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Synthesis, Functionalisation and Biological Evaluation of Tetrahydroxanthones

by

Samiullah

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick
January 2012

CONTENTS

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I thank the University of Balochistan for funding this research.

DECLARATION

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick carried out between January 2008 and January 2012.

The research reported in this thesis has not been submitted, either wholly or in part, for a degree at another institution.

ABSTRACT

This thesis describes the development of new methods for the synthesis of mono-, di- and trihydroxylated tetrahydroxanthones which are structural elements of a range of important natural products including the anti-cancer agents known as the kigamicins.

In Chapter One, work on the isolation, biological significance and chemical synthesis of xanthones, dihydroxanthones, and tetrahydroxanthones is reviewed, with special focus on the polycyclic tetrahydroxanthone natural products.

Chapter Two describes the development of methods for the synthesis of tetrahydroxanthones mimicking the ABC rings of kigamicin A which contain a hydroxyl group at C-3 of the saturated ring. A 5 step synthesis of **228** was achieved via palladium catalysed assembly of tetrahydroxanthone nucleus, followed by enantiocontrolled reduction of the C=O group via asymmetric transfer hydrogenation, and glycosidation using a novel trichloroacetimidate donor **225**.

In Chapter Three, a short route to the *cis* and *trans*1,4-diol functionality found in the tetrahydroxanthone fragment of 1,3,5-trihydroxy-8-*β*-D-glucopyranosyl, puniceaside B, puniceaside C, albofungin, and simaomicins is achieved. Excellent enantiocontrol (99% ee) was realised through use of an asymmetric ketone transfer hydrogenation. Subsequent enolate hydroxylation with the Davis oxaziridine facilitated installation of the second hydroxyl group albeit with low levels of diastereocontrol. The structure of *cis*-**277** was verified by X-ray crystallography after conversion to the corresponding diacetate **279**. Similar enolate hydroxylations were used to access the triol substitution patterns found in kibdelones and isokibdelones. Attempts to develop synthetic routes to the fully functionalised A-ring fragments of the actinoplanones and kigamicins are described. This culminated in the preparation of advanced synthetic intermediate **322** in 4 steps from hydroxyl selenide tetrahydroxanthone. In a key step in this sequence, an unusual *syn*-selective dihydroxylation of a PMB-protected homoallylic alcohol (**321**) was unearthed. Finally, the biological effects of the new dihydroxanthones, dihydroxy, and trihydroxytetrahydroxanthones synthesised in the laboratory were evaluated against human pancreatic cancer cell line (PANC-1), grown separately in nutrient rich medium (NRM) and nutrient deprived medium (NDM).

In Chapter Four, detailed experimental and characterisation data for the new compounds are described.

ABREVIATIONS

atm	Atmosphere
Bn	benzyl
Bz	Benzoyl
Br	broad
Calcd	calculated
CAN	Cerium(IV) ammonium nitrate
cat.	catalytic
COSY	Correlation Spectroscopy
d	day
DBU	1,3-Diazobicyclo[5.4.0]undecane
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	Diethyl azodicarboxylate
decomp.	decomposed
DIBAL	Di-*iso*-butylaluminium hydride
DMAP	*N*,*N*-Dimethylaminopyridine
DMEDA	*N,N*′-Dimethylethylenediamine
DMF	*N*,*N*′-Dimethylformamide
DMPU	*N*,*N*′-Dimethylpropylene urea
DMSO	Dimethyl sulphoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	Electron Impact
equiv	equivalent
ES	Electrospray
FT	Fourier Transform
GCMS	Gas Chromatography Mass Spectroscopy
h	hour

HMBC	Heteronuclear Multiple Bond Coherence
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRFABMS	High Resolution Fast Atom Bombardment Mass Spectoscopy
HRMS	High Resolution Mass Spectroscopy
IR	Infrared
J	Coupling constant
LCMS	Liquid chromatography-Mass Spectroscopy
LDA	Lithium Di-*iso*-propylamide
lit.	literature
LUMO	Lowest Unoccupied Molecular Orbital
min	minute
MO	Molecular Orbital
mol.	molar
M.p.	Melting point
Ms	Methanesulphonyl
NAP	2-Methylnaphthyl
NDM	Nutrient deprived medium
NRM	Nutrient rich medium
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser effect
p	*para*
PMB	*para*-Methoxybenzyl
ppm	parts per million
Rf	Retention factor
rt	room temperature
S_N2	Nucleophilic Substitution Bimolecular

t	time
t_r	retention time
T	temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tlc	thin layer chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TBDMS	*tert*. butyldimethysilyl
Ts	*para*-Toluenesulfonyl
TTN	Thallium trinitrate
UV	Ultraviolet
VEGF	Vascular Endothelial Growth Factor
v/v	volume per unit volume
wt	weight
w/w	weight per unit weight

CHAPTER 1:
INTRODUCTION

1 Introduction

Xanthones and partially hydrogenated di- or tetrahydroxanthones are not only widespread classes of natural products, but also occur as polyhydroxlated fragments of the polycyclic natural products. This thesis describes the synthesis, structural studies and functionalisation of simple di- and tetrahydroxanthones to probe the pharmacophore in the natural products possessing these components.

1.1 Xanthones

The term xanthone (from the Greek 'xanthos' meaning yellow), designates the organic compound dibenzo-γ-pyrone **1** (*Figure 1*).[1] The basic xanthone skeleton is symmetric and has a mixed biogenetic origin in vascular plants. Its carbons are often numbered according to biosynthetic convention, in which carbons 1 to 4 are assigned to the acetate derived ring and carbons 5 to 8 to the shikimate derived ring.[2]

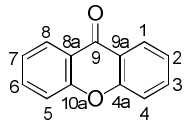

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Figure 1. Dibenzo-γ-pyrone **1**

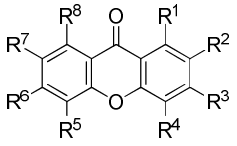
Xanthones are natural polyhydroxylated secondary metabolites that occur in higher plant families, fungi and lichen. They also occur sporadically in the rest of the plant kingdom. Most of the natural xanthones have been obtained from the four families: Guttiferae, Gentianaceae, Moraceae and Polygalaceae. However, some of them have also been isolated from other plant families such as Leguminosea, Loganiaceae, Lythraceae and Rhamnaceae.[3]

1.1.1 Classification of Xanthones

Xanthones are generally classified into five major groups depending on the substituents on their skeleton: simple oxygenated xanthones, prenylated xanthones, xanthone glycosides, xanthonolignoids and miscellaneous xanthones.[4]

1.1.1.1 *Oxygenated Xanthones*

The oxygenated xanthones have been further divided into sub classes according to the degree of oxygenation of the basic xanthone skeleton, which include the Mono-**2**-**4**, Di-**5**, **6**, Tri-**7**, **8**, Tetra-**9**, and Penta-**10**, oxygenated xanthones (*Figure 2*).



Mono-oxygenated xanthones R^2 = OH **2,** R^2= OMe **3,** R^4 = OH **4**
Dioxygenated xathones R^1 = OH, R^5= OH **5,** R^1 = OH, R^7= OH **6**
Trioxygenated xanthones R^1 = OH, R^3= OH, R^5= OH **7**, R^1 = OH, R^5 = OH, R^6= OH **8**
Tetraoxygenated xanthones R^1 = OH, R^3= OH, R^5= OH, R^6 = OH **9**
Pentaoxygenated xanthones R^1 = OH, R^2 = OMe, R^3= OMe, R^7= OMe, R^8 = OH **10**

Figure 2

Only a small number of mono-oxygenated xanthones **2**, **3**, **4** have been isolated from plants. Di-oxygenated xanthones **5** and **6** are relatively common, usually oxygenated in 1,5- or 1,7- positions of the xanthone nucleus. Tri **7**, **8** and tetra-oxygenated xanthones **9** are the most common class of these natural products. However, penta-oxygenated xanthones **10** are very rarely found in the plant kingdom.

