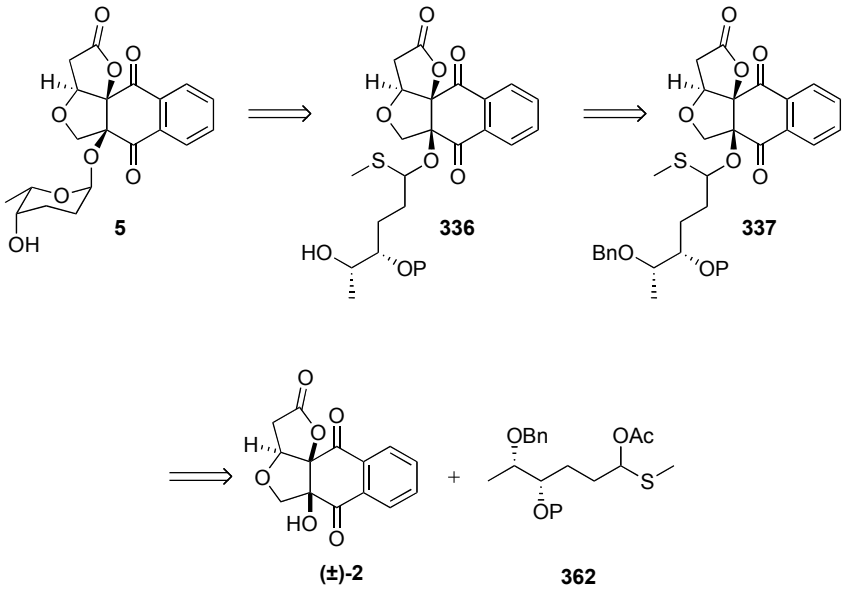
[a]Typical reaction conditions were performed on a 100 mg scale in CH_2Cl_2, in the presence of 4Å molecular sieves and stirred overnight.

In all the experiments however, intramolecular elimination of the sulfonium ion **358** to the sulfanyl alkene **359** occurred preferentially over intermolecular attack of the aglycone alcohol **360** (Scheme 91 and Table 1, entries 1 and 2).

In an attempt to enhance the probability of an intermolecular reaction, experiments were carried out with a large excess of alcohol **360** with various orders of addition (Table 1, entries 3 and 4). None however had a positive effect on the outcome of the reaction, with all providing the sulfanyl alkene **359** as the only product of the reaction. The use of such a method for the glycosidation of alcohols was consequently considered ineffective and as a result was abandoned.

5.3 Experiments Towards Glycosidation *via* Sulfanyl Acetate 362

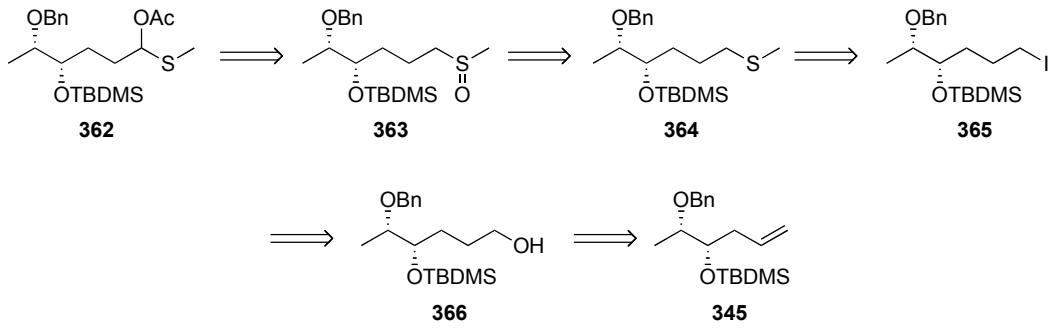
In parallel to the above work, was envisaged a similar approach to glycosidation, employing the alternative sulfanyl acetate **362** as the glycosyl donor. We proposed that glycosidation *via* the sulfonium ion could be initiated by treatment of sulfanyl acetate **362** with a Lewis acid. Again, mono-thio-acetal **337** could undergo cyclisation to target compound **5** upon activation (Scheme 92).



Scheme 92: Retrosynthetic Analysis of *O*-Glycoside **5** *via* Sulfanyl Acetate **362**.

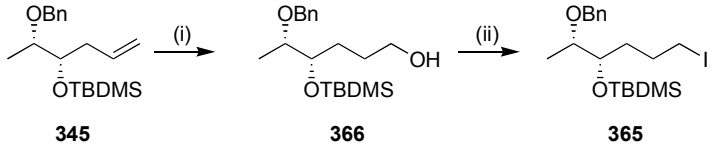
5.3.1 Experiments Towards the Synthesis of Sulfanyl Acetate **362**

We proposed the use of a Pummerer rearrangement for the synthesis of sulfanyl acetate **362** from sulfoxide **363**. This in turn could be prepared from sulfide **364** *via* oxidation which in turn could be prepared from iodide **365**. In a similar approach to that for sulfanyl sulfoxide **342**, iodide **365** could be prepared form alcohol **366** which, using the known procedure of Barrett and co-workers,[28] could be synthesised from previously prepared alkene **345** (Scheme 93).



Scheme 93: Retrosynthetic Analysis of Sulfanyl Acetate **362**.

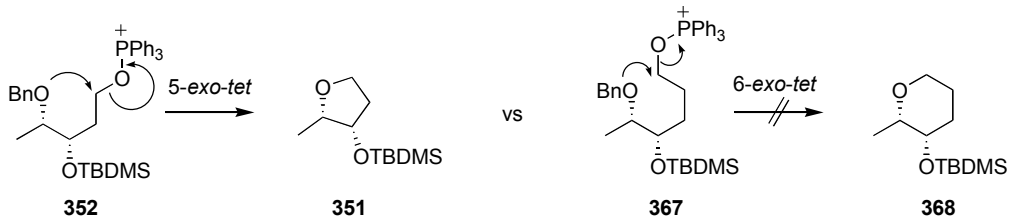
Starting from alkene **345**, hydroboration furnished alcohol **366** in 91% yield. Iodination using the previously employed reaction conditions with alcohol **344** (Scheme 86) gave iodide **365** exclusively in 65% yield (Scheme 94).



Reagents and Conditions: (i) a) Cyclohexene, $BH_3{\cdot}SMe_2$, THF, 0 °C, 2 h; b) **345**, 12 h; c) NaOH, H_2O_2, 50 °C, 3 h, 91%; (ii) I_2, PPh_3, imid., CH_2Cl_2, 0 °C, 7 h, 65%.

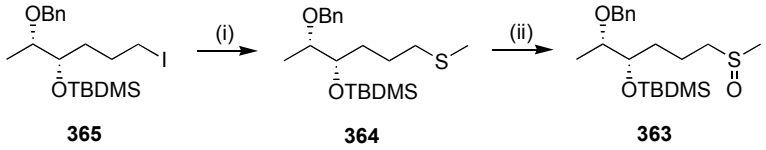
Scheme 94: Synthesis of Iodide **365**.

The corresponding 6-*exo-tet* cyclisation product **351**, previously formed during the iodination of alcohol **344** *via* a 5-*exo-tet* process (Scheme 87), was not detected in the reaction mixture (Scheme 95). According to Baldwin's rules[170] both processes are just as favourable and consequently it was thought that due to the longer chain in the alkoxy triphenyl phosphonium species **367**, the two reacting centers were less likely to come together and consequently undergo the ring forming reaction (Scheme 95).



Scheme 95: 5-*exo-tet* versus 6-*exo-tet*.

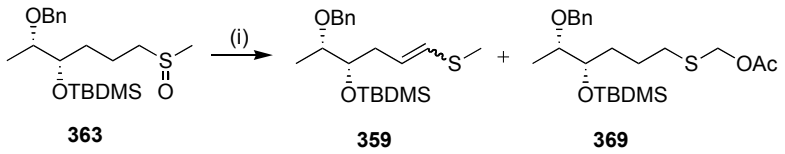
Reaction of the resulting iodide **365** with sodium thiomethoxide followed by oxidation with *m*-CPBA provided sulfoxide **363** in 88% overall yield (Scheme 96).



Reagents and Conditions: (i) NaSMe, EtOH, 6 h, 99%; (ii) *m*-CPBA, CH_2Cl_2, –78 °C, 2 h, 89%.

Scheme 96: Synthesis of Sulfoxide **363**.

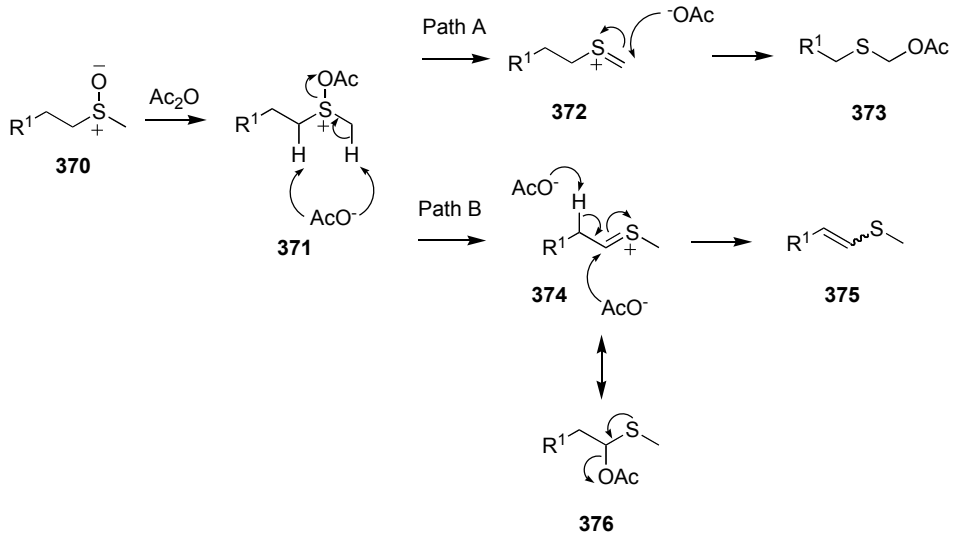
However, during the subsequent Pummerer rearrangement of sulfoxide **363** with sodium acetate in acetic anhydride, a 1:1 mixture of sulfanyl alkene **359** was produced along with acetate **369** (the undesired regiomeric isomer of acetate **362**) (Scheme 97).



Reagents and Conditions: (i) NaOAc, Ac_2O, reflux, 15 h, **359** = 40% and **369** = 40%.

Scheme 97: Pummerer Rearrangement of Sulfoxide **363**.

The formation of the sulfanyl alkene **359** was again due to the successful competition of elimination (Scheme 98, Path B) over the formation of the desired Pummerer rearrangement product **367** and was not surprising given the outcome of the previous experiments (Scheme 91). At the same time, the alternative Pummerer rearrangement product **369** was produced *via* sulfonium species **372** (Scheme 98).



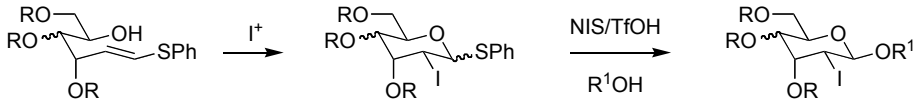
Scheme 98: Mechanism of the Pummerer Rearrangement.

In light of these results, and taking into account the preference for elimination over glycosidation with sulfanyl sulfoxide **342**, the use of such substrates for further experimentation into the glycosidation reaction with ABCD alcohol **(±)-2** was brought to an end.

5.4 Conclusions and Future Work

The synthesis of sulfanyl sulfoxide **342**—with the aim of carrying out further glycosidation experiments—has been conducted in good overall yield. Regrettably, the successful coupling of the corresponding activated sulfonium species **358** was not realised, due to its rapid intramolecular elimination to sulfanyl alkene **359**. This undesired side reaction was also found to prevent the formation of sulfanyl acetate **362** during the Pummerer rearrangement of sulfoxide **363**.

Recently however, the use of similar sulfanyl alkenes **377** in the synthesis of 2-deoxy-glycosides **379** has been shown to occur *via* an electrophilic iodine induced cyclisation reaction (Scheme 99).[171-173]



377 **378** 39-81%, α:β > 1:10 **379**

Scheme 99: Synthesis of 2-Deoxy-Glycosides **379** from Sulfanyl Alkenes **377**.

The possible activation of sulfanyl alkene **359**—formed as a by-product from both the activation of sulfanyl sulfoxide **342** and the Pummerer rearrangement of sulfoxide **363**—may allow for the successful future coupling to ABCD alcohol **(±)-2**.

Chapter 6: Results and Discussion: Investigations into Palladium Catalysed Glycosidation

6.1 Introduction

Following our unsuccessful attempts to employ sulfonium ions in the glycosidation of model alcohol **(±)-2** (Chapter 5), our attention turned to a different strategy that relied on a palladium catalysed glycosidation reaction.

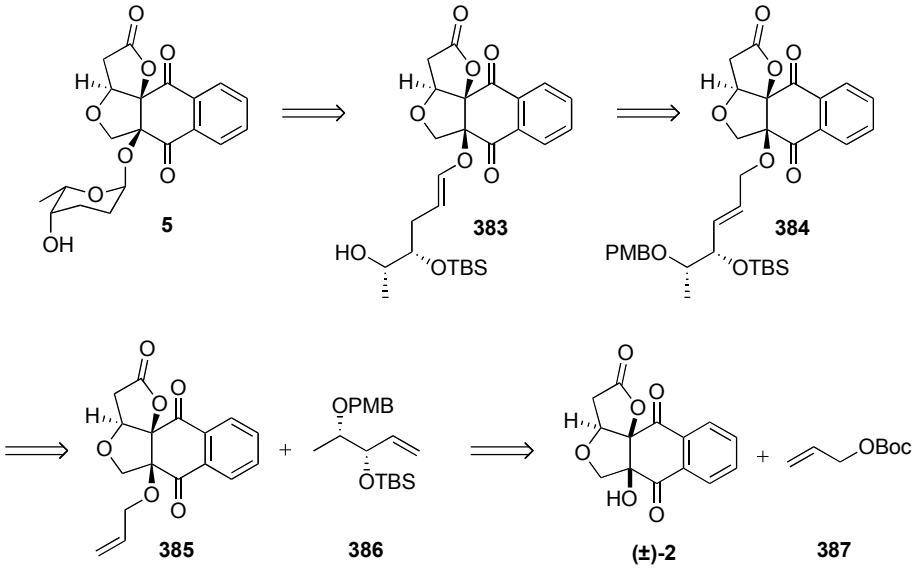
The palladium-catalysed allylation reaction of *O*-nucleophiles represents a fundamentally important cross-coupling reaction for the construction of C-O bonds in organic chemistry.[174-176] Until recently, due to poor nucleophilicity, most examples in this reaction class have been limited to intramolecular allylations,[177, 178] substrate specific systems[179, 180] and metal alkoxides.[181-183] However, the use of a mild palladium catalysed allylation reaction between aliphatic alcohols **380** and allyl carbonates **381** has recently been developed by Haight and co-workers and demonstrates the efficient coupling of tertiary alcohols without the need for the preparation of metal alkoxides (Scheme 100).[184, 185]



Scheme 100: Haight's Palladium-Catalysed Allylation of Aliphatic Alcohols **380**.

6.2 Previous Investigations Using an Allylation-Isomerisation Approach

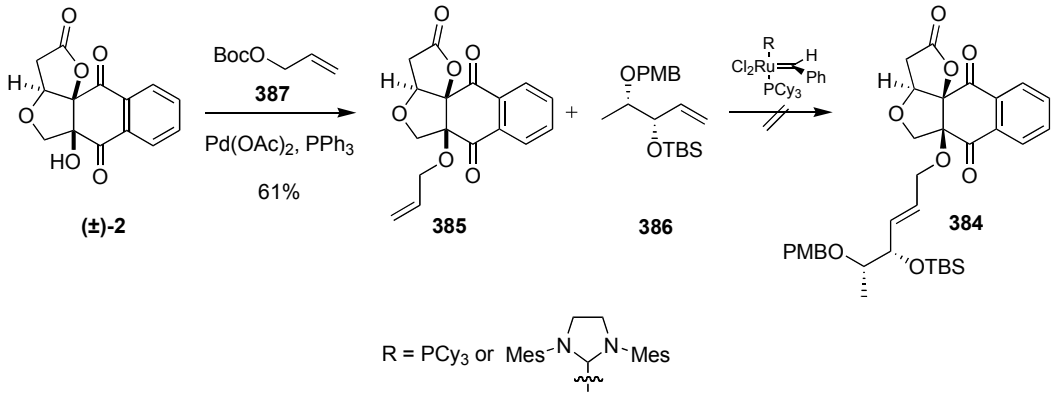
In previous studies within the Barrett group, Henderson successfully introduced an open chain form of the lactonamycin (**1**) 2,3,6-trideoxy sugar onto model ABCD alcohol **(±)-2** using Haight's palladium catalysed methodology.[42] Initially, an allylation-cross-metathesis-isomerisation approach was envisaged, the retrosynthetic analysis of which is outlined in Scheme 101.



Scheme 101: Henderson's Retrosynthetic Analysis of *O*-Glycoside **5** *via* an Allylation Cross-Metathesis-Isomerisation Approach.

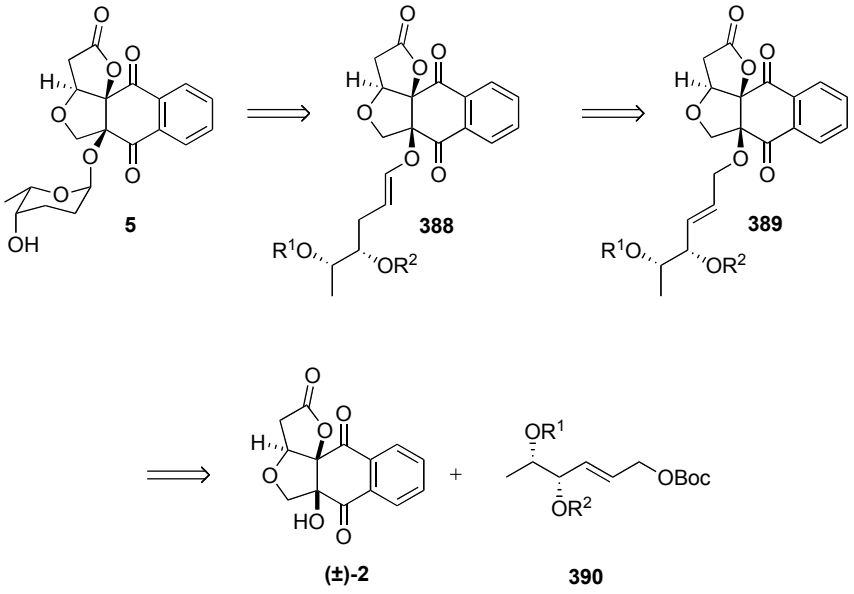
Henderson envisaged the use of a palladium catalysed allylation reaction of ABCD alcohol **(±)-2** with *tert*-butyl carbonate allylic alcohol **387** to provide allyl ether **385**. Grubbs' cross-metathesis with olefin **386** would allow for the introduction of the remaining carbon backbone of the sugar residue to give **384**, which, after transition metal catalysed olefin isomerisation would provide vinyl ether **383**. It was anticipated that after removal of the PMB protecting group, mild acid catalysis would promote cyclisation to target compound **5** after deprotection (Scheme 101).

Successful reaction of *tert*-butyl carbonate **387** with ABCD alcohol **(±)-2** was accomplished in refluxing THF, using palladium(II) acetate and triphenylphosphine, in 61% yield. However, Henderson's efforts to bring about the cross-metathesis with olefin **386** failed to furnish the desired product **384** (Scheme 102).[42]



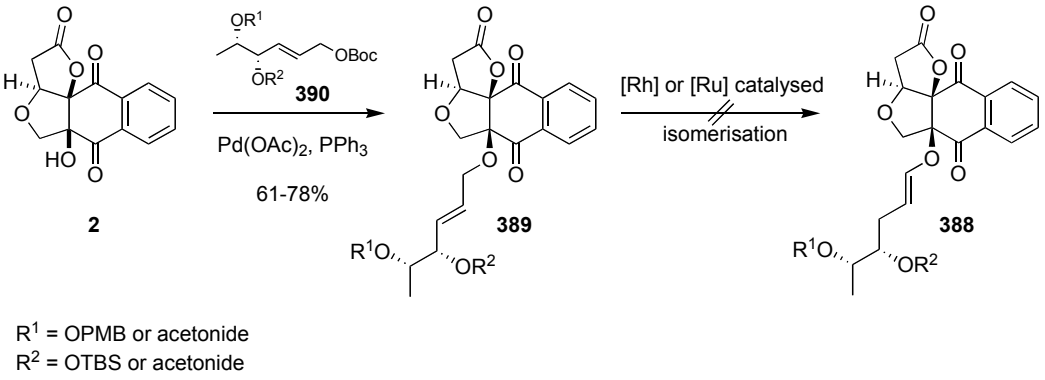
Scheme 102: Henderson's Attempted Cross Metathesis of Allyl Ether **385** with Olefin **386**.

As a result, Henderson considered an alternative approach varying only slightly from the original methodology. It was hoped that direct allylation of ABCD alcohol **(±)-2** with the *tert*-butyl carbonate protected open chain alcohol **390** could be achieved, thus eliminating the need for the problematic cross-metathesis step (Scheme 103).



Scheme 103: Henderson's Modified Retrosynthetic Using *tert*-Butyl Carbonate **390**.

A number of protected *tert*-butyl carbonates **390** were coupled successfully to ABCD alcohol **(±)-2** in yields between 61 and 78% (Scheme 104). The next key step was the isomerisation of the allylic double bond, however the use of either rhodium(III) chloride,[186] Wilkinson's catalyst[187] or *tris*(triphenylphosphine)ruthenium(II) chloride[188] under a variety of conditions failed to give any of the desired product **388**.



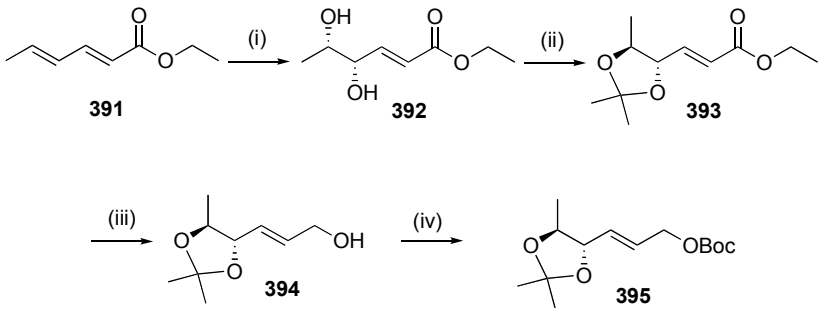
Scheme 104: Henderson's Attempted Rhodium or Ruthenium Catalysed Isomerisation of Allyl Ether **389**.

In most cases, starting material **389** or very polar products which were attributed to cleavage of the sensitive acetonide protecting group, were isolated. However, when rhodium (III) chloride was used, a significant amount of ABCD alcohol **(±)-2** was recovered. Indeed, the use of allyl ethers have found general use as temporary hydroxyl protecting groups[189] and can be cleaved *in situ* following transition metal catalysed isomerisation.[190]

6.3 Allylation-Isomerisation Approach with Alternative Isomerisation Catalysts

The transition metal catalysed double bond migration as a method of isomerisation in *O*-allyl systems has been well documented in organic synthesis.[191, 192] An extensive survey of the literature has revealed several additional procedures that may be of significant importance for the successful isomerisation of allyl ether **389** to enol ether **388**. Given Henderson's previous success with the palladium-catalysed cross-coupling reactions between ABCD alcohol **(±)-2** and *tert*-butyl carbonate **390**, it was decided that further investigations into the isomerisation reaction were required to fully discount this approach.

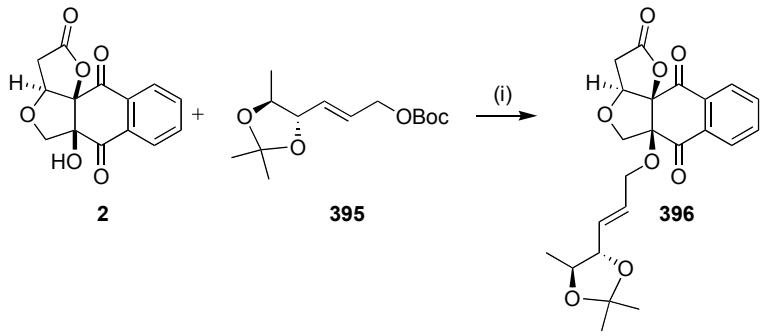
In order to fully explore the isomerisation reactions, the *tert*-butyl carbonate protected allylic alcohol **395** was prepared in large scale, using the procedure described by Henderson (Scheme 105).[42] Sharpless asymmetric dihydroxylation[193] of ethyl sorbate (**391**) with AD-mix-α provided diol **392** in 59% yield, subsequent protection by treatment with 2,2-dimethoxy-propane in the presence of *para*-toluene sulfonic acid gave the desired acetonide **393** in 89% yield. Reduction using di*iso*butylaluminium hydride and protection of the resulting alcohol **394** as the *tert*-butyl carbonate allylic alcohol gave the desired coupling partner **395** in 52% overall yield (Scheme 105).



Reagents and Conditions: (i) AD-α-mix, $Me_2SO_2NH_2$, *t*-BuOH, 0 °C, 18 h, 59%; (ii) 2,2-dimethoxypropane, TsOH, 0 °C, 1 h, 89%; (iii) DIBAl-H, –78 °C, 5 h, 71%; (iv) Boc_2O, NEt_3, DMAP, 1 h, 72%.

Scheme 105: Synthesis of *tert*-Butyl Carbonate Protected Allylic Alcohol **395**.

With the *tert*-butyl carbonate protected allylic alcohol **395** in hand, its coupling to ABCD alcohol **(±)-2** was achieved according to the procedure described by Henderson (Scheme 106).[42]



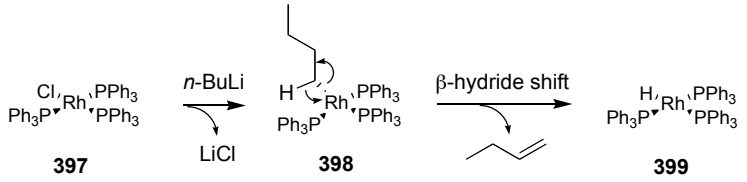
Reagents and Conditions: (i) $Pd(OAc)_2$, PPh_3, THF, 65 °C, 6 h, 36-45%.

Scheme 106: Synthesis of Allyl Ether **396**.

The coupled allyl ether **396** was obtained in moderate yields (36-45%), nevertheless, sufficient material was available to investigate the following isomerisation reaction (Scheme 106).

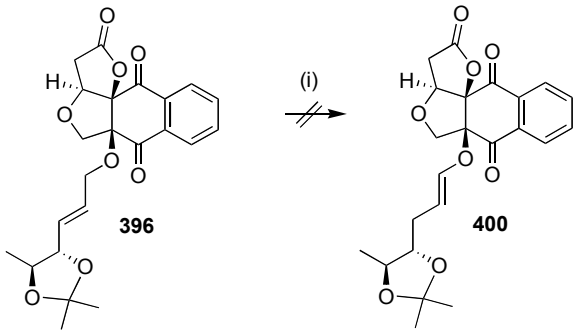
6.3.1 Rhodium Hydride Catalysts

A procedure described by Boons and co-workers[194] has shown that the reaction of Wilkinson's catalyst (**397**) with *n*-butyllithium results in a rhodium catalyst capable of isomerising a wide range of substituted and unsubstituted allyl ethers without cleavage of the resulting enol ether bond, thus potentially circumventing the problem that was observed in Henderson's previous experiments (Section 6.2).[42] Boons and co-workers have postulated that under the reaction conditions, the active isomerisation catalyst—*tris*(triphenylphosphine)rhodium(I) hydride (**399**)—is formed *via* a β-hydride shift of the butyl rhodium complex **398** formed in a substitution reaction between *n*-butyllithium and the chloride in Wilkinson's catalyst (**397**) (Scheme 107).[195]



Scheme 107: Formation of Rhodium Hydride Species **399**.

The isomerisation of allyl ether **396** to enol ether **400** (Scheme 108) under the action of the rhodium(I) hydride catalyst **399** described above was investigated and the results summarised in Table 2.



Reagents and Conditions: (i) See Table 2.

Scheme 108: Attempted Isomerisation of Allyl Ether **396**.

Table 2: Investigations into the Isomerisation of Allyl Ether **396**.

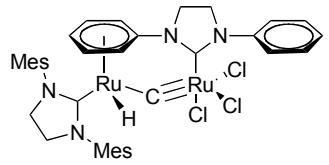
Entry[a]	$Rh(PPh_3)_3Cl$ (mol %)	*n*-BuLi (mol%)	Result[c]
1[b]	10	15	No reaction.
2	100	150	Mixture of unidentifiable products.
3	100	100	Mixture of unidentifiable products.

[a]Typical reaction conditions were performed on a 50 mg scale, with a THF solution of the preformed [Rh]H catalyst added *via* cannula to a solution of allyl ether **396** and heated to 65 °C for 2 h. [b]Conditions reported by Boons and co-workers.[190] [c]Determined by crude ^{1}H NMR spectroscopy.

Initial experiments using catalytic quantities of the rhodium hydride complex **399** (Table 2, entry 1) gave no reaction after 2 hours in refluxing THF. This was attributed to the deactivation of the transition metal complex through coordination to Lewis basic sites on model ABCD alcohol **(±)-2**. Upon treatment with equimolar amounts of the preformed catalyst (Table 2, entry 2), no reaction was observed until reflux was reached upon which complete decomposition was detected after 2 hours. This was initially thought to be due to the excess *n*-butyllithium used in the formation of the active rhodium species **399**; yet lowering the number of equivalents of *n*-butyllithium to one (Table 2, entry 3) gave an identical crude ^{1}H NMR spectra. To verify this chemistry, the isomerisation of allyl benzyl ether was conducted successfully, the product of which was found to be spectroscopically identical to that described in literature.[195] It was deemed that the use of *n*-butyllithium for the preparation of the rhodium hydride complex **399** was resulting in decomposition of the sensitive ABCD alcohol **(±)-2**. Therefore, this methodology was considered unsuitable for the required isomerisation.

6.3.2 Ruthenium Hydride Catalysts

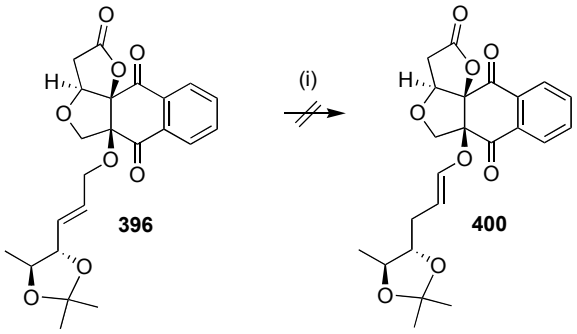
In related investigations, Snapper and co-workers[196] have described a novel olefin metathesis-double bond migration sequence, that was presumed to be catalysed by a ruthenium hydride species. Later work by Schmidt and co-workers reported similar double bond migrations, catalysed by the addition of hydride donors[197] such as sodium borohydride and sodium hydride, or additives[198] such as ethyl vinyl ether to Grubbs catalyst. A possible active species for these double bond isomerisations was recently identified by Grubbs and co-workers as being the ruthenium hydride catalyst **401** (Figure 12).[199]



401

Figure 12: Ruthenium Hydride Species **401**.

Experiments towards the double bond migration of ally ether **396** were consequently conducted using a number of these methods (Scheme 109, Table 3).



Reagents and Conditions: (i) See Table 3.

Scheme 109: Attempted Isomerisation of Allyl Ether **396**.

Table 3: Investigations into the Isomerisation of Allyl Ether **396**.

Entry[a]	Catalyst	Additive	Time (h)	Result[b]
1	Grubbs II (5 mol%)	NaH (30 mol%)	16	No reaction.
2	Grubbs II (110 mol%)	NaH (115 mol%)	1	Mixture of unidentifiable products.
3	Grubbs II (5 mol%)	$NaBH_4$ (30 mol%)	21	No reaction.
4	Grubbs II (110 mol%)	$NaBH_4$ (115 mol%)	2	Mixture of unidentifiable products.
5	Grubbs II (110 mol%)	Ethyl vinyl ether	21	No reaction.
6	Grubbs I (110 mol%)	Ethyl vinyl ether	21	No reaction.

[a]Typical reaction conditions were performed on a 50 mg scale, with a preformed solution of catalyst added *via* cannula to a solution of allyl ether **396** and refluxed at 110 °C in toluene. [b]Determined by crude ^{1}H NMR spectroscopy.

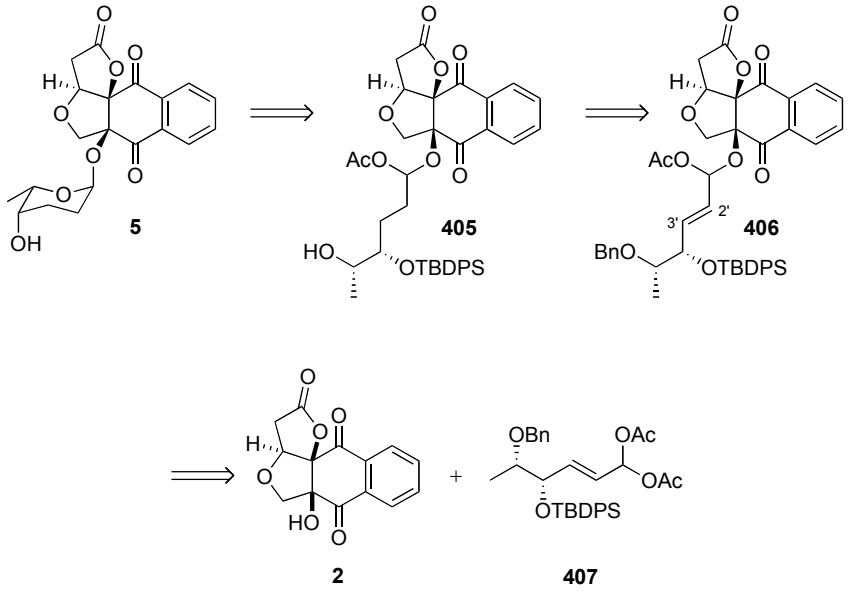
Unfortunately, the isomerisation of allyl ether **396** using these preformed ruthenium hydride catalysts proved to be ineffective. As before, it was found that the use of strong additives such as sodium borohydride or sodium hydride led to the production of a mixture of unidentifiable products of the sensitive ABCD system **(±)-2** (Table 3, entries 2 and 4). However, the use of ethyl vinyl ether as the additive, led to complete recovery of starting material **(±)-2** (Table 3, entries 5 and 6). Again, this chemistry was verified with

all three additives for the isomerisation of allyl benzyl ether, the product of which was found to be spectroscopically identical to that described in the literature.[195] This result led us to the conclusion that such isomerisation catalysts were not suitable for use with our highly sensitive system. The use of the allylation-isomerisation approach was consequently abandoned.

6.4 Alternative Allylation-Cyclisation Approach

6.4.1 Palladium Catalysed Allylation with *Gem*-Diacetate **407**

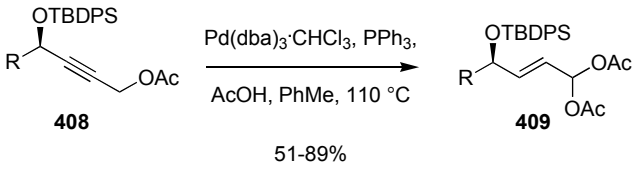
Whilst the isomerisation of allyl ether **396** proved to be ineffective, we were encouraged by the success of the coupling reaction between the open chain sugar **395** and model ABCD alcohol **(±)-2**. We therefore envisaged an alternative method to achieve ring closure, the key to which involved the use of *gem*-diacetate **407** (Scheme 110).



Scheme 110: Retrosynthetic Analysis of *O*-Glycoside **5** *via gem*-Diacetate **407**.

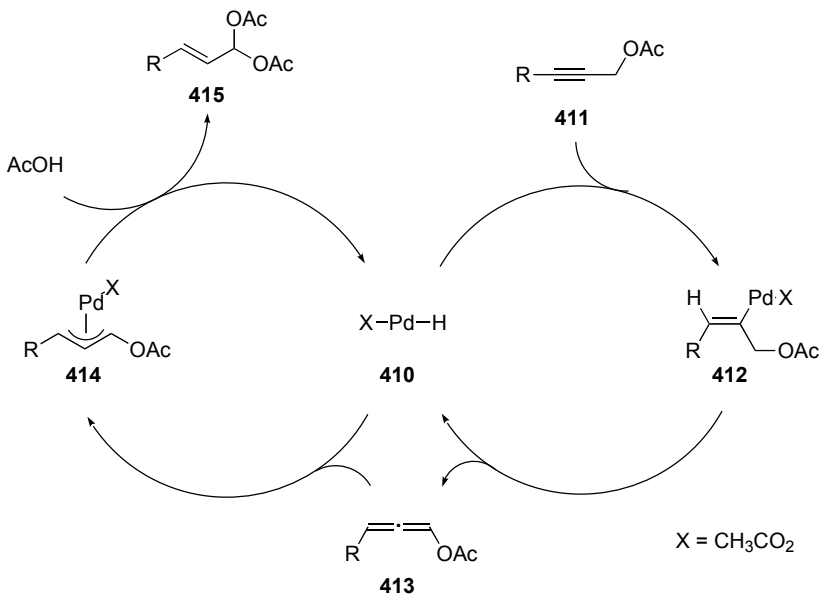
In this approach, we hoped that *gem*-diacetate **407**, in a variation of Haight's methodology,[184, 185] would couple to ABCD alcohol **(±)-2** to provide allyl ether **406**. Hydrogenation to simultaneously remove the benzyl ether as well as unsaturation between C-2' and C-3' would provide alcohol **405**, which upon mild acid catalysis and deprotection would give the desired glycoside **5** (Scheme 110).

To this end, we envisaged the use of Trost's palladium catalysed rearrangement and addition reaction of propargylic alcohols to provide the required *gem*-diacetate **407**.[200-202] In this series of papers, Trost has shown that the reaction of protected propargylic alcohols **408** with acetic acid under palladium catalysis results in the formation of *gem*-diacetates **409** as illustrated in Scheme 111.



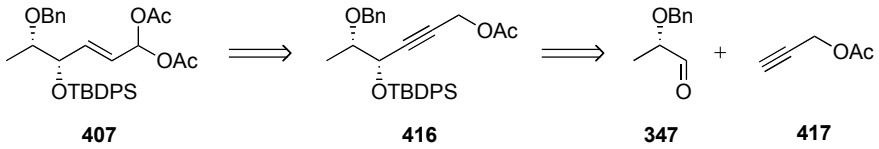
Scheme 111: Trost's Catalysed Rearrangement and Addition Reaction of Propargylic Alcohols **408**.

It is thought that the mechanism of the reaction occurs *via* the π-allylpalladium species **414** (Scheme 112).[203] The initial step, to produce the vinyl palladium species **412**, occurs *via* hydropalladation of alkyne **411** with the hydrodopalladium species **410** generated from the reaction between Pd(0) and acetic acid. This in turn undergoes β-elimination to both regenerate the active hydrodopalladium species **410** and provide the intermediate allene species **413**. Following this, hydrodopalladation with the active catalyst **410** provides the π-allylpalladium species **414** which subsequently reacts further with acetic acid to provide the desired product **415** (Scheme 112).



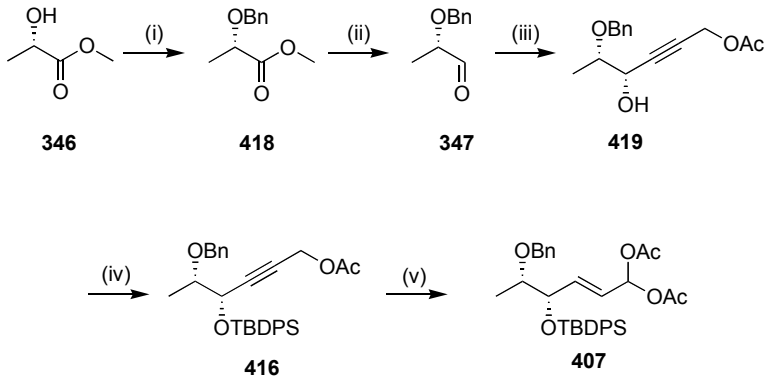
Scheme 112: Catalytic Cycle for the Palladium/Acetic Acid Catalysed Formation of *gem*-Diacetates **415**.

It was found that the *tert*-butyldiphenyl silyl protecting group played an essential role in directing the palladium-mediated oxidative addition of acetic acid towards the primary acetate and away from the sterically encumbered silyl protected alcohol.[201, 202, 204] Indeed, yields were found to be significantly lower when the *tert*-butyldimethyl silyl protecting group was used. As a result we envisaged the use of *tert*-butyldiphenyl silyl ether **416** as a precursor to the formation of *gem*-diacetate **407**. This in turn would be prepared from the addition of propargylic acetate **417** to aldehyde **347** in a procedure described by Carreira and co-workers (Scheme 113).[204]



Scheme 113: Retrosynthetic Analysis of *gem*-Diacetate **407**.

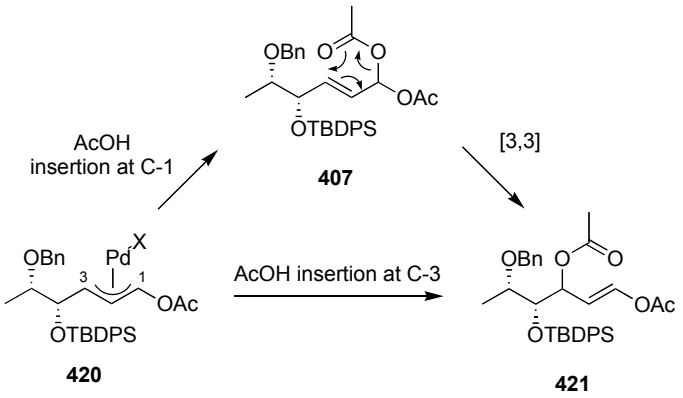
Aldehyde **347** was prepared from readily available methyl-(*S*)-lactate (**346**) *via* protection as the benzyl ether using sodium hydride and benzyl bromide followed by reduction with diisobutylaluminium hydride in 84% overall yield (Scheme 114). The direct addition of propargyl acetate to aldehyde **347** using stoichiometric zinc(II) triflate and (+)-*N*-methylephedrine gave alcohol **419** in 71% yield as essentially one diastereoisomer (*dr* > 95:5 by ^{1}H NMR). Subsequent protection with *tert*-butyldiphenyl silyl chloride and imidazole provided the propargylic acetate **416** which under Trost's palladium catalysed rearrangement-addition reaction conditions[201, 202] provided *gem*-diacetate **407** in 52% yield.