1.1.1.2 *Prenylated xanthones*

Prenylated xanthones are polyhydroxylated xanthones having an isopentenyl group attached to the basic xanthone skeleton. Mono, di and tri-prenylated xanthones have been isolated, sometimes the prenyl groups have further modifications. The most characteristic modification is the oxidative cyclisation of the prenyl group with an *ortho*-hydroxyl group to the chromene ring. Structure elucidation and characterisation of these natural products has been simplified by the characteristic NMR patterns that these prenylated groups manifest. The mono-prenylated dihydroxyxanthones include Guanandine (**11**) and *iso*-Guanandine (**12**) isolated from the family Clusiaseae (*Figure 3*). [5]

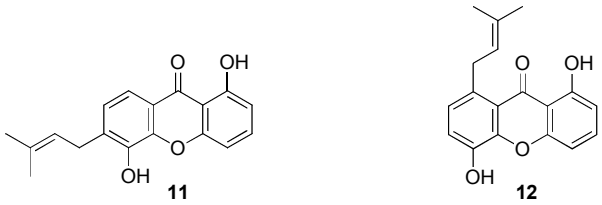


Figure 3

In compounds **13** and **14**, the prenyl group has oxidatively cyclised to the chromene group. These compounds have been isolated from different generae of plants (*Figure 4*).

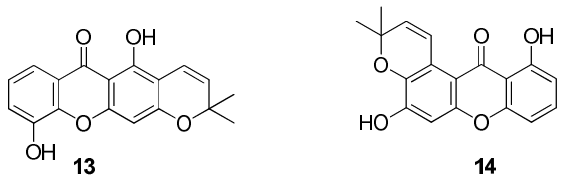


Figure 4

1.1.1.3 *Xanthone glycosides*

Naturally occurring xanthone glycosides have been differentiated into *C*-glycosides and *O*-glycosides. *C*-Glycosidic xanthones have a C-C bond linkage resistant to acidic and enzymatic hydrolysis attached to the skeleton, where as *O*-glycoside xanthones present a typical glycosidic linkage susceptible to such hydrolysis conditions.[6] Mangiferin is one of the first C-glycoside xanthones isolated. It was discovered from *mangifera indica* in 1908 by Wiechowski,[7] the structure being established as 2-C-*β*-D-glucopyranosyl-1,3,6,7-tetrahydroxy xanthone (**15**) (*Figure 5*).[8,9] Until 1969 only three *O*-glycoside xanthones were known, including Swertianoline **16** (*Figure 5*). However, more than twenty *O*-glycoside xanthones have been discovered in the last 20 years.[10, 11]

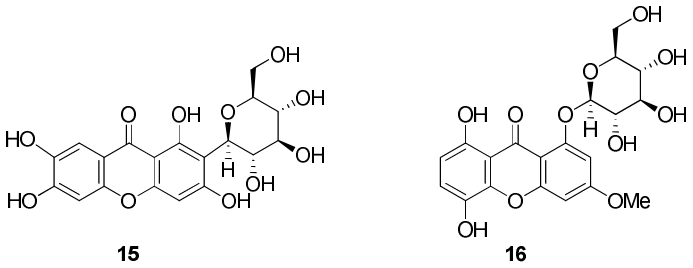


Figure 5

Guo *et al* have recently isolated 2,2-fused dimeric swertibisxanthone-1,8-*O*-*β*-D-glucopyroanside **17** from *swertia punicea* and a carbon linked 3-*O*-dimethylswertipunicoside **18** from the same species (*Figure 6*).[12]

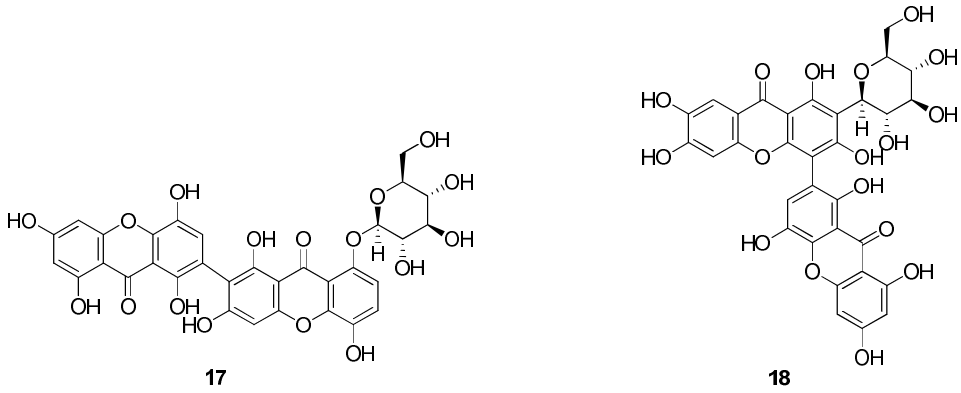


Figure 6

1.1.1.4 *Xanthonoligonoides*

Xanthonoligonoids are relatively rare and occur only in some generae of *Guttiferrae*. These natural products are formed from the fusion of the xanthone nucleus with that of a lignoid. Cadensin D **19** belongs to this class of xanthones and was isolated from *Guttifrae* family (*Figure 7*) .[13]

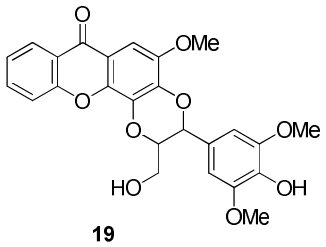


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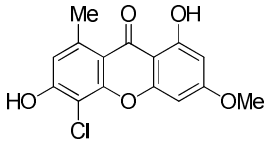
Figure 7

1.1.1.5 *Miscellaneous xanthones*

These xanthones present a random type of substitutions and have been isolated from different plants including lichens. 4-Chloro-3,8-dihydroxy-6-methoxy-1-methylxanthone (**20**) isolated from *H.ascyron* and a sulphonated xanthone **21** from *H.sampsonii*[14] are illustrative examples (*Figure 8*).[15]



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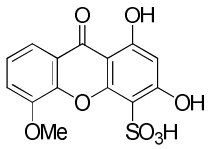

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Figure 8

One of the significant features of most of the naturally occurring xanthones is the presence of a hydroxyl group at C-1. This confers similar optical properties in all such xanthones, namely a yellow colour, which turns green with ferric chloride in ethanolic solution, and a more intense yellow colour when in contact with 2N NaOH solution.[1]

1.2 Isolation and structural elucidation of Xanthones

Xanthones are present in non-polar or medium-polar extracts of plants. They are efficiently extracted using ultrasonic extractions or extraction with ethanol. An increasing number of bioactive xanthones have been isolated by bioassay-guided fractionation methods.[16] They are usually separated by chromatography using different mixtures of solvents[17] and are also identified by comparison with known samples by

TLC[18] and purified by HPLC.[19, 20] The structures of the simple xanthones have been determined mainly from the ultraviolet,[21] infrared,[22] and nuclear magnetic resonance spectroscopy.[23]

Since the occurrence of these natural products is limited due to their biosynthesis, there is growing interest in the development of synthetic xanthones with varied substituent positions. The classic methods used for the synthesis of xanthones include the Michael-Kostanecki, Ullman, Robinson-Nishikawa, Ashina-Tanase and the Friedal-Crafts methods.[1]

1.3 Biological Activities of Xanthones

Mono, di, and the polyhydroxylated xanthones are found to be tuberculostatic, antibacterial, antihepatotoxic, and are active against ulcers.[24] Prenylated xanthones have been shown to have antibacterial, antifungal and antioxidative activities.[25] Xanthone glycosides have shown to be cytotoxic towards specific cancer lines and have also shown interesting coagulant activity.[26] Monoxanthone glycosides show less tuberculostatic activities than those found in simple oxygenated xanthones, while bisxanthone glycosides exhibit very high neuroprotective activities.[12] Xanthonoligonoids display antifungal activity.[27] Some sulfonated xanthonoids exhibit significant cytotoxicity against the P388 cancer cell line.[28]

1.4 Introduction to partially hydrogenated di- and tetrahydroxanthones

Xanthones, and partially hydrogenated, di- or tetrahydroxanthones are classes of natural products that are widely distributed in fungi[29], lichenes[30] and ferns.[31, 32] Due to their prominent activity they are classified as mycotoxins (myco meaning ‘fungus’).[33]

Mycotoxins are low molecular weight, non volatile secondary metabolic products. Many mycotoxins are produced by a single species of fungi, however most of them are produced by more than a single species. Some of these mycotoxins are also isolated from higher plants and bacteria. [34]

1.4.1 Dihydroxanthones

1.4.1.1 Isolation and structural elucidation of Dihydroxanthones

In 1994, Nobuo *et al* reported the isolation of nidulallins A (**22**) the first member of the dihydroxanthone class of natural products, from the dichloromethane extract of rice culture *Emericella nidulans* (*Figure 9*).[35]

Electron impact ionisation mass spectrometry and elemental analysis gave molecular formula $C_{16}H_{14}O_6$ for nidulallin A (**22**). The IR absorptions bands at 3400, 1740, and 1650 cm^{-1} suggested the presence of hydroxyl, ester, and carbonyl functional groups respectively. The ^{1}H, ^{13}C NMR and the decoupling experiments together with the UV absorption maxima suggested a dihydroxanthone moiety. To determine the structure of nidulallin unambiguously X-ray analysis was undertaken and the relative stereochemistry of the dihydroxanthone **22** was confirmed as shown below (*Figure 9*). The absolute configuration of nidulallin **22** was determined by ^{1}H-NMR analysis of (+)-*R*- and (-)-*S*-*α*-methoxy-*α*-trimethylphenyl acetates of **22** by a modified Mosher's method.[36]

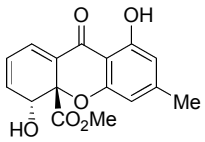

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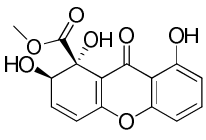
Figure 9

1.4.1.2 Globosuxanthone A

Chaetomium is a large genus of the fungal family *Chaetomiacaea* comprising over a hundred species.[37] The ethyl acetate extract from the fungal strain *chaetomium globosum Ames* isolated from the rhizosphere of the christmas cactus, *opuntia leptocaults* DC, exhibited significant cytotoxicity against seven human cancer cell lines. Bioactivity guided fractionation of this extract resulted in the isolation of a novel dihydroxanthone named as globosuxanthone A (**23**) (*Figure 10*).[38]



23

Figure 10

The structure of globosuxanthone A **23** was deduced as a basic xanthone skeleton containing a methyl ester and *trans* vicinal diol with a characteristic hydroxyl group at C-8. High resolution fast atom bombardment mass spectoscopy (HRFABMS) indicated a molecular formula of $C_{15}H_{12}O_6$, and characteristic IR peaks at 3440, 1734, and 1654 cm^{-1} suggested the presence of hydroxyl, ester and conjugated carbonyl group respectively. ^{1}H and ^{13}C NMR indicated ten degrees of unsaturation suggesting a dihydroxanthone. The complete structure and relative configuration of C-1 and C-2 of **23** were determined to by single crystal X-ray diffraction.

Prior to this discovery only two other 1,2-dihydroxanthones **24** and **25** have been isolated from *Aspergillus*. The structures of **24** and **25** were established by NMR, IR, and mass spectrometry (*Figure 11*).[39]

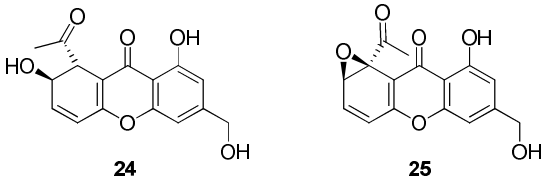


Figure 11

1.4.1.3 Biological Activities of Dihydroxanthones

Nidulallin **22** is a highly active anticancer dihydroxanthone. Globosuxanthone A **23** was evaluated for *in vitro* cytotoxicity against a panel of human solid tumour cell lines and was found to have significant activity. In an initial step of evaluating the potential of this dihydroxanthone as a lead molecule for drug development, the reversibility of cytotoxic acitivity was examined using a mouse cancer lines.[38] The irreversible cytoxicity of **23** was confirmed by clonagenic assays.[40] Dihydroxanthone **24** has been found to inhibit VEGF induced endothelial cell growth[39] and **25** has been reported to inhibit the myosin light chain kinase.[41]

1.4.2 Tetrahydroxanthones

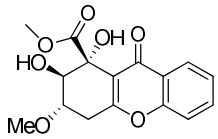
Over 600 xanthones are known, of which more than 100 contain the basic tetrahydroxanthone skeleton. These tetrahydroxanthones belong to the class of mycotoxins that occur in many fungi.[42]

They are produced both as monomeric and dimeric units in natural products. The monomeric tetrahydroxanthones include the globosuxanthone B **26** (*Figure 12*), *α*- and

β- diversonolic esters (**27** and **28** respecitvely), diversonol **29** (*Figure 13*) and the recently isolated secalonic acids **31**, **32** (*Figure 15*). [43, 44]

A tetrahydroxanthone structurally related to the dihydroxanthone A **23** named globosuxanthone B **26** (*Figure 12*) was isolated as a colourless gum from the ethyl acetate extract of *chaetomium globosum***.**[38] HRFABMS indicated a molecular formula of $C_{16}H_{16}O_6$, showing nine degrees of unsaturation. This in combination with ^{1}H NMR and ^{13}C NMR showed the same methyl ester as in globosuxanthone A **23**. The additional methoxy group and the absence of two olefinic hydrogens instead suggested a tetrahydroxanthone. Furthermore, the IR absorption bands of 3460, 1730, 1660 and 1590 cm^{-1} indicated the presence of hydroxyl, ester and conjugated carbonyl groups respectively.

Based on the structural similarity of **26** to **23** the same relative configuration at C-1 and C-2 was assumed. The coupling constants observed between H-2 and H-3 (9.1 Hz) suggested a diaxial relationship between the two hydrogens. Thus, the structure of globosuxanthone B **26** was deduced as depicted in (*Figure 12*).



1R*, 2R*, 3S*- **26**

Figure 12

These examples are representative of a growing family of monomeric tetrahydroxanthone natural products (*Figure 13*).

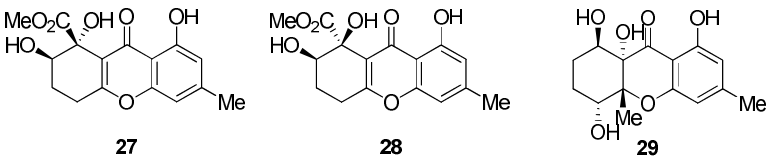
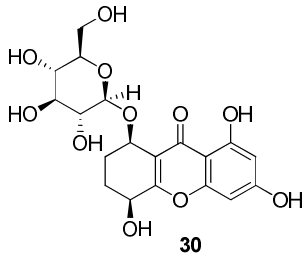


Figure 13

The first *O*-glycoside monomeric tetrahydroxanthone was isolated from *Gentiana campestris*. Its structure was elucidated as 1,3,5-trihydroxy-8-*β*-D-glucopyranosyl tetrahydroxanthone (**30**) (*Figure 14*).[45]



30

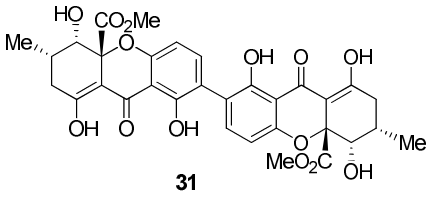
Figure 14

The occurrence of the monomeric tetrahydroxanthone glycoside **30** is of biogenic importance because the corresponding xanthone glycoside, possessing the same oxidation pattern and glycosidated at the same position is present in high quantities.