Reagents and Conditions: (i) NaH, BnBr, THF, 0 °C, 12 h, 90% (ii) DIBAl-H, CH_2Cl_2, –78 °C, 6 h 93% (iii) Propargyl acetate, (+)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N, PhMe, 5 h, 71%, d.r. > 95:5 (iv) TBDPSCl, imid., DMF, 18 h, 100%; (v) $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, AcOH, PhMe, 110 °C, 24 h, 52%.

Scheme 114: Synthesis of *gem*-Diacetate **407** *via* Carreira's Methodology.

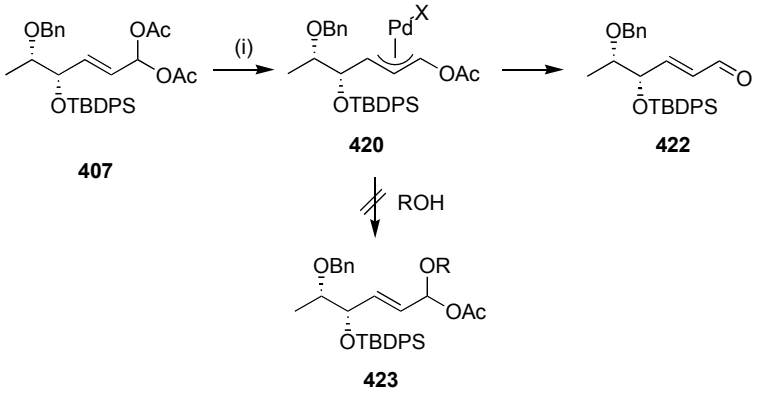
A significant amount of side-product (~40%) was isolated from the palladium rearrangement-addition reaction which, after ^{1}H NMR analysis, was determined to be a diastereoisomeric mixture of diacetate **421**. This could be formed from either the oxidative addition of acetic acid at C-3 on the palladium π-allylpalladium species **420** or from the thermally induced [3,3]-sigmatropic rearrangement of *gem*-diacetate **407** (Scheme 115).



Scheme 115: Proposed Formation of Diacetate **421**.

Reduction of the reaction time did not result in the suppression of by-product **421** formation. Nevertheless a significant quantity of *gem*-diacetate **407**, required for the subsequent coupling experiments, was obtained.

Initial experiments focused on the coupling of simple aliphatic alcohols with *gem*-diacetate **407** using a variety of reaction conditions, the results of which are summarised in Table 4 (Scheme 116).



407 **420** **422** **423**

Reagents and Conditions: (i) See Table 4.

Scheme 116: Attempted Coupling of Aliphatic Alcohols with *Gem*-Diacetate **407**.

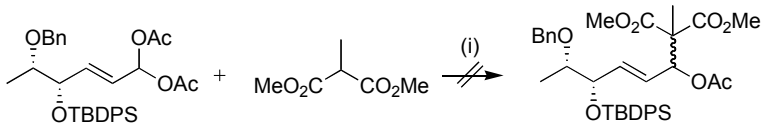
Table 4: Investigations into the Coupling of Aliphatic Alcohols with *Gem*-Diacetate **407**.

Entry[a]	Alcohol (ROH)	Conditions	Result[d]
1	Adamantan-1-ol	$Pd(OAc)_2$, PPh_3, reflux, 20 h	Recovered alcohol (ROH).
2	Adamantan-1-ol	$Pd_2Cl_2(CH_3CH{=}CH_2)_2$, reflux, 18 h	ROH + aldehyde **422** (5%).
3	*t*-BuOH	$Pd(OAc)_2$, PPh_3, reflux, 20 h	ROH + aldehyde **422** (12%).
4[b]		$Pd(OAc)_2$, PPh_3, reflux, 20 h	ROH + aldehyde **422** (16%).
5[b]	NaO*t*-Bu	$Pd(OAc)_2$, PPh_3, reflux, 18 h	Aldehyde **422** (23%).
6[b]	NaO*t*-Bu	$Pd_2Cl_2(CH_3CH{=}CH_2)_2$, reflux, PPh_3, 18 h	Aldehyde **422** (28%).
7[c]	$Zn(Ot\text{-}Bu)_2$	$Pd(PPh_3)_4$, 2 h	Aldehyde **422** (12%).

[a] Typical reaction conditions were performed in THF on a 100 mg scale using 2.0 equivalents of *gem*-diacetate **407**. [b] Alkoxide prepared from reaction of alcohol with sodium hydride. [c] Zinc alkoxide prepared by reaction of alcohol with diethyl zinc. [d] Determined by crude ^{1}H NMR spectroscopy.

Disappointingly, the desired coupled products **423** were not detected by ^{1}H NMR spectroscopy and in the majority of cases aldehyde **422** was identified as the only product of the reaction (Table 4, entries 1 to 7). Attempts at increasing the nucleophilicity of the alcohols by preforming the alkoxides with sodium hydride (Table 4, entries 4-6) or diethyl zinc[183] (Table 4, entry 7) offered no improvements.

To verify the reactivity of *gem*-diacetate **407**, the palladium catalysed reaction with sodium dimethyl methylmalonate **424**—the nucleophile described in Trost's[201] original procedure—was performed. Again, none of the desired product **425** was detected by ^{1}H NMR analysis (Scheme 117).

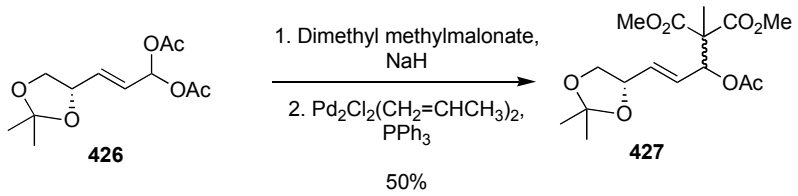


407 **424** **425**

Reagents and Conditions: (i) *a*) NaH, THF, –5 °C, 30 min; *b*) $Pd_2Cl_2(CH_2{=}CHCH_3)_2$, PPh_3, THF, 5 h.

Scheme 117: Attempted Coupling of Sodium Dimethyl Methylmalonate **424** with *gem*-Diacetate **407**

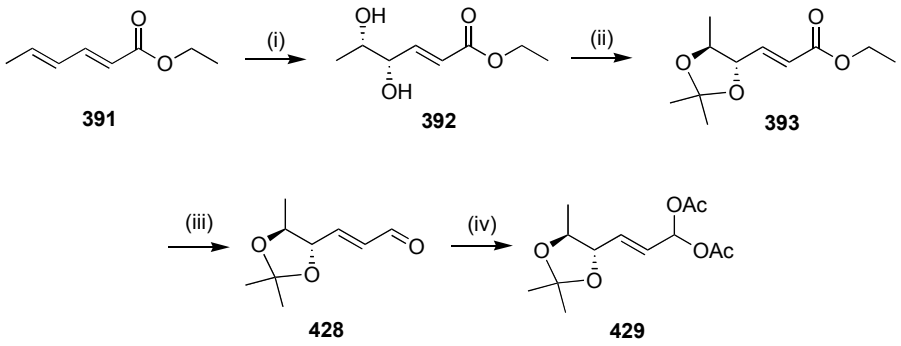
The failure of this experiment led us to conclude that the sterically demanding *tert*-butyldiphenyl silyl protecting group, although essential for the successful synthesis of diacetate **407**, was blocking its reactivity. Trost in fact indicates that "with sterically more congested substrates alkylation does not even take place at elevated temperatures".[201] To overcome the steric congestion, an alternative protecting group for the diol functionality was sought. Surveying some of the substrates used by Trost revealed the use of the sterically less hindered acetonide protected diol **426** in a similar coupling reaction (Scheme 118).



Scheme 118: Trost's Palladium Catalysed Coupling of *Gem*-Diacetate **426** with Dimethyl Methylmalonate.

Less sterically encumbered in nature, we envisaged that the use of acetonide for the protection of the diol functionality of *gem*-diacetate **407** might provide the reactivity required for the successful palladium catalysed coupling with ABCD alcohol **(±)-2**.

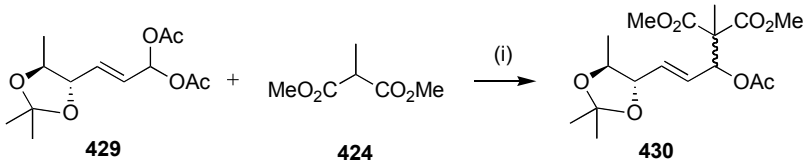
Consequently, *gem*-diacetate **429** was prepared from α,β-unsaturated aldehyde **428** by the protocol described by Trost and co-workers.[201] Ethyl sorbate (**391**) was converted, as before (Scheme 105), to diol **392** by the Sharpless asymmetric dihydroxylation with AD-mix-α in 45% yield. Protection by treatment with 2,2-dimethoxypropane in the presence of *para*-toluene sulfonic acid provided the desired protected diol **393** in 91% yield. This was then reduced using diisobutylaluminium hydride at –78 °C to α,β-unsaturated aldehyde **428** and treated with iron(III) chloride in the presence of acetic anhydride at 0 °C to give *gem*-diacetate **429** in 40% overall yield (Scheme 119).



Reagents and Conditions: (i) AD-α-mix, $Me_2SO_2NH_2$, *t*-BuOH, 0 °C, 18 h, 45%; (ii) 2,2-dimethoxypropnae, TsOH, 0 °C, 1 h, 91%; (iii) DIBAl-H, –78 °C, 5 h, 63%; (iv) $FeCl_3$, Ac_2O, CH_2Cl_2, 0 °C, 24 h, 64%.

Scheme 119: Synthesis of *gem*-Diacetate **429**.

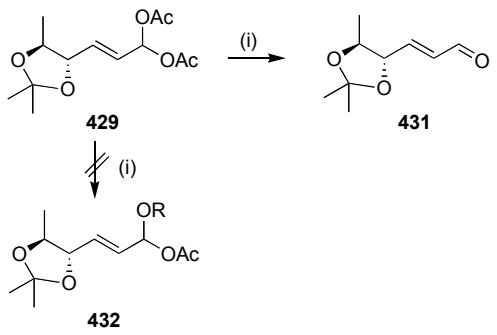
Gem-diacetate **429**, was successfully coupled to dimethyl methylmalonate using Trost's palladium catalysed conditions[201] in 44% yield. This result verified the reactivity of *gem*-diacetate **429** towards the palladium catalysed reaction conditions (Scheme 120).



Reagents and Conditions: (i) a) $HCCH_3(CO_2Me)_2$, NaH, THF, –5 °C, 30 min b) $Pd_2Cl_2(CH_2{=}CHCH_3)_2$, PPh_3, THF, 6 h, 44%.

Scheme 120: Coupling of *gem*-Diacetate **429** to Dimethyl Methylmalonate **424**.

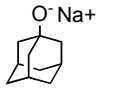
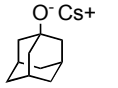
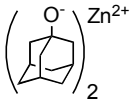
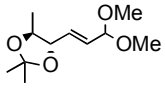
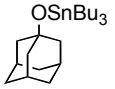
This new coupling partner **429** was subsequently used in initial coupling experiments with a selection of tertiary alcohols **(**Scheme 121**)**, the results of which are summarised in Table 5.



Reagents and Conditions: (i) See Table 5.

Scheme 121: Attempted Coupling of Aliphatic Alcohols to *Gem*-Diacetate **429**.

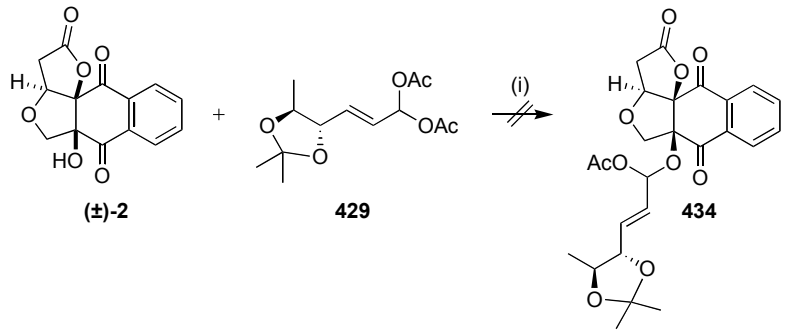
Table 5: Investigations into the Coupling of Aliphatic Alcohols to *Gem*-Diacetate **429**.

Entry[a]	Alcohol	Conditions	Result[f]
1	Adamantan-1-ol	$Pd(OAc)_2$, PPh_3, reflux, 48 h	Recovered alcohol (ROH) + aldehyde **431**
1[b]		$Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, reflux, 48 h	ROH + aldehyde **431**.
2[c]		$Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, reflux, 24 h	ROH + aldehyde **431**.
3[d]		$Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, reflux, 24 h	ROH + aldehyde **431**.
4[e]	$SnBu_3OMe$	$Pd(PPh_3)$, 3 h	 **433** 65%[g]
5[e]		$Pd(PPh_3)_4$, THF, 3 h	ROH + aldehyde **431**.

[a]Typical reaction conditions were performed in THF on a 100 mg scale using 2.0 equivalents of *gem*-diacetate **429**. [b] Sodium alkoxide prepared by reaction of alcohol with sodium hydride. [c] Zinc alkoxide prepared by reaction of alcohol with diethyl zinc. [d]Cesium alkoxide prepared by reaction of alcohol with cesium carbonate. [e]Tin alkoxide prepared by reaction of alcohol with sodium hydride followed by tributyltin chloride. [f]Determined by crude ^1H NMR spectroscopy. [g]Isolated yield.

Exposure of adamantan-1-ol to *gem*-diacetate **429** using Haight's[184, 185] original palladium catalysed reaction conditions failed to furnish any of the coupled product **432** (Table 5, Entry 1). In an attempt to tune the nucleophilicity of the incoming alcohol to the π-allyl palladium species, a number of metal alkoxides were prepared (Table 5, entries 2 to 5). Most were unsuccessful and only starting material was observed by ^{1}H NMR spectroscopy. However, exposure of *gem*-diacetate **429** to tributyltin methoxide provided the *di*-coupled product **433** in 60% yield (Table 5, entry 4). Application of this procedure to the sterically more demanding adamantan-1-ol, in a hope to achieve *mono*-alkylation was unsuccessful and gave starting material back (Table 5, Entry 5).

The reaction between model ABCD alcohol **(±)-2** and *gem*-diacetate **429** was performed to exclusively rule out this approach to the glycosidation reaction. Again, none of the desired coupled product was obtained upon crude ^{1}H NMR analysis (Scheme 122).



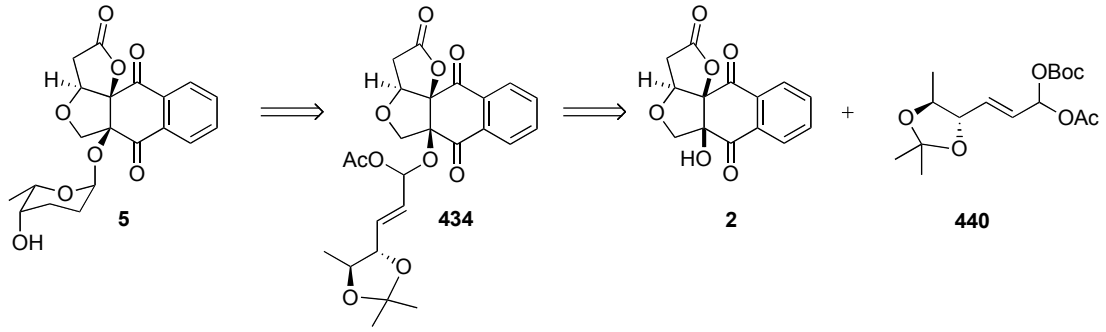
Reagents and Conditions: (i) $Pd(OAc)_2$, PPh_3 or $Pd(PPh_3)_4$, THF, reflux, 24 h.

Scheme 122: Attempted Coupling of *gem*-Diacetate **429** to ABCD Alcohol **2**.

These results clearly indicated the inherent lack of reactivity of ABCD alcohol **(±)-2** as well as simple aliphatic alcohols towards *gem*-diacetate **429**. The use of *gem*-diacetates as an approach for the glycosidation of lactonamycinone (**9**) was consequently abandoned.

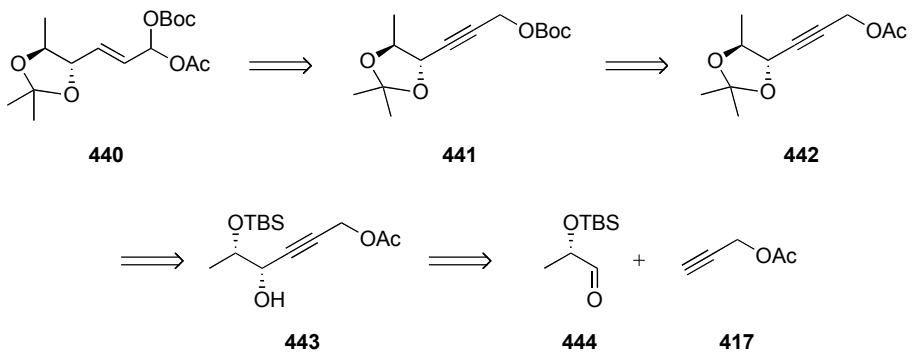
6.4.2 Experiments Towards the Palladium Catalysed Allylation Reaction with Boc Acetate **440**

Given that the reaction of ABCD alcohol **(±)-2** with *tert*-butyl carbonate protected allylic alcohol **395** has been shown to be successful (Scheme 106),[42] the use of the alternative coupling partner **440** was envisaged. It was hoped that Boc acetate **440** would provide the reactivity required for the successful coupling to ABCD alcohol **(±)-2**. With the coupled product **434** in hand, simple acid deprotection and cyclisation would provide glycoside **5** (Scheme 123).



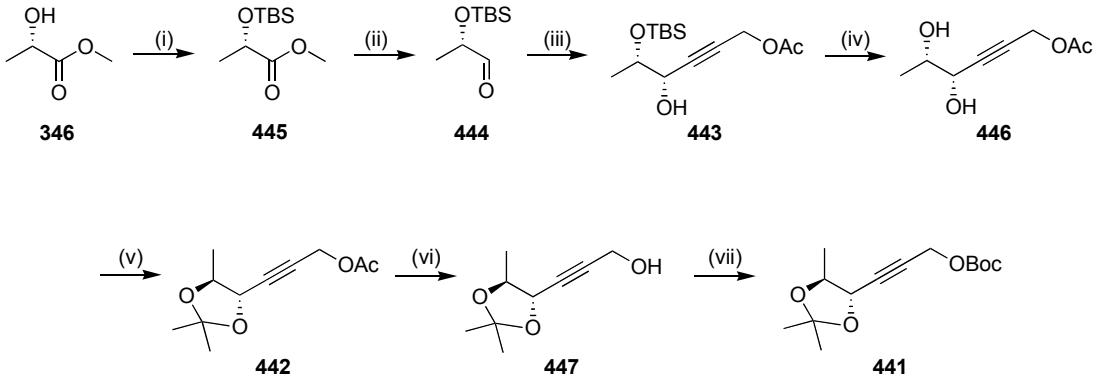
Scheme 123: Retrosynthetic Analysis of *O*-Glycoside **5** *via* Boc Acetate **440**.

We envisaged that it should be possible to extend Trost's palladium catalysed rearrangement reaction to provide Boc acetate **440** (Scheme 124).[200-202] Addition of propargyl acetate **417** to aldehyde **444** using Carreira's methodology[204] would provide alcohol **443**, deprotection and acetonide protection to **442** followed by conversion to the *tert*-butyl carbonate protected propargylic alcohol **441** would allow for further manipulation to Boc acetate **440** (Scheme 124).



Scheme 124: Retrosynthetic Analysis of Boc Acetate **440**.

With this aim, *tert*-butyl carbonate protected propargylic alcohol **440** was prepared starting from commercially available (*S*)-methyl lactate (**346**) (Scheme 125).

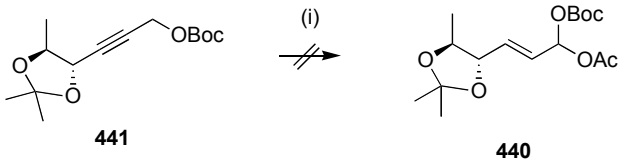


Reagents and Conditions: (i) TBSCl, Imid., DMAP, DMF, 12 h, 97%; (ii) DIBAL-H, CH_2Cl_2, –78 °C, 6 h, 86%; (iii) Propargylic acetate, (+)-*N*-methylephidrine, $Zn(OTf)_2$, Et_3N, PhMe, 5 h, 46%, d.r. > 95:5; (iv) $HF{\cdot}H_2O$, CH_3CN, 4 h, 92%; (v) 2,2-dimethoxypropnae, TsOH, 0 °C, 1 h, 99%; (vi) DIBAl-H, CH_2Cl_2, –78 °C, 5 h, 97%; (vii) Boc_2O, NEt_3, DMAP, 1 h, 72%.

Scheme 125: Synthesis of *tert*-Butyl Carbonate Protected Propargylic Alcohol **441**.

Protection of (*S*)-methyl lactate (**346**) using *tert*-butyldimethyl silyl chloride and imidazole with a catalytic quantity of DMAP followed by reduction using diisobutylaluminium hydride provided aldehyde **444** in 83% overall yield. Addition of propargylic acetate using Carreira's procedure[204] gave the desired alcohol **443** in 46% yield (d.r. > 95:5 by ^{1}H NMR). Several functional group interconversions were then required to allow access to Boc acetate **440**. Firstly, deprotection of the *tert*-butyldimethyl silyl protecting group using aqueous hydrogen fluoride gave diol **446** in 92% yield. Protection to the acetonide **442**, followed by reduction of the acetate group using diisobutylaluminium hydride provided propargylic alcohol **447** in 96% overall yield. Finally, protection using di-*tert*-butyldicarbonate, triethylamine and DMAP gave the *tert*-butyl carbonate protected propargylic alcohol **441** in 72% yield.

With the Boc protected propargyl alcohol **441** in hand, attention turned to Trost's palladium catalysed rearrangement reaction with acetic acid (Scheme 126). The results are summarised in Table 6.



441 **440**

Reagents and Conditions: (i) See Table 6.

Scheme 126: Attempted Catalysed Rearrangement and Addition Reaction of Acetic Acid to *tert*-butyl carbonate protected propargylic alcohol **441**.

Table 6: Investigations into the Synthesis of Boc Acetate **440**.

Entry[a]	Conditions	Result[b]
1	$Pd_2(dba)_3{\cdot}CHCl_3$, AcOH, PPh_3, PhMe, 110 °C, 15 h	Mixture of unidentifiable products
2	$Pd(PPh_3)_4$, AcOH, THF, 80 °C, 12 h.	Mixture of unidentifiable products
3	$Pd(PPh_3)_4$, AcOH, 1,2-DCE, 100 °C, 13 h.	Mixture of unidentifiable products

[a]Typical reaction conditions were performed on a 100 mg scale using 1.05 equivalents of acetic acid. [b]Determined by crude ^{1}H NMR spectroscopy.

Unfortunately, the attempted formation of Boc acetate **440** proved to be unsuccessful. In all cases, after prolonged reaction times complete decomposition of the starting material **441** to a mixture of unidentifiable products was observed by crude ^{1}H NMR analysis. In light of these results, the use of this approach to glycosidation was abandoned.

6.5 Conclusions and Future Work

The synthesis of open chain glycoside **395** was prepared as before and coupled to ABCD model alcohol **2** using a palladium catalysed *O*-allylation reaction to give allyl ether **396**.[42] The use of both ruthenium and rhodium hydride transition metal catalysts for the isomerisation to vinyl ether **400** proved to be ineffective and mainly resulted in decomposition of the highly sensitive ABCD model alcohol **(±)-2**.

Next, we anticipated that *gem*-diacetates **407** and **429** could be employed in a similar strategy for their coupling to ABCD alcohol **(±)-2**. These were successfully synthesised, however they proved to be unreactive towards a variety of model alcohols**.**

In a third approach, the synthesis of *tert*-butyl carbonate protected propargylic alcohol **441** was conducted in a hope to prepare Boc acetate **440** as a more reactive coupling partner. However, the use of Trost's palladium catalysed rearrangement and addition reaction failed to provide the desired coupling partner **440**.

Following our disappointing results with the palladium catalysed allylation strategy, we next turned our attention to O'Doherty's glycosidation approach.

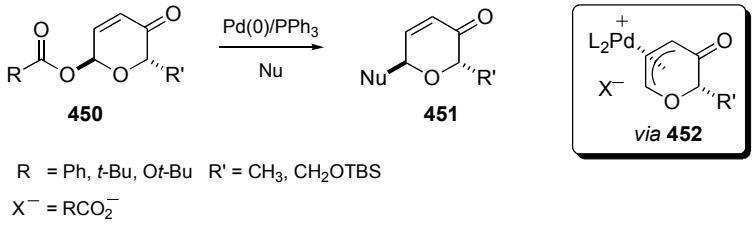
Chapter 7: Results and Discussion: Investigations into the O'Doherty Glycosidation

7.1 Introduction

Following the success of the palladium(0) catalysed *O*-allylation reaction between ABCD alcohol **(±)-2** and *tert*-butyl carbonate protected allylic alcohol **395** (Chapter 6), we considered the use of an alternative cyclic sugar derivative in a similar palladium-catalysed coupling reaction. We envisaged that the resulting glycoside may prove easier to manipulate into the 2,3,6-trideoxy sugar in lactonamycin (**1**), by avoiding the troublesome isomerisation reaction.

The use of such an approach has been recently reported by O'Doherty and co-workers where non-classical palladium-catalysed allylation reactions have been employed for the syntheses of several sugar containing natural products.[205-214] This novel palladium π-allyl approach proceeds in excellent yields with high levels of stereocontrol at the anomeric centre and as well as being a catalytic process, operates under very mild reaction conditions.

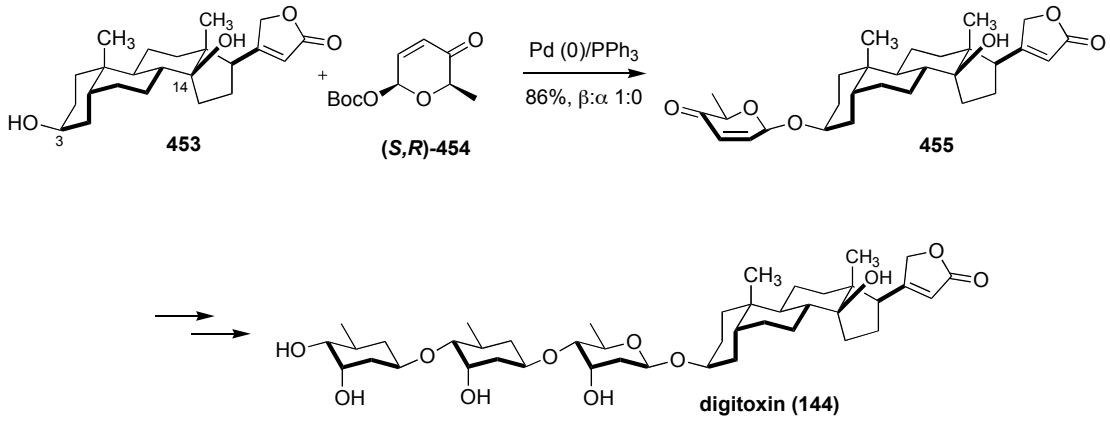
O'Doherty's methodology relies on the successful generation of a diastereisomeric π-allyl palladium intermediate **452** from the reaction between palladium(0) and optically active pyranones such as **450** (Scheme 127).



Scheme 127: O'Doherty's Palladium Coupling Reaction.

The origin of the high stereocontrol comes about by the preferential approach of the incoming palladium(0) species from the opposite face to that of the *tert*-butoxycarboxy leaving group, to give the diastereomeric π-allyl palladium intermediate **452**. A nucleophilic species then transforms the π-allyl palladium species **452** into the corresponding α or β glycoside **451** *via* an additional inversion of stereochemistry. The process of double inversion at the stereogenic centre allows for the complete retention of stereochemistry at the anomeric position to give the glycoside **451** with excellent stereocontrol (Scheme 127).

One noteworthy example is outlined below and illustrates the efficient and stereoselective coupling between digitoxigenin (**453**) and pyranone **(*S*,*R*)-454** to give the naturally occurring trisaccharide, digitoxin (**144**) (Scheme 128).[214]



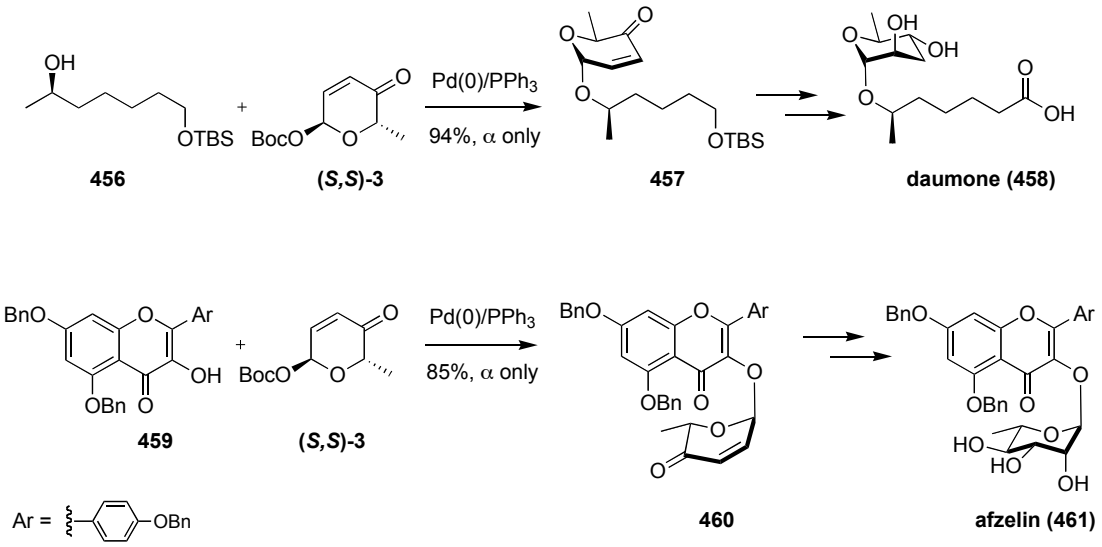
Scheme 128: O'Doherty's Synthesis of Digitoxin (**144**).

Combined with the excellent yields, complete chemoselectivity to β-glycoside **455** was observed during the glycosidation step. In particular, reaction at the C-3 secondary alcohol occurred exclusively over the more sterically congested C-14 tertiary alcohol. Following several structural manipulations of the sugar unit, it was shown that two

additional glycosidation cycles again proceeded with the same selectivity towards the sterically less congested sugar alcohol (Scheme 128).

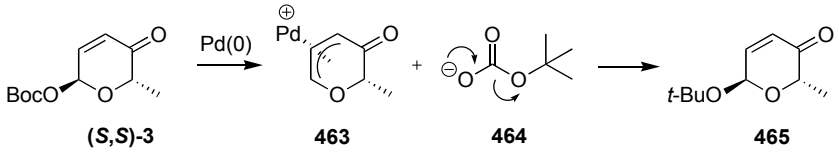
However, the application of this approach towards the glycosidation of lactonamycinone (**9**) was not without its concerns. Taking into account the complete lack of reactivity of the tertiary alcohol in digitoxigenin (**453**) during O'Doherty's studies, there was a high chance that a similar observation may be encountered with ABCD alcohol **(±)-2**.

Furthermore, the majority of glycosidations published by O'Doherty on this subject, showed the application of this strategy to unhindered secondary alcohols. The synthesis of daumone (**458**) and afzelin (**461**) are two typical examples; once more, yields were high and complete diastereoselectivity was observed (Scheme 129).[208, 212]



Scheme 129: O'Doherty's Synthesis of Daumone (**458**) and Afzelin (**461**).

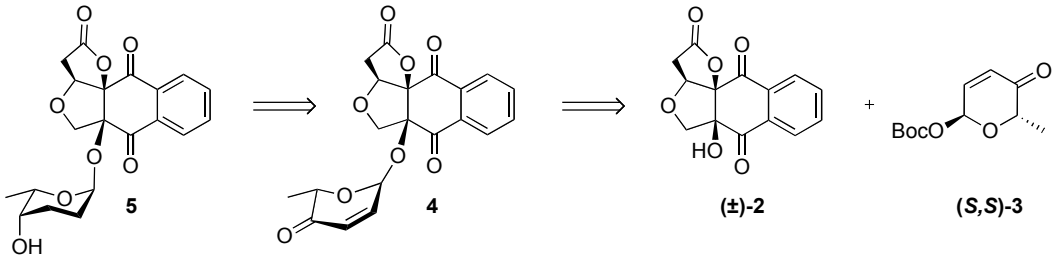
In addition to these concerns, in the one paper that described the glycosidation of the tertiary alcohol adamantan-1-ol, O'Doherty observed the production of a significant amount of a *tert*-butyl acetal by-product **465** during the course of the reaction.[205] He postulated that this was due to the successful competition between *tert*-butanol (generated from the decarboxylation of the *tert*-butoxycarboxy leaving group **464** and the substrate alcohol for the intermediate π-allyl palladium complex **463** (Scheme 130).



Scheme 130: Generation of *tert*-Butyl Acetal By-Product **465**.

7.2 Application of O'Doherty's Glycosidation Strategy to Lactonamycin (1)

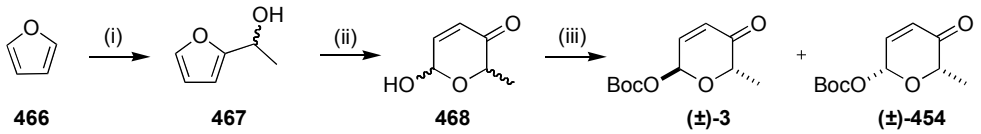
In light of this novel chemistry, coupled with the previous success with Haight's[184] palladium(0) catalysed *O*-allylation reactions described in Chapter 6, we considered the application of this methodology to the glycosidation of ABCD alcohol **(±)-2**. After the coupling of pyranone **(*S*,*S*)-3** to ABCD alcohol **(±)-2**, a sequence of reductions of the sugar ring should provide the desired 2,3,6-trideoxy sugar unit in glycoside **5** (Scheme 131).



Scheme 131: Retrosynthetic Approach to Glycoside **5** Using O'Doherty's Glycosidation Methodology.

7.2.1 Glycosidation Studies

In order to test O'Doherty's methodology, pyranones **(±)-3** and **(±)-454** were prepared from racemic 1-(2-furyl)ethanol (**466**) employing the procedure described by O'Doherty and co-workers (Scheme 132).[207, 208]



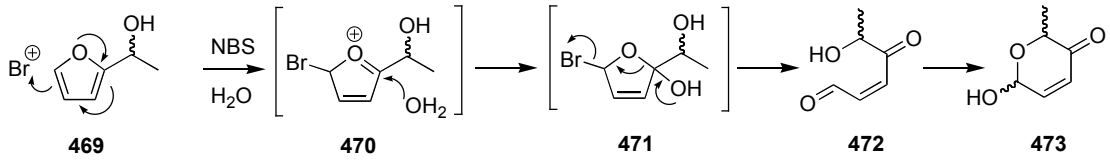
466 **467** **468** **(±)-3** **(±)-454**

Reagents and Conditions: (i) a) *n*-BuLi, THF, –78 °C b) CH_3CHO, 15 h, 61%; (ii) $NaHCO_3$, NaOAc, NBS, THF/H_2O, 0 °C, 1h, 83%; (iii) Boc_2O, DMAP, CH_2Cl_2, –78 to 23 °C, 1 h, 89% (**(±)-3** : **(±)-454**, 3.2 : 1).

Scheme 132: Synthesis of Boc Pyranones **(±)-3** and **(±)-454**.

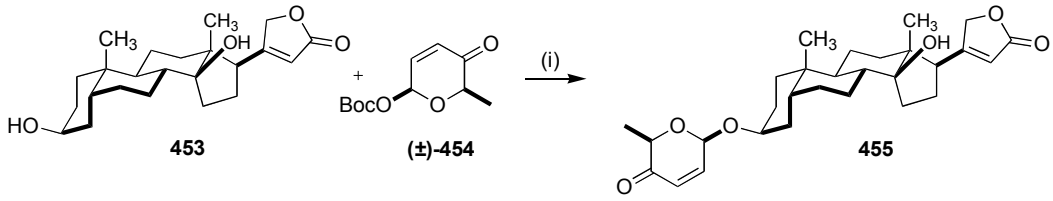
1-(2-Furyl)ethanol (**467**) was synthesised in 61% yield by treatment of furan (**466**) with *n*-butyllithium and acetaldehyde at –78 °C. Conversion to pyranone hemi-acetal **468** following Georgiadis' modification[215] of the Achmatowicz reaction[216] was achieved in 83% yield by treatment with sodium bicarbonate, sodium acetate and NBS at 0 °C. Protection with di-*tert*-butyl dicarbonate and DMAP gave a 3.2 : 1 mixture of pyranones **(±)-3** and **(±)-454** in 89% yield (Scheme 132). Crucially, both diastereoisomers were separable by silica gel flash column chromatography.

The key transformation for this synthesis; the Achmatowicz reaction, follows the oxidative rearrangement of furfuryl alcohol derivatives such as furan **469** to 2*H*-pyran-3(6*H*)-ones **473**.[217] The crucial step involves the oxidation of the furan ring **469** by NBS[215] to give the intermediate 2,5-dihydrofuran **471**.[218] This intermediate then proceeds to rearrange *via* the keto-aldehyde **472** to give the more stable hemiacetal **473** under the acidic conditions (Scheme 133).



Scheme 133: Mechanism of the Achmatowicz Reaction.

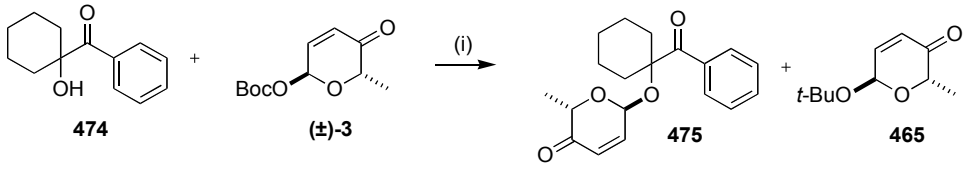
Reacting two equivalents of pyranone **(±)-454** with commercially available digitoxigenin (**453**) in the presence of tris(dibenzylideneacetone)dipalladium(0) and triphenylphosphine gave complete conversion to glycoside **455** as a 1:1 mixture of diastereoisomers and with comparable yields to those reported by O'Doherty and co-workers (Scheme 134).[214]



Reagents and Conditions: (i) Pd_2dba_3, PPh_3, CH_2Cl_2/THF, 0 °C, 8 h, 79%.

Scheme 134: Glycosidation of Digitoxigenin (**453**).

In an attempt to extend this methodology to more hindered substrate alcohols, O'Doherty's glycosidation conditions were applied to commercially available 1-hydroxycyclohexyl phenyl ketone (**474**) (Scheme 135), the results of which are summarised in Table 7.



Reagents and Conditions: (i) See Table 7.

Scheme 135: Glycosidation of 1-Hydroxycyclohexyl Phenyl Ketone (**474**).

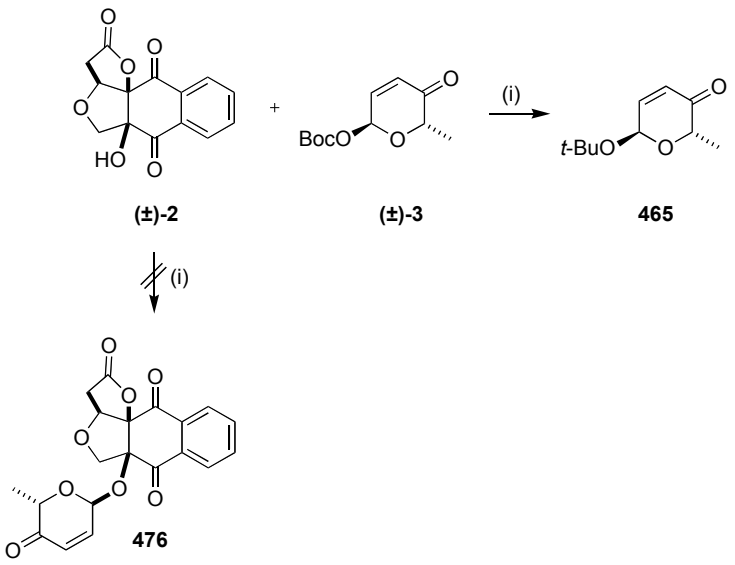
Table 7: Glycosidation of Alcohol **474** Using O'Doherty's Reaction Conditons.

Entry[a]	Temp. (°C)	Ratio **474** : **(±)-3**	Time (h)	Observed Ratio **474** : **475** : **465**[b]
1	0	1 : 2	12	0.6 : 0.4 : 1.6
2	23	1 : 2	12	0.6 : 0.4 : 1.6
3	75	1 : 2	0.5[c]	0.6 : 0.4 : 1.6
4	23	1 : 4	12	0.5 : 0.5 : 3.5

[a]Typical reaction conditions were performed using Pd_2dba_3 (2.5 mol%) and PPh_3 (10 mol%) in a 0.5 M CH_2Cl_2 solution. [b]Ratio determined by crude ^1H NMR. [c]This reaction was performed under microwave conditions.