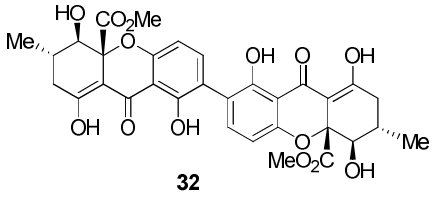
1.4.2.1 Dimers of Tetrahydroxathones

The ergochromes (ergoflavins, ergochrysin, secalonic acids) are an important class of mycotoxins produced by a variety of microorganisms. Currently 22 members of the ergochrome family have been isolated and structurally identified as dimers of tetrahydro-monoxanthones. The natural products secalonic acids and ergochromes being important examples.[46]

Secalonic acid B **31** and D **32** are 2,2'-fused symmetrical tetrahydroxanthone dimers that differ only in the stereochemistry of functional groups in the partially saturated rings (*Figure 15*).[44]



31

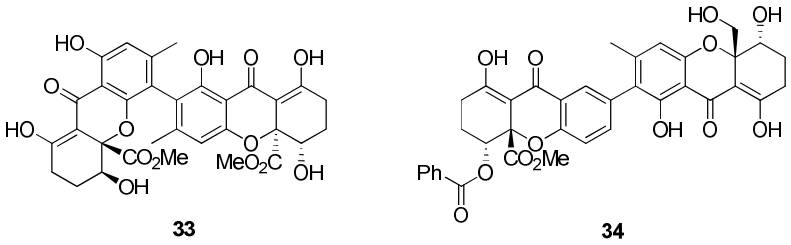


32

Figure 15

More recently, a number of new tetrahydroxanthones, such as rugulotrosin **33** and xanthanol **34** were isolated from moulds.[47]

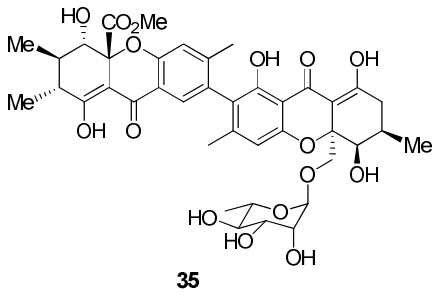
Rugulotrosin B **33** is an example of 2,4'-fused dimeric tetrahydroxanthone while xanthonol **34** is a novel unsymmetrical dimeric xanthone that was isolated from the fermentation broth of a nonsporulating fungal species (*Figure 16*).[48]



33 34

Figure 16

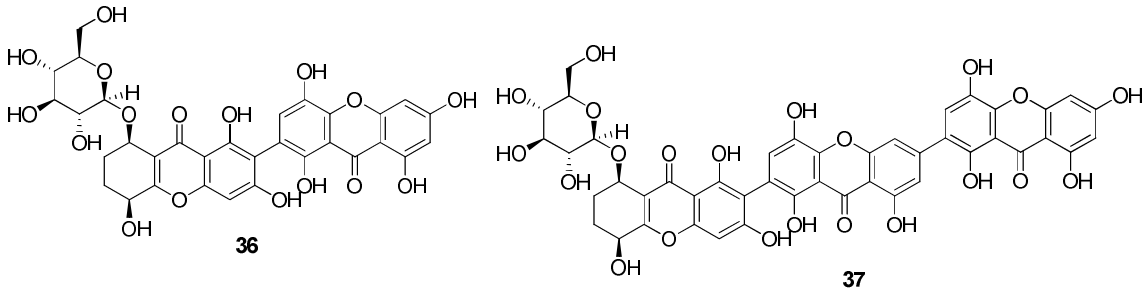
An unsymmetrical *O*-glycoside tetrahydroxanthone dimer hirtusneanoside **35** was isolated from the *n*-butanol extract of *Usnea hirta.*[49] Its structure and the absolute configuration was determined using extensive spectroscopic data (UV, IR, CD, 1D and 2D NMR) and chemical degradation. The tetrahydroxanthone dimer **35** has a unique structure containing an L-rhamnopyranside (*Figure 17*).



35

Figure 17

In 2010, Guo *et al* isolated the unsymmetrical dimeric puniceaside B **36** and trimeric *O*-glycoside puniceaside C **37** from *Swertia punicea* (*Figure 18*). [12]



36 37

Figure 18

1.4.2.2 Biological Activities of Monomeric and Dimeric Tetrahydroxanthones

All the above monomeric tetrahydroxanthones show striking anticancer and antibiotic activities.[38] The dimeric tetrahydroxanthone *O*-glycosides showed highly potent neuroprotective activity.[12] The xanthone structure is a very interesting framework that

has a large variety of pharmacological activities. The biological activity of xanthones, dihydroxanthones and tetrahydroxanthones is due to their tricyclic scaffold but varies depending on the nature and the position of the substituents. These natural products possess antioxidant, anti-inflammatory, immunomodulatory, and antiviral effects.[48] The diversity of substituents and the heterocyclic nature of these natural products have made them exhibit some important pharmacological properties, such as antioxidative, antitumour, antiulcer, antimicrobial, antiheptotoxic and CNS depressant activities. [50]

1.5 Xanthones, Dihydroxanthones, and Tetrahydroxanthones in Polycyclic Natural Product Frameworks.

The polycyclic xanthones form a small but distinct family of more than twenty natural products.[51] The polycyclic xanthones are one of the largest subgroups of polyketides being assembled by a type-2 polyketide synthase.[52]

The genus streptomyces is a prodigious source of structurally variegated secondary metabolites. A new species *Streptomycis cervinus* in this genus was discovered and a collaborative effort led to the isolation and structure determination of novel antibiotics cervinomycin A_1 **38** and A_2 **39** (*Figure 19*).[53]

Cervinomycins **38** and **39** belong to a small but esoteric group of antibiotics all of which possess xanthone and isoquinolone moieties fused angularly in a polycyclic framework (*Figure 19*).[54]

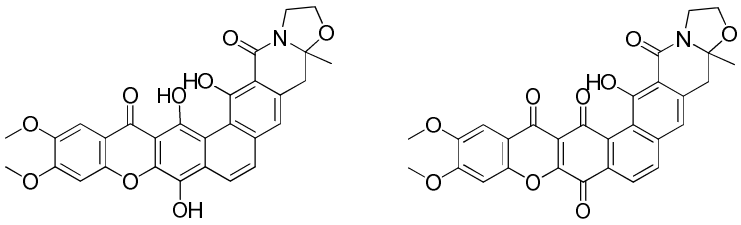
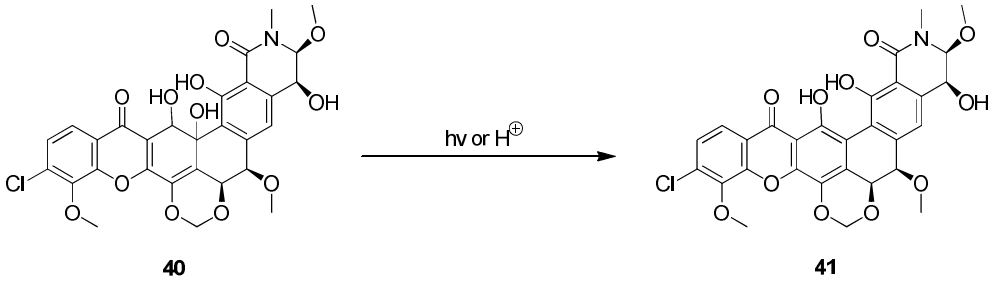


Figure 19

The lure of novel structural features and their promising biological activities generated considerable synthetic interest in these compounds. The first total synthesis of cervinomycins **38** and **39** was reported in 1989 by Kelly *et al*, followed in the following decade by several other syntheses based upon alternative synthetic strategies.[55, 56]

Lysolipin **40** which is a product of *Streptomyces violaceoniger* and immediate precursor of the lysolipin I **41**, formed after dehydration, is another member of the polycyclic

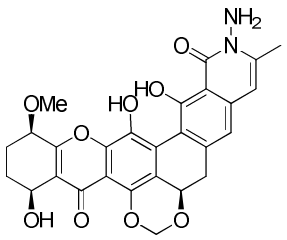
xanthone natural product family (*Scheme 1*). [50] Lysolipins **40**, and **41** were the second group of polycyclic xanthone family of antibiotics to be discovered. [57]



40 **41**

Scheme 1

Albofungin **42** is a tetrahydroxanthone containing polycyclic angularly fused metabolite isolated from *Actinomyces albus var fungatus*.[58] The basic framework of albofungin was determined by Slovieva *et al* in 1972, while the absolute configuration and stereochemistry were established by Gurevich *et al* two years later. The helicity of the fused rings and hence the absolute configuration of methylenedioxy ring was determined using CD spectroscopy conducted on albofungin and its degradation products (*Figure 20*).[59]



42

Figure 20

Structurally related to albofungin **42** are actinoplanones **45** and **46** (*Figure 22*) and simaomicins *α*-**43** and *β*-**44** (*Figure 21*), which are hexacyclic xanthones produced by *actinomadura madurae simaoensis*.[60] The structure of simaomicins *α*-**43** and *β*-**44** was established using X-ray crystallography alongside spectroscopic methods. The structure of simaomicins *α*-**43** and *β*-**44** are unique within the polycyclic tetrahydroxanthone natural products in that the methylenedioxy ring is in line with the xanthone rather than the pyridone unit. Such a heterocyclic ring is common to all these natural products with the exception of the cervinomycins **38**, **39** (*Figure 19*). [61]

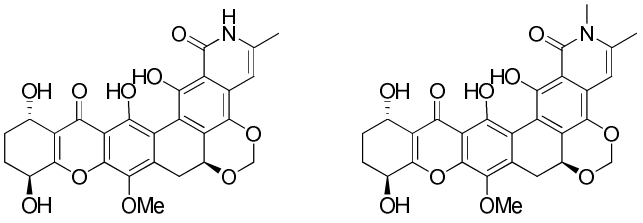


Figure 21

Two polycyclic xanthones named actinoplanones A **45** and B **46** were isolated from the culture broth of *Actinoplanes actinoplanaceae* by Kobayashi *et al* in 1988 (*Figure 22*).[62] The structures of **45** and **46** were determined by a detailed study of 2D heteronuclear correlation NMR experiments. The absolute configurations of the asymmetric carbons being established by CD spectra alongside ^{1}H and ^{13}C NMR analysis of chiral Mosher derivatives.

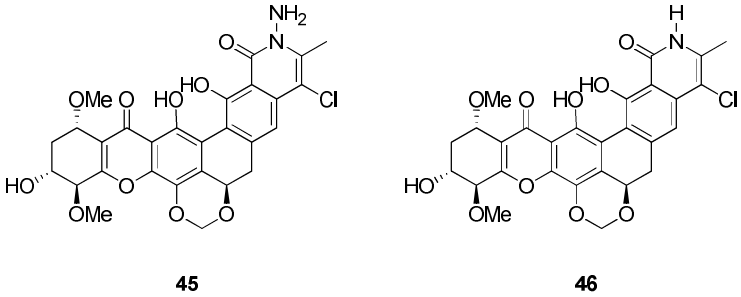
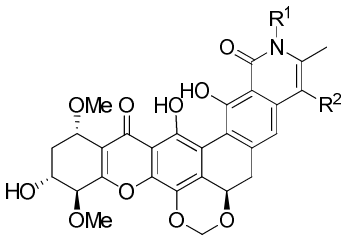


Figure 22

In a continued search for polycyclic xanthone antibiotics, a further five analogues of actinoplanones were isolated from the culture broth of the same species *Actinoplanes* species by the same research group later that year. The new analogues were named as actinoplanone C **47**, D **48**, E **49**, F **50**, and G **51**.[63]

All these (**C-G**) exhibited similar physico-chemical properties to those of actinoplanones (**A**, and **B**). In the ^{1}H and ^{13}C NMR, similar spectral patterns were observed between the newly isolated polycyclic xanthones and the actinoplanone A (**45**), except in the region of the pyridone ring (*Figure 23*).



Actinoplanone C ; $R^1 = NH_2$, $R^2 = H$ **47**
Actinoplanone D ; $R^1 = H$, $R^2 = H$ **48**
Actinoplanone E ; $R^1 = N=C(CH_3)_2$, $R^2 = Cl$ **49**
Actinoplanone F ; $R^1 = N=C(CH_3)COCH_3$, $R^2 = Cl$ **50**
Actinoplanone G ; $R^1 = N=C(CH_3)COCH_3$, $R^2 = H$ **51**

Figure 23

During a search for new bioactive metabolites from Australian microorganisms, an isolate of the rare actinomycete was examined by Capon and co-workers in 2007. Bioassay profiling of the methanolic extract derived from a culture of *kibdelosporangium* sp. (MST-108465) uncovered an unusual combination of potent antibacterial, nematocidal and cytotoxic activities.[64]

HPLC analysis of the secondary metabolites showed the presence of a family of non-polar metabolites displaying distinctive UV- visible spectra.

An electronic search of data sets comprising HPLC-DAD-ELSD profiles for over 1500 natural products and 6000 annotated microorganisms failed to identify these non-polar metabolites, suggesting that these metabolites were novel.

A scaled up solid and liquid phase fermentation of the *kibdelosporangium sp.* optimised for the production of cytotoxic metabolites yielded a family of 10 polycyclic xanthone natural products exemplified by kibdelone A (**52**) (*Figure 24*). Kibdelones are hexacyclic tetrahydroxanthone natural products featuring two fully substituted aryl rings, two fully substituted heteroaryl rings, three stereogenic centres in the saturated ring and a halogenated ring.

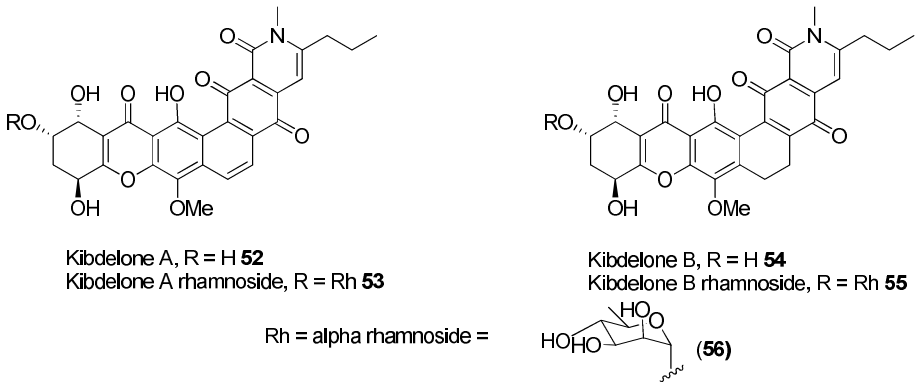


Figure 24

The other isomers of kibdelones include oxokibdelone **59** which contains a ketone in the saturated ring (*Figure 25*).[64] Recently, two total syntheses of the kibdelone family member have been reported, these are described in section 1.7.