However, as expected, in all cases only a limited amount of glycoside **475** was detected by crude ^1H NMR spectroscopic analysis, with the major product of the reaction detected as the previously reported *tert*-butyl acetal by-product **465**.[205] Conducting the experiments at 0, 23 and 75 °C (microwave) provided ratios of 0.6 : 0.4 of substrate alcohol **474** to glycoside **475** (Table 7, entries 1, 2 and 3). Increasing the equivalents of pyranone **(±)-3** to four, as expected had a slight positive effect on the ratio of the desired product, yet was limited to only to 50% conversion (Table 7, entry 4). The use of a large excess of pyranone **(±)-3** however, was not an attractive solution for the suppression of the unwanted side reaction.

Despite these results, the attempted coupling of ABCD alcohol **(±)-2** to pyranone **(±)-3** was conducted to test the scope of O'Doherty's reaction conditions with our hindered substrate alcohol (Scheme 136).



Reagents and Conditions: (i) Pd_2dba_3, PPh_3, CH_2Cl_2, 0 °C, 5 h.

Scheme 136: Attempted Glycosidation of ABCD Alcohol **(±)-2** with Pyranone **(±)-3**.

Unfortunately, the desired glycoside **476** was not detected by crude ^{1}H NMR analysis. Instead complete conversion of pyranone **(±)-3** to the *tert*-butyl acetal by-product **465** occurred and indicated the successful competition of *tert*-butanol for the reactive π-allyl palladium species **463**.

These results confirmed that the reactivity of ABCD alcohol **(±)-2** towards the π-allyl palladium complex **463** was significantly lower than that of *tert*-butanol, as was to be expected. In light of these results it was apparent that a method for the removal of *tert*-butanol from the reaction mixture was necessary if this methodology were to be successful with our substrate alcohol **(±)-2**.

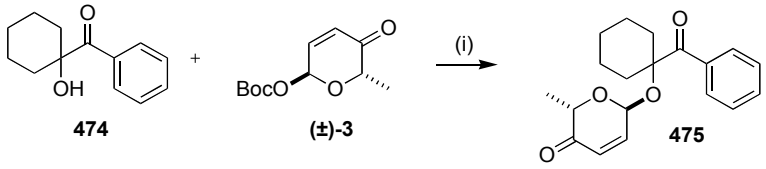
We speculated that it might be possible to scavenge the *tert*-butanol generated during the reaction by the use of molecular sieves. Molecular sieves of the type 3A and 4A (Table 8, entries 1 and 2) are commonly know to trap water molecules (molecular volume 3.2 Å) in moisture sensitive reactions.[219, 220] We postulated that molecules such as *tert*-butanol could potentially be removed form the reaction mixture by the larger pore size molecular sieves (Table 8, entries 3, 4 and 5).

Table 8: Adsorption Properties of Various Commercially Available Molecular Sieves.[221]

Entry	Type	Pore Diameter (Å)	Adsorbs
1	3A	3	NH_3, H_2O, (not C_2H_6)
2	4A	4	H_2O, CO_2, SO_2, H_2S, C_2H_4, C_2H_6, C_3H_6, EtOH. Will not adsorb C_3H_8 and higher hydrocarbons.
3	5A	5	Linear hydrocarbons to *n*-C_4H_{10}, alcohols to C_4H_9OH. Will not adsorb isocompounds or rings greater than C_4.
4	10X	8	Branched hydrocarbons and aromatics.
5	13X	10	di-*n*-butylamine (not tri-*n*-butylamine).

Given that the average size of a *tert*-butanol molecule is approximately 5.6 Å,[222] we elected to use readily available molecular sieves of the type 13X (Table 8, entry 5) to potentially provide a method for eliminating *tert*-butanol from the reaction mixture.

In order to test our hypothesis, we carried out O'Doherty's original glycosidation reaction conditions between hydroxy ketone **474** and pyranone **(±)-3**, using molecular sieves 13X as an additive (Scheme 137).



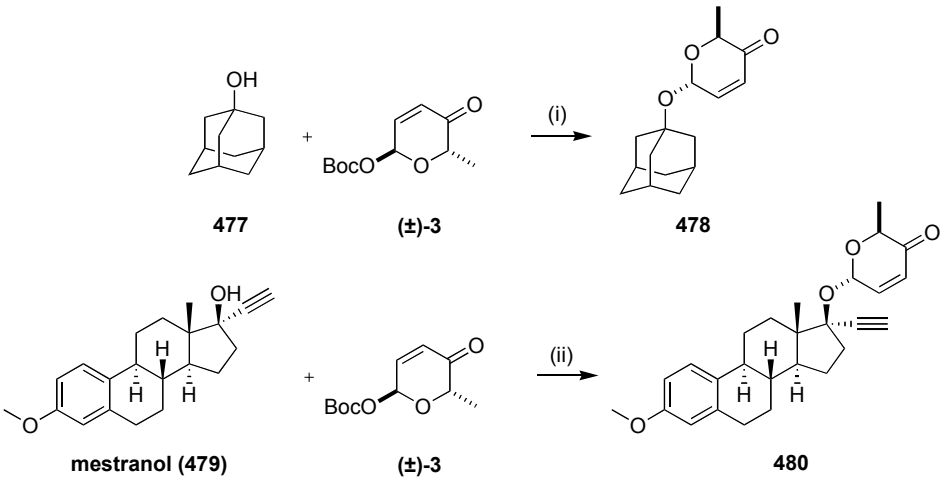
Reagents and Conditions: (i) **(±)-3** (2 eq), Pd_2dba_3, PPh_3, molecular sieves 13X, CH_2Cl_2, 6 h, 78%.

Scheme 137: Glycosidation of Hydroxy Ketone (**474**) Using Molecular Sieves 13X.

These results were superior to the 40% maximum yield obtained using O'Doherty's original procedure and under these new reaction conditions, we were able to obtain a 78% isolated yield of the coupled product **475**.

Interestingly, the molecular sieves did not completely prevent the undesired side reaction. Complete conversion of the remaining unreacted pyranone **(±)-3** to the *tert*-butyl acetal by-product **465** was observed and suggested that the side reaction was still occurring, but at a much slower rate. We postulated that this may be due to; (i) the slow rate of heterogeneous trapping of the *tert*-butanol molecules compared to the homogenous reaction with the π-allyl palladium complex **463** or (ii) the acidic nature of the molecular sieves, slowing down the rate of decarboxylation of the *tert*-butoxycarboxylate anion (**464**), thus minimising the amount of *tert*-butanol in the reaction mixture.

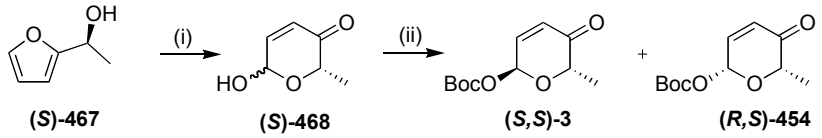
To confirm the new reaction conditions, this methodology was extended to alternative tertiary alcohols. Both adamantan-1-ol (**477**) and mestranol (**479**) were successfully employed in the coupling to pyranone **(±)-3** under the modified reaction conditions (Scheme 138). Both glycosides **478** and **480** were synthesised in excellent yields and demonstrated the importance of using molecular sieves 13X for the glycosidation of hindered substrate alcohols with this methodology.



Reagents and Conditions: (i) **(±)-3** (2 eq), Pd_2dba_3, PPh_3, molecular sieves 13X, CH_2Cl_2, 5 h, 98% conversion (by ^1H NMR analysis); (ii) **(±)-3** (2 eq), Pd_2dba_3, PPh_3, molecular sieves 13X, CH_2Cl_2, 6 h, 100%.

Scheme 138: Glycosidation of Adamantan-1-ol (**477**) and Mestranol (**479**) using O'Doherty Reaction Conditions with Molecular Sieves 13X as an Additive.

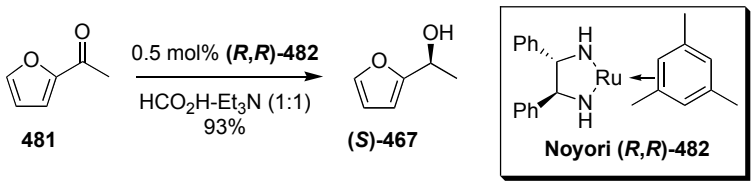
With these encouraging results in hand, experiments towards the coupling of ABCD alcohol **(±)-2** using molecular sieves 13X as a *tert*-butanol scavenger were conducted. Enantiomerically pure pyranone **(*S,S*)-3** was prepared as before, starting from commercially available (*S*)-furyl ethanol (**(*S*)-467**) (Scheme 139).



Reagents and Conditions: (i) $NaHCO_3$, NaOAc, NBS, THF/H_2O, 0 °C, 1 h, 83%; (ii) Boc_2O, DMAP, CH_2Cl_2, –78 to 25 °C, 1 h, 89%, **(*S,*S)-3** : **(*R,*S)-454**, 3.2 : 1.

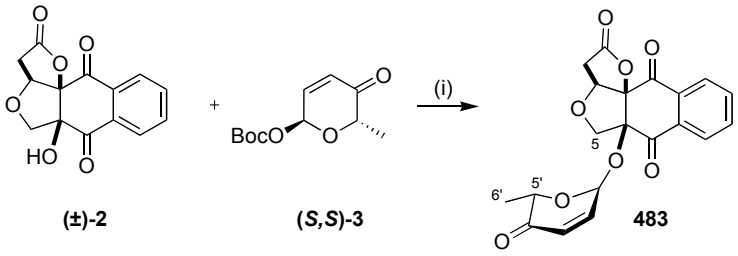
Scheme 139: Synthesis of Pyranones **(*S,S*)-3** and **(*R,S*)-454**.

It is noteworthy to mention here that chiral furyl alcohols such as **(*S*)-467** can be prepared easily from Noyori's reduction[223] of the corresponding acylfuran **481** as demonstrated by O'Doherty and co-workers.[208-210, 212]



Scheme 140: O'Doherty's Modified Noyori Conditions for the Enantioselective Reduction of Acylfurans **481**.

Accordingly, enantiomerically pure pyranone **(*S,S*)-3** was allowed to react with racemic ABCD alcohol **(±)-2** using O' Doherty reaction conditions with molecular sieves 13X as an additive (Scheme 141).



Reagents and Conditions: (i) **(*S,S*)-3** (2 eq), Pd_2dba_3, PPh_3, molecular sieves 13X, CH_2Cl_2, 5 h, 95% (1:1 mixture of diastereoisomers).

Scheme 141: Glycosidation of ABCD Alcohol **(±)-2** Using O'Doherty's Reaction Conditions with molecular sieves 13X.

By thin layer chromatography, complete consumption of the starting material **(±)-2** and the appearance of a new product was detected after 5 hours. Spectroscopic analysis after purification by silica gel column chromatography revealed the expected sugar signals in the ^{1}H and ^{13}C NMR spectra, consequently providing evidence that the coupling reaction had been successful. In addition, two sets of signals were apparent and indicated a 1 : 1 mixture of diastereoisomers of the coupled product **483**, as was expected.

Comparison of the new ^{1}H NMR data to the original ABCD alcohol **(±)-2** and lactonamycin (**1**)[1] provided further evidence for the formation of the coupled product **483** (Figure 13).

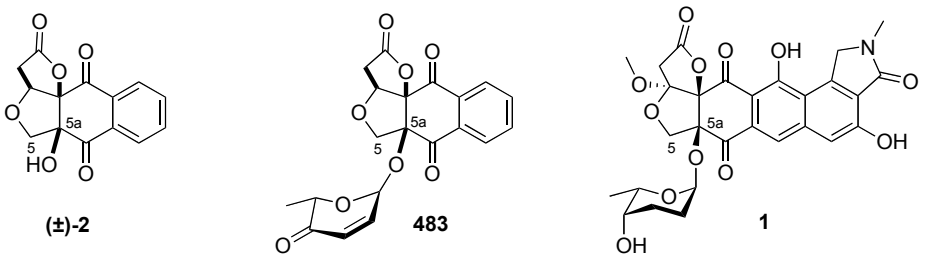


Figure 13: Comparison of the ^{1}H and ^{13}C NMR Shifts of ABCD Alcohol **(±)-2**, Coupled Product **483** and Lactonamycin (**1**).

Specifically, a significant change in the chemical shifts of the H-5 protons from 4.45 ppm (in the starting material **(±)-2**) to 4.75 and 4.85 ppm (in the diastereoisomeric mixture **483**) was observed and were comparable to the corresponding H-5 chemical shifts of lactonamycin (**1**)[1] (4.93 ppm) (Figure 13). Analysis of the ^{13}C NMR spectrum of the diastereoisomeric mixture **483** also revealed significant similarities to lactonamycin (**1**).[1] Of particular interest was the shift in the C-5 and C-5a signals from 75.2 and 83.6 ppm in the model ABCD alcohol **(±)-2** to 72.3 and 73.4 ppm (C-5) and 87.2 and 87.0 ppm (C-5a) in the coupled product **483**. Again, these signals showed similarity to those of

lactonamycin (**1**)[1] (73.8 ppm (C-5) and 86.4 ppm (C-5a)) (Figure 13). Mass spectroscopy of the diastereomeric mixture also confirmed the synthesis of the coupled product **483**.

Further purification of the diastereomeric mixture **483** by crystallisation from *tert*-butyl methyl ether, fortuitously provided crystals of a single diastereoisomer **484** in 40% yield, and was observed by the disappearance of one of the sets of signals in the ^{1}H and ^{13}C NMR spectra. Regrettably, attempts at crystallisation of the remaining diastereoisomer **4** were unsuccessful, however, adequate purity was achieved by standard silica gel flash column chromatography. Optical rotation of both diastereoisomers **484** and **4** were significantly different, giving values of +35.8 and –127.5 respectively.

Comparison of the ^{1}H NMR spectra of both diastereoisomers revealed a significant difference in the chemical shift of the H-5' and H-6' sugar protons. It was hoped that upon comparison to the ^{1}H NMR spectrum of lactonamycin (**1**), that the identity of the two diastereoisomers could be determined. Indeed, the ^{1}H NMR spectrum of diastereoisomer **4** displayed a higher degree of similarity to lactonamycin (**1**),[1] as was exemplified by the H-5' and H-6' signals (Figure 14).

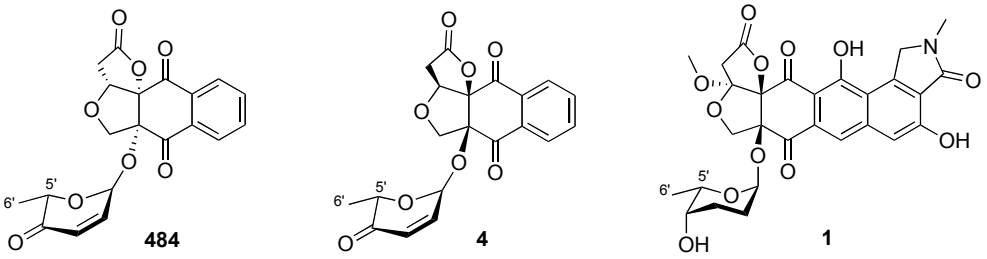


Figure 14: Comparison of the ^{1}H NMR shifts of lactonamycin (**1**) and Diastereoisomers **484** and **4**.

The identity of both diastereoisomers **484** and **4** was tentatively assigned (as indicated in Figure 14) according to the NMR data obtained. At a later stage, X-ray quality crystals of diastereoisomer **484** were acquired. The X-ray data obtained confirmed the synthesis of the coupled glycoside **484** and provided conclusive evidence for the absolute stereochemistry of both the C-1' and C-5' positions on the sugar ring and that of the ring junctions at C-3a, C-5a and C-11a. The crystalline material **484** was consequently shown to be of the opposite configuration to that of the natural product (**1**) (Figure 15).

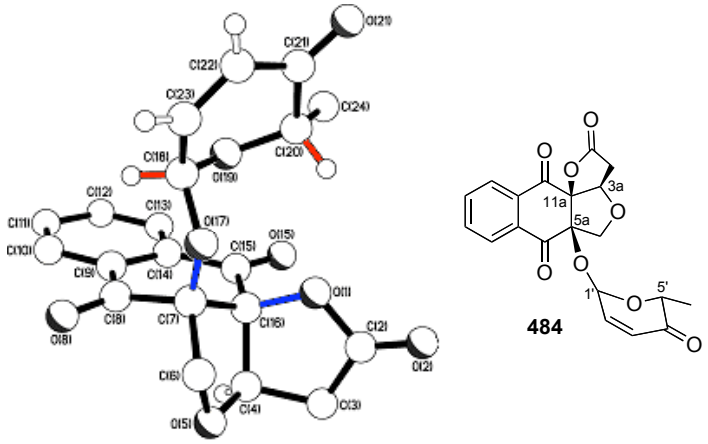
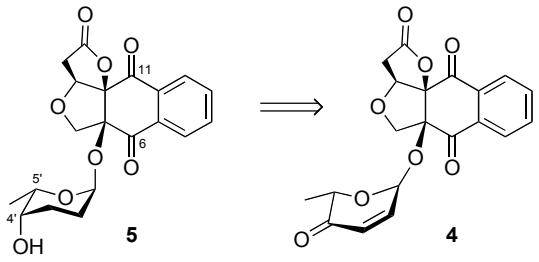


Figure 15: X-ray Crystal Structure of Diastereoisomer **484**.

7.2.2 Investigations into Sugar Ring Reduction

With the glycosidic bond in place, our attention focused towards the reduction of the appended sugar moiety in glycoside **4**. Two functional group manipulations were required in order to reveal the necessary functionality in the final glycoside unit **5** (Scheme 142).



Scheme 142: Functional Group Interconversion of Glycoside **5** to Glycoside **4**.

Reduction of the double bond and the ketone functionality of glycoside **4** necessitated chemoselective transformations to avoid the reduction of the benzylic ketones at C-6 and C-11. Additionally, high stereoselectivity was required for the reduction of the sugar ketone to provide the desired *syn* relationship between the C-4' alcohol and the C-5' methyl in the final glycoside unit (Scheme 142).

7.2.3 Chemoselective Reduction Strategy

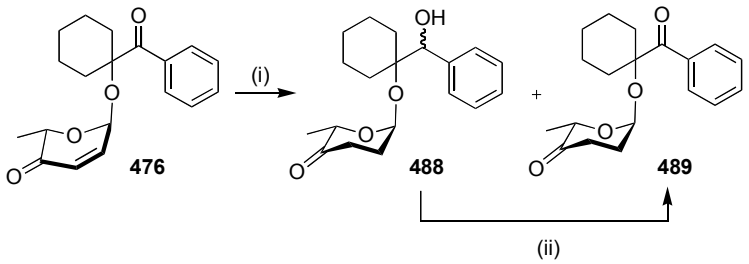
We envisaged that reduction of the sugar double bond in glycoside **4**, prior to ketone reduction would result in a distinct difference in reactivity between the benzylic ketones and the sugar ring ketone in the resulting product **485**, to allow for a successful chemoselective transformation (Figure 16).



Figure 16: Comparing Ketone Reactivities in Glycosides **4** and **485**.

7.2.3.1 Investigations into Double Bond Reduction

Due to limited quantities of glycoside **4** an initial set of experiments were conducted on model system **476**. Hydrogenation was employed as a selective and mild method for the reduction to the saturated glycoside **489** (Scheme 143).

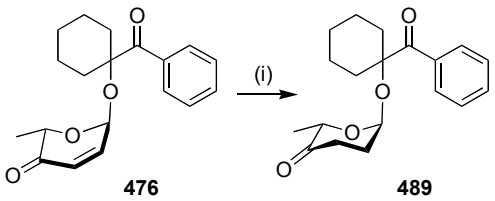


Reagents and Conditions: (i) H_2, 10% Pd/C, EtOAc, 1 h, **488** = 58% and **489** = 28%; (ii) DMP, CH_2Cl_2, 0 °C, 1 h, 81%.

Scheme 143: Hydrogenation of **476** Over Palladium on Charcoal.

Subjecting glycoside **476** to classical hydrogenative conditions, for 1 h at room temperature afforded over reduction to alcohol **488** as the major product of the reaction in 58% yield and gave the desired product **489** in only 28% yield (Scheme 143). Nevertheless, the undesired alcohol **488** could be easily oxidised using DMP in dichloromethane, to provide ketone **489** in 84% overall yield.

The use of an additional oxidation step however was not a desirable option for our synthesis and consequently an alternative procedure was sought. A recent protocol described by Sajiki and co-workers described the successful use of diphenyl sulfide and palladium on charcoal as a poisoned catalyst system for the chemoselective hydrogenation of double bonds.[224] Application of this methodology to glycoside **476** provided ketone **489** in 89% yield; moreover, no over reduction to alcohol **488** was detected (Scheme 144).

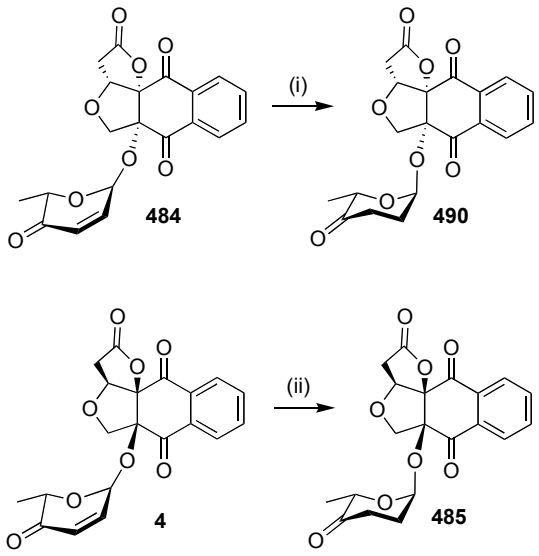


Reagents and Conditions: (i) H_2, 10% Pd/C, Ph_2S, MeOH, 24 h, 89%.

Scheme 144: Synthesis of Ketone **489** Using a Poisoned Catalyst System.

At this stage, the identity of the diastereoisomers **484** and **4** had not been categorically proven by X-ray crystal analysis and as a result both diastereoisomers were taken forward in the subsequent reaction steps.

Subjecting glycosides **484** and **4** to the tested poisoned catalyst system for the chemoselective hydrogenation of the sugar ring double bonds provided ketones **490** and **485** in good yields with no detection of the over reduced products (Scheme 145).



Reagents and Conditions: (i) H_2, 10% Pd/C, Ph_2S, MeOH, 5 h, 87%; (ii) H_2, 10% Pd/C, Ph_2S, MeOH, 5 h, 83%.

Scheme 145: Reduction of glycosides **484** and **4** Under Poisoned Reaction Conditions.

Analysis of the ^{1}H NMR data for both diastereoisomers **490** and **485** indicated the reduction of the unsaturated C-2' and C-3' positions by the disappearance of the alkene signals in the 6.08-6.66 ppm region of the spectra and the appearance of the CH_2 signals at 1.89-2.42 ppm. A similar observation was found for the ^{13}C NMR spectra. Comparison of the ^{1}H NMR data for these compounds **490** and **485** to lactonamycin (**1**)[1] again showed similarities (Figure 17).

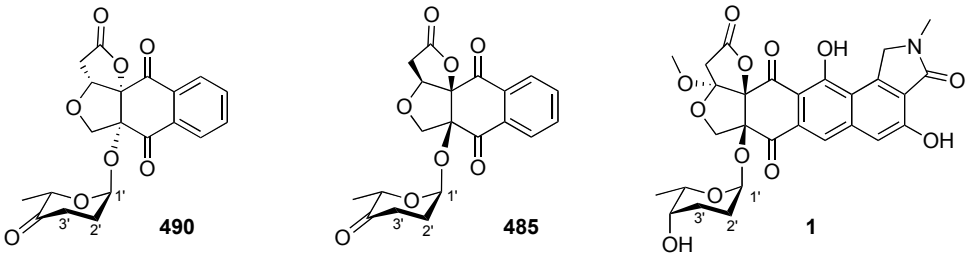


Figure 17: Comparison of the ^{1}H NMR shifts of lactonamycin (**1**)[1] and Diastereoisomers **490** and **485**.

X-ray quality crystals of ketone **490** were later obtained by crystallisation from *tert*-butyl methylether and the X-ray data obtained confirmed its structure (Figure 18).

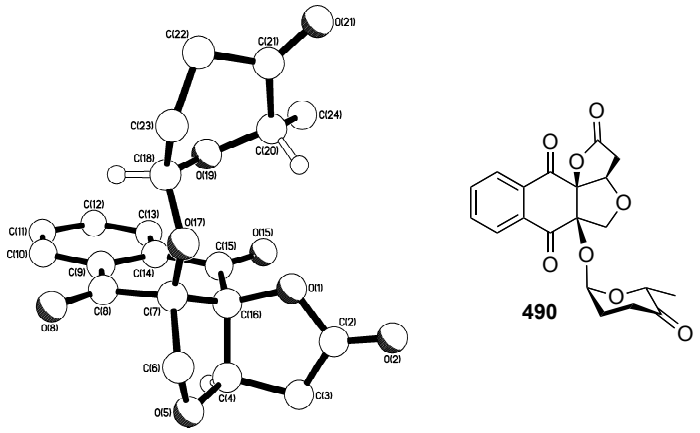
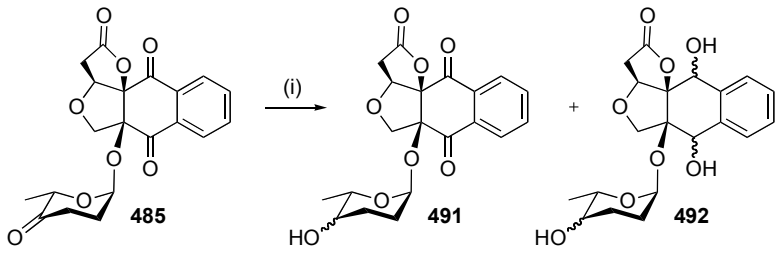


Figure 18: X-ray Crystal Structure of Ketone **490**.

Again, due to the amorphous nature of diastereoisomer **485**, X-ray data for this compound was not attainable.

7.2.3.2 Investigations into Ketone Reduction

The use of a chemoselective reducing agent was essential in order to avoid the additional reduction of the benzylic ketones in glycoside **485** (Scheme 146). We anticipated that by using bulky reducing agents or deactivated hydride donors we could tune the selectivity accordingly. A number of conditions were attempted and are summarised in Table 9.



Reagents and Conditions: (i) see Table 9.

Scheme 146: Reduction of Ketone **485**.

Table 9: Investigations into the Chemoselective Reduction of Ketone **485**.

Entry[a]	Reducing Agent	Eq.	T (°C)	Time (h)	Solvent	Result[b]
1	$Li(Ot\text{-}Bu)_3AlH$[c]	1.05	0	0.8	Et_2O/THF	Mixture of unidentifiable compounds
2	$Li(Ot\text{-}Bu)_3AlH$[c]	1.05	–78	3	CH_2Cl_2	Mixture of unidentifiable compounds and SM
3	$Li(Ot\text{-}Bu)_3AlH$[c]	2.0	–78	3	CH_2Cl_2	Mixture of unidentifiable compounds
4	$NaBH_4$	0.25	–78	2	CH_2Cl_2/MeOH	Mixture of unidentifiable compounds
5	LS-Selectride®[c]	1.1	–50	4	THF	Mixture of unidentifiable compounds and SM
6	$Na(OAc)_3BH$	1.1	60	24	THF	Starting material

[a]Typical reaction conditions were performed on a 25 mg scale. [b]Analysis carried out by crude ^{1}H NMR. [c]Reagent added as a 1M solution in THF.

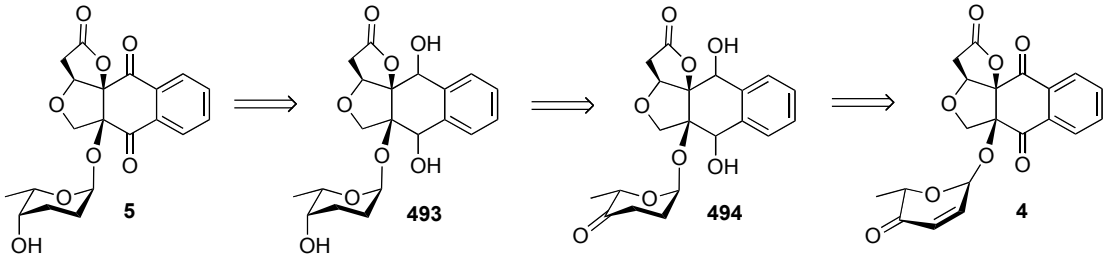
Dissapointingly, in all of the experiments conducted, the desired alcohol **491** was not detected by crude ^{1}H NMR analysis. Reduction with lithium-tri-(*tert*-butoxy)-aluminium hydride at both 0 and –78 °C gave a mixture of unidentifiable products as observed by multiple signals in ^{1}H NMR spectra (Table 9, entries 1 to 3). The mixture of compounds was attributed to the various reduction products as a result of the lack of chemoselectivity. The use of sodium borohydide at –78 °C also provided a mixture of unidentifiable products (Table 9, entry 4) and employing a bulkier reducing agent such as LS-selectride® also offered no improvements towards selectivity (Table 9, entry 5).

In light of these results, a finer balance between the reactivity of the reducing agent and the sugar ring ketone was required. It was thought that sodium triacetoxy borohydride would display chemoselectivity towards the aliphatic ring ketone as a result of the deactivation of the boron-hydrogen bond by the electron withdrawing nature of the acetate groups. However subjecting ketone **485** to sodium triacetoxy borohydride gave no reaction, even at elevated temperatures (Table 9, entry 6).

It was clear at this stage that an alternative strategy was required to obtain the correct oxidation level in the sugar unit of glycoside **485**. The forthcoming section describes the efforts made towards this goal.

7.2.4 Chemoselective Reduction-Oxidation Strategy

The use of a chemoselective reduction-oxidation strategy to provide glycoside **5** was proposed (Scheme 147). Using hydrogenative conditions for the simultaneous reduction of the benzylic ketones and the double bond of glycoside **4** to provide diol **494**, would allow for a simple stereoselective reduction of the aliphatic ketone functionality to triol **493**. Following these reductions, a chemoselective oxidation of the two benzylic alcohols would provide the desired compound **5**.

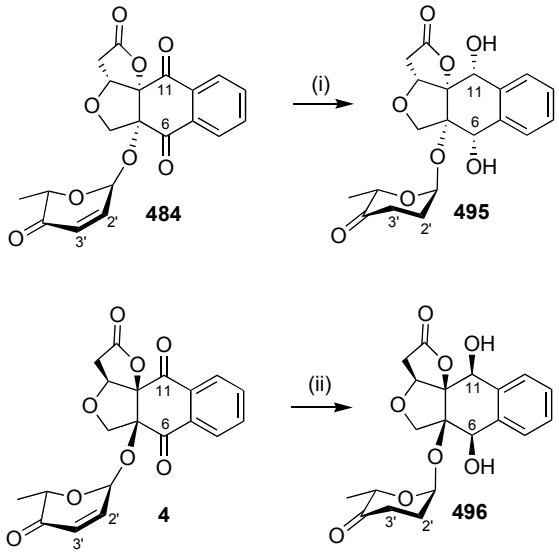


Scheme 147: Retrosynthetic Analysis of Glycoside **5** Using a Chemoselective Reduction-Oxidation Strategy.

7.2.4.1 Investigations into Reductions

Again, at this stage the identity of the diastereoisomeric glycosides **484** and **4** had not been fully corroborated by X-ray analysis, consequently both were taken through in the forthcoming reaction sequences.

Subjecting diastereomeric glycosides **484** and **4** to the hydrogenation conditions used previously (Scheme 143) brought about the reduction to diols **495** and **496** (Scheme 148). Their structure was assigned by the new CH_2 (H-2' and H-3'), alcohol and CH ether (H-6 and H-11) signals in the ^1H NMR spectra. In addition, evidence was also obtained by disappearance of the alkene, C-2' and C-3' signals and the carbonyl C-6 and C-11 signals in the ^{13}C NMR spectrum. Infrared spectroscopy also confirmed the existence of the alcohol functionalities.



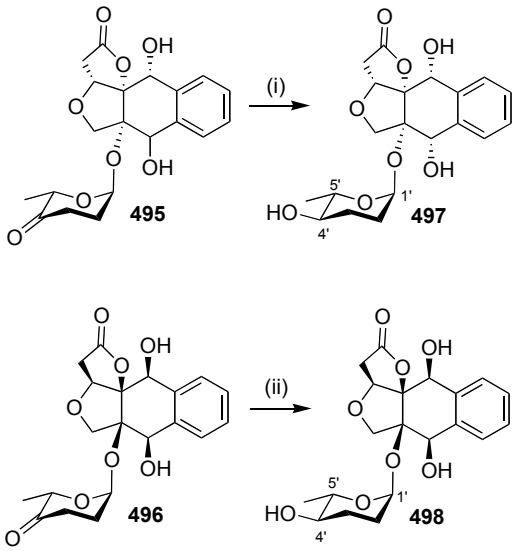
Reagents and Conditions: (i) H_2, 10% Pd/C, EtOAc, 14 h, 85%; (ii) H_2, 10% Pd/C, EtOAc, 14 h, 83%.

Scheme 148: Hydrogenation of Glycosides **484** and **4**.

Unexpectedly and to our delight, ^1H NMR analysis revealed only one set of signals for both reactions, indicating that the transformation had occurred with excellent

stereocontrol providing single diastereoisomers for the two diols **495** and **496**. We postulated that this was a result of the interaction of the palladium surface with the least hindered face of the ring systems, therefore bringing about a diastereoselective reduction. Accordingly, we proposed the stereochemistry for diols **495** and **496** as depicted in Scheme 148. NOESY correlations between the H-6 and H-11 protons confirmed the *syn* relative stereochemistry between the 6 and 11 positions, however the absolute stereochemistry could not be determined (Scheme 148).

With the required diols **495** and **496** in hand, experiments towards the stereoselective reduction of the sugar ketone were conducted. Reaction with sodium borohydride in a 1:1 mixture of methanol/dichloromethane at –78 °C gave triols **497** and **498** as single diastereoisomers as determined by the ^{1}H and ^{13}C NMR and spectra (Scheme 149).



Reagents and Conditions: (i) $NaBH_4$, $MeOH/CH_2Cl_2$, –78 °C, 30 min, 87%; (ii) $NaBH_4$, $MeOH/CH_2Cl_2$, –78 °C, 30 min, 77%.

Scheme 149: Sodium Borohydride Reduction of Triols **495** and **496**.

The preference for axial attack on 6-membered ring ketones by small nucleophiles, resulting in a highly stereochemical transformation, has been suggested to be a result of the "Felkin-Anh factor of antiperiplanarity between the incoming nucleophile and the adjacent axial hydrogens".[225] Taking this into consideration—and assuming the adoption of an axial configuration at C-1' due to the anomeric effect—an *anti* relationship between the C-4' alcohol and C-5' methyl in glycosides **497** and **498** was predicted (Figure 19).

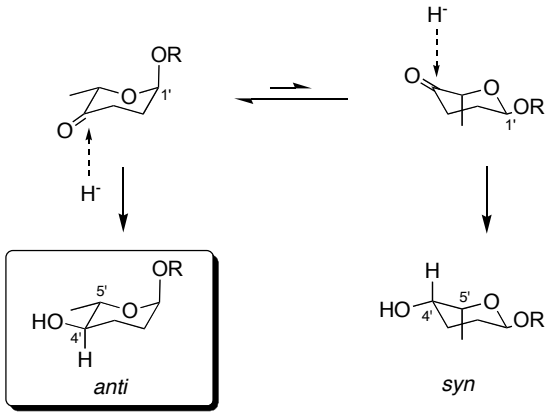


Figure 19: Prediction of *anti* Relationship Between C-4 and C-5.

NOESY experiments showed no correlation between the H-4' and H-5' ring protons and confirmed the *anti*-relationship between the two ring substituents. This was further corroborated by the large coupling constants of the antiperiplanar ring protons H-4' and H-5' (Figure 20).

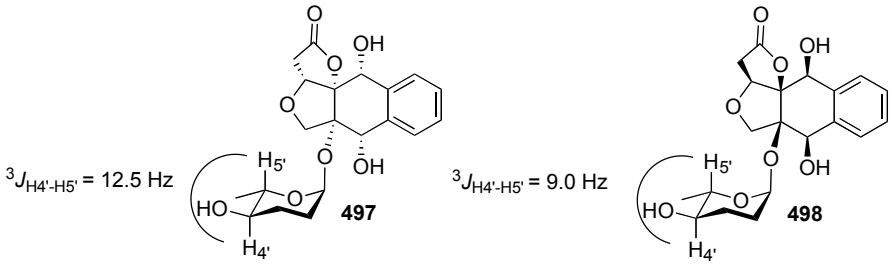


Figure 20: ^3J Coupling Constants of Triols **497** and **498**.

Conclusive evidence for the stereochemistry of diastereoisomer **498** was obtained in the form of an X-ray crystal structure and verified the proposed stereochemistry at the C-6, C-11 and H-4' positions. Furthermore, the stereochemistry (aside from the C-4' alcohol) matched that of lactonamycin (**1**) (Figure 21).

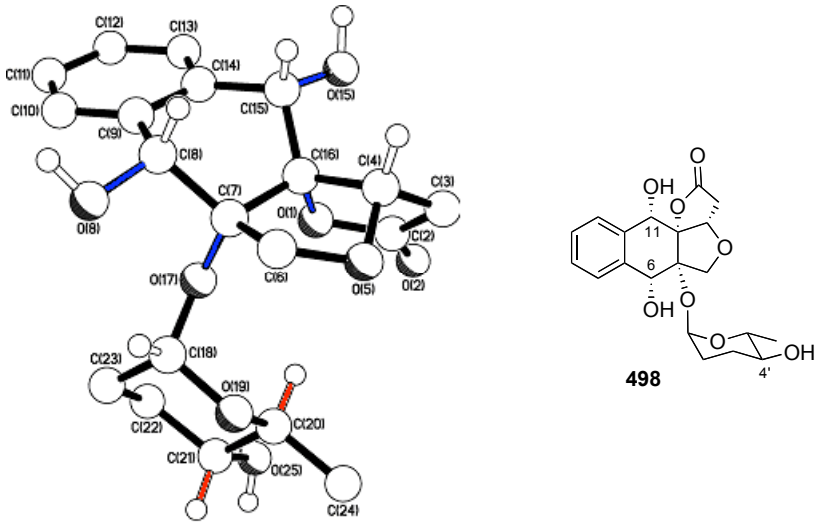


Figure 21: X-ray Crystal Structure of Triol **498**.

Whilst these results were encouraging, the stereochemistry of the sugar alcohol of triol **498** was nevertheless the opposite configuration to that of the axial alcohol in lactonamycin (**1**). Complementary to the preferential attack by small nucleophiles from an axial trajectory is the capacity for large nucleophiles to predominantly approach ring ketones equatorially (Figure 22).

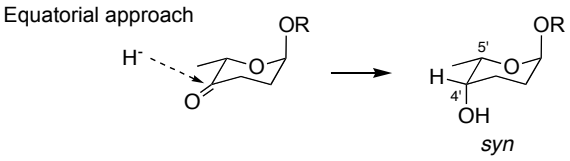
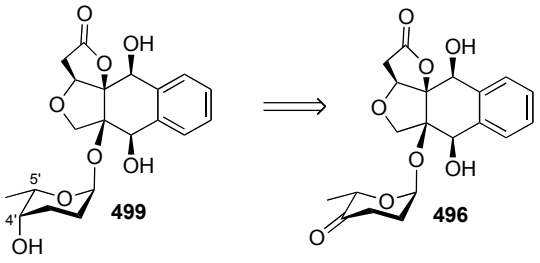


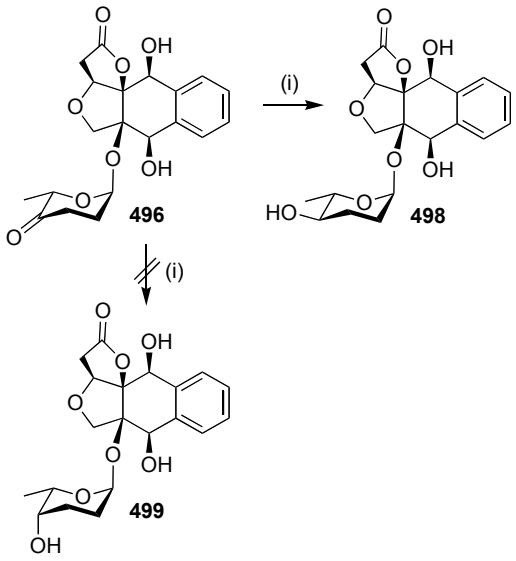
Figure 22: Predicted use of Bulky Reducing Agents to Provide a *syn* Relationship Between C-4' and C-5'.

Brown and co-workers have shown that highly hindered reducing agents such as LS-Selectride® almost always result in the formation of the axial alcohol.[226] Thus, it was proposed that bulkier reducing agents could provide the required *syn* configuration between the C-4' and C-5' substituents in triol **499** (Scheme 150).



Scheme 150: Retrosynthetic Analysis of Triol **499**.

To evaluate our approach, we first investigated the reduction with the classical bulky borohydride reducing agent, LS-Selectride® (Scheme 151, Table 10).



Reagents and Conditions: (i) see Table 10.

Scheme 151: Reduction of Ketone **496** with Bulky Reducing Agents.

Table 10: Investigations into the Diastereoselective Reduction of Ketone **496**.

Entry[a]	Reducing Agent	Solvent	**499** : **498**[b]
1	LS-Selectride®[c]	THF	0 : 1
2	LS-Selectride®[c]	CH_2Cl_2	0 : 1
3	Li(O*t*-Bu)$_3$AlH[c]	THF	0 : 1

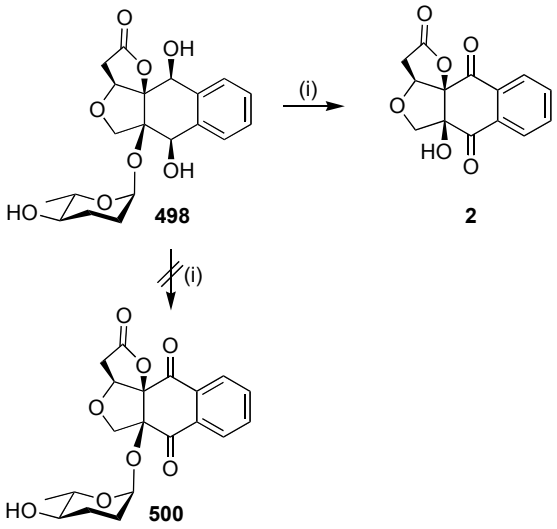
[a]Typical reaction conditions were performed on a 25 mg scale using 1.05 equivalents of reducing agent at –78 °C for 2 h. [b]Analysis carried out by crude ^{1}H NMR. [c]Reagent added as a 1M solution in THF.

The use of such reagents unfortunately showed no affinity towards the production of the *syn* isomer **499** and provided the *anti* isomer **498** as the only product with both LS-Selectride® and lithium tri-*tert*-butoxy aluminum hydride (Table 10, entries 1 to 3). This stereochemical outcome was attributed to the highly congested environment of the upper face of the sugar ring consequently preventing the approach of the bulky reducing agent from this trajectory. Given the outcome of both these experiments and that the reduction with sodium borohydride offered excellent stereocontrol albeit to the alternative *anti*-stereoisomer **498**, it was decided that the *anti*-isomer **498** would be taken through and converted at the end of the sequence to the corresponding *syn*-isomer **5** by the use of standard Mitsunobu chemistry.[145, 227]

7.2.4.2 Investigations into oxidation

At this stage, one final chemoselective oxidation step was required to complete the oxidation pattern of the western core of lactonamycin (**1**). Manganese(IV) dioxide is known[228, 229] to display high selectivity for the oxidation of benzylic and allylic alcohols and was consequently used in the subsequent transformation.

In general, manganese(IV) dioxide oxidations are conducted in solvents such as saturated hydrocarbons, chlorinated hydrocarbons, aromatic solvents and acetonitrile. The use of other solvents such as acetone, alcohols, dimethylsulfoxide or ethylacetate can significantly deactivate the manganese(IV) dioxide surface and tend not to be used. Choice of solvent was therefore limited and due to the high polarity of triol **498**, acetonitrile and dichloromethane were the only two solvents suitable for the oxidation (Scheme 152).



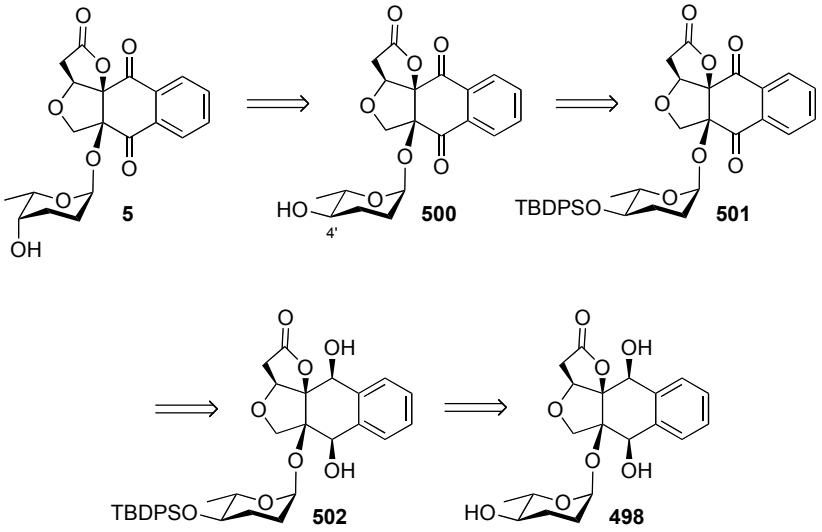
Reagents and Conditions: (i) MnO_2, CH_3CN or CH_2Cl_2, 25 °C, 16 h.

Scheme 152: Attempted Selective Benzylic Oxidation of Triol **498**.

When the manganese(IV) dioxide oxidation of triol **498** was conducted in either dichloromethane or acetonitrile a single product was isolated. Crude ^1H NMR analysis of both reaction mixtures indicated that in addition to benzylic oxidation, fragmentation of the sensitive glycosidic linkage was also taking place. As a result, the original ABCD alcohol **2** was isolated as the main product of both reactions (Scheme 152). Despite the mild reaction conditions employed in this procedure, the glycosidic bond was readily hydrolysed and it was thought that the manganese(II) species, generated during the

course of the reaction was acting as a mild Lewis acid, activating the glycosidic bond towards cleavage.

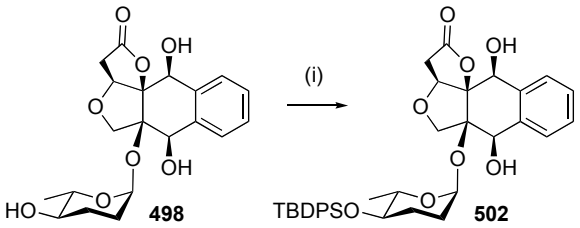
Whilst this was a disappointing result, an alternative route to the desired compound **5** *via* the mono-protected triol **502** was considered. By selectively protecting the sugar alcohol of triol **498**, the required oxidation level of the ABCD fragment could be achieved through the use of a simple oxidation step to give glycoside **501**. Deprotection of the silyl ether and inversion of the C-4' alcohol would then provide target compound **5** (Scheme 153).



Scheme 153: Retrosynthetic Analysis *via* Mono-Protected Triol **502**.

The main obstacle in undertaking this new approach was the successful differentiation between the secondary sugar alcohol and the secondary core ring alcohols during the chemoselective protection step. Although the differences were slight, it was hoped that the core ring alcohols—surrounded by a more sterically congested environment—would be sufficiently less reactive to remain unchanged during the protection process. The use of a bulky protecting reagent such as *tert*-butyl(diphenyl)silyl chloride was desirable for the success of such a transformation.

Consequently, triol **498** was treated with *tert*-butyl(diphenyl)silyl chloride in the presence of imidazole at 0 °C. An increase in temperature to 70 °C was required for the desired transformation to take place. The desired monoprotected triol **502** was isolated in a low yield 23%, with 67% recovery of starting material **498** (Scheme 154). No other protection products were detected by thin layer chromatography or by ^{1}H NMR analysis of the crude reaction mixture.

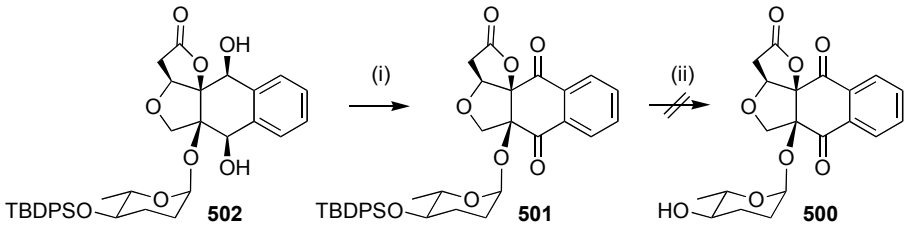


Reagents and Conditions: (i) TBDPSCl (1.2 eq), imid., DMF, 70 °C, 22 h, 23% and 69% recovered **498**.

Scheme 154: Mono-Protection of Triol **498**.

Increasing the number of equivalents of silyl chloride to 1.5 and lengthening the reaction times to 48 hours provided no improvements on the yield of the reaction. However, despite the low yields, these results were encouraging because they clearly showed that these substrates could be successfully mono-protected at the sugar alcohol, even at elevated temperatures.

Despite the low yields of the mono-protection step, it was decided to progress into the final steps of the investigation in order to validate the remaining chemistry. Accordingly, oxidation of mono-protected triol **502** by exposure to DMP in dichloromethane at 0 °C gave diketone **501** in excellent yield (Scheme 155).



Reagents and Conditions: (i) DMP, CH_2Cl_2, 0 °C, 20 min., 93% (ii) See Table 11.

Scheme 155: Synthesis of Diketone **501** and its Attempted Deprotection to Alcohol **500**.

At this late stage, the successful deprotection of the *tert*-butyl(diphenyl)silyl ether was essential for application of this route to the real system. At our disposal was a vast array of deprotecting agents, a large number of which were tested on substrate **501** (Table 11).

Table 11: Investigations into the Deprotection of *tert*-Butyl(diphenyl)silyl Ether **501**.

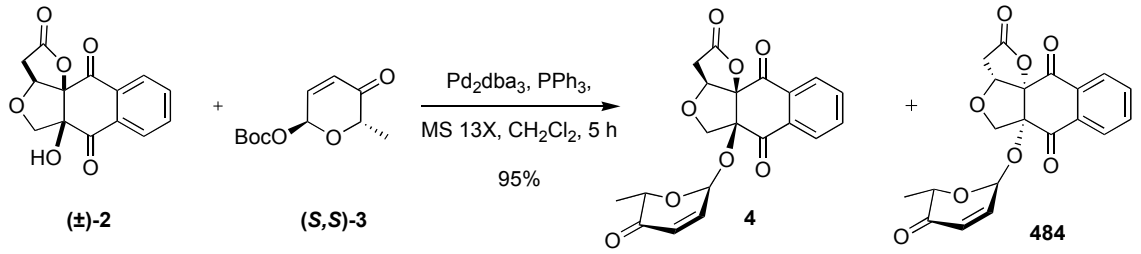
Entry[a]	Deprotecting Agent	Eq.	T (°C)	Time (h)	Solvent	Result[b]
1	TBAF[c]	2.0	23	1	THF	Mixture of unidentifiable compounds.
2	HF·Pyridine[d]	5.0	23	25	THF	ABCD alcohol **2**.
3	$H_2[SiF_6]$	1.2	23	3	CH_3CN/*t*-BuOH	ABCD alcohol **2**.
4	CsF	2.0	130	5	DMF	No reaction.
5	NH_4F	15.5	65	6	MeOH	No reaction.
6	NH_4F	15.5	130	5	DMF	No reaction.

[a]Typical reaction conditions were performed on a 15 mg scale. [b]Analysis carried out by crude ^1H NMR. [c]Reagent added as a 1M solution in THF. [d]Reaction mixture buffered with pyridine.

Using TBAF unfortunately led to decomposition of the starting material **501**, presumably due to the strongly basic conditions, and provided a mixture of unidentifiable products by crude ^{1}H NMR analysis (Table 11, entry 1). The hydrogen fluoride pyridine complex was used and buffered with extra pyridine to avoid cleavage of the glycoside linkage, unfortunately, the conditions were nevertheless too acidic and ABCD alcohol **2** was found to be the main product of the reaction (Table 11, entry 2). The same observation was also found with hexafluorosilicic acid (Table 11, entry 3). It was hoped that the use of fluoride salts would avoid the cleavage of glycosidic bond. Unfortunately, both reaction with cesium fluoride and ammonium fluoride at elevated temperatures resulted in complete recovery of starting material **501** (Table 11, entries 4 to 6). Due to lack of material and limited time, no further investigations into the deprotection or into the use of alternative protecting groups were conducted.

7.3 Conclusions and Future Work

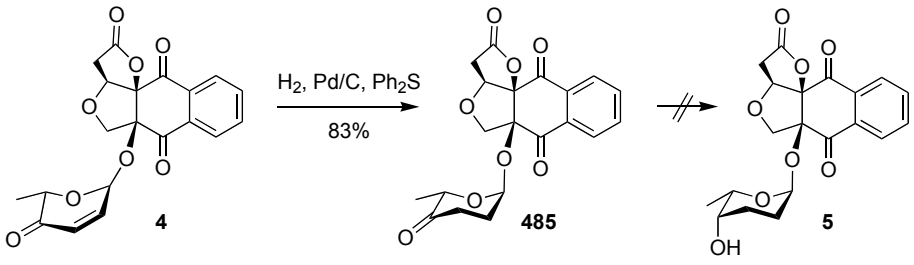
As part of the studies towards the total synthesis of lactonamycin (**1**), this thesis has shown that the use of molecular sieves 13X—for the application of O'Doherty's palladium catalysed *O*-allylation reaction with pyranone **(±)-3**—is essential for the successful coupling to hindered alcohols such as ABCD alcohol **(±)-2**. The synthesis of glycosides **4** and **484**, using these modified reaction conditions was carried out in excellent yields and selectivities (Scheme 156).



Scheme 156: Glycosidation of ABCD alcohol **(±)-2** with pyranone **(*S*,*S*)-3** based on a modified version of the O'Doherty glycosidation.

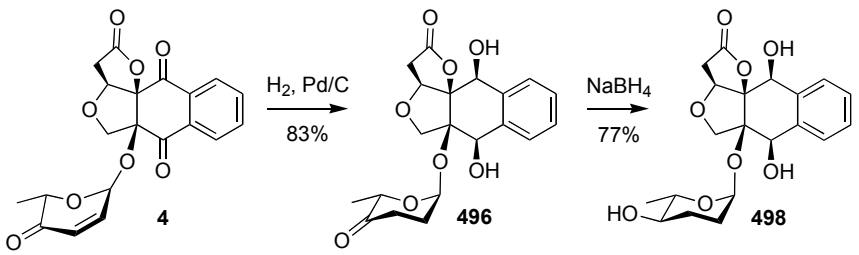
Crucially, separation of both diastereoisomers could be achieved by crystallisation of diastereoisomer **484** from *tert*-butyl methylether. Their tentative assignment was conducted by comparison to the ^{1}H and ^{13}C NMR spectra of lactonamycin (**1**)[1] and was later confirmed by the X-ray crystal structures of glycosides **484** and **490** and triol **498**.

Chemoselective reduction of the sugar double bond of glycoside **4** was achieved using poisoned hydrogenative reduction conditions with palladium on charcoal to provide glycosides **485** in excellent yield. Unfortunately, the chemoselective reduction of glycoside **485** to target compound **5** was unsuccessful producing only a mixture of unidentifiable products (Scheme 157).



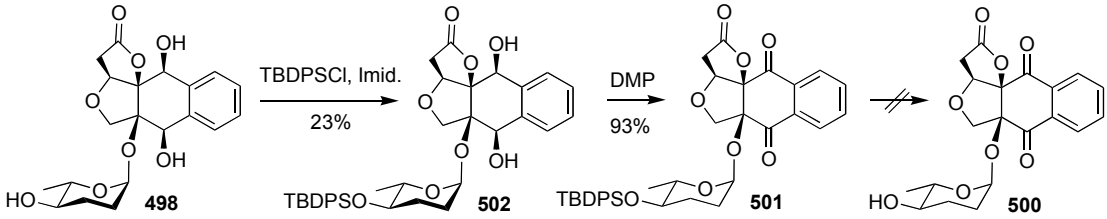
Scheme 157: Chemoselctive Reduction Strategy.

Our strategy therefore changed to allow for a chemoselective reduction-oxidation approach. Simultaneous reduction of the benzylic ketones and sugar double bond in glycoside **4** under hydrogenative reduction conditions fortuitously provided diol **496** as a single diastereoisomer. Subsequent reduction with sodium borohydride was also highly stereoselective and provided triol **498** in good yields (Scheme 158).



Scheme 158: Synthesis of Triol **498**.

The stereochemistry of the C-4' alcohol however, was opposite to that of the natural product **1**, several attempts to effect reduction to the *syn*-isomer **499** with bulkier reducing agents were unsuccessful. It was decided therefore, to carry forward the *anti* diastereoisomer **498**, and alter its stereochemistry at the end of the sequence to the corresponding *syn*-alcohol **5** by the use of Mitsunobu chemistry.[144, 145] Chemoselective oxidation of the triol **498** proved problematic however and provided the ABCD alcohol **2** exclusively after work up. On the other hand, the chemoselective protection of triol **498** with *tert*-butyl(diphenyl)silyl chloride at 70 °C was successful, despite major recovery of starting material **498** (Scheme 159). The future use of additives such as sodium bromide, sodium iodide or silver nitrate to activate the silylating agent may provide the required reactivity to achieve complete conversion.



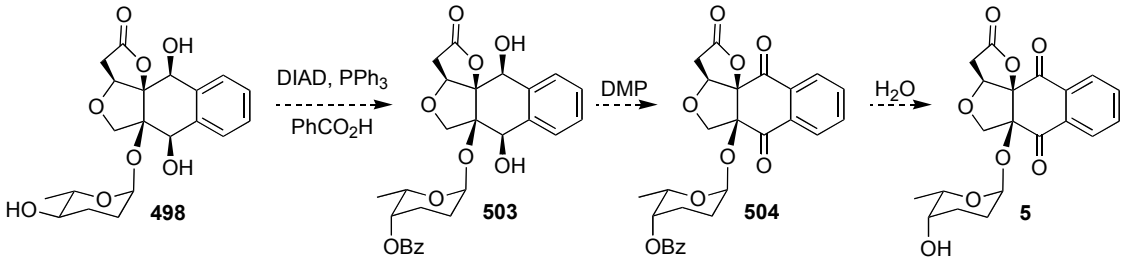
Scheme 159: Attempted Synthesis of Alcohol **500**.

Oxidation of silyl ether **502** ether using DMP proceeded smoothly to provide diketone **501** in excellent yield, however its deprotection to the final glycoside **500** could not be effected (Scheme 159).

Decomposition or cleavage to the ABCD alcohol **2** was observed when using strongly basic or acidic conditions respectively and no reaction was observed with either ammonium fluoride or cesium fluoride. It might be possible to activate the reactivity of the fluoride ions through the use of nonpolar protic solvents such as *tert*-butanol. In a recent publication, Kim and co-workers[230] described the greatly enhanced reactivity of alkali metal fluorides when using *tert* alcohols as the reaction medium as opposed to using conventional dipolar aprotic solvents. They described this effect as a result of the effective hydrogen bonding of the *tert*-alcohol solvent with the fluoride ion, therefore reducing the strength of the ionic bonding of the alkali metal fluorides. It may therefore be possible to increase the reactivity towards deprotection to alcohol **500** through the use of *tert* butanol as solvent.

On the other hand, the use of an alternative protecting group for the chemoselective protection of triol **498** may be required. The use of protecting groups such as *tert* butyl dimethyl silyl or triisopropyl silyl ether may offer a means to improving the yield of the mono-protection step since these groups are sterically less congested. In addition, the deprotection of such protecting groups may be conducted successfully under the conditions described in Table 11.

Alternatively, the use of a Mitsunobu reaction[144, 145] with triol **498** could potentially provide a chemoselective process to combine the protection and inversion steps (Scheme 160). If the chemoselective Mitsunobu reaction were successful, oxidation of the benzylic positions followed by hydrolysis of the benzoate ester **504** would provide the desired glycoside **5**.



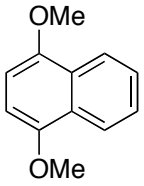
Scheme 160: Using a Mitsunobu Reaction for the Selective Protection of Triol **498**.

Overall, the use of a modified version of O'Doherty's glycosidation protocol has been investigated and optimised using the ABCD model system **(±)-2** of lactonamycin (**1**). Further work is required in order to reveal the final functionality on the sugar unit of glycoside **5**.

Chapter 8: Experimental Section

Melting points were obtained on a Reichert-Thermovar melting point apparatus and are uncorrected. Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100 mL. Infrared spectra were recorded on a Unicam FTIR spectrometer with automated background subtraction. Samples were prepared as thin films on sodium chloride plates. Reported absorptions are strong or medium strength unless stated otherwise and given in wavenumbers (cm^{-1}). ^{1}H NMR spectra were recorded on a Bruker DRX-300 or DRX-400 spectrometer operating at 300 or 400 MHz respectively or an AM 500 spectrometer operating at 500 MHz. ^{13}C NMR spectra were recorded on a Bruker DRX-300 or DRX-400 spectrometer operating at 75 or 100 MHz respectively or an AM 500 spectrometer operating at 125 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to a residual solvent peak. Coupling constants (*J*) are quoted in Hertz (Hz) to the nearest 0.5 Hz. Spectra recorded at 100 or 125 MHz (13C NMR) and 400 or 500 MHz (1H NMR) were carried out by the Imperial College London Department of Chemistry NMR Service. Low and high resolution mass spectrometry (EI, CI, FAB) were recorded by the Imperial College London Department of Chemistry Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. Elemental analyses were determined by the University of North London Analytical Service. All manipulations of air or moisture sensitive materials were carried out in oven or flame dried glassware under an inert atmosphere of nitrogen. Solvents were distilled from CaH_2 (dichloromethane, toluene, triethylamine, pyridine, *n*-hexane), Na/Ph_2CO (tetrahydrofuran, diethyl ether) or obtained as dry or anhydrous from Aldrich Chemical Company (*N*,*N*-dimethylformamide, acetonitrile) or BDH (ethanol). Other solvents and all reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All flash and dry flash column chromatography was carried out on BDH silica gel 60, particle size 40-63 mm unless otherwise stated. Thin layer chromatography (TLC) was performed on pre-coated aluminium backed or glass backed plates (Merck Kieselgel 60 F254), and visualised with ultraviolet light (254 nm) or potassium permanganate ($KMnO_4$), vanillin or anisaldehyde stains as deemed appropriate.

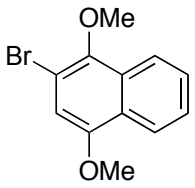
1,4-Dimethoxy-naphthalene[123] (241)



To a solution of 1,4-naphthoquinone (**240**) (5.00 g, 31.6 mmol, 1.0 eq) in MeOH (100 mL), was added $SnCl_2$ (9.35 g, 49.3 mmol, 1.6 eq). HCl gas was bubbled through the stirred reaction mixture for 1 h and heated at reflux for 18 h. The solution was cooled and the pink solid collected by filtration and washed with cold MeOH (50 mL) to give pale pink crystals (2.77 g, 47%). The remaining solution was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% CH_2Cl_2/Petroleum ether) to give naphthalene **241** as white crystals (1.87 g, 31%);

M.p. (MeOH) 86-87 °C [lit.[123] m.p. 86-87 °C]; R_f 0.72 (30% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 6H, OCH_3), 6.70 (s, 2H, ArH), 7.53 (dd, 2H, *J* = 6.5, 3.5 Hz, ArH), 8.25 (dd, 2H, *J* = 6.5, 3.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 103.3, 121.9, 126.0, 126.4, 149.6.

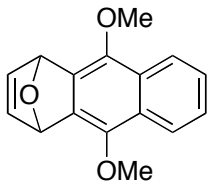
2-Bromo-1,4-dimethoxy-naphthalene[123] (233)



To a solution of 1,4-dimethoxy naphthalene (**241**) (2.68 g, 14.2 mmol, 1.0 eq) and iron powder (15 mg, 0.25 mmol, 1.7 mol%) in CH_2Cl_2 (40 mL) under N_2 was added drop-wise, over an hour, a solution of bromine (730 μL, 14.2 mmol, 1.0 eq) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 1 h, and then the brown mixture poured into H_2O (100 mL). The organic layer was separated and the aqueous portion extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with 10% aqueous KOH solution (3 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% CH_2Cl_2/Petroleum ether) to give bromide **233** as a pale yellow oil (3.60 g, 95%);

R_f 0.66 (15% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 6.89 (s, 1H, ArH), 7.47-7.59 (m, 2H, ArH), 8.06-8.10 (m, 1H, ArH), 8.20-8.23 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 61.3, 107.7, 111.8, 121.7, 122.5, 125.6, 125.7, 127.3, 128.8, 146.6, 152.1.

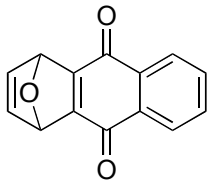
1,4-Dihydro-9,10-dimethoxy-1,4-epoxyanthracene[123] (234)



To a solution of bromide **233** (2.71 g, 10.1 mmol, 1.0 eq) in THF (20 mL) was added $NaNH_2$ (7.92 g, 20.3 mmol, 20 eq) and freshly distilled furan (37.0 mL, 505 mmol, 50 eq). The reaction mixture was stirred at 55 °C for 20 h after which H_2O (50 mL) was added slowly. The organic layer was separated and the aqueous portions extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% CH_2Cl_2/Petroleum ether) to give adduct **234** as a tan coloured solid (2.08 g, 81%);

M.p. (Et_2O/Petroleum ether) 89-91 °C [lit.[123] m.p. 92-93 °C]; R_f 0.17 (15% EtOAc/ Petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 6H, CH_3), 6.15 (*app*. s, 2H, OCH), 6.97 (*app*. s, 2H, CH=CH), 7.46-7.49 (m, 2H, ArH), 8.02-8.06 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.3, 80.4, 122.5, 126.4, 128.0, 128.4, 140.9, 144.2.

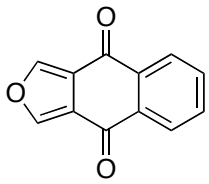
1,4-Dihydro-1,4-epoxyanthracene-9,10-dione[123] (235)



To a solution of adduct **234** (2.05 g, 8.05 mmol, 1.0 eq) in CH_3CN (45 mL) and H_2O (12 mL) was added AgO (4.29 g, 35.0 mmol, 4.3 eq) and HNO_3 (0.13 mL, 1.80 mmol, 0.2 eq). After the solution turned orange the reaction mixture was diluted with CH_2Cl_2 (25 mL) and H_2O (20 mL). The organic layer was separated and the aqueous portion extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with H_2O (3 x 15 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give naphthoquinone **235** as an orange solid (85 mg, 5%);

M.p. ($CHCl_3$/Petroleum ether) 178-180 °C [lit.[123] m.p. 180-181 °C]; R_f 0.43 (10% EtOAc /Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (*app*. s, 2H, CH), 7.18 (*app*. s, 2H, CH=CH), 7.69 (dd, 2H, *J* = 5.5, 3.5 Hz, ArH), 8.02 (dd, 2H, *J* = 5.5, 3.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.3, 126.5, 132.5, 133.9, 143.3, 163.0, 180.5.

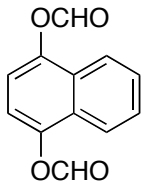
Naphtho[2,3-c]furan-4,9-dione[123] (237)



A solution of naphthoquinone **235** (80 mg, 0.38 mmol, 1.0 eq) and 3,6-di(2'-pyridyl)-5-tetrazine (70 mg, 0.38 mmol, 1.0 eq) in THF (2 mL) under N_2 was heated at reflux for 12 h. The mixture was cooled, poured into $CHCl_3$ (20 mL) and washed with 1M HCl (3 x 10 mL) and water (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (15% EtOAc/Petroleum ether) to give furan **237** as a brown crystalline solid (63 mg, 82%):

M.p. ($CHCl_3$/Petroleum ether) 222-237 °C dec. [lit.[123] m.p. 217-238 °C dec.]; R_f 0.32 (30% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, 2H, *J* = 6.0, 3.5 Hz, ArH), 8.23 (s, 2H, OCH), 8.31 (dd, 2H, *J* = 6.0, 3.5 Hz, ArH).

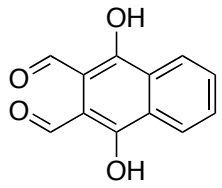
Naphthalene-1,4-diformate (250)



To a solution of 1,4-dihydroxynaphthalene (**245**) (1.0 g, 6.50 mmol, 1.0 eq) and formic acid (0.58 mL, 15.0 mmol, 2.4 eq) in acetone (20 mL) was added DCC (3.60 g, 17.5 mmol, 1.0 eq). The reaction mixture was stirred at 30 °C for 45 min, cooled to rt, filtered and concentrated under reduced pressure to give **250** as a black viscous oil which was used crude without further purification (1.95 g, 90%);

R_f 0.67 (30% EtOAc/Petroleum ether); IR (film) ν_{max} 1742, 1599, 1463, 1390, 1262, 1215, 1154, 1115, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 2H, ArH), 7.61 (dd, 2H, *J* = 6.5, 3.5 Hz, ArH), 7.97 (dd, 2H, *J* = 6.5, 3.5 Hz, ArH), 8.50 (s, 2H, OCHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.2, 117.1, 121.6, 127.8, 144.0, 159.3 MS *m/z* (CI; NH_3); 234 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{12}H_8O_4$ $[M+NH_4]^+$; 234.0766, found; 234.0766.

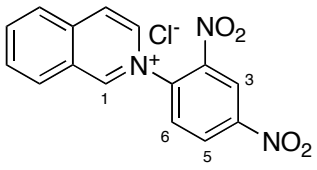
1,4-Dihydroxy-naphthalene-2,3-dicarbaldehyde (246)



To a solution of diformate **250** (200 mg, 0.93 mmol, 1.0 eq) in 1,2-DCE (10 mL) at –20 °C was added slowly BBr_3 (1.10 mL, 1.11 mmol, 1.2 eq). The reaction mixture was allowed to warm up to 30 °C over 30 min and stirred for 21 h. The reaction mixture was cooled to 0 °C and diluted with MeOH (5 mL) and H_2O (5 mL) and concentrated under reduced pressure to half the volume. The aqueous mixture was extracted with Et_2O (2 x 25 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure to give **246** as a brown oil which was used crude without further purification (46 mg, 23%);

R_f 0.38 (30% EtOAc/Petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, 2H, *J* = 6.5, 3.5 Hz, ArH), 8.13 (dd, 2H, *J* = 6.5, 3.5 Hz, ArH), 9.70 (s, 2H, CHO), 12.19 (s, 2H, OH).

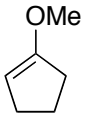
2-(2,4-Dinitro-phenyl)-isoquinolinium chloride[135] (258)



A mixture of finely powdered 1-chloro-2,4-dinitrobenzene (**257**) (6.00 g, 29.6 mmol, 1.0 eq) and isoquinoline (**256**) (3.48 mL, 29.6 mmol, 1.0 eq) was heated to 80 °C. After stirring for 15 min, acetone (2 mL) was added, and the reaction mixture heated at reflux for 2 h. The precipitate was collected, washed with acetone (3 x 25 mL) and crystallised from MeOH/EtOAc/hexane to give dinitro-phenyl salt **258** as pale yellow crystals (6.64 g, 66%);

M.p. (MeOH/EtOAc/hexane) 205-207 °C [lit.[135] m.p. 199-200 °C]; ^{1}H NMR (300 MHz, d_6-DMSO,) δ 8.21 (t, 1H, *J* = 8.0 Hz, ArH), 8.45 (t, 1H, *J* = 8.0 Hz, ArH), 8.55 (d, 1H, *J* = 8.5 Hz, H_5), 8.60 (d, 1H, *J* = 8.5 Hz, H_6), 8.68 (d, 1H, *J* = 8.0 Hz, ArH), 8.88 (d, 1H, *J* = 7.0 Hz, ArH), 9.04 (dd, 1H, *J* = 8.0, 2.5 Hz, ArH), 9.15-9.16 (m, 2H, ArH and H_3), 10.71 (s, 1H, H_1); ^{13}C NMR (75 MHz, d_6-DMSO) δ 122.1, 125.8, 127.2, 128.2, 130.8, 132.2, 132.4, 132.7, 136.0, 138.5, 139.4, 139.5, 143.7, 149.5, 152.8.

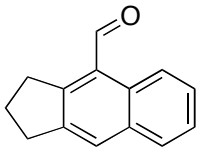
1-Methoxy-cyclopentene[136] (259)



To a stirred mixture of cyclopentanone (25.1 mL, 285 mmol, 1.0 eq) and trimethylorthoformate (34.1 mL, 310 mmol, 1.1 eq) was added *p*-toluenesulfonic acid monohydrate (270 mg, 1.42 mmol, 0.5 mol%). After stirring at rt for 48 h, the reaction mixture was distilled at atmospheric pressure to give cylcopentene **259** as a colourless liquid (18.61 g, 66%);

B.p. 111 °C [b.p. lit.[136] 112.5-113.5 °C]; R_f 0.79 (30% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78-1.98 (m, 2H, CH_2), 2.33-2.24 (m, 4H, CH_2), 3.56 (s, 3H, OCH_3), 4.41 (*br-s*, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 28.8, 31.7, 56.5, 93.2, 161.0.

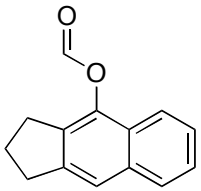
2,3-Dihydro-1H-cyclopenta[b]naphthalene-4-carbaldehyde[133, 231] (261)



To a stirred suspension of DNP salt **258** (2.00 g, 6.03 mmol, 1.0 eq) and $CaCO_3$ (3.38 g, 33.8 mmol, 5.6 eq) in MeOH (15 mL) was added 1-methoxy-1-cyclopentene (**259**) (6.8 g, 69.3 mmol, 11.5 eq). After stirring at rt for 24 h, the resulting suspension was filtered through celite, diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the resulting residue stirred at 35 °C with Amberlyst-15 resin (1.2 g) in THF (50 mL) and H_2O (2 mL) for 21 h. After filtration and concentration under reduced pressure, the residue was added immediately in THF (20 mL) to a solution of NaOH (1.6 g) in H_2O (16 mL) and MeOH (40 mL) and heated at reflux for 5 min. The dark red solution was concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (30% Et_2O/Petroleum ether) to give naphthalene **261** as a red solid (505 mg, 43%);

M.p. (EtOAc/Petroleum ether) 120 °C [lit.[133, 231] m.p. 121 °C]; R_f 0.51 (15% EtOAc /Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (*app*. quin., 2H, *J* = 7.5 Hz, CH_2), 3.09 (t, 2H, *J* = 7.5 Hz, CH_2), 3.47 (t, 2H, *J* = 7.5 Hz, CH_2), 7.50 (t, 1H, *J* = 8.0 Hz, ArH), 7.60 (t, 1H, *J* = 8.0 Hz, ArH), 7.82 (d, 1H, *J* = 8.0 Hz, ArH), 7.91 (s, 1H, ArH), 9.09 (d, 1H, *J* = 8.0 Hz, ArH), 10.85 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 31.7, 31.8, 124.3, 125.6, 126.0, 127.9, 128.2, 129.5, 130.4, 133.3, 143.5, 152.0, 192.5.

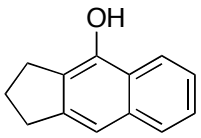
Formic acid 2,3-dihydro-1H-cyclopenta[b]naphthalen-4-yl ester[134] (262)



To a solution of naphthaldehyde **261** (355 mg, 1.80 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) under N_2 was added *m*-CPBA (625 mg, 3.60 mmol, 2.0 eq). The reaction mixture was stirred at rt for 24 h, KF (420 mg, 7.2 mmol, 4.0 eq) was added and the reaction mixture stirred for a further 5 h. The solid residue was removed by filtration and washed with CH_2Cl_2 (40 mL). The yellow solution was concentrated under reduced pressure to give formate **262** as a yellow solid that required no further purification (160 mg, 99%);

M.p. (EtOAc/Petroleum ether) 121-123 °C; R_f 0.51 (15% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (*app.* quin., 2H, *J* = 7.5 Hz, H_6), 2.95 (t, 2H, *J* = 7.5 Hz, CH_2), 3.08 (t, 2H, *J* = 7.5 Hz, CH_2), 7.45-7.46 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.83-7.86 (m, 2H, ArH), 8.45 (s, 1H, OCHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 30.1, 33.1, 120.6, 121.0, 125.8, 126.2, 126.3, 133.4, 134.0, 134.5, 140.9, 144.4, 159.1.

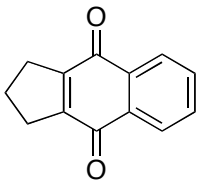
2,3-Dihydro-1H-cyclopenta[b]naphthalen-4-ol[134] **(263)**



To a solution of formate ester **262** (375 mg, 1.80 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) was added basic aluminium oxide (1.0 g). The reaction mixture was allowed to stir at rt for 24 h. The yellow solution was filtered, washed with 50% CH_2Cl_2/MeOH (3 x 20 mL), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give **263** as a red solid (225 mg, 69%);

M.p. (EtOAc/Petroleum ether) 93-95 °C [lit.[134] m.p. 92-99 °C]; R_f 0.52 (15% EtOAc /Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (*app*. quin., 2H, *J* = 7.5 Hz, CH_2), 2.95 (t, 2H, *J* = 7.5 Hz, CH_2), 3.06 (t, 2H, *J* = 7.5 Hz, CH_2), 5.26 (*br-s*, 1H, OH), 7.30 (s, 1H, ArH), 7.39-7.42 (m, 2H, ArH), 7.72-7.74 (m, 1H, ArH), 8.08-8.12 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.01, 28.4, 33.2, 115.0, 121.1, 124.2, 125.5, 126.3, 127.4, 133.5, 144.5, 146.5, 151.3.

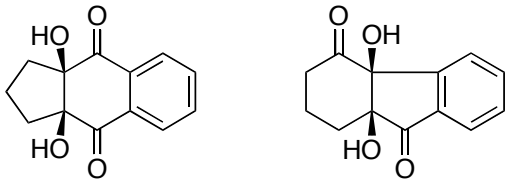
2,3-Dihydro-1H-cyclopenta[b]naphthalene-1,4-dione[134] (255)



To a solution of naphthol **263** (225 mg, 1.20 mmol, 1.0 eq) in THF (10 mL) was added salcomine (200 mg, 0.60 mmol, 0.5 eq). The reaction mixture was purged with O_2 for 10 min and allowed to stir under an atmosphere of O_2 for 3 h. The solution was concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (100% CH_2Cl_2) to give naphthoquinone **255** as a bright yellow crystalline solid (189 mg, 78%);

M.p. (EtOAc) 162-164 °C [lit.[134] m.p. 163-165 °C]; R_f 0.46 (15% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (quin., 2H, *J* = 7.5 Hz, CH_2), 2.89 (t, 4H, *J* = 7.5 Hz, CH_2), 7.64 (dd, 2H, *J* = 5.5, 3.5 Hz, ArH), 8.00 (dd, 2H, *J* = 5.5, 3.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 31.2, 126.2, 133.2, 133.4, 151.3, 183.9.

(±)-3a,9a-Dihydroxy-2,3,3a,9a-tetrahydro-1H-cyclopenta[*b*]naphthalene-4,9-dione (254) and (±)-4a,9a-Dihydroxy-2,3,4a,9a-tetrahydro-1H-fluorene-4,9-dione (264)



To a solution of naphthoquinone **255** (290 mg, 1.50 mmol, 1.0 eq) in acetone (12 mL) and H_2O (3 mL) was added NMO (260 mg, 2.20 mmol, 1.5 eq) and OsO_4 (370 μL, 2.5 % wt in *t*-BuOH, 2.5 mol%). The reaction mixture was stirred at rt for 18 h and diluted with aqueous Na_2SO_4 (2 mL). After 45 min the mixture was concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (30-40% EtOAc/Petroleum ether) to give diol **254** as a white solid (118 mg, 35%);

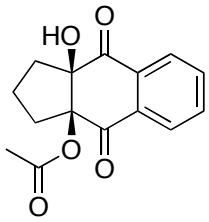
M.p. (EtOAc/Petroleum ether) 136-137 °C; R_f 0.35 (40% EtOAc/Petroleum ether); IR (film) ν_{max} 3424, 2952, 2924, 1715, 1598, 1196, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89-1.99 (m, 4H, CH_2), 2.28-2.36 (m, 2H, CH_2), 3.87 (s, 2H, OH), 7.76 (dd, 2H, *J* = 5.5, 3.5 Hz, ArH), 8.08 (d, 2H, *J* = 5.5, 3.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 34.2, 86.3, 127.8, 132.8, 135.1, 196.4; MS (CI; NH_3) *m/z* 250 $[M+NH_4]^+$, 232 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{13}H_{12}O_4$ $[M+H]^+$; 250.1079, found; 250.1078;

Further elution gave diol **264** as a white solid (146 mg, 43%);

M.p. (EtOAc/Petroleum ether) 141 °C; R_f 0.21 (40% EtOAc/Petroleum ether); IR (film) ν_{max} 3406, 2961, 2936, 2877, 1729, 1598, 1588, 1462, 1396, 1323, 1191, 1143, 1107, 1082, 948, 892, 770, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85-2.61 (m, 6H, CH_2), 3.67 (s, 1H, OH), 4.88 (s, 1H, OH), 7.23 (d, 1H, *J* = 7.5 Hz, ArH), 7.54 (dt, 1H, *J* = 7.5, 1.0 Hz, ArH), 7.65 (dt, 1H, *J* = 7.5, 1.0 Hz, ArH), 7.80 (d, 1H, *J* = 7.5 Hz, ArH); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 21.4, 32.8, 37.6, 80.9, 84.9, 124.6, 125.4, 131.3, 133.8, 136.3, 149.2, 204.2, 209.4; MS (CI; NH_3) *m/z* 250 $[M+NH_4]^+$, 232 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{13}H_{12}O_4$ $[M+NH_4]^+$; 250.1079, found; 250.1072; X-ray crystal data $C_{13}H_{12}O_4$, M = 232.23, orthorhombic, a = 8.9268(4) Å, b = 10.3780(4) Å, c = 23.4422(9) Å, α = 90°, β = 90°, γ = 90°, V = 2171.74(15) $Å^3$, Z = 8, D_C = 1.421 Mg/m^3, μ(Cu-Kα) = 0.106 mm^{-1}, T = 976 K, colourless blocks, 20077 independent measured reflections, 3751 independent observed reflections [F>4σ(F)], 162 parameters.

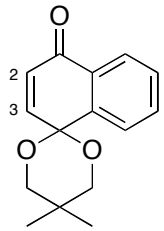
(±)-Acetic acid 9a-hydroxy-4,9-dioxo-1,2,3,4,9,9a-hexahydro-cyclopenta[*b*] naphthalen-3a-yl ester (253)



To a solution of diol **254** (118 mg, 0.50 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) was added pyridine (50.0 μL, 0.53 mmol, 1.05 eq) and DMAP (5 mg). The reaction mixture was allowed to stir at rt for 20 h after which H_2O (5 mL) was added. The aqueous mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give mono-acetate **253** as a white solid (127 mg, 91%);

M.p. (EtOAc/Petroleum ether) 110-113 °C; R_f 0.39 (30% EtOAc/Petroleum ether); IR (film) ν_{max} 3472, 2971, 2934, 2876, 1736, 1695, 1596, 1437, 1371, 1272, 1248, 1143, 1098, 1069, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97-2.02 (m, 4H, CH_2), 2.05 (s, 3H, $OCOCH_3$), 2.29-2.65 (m, 2H, CH_2), 4.18 (*br*-s, 1H, OH), 7.69-7.78 (m, 2H, ArH), 7.95-8.02 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 20.5, 37.3, 41.6, 82.2, 88.7, 127.0, 127.6, 133.2, 133.5, 134.3, 134.7, 171.5, 194.8, 197.6; MS (CI; NH_3) *m/z* 292 $[M+NH_4]^+$, 275 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{15}H_{14}O_5$ $[M+NH_4]^+$; 292.1185, found; 292.1184.