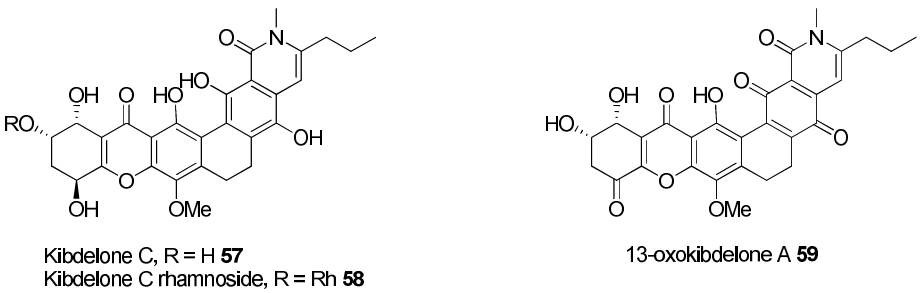
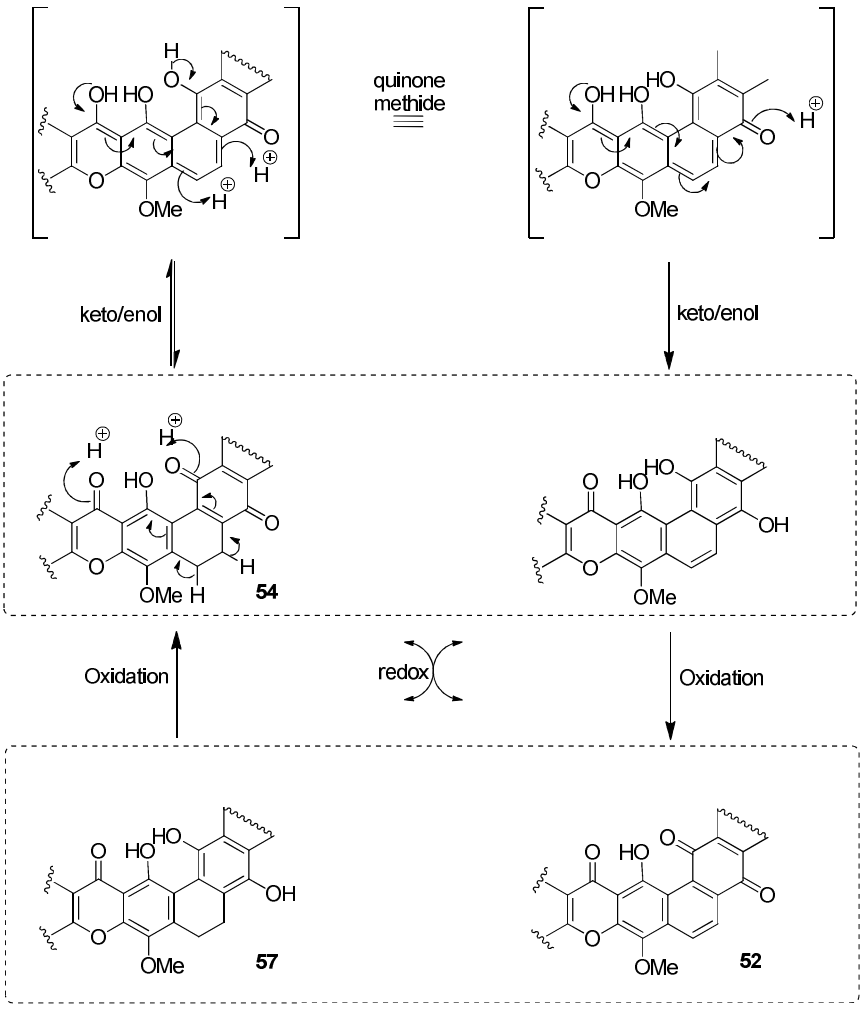


Figure 25

An interesting property of these compounds is the facile equilibration of kibdelone B **54** and C **57** to a mixture of A **52** and C **57** through keto-enol tautomerism followed by quinone-hydroquinone redox reactions proposed by Capon *et al* (*Scheme 2*).[64]



Scheme 2 : A plausible mechanism for the equilibration of kibdelones **52**-**57**.

On standing in MeOH, purified kibdelone A **52** or kibdelone B **54** evolves to an equilibrium mixture of **52** : **54** : **57** in approximately 3 : 1 : 2 ratio.

Other kibdelone analogues discovered include the 25-methoxy-24-oxokibdelone C **60**, 25-hydroxoxy-24-oxokibdelone C **61** and the hydroquinone **62** (*Figure 26*).

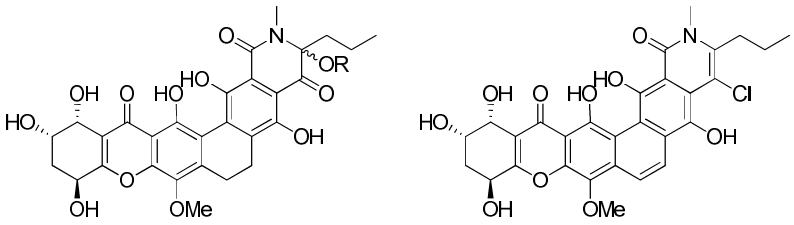


Figure 26

A family of biosynthetically related co-metabolites called the isokibdelones were isolated from a mixed media fermentation of the *kibdelosporangium sp.* (MST-108465)

by Capon *et al* subsequent to the isolation of the kibdelones.[65] Isokibdelones possess the same hexacyclic tetrahydroxanthones however, the isokibdelones feature an polyketide heterocyclic skeleton unprecedented in traditional polyketide biosynthesis.

Isokibdelone A (**63**) comprises a tetrahydroxanthone angularly fused to a halogenated quinone moiety where as isokibdelone A rhamnoside **64** contains a rhamnoside **56** attached through oxygen at C-11. The other members of the isokibdelone family include the quinone isokibdelone B (**65**) and the corresponding hydroquinone isokibdelone C (**66**) (*Figure 27*).

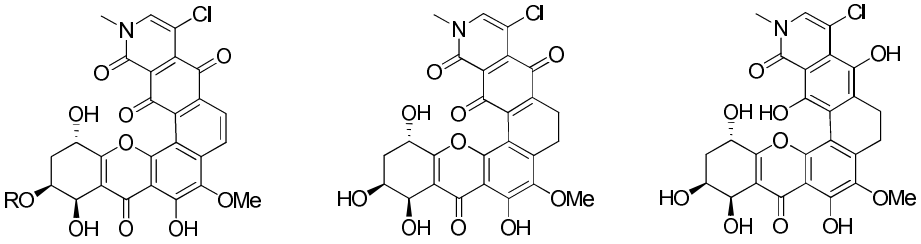


Figure 27

The isokibdelones are not as potent nematocidal, antibiotic or anticancer agents as the kibdelones. However, this study does uncover structure activity relationships (SAR) within this family of natural products.

One final class of polycyclic xanthones that have been isolated from natural sources are the kigamicins. Since, these are the main focus of my thesis work, these are discussed separately in section 1.6.

1.5.1 Biological Activities of Polycyclic Natural products

Cervinomycins **38** and **39** are antibiotics having strong inhibitory activities against anaerobic bacteria and mycoplasma. Lysolipins **40** and **41** are antibacterial, antifungal, as well as cytotoxic xanthone natural products.[57] Albofungin **42** is a highly active antibiotic against gram positive bacteria and yeasts.[66] Simaomicins α-**43** and β-**44** are primarily active against gram positive bacteria. It is however, the antiparasitic activity of the simaomicins versus the single cell animal of the genus *Eimeria* that has generated greatest interest. Simaomicin α-**43** is the most potent natural anticoccidal agent for the treatment of *E.tenella* infections ever reported.[60] Actinoplanones **45** and **46** are strongly cytotoxic against HeLa cells. These polycyclic xanthones also show antifungal and antibacterial activities, with **45** active against gram negative bacteria. Actinoplanone **45**

is shown to inhibit DNA synthesis while RNA and protein inhibition was comparatively weak. All the actinoplanones showed strong cytotoxicity against HeLa cells, particularly actinoplanone C **47** and G **51** which exhibited IC_{50} values at less than 0.00004 μg/mL.[63] Among all the other known polycyclic xanthones, only albofungin **42** has been reported to show cytotoxicity against HeLa cells and prolong the life of mice into which *Ehrlich ascites* tumour cells have been transplanted.[58] Kibdelones (**52-62**) possess potent nematocidal and antibiotic activities. They are also impressive anticancer agents displaying GI_{50} in the low nanomolar range against a panel of human cancer cell lines.[64]

1.6 Kigamicins

The polycyclic tetrahydroxanthone natural products known as kigamicins (**67-71**), named after 'kiga,' a Japanese word meaning starvation, were first extracted from the culture broths of *Amycolatopsis* sp. ML630-mF1 during the course of screening for new antitumor antibiotics by Kunimoto *et al*.[67] Kigamicins (**67-71**) are potential antitumor agents against pancreatic cancers. They selectively target pancreatic cancer cells growing under nutrient starved conditions.[68, 69] Most of the research so far conducted on the kigamicins (**67-71**) has been on their isolation,[67] determination of their structure, [70] absolute configuration, [71] and biological activities (*Figure 28*).[72]