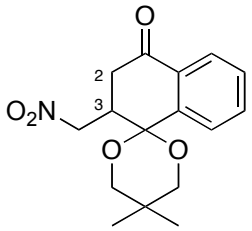
4,4-(2,2-Dimethyl-1,3-propylenedioxy)naphthalen-1(*4H*)-one[29] (271)



A solution of 4-methoxy-1-naphthol (**270**) (25.0 g, 144 mmol, 1.0 eq) in CH_2Cl_2 (350 mL) and THF (25 mL) was added *via* a dropping funnel to a mechanically stirred solution of 2,2-dimethyl-1,3-propandiol (85.0 g, 720 mmol, 5.0 eq) and PIFA (80.0 g, 173 mmol, 1.2 eq) in CH_2Cl_2 (600 mL) so as to maintain a temperature of 0 ± 5 °C. Cooling was removed and stirring continued for 1 h allowing the reaction mixture to warm to rt. Sat. aq. Na_2CO_3 (400 mL) was added and after 30 min of vigorous stirring the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure to half the volume and washed with sat. aq. Na_2CO_3 (300 mL), water (250 mL) and brine (250 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by crystallisation (20% EtOAc/Petroleum ether) to give mono-ketal **271** as a white crystalline solid (23.2 g, 66%);

M.p. (EtOAc/Petroleum ether); 138–140 °C [lit.[29] m.p. 139-141 °C]; R_f 0.45 (30%, EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.63 (d, 2H, *J* = 11.5 Hz, CH_2), 4.03 (d, 2H, *J* = 11.5 Hz, CH_2), 6.45 (d, 1H, *J* = 11.0 Hz, H_2), 7.49 (t, 1H, *J* = 7.0 Hz, ArH), 7.68 (t, 1H, *J* = 7.0 Hz, ArH), 7.78 (d, 1H, *J* = 11.0 Hz, H_3), 7.99 (d, 1H, *J* = 7.0 Hz, ArH), 8.05 (d, 1H, *J* = 7.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.6, 30.2, 71.9, 72.0, 90.5, 126.0, 126.8, 129.3, 129.4, 133.7, 137.4, 137.5, 142.3, 183.9.

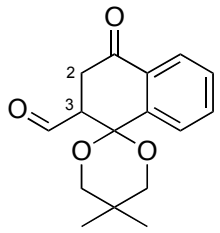
(±)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-nitromethyl-2,3-dihydronaphthalen-1(*2H*)-one[29] (272)



To a solution of mono-ketal **271** (30.0 g, 123 mmol, 1.0 eq) in MeOH (95 mL) was added $MeNO_2$ (47.0 mL, 850 mmol, 7.0 eq) followed by Et_3N (18.0 mL, 130 mmol, 1.1 eq) and the mixture stirred at rt for 3.5 h. The product crystallised from the reaction mixture and was filtered, air dried and re-crystallised from MeOH to give nitro compound **272** as off-white crystals (31.4 g, 83%);

M.p. (MeOH) 146–147 °C; [lit.[29] m.p. 146-147 °C] R_f 0.71 (30%, EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.70 (dd, 1H, *J* = 18.0, 1.0 Hz, H_2), 3.05 (dd, 1H, *J* = 18.0, 4.0 Hz, H_2), 3.56 (*app*. t, 2H, *J* = 11.5 Hz, CH_2), 3.78 (dd, 2H, *J* = 11.5, 5.5 Hz, CH_2), 4.04-4.07 (m, 2H, CH_2NO_2), 4.44-4.48 (m, 1H, H_3) 7.47 (dt, 1H, *J* = 7.5, 1.0 Hz, ArH), 7.64 (dt, 1H, *J* = 7.5, 1.0 Hz, ArH) 7.85 (d, 1H, *J* = 7.5 Hz, ArH), 7.95 (d, 1H, *J* = 7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.2, 30.1, 34.5, 37.6, 70.6, 71.7, 75.9, 95.7, 125.8, 127.0, 129.8, 131.1, 134.6, 140.8, 194.4.

(±)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-carbaldehyde-2,3-dihydronaphthalen-1(*2H*)-one[29] (273)

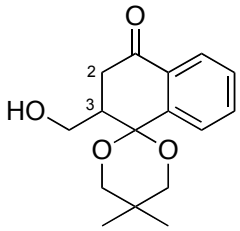


To a mechanically stirred slurry of nitro compound **272** (23.0 g, 75.0 mmol, 1.0 eq) in MeOH (300 mL) kept at 0 °C under N_2 was added a freshly prepared methanolic (480 mL) solution of KOH (4.75 g, 83.0 mmol, 1.1 eq) over 45 min. The resulting nitronate solution was stirred at 0 °C for 15 min and then a solution of $KMnO_4$ (8.0 g, 50.0 mmol, 0.7 eq) and $MgSO_4$ (6.70 g, 55.5 mmol, 0.7 eq) in H_2O (1.1 L) was added drop-wise, with vigorous stirring at a rate that maintained T = 0 °C ± 2 °C. The reaction mixture was stirred at 0 °C for 2 hours and then filtered through celite eluting with Et_2O (600 mL). The filtrate was reduced to half the volume, diluted with brine (300 mL) and the aqueous layer separated and extracted with a mixture of Et_2O and EtOAc (50%; 3 x 400 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure (bath temperature not permitted to exceed 35 °C) and the crude yellow crystals re-crystallised (EtOAc/Petroleum ether) to give aldehyde **273** as fine white needles (12.8 g, 62%);

M.p. (EtOAc/Petroleum ether) 144-145 °C; [lit.[29] m.p. 143-145 °C]; R_f 0.58 (40% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 2.80 (dd, 1H, *J* = 17.5, 5.0 Hz, H_2), 3.02 (dd, 1H, *J* = 17.5, 2.5 Hz, H_2), 3.58 (dd, 1H, *J* = 11.5, 2.5 Hz, CH_2), 3.76 (dd, 1H, *J* = 11.5, 2.5 Hz, CH_2), 3.78 (d, 1H, *J* = 11.5 Hz, CH_2), 4.09 (d, 1H, *J* = 11.5 Hz, CH_2), 4.19 (dd, 1H, *J* = 5.0, 2.5 Hz, H_3), 7.44 (dt, 1H, *J* = 8.0, 1.5 Hz, ArH), 7.62 (dt, 1H, *J* = 8.0, 1.5 Hz, ArH), 7.89 (dd, 1H, *J* = 8.0, 1.5 Hz, ArH), 7.95 (dd, 1H, *J* = 8.0, 1.5 Hz, ArH), 9.63 (d, 1H, CHO); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 22.3, 23.3, 30.2, 34.5, 46.6, 71.1, 71.9, 95.7, 125.3, 127.0, 129.8, 131.3, 134.3, 140.7, 194.6, 200.4.

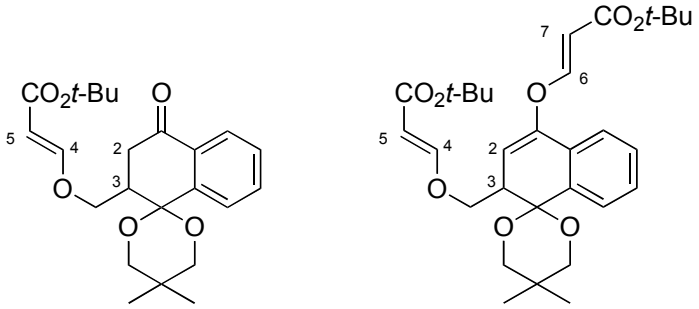
(±)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-hydroxymethyl-2,3-dihydronaphthalen-1(*2H*)-one[29] (274)



To a solution of aldehyde **273** (20.0 g, 73.0 mmol, 1.0 eq) in MeOH (500 mL) at –5 °C was added sodium borohydride (700 mg, 18.2 mmol, 0.25 eq) in small portions over 15 min. After stirring for 2 h, acetic acid (1.80 mL) was added and the reaction mixture concentrated under reduced pressure. The resulting residue was slurried in EtOAc (30 mL), stirred for 30 min at 40 °C and filtered cold though celite to remove insolubles. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography (10% Et_2O/Petroleum ether) to give alcohol **274** as a colourless oil (19.0 g, 95%);

R_f 0.28 (40% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.72 (d, 1H, *J* = 17.5 Hz, H_2), 2.95 (dd, 1H, *J* = 17.5, 4.5 Hz, H_2), 3.43-3.71 (m, 6H, H_3, CH_2 and OH), 3.83 (d, 1H, *J* = 11.5 Hz, CH_2OH), 3.94 (d, 1H, *J* = 11.5 Hz, CH_2OH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.64 (t, 1H, *J* = 8.0 Hz, ArH), 7.91 (d, 1H, *J* = 8.0 Hz, ArH), 7.95 (d, 1H, *J* = 8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.4, 30.1, 36.3, 37.5, 62.7, 70.8, 71.4, 97.4, 125.7, 126.5, 129.3, 131.5, 134.3, 141.6, 196.6.

(±)-(*E*)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-methyloxy(acrylic acid *t*-butyl ester)-2,3-dihydronaphthalen-1(*2H*)-one[29] (276) and (±)-(*E*)-4,4-(2,2-Dimethyl-1,3-propylenedioxy-3-[4-(2-*tert*-Butoxycarbonyl-vinyloxy)-1,2-dihydro-naphthalen-2-ylmethoxy]-acrylic acid *tert*-butyl ester[29] (277)



To a solution of NMM (1.10 mL, 10.0 mmol, 1.05 eq) in Et_2O (10 mL) was added *tert*—butyl propiolate (1.70 mL, 12.3 mmol, 1.3 eq) and the mixture stirred at rt for 30 min. A solution of alcohol **274** (2.62 g, 9.50 mmol, 1.0 eq) in Et_2O (10 mL) was then added and stirring continued for 12 h. The mixture was diluted with Et_2O (100 mL) and water (100 mL) the layers separated and the aqueous portion extracted with Et_2O (100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% Et_2O/Petroleum ether) to give divinyl ether **277** as a colourless oil (370 mg, 19%);

R_f 0.73 (30% EtOAc/Petroleum ether); IR (film) ν_{max} 2976, 2931, 2871, 1711, 1642, 1624, 1367, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.42 (s, 9H, $CO_2C(CH_3)_3$), 1.47 (s, 9H, $CO_2C(CH_3)_3$), 3.40-3.88 (m, 7H, H_3 and OCH_2), 4.98 (d, 1H, J = 12.5 Hz, H_4), 5.51 (d, 1H, J = 7.0 Hz, H_2), 5.57 (d, 1H, J = 12.0 Hz, H_6), 7.40 (d, 1H, J = 12.5 Hz, H_5), 7.45-7.37 (m, 3H, ArH), 7.62 (d, 1H, J = 12.0 Hz, H_7), 7.78-7.76 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 23.3, 28.1 (3C), 28.2 (3C), 30.54, 70.4, 70.6, 71.2, 79.7, 80.2, 96.5, 98.4, 104.6, 105.3, 122.3, 125.0, 128.7, 129.1, 129.3, 135.5, 150.6, 156.9, 161.3, 166.4, 166.9; MS *m/z* (CI; NH_3) 546 $[M+NH_4]^+$, 529 $[M+H]^+$; HRMS

(CI) Calculated for $C_{30}H_{40}O_8$ $[M+H_4]^+$; 529.2801, found; 529.2799; Microanalysis calculated for $C_{30}H_{40}O_8$; C 68.16, H 7.63; found C 68.25, H 7.70%.

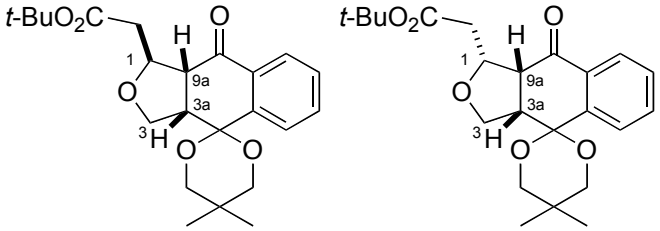
Further elution gave vinyl ether **276** as a colourless oil (3.09 mg, 81%);

R_f 0.67 (30% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 2.76 (dd, 1H, *J* = 17.5, 2.5 Hz, H_2), 2.90 (dd, 1H, *J* = 17.5, 4.5 Hz, H_2), 3.49-3.53 (m, 1H, OCH_2), 3.50 (dd, 1H, *J* = 10.5, 2.0 Hz, OCH_2), 3.64-3.68 (m, 2H, CH and OCH_2), 3.83-3.88 (m, 2H, OCH_2), 3.90 (dd, 1H, *J* = 10.5, 4.5 Hz, CH=CHOCH_2), 4.99 (d, 1H, *J* = 13.0 Hz, H_5), 7.42 (d, 1H, *J* = 13.0 Hz, H_4), 7.51 (dt, 1H, *J* = 7.5, 1.0 Hz, ArH), 7.69 (dt, 1H, *J* = 7.5, 1.0 Hz, ArH), 7.93 (dd, 1H, *J* = 7.5, 1.0 Hz, ArH), 8.01 (dd, 1H, *J* = 7.5, 1.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.3, 28.2 (3C), 30.0, 34.2, 36.9, 69.5, 70.4, 71.5, 79.8, 95.9, 98.7, 125.7, 126.5, 129.4, 131.5, 134.3, 141.4, 161.0, 166.8, 195.5.

Alternative procedure;

To a solution of alcohol **274** (13.8 g, 50.0 mmol, 1.0 eq) and *tert*-butyl propiolate (8.20 g, 65.0 mmol, 1.3 eq) in CH_2Cl_2 (200 mL) was added DMAP (1.22 g, 10.0 mmol, 0.2 eq) and the reaction mixture stirred at rt for 18 h. The mixture was diluted with water (200 mL), the layers separated and the aqueous portion extracted with CH_2Cl_2 (200 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% Et_2O/Petroleum ether) to give vinyl ether **276** as a colourless oil (18.5 g, 92%).

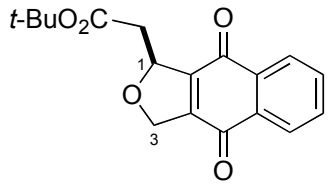
(±)-(1*SR*,3a*SR*,9a*RS*)-*tert*-Butyl 4,4-(2,2-dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate[29] (278) and (±)-(1*RS*,3a*SR*,9a*RS*)-*tert*-Butyl 4,4-(2,2-dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate[29] (279)



To a stirred solution of vinyl ether **276** (9.70 g, 24.0 mmol, 1.0 eq) in CH_2Cl_2 (120 mL) was added Barton's base (4.85 mL, 24.0 mmol, 1.0 eq) at rt and under N_2. The reaction mixture was stirred at rt for 8 h, diluted with CH_2Cl_2 (150 mL) and H_2O (150 mL) and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (150 mL) and the combined organic extracts washed with H_2O (2 x 50 mL) and brine (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (15% EtOAc/Petroleum ether) to give a 1 : 1 mixture of tetrahydrofurans **278** and **279** as a colourless oil (9.70 g, 100%);

R_f 0.38 (15% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) *both isomers* δ 0.96 (s, 6H, CH_3), 1.17 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.50 (s, 9H, $OC(CH_3)_3$), 2.37 (dd, 1H, *J* = 8.5, 17.0 Hz, H_{9a}), 2.59-2.77 (m, 3H, H_{3a} and $CH_2CO_2C(CH_3)_3$), 3.09 (dd, 1H, *J* = 9.0, 5.0 Hz, H_{9a}), 3.27-4.13 (m, 8H, H_{3a}, OCH_2, H_3 and $CH_2CO_2C(CH_3)_3$), 4.35 (dt, 1H, *J* = 8.5, 4.5 Hz, H_1), 4.43 (dt, 1H, *J* = 10.0, 5.0 Hz, H_1), 7.51 (*app*. q, 2H, *J* = 8.0 Hz, ArH), 7.62-7.70 (m, 2H, ArH), 7.80 (dd, 1H, *J* = 8.0, 0.8 Hz, ArH), 7.86-7.91 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *both isomers* δ 22.5 (2C), 23.1 (2C), 28.1 (6C), 30.2 (2C), 37.3, 39.7, 40.3, 41.4, 51.4, 52.9, 68.1, 69.2, 71.0, 71.1, 71.3 (2C), 79.4, 80.4, 80.9, 81.1, 95.5, 96.3, 125.2, 125.4, 126.2, 127.2, 129.3 (2C), 132.3, 133.1, 133.7, 134.3, 141.1, 141.4, 169.8, 170.3, 197.0, 197.4.

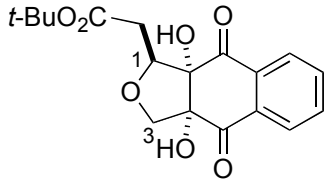
(±)-*tert*-Butyl (4,9-dioxo-1,3,4,9-tetrahydronaphtho[2,3-*c*]furan-1-yl)acetate[29] (280)

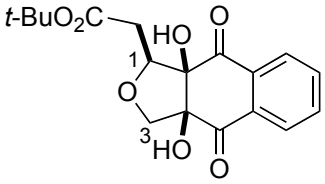


To a stirred solution of tetrahydrofurans **278** and **279** (13.2 g, 32.8 mmol, 1.0 eq) in acetone (1.2 L) was added *para*-toluene sulfonic acid monohydrate (9.30 g, 49.0 mmol, 1.5 eq). After stirring for 24 h at rt, sat. aq. $NaHCO_3$ (500 mL) was added and the mixture extracted with EtOAc (2 x 300 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (15% EtOAc/Petroleum ether) to give quinone **280** as a bright yellow solid (9.88 g, 96%);

M.p. (EtOAc/Petroleum ether) 81-84 °C; R_f 0.38 (30% EtOAc/Petroleum ether); ^{1}H NMR δ (400 MHz, $CDCl_3$) 1.36 (s, 3H, $CO_2C(CH_3)_3$), 2.79 (dd, 1H, *J* = 15.5, 7.0 Hz, C*H*$_2CO_2C(CH_3)_3$), 2.98 (dd, 1H, *J* = 15.5, 3.5 Hz, C*H*$_2CO_2C(CH_3)_3$), 5.03 (dd, 1H, *J* = 16.0, 4.5 Hz, H_3), 5.11 (dd, 1H, *J* = 16.0, 6.0 Hz, H_3), 5.59-5.62 (m, 1H, H_1), 7.71-7.77 (m, 2H, ArH), 8.03-8.11 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0 (3C), 40.2, 72.5, 81.1, 82.0, 126.4, 126.5, 132.9, 133.0, 133.9, 134.0, 146.6, 146.7, 169.3, 181.4, 181.6.

(±)-(1*SR*,3a*SR*,9a*RS*)-(3a,9a-Dihydroxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydro-naphtho[2,3-c]furan-1-yl)-acetic acid tert-butyl ester[29] (281) and
(±)-(1*SR*,3a*RS*,9a*SR*)-(3a,9a-Dihydroxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydro-naphtho[2,3-c]furan-1-yl)-acetic acid tert-butyl ester[29] (282)

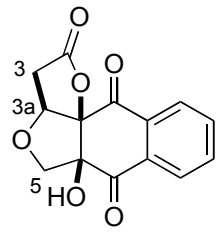




To a solution of naphthoquinone **280** (2.60 g, 8.25 mmol, 1.0 eq) in acetone and water (10:1; 57 mL) were added NMO (3.0 g, 25.3 mmol, 3.0 eq) and OsO_4 in *t*-BuOH (2.5 wt %; 2.81 mL, 0.47 mmol, 0.05 eq). After stirring at rt for 4 h, 1M aq. citric acid was added (50 mL) and the mixture was stirred for a further 25 min. The reaction mixture was diluted with EtOAc (200 mL), washed with 1M aq. citric acid (2 x 100 mL) and the aqueous portion extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude residue purified by silica gel flash column chromatography (50% EtOAc/petroleum ether) to give a 1 : 1 mixture of diols **281** and **282** as a white solid (2.56 g, 89%):

R_f 0.60 (60% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) *both isomers* δ 1.38 and 1.40 (s, 9H, $CO_2C(CH_3)_3$), 2.45 and 2.62 (dd, 1H, *J* = 8.0, 17.0 and 7.0, 16.5 Hz, $CH_2CO_2C(CH_3)_3$), 2.70 and 2.69 (dd, 1H, *J* = 6.0, 17.0 and 7.0, 16.5 Hz, CH_2 $CO_2C(CH_3)_3$), 3.60 and 4.15 (*br*. s, 1H, OH), 3.97 and 3.87 (d, 1H, *J* = 10.5 and 9.0 Hz, H_3), 4.24 and 4.52 (d, 1H, *J* = 10.5 and 9.0 Hz, H_3), 4.41 and 4.56 (dd and t, 1H, *J* = 6.0, 8.0 and 7.0 Hz, H_1), 4.60 and 5.10 (*br*. s, 1H, OH), 7.77-7.87 (m, 2H, ArH), 7.98-8.09 (m, 2H, ArH).

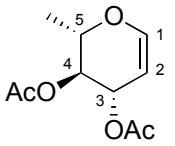
(±)-(3a*SR*,5a*SR*,11a*RS*)-5a-Hydroxy-3,3a,5,5a-tetrahydro-furo[3,2-b]naphtho[2,3-c]furan-2,6,11-trione[19, 20] (±)-(2)



To a solution of diols **281** and **282** (2.56 g, 7.35 mmol, 1.0 eq) in CH_2Cl_2 (45 mL) at 0 °C was added a mixture of TFA and H_2O (9:1; 5.4 mL). After 10 min. at 0 °C and a further 12 h at rt, the mixture was concentrated under reduced pressure and diluted with CH_2Cl_2 (50 mL). The mixture was washed with sat. aq. $NaHCO_3$ (40 mL), the aqueous portion extracted with EtOAc (2 x 50 mL) and the combined organic extracts washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (50% EtOAc/petroleum ether) and crystallisation (EtOAc/hexanes) to give ABCD alcohol **(±)-2** as a white solid (1.04 g, 52%);

M.p. (EtOAc/Petroleum ether) 172-174 °C [lit.[19, 20] m.p. 173 °C dec.]; R_f 0.23 (50% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (dd, 1H, *J* = 2.0, 19.0 Hz, H_3), 2.92 (dd, 1H, *J* = 7.0, 19.0 Hz, H_3), 3.52 (s, 1H, OH), 3.94 (d, 1H, *J* = 10.0 Hz, H_5), 4.35 (d, 1H, *J* = 10.0 Hz, H_5), 4.75 (dd, 1H, *J* = 2.0, 7.0 Hz, H_{3a}), 7.89-7.94 (m, 2H, ArH), 8.15 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9, 75.2, 80.9, 83.6, 91.9, 128.1, 128.3, 132.2, 133.2, 135.8, 136.3, 173.4, 189.2, 191.7.

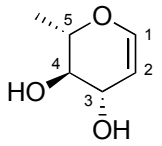
(3*S*,4*S*,5*S*)-Acetic acid 4-acetoxy-5-methyl-3,4-dihydro-2H-pyran-3-yl ester[141] (304)



L-Rhamnose (**303**) (10.0 g, 61.0 mmol, 1.0 eq) was added to a mixture of acetic anhydride (34 mL, 360 mmol, 6.0 eq) and 70% perchloric acid (0.2 mL, 6.0 mmol, 0.1 eq) in a 3-necked flask, in such a way as to maintain a temperature of 35 ± 5 °C. After stirring for 2 h PBr_3 (3.30 mL, 34.5 mmol, 0.5 eq) was added drop-wise, maintaining the temperature below 10 °C. H_2O (3.3 mL) was added drop-wise and the reaction stirred at rt for 2 h. To a cooled solution (–10 °C) of NaOAc (22.0 g, 270 mmol, 4.5 eq), H_2O (70 mL) and AcOH (30 mL) were added zinc powder (20.0 g, 305 mmol, 5.0 eq) and aq. $CuSO_4$ (6.5 mL, 1M) so as to maintain a temperature of 5 ± 5 °C. After disappearance of the blue colour and development of H_2, the crude bromo-aceto-rhamnose solution (prepared above) was added drop-wise to the mixture keeping the reaction temperature at –5 ± 2 °C. After stirring at this temperature for 18 h ice/H_2O (100 mL) was added and the reaction mixture stirred for 5 min. Any unreacted zinc and copper was filtered off and the filtrate extracted with CH_2Cl_2 (5 x 25 mL). The combined organic extracts were washed with ice/water (100 mL) and sat. aq. $NaHCO_3$ (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (100% CH_2Cl_2) to give diacetate **304** as a colourless oil (4.59 g, 39%);

R_f 0.36 (100% CH_2Cl_2); $[\alpha]_D^{22}$ +62.8 (c = 1.0, CH_2Cl_2) [lit[141] $[\alpha]_D^{22}$ +76.5 (*c* = 1.0, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (dd, 1H, *J* = 2.0 Hz, 6.5 Hz, CH_3), 1.96 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 3.98-4.09 (m, 1H, H_5), 4.68-4.73 (m, 1H, H_4), 4.92-4.98 (m, 1H, H_2), 5.24-5.28 (m, 1H, H_3), 6.34-6.37 (m, 1H, H_1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.9, 21.1, 68.3, 71.8, 72.5, 98.8, 146.0, 169.9, 170.6.

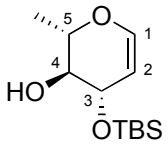
(3*S*,4*R*,5*S*)-5-Methyl-1,2-dihydro-2H-pyran-3,4-diol[141] (305)



To a solution of diacetate **304** (4.5 g, 21.0 mmol, 1.0 eq) in MeOH (35 mL) was added K_2CO_3 (45 mg, 0.3 mmol, 0.02 eq). The reaction mixture was stirred at rt for 2 h and concentrated under reduced pressure to give diol **305** as a white solid that required no further purification (2.79 g, 100%);

R_f 0.00 (100% CH_2Cl_2); $[\alpha]_D^{22}$ +24.3 (*c* = 1.0, CH_2Cl_2) [lit[141] $[\alpha]_D^{22}$ + 25.7 (*c* = 1.0, $CHCl_3$)]; ^{1}H NMR (300 MHz. $CDCl_3$) δ 1.31 (d, 3H, *J* = 6.5 Hz, CH_3), 3.22-3.44 (m, 1H, H_4), 3.68-3.79 (m, 1H, H_5), 4.06-4.09 (m, 1H, H_3), 4.63-4.66 (m, 1H, H_2), 4.85 (*br*. s, 2H, OH), 6.25-6.27 (m, 1H, H_1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 48.4, 74.7, 74.8, 103.4, 143.9.

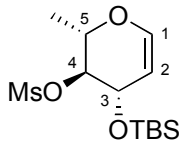
(3*S*,4*S*,5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-methyl-3,4-dihydro-2H-pyran-4-ol[141] (302)



To a solution of diol **305** (2.79 g, 21.4 mmol, 1.0 eq) and imidazole (2.92 g, 42.9 mmol, 2.0 eq) in DMF (30 mL) was added TBSCl (3.72 g, 24.7 mmol, 1.2 eq) and stirred for 2.5 h. Et_2O (100 mL) was added and the reaction mixture washed with H_2O (3 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give alcohol **302** as a pale yellow oil that required no further purification (5.25 g, 100%);

R_f 0.27 (100% CH_2Cl_2); $[\alpha]_D^{22}$ +74.3 (c = 1.0, CH_2Cl_2) [lit[141] $[\alpha]_D^{22}$ +76.5 (*c* = 1.0, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$) 0.88 (s, 9H, $SiC(CH_3)_3$), 1.34 (d, 3H, *J* = 6.5 Hz, CH_3), 2.25 (*br.* s, 1H, OH), 3.43 (t, 1H, *J* = 8.5 Hz, H_4), 3.88 (qd, 1H, *J* = 6.5, 8.5 Hz, H_5), 4.17 (td, 1H, *J* = 2.5, 6.5 Hz, H_3), 4.59 (ddd, 1H, *J* = 0.5, 2.5, 6.5 Hz, H_2), 6.22 (dd, 1H, *J* = 2.0, 6.0 Hz, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.5, –4.3, 17.3, 18.1, 25.9 (3C), 70.3, 74.4, 74.9, 103.5, 143.7.

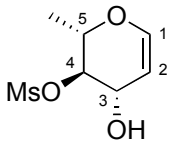
(3*S*,4*S*,5*S*)-Methanesulfonic acid 3-(*tert*-butyl-dimethyl-silanyloxy)-5-methyl-3,4-dihydro-2H-pyran-4-yl ester[141] (301)



To a solution of alcohol **302** (5.25 g, 21.4 mmol, 1.0 eq) in pyridine (100 mL) at 0 °C was added MsCl (3.38 mL, 42.9 mmol, 2.0 eq) and stirred for 18 h at rt. The reaction mixture was diluted with Et_2O (150 mL) and washed with water (3 x 100 mL). The aqueous portion extracted with Et_2O (2 x 50 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (80% CH_2Cl_2/Petroleum ether) to give mesylate **301** as a colourless oil that required no further purification (5.69 g, 82%);

R_f 0.77 (100% CH_2Cl_2); $[\alpha]_D^{22}$ +45.0 (c = 1.0, CH_2Cl_2) [lit[141] $[\alpha]_D^{22}$ +52.9 (*c* = 1.03, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$) 0.85 (s, 9H, $SiC(CH_3)_3$), 1.39 (dd, 1H, *J* = 1.0, 6.5 Hz, CH_3), 3.04 (s, 3H, SO_2CH_3), 4.11 (*app.* quin., 1H, *J* = 6.5 Hz, H_5), 4.32-4.35 (m, 1H, H_3), 4.49-4.54 (m, 1H, H_4), 4.67 (ddd, 1H, *J* = 1.0, 3.0, 6.0 Hz, H_2), 6.27 (d, 1H, *J* = 6.0 Hz, H_1); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.4, –4.3, 16.9, 18.0, 25.8 (3C), 39.0, 66.6, 72.6, 82.2, 102.2, 143.7.

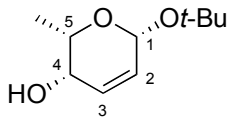
(3*S*,4*R*,5*S*)-Methanesulfonic acid 3-hydroxy-5-methyl-3,4-dihydro-2H-pyran-4-yl ester[141] (300)



To a solution of TBS ether **301** (5.69 g, 17.6 mmol, 1.0 eq) in THF (150 mL) at 0 °C was added TBAF (1M in THF, 17.6 mL, 17.6 mmol, 1.0 eq) and stirred at rt for 20 min. The reaction mixture was diluted with H_2O (75 mL) and Et_2O (75 mL) and the layers separated. The aqueous portion was extracted with E_2O (2 x 70 mL) and the combined organic extracts washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give alcohol **300** as an off white solid that required no further purification (4.26 g, 116%);

M.p. (EtOAc/Petroleum ether) 73-75 °C [lit.[141] m.p. 74-76 °C dec.]; R_f 0.07 (CH_2Cl_2); $[\alpha]_D^{22}$ –21.3 (c = 1.0, CH_2Cl_2) [lit[141] $[\alpha]_D^{22}$ –14.8 (*c* = 1.65, CH_2Cl_2)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, 3H, *J* = 6.5 Hz, CH_3), 2.71-2.80 (d, 1H, *J* = 3.0 Hz, OH), 3.18 (s, 3H, SO_2CH_3), 3.91-3.02 (m, 1H, H_3), 4.43-4.46 (m, 2H, H_4 and H_5), 4.75 (dd, 1H, *J* = 2.0, 6.0 Hz, H_2), 6.32 (d, 1H, *J* = 6.0 Hz, H_1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 39.0, 68.0, 72.6, 84.1, 102.7, 144.9.

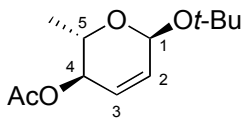
(1*R*,4*S*,5*S*)-1-*tert*-Butoxy-5-methyl-1,4-dihydro-2H-pyran-4-ol (307)



To a solution of mesylate **300** (50 mg, 0.24 mmol, 1.0 eq) in Et_2O (4 mL) at 0 °C was added *t*-BuOK (1 M in THF, 240 μL, 0.24 mmol, 1.0 eq), stirred at rt for 15 min and *t*-BuOH (5 mL) was added. After stirring at rt for 2 h, H_2O (5 mL) was added and the reaction mixture extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give glycoside **307** as a colourless oil (27 mg, 62%);

R_f 0.39 (10% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H, CH_3), 1.24 (s, 9H, $C(CH_3)_3$), 1.88 (d, 1H, *J* = 11.5 Hz, OH), 3.56 (m, 1H, H_4), 3.66 (dq, 1H, *J* = 2.0, 6.5 Hz, H_5), 5.15 (s, 1H, H_1), 5.68 (d, 1H, *J* = 10.0 Hz, H_2), 6.06 (dd, 1H, *J* = 5.0, 10.0Hz, H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 28.7 (3C), 64.6, 71.5, 75.9, 92.9, 130.7, 132.7; MS *m/z* (CI; NH_3); 204 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{10}H_{18}O_3$ $[M+NH_4]^+$; 204.1600, found; 204.1594.

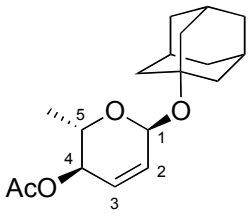
(1*S*,4*R*,5*S*)-Acetic acid 1-*tert*-butoxy-5-methyl-1,4-dihydro-2H-pyran-4-yl ester[233] (313)



To a solution of diacetate **304** (960 mg, 4.5 mmol, 1.0 eq) and *t*-butanol (0.9 mL, 9.0 mmol, 2.0 eq) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added $BF_3{\cdot}OEt_2$ (30 μL, 0.23 mmol, 0.05 eq). The reaction mixture was stirred at rt for 2 h and diluted with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give glycoside **313** as a colourless oil (640 mg, 63%, 5:1 mixture of diastereoisomers);

R_f 0.76 (20% EtOAc/Petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) *major isomer* δ 1.10 (d, 3H, *J* = 6.0 Hz, CH_3), 1.20 (s, 9H, $C(CH_3)_3$), 1.98 (s, 3H, $OCOCH_3$), 3.90-4.00 (m, 1H, H_5), 4.92 (dd, 1H, *J* = 1.0, 9.5 Hz, H_4), 5.17 (s, 1H, H_1), 5.63 (dd, 1H, *J* = 1.0, 10.0 Hz, H_3), 5.73 (d, 1H, *J* = 10.0 Hz, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 21.1, 28.8 (3C), 64.3, 71.0, 75.0, 88.9, 128.8, 129.5, 170.6.

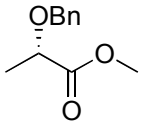
(1*S*,4*R*,5*S*)-Acetic acid 1-(adamantan-1-yloxy)-5-methyl-1,4-dihydro-2H-pyran-4-yl ester (314)



To a solution of diacetate **304** (960 mg, 4.5 mmol, 1.0 eq) and adamantan-1-ol (1.36 g, 9.0 mmol, 2.0 eq) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added $BF_3{\cdot}OEt_2$ (30 μL, 0.23 mmol, 0.05 eq). The reaction mixture was stirred at rt for 1.5 h, diluted with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give glycoside **314** as a colourless oil (900 mg, 66%, 5:1 mixture of diastereoisomers);

R_f 0.68 (20% EtOAc/Petroleum ether); IR (film) ν_{max} 2913, 2900, 2848, 1737, 1234, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *major isomer* δ 1.11 (d, 3H, *J* = 6.0 Hz, CH_3), 1.55 (s, 6H, CH_2), 1.77 (s, 6H, CH_2), 1.99 (s, 3H, $OCOCH_3$), 2.07 (s, 3H, CH), 3.93-4.08 (m, 1H, H_5), 4.92 (dd, 1H, *J* = 1.5, 9.0 Hz, H_4), 5.30 (s, 1H, H_1), 5.63 (ddd, 1H, *J* = 2.0, 2.5, 10.0 Hz, H_3), 5.73 (d, 1H, *J* = 10.0 Hz, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 21.1, 30.7 (3C), 36.3 (3C), 42.7 (3C), 64.3, 71.0, 74.4, 87.5, 128.9, 129.7, 170.6.

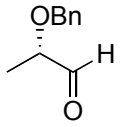
(2*S*)-2-Benzyloxy-propionic acid methyl ester[161] (418)



To a suspension of NaH (7.84 g, 196 mmol, 1.02 eq) in THF (150 mL) at 0 °C was added slowly methyl-(*S*)-lactate (**346**) (20.0 g, 192 mmol, 1.0 eq). The reaction mixture was stirred at rt for 40 min, then benzyl bromide (24.0 mL, 200 mmol, 1.02 eq) was added. After stirring at rt for 24 h, sat. aq. NH_4Cl (50 mL) was added and the reaction mixture extracted with Et_2O (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (5% EtOAc/Petroleum ether) to give benzyl ether **418** as a pale yellow oil (32.3 g, 86%);

R_f 0.55 (30% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, 3H, *J* = 7.0 Hz, CH_3), 3.69 (s, 3H, OCH_3), 3.88 (q, 1H, *J* = 7.0 Hz, CH), 4.40 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.65 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.22-7.34 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 51.9, 72.0, 74.0, 128.0 (3C), 128.5 (2C), 137.7, 173.6.

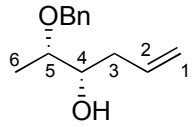
(2*S*)- 2-Benzyloxy-propionaldehyde[161] (347)



To a solution of methyl ester **418** (30.0 g, 154 mmol, 1.0 eq) in CH_2Cl_2 (250 mL) under N_2 at –78 °C, was added drop-wise DIBAl-H (1 M in hexanes, 169 mL, 169 mmol, 1.1 eq). After stirring at –78 °C for 6h, sat. aq. sodium potassium tartate (250 mL) was added, warmed to rt and stirred for 1 h. The layers were separated and the aqueous portion extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with H_2O (3 x 150 mL), brine (3 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (30% EtOAc/Petroleum ether) to give aldehyde **347** as a colourless oil (15.5 g, 61%);

R_f 0.57 (10% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (dd, 3H, *J* = 0.5, 7.0 Hz, CH_3), 3.89 (dq, 1H, *J* = 1.5, 7.0 Hz, CH), 4.58-4.68 (m, 2H, OCH_2Ph), 7.28-7.40 (m, 5H, ArH), 9.67 (dd, 1H, *J* = 0.5, 1.5 Hz, CHO).

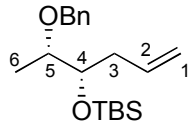
(4*S*,5*S*)-5-Benzyloxy-2-hexen-4-ol[161] (348)



To a solution of aldehyde **347** (14.5 g, 88.0 mmol, 1.0 eq) in CH_2Cl_2 (200 mL) under N_2 at –78 °C, was added magnesium bromide diethyl etherate (28.5 g, 100 mmol, 1.2 eq). The mixture was maintained at –78 °C for 45 min and then allylmagnesium bromide (1 M in Et_2O, 100 mL, 100 mmol, 1.15 eq) was added drop-wise. The reaction mixture was kept at –78 °C for 2 h and stirred for a further 12 h at rt. Sat. aq. $NaHCO_3$ (200 mL) was slowly added, the layers separated and the aqueous portion extracted with CH_2Cl_2 (100 mL). The combined organic extracts were washed with H_2O (3 x 100 mL), brine (3 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give alcohol **348** as a colourless oil (15.7 g, 87%);

R_f 0.54 (10% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +24.2 (c = 1.0, CH_2Cl_2) [lit.[161] +26.3 (c = 1.0, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 3H, *J* = 6.0 Hz, H_6), 2.16-2.40 (m, 2H, H_3), 2.79 (*br*-s, 1H, OH), 3.40-3.47 (m, 1H, H_5), 3.49-3.57 (m, 1H, H_4), 4.43 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 4.67 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 5.07-5.15 (m, 2H, H_1), 5.80-5.98 (m, 1H, H_2), 7.28-7.35 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 37.6, 71.1, 74.3, 77.6, 117.2, 127.8, 127.9 (2C), 128.5 (2C), 135.1, 138.5.

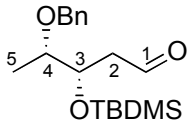
(4*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-benzyloxy-2-hexene[161] (**345)**



To a solution of alcohol **348** (14.8 g, 70.0 mmol, 1.0 eq) in DMF (120 mL) under N_2 was added imidazole (6.40 g, 95.0 mmol, 1.4 eq) and DMAP (450 mg, 3.60 mmol, 0.05 eq). A solution of TBSCl (13.7 g, 91.0 mmol, 1.3 eq) in DMF (60 mL) was added drop-wise and the mixture maintained at rt for 16 h. MeOH (100 mL) and Et_2O (200 mL) were added followed by sat. aq. NH_4Cl (250 mL), the layers separated and the organic portion washed with water (3 x 100 mL) and brine (3 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/Petroleum ether) to give TBS ether **345** as a colourless oil (20.8 g, 90%);

R_f 0.92 (10 % EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.18 (d, 3H, J = 6.5 Hz, H_6), 2.12-2.23 (m, 1H, H_3), 2.41-2.50 (m, 1H, H_3), 3.50-3.57 (m, 1H, H_5), 3.77-3.82 (m, 1H, H_4), 4.53 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.64 (d, 1H, J = 12.0 Hz, OCH_2Ph), 5.03-5.14 (m, 2H, H_1), 5.80-5.95 (m, 1H, H_2), 7.25-7.37 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.4, –4.4, 14.0, 18.2, 26.0 (3C), 36.4, 71.1, 73.9, 77.4, 116.6, 127.5, 127.6 (2C), 128.4 (2C), 136.2, 139.1.