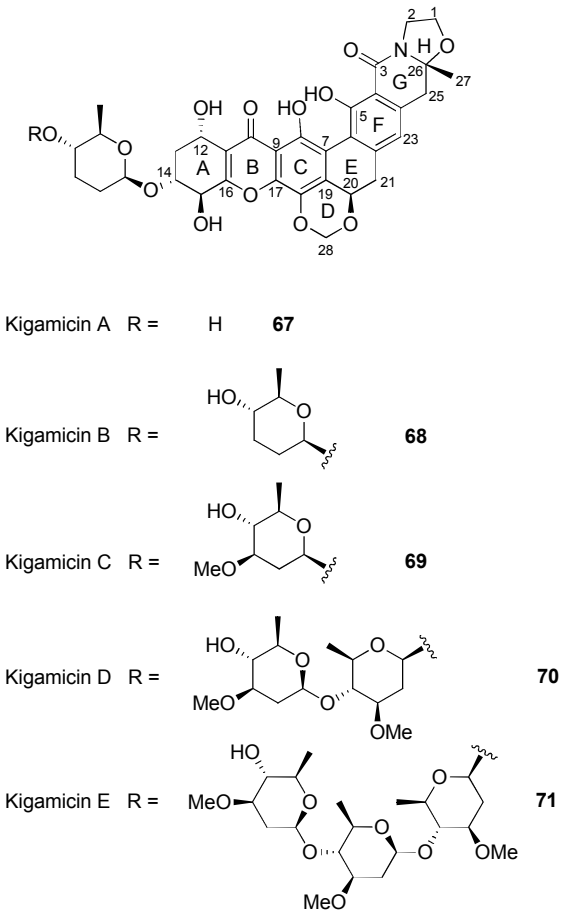


Figure 28 : Structure of Kigamicins A-E

1.6.1 Extraction and isolation of the kigamicins

The kigamicins (**67-71**) were first isolated from the culture broth of *Amycolatopsis* sp. ML630-mF1 by Kunimoto *et al* in 2003.[67] The culture filtrate (10,270 mL) from strain *Amycolatopsis* sp. ML630-mF1 was adjusted to pH 2.0 and extracted with butyl acetate. Silica gel column chromatography of the dried paste with different mixture of CH_3Cl and MeOH resulted in an active eluate which was further separated into two parts. Each eluate was charged onto a reverse phase ODS column and developed with a mixture of CH_3CN and H_2O. The first eluate provided three active fractions containing kigamicin C (**69**), D (**70**), and E (**71**) respectively as the main components. Each fraction was further purified by chromatography using reverse phase HPLC with the same solvent system. Thus kigamicin C (**69**) (31.6 mg), D (**70**) (85.3 mg) and E (**71**) (19.4 mg) were purified as yellow powders. The second eluate from the silica gel column chromatography was applied on reverse phase ODS column resulting in the isolation of kigamicin A (**67**) (25.8 mg). Kigamicin B (**68**) (4.1 mg) was purified from another culture (3 litres) by almost the same purification steps along with some kigamicin C (**69**) (14.9 mg), D (**70**) (46.6 mg) and E (**71**) (21.8 mg) subsequently.

Tan *et al* also isolated kigamicins from a novel species of Actinomycete, the *Amycolatopsis regifaucium* in 2007.[73]

1.6.2 Structure determination of kigamicins

The structural studies were first carried out for kigamicin D (**70**), the major component of these antibiotics. The structures of other components were determined subsequently by comparing their spectral data with kigamicin D.[70]

The molecular formula of kigamicin D was established as $C_{48}H_{59}NO_{19}$ (MW 953 g/mol) on the basis of HRESI-MS and NMR data. The UV spectrum of **70** showed characteristic absorption maxima at 227, 253, 306, and 384 nm similar to that of actinoplanones (**45-51**) suggesting the presence of polycyclic xanthone chromophore. IR absorption bands showed the presence of hydroxyl (3450, 1062 cm^{-1}), conjugated carbonyl (1650 cm^{-1}), and γ-pyrone (1620 cm^{-1}) functions in the natural product. The ^{13}C NMR, DEPT and HMQC spectra of **70** in $CDCl_3$ revealed the presence of 48 carbon signals comprising of six methyl, ten methylene, sixteen methine and sixteen quaternary carbons. The ^{1}H NMR spectrum indicated the presence of five deuterium exchangeable hydrogens. The seven spin systems observed in ^{1}H-^{1}H COSY and the HMBC analysis of **70** revealed the presence of an aglycon moiety, a 2,3,6-trideoxyhexose (D-amicetose) moiety and two 2,6-dideoxyhexose (oleandrose) moieties.

The aglycon was found to be similar to albofungin **42** (*Figure 20*). However, a five membered nitrogen containing ring in kigamicin D was replaced by the six membered heterocyclic rings in albofungin **42**. The long range coupling in the HMBC spectrum confirmed the glycosidic linkage.

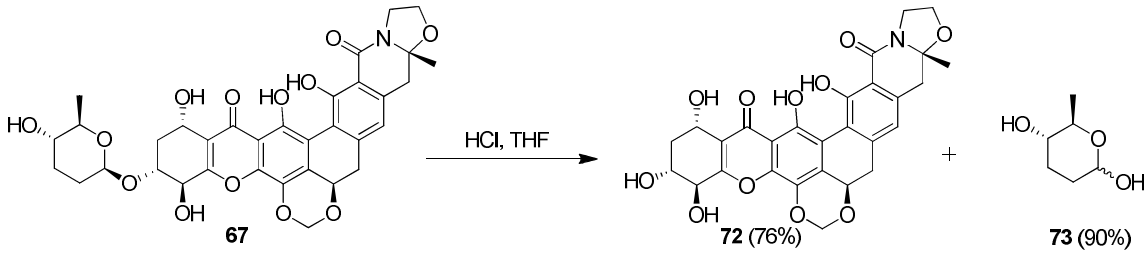
The molecular formula of kigamicin A (**67**), B (**68**), C (**69**), and E (**71**), were established to be $C_{34}H_{35}NO_{13}$ (MW 665 g/mol), $C_{40}H_{45}NO_{15}$ (MW 779 g/mol), $C_{41}H_{47}NO_{16}$ (MW 809 g/mol) and $C_{55}H_{71}NO_{22}$ (MW 953 g/mol) respectively from the HRESI-MS and NMR data. The UV and IR spectra of **67**, **68**, **69**, and **71** were very similar to those of **70**. The ^{1}H and ^{13}C NMR data showed the presence of a common aglycon in all the kigamicins, and the presence of one D-amicetose moiety in **67**, two D-amicetose moieties in **68**, one D-amicetose and one oleandrose moiety in **69**, and one D-amicetose and three oleandrose moieties in **71.**

Thus, the structures of kigamicins (**67-71**) have been determined to consist of fused octacyclic aglycon and deoxy sugars. The absolute configuration of kigamicins A (**67**),

C (**69**), and D (**70**), were determined a year later by Someno *et al* by NMR analysis, chemical degradation studies and X-ray crystallographic analyses.[71]

Determination of the stereochemistry was first conducted for kigamicin A **67**, because other members of the class could not be crystallised in the solvents investigated. Kigamicin A (**67**) was crystallised from hot MeOH/H_2O to give yellow plate like crystals. The relative stereochemistry of **67** was conclusively determined by X-ray analysis (*Figure 29*).

In order to determine the absolute stereochemistry of kigamicin A (**67**), the configuration of D-amicetose was examined by measuring its optical rotation after acidic hydrolysis of the natural product (*Scheme 30*).