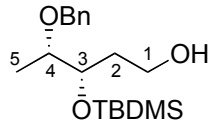
(3*S*,4*S*)-4-Benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-pentan-1-al (350)



Ozone was bubbled through a solution of alkene **345** (5.0 g, 15.6 mmol, 1.0 eq) in CH_2Cl_2 (100 mL) at –78 °C until the blue colour persisted. PPh_3 (6.14 g, 23.4 mmol, 1.5 eq) was added and stirring was continued for 1.5 h at –78 °C. After warming to rt, the reaction mixture was adsorbed onto silica (~5 g) and purified by silica gel flash column chromatography (5% EtOAc/Petroleum ether) to give aldehyde **350** as a colourless oil (4.72 g, 94%);

R_f 0.48 (10% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +5.0 (*c* = 1.0, CH_2Cl_2); IR (film) ν_{max} 2954, 2929, 2886, 2858, 1714, 1454, 1386, 1255, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05, (s, 3H, $Si(CH_3)_2$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.19 (d, 3H, *J* = 6.5 Hz, H_5), 2.53 (ddd, 1H, *J* = 3.0, 7.5, 16.0 Hz, H_2), 2.71 (ddd, 1H, *J* = 1.5, 4.5, 16.0 Hz, H_2), 3.60 (dq, 2H, *J* = 4.5, 6.5 Hz, H_4), 4.37 (td, 1H, *J* = 4.5, 8.0 Hz, H_3), 4.50 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.63 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.29-7.40 (m, 5H, ArH), 9.23 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.5, –4.6, 13.5, 18.0, 25.7 (3C), 46.0, 68.9, 71.0, 76.5, 127.6, 127.7 (2C), 128.4 (2C), 138.4, 201.8; MS *m/z* (CI; NH_3) 340 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{18}H_{30}O_3Si$ $[M+NH_4]^+$; 340.2308, found; 340.2310.

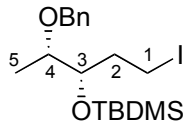
(3*S*,4*S*)-4-Benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-pentan-1-ol (344)

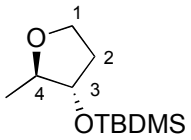


To a solution of aldehyde **350** (4.72 g, 14.6 mmol, 1.0 eq) in MeOH (150 mL) at 0 °C was added portion-wise $NaBH_4$ (609 mg, 16.1 mmol, 1.1 eq). The reaction mixture was stirred for 30 min and then quenched with AcOH (5 mL). The mixture was then concentrated under reduced pressure and the resulting residue slurried in EtOAc (50 mL), stirred for 30 min at 40 °C and filtered cold through celite. The filtrate was concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give alcohol **344** as a colourless oil (4.70 g, 99%);

R_f 0.51 (30% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +21.0 (*c* = 1.0, CH_2Cl_2); IR (film) ν_{max} 3415, 1954, 2929, 2885, 2856, 1461, 1255, 1093, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02, (s, 3H, $Si(CH_3)_2$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.90 (s, 9H, $Si(CH_3)_3$), 1.20 (d, 3H, *J* = 6.5 Hz, H_5), 1.68 (dddd, 1H, *J* = 5.0, 6.0, 7.5, 14.0 Hz, H_2), 1.93 (tdd, 1H, *J* = 5.0, 8.0, 13.0 Hz, H_2), 2.64 (*br.* s, 1H, OH), 3.58 (dq, 1H, *J* = 5.0, 6.5 Hz, H_1), 3.68-3.79 (m, 1H, H_1), 3.95 (td, 1H, *J* = 5.0, 7.5 Hz, H_3), 4.53 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.65 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.29-7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.8, –4.6, 13.4, 18.0, 25.8 (3C), 34.1, 60.3, 71.1, 72.2, 77.2, 127.2 (3C), 128.4 (2C), 138.5; MS *m/z* (CI; NH_3) 325 $[M+H]^+$, 342 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{18}H_{32}O_3Si$ $[M+NH_4]^+$; 325.2199, found; 325.2196.

(3*S*,4*S*)-4-Benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-1-iodo-pentane (343) and (3*S,*4*R*)-4-Methyl-3-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-furan (351)





A solution of PPh_3 (5.70 g, 21.7 mmol, 1.5 eq) in CH_2Cl_2 (50 mL) was cooled to 0 °C and I_2 (5.51 g, 21.7 mmol, 1.5 eq) was added in one portion. The reaction mixture was stirred at 0 °C for 10 min and a solution of alcohol **350** (4.70 g, 14.5 mmol, 1.0 eq) and imidazole (2.86 g, 42.0 mmol, 2.9 eq) was added *via* cannula. The reaction mixture was allowed to warm up to rt and stirred for 4 h before quenching with sat. aq. $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 75 mL). The combined organics were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (5% EtOAc/Petroleum ether) to give iodide **343** as a colourless oil (2.46 g, 39%);

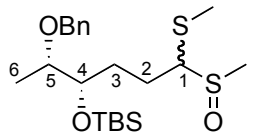
R_f 0.52 (5% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +16.4 (*c* = 1.0, CH_2Cl_2); IR (film) ν_{max} 2954, 2929, 2885, 2858, 1720, 1471, 1253, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H, $Si(CH_3)_2$), 0.12 (s, 3H, $Si(CH_3)_2$), 0.91 (s, 9H, $Si(CH_3)_3$), 1.20 (d, 3H, *J* = 6.5 Hz, H_5), 1.86-1.97 (m, 1H, H_2), 2.15-2.23 (m, 1H, H_2), 3.19 (dt, 1H, *J* = 7.0, 9.0 Hz, H_1), 3.36 (ddd, 1H, *J* = 5.0, 7.0, 9.0 Hz, H_1), 3.52-3.58 (m, 1H, H_4), 3.90 (ddd, 1H, *J* = 3.0, 4.5, 8.5 Hz, H_3), 4.56 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.62 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.29-7.41 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.4 (2C), 4.5, 13.7, 18.0, 25.9 (3C), 34.9, 71.0, 72.8, 76.5, 127.6, 127.7 (2C), 128.4 (2C), 138.7; MS *m/z* (CI; NH_3) 435 $[M+H]^+$, 452 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{18}H_{31}IO_2Si$ $[M+H]^+$; 435.1216, found; 435.1214.

Further elution gave tetrahydrofuran **351** as a colourless oil (1.85 g, 59%);

R_f 0.46 (5% EtOAc/Petroleum ether); IR (film) ν_{max} 2931, 2856, 1427, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.92 (s, 9H,

$Si(CH_3)_3$), 1.21 (d, 3H, *J* = 6.5 Hz, CH_3), 1.84-1.91 (m, 1H, H_2), 2.12 (dtd, 1H, *J* = 5.5, 8.5, 13.0 Hz, H_2), 3.75 (dt, 1H, *J* = 4.5, 8.5 Hz, H_1), 3.79-3.85 (m, 1H, H_1), 4.02 (q, 1H, *J* = 8.0 Hz, H_4), 4.19-4.21 (m, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.0, –4.7, 14.8, 18.2, 25.8 (3C), 36.3, 65.8, 73.5, 78.8; MS *m/z* (CI; NH_3) 217 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{11}H_{24}O_2Si$ $[M+H]^+$; 217.1624, found; 217.1627.

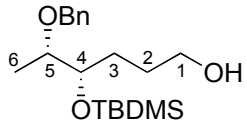
(1*RS*,4*S*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-methanesulfinyl-1-methylsulfanyl-hexane (342)



To a solution of FAMSO (502 μL, 4.94 mmol, 1.0 eq) in THF (50 mL) at –20 °C was added *n*-butyllithium (1.6 M in hexanes, 3.09 mL, 4.94 mmol, 1.5 eq) drop-wise and stirred for 45 min. Iodide **343** (1.43 g, 3.29 mmol, 1.0 eq) was added and the reaction mixture stirred at rt for 45 min before sat. aq. NH_4Cl (30 mL) was added. The layers were separated and the aqueous portion extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (50% EtOAc/Petroleum ether) to give sulfanyl sulfoxide **342** as a colourless oil (1.20 g, 85%);

R_f 0.38 (50% EtOAc/Petroleum ether); IR (film) ν_{max} 2952, 2927, 2856, 1454, 1375, 1253, 1091, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *all isomers* δ –0.1 (s, 3H, $Si(CH_3)_2$), and 0.4 (s, 3H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.16 (d, 1H, *J* = 6.5 Hz, H_6), 1.44-2.19 (m, 4H, H_2 and H_3), 2.14, 2.15, 2.25 and 2.27 (s, 3H, SCH_3), 2.50, 2.53, 2.65 and 2.69 (s, 3H, $SOCH_3$), 3.41-3.53 (m, 2H, H_4 and H_1), 3.73-3.81 (m, 1H, H_5), 4.48 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.59 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.26-7.36 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *all isomers* δ –4.6, –4.5, –4.4, 12.8, 13.4, 13.7, 15.4, 15.6, 18.0, 21.9, 23.6, 23.9, 25.9, 28.0, 28.6, 28.7, 29.3, 32.2, 32.5, 35.9, 36.6, 66.1, 66.5, 67.6, 68.1, 71.0, 72.9, 73.1, 73.4, 127.5, 127.6, 128.3, 138.7, 138.8; MS *m/z* (CI; NH_3) 431 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{21}H_{38}O_3S_2Si$ $[M+H]^+$; 431.2110, found; 431.2111.

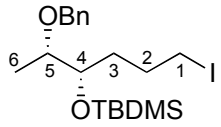
(4*S*,5*S*)-5-benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-hexanol[161] (366)



To a stirred solution of cyclohexene (64.0 mL, 632 mmol, 10.0 eq) in THF (100 mL) at 0 °C and under N_2 was added $BH_3{\cdot}SMe_2$ (2 M in THF, 158 mL, 316 mmol, 5.0 eq). After 30 min, THF (100 mL) was added and the mixture stirred at 0 °C for 1.5 h. A solution of alkene **345** (20.3 g, 63.0 mmol, 1.0 eq) in THF (100 mL) was added and the mixture stirred at rt for 12 h. H_2O (100 mL), 3 M aqueous NaOH (50 mL) and 30% aqueous H_2O_2 (50 mL) were carefully added and the mixture stirred at 50 °C for 3 h. After cooling to rt, the layers were separated and the aqueous portion extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (15% EtOAc/Petroleum ether) to give alcohol **366** as a colourless oil (20.7 g, 96%);

R_f 0.31 (15% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.02 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.12 (d, 3H, J = 6.5 Hz, H_6), 1.40-1.67 (m, 4H, H_2 and H_3), 2.46 (*br*. s, 1H, OH), 3.49-3.76 (m, 4H, H_1, H_4 and H_5), 4.48 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.59 (d, 1H, J = 12.0 Hz, OCH_2Ph), 7.25-7.32 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.4, –4.5, 13.8, 18.1, 25.7 (3C), 27.7, 29.2, 63.0, 71.1, 73.8, 77.4, 127.6, 127.7 (2C), 128.4 (2C), 138.9.

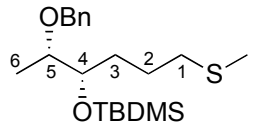
(4*S*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-iodo-hexane (365)



To a solution of PPh_3 (650 mg, 2.5 mmol, 1.1 eq) in CH_2Cl_2 (15 mL) at 0 °C and under N_2 was added I_2 (630 mg, 2.5 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 10 min and a solution of alcohol **366** (1.04 g, 2.2 mmol, 1.0 eq) and imidazole (445 mg, 6.5 mmol, 2.9 eq) in CH_2Cl_2 (10 mL) was added *via* cannula. After stirring at rt for 7 h, sat. aq. $NaHCO_3$ (30 mL) was added, the layers separated and the aqueous portion extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography to give iodide **365** as a colourless oil (840 mg, 65%);

R_f 0.55 (10% Et_2O/Petroleum ether); $[\alpha]_D^{22}$ –3.2 (c = 1.0, CH_2Cl_2); IR (film) ν_{max} 2954, 2929, 2856, 1255, 1087, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.18 (d, 3H, *J* = 6.5 Hz, H_6), 1.47-2.05 (m, 4H, H_2 and H_3), 3.22 (dt, 2H, *J* = 2.5, 7.0 Hz, H_1), 3.49-3.55 (m, 1H, H_5), 3.73-3.77 (m, 1H, H_4), 4.53 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.65 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.29-7.41 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6, –4.4, 7.3, 13.7, 18.1, 25.9 (3C), 30.4, 32.2, 71.1, 72.9, 77.2, 127.5, 127.6 (2C), 128.4 (2C), 138.9; MS *m/z* (CI; NH_3) 449 $[M+H]^+$, 466 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{19}H_{33}IO_2Si$ $[M+H]^+$; 449.1380, found; 449.1380.

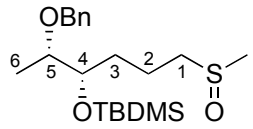
(4*S*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-Methylsulfanyl-hexane (364)



To a solution of iodide **365** (100 mg, 0.2 mmol, 1.0 eq) in EtOH (5 mL) was added NaSMe (23 mg, 0.3 mmol, 1.5 eq). After stirring for 6 h, sat. aq. NH_4Cl (20 mL) was added, the layers separated and the aqueous portion extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give sulfide **364** as a colourless oil that required no further purification (81 mg, 99%);

R_f 0.50 (10% Et_2O/Petroleum ether); $[\alpha]_D^{22}$ –3.2 (c = 1.0, CH_2Cl_2); IR (film) ν_{max} 2952, 2929, 2856, 1255, 1085, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.17 (d, 3H, *J* = 6.5 Hz, H_6), 1.45-1.83 (m, 4H, H_2 and H_3), 2.12 (s, 3H, SCH_3), 2.47-2.61 (m, 2H, H_1), 3.49-3.55 (m, 1H, H_5), 3.74 (ddd, 1H, *J* = 3.0, 4.5, 7.5 Hz, H_4), 4.53 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.64 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.28-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6, –4.4, 13.7, 15.5, 18.1, 25.9 (3C), 30.3, 34.4, 34.5, 71.0, 73.5, 77.4, 127.5, 127.6 (3C), 128.3 (2C), 140.0; MS *m/z* (CI; NH_3) 369 $[M+H]^+$, 386 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{36}O_2SSi$ $[M+H]^+$; 369.2309, found; 369.2297.

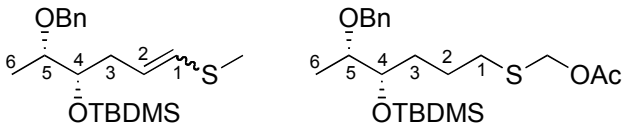
(4*S*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-methylsulfinyl-hexane (363)



To a solution of sulfide **364** (81 mg, 0.22 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at –78 °C was added *m*-CPBA (34 mg, 0.20 mmol, 0.9 eq). The reaction mixture was stirred at –78 °C for 2 h and for a further 30 min at rt after which sat. aq. $NaHCO_3$ (30 mL) was added. The layers were separated and the organic portion washed with sat. aq. $NaHCO_3$ (2 x 30 mL), dried and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (50% EtOAc/Petroleum ether) to give sulfoxide **363** as a colourless oil (75 mg, 89%);

R_f 0.36 (90% EtOAc/Petroleum ether); IR (film) ν_{max} 2054, 2930, 2857, 1471, 1435, 1361, 1257, 1082, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both isomers* δ 0.00 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.15 (d, 3H, *J* = 6.5 Hz, H_6), 1.43-1.94 (m, 4H, H_2 and H_3), 2.58 and 2.59 (s, 3H, $SOCH_3$), 2.63-2.73 (m, 1H, H_1), 2.78-2.86 (m, 1H, H_1), 3.48-3.56 (m, 1H, H_5), 3.70-3.76 (m, 1H, H_4), 4.49 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.62 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 7.28-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *both isomers* δ –4.6, –4.4, 13.5, 18.0, 19.2, 19.4, 25.8 (3C), 30.1, 30.3, 38.4, 38.5, 55.0, 55.1, 71.0, 73.1, 77.0, 77.1, 127.6 (3C), 128.4 (2C), 138.8; MS *m/z* (CI; NH_3) 385 $[M+H]^+$, 402 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{36}O_3SSi$ $[M+H]^+$; 385.2233, found; 385.2245.

(4*S*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-Methylsulfanyl-hex-2-ene (359) and (4*S*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-1-Acetoxymethyl-sulfanyl-hexane (369)



A mixture of sulfoxide **363** (115 mg, 0.3 mmol, 1.0 eq) and anhydrous NaOAc (245 mg, 3.0 mmol, 10.0 eq) in Ac_2O (3 mL) was heated at reflux for 15 hours. Ac_2O was removed by azeotropic distillation with toluene (3 x 5 mL) and the resulting residue was dissolved in CH_2Cl_2 (25 mL) and filtered to remove NaOAc. The filtrate was concentrated and purified by silica gel flash column chromatography to give sulfanyl alkene **359** as a colourless oil (44 mg, 40%, *E* : *Z* = 5 : 3);

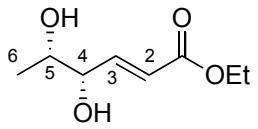
R_f 0.53 (10% EtOAc/Petroleum ether); IR (film) ν_{max} 2952, 2927, 2885, 2856, 1461, 1255, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both isomers* δ 0.01 and 0.02 (s, 3H, $Si(CH_3)_2$), 0.05 and 0.07 (s, 3H, $Si(CH_3)_2$), 0.90 (s, 9H, $Si(CH_3)_3$), 1.17 and 1.18 (d, 3H, *J* = 6.5 and 6.0 Hz, H_6), 2.15-2.34 (m, 1H, H_3), 2.23 and 2.32 (s, 3H, SCH_3), 2.42-2.49 (m, 1H, H_3), 3.49-3.55 (m, 1H, H_4), 3.71-3.75 and 3.81-3.85 (m, 1H, H_5), 4.52 and 4.57 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.62 and 4.63 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 5.44 and 5.62-5.68 (td and m, 1H, *J* = 7.5, 5.0 Hz, H_2), 5.96 and 6.01 (d, 1H, *J* = 9.5 Hz and 15.0 Hz, H_1), 7.28-7.39 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *both* isomers δ –4.5, –4.4, 13.7, 13.8, 14.3, 14.8, 15.5, 17.1, 18.1, 25.9 (3C), 30.3, 31.8, 34.5, 35.3, 71.0, 73.5, 73.8, 77.2, 124.2, 125.5, 125.8, 127.4, 127.5, 127.6, 127.9, 128.3, 138.6; MS *m/z* (CI; NH_3) 367 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{34}O_2SSi$ $[M+H]^+$; 367.2134, found; 367.2134.

Further elution gave sulfanyl acetate **369** as a colourless oil (51 mg, 40%);

R_f 0.41 (10% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ –1.6 (*c* = 1.0, CH_2Cl_2); IR (film) ν_{max} 2952, 2929, 2885, 2856, 1747, 1255, 1200, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s,

3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.15 (d, 3H, *J* = 6.5 Hz, H_6), 1.43-1.85 (m, 4H, H_2 and H_3), 2.11 (s, 3H, $OCOCH_3$), 2.65-2.75 (m, 2H, H_1), 3.48-3.54 (m, 1H, H_5), 3.73 (ddd, 1H, *J* = 3.0, 4.5, 8.0 Hz, H_4), 4.51 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.63 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 5.17 (s, 2H, SCH_2), 7.29-7.39 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6, –4.4, 13.6, 18.0, 21.1, 25.9 (3C), 26.5, 30.2, 32.7, 66.7, 71.0, 73.4, 76.7, 127.5, 127.6 (2C), 128.3 (2C), 138.9, 170.7; MS *m/z* (CI; NH_3) 444 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{22}H_{38}O_4SSi$ $[M+NH_4]^+$; 444.2611, found; 444.2614.

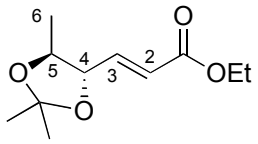
(*E*)-(4*S*,5*S*)-Ethyl-4,5-dihydroxy-2-hexenoate[42] (392)



AD-mix-α containing $K_3Fe(CN)_6$ (17.62 g, 53.6 mmol, 3.0 eq), K_2CO_3 (7.39 g, 53.6 mmol, 3.0 eq), $(DHQ)_2$-PHAL (2.78 g, 3.57 mmol, 0.2 eq) and OsO_4 (0.45 g, 1.79 mmol, 0.1 eq) was added to a stirred solution of $MeSO_2NH_2$ (1.70 g, 17.9 mmol, 1.0 eq) in *t*-BuOH (75 mL) and water (75 mL) and cooled to 0 °C. Ethyl sorbate (**391**) (2.50 g, 17.9 mmol, 1.0 eq) was then added and the mixture stirred vigorously for 14 h at 0 °C. The reaction mixture was quenched with sat. aq. Na_2SO_3 (30 mL) and stirred at rt for 15 min after which EtOAc (50 mL) was added and the layers separated. The aqueous portion was extracted with EtOAc (2 x 50 mL) and the combined organic extracts washed with 1M KOH (20 mL), brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (50% EtOAc/Petroleum ether) to give diol **392** as a colourless oil (1.91 g, 59%);

R_f 0.21 (50% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ –22.4 (*c* = 1.0, CH_2Cl_2) [lit.[42] $[\alpha]_D^{22}$ –54.8 (*c* = 1.17, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3H, *J* = 6.5 Hz, H_6), 1.27 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 2.72 (s, 1H, OH), 3.02 (s, 1H, OH), 3.69 (m, 1H, H_5), 4.03 (m, 1H, H_4), 4.17 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 6.11 (dd, 1H, *J* = 15.5, 1.5 Hz, H_2), 6.89 (dd, 1H, *J* = 15.5, 5.0 Hz, H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.2, 60.8, 70.3, 75.7, 122.6, 146.6, 166.5.

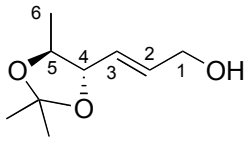
(*E*)-(4*S*,5*S*)-Ethyl-4,5-(*iso*-propylidenedioxy)-2-hexenoate[42] (393)



To solution of diol **392** (535 mg, 3.09 mmol, 1.0 eq) in 2,2-dimethoxypropane (20 mL) 0 °C was added $TsOH{\cdot}H_2O$ (30 mg, 0.16 mmol, 0.05 eq). The solution was allowed to stir at rt for 1 h and K_2CO_3 (1.0 g) was added. The mixture was diluted with Et_2O (50 mL) and water (25 mL) and the layers separated. The organic portion was washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give acetonide **393** as a colourless oil (580 mg, 89%);

R_f 0.46 (20% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ –12.2 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.33 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 1.34 (d, 3H, *J* = 6.0 Hz, H_6), 1.44 (s, 3H, $C(CH_3)_2$), 1.47 (s, 3H, $C(CH_3)_2$), 3.86 (m, 1H, H_5), 4.10 (ddd, 1H, *J* = 1.5, 6.0, 8.5 Hz, H_4), 4.22 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 6.14 (dd, 1H, *J* = 1.0, 13.5 Hz, H_2), 6.88 (dd, 1H, *J* = 5.0, 13.5 Hz, H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 16.6, 26.6, 27.2, 60.5, 76.4, 81.6, 109.2, 122.8, 143.4, 165.8.

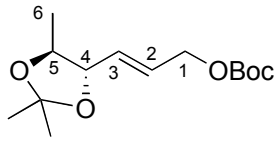
(*E*)-(4*S*,5*S*)-4,5-(*iso*-Propylidenedioxy) hex-2-en-1-ol[42] (394)



To a solution of ester **393** (515 mg, 2.40 mmol, 1.0 eq) in Et_2O (50 mL) at –78 °C was added drop-wise DIBAl-H (20 wt% in toluene, 3.41 mL, 5.99 mmol, 2.5 eq) over 10 min. The reaction mixture was stirred for 2 h at –78 °C and then diluted with MeOH (3 mL) and sat. aq. sodium potassium tartate (20 mL). The mixture was allowed to warm to rt and stirred vigorously for 1 h. The reaction mixture was diluted with Et_2O (25 mL) and water (10 mL) and the layers separated. The aqueous portion was extracted with Et_2O (25 mL) and the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give alcohol **394** as a colourless oil (290 mg, 71%);

R_f 0.27 (50% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ –6.2 (*c* = 1.0, CH_2Cl_2) [lit.[42] $[\alpha]_D^{22}$ –3.0 (*c* = 1.0, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, *J* = 6.0 Hz, H_6), 1.41 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 1.91 (*br.* s, 1H, OH), 3.78 (dq, 1H, *J* = 6.0, 8.0 Hz, H_5), 3.95 (*app.* t, 1H, *J* = 8.0 Hz, H_4), 4.17 (d, 2H, *J* = 4.5 Hz, H_1), 5.68 (dd, 1H, *J* = 15.5, 8.0 Hz, H_3), 5.98 (dt, 1H, *J* = 15.5, 4.5 Hz, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 27.3, 27.7, 63.0, 77.0, 83.5, 108.5, 127.6, 134.6.

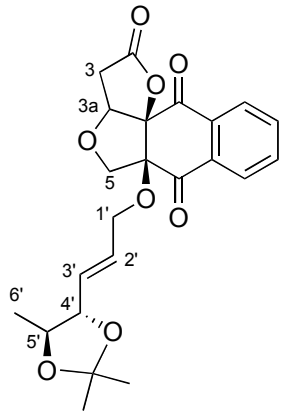
(*E*)-(4*S*,5*S*)-4,5-(*iso*-Propylidenedioxy)-hex-2-en-1-ol *tert*-butyl carbonate[42] (395)



To a solution of alcohol **394** (290 mg, 1.68 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) was added drop-wise over 15 min to a stirred solution of di-*tert*-butyl carbonate (1.09 g, 5.0 mmol, 3.0 eq), Et_3N (0.70 mL, 5.0 mmol, 3.0 eq) and DMAP (10 mg, 0.08 mmol, 0.05 eq) in CH_2Cl_2 (3 mL) at rt. The mixture was allowed to stir for 1 h and then diluted with Et_2O (25 mL) and water (10 mL) and the layers separated. The organic layer was washed with sat. aq. $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give *tert*-butyl carbonate **395** as a colourless oil (235 mg, 72%);

R_f 0.46 (30% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +2.2 (*c* = 1.0, CH_2Cl_2) [lit.[42] $[\alpha]_D^{22}$ +1.3 (*c* = 1.0, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (dd, 3H, *J* = 6.0, 1.0 Hz, H_6), 1.33 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 1.42 (s, 9H, $C(CH_3)_3$), 3.67-3.78 (m, 1H, H_5), 3.87 (*app*. t, 1H, *J* = 7.5 Hz, H_4), 4.51 (d, 2H, *J* = 5.5 Hz, H_1), 5.69 (ddd, 1H, *J* = 15.5, 7.0, 1.0 Hz, H_3), 5.86 (dtd, 1H, *J* = 15.5, 5.5, 0.5 Hz, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 26.9, 27.3, 27.8 (3C), 66.3, 76.6, 82.3, 82.8, 108.5, 128.2, 130.9, 153.2.

(±)-5a-((E)-(4*S*, 5*S*)-4,5-(*iso*-Propylidenedioxy)hex-2-en-1-oxy)-3,3a,5,5a-tetrahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione[42] (396)

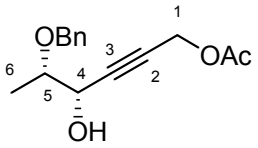


To a cooled (0°C) solution of hydroxy ketone **(±)-2** (300 mg, 1.1 mmol, 1.0 eq) and *tert*-butyl carbonate **395** (1.2 g, 4.4 mmol, 4.0 eq) in de-gassed THF (5 mL) was added $Pd(OAc)_2$ (10 mg, 0.05 mmol, 0.05 eq) and triphenylphosphine (30 mg, 0.1 mmol, 0.1 eq). The solution was evacuated and purged three times with nitrogen and heated to reflux for 6 h. After dilution with THF (30 mL) a solution of bleach (1 mL of ca. 5 wt %) was added and the mixture stirred vigorously for 30 min and then filtered though a short plug of Celite. The filtrate was diluted with EtOAc (50 mL) and washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give allyl ether **396** as an orange oil (29 mg, 61%, 1:1 mixture of diastereoisomers:

R_f 0.58 (60% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) *both isomers* δ 1.24 (d, 3H, *J* = 5.5 Hz, $H_{6'}$), 1.39 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 2.76 (d, 1H, *J* = 18.5 Hz, H_3), 2.90 (dd, 1H, *J* = 6.0, 18.5 Hz, H_3), 3.63-3.74 (m, 1H, $H_{5'}$), 3.86 (*app*. t, 1H, *J* = 7.5 Hz, $H_{4'}$), 3.92 (dd, 1H, J = 5.0, 11.5 Hz, $H_{1'}$), 4.04 (d, 1H, *J* = 8.5 Hz, H_5), 4.07 (dd, 1H, *J* = 5.0 and 11.0 Hz, $H_{1'}$), 4.70 (d, 1H, *J* = 6.0 Hz, H_{3a}), 4.73 and 4.75 (d, 1H, *J* = 8.5 Hz, H_5), 5.60 (dd, 1H, *J* = 7.5, 15.5, $H_{3'}$), 5.77 (dt, 1H, *J* = 5.0, 15.5 Hz, $H_{2'}$), 7.87-7.98 (m, 2H, ArH), 8.21-8.28 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) *both isomers*

δ 17.0, 27.5, 27.7, 35.9, 68.6, 71.2, 76.9, 81.0, 83.1, 89.0, 92.5, 108.9, 128.1, 128.6, 129.5, 130.7, 131.0, 132.5, 134.1, 136.1, 136.4, 174.1, 189.1, 191.6.

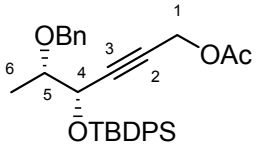
(4*S*,5*S*)-1-Acetic acid-5-benzyloxy-4-hydroxy-hex-2-ynyl ester (419)



To a suspension of dry $Zn(OTf)_2$ (10.16 g, 27.9 mmol, 1.1 eq) and (+)-*N*-methylephedrine (5.46 g, 30.5 mmol, 1.2 eq) in toluene (80 mL) under N_2 was added drop-wise NEt_3 (4.25 mL, 30.5 mmol, 1.2 eq) to afford a turbid milky reaction mixture. After stirring for 2h a solution of propargyl acetate (3.02 mL, 30.5 mL, 1.2 eq) in toluene (20 mL) was added drop-wise and after 15 min aldehyde **347** (4.17 g, 25.4 mmol, 1.0 eq) was added drop-wise and stirred for 5 h. Sat. aq. NH_4Cl (100 mL) was slowly added, the layers separated and the aqueous portion extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with NH_4Cl (3 x 50 mL) and brine (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20-30% EtOAc/Petroleum ether) to give alcohol **419** as a colourless oil (3.23 g, 48%);

R_f 0.38 (40% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +11.2 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 3451, 3063, 3030, 2980, 2934, 2875, 1745, 1496, 1453, 1377, 1225, 1131, 1099, 1061, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J* = 6.0 Hz, H_6), 2.11 (s, 3H, $OCOCH_3$), 3.00 (*br.* s, 1H, OH), 3.67 (*app.* quin., 1H, *J* = 6.0 Hz, H_5), 4.32-4.34 (m, 1H, H_4), 4.60 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 4.72 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 4.74 (s, 2H, H_1), 7.29-7.439 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 20.7, 52.3, 66.3, 71.7, 76.9, 79.9, 85.2, 127.9 (2C), 128.0 (2C), 128.5, 138.0, 170.3; MS *m/z* (CI; NH_3) 280 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{15}H_{18}O_4$ $[M+NH_4]^+$; 280.1549, found; 280.1584.

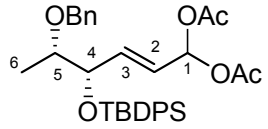
(4*S*,5*S*)-1-Acetic acid-5-benzyloxy-4-(*tert*-butyl-diphenyl-silanyloxy)-hex-2-ynyl ester (416)



To a stirred solution of alcohol **419** (3.23 g, 12.3 mmol, 1.0 eq) and imidazole (2.10 g, 30.8 mmol, 2.5 eq) in DMF (10 mL) under N_2 was added drop-wise TBDPSCl (3.84 mL, 14.8 mmol, 1.2 eq) and the mixture stirred at rt for 12 h. Et_2O (50 mL) was added, and the reaction mixture washed with H_2O (3 x 50 mL) and brine (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give TBDPS ether **416** as a colourless oil (6.77 g, 100%);

R_f 0.31 (50% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +22.3 (c = 1.0, CH_2Cl_2); IR (film) ν_{max} 3070, 2957, 2932, 2889, 2957, 1749, 1471, 1427, 1377, 1223, 1111, 1027, 822, 740, 701, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H, $SiC(CH_3)$), 1.41 (d, 3H, *J* = 6.0 Hz, H_6), 2.08 (s, 3H, $OCOCH_3$), 3.60 (*app.* quin., 1H, *J* = 6.0 Hz, H_5), 4.43 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.51 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.58-4.62 (m, 3H, H_4 and H_1), 7.27-7.51(m, 9H, ArH), 7.73-7.75 (m, 2H, ArH), 7.78-7.82 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 19.1, 20.8, 26.7, 27.0, 52.4, 66.6, 71.4, 77.2, 80.4, 85.4, 127.5 (2*C*), 127.7 (4*C*), 128.3 (2*C*), 129.6, 129.8, 130.0, 133.3 (2*C*), 134.9, 135.5, 135.9, 136.2, 136.3, 138.5, 170.2; MS *m/z* (CI; NH_3) 518 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{31}H_{36}O_4Si$ $[M+NH_4]^+$; 518.2727, found; 518.2728

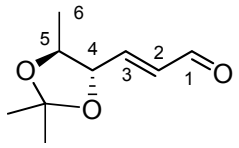
(4*S*,5*S*)-1-Acetic acid-1-acetoxy-5-benzyloxy-4-(*tert*-butyl-diphenyl-silanyloxy)-hex-2-enyl ester (407)



Tris(dibenzylideneacetone)dipalladium (0)-chloroform (280 mg, 0.27 mmol, 0.02 eq) and PPh_3 (815 mg, 3.1 mmol, 0.23 eq) were dissolved in toluene (100 mL) under N_2 and after 10 min a clear yellow solution formed. This was followed by drop-wise addition of freshly distilled acetic acid (1.35 mL, 23.7 mmol, 1.75 eq) and after 20 min a solution of propargyl acetate **416** (6.77 g, 13.5 mmol, 1.0 eq) in toluene (50 mL) was added drop-wise at rt. The reaction mixture was heated at reflux for 18 h and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/Petroleum ether) to give *gem*-diacetate **407** as a colourless oil (3.95 g, 52%);

R_f 0.61 (10% EtOAc/Petroleum ether); IR (film) ν_{max} 3070, 3049, 3031, 2959, 2932, 2891, 2858, 1763, 1427, 1371, 1242, 1204, 1111, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (m, 9H, $SiC(CH_3)_2$ and H_6), 2.12 (s, 6H, $OCOCH_3$), 3.43 (dq, 1H, *J* = 6.0, 6.5 Hz, H_5), 4.25 (s, 2H, OCH_2Ph), 4.49-4.52 (m, 1H, H_4), 5.85 (ddd, 1H, *J* = 1.5, 6.0, 15.5 Hz, H_3), 6.18 (dd, 1H, *J* = 4.5, 15.5 Hz, H_2), 7.17-7.48 (m, 12H, ArH and H_1), 7.67-7.72 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.4, 20.9 (2C), 27.1 (3C), 71.0, 73.1, 77.3, 89.3, 124.7, 127.5, 127.6 (2C), 127.7 (3C), 128.3 (2C), 129.8, 130.0, 133.4 (3C), 133.8, 135.6, 135.9, 136.2, 138.6, 168.5, 168.6; MS *m/z* (CI; NH_3) 578 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{33}H_{40}O_6Si$ $[M+NH_4]^+$; 578.2925, found; 578.2922.

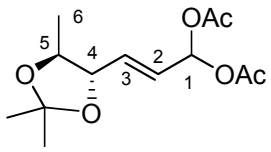
(*E*)-(4*S*,5*S*)-4,5-(*iso*-Propylidenedioxy)-hex-2-en-1-al (428)



To a solution of ester **393** (5.09 g, 23.8 mmol, 1.0 eq) in CH_2Cl_2 (250 mL) at –78 °C was added drop-wise DIBAL-H (1M in hexanes, 24 mL, 24.0 mmol, 1.01 eq). The reaction mixture was allowed to stir at –78°C for 5 h and then quenched with satd. aq. sodium potassium tartate (250 mL), allowed to warm up to room temperature and stirred for 1 h. The layers were separated and the aqueous portion extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (15% EtOAc/Petroleum ether) to give aldehyde **428** as a colourless oil (2.94 g, 79%);

R_f 0.20 (30% Et_2O/Petroleum ether); $[\alpha]_D^{22}$ + 5.6 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, 3H, *J* = 6.0 Hz, H_6), 1.36 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 3.79-3.86 (m, 1H, H_5), 4.14 (m, 1H, H_4), 6.31 (dd, 1H, *J* = 8.0, 15.5 Hz, H_2), 6.69 (dd, 1H, *J* = 5.5, 15.5 Hz, H_3), 9.54 (d, 1H, *J* = 8.0 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 26.5, 27.2, 76.4, 81.5, 109.5, 132.7, 151.7, 192.9.

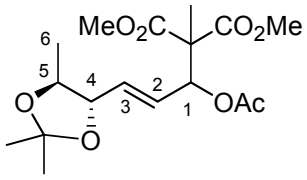
(*E*)-(4*S*,5*S*)-4,5-(*iso*-Propylidenedioxy)-hex-2-en-1,1-diacetoxy (429)



To a solution of aldehyde **428** (1.83 g, 10.8 mmol, 1.0 eq) in CH_2Cl_2 (100 mL) at 0 °C was added acetic anhydride (2.03 mL, 21.5 mL, 2.0 eq) and $FeCl_3$ (17 mg, 0.11 mmol, 0.01 eq). The reaction mixture was stirred at 0 °C for 4 h, quenched with satd. aq. Na_2CO_3 (100 mL) and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts washed with brine (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (15% EtOAc/Petroleum ether) to give *gem*-diacetate **429** as a colourless oil (1.87 g, 64%);

R_f 0.70 (50% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ + 1.2 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 2985, 2935, 2876, 1825, 1764, 1434, 1372, 1239, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3H, *J* = 6.0 Hz, H_6), 1.38 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 2.06 (s, 6H, $OCOCH_3$), 3.76 (qd, 1H, *J* = 6.0, 8.0 Hz, H_5), 3.93 (dd, 1H, *J* = 6.0, 8.0 Hz, H_4), 5.86 (dd, 1H, *J* = 5.5, 15.5 Hz, H_2), 5.96 (dd, 1H, *J* = 6.0, 15.5 Hz, H_3), 7.13 (d, 1H, *J* = 5.5 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 20.8 (2C), 26.8, 27.3, 76.7, 81.6, 88.4, 108.9, 126.5, 132.9, 168.6 (2C); MS *m/z* (CI; NH_3) 290 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{13}H_{20}O_6$ $[M+NH_4]^+$; 290.1604, found; 290.1604.

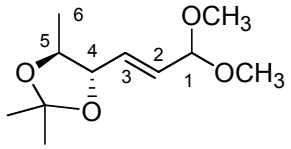
(*E*)-(4*S*,5*S*)-4,5-(*iso*-Propylidenedioxy)-hex-2-en-1-acetoxy-1-dimethylmethyl malonate (430)



To a suspension of NaH (30 mg, 0.74 mmol, 1.5 eq) in THF (1 mL) was added dimethylmethyl malonate (**424**) (138 μL, 1.04 mmol, 2.1 eq). The mixture was stirred at rt until the evolution of H_2 ceased. To this mixture was added, *via* cannula, a solution of *gem*-diacetate **429** (135 mg, 0.5 mmol, 1.0 eq), $Pd_2dba_3{\cdot}CHCl_3$ (13 mg, 0.10 mmol, 0.03 eq) and PPh_3 (26 mg, 0.10 mmol, 0.2 eq). After stirring at rt for 6 h, the mixture was quenched with 10% aq. $NaHSO_4$ (5 mL), extracted with ether (3 x 3 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give dimethylmethyl malonate **430** as a pale yellow oil (79 mg, 44%);

R_f 0.50 (50% Et_2O/Petroleum ether); IR (film) ν_{max} 2985, 2954, 2930, 1742, 1378, 1227, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3H, *J* = 6.0 Hz, H_6), 1.40 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CO_2CH_3)CH_3$), 2.06 (s, 3H, $OCOCH_3$), 3.72 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.70-3.75 (m, 1H, H_5), 3.93 (dd, 1H, *J* = 6.0, 8.0 Hz, H_4), 5.74 (dd, 1H, *J* = 6.0, 15.5 Hz, H_2), 5.83 (dd, 1H, *J* = 6.0, 15.5 Hz, H_3), 5.98 (d, 1H, *J* = 6.0 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 16.5, 20.9, 26.8, 27.3, 52.8 (2C), 57.5, 73.7, 76.7, 82.6 108.7, 127.1, 132.3, 169.2, 169.6, 169.9; MS *m/z* (CI; NH_3) 376 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{17}H_{26}O_8$ $[M+NH_4]^+$; 376.1971, found; 376.1969.

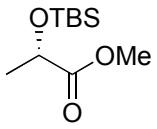
(*E*)-(4*S*,5*S*)-1,1-dimethoxy-4,5-(*iso*-Propylidenedioxy)-hex-2-ene (433)



To a stirred solution of *gem*-diacetate **429** (150 mg, 0.55 mmol, 1.0 eq) and $Pd(PPh_3)_4$ (170 mg, 0.15 mmol, 0.30 eq) in THF (4 mL) was added drop-wise methoxy tributyltin (450 μL, 1.47 mmol, 2.7 eq). The reaction mixture was allowed to stir at rt for 3 h and the crude reaction mixture concentrated under reduced pressure and purified by silica gel flash column chromatography (20% Et_2O/Petroleum ether) to give methyl ether **433** as a pale yellow oil that slowly decomposed on standing (77 mg, 65%);

R_f 0.53 (30% EtOAc/Petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, 3H, *J* = 6.0 Hz, H_6), 1.40 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 3.30 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.79 (qd, 1H, *J* = 6.0, 8.5 Hz, H_5), 3.95 (dd, 1H, *J* = 6.5 Hz, 8.5 Hz, H_4), 4.82 (d, 1H, *J* = 4.0 Hz, H_1), 5.76 (dd, 1H, *J* = 4.0, 15.5 Hz, H_2), 5.84 (dd, 1H, *J* = 6.5, 15.5 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 26.8, 27.3, 52.5, 52.7, 76.6, 82.8, 101.7, 108.6, 130.5, 131.2.

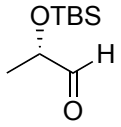
(2*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-propionic acid methyl ester[234] (445)



To a stirred solution of (*S*)-Methyl lactate (**346**) (20.0 g, 192 mmol, 1.0 eq) and imidazole (52.0 g, 768 mmol, 4.0 eq) in DMF (400 mL) under N_2 was added portion-wise TBSCl (49.5 g, 328 mmol, 1.7 eq) and the mixture stirred at rt for 12 h. Et_2O (500 mL) was added, the layers separated and the organic portion washed with H_2O (3 x 250 mL) and brine (3 x 250 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give **445** as a colourless oil (40.6 g, 97%);

R_f 0.25 (10% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ –65.3 (c = 1.0, CH_2Cl_2) [lit.[234] $[\alpha]_D^{25}$ –31.7 (*c* = 0.66, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.36 (d, 3H, *J* = 6.5 Hz, CH_3), 3.69 (s, 3H, OCH_3), 4.30 (q, 1H, *J* = 6.5 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.3, –5.0, 18.3, 21.3, 25.7 (3C), 51.8, 68.3, 174.5.

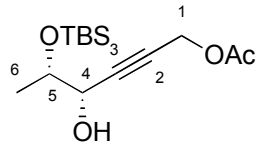
(2*S*)-*tert*-Butyl-dimethyl-silanyloxy)-propanal[234] (444)



To a solution of methyl ester **445** (35.0 g, 160 mmol, 1.0 eq) in CH_2Cl_2 (500 mL) under N_2 at –78 °C was added drop-wise DIBAl-H (1 M in hexanes, 168 mL, 168 mmol, 1.05 eq). The reaction mixture was stirred at –78 °C for 5 h and then quenched with satd. aq. sodium potassium tartate (500 mL) and allowed to warm up to rt. The layers were separated and the aqueous portion extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by distillation under reduced pressure to give aldehyde **444** as a colourless oil (26.0 g, 86%);

B.p. 134 °C (1 atm.); R_f 0.64 (30% Et_2O/Petroleum ether); $[\alpha]_D^{22}$ –47.0 (c = 1.0, $CHCl_3$) [lit.[234] $[\alpha]_D^{25}$ –6.13 (*c* = 1.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.24 (d, 3H, *J* = 6.5 Hz, CH_3), 4.06 (q, 1H, *J* = 6.5 Hz, CH), 9.57 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.0, –4.9, 18.1, 18.4, 25.6 (3C), 73.7, 203.7.

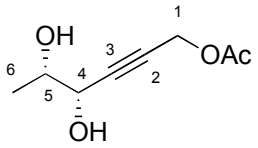
(4*S*,5*S*)-1-acetoxy-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-hydroxy-hex-2-ynyl (443)



To a suspension of dry $Zn(OTf)_2$ (42.5 g, 117 mmol, 1.1 eq) and (+)-*N*-methyl-ephidrine (22.9 g, 127 mmol, 1.2 eq) in toluene (300 mL) under N_2 was added NEt_3 (17.8 mL, 127 mmol, 1.2 eq) to afford a turbid milky reaction mixture. After 2 h at rt a solution of propargyl acetate (12.6 mL, 127 mmol, 1.2 eq) in toluene (50 mL) was added followed by aldehyde **444** (20.0 g, 106 mmol, 1.0 eq). After stirring at rt for 5 h, sat. aq. NH_4Cl (300 mL) was slowly added, the layers separated and the aqueous portion extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with NH_4Cl (3 x 150 mL) and brine (3 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% Et_2O/Petroleum ether) to give alcohol **443** as a colourless oil (14.0 g, 46%);

R_f 0.28 (30% Et_2O/Petroleum ether); $[\alpha]_D^{22}$ +10.1 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 3441, 2954, 2931, 2887, 2857, 1746, 1463, 1378, 1231, 1133, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.21 (d, 3H, *J* = 6.0 Hz, H_6), 2.06 (s, 3H, $OCOCH_3$), 2.65 (*br.* s, 1H, OH), 3.85 (*app*. quin., 1H, *J* = 6.0 Hz, H_5), 4.09 (d, 1H, *J* = 6.0 Hz, H_4), 4.68 (s, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.8, –4.5, 18.0, 20.0, 20.7, 25.7 (3C), 52.2, 67.1, 71.6, 79.1, 85.9, 170.2; MS *m/z* (CI; NH_3) 304 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{14}H_{26}O_4Si$ $[M+NH_4]^+$; 304.1944, found; 304.1947

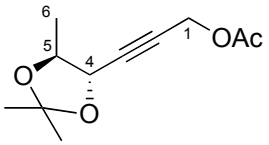
(4*S*,5*S*)-1-Acetoxy-hex-4-yn-2,3-diol (446)



To a solution of alcohol **443** (500 mg, 1.75 mmol, 1.0 eq) in MeCN (15 mL) at 0 °C was added drop-wise a solution of HF (615 μL, 48% in H_2O). After stirring at rt for 4 h, sat. aq. $NaHCO_3$ (50 mL) was slowly added, the layers separated and the aqueous portion extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ (3 x 50 mL) and brine (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% Et_2O/Petroleum ether) to give diol **446** as a colourless oil (286 mg, 92%);

R_f 0.42 (80% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +3.05 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 3398, 2980, 2936, 1738, 1436, 1378, 1237, 1126, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3H, *J* = 6.5 Hz, H_6), 2.08 (s, 3H, $OCOCH_3$), 3.76-3.80 (m, 3H, OH and H_5), 4.12 (d, 1H, *J* = 6.5 Hz, H_4), 4.69 (s, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 20.7, 52.3, 67.2, 70.9, 80.0, 85.2, 170.7; MS *m/z* (CI; NH_3) 190 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_8H_{12}O_4$ $[M+NH_4]^+$; 190.1079, found; 190.1073.

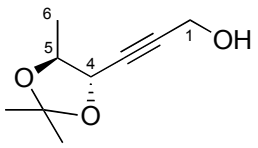
(4*S*,5*S*)-Acetic acid 4,5-(*iso*-Propylidenedioxy)-prop-2-ynyl ester (442)



To a solution of diol **446** (4.2 g, 24.4 mmol, 1.0 eq) in 2,2-dimethoxy propane (300 mL) at 0 °C was added *p*-TsOH (465 mg, 2.4 mmol, 0.1 eq). After stirring at rt for 1 h, solid K_2CO_3 (1.0 g) was added and the solution diluted with Et_2O (150 mL) and H_2O (75 mL). The layers were separated and the organic portion washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% Et_2O/Petroleum ether) to give acetonide **442** as a colourless oil (5.13 g, 99%);

R_f 0.42 (20% Et_2O/Petroleum ether); $[\alpha]_D^{22}$ +14.4 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 2986, 2936, 2893, 1748, 1448, 1380, 1226, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, 3H, *J* = 6.0 Hz, H_6), 1.37 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 2.05 (s, 3H, $OCOCH_3$), 4.03-4.09 (m, 1H, H_5), 4.13-4.21 (m, 1H, H_4), 4.68 (s, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 20.6, 26.2, 27.1, 50.7, 71.7, 77.4, 80.7, 82.7, 109.7, 170.1; MS *m/z* (CI; NH_3) 230 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{11}H_{16}O_4$ $[M+NH_4]^+$; 230.1392, found; 230.1398.

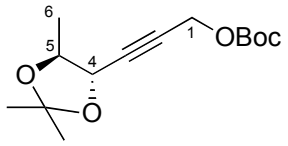
(4*S*,5*S*)-4,5-(*iso*-Propylidenedioxy)-prop-2-ynyl-1-ol (447)



To a solution of acetate **442** (5.00 g, 23.6 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) at –78 °C was added drop-wise a solution of DIBAl-H (1 M in hexanes, 30.1 mL, 30.1 mmol, 1.30 eq). After stirring at –78 °C for 5 h, satd. aq. sodium potassium tartate (50 mL) was added and the reaction mixture allowed to warm up to rt. The layers were separated and the aqueous portion extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine (3 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20% EtOAc/Petroleum ether) to give alcohol **447** as a colourless oil (3.90 g, 97%);

R_f 0.42 (40% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +0.9 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 3429, 2986, 2934, 2893, 1453, 1380, 1237, 1169, 1113, 1090, 1023, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J* = 6.0 Hz, H_6), 1.39 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 2.85 (*br*. s, 1H, OH), 4.02-4.10 (m, 1H, H_5), 4.12-4.18 (m, 1H, H_4), 4.28 (s, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 26.3, 27.1, 50.7, 71.9, 77.4, 81.1, 85.3, 109.5; MS *m/z* (CI; NH_3) 171, $[M+H]^+$, 188 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_9H_{14}O_3$ $[M+H]^+$; 171.1021, found; 171.1025.

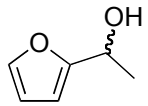
(4*S*,5*S*)-Carbonic acid *tert*-butyl ester 4,5-(*iso*-propylidenedioxy)-prop-2-ynyl ester (441)



To a solution of Boc_2O (5.51 g, 25.2 mmol, 1.1 eq), Et_3N (6.4 mL, 45.9 mmol, 2.0 eq) and DMAP (140 mg, 1.1 mmol, 0.05 eq) in CH_2Cl_2 (50 mL) was added drop-wise a solution of alcohol **447** (3.9 g, 22.9 mmol, 1.0 eq) in CH_2Cl_2 (10 mL). After stirring at rt for 1 h, EtOAc (50 ml) and H_2O (50 mL) were added, the layers separated and the aqueous portion extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give *tert*-butyl carbonate **441** as a colourless oil (4.44 g, 72 %);

R_f 0.67 (20% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ +1.0 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} 2984, 2936, 2893, 1747, 1456, 1371, 1277, 1255, 1161, 1092, 1032, 857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (dd, 3H, *J* = 1.0 Hz, 6.0 Hz, H_6), 1.38 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 1.47 (s, 9H, $C(CH_3)_3$), 4.04-4.10 (m, 1H, H_5), 4.13-4.15 (m, 1H, H_4), 4.69 (s, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 26.2, 27.1, 27.6 (3C), 54.5, 71.7, 77.3, 80.4, 82.9, 83.2, 109.7, 152.6; MS *m/z* (CI; NH_3) 288 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{14}H_{22}O_5$ $[M+NH_4]^+$; 288.1811, found; 288.1800.

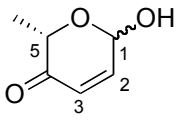
(±)-1-Furan-2-yl-ethanol[235] (467)



To a solution of freshly distilled furan (**466**) (10.0 mL, 138 mmol, 1.0 eq) in THF (50 mL) at 0 °C was added drop-wise *n*-butyllithium (2.5 M in hexanes, 60.5 mL, 151 mmol, 1.1 eq). The reaction mixture was stirred at rt for 1 h and then re-cooled to 0 °C. Freshly distilled acetaldehyde (10.0 mL, 179 mmol, 1.3 eq) was added over 10 min and the reaction mixture was allowed to warm to rt. After 15 h a mixture of H_2O/THF (1 : 1 v/v, 100 mL) was added and the reaction mixture extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with H_2O (3 x 30 mL), satd. aq. citric acid (3 x 30 mL) and brine (3 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by distillation under reduced pressure to give alcohol **467** as a colourless oil (9.40 g, 61%);

B.p. 39 °C (0.3 mmHg); R_f 0.59 (50% EtOAc/Petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 3H, J = 6.5 Hz, CH_3), 4.78 (m, 1H, C*H*OH), 6.15 (m, 1H, ArH), 6.25 (m, 1H, ArH), 7.29 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 63.4, 105.1, 110.1, 141.8, 157.8.

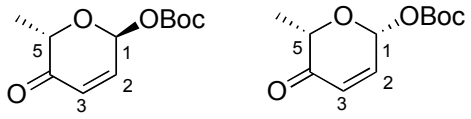
(1*RS*,5*S*)-1-Hydroxy-5-methyl-6H-pyran-4-one[210] (468)



To a solution of (*S*)-furyl-ethanol **467** (2.5 g, 22.3 mmol, 1.0 eq) in THF (55 mL) and H_2O (20 mL) at 0 °C was added solid $NaHCO_3$ (3.75 g, 44.6 mmol, 2.0 eq), NaOAC (1.83 g, 22.3 mmol, 1.0 eq) and NBS (3.97 g, 22.3 mmol, 1.0 eq). After 1 h at 0 °C sat. aq. $NaHCO_3$ (5 mL) was added and the reaction mixture extracted with Et_2O (3 x 60 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (35% EtOAc/petroleum ether) to give alcohol **468** as a colourless oil (2.37 g, 83%);

R_f 0.38 (50% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) *both isomers* δ 1.33 and 1.39 (d, 3H, *J* = 7.0 and 6.5 Hz, CH_3), 4.19 and 4.67 (dq and d, 1H, *J* = 1.0, 6.5 and 7.0 Hz, H_5), 4.80 and 5.15 (d, 1H, *J* = 5.0 and 7.5 Hz, OH), 5.58 and 6.06 (m, 1H, H_1), 6.06 (d and dd, 1H, *J* = 10.0 and 1.5, 10.5 Hz, H_3), 6.89 and 6.93 (dd, 1H, *J* = 3.5, 10.0 and 1.5, 10.5 Hz, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 16.1, 70.4, 75.1, 87.5, 90.9, 126.9, 128.3, 145.2, 148.9, 197.1, 197.7.

(1*S*,5*S*)-Carbonic acid *tert*-butyl ester 5-methyl-4-oxo-4,5-dihydro-2H-pyran-1-yl ester[210] (3) and (1*R*,5*S*)-Carbonic acid *tert*-butyl ester 5-methyl-4-oxo-4,5-dihydro-2H-pyran-1-yl ester (454)



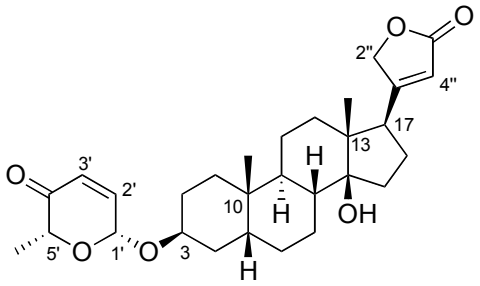
To a solution of alcohol **468** (1.0 g, 7.8 mmol, 1.0 eq) in CH_2Cl_2 (8 mL) at –78 °C was added a solution of Boc_2O (2.04 g, 9.4 mmol, 1.2 eq) and DMAP (95 mg, 0.78 mmol, 0.1 eq) in CH_2Cl_2 (1 mL). The reaction mixture was warmed up to rt and after 30 min sat. aq. $NaHCO_3$ (35 mL) was added. The reaction mixture was extracted with Et_2O (3 x 35 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/petroleum ether) to give *tert*-butyl carbonate **(*S*,*S*)-3** as a colourless oil (1.21 g, 68%);

R_f 0.42 (10% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ + 102.3 (*c* = 1.0, CH_2Cl_2) [lit[210] $[\alpha]_D^{25}$ +98 (*c* = 1.0, CH_2Cl_2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 3H, *J* = 7.0 Hz, CH_3), 1.53 (s, 9H, $OCOC(CH_3)_3$), 4.65 (q, 1H, *J* = 7.0 Hz, H_5), 6.21 (d, 1H, *J* = 10.0 Hz, H_3), 6.34 (d, 1H, *J* = 3.5 Hz, H_1), 6.88 (dd, 1H, *J* = 3.5, 10.0 Hz, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 27.7 (3C), 72.2, 83.6, 89.2, 128.4, 141.0, 151.9, 195.8;

Further elution gave *tert*-butyl carbonate **(*R*,*S*)-454** (375 mg, 21%) as colourless oil;

R_f 0.38 (10% EtOAc/Petroleum ether); $[\alpha]_D^{22}$ –39.6 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, 3H, *J* = 7.0 Hz, CH_3), 1.51 (s, 9H, $OCOC(CH_3)_3$), 4.35 (q, 1H, *J* = 7.0 Hz, H_5), 6.20 (dd, 1H, *J* = 1.0, 10.5 Hz, H_3), 6.36 (dd, 1H, *J* = 1.0, 2.5 Hz, H_1), 6.89 (dd, 1H, *J* = 2.5, 10.5 Hz, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 27.7 (3C), 75.7, 83.6, 89.9, 128.3, 142.9, 151.8, 195.9.

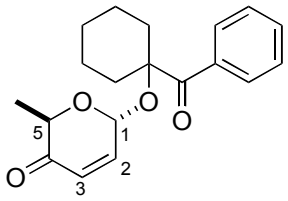
(1'*RS*,5'*RS*)-1'-(3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*R*,17*R*)-14-Hydroxy-10,13-dimethyl-17-(5-oxo-2,5-dihydro-furan-3-yl)-hexadecahydro-cyclopenta[a]phenanthren-3-yloxy]-5'-methyl-6H-pyran-4'-one[214] (455)



To a solution of pyranone **454** (204 mg, 0.89 mmol, 1.0 eq) and digitoxigenin (**453**) (502 mg, 1.34 mmol, 1.5 eq) in CH_2Cl_2/THF (3 mL, 4:1 v/v) at 0 °C and under N_2 was added a solution of $Pd_2(dba)_3$ (20 mg, 2.5 mol%) and PPh_3 (23 mg, 10 mol%) in CH_2Cl_2 (0.5 mL) upon which the maroon coloured solution turned dark green. After 8 h at 0 °C sat. aq. $NaHCO_3$ (5 mL) was added and the reaction mixture extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (40% EtOAc/petroleum ether) to give glycoside **455** as a white solid (341 mg, 79%);

R_f 0.45 (60% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.18-1.90 (m, 18H, CH_2), 1.43 (d, 3H, *J* = 7.0 Hz, CH_3-C5'), 2.07-2.19 (m, 3H, CH), 2.75-2.79 (m, 1H, H_{17}), 4.14-4.19 (m, 2H, $H_{5'}$ and H_3), 4.80 (dd, 1H, *J* = 1.0, 18.0 Hz, $H_{2''}$), 5.00 (d, 1H, *J* = 1.0, 18.0 Hz, $H_{2''}$), 5.39 (m, 1H, $H_{4''}$), 5.85 (m, 1H, $H_{1'}$), 6.09 (dd, 1H, *J* = 1.5, 10.5 Hz, $H_{3'}$), 6.88 (dd, 1H, *J* = 1.5, 10.5 Hz, $H_{2'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 16.9, 21.1, 21.4, 23.7, 26.5, 26.6, 26.9, 29.8, 30.1, 33.0, 35.2, 35.7, 36.4, 40.0, 41.7, 49.7, 50.9, 73.6 (2*C*), 75.1, 85.4, 93.9, 117.4, 128.0, 148.0, 174.8, 175.1, 197.2.

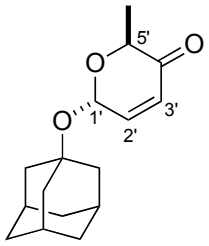
(±)-(1*RS*,5*RS*)-1-(1-Benzoyl-cyclohexyloxy)-5-methyl-6H-pyran-4-one (475)



To a flame dried flask under N_2, was added pyranone **3** (112 mg, 0.49 mmol, 2.0 eq), 1-hydroxycyclohexyl phenyl ketone (**474**) (50 mg, 0.24 mmol, 1.0 eq), $Pd_2(dba)_3$ (11 mg, 2.5 mol%), PPh_3 (13 mg, 10 mol%) and molecular sieves 13X. CH_2Cl_2 (0.8 mL) was added and after 5 min the maroon coloured solution turned dark green. After 6 h at rt the reaction mixture was filtered through celite, concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (100% CH_2Cl_2) to give glycoside **475** as a colourless oil that slowly solidified upon standing (60 mg, 78%);

R_f 0.55 (20% EtOAc/Petroleum ether); IR (film) ν_{max} 2936, 2858, 1701, 1678, 1447, 1243, 1079, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 7.0 Hz, CH_3), 1.32-1.41 (m, 1H CH_2), 1.59-1.76 (m, 5H, CH_2), 1.88-1.95 (m, 1H, CH_2), 2.04-2.11 (m, 1H, CH_2), 2.16-2.26 (m, 2H, CH_2), 4.42 (q, 1H, *J* = 7.0 Hz, H_5), 5.23 (d, 1H, *J* = 3.5 Hz, H_1), 6.00 (d, 1H, *J* = 10.0 Hz, H_3), 6.38 (dd, 1H, *J* = 3.5, 10.0 Hz, H_2), 7.44 (t, 2H, *J* = 7.5 Hz, ArH), 7.54 (t, 1H, *J* = 7.5 Hz, ArH), 8.15 (d, 2H, *J* = 7.5 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 21.7, 21.9, 25.3, 33.1, 33.8, 71.2, 85.6, 89.8, 127.0, 128.3 (2C), 130.1 (2C), 132.8, 134.9, 143.6, 197.0, 202.2; MS *m/z* (CI; NH_3) 332 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{19}H_{22}O_4$ $[M+H]^+$; 315.1610, found; 315.1607.

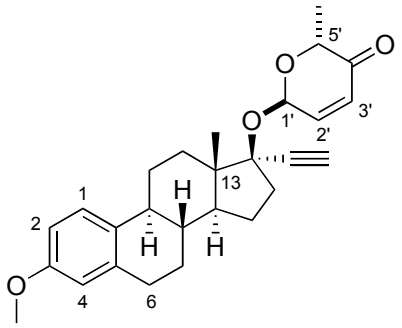
(1'*RS*,5'*RS*)-1'(adamantan-1-yloxy)-5'-methyl-6H-pyran-4-one[206] (478)



To a flame dried flask under N_2, was added pyranone **3** (150 mg, 0.66 mmol, 2.0 eq), adamantan-1-ol (50 mg, 0.33 mmol, 1.0 eq), $Pd_2(dba)_3$ (8 mg, 2.5 mol%), PPh_3 (9 mg, 10 mol%) and molecular sieves 13X. CH_2Cl_2 (0.7 mL) was added and after 5 min the maroon coloured solution turned dark green. After 5 h at rt the reaction mixture was filtered through celite and concentrated under reduced pressure to give an inseparable 1.35 : 1 mixture of *tert*-butyl acetal by-product **465** and glycoside **478** as a white solid (132 mg, 100% conversion by ^{1}H NMR);

R_f 0.45 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ.1.35 (d, 1H, J = 7.0 Hz, CH_3), 1.62-1.72 (m, 6H, CH_2), 1.84-1.91 (m, 6H, CH_2), 2.19 (*br*. s, 3H, CH), 4.61-4.69 (m, 3H, $H_{5'}$), 5.60 (d, 1H, J = 3.5 Hz, $H_{1'}$), 6.04 (d, 1H, J = 10.0 Hz, $H_{3'}$), 6.76 (dd, 1H, J = 3.5, 10.0 Hz, $H_{2'}$).

(1'*RS*,5'*RS*)-1'-((8*S*,9*S*,13*S*,14*R*,17*R*)-17-Ethynyl-2-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yloxy)-5'-methyl-6H-pyran-4-one (480)

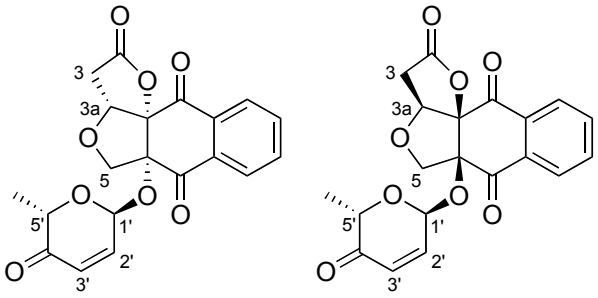


To a flame dried flask under N_2, was added pyranone **3** (37 mg, 0.16 mmol, 2.0 eq), mestranol (**479**) (25 mg, 0.08 mmol, 1.0 eq), $Pd_2(dba)_3$ (2 mg, 2.5 mol%), PPh_3 (2 mg, 10 mol%) and molecular sieves 13X. CH_2Cl_2 (0.8 mL) was added and after 5 min the maroon coloured solution turned dark green. After 6 h at rt the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give glycoside **480** as a white crystalline solid (34 mg, 100%, 1:1 mixture of diastereoisomers);

M.p. 114-117 °C (*t*-BuOMe/Petroleum ether); R_f 0.50 (20% EtOAc/Petroleum ether); IR (film) 3275, 2980, 2934, 2870, 1699, 1499, 1254, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both isomers* δ 0.92 and 0.93 (s, 3H, CH_3-C13), 1.40 and 1.41 (d, 3H, *J* = 7.0 and 6.5 Hz, CH_3-C5'), 1.43-2.40 (m, 13H, CH and CH_2), 2.76 and 2.77 (s, 1H, C≡CH), 2.87-2.91 (m, 2H, H_6), 3.81 (s, 3H, OCH_3), 4.59 and 4.71 (q, 1H, *J* = 7.0 and 6.5 Hz, $H_{5'}$), 5.77 and 5.91 (d, 1H, *J* = 3.5 Hz, $H_{6'}$), 6.09 and 6.10 (d, 1H, *J* = 10.0 Hz, $H_{2'}$), 6.66 (d, 1H, *J* = 2.5 Hz, H_4), 6.74 (dd, 1H, *J* = 2.5, 8.5 Hz, H_2), 6.81 and 6.84 (dd, 1H, *J* = 3.5, 10.0 Hz, 1 dia., $H_{2'}$), 7.24 (d, 1H, *J* = 8.5 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) *both isomers* δ 12.9, 13.0, 15.3, 22.2, 23.2, 26.3, 26.4, 27.2, 27.3, 29.8, 32.8, 32.9, 37.0, 37.7, 39.1, 39.4, 43.4, 43.6, 47.6, 48.2, 48.4, 49.7, 55.2, 70.6, 71.1, 84.1, 84.5, 86.2, 86.7, 90.2, 90.4, 111.5, 113.8, 126.4, 126.8, 132.5, 137.9, 144.7, 157.5, 197.4; MS *m/z*

(CI; NH_3) 421 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{27}H_{32}O_4$ $[M+H]^+$; 421.2379, found; 421.2383.

(3a*R*,5a*R*,11a*S*)-5a-((1'*S*,5'*S*)-5'-Methyl-4'-oxo-4',5'-dihydro-2H-pyran-1'-yloxy)-3,3a,5,5a-tetrahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione (484) and (3a*S*,5a*S*,11a*R*)-5a-((1'*S*,5'*S*)-5'-Methyl-4'-oxo-4',5'-dihydro-2H-pyran-1'-yloxy)-3,3a,5,5a-tetrahydro-furo[3,2-b]naphtho[2,3-c]furan-2,6,11-trione (4)



To a flame dried flask under N_2, was added pyranone **(*S*,*S*)-3** (166 mg, 0.73 mmol, 2.0 eq), hydroxy-ketone **(±)-2** (100 mg, 0.36 mmol, 1.0 eq), $Pd_2(dba)_3$ (8 mg, 2.5 mol%), PPh_3 (10 mg, 10 mol%) and molecular sieves 13X (~1g). CH_2Cl_2 (4 mL) was added and after 5 min. the maroon coloured solution turned dark green. After 5 h at rt the reaction mixture was filtered through celite®, concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (2% MeOH/$CHCl_3$) to give a 1:1 mixture of glycosides **484** and **4**. Recrystallisation from CH_2Cl_2/^{t}BuOMe gave glycoside **484** as a white crystalline solid (56 mg, 40%);

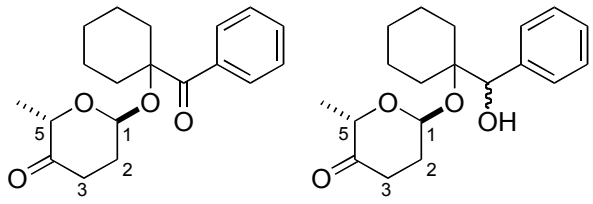
M.p. (CH_2Cl_2/^{t}BuOMe) 198-203 °C; $[\alpha]_D^{22}$ +35.8 (*c* = 1.0, CH_2Cl_2); R_f 0.40 (40% EtOAc/Petroleum ether); IR (film) ν_{max} 2926, 2256, 1803, 1701, 1593, 1398, 1375, 1272, 1060, 935 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, 3H, *J* = 6.5 Hz, CH_3), 2.77 (d, 1H, *J* = 18.5 Hz, H_3), 2.89 (dd, 1H, *J* = 6.5, 18.5 Hz, H_3), 4.07 (d, 1H, *J* = 9.0 Hz, H_5), 4.73-4.78 (m, 2H, H_{3a} and $H_{5'}$), 4.85 (d, 1H, *J* = 9.0 Hz, H_5), 5.20 (d, 1H, *J* = 3.5 Hz, $H_{1'}$), 6.09 (d, 1H, *J* = 10.5 Hz, $H_{3'}$), 6.66 (dd, 1H, *J* = 3.5, 10.5 Hz, $H_{2'}$), 7.92-7.97 (m, 2H, ArH), 8.27-8.30 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 35.6, 72.2, 72.3, 81.7, 87.2, 90.7, 91.9, 128.0 (2*C*), 128.2, 132.3, 134.0, 135.7, 136.4, 140.6, 173.6, 187.6, 192.4, 195.6; MS *m/z* (CI; NH_3) 402 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{20}NO_8$ $[M+NH_4]^+$; 402.1189, found; 402.1202; Anal. Calcd. for $C_{20}H_{16}O_8$; C, 62.50; H, 4.20;

found; C, 62.57; H, 4.18; X-ray crystal data $C_{20}H_{16}O_8$, M = 472.47, Monoclinic, P2(1), a = 9.5417(3) Å, b = 9.27423(19) Å, c = 13.5694(3) Å, α = 90°, β = 105.346(3)°, γ = 90°, V = 1157.97(8) Å^3, Z = 2, D_C = 1.355 Mg/m^3, μ(Cu-Kα) = 0.103 mm^{-1}, T = 173 K, colourless prisms, 18151 independent measured reflections, 5187 independent observed reflections [F>4σ(F)], 320 parameters.

Concentration of the mother liquor and further chromatography gave glycoside **4** as a white amorphous solid (53 mg, 39%);

$[\alpha]_D^{22}$ –127.5 (*c* = 1.0, $CHCl_3$); R_f 0.40 (40% EtOAc/Petroleum ether); IR (film) ν_{max} 2926, 2256, 1803, 1701, 1593, 1398, 1375, 1272, 1060, 935 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, *J* = 6.5 Hz, CH_3), 2.79 (d, 1H, *J* = 19.0 Hz, H_3), 2.95 (dd, 1H, *J* = 6.0, 19.0 Hz, H_3), 4.09 (d, 1H, *J* = 9.0 Hz, H_5), 4.26 (q, 1H, *J* = 6.5 Hz, $H_{5'}$), 4.75 (d, 1H, *J* = 9.0 Hz, H_5), 4.81 (d, 1H, *J* = 6.0 Hz, H_{3a}), 5.40 (d, 1H, *J* = 3.5 Hz, $H_{1'}$), 6.08 (d, 1H, *J* = 10.0 Hz, $H_{3'}$), 6.76 (dd, 1H, *J* = 3.5, 10.0 Hz, $H_{2'}$), 7.89-7.96 (m, 2H, ArH), 8.20-8.29 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 35.4, 70.9, 73.4, 82.1, 87.0, 91.3, 91.7, 127.8, 127.9, 128.1, 131.8, 133.6, 135.6, 135.9, 140.5, 173.5, 189.0, 192.0, 195.3; MS *m/z* (CI; NH_3) 402 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{20}NO_8$ $[M+NH_4]^+$; 402.1189, found; 402.1196.

(±)-(1*S*,5*S*)-1-(1-Benzoyl-cyclohexyloxy)-5-methyl-dihydro-pyran-4-one (489) and (±)-(1*S*,5*S*)-1-[(1*RS*)-1-(Hydroxy-phenyl-methyl)-cyclohexyloxy]-5-methyl-dihydro-pyran-4-one (488)



To a solution of pyranone **476** (250 mg, 0.80 mmol, 1.0 eq) in EtOAc (40 mL) was added 10% Pd/C (835 mg, 0.80 mmol, 1.0 eq). The reaction mixture was degassed and flushed with H_2 three times, then placed under H_2 (balloon). After stirring at rt for 18 h the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/Petroleum ether) to give pyranone **489** as a white crystalline solid (70 mg, 28%);

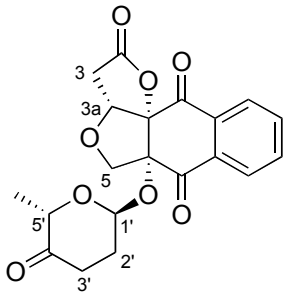
M.p. (EtOAc/hexane) 129-130 °C; R_f 0.50 (20% EtOAc/Petroleum ether); IR (film) ν_{max} 2936, 2858, 1730, 1678, 1596, 1447, 1246, 1038, 1024, 1001, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J* = 7.0 Hz, CH_3), 1.54-2.07 (m, 9H CH_2), 2.15-2.29 (m, 3H, H_2 and CH_2), 2.35-2.39 (m, 2H, H_3), 3.92 (q, 1H, *J* = 7.0 Hz, H_5), 5.21 (m, 1H, H_1), 7.44 (t, 2H, *J* = 7.5 Hz, ArH), 7.54 (t, 1H, *J* = 7.5 Hz, ArH), 8.28 (d, 2H, *J* = 7.5 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.7, 21.8, 25.5, 27.5, 29.7, 33.4, 34.8, 71.9, 83.8, 93.3, 128.1, 130.3 (2C), 132.5 (2C), 134.7, 202.0, 211.9; MS *m/z* (CI; NH_3) 317 $[M+H]^+$; HRMS (CI; NH_3) calculated for $C_{19}H_{24}O_4$ $[M+H]^+$; 317.1766, found; 317.1766.

Further elution gave alcohol **488** as a colourless oil (147 mg, 58%, 1:1 mixture of unassigned diastereoisomers);

R_f 0.34 (20% EtOAc/Petroleum ether); IR (film) ν_{max} 3509, 2937, 2859, 1729, 1452, 1089, 1027, 998 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both isomers* δ 1.00-1.89 (m, 1H,

CH_2), 1.28-1.43 (m, 3H, CH_2), 1.34 and 1.35 (d, 3H, *J* = 7.0 Hz, CH_3), 1.46-2.00 (m, 6H, CH_2), 2.10-2.49 (m, 1H, H_2), 2.51-2.64 (m, 2H, H_3), 3.53 (d, 1H, *J* = 3.5 Hz, OH), 4.57 and 4.59 (q, 1H, *J* = 7.0 Hz, H_5), 4.68 (*br*. s, 1H, OH), 4.65 and 4.83 (s and d, 1H, *J* = 3.5 Hz, C*H*OH), 5.51 and 5.52 (t, 1H, *J* = 5.5 and 6.5 Hz, H_1), 7.28-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *both isomers* δ 14.8, 14.9, 21.0, 21.2, 21.3, 21.6, 24.5, 25.6 (2C), 28.6, 29.4, 29.7, 29.8, 33.8 (2C), 34.1, 71.6, 71.7, 78.3, 80.6, 81.4, 82.3, 91.3, 91.4, 127.5, 127.6, 127.7 (2C), 127.8 (2C), 127.9 (2C), 128.0 (2C), 140.0, 140.6, 210.2; 210.8; MS *m/z* (CI; NH_3) 336 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{19}H_{26}O_4$ $[M+H]^+$; 319.1923, found; 319.1923.

(3a*R*,5a*R*,11a*S*)-5a-((1'*S*,5'*S*)-5'-Methyl-4-oxo-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a-tetrahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione (490)

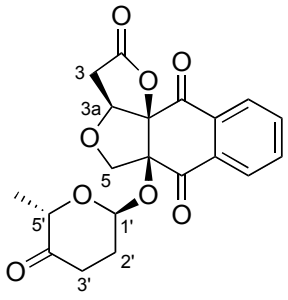


To a solution of glycoside **484** (24 mg, 0.06 mmol, 1.0 eq) and diphenylsulfide (10 μL, 0.06 mmol, 1.0 eq) in MeOH (3.5 mL) was added 10% Pd/C (69 mg, 0.06 mmol, 1.0 eq). The reaction mixture was degassed and flushed with H_2 three times, then placed under H_2 (balloon). After stirring at rt for 5 h the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (50% EtOAc/Petroleum ether) to give ketone **490** as a white crystalline solid (21 mg, 87%);

M.p. (CH_2Cl_2/*t*-BuOMe) 215 °C; $[\alpha]_D^{22}$ –72.0 (*c* = 1.0, CH_2Cl_2); R_f 0.62 (60% EtOAc/Petroleum ether); IR (film) ν_{max} 1085, 1698, 1590, 1274, 1122, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, 3H, *J* = 6.5 Hz, CH_3), 1.92-2.01 (m, 1H, $1H_{2'}$), 2.18-2.29 (m, 2H, $H_{2'}$ and $H_{3'}$), 2.33-2.40 (m, 1H, $1H_{3'}$), 2.76 (d, 1H, *J* = 19.0 Hz, H_3), 2.90 (dd, 1H, *J* = 6.5, 19.0 Hz, H_3), 4.04 (d, 1H, *J* = 9.0 Hz, H_5), 4.46 (q, 1H, *J* = 6.5 Hz, $H_{5'}$), 4.73 (d, 1H, *J* = 6.0 Hz, H_{3a}), 4.82 (d, 1H, *J* = 9.0 Hz, H_5), 5.00 (t, 1H, *J* = 6.0 Hz, $H_{1'}$), 7.90-7.97 (m, 2H, ArH), 8.25-8.30 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.2, 32.7, 35.7, 72.8, 73.1, 81.8, 86.8, 91.9, 94.9, 127.9, 128.0, 132.2, 134.0, 135.6, 136.2, 173.9, 187.7, 192.9, 210.1; MS *m/z* (CI; NH_3) 404 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{22}NO_8$ $[M+NH_4]^+$; 404.1359, found; 404.1353; X-ray crystal data $C_{20}H_{18}O_8 \cdot C_5H_{12}O$, M = 474.49, Monoclinic, P2(1), a = 9.53423(8) Å, b = 9.22204(6) Å, c = 13.77287(11) Å, α = 90°, β = 104.5013(8)°, γ = 90°, V = 1172.40(6) $Å^3$, Z = 2, D_c = 1.344 Mg/m^3, μ(Cu-Kα) = 0.853 mm^{-1}, T = 173 K, colourless blocks, 18283

independent measured reflections, 3638 independent observed reflections [F>4s(F)], 329 parameters.

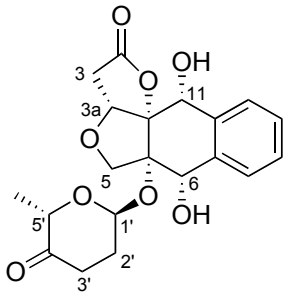
(3a*S*,5a*S*,11a*R*)-5a-((1'*S*,5'*S*)-5'-Methyl-4-oxo-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a-tetrahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione (485)



To a solution of glycoside **4** (24 mg, 0.06 mmol, 1.0 eq) and diphenylsulfide (10 μL, 0.06 mmol, 1.0 eq) in MeOH (3.5 mL) was added 10% Pd/C (69 mg, 0.06 mmol, 1.0 eq). The reaction mixture was degassed and flushed with H_2 three times, then placed under H_2 (balloon). After stirring at rt for 5 h the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (40% EtOAc/Petroleum ether) to give ketone **485** as a colourless oil (20 mg, 83%);

$[\alpha]_D^{22}$ –232.1 (*c* = 1.0, $CHCl_3$); R_f 0.45 (40% EtOAc/Petroleum ether); IR (film) ν_{max} 2940, 1806, 1732, 1698, 1594, 1271, 1160, 1061, 1007, 936 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, 3H, *J* = 6.5 Hz, CH_3), 1.89-2.03 (m, 1H, $1H_{2'}$), 2.22-2.42 (m, 3H, $H_{3'}$ and $H_{2'}$), 2.78 (dd, 1H, *J* = 1.0, 19.0 Hz, H_3), 2.93 (dd, 1H, *J* = 7.0, 19.0 Hz, H_3), 4.04 (q, 1H, *J* = 6.5 Hz, $H_{5'}$), 4.07 (d, 1H, *J* = 9.0 Hz, H_5), 4.75 (d, 1H, *J* = 9.0 Hz, H_5), 4.78 (dd, 1H, *J* = 1.0, 7.0 Hz, H_{3a}), 5.24 (t, 1H, *J* = 5.5 Hz, $H_{1'}$), 7.87-7.94 (m, 2H, ArH), 8.20-8.24 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 27.3, 32.7, 35.4, 71.8, 73.5, 82.0, 86.8, 91.5, 95.8, 127.7, 127.8, 131.8, 133.7, 135.3, 135.8, 173.6, 189.3, 192.6, 209.5; MS *m/z* (CI; NH_3) 402 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{22}NO_8$ $[M+NH_4]^+$; 404.1345, found; 404.1352.

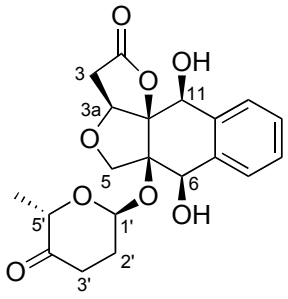
(3a*R*,5a*S*,6*S*,11*R*,11a*S*)-6,11-Dihydroxy-5a-((1'*S*,5'*S*)-5'-Methyl-4-oxo-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a,6,11-hexahydro-furo[3,2-b]naphtho[2,3-c]furan-2-one (495)



To a solution of glycoside **484** (100 mg, 0.26 mmol, 1.0 eq) in EtOAc (11 mL) was added 10% Pd/C (290 mg, 0.26 mmol, 1.0 eq). The reaction mixture was degassed and flushed with H_2 three times, then placed under H_2 (balloon). After stirring at rt for 14 h the reaction mixture was filtered through celite® and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (60% EtOAc/petroleum ether) to give diol **495** as a white solid (86 mg, 85%);

M.p. (EtOAc/CH_2Cl_2) >250 °C dec.; $[\alpha]_D^{22}$ –108.1 (*c* = 0.8, $CHCl_3$); R_f 0.48 (10% MeOH/$CHCl_3$); IR (film) ν_{max} 3424, 2925, 1778, 1724, 1178, 1062, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J* = 6.5 Hz, CH_3), 2.07-2.17 (m, 1H, $H_{2'}$), 2.38-2.52 (m, 3H, $H_{2'}$ and $H_{3'}$), 2.76 (d, 1H, *J* = 18.5 Hz, H_3), 2.91 (dd, 1H, *J* = 6.0, 18.5 Hz, H_3), 3.44 (d, 1H, *J* = 11.5 Hz, H_5), 4.04 (d, 1H, *J* = 6.0 Hz, H_{3a}), 4.05-4.27 (m, 2H, OH), 4.60 (q, 1H, *J* = 6.5 Hz, $H_{5'}$), 4.57 (*br*. s, 1H, H_6), 4.69 (*br*. s, 1H, H_{11}), 4.73 (d, 1H, *J* = 11.5 Hz, H_5), 5.43 (t, 1H, *J* = 5.5 Hz, $H_{1'}$), 7.42-7.44 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 28.1, 33.4, 35.1, 71.7, 72.5, 74.2, 77.2, 81.9, 86.4, 94.0, 94.3, 127.7, 128.2, 129.6, 129.8, 135.3, 135.6, 174.1, 210.3; MS *m/z* (CI; NH_3) 408 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{26}NO_8$ $[M+NH_4]^+$; 408.1658, found; 408.1663; Anal. Calcd. for $C_{20}H_{22}O_8$; C, 61.53; H, 5.68; found; C, 61.55; H, 5.73.

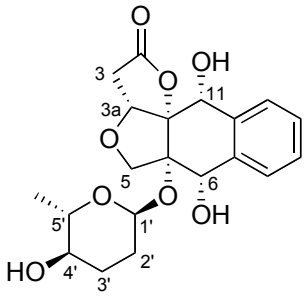
(3a*S*,5a*R*,6*R*,11*S*,11a*R*)-6,11-Dihydroxy-5a-((1'*S*,5'*S*)-5'-Methyl-4-oxo-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a,6,11-hexahydro-furo[3,2-b]naphtho[2,3-c]furan-2-one (496)



To a solution of glycoside **4** (176 mg, 0.46 mmol, 1.0 eq) in EtOAc (18 mL) was added 10% Pd/C (503 mg, 0.46 mmol, 1.0 eq). The reaction mixture was degassed and flushed with H_2 three times, then placed under H_2 (balloon). After stirring at rt for 14 h the reaction mixture was filtered through celite® and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (60% EtOAc/petroleum ether) to give **496** as a white solid (147 mg, 83%);

M.p. ($CHCl_3$) 244-246 °C; $[\alpha]_D^{22}$ –162.5 (*c* = 0.6, CH_2Cl_2); R_f 0.39 (80% EtOAc/ petroleum ether); IR (film) v_{max} 3349, 2979, 2935, 2861, 1787, 1735, 1442, 1201, 1058, 981 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, 3H, *J* = 6.5 Hz, CH_3), 1.94-2.04 (m, 1H, $1H_{2'}$), 2.30 (ddd, 1H, *J* = 4.0, 8.5, 17.0 Hz, $H_{3'}$), 2.39-2.50 (m, 2H, $H_{3'}$ and $H_{2'}$), 2.77 (dd, 1H, *J* = 1.5, 18.5 Hz, H_3), 2.93 (dd, 1H, *J* = 6.0, 18.5 Hz, H_3), 3.35 (d, 1H, *J* = 9.0 Hz, OH), 3.73 (d, 1H, *J* = 10.5 Hz, H_5), 4.30 (d, 1H, *J* = 10.5 Hz, H_5), 4.42 (dd, 1H, *J* = 1.5, 6.0 Hz, H_{3a}), 4.54 (q, 1H, *J* = 6.5 Hz, $H_{5'}$), 4.64 (d, 1H, *J* = 9.0 Hz, H_6), 4.74 (d, 1H, *J* = 8.0 Hz, OH), 4.93 (t, 1H, *J* = 6.0 Hz, $H_{1'}$), 5.31 (d, 1H, *J* = 8.0 Hz, H_{11}), 7.45-7.50 (m, 3H, ArH), 7.55-7.56 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 27.5, 33.4, 35.0, 71.0, 71.6, 71.8, 79.6, 82.4, 88.4, 94.6, 95.0, 125.6 (2C), 128.9, 129.2, 134.9, 136.8, 174.3, 209.7; MS *m/z* (CI; NH_3) 408 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{26}NO_8$ $[M+NH_4]^+$; 408.1658, found; 408.1678; Anal. Calcd. for $C_{20}H_{22}O_8$; C, 61.53; H, 5.68; found; C, 61.48; H, 5.60.

(3a*R*,5a*S*,6*S*,11*R*,11a*S*)-6,11-Dihydroxy-5a-((1'*S*,4'*R*,5'*S*)-4'-hydroxy-5'-methyl-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a,6,11-hexahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2-one (497)

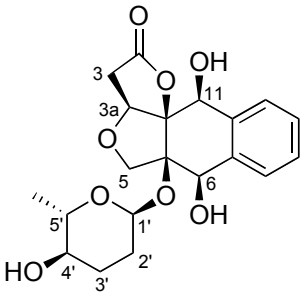


To a solution of ketone **495** (90 mg, 0.23 mmol, 1.0 eq) in MeOH/CH_2Cl_2 (1;1 v/v, 8 mL) at –78 °C and under N_2 was added $NaBH_4$ (10 mg, 0.25 mmol, 1.1 eq). The reaction mixture was stirred at –78 °C for 30 min. before quenching with H_2O (2 mL). The layers were separated and the aqueous portion extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (70% EtOAc/petroleum ether) to give alcohol **497** as a white solid that decomposed slowly on standing (78 mg, 87%);

M.p. (CH_2Cl_2) >250 °C dec.; $[\alpha]_D^{22}$ –31.7 (*c* = 1.0, CH_2Cl_2); R_f 0.42 (90% EtOAc/Petroleum ether); IR (film) ν_{max} 3399, 2967, 2935, 2873, 1776, 1211, 1182, 1049, 981 cm^{-1}; ^1H NMR (400 MHz, THF-d_8) δ 1.17 (d, 3H, *J* = 6.0 Hz, CH_3), 1.46-1.52 (m, 3H, $H_{3'}$ and $H_{2'}$), 1.71-1.73 (m, 1H, $H_{2'}$), 2.55 (d, 1H, *J* = 18.0 Hz, H_3), 2.88 (dd, 1H, *J* = 6.5, 18.0 Hz, H_3), 2.93-2.99 (m, 1H, $H_{4'}$), 3.70-3.76 (m, 1H, $H_{5'}$), 3.82 (d, 1H, *J* = 11.0 Hz, H_5), 4.31 (d, 1H, *J* = 9.5 Hz, OH), 4.45 (d, 1H, *J* = 6.5 Hz, H_{3a}), 4.62 (d, 1H, *J* = 9.5 Hz, H_6), 4.71 (d, 1H, *J* = 9.0 Hz, OH), 4.86 (d, 1H, *J* = 11.0 Hz, H_5), 4.97 (s, 1H, $H_{1'}$), 5.21 (d, 1H, *J* = 9.0 Hz, H_{11}), 7.24-7.30 (m, 2H, ArH), 7.41-7.43 (m, 1H, ArH), 7.50-7.52 (m, 1H, ArH); ^{13}C NMR (100 MHz, THF-d_8) δ 15.9, 25.3, 27.8, 33.4, 68.1, 68.6, 69.5, 70.4, 72.5, 80.4, 86.2, 90.9, 93.4, 121.1, 121.3, 124.6, 124.8, 134.7, 136.3, 172.0; MS *m/z* (CI; NH_3) 410

$[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{28}NO_8$ $[M+NH_4]^+$; 410.1815, found; 410.1832.

(3a*S*,5a*R*,6*R*,11*S*,11a*R*)-6,11-Dihydroxy-5a-((1'*S*,4'*R*,5'*S*)-4'-hydroxy-5'-methyl-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a,6,11-hexahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2-one (498)

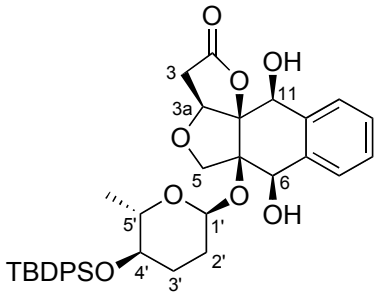


To a solution of ketone **496** (51 mg, 0.13 mmol, 1.0 eq) in MeOH/CH_2Cl_2 (1;1 v/v, 4 mL) at –78 °C and under N_2 was added $NaBH_4$ (6 mg, 0.16 mmol, 1.2 eq). The reaction mixture was stirred at –78 °C for 30 min. before quenching with H_2O (2 mL). The layers were separated and the aqueous portion extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (70% EtOAc/petroleum ether) to give alcohol **498** as a white solid that decomposed slowly on standing (40 mg, 77%);

M.p. (MeOH/CH_3CN) >250 °C dec.; $[\alpha]_D^{22}$ +25.7 (*c* = 1.0, CH_2Cl_2); R_f 0.42 (90% EtOAc/Petroleum ether); IR (film) ν_{max} 3380, 2964, 2931, 2873, 1778, 1457, 1263, 1205, 1176, 1139, 1108, 1076, 1049, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, 3H, *J* = 6.0 Hz, CH_3), 1.68-1.88 (m, 3H, $H_{2'}$ and $H_{3'}$), 2.02-2.06 (m, 1H, $H_{2'}$), 2.75 (dd, 1H, *J* = 1.5, 18.5 Hz, H_3), 2.88 (dd, 1H, *J* = 6.5, 18.5 Hz, H_3), 3.25-3.35 (m, 1H, $H_{4'}$), 3.59 (d, 1H, *J* = 10.5 Hz, H_5), 3.84 (d, 1H, *J* = 10.5 Hz, OH), 3.94 (dq, 1H, *J* = 6.5, 9.0 Hz, $H_{5'}$), 4.22-4.27 (m, 2H, H_{3a} and 1H_5), 4.55 (d, 1H, *J* = 10.5 Hz, H_6), 4.69 (d, 1H, *J* = 6.5 Hz, OH), 4.93-4.95 (m, 1H, $H_{1'}$), 5.90 (d, 1H, *J* = 6.5 Hz, H_{11}), 7.44-7.48 (m, 3H, ArH), 7.50-7.52 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 27.029.2, 35.0, 71.0, 71.5, 71.7, 72.1, 79.6, 82.5, 88.4, 93.9, 94.6, 126.5, 126.7, 129.1, 129.4, 135.3, 137.1, 174.4; MS *m/z* (CI; NH_3) 410 $[M+NH_4]^+$; HRMS (CI; NH_3) calculated for $C_{20}H_{24}O_8$ $[M+NH_4]^+$;

410.1815, found; 410.1805; X-ray crystal data $C_{20}H_{24}O_8 \cdot 0.5CH_2Cl_2$, M = 434.86, Tetragonal, P4(3)2(1)2, a = 10.64714(5) Å, b = 10.64714(5) Å, c = 35.2714(2) Å, α = 90°, β = 90°, γ = 90°, V = 3998.43(15) Å^3, Z = 8, D_C = 1.455 Mg/m^3, μ(Cu-Kα) = 2.107 mm^{-1}, T = 173 K, colourless tablets, 51689 independent measured reflections, 3242 independent observed reflections [F>4σ(F)], 316 parameters.

(3a*S*,5a*R*,6*R*,11*S*,11a*R*)-6,11-Dihydroxy-5a-((1'S,4'R,5'S)-4'-(*tert*-Butyl-diphenyl-silanyloxy)-5'-methyl-tetrahydro-pyran-1'-yloxy)-3,3a,5,5a,6,11-hexahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2-one (502)

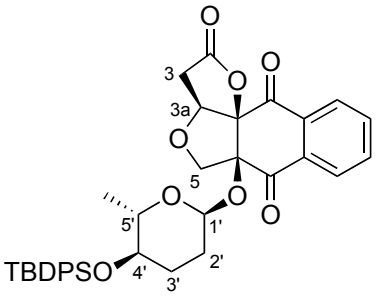


To a solution of alcohol **498** (75 mg, 0.19 mmol, 1.0 eq) in DMF (2 mL) at rt and under N_2 were added imidazole (33 mg, 0.48 mmol, 2.5 eq) and TBDPSCl (60 μL, 0.23 mmol, 1.2 eq). The reaction mixture was stirred at 70 °C for 22 h before quenching with sat. aq. NH_4Cl (5 mL). The layers were separated and the aqueous portion extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (70% EtOAc/petroleum ether) to give recovered starting material **498** (52 mg, 69%) and silyl ether **502** as a white solid (27 mg, 23%);

M.p. ($CHCl_3$) >250 °C dec.; $[\alpha]_D^{22}$ –47.4 (*c* = 1.0, $CHCl_3$); R_f 0.46 (10% MeOH/$CHCl_3$); IR (film) ν_{max} 3365, 2958, 2929, 2858, 1791, 1132, 1110, 1085, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H, $SiC(CH_3)_3$), 1.27 (d, 3H, *J* = 6.0 Hz, CH_3), 1.37 (dt, 1H, *J* = 4.0, 14.5 Hz, $H_{2'}$), 1.52-1.57 (m, 1H, $H_{2'}$), 1.77-1.87 (m, 2H, $H_{3'}$), 2.72 (dd, 1H, *J* = 1.0, 18.5 Hz, H_3), 2.87 (dd, 1H, *J* = 6.5, 18.5 Hz, H_3), 3.32 (m, 1H, $H_{4'}$), 3.66 (d, 1H, *J* = 10.5 Hz, H_5), 3.88 (m, 1H, OH), 4.07 (dq, *J* = 6.0, 8.5 Hz, $H_{5'}$), 4.30 (d, 1H, *J* = 10.5 Hz, H_5), 4.31-4.32 (m, 1H, H_{3a}), 4.55 (m, 1H, 1H, OH), 4.66-4.68 (m, 2H, $H_{1'}$ and H_6), 5.85 (d, 1H, *J* = 7.5 Hz, H_{11}), 7.38-7.50 (m, 10H, ArH), 7.68-7.71 (ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 19.3, 27.0, 27.2, 28.9, 35.0, 71.2, 72.0, 73.4 (2C), 79.8, 82.5, 88.4, 93.8, 94.7, 125.8, 126.2, 127.5, 127.7, 128.9, 129.2, 129.7, 129.8, 133.5, 134.3,

135.3, 135.9, 136.5, 137.2, 174.5; MS *m/z* (ES^+; Na) 653 $[M+Na]^+$; HRMS (ES^+; Na) calculated for $C_{36}H_{42}O_8SiNa$ $[M+Na]^+$; 653.2547, found; 653.2540.

(3a*S*,5a*R*,11a*R*)-5a-[(1'S,4'R,5'S)-4'-(*tert*-Butyl-diphenyl-silanyloxy)-5'-methyl-tetrahydro-pyran-1'-yloxy]-3,3a,5,5a-tetrahydro-furo[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione (501)



To a solution of diol **502** (18 mg, 0.03 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) at 0 °C and under N_2 was added DMP (30 mg, 0.07 mmol, 2.5 eq). The reaction mixture was stirred for 20 min at 0 °C and then for a further 20 min at rt before quenching with sat. aq. $Na_2S_2O_3$ (2 mL). EtOAc (5 mL) was added, the layers separated and the aqueous portion extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude product purified by silica gel flash column chromatography (30% EtOAc/petroleum ether) to give dione **501** as a colourless oil (17 mg, 93%);

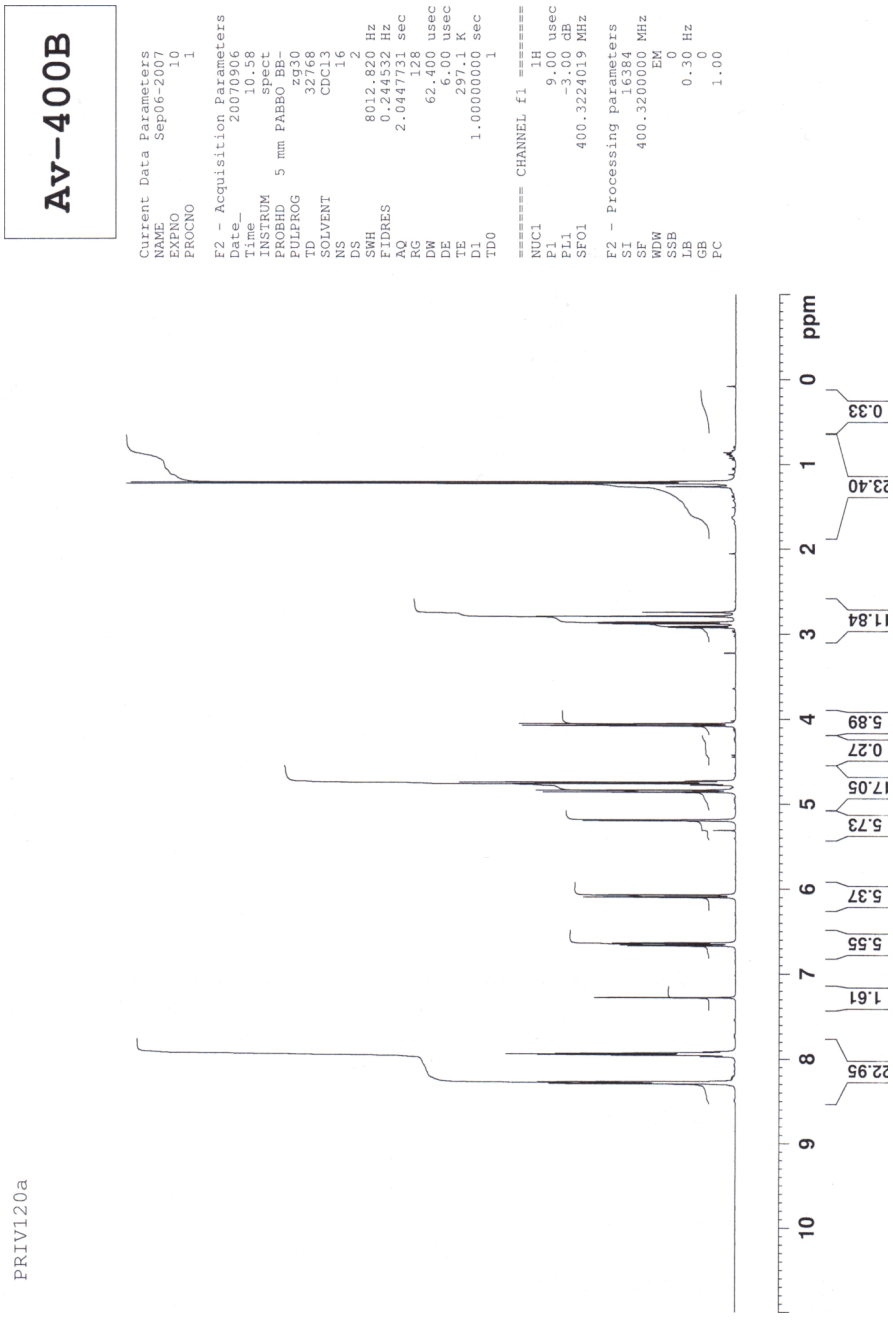
$[\alpha]_D^{22}$ –43.4 (*c* = 1.0, $CHCl_3$); R_f 0.48 (40% EtOAc/Petroleum ether); IR (film) ν_{max} 2931, 2858, 1805, 1698, 1592. 1427. 1300, 1160, 1112, 1089, 1060, 935, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, 3H, *J* = 6.0 Hz, CH_3), 1.04 (s, 9H, $SiC(CH_3)_3$), 1.32-1.38 (m, 1H, $H_{2'}$), 1.48-1.53 (m, 1H, $H_{2'}$), 1.67-1.77 (m, 2H, $H_{3'}$), 2.76 (d, 1H, *J* = 19.0 Hz, H_3), 2.89 (dd, 1H, *J* = 6.5, 19.0 Hz, H_3), 3.14 (dt, 1H, *J* = 4.0, 10.0 Hz, $H_{4'}$), 3.53 (dq, 1H, *J* = 6.0, 9.0 Hz, $H_{5'}$), 4.02 (d, 1H, *J* = 9.0 Hz, H_5), 4.73 (d, 1H, *J* = 6.5 Hz, H_{3a}), 4.77 (d, 1H, *J* = 3.5 Hz, $H_{1'}$), 4.82 (d, 1H, *J* = 9.0 Hz, H_5), 7.33-7.44 (m, 6H, ArH), 7.63-7.65 (m, 4H, ArH), 7.83-7.90 (m, 2H. ArH), 8.18-8.24 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.3, 27.0, 27.3, 28.9, 29.7, 35.6, 70.9, 73.2 (2C), 81.8, 87.3, 91.6, 95.4, 127.4, 127.6, 127.7, 127.8, 129.6, 129.7, 131.5, 133.4, 134.2, 134.3, 134.8, 135.0, 135.7, 135.9, 173.8, 189.2, 192.0; MS *m/z* (ES^+; Na) 649 $[M+Na]^+$; HRMS (CI; NH_3) calculated

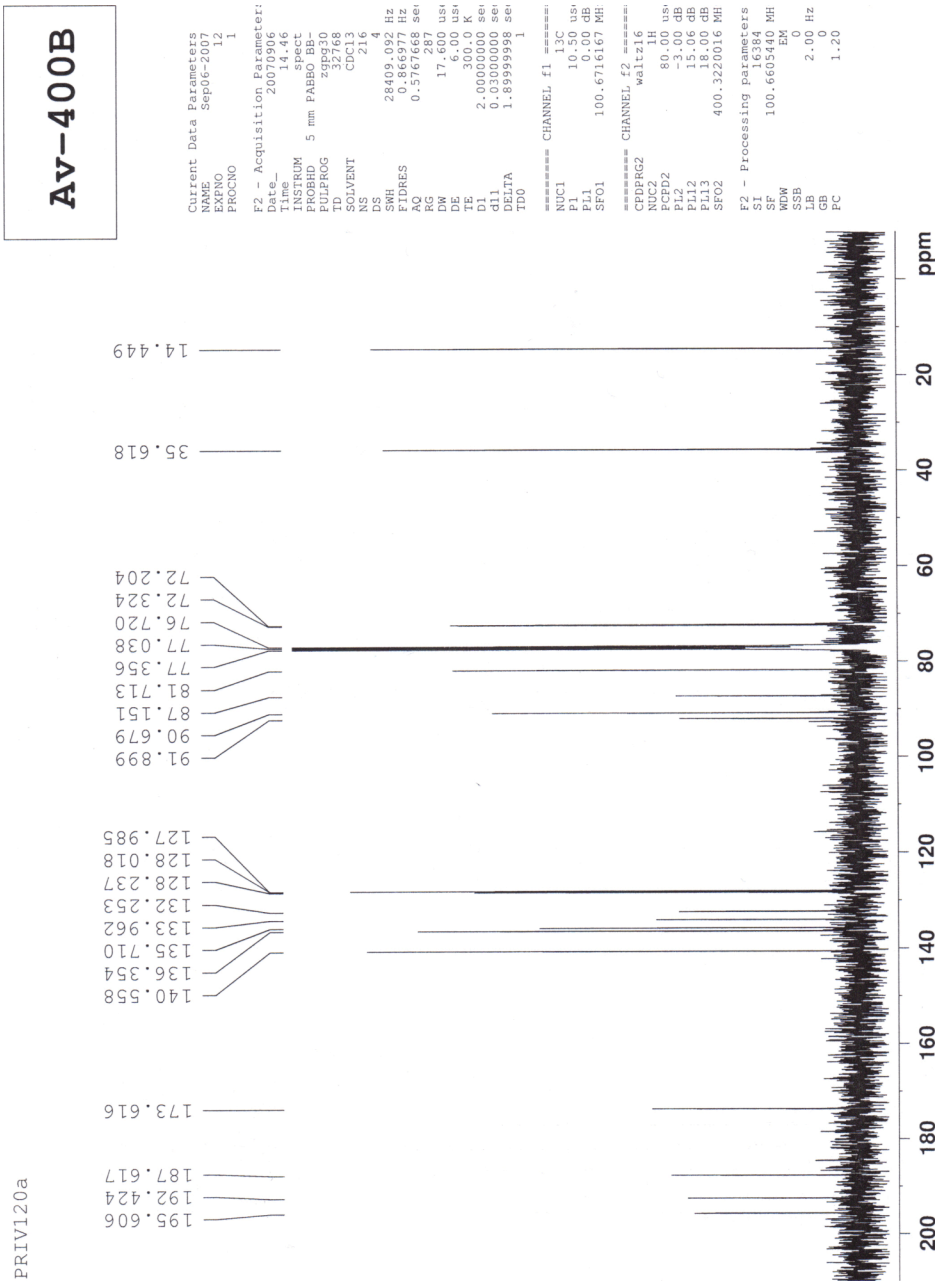
for $C_{36}H_{38}O_8SiNa$ $[M+Na]^+$; 649.2234, found; 649.2251. Anal. Calcd. for $C_{36}H_{38}O_8Si$; C, 68.99; H, 6.11; found; C, 69.08; H, 6.08.

Appendices

Appendix 1

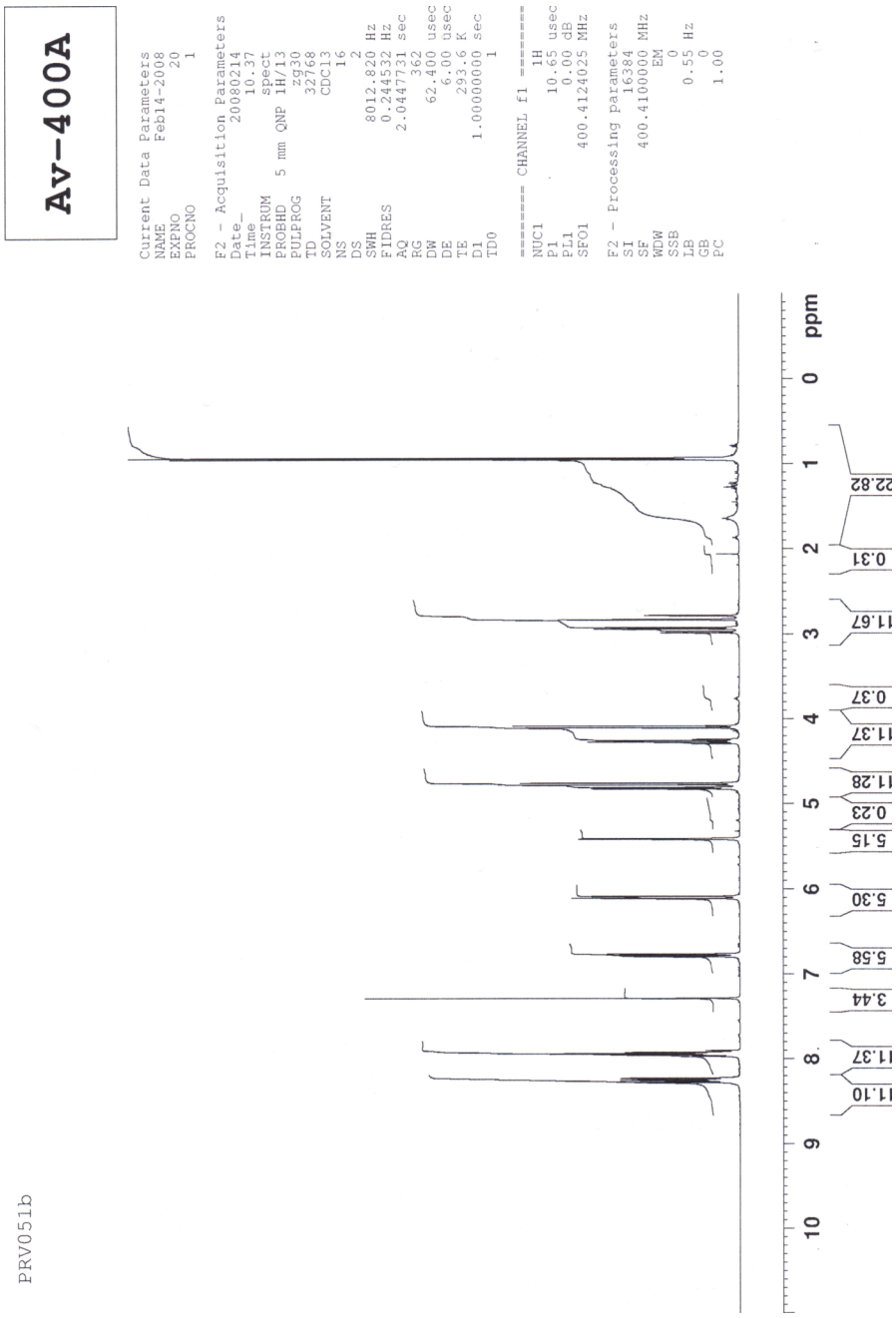
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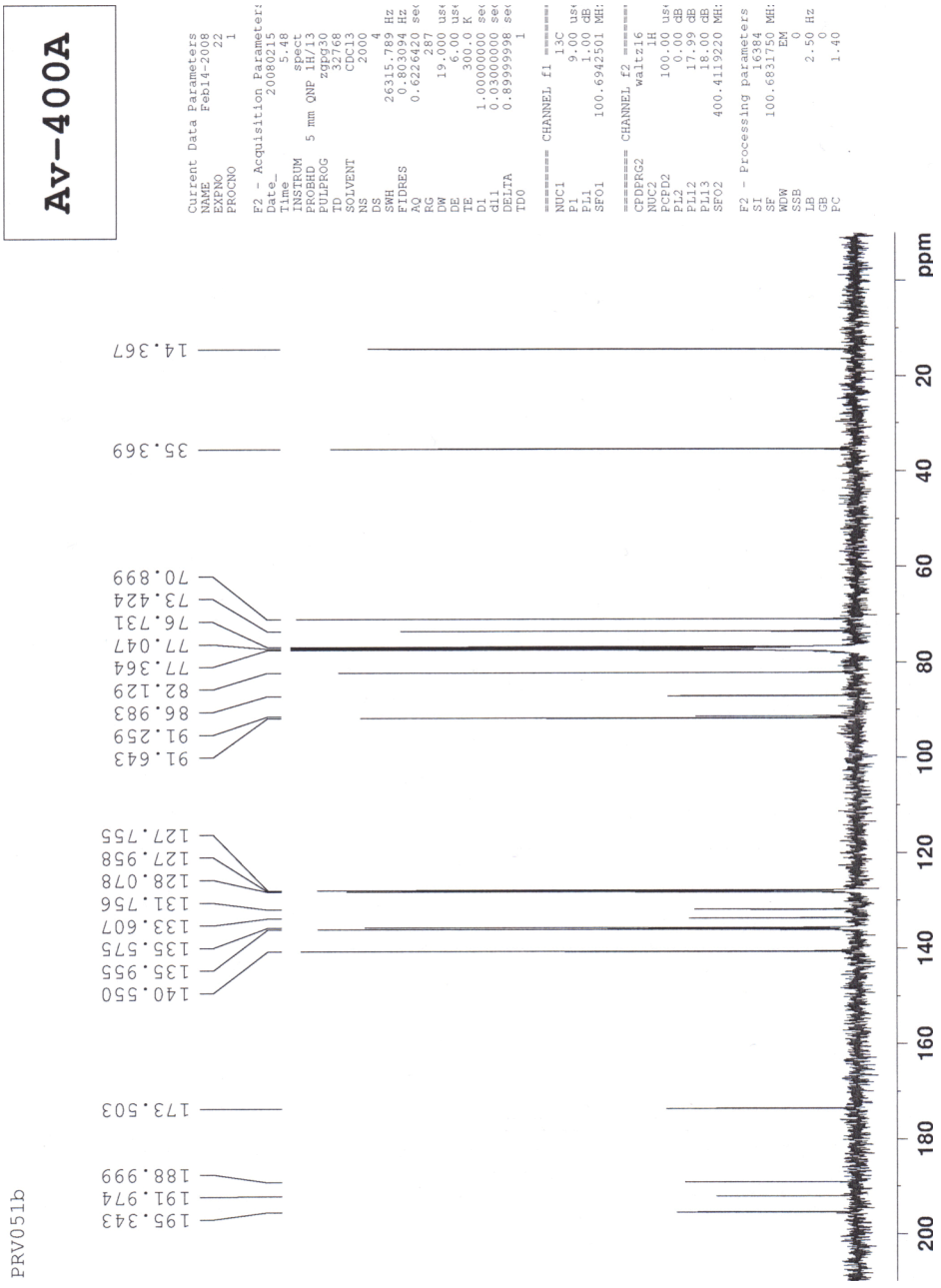



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Appendix 2

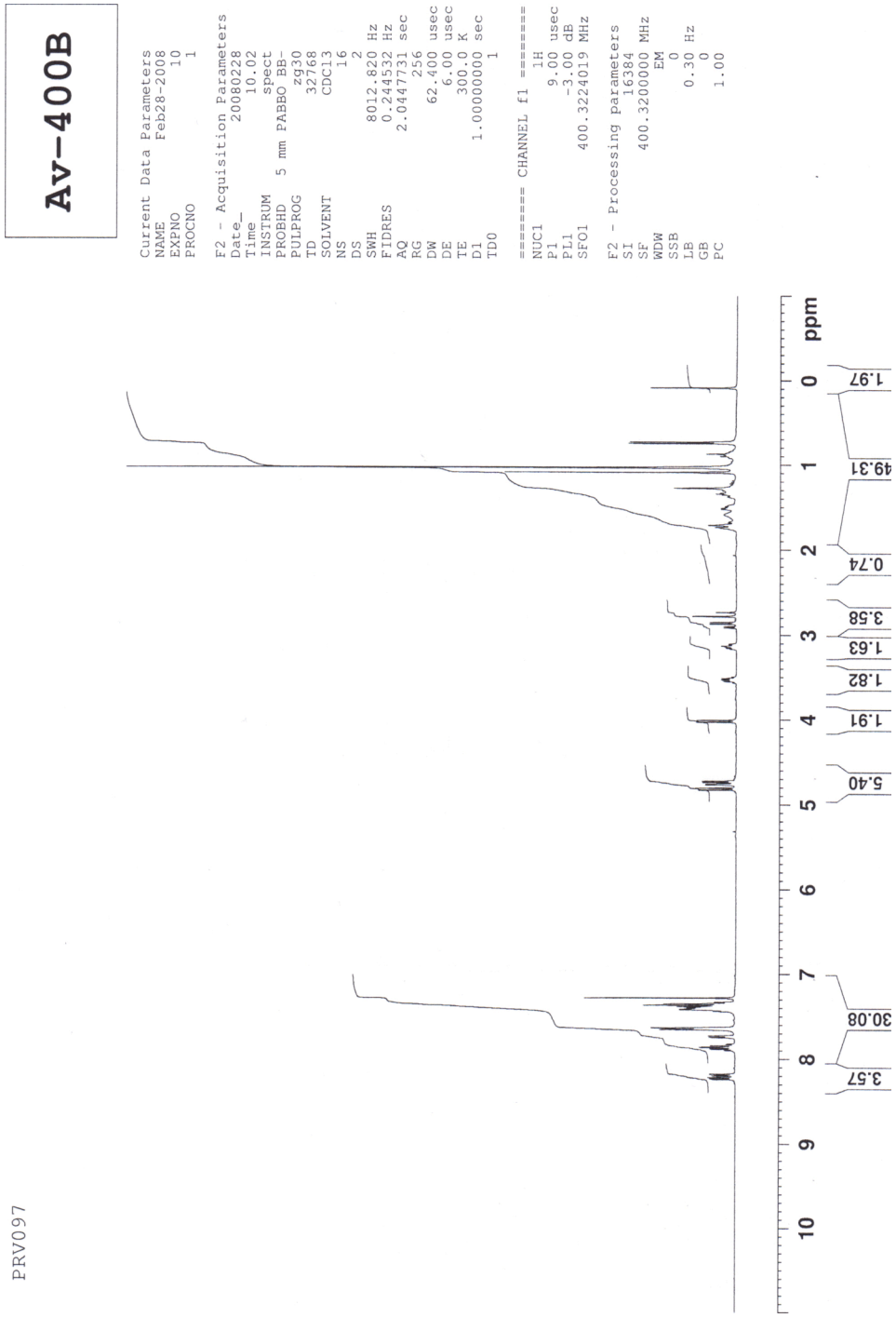
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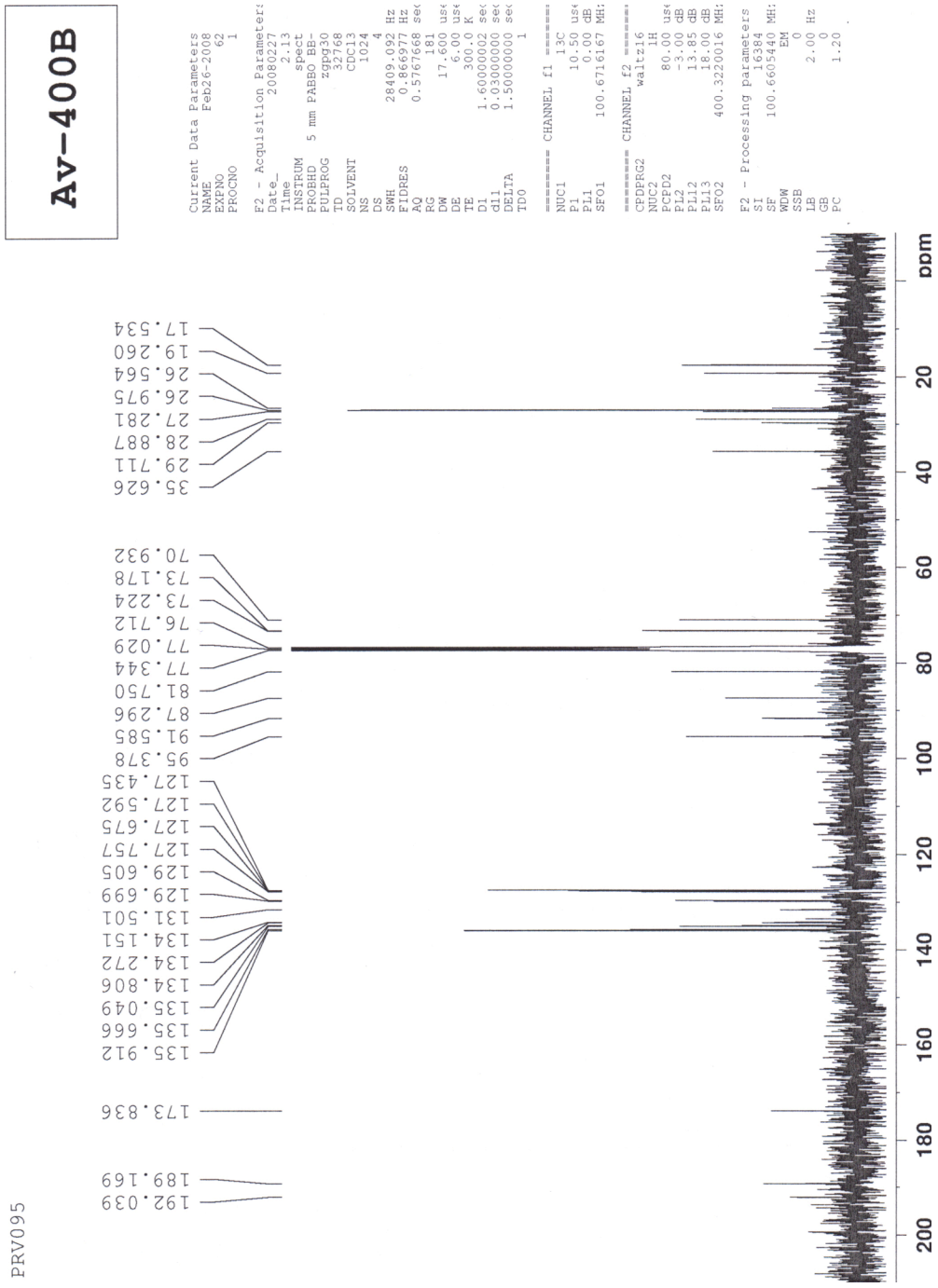



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PL13 18.00 dB
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WDW EM
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77.364
82.129
86.983
91.259
91.643
127.755
127.958
128.078
131.756
133.607
135.575
135.955
140.550
173.503
188.999
191.974
195.343
200
180
160
140
120
100
80
60
40
20
ppm

Appendix 3

^{1}H and ^{13}C NMR data for glycoside **501**:




Av-400B
PRV095
Current Data Parameters
NAME Feb26-2008
EXPNO 62
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080227
Time 2.13
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1024
DS 4
SWH 28409.092 Hz
FIDRES 0.866977 Hz
AQ 0.5767668 sec
RG 181
DW 17.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.60000002 sec
d11 0.03000000 sec
DELTA 1.50000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SFO1 100.6716167 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 13.85 dB
PL13 18.00 dB
SFO2 400.3220016 MHz
F2 - Processing parameters
SI 16384
SF 100.6605440 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.20
35.626
29.711
28.887
27.281
26.975
26.564
19.260
17.534
70.932
73.178
73.224
76.712
77.029
77.344
81.750
87.296
91.585
95.378
127.435
127.592
127.675
127.757
129.605
129.699
131.501
134.151
134.272
134.806
135.049
135.666
135.912
173.836
189.169
192.039
200
180
160
140
120
100
80
60
40
20
ppm

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