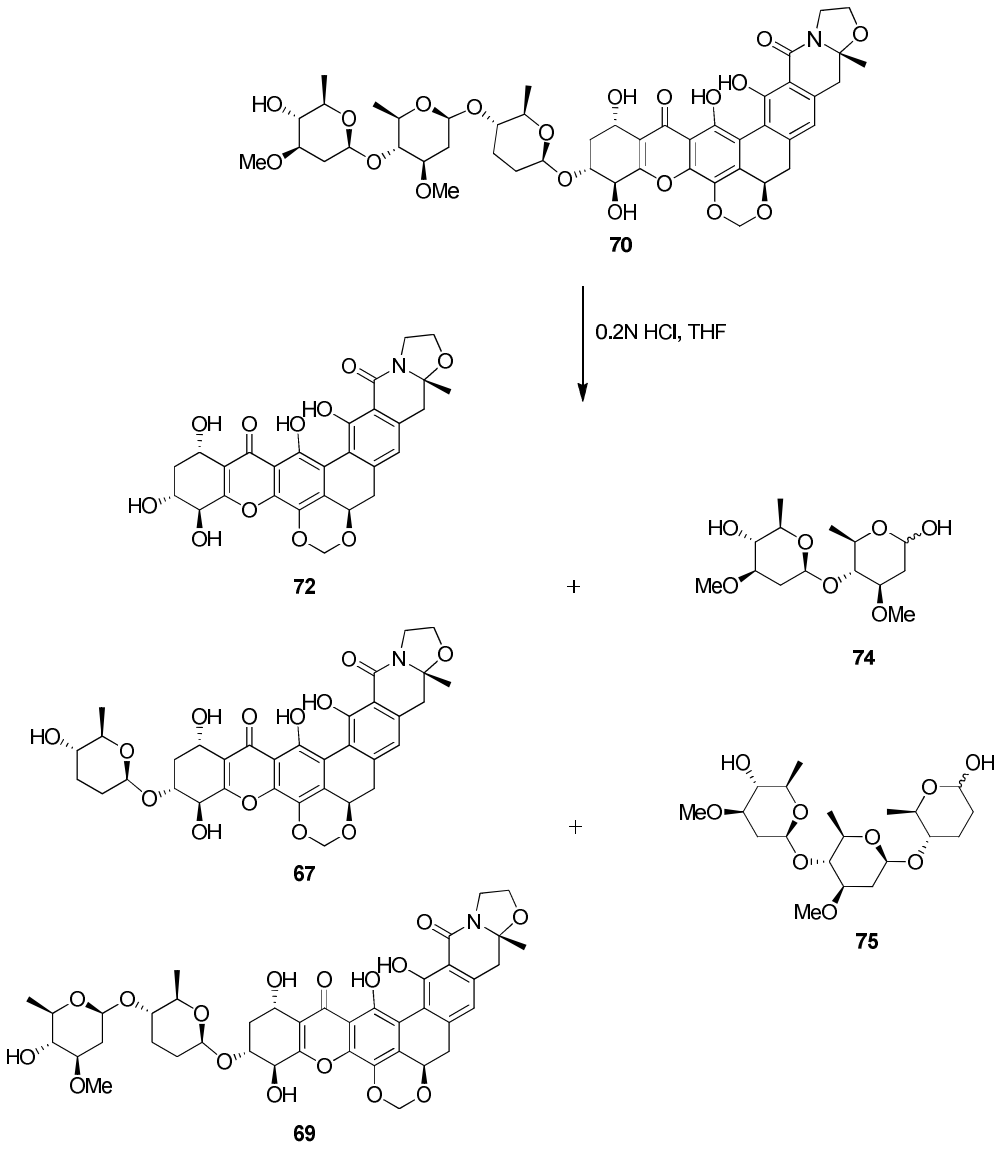


Scheme 3

Treatment of kigamicin A with 1N HCl in THF at room temperature for 18 hours gave the aglycon **72** of fused octacyclic ring system containing seven six membered rings and one oxazolidine in 76 % yield and amicetose **73** in 90 % yield (*Scheme 3*). The aglycon part was spectroscopically identical with the octacyclic component found in the kigamicins themselves. The optical rotation value for **73**, $[\alpha]_D^{22}$ = + 42.5 (*c* = 0.7, Me_2CO), was close to that reported for D-amicetose $[\alpha]_D^{22}$ = + 43.6 (*c* = 1.0, Me_2CO). Therefore, it was concluded that kigamicin A possesses this sugar in the D-form. Taking the configuration of D-amicetose into consideration, the absolute configuration of kigamicin A was thus established as shown in Figure 29. In addition, the coupling constants of anomeric hydrogen (*J* = 2.0, 9.0 Hz) indicated the presence of *β*-D-amicetose, which is consistent with the results obtained from the X-ray analysis.

Kigamicin D (**70**) contains one amicetose and two oleandrose moieties. Since there are discrepancies between the reported optical rotation values of oleandrose, and since the complete separation of D-amicetose and oleandrose when kigamicin D was hydrolysed was found to be difficult, attempts were made to obtain crystalline di- or tri-saccharides containing D-amicetose and oleandrose. Mild acid hydrolysis of **70** yielded amicetose,

oleandrose, as well as aglycon **72**, kigamicin A **67,** kigamicin C **69**, disaccharide **74** and trisaccharide **75** (*Scheme 4*).



Scheme 4

Compounds **74** and **75** were crystallised from EtOAc/*n*-hexane and ether/*n*-hexane to give colourless crystals. The X-ray structural analysis of **75** revealed the presence of anomeric mixture (α : β = 55 : 45). Since the absolute configuration of the D-amicetose was known to be the D-form, the two oleandrose moieties were established to be also the D-forms. On the basis of the above investigation, the absolute structure of kigamicin D (**70**) was deduced as depicted in Figure 29 having an octacyclic aglycon, D-amicetose, and two D-oleandrose moieties.

1.6.3 Biological activity of the kigamicins

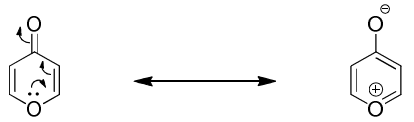
The biological activity of the kigamicins has been extensively studied by Lu *et al.*[69] Masuda *et al* while determining the spectrum of activity of kigamicin D against various human cancers, found kigamicin D to be a novel anticancer agent that targets the tolerance of cancer cells to nutrient starvation.[72] They have shown that kigamicin D displays a preferential cytotoxicity to cancerous cells grown under nutrient deprived conditions. Both tolerance to nutrient starvation and angiogenesis (development of new blood capillaries) are essential for cancer progression because of the insufficient supply of nutrients to tumour cells. Chronic nutrient starvation seldom occurs in normal tissue therefore nutrient deficiency in tumours provides a novel cancer therapy for which the phrase has been coined "anti-austerity." Selective killing of pancreatic cancer cells in nutrient starved conditions was determined by comparing cell survival after 24 hours incubation in nutrient deprived medium (NDM), against that in nutrient rich medium (NRM). Under nutrient starved conditions, kigamicin A, B, C, and D inhibited PANC-1 (pancreatic cancer cells) survival at 100 times lower concentrations than in normal media. Kigamicins induced cell death in melphalan-resistant myeloma cells at very low concentrations (0.004 nM). They also selectively killed the malignant plasma cells at very low concentrations while sparing the normal lymphocytes.[69] Kigamicins showed antimicrobial activity against Gram-positive bacteria including methicillin resistant staphylococcus aureus (MRSA). Kigamicin D **70** inhibited the growth of various mouse tumour cell lines, with an IC_{50} of 1 μg/mL.

Oral administration of kigamicin D showed a strong antitumor effect in human tumour xenograft models of pancreatic tumours. It showed a weak effect against lung cancer, and no effect against colon cancers. However, it has also been reported that kigamicin D **70** shows the same selective cytotoxicity against normal human cells such as lung fibroblast and prostate stromal cells under nutrient starved conditions. Thus, these natural products represent interesting molecules for further study.[74]

1.7 Synthetic strategies for the synthesis of dihydro and tetrahydroxanthones natural products.

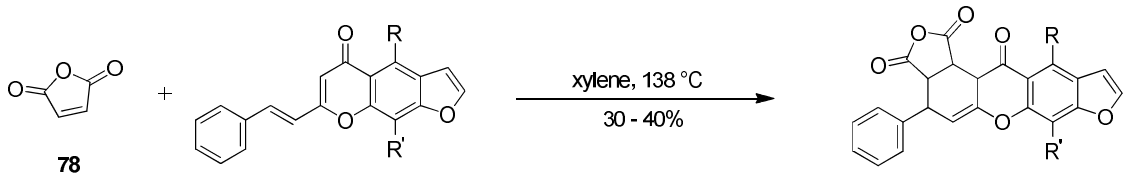
To date, there have been no synthetic studies reported concerned with the synthesis of the kigamicins (**67-71**) or their analogues. This section provides a broader overview to the field of tetrahydroxanthone synthesis.

In 1954, Alexander *et al* suggested that the double bond in γ-pyrones **76** should allow them to act as dienophiles in Diels Alder reactions thus allowing the synthesis of xanthone derivatives. However, the formation of the zwitterion **77** by resonance delocalisation reduces this reactivity somewhat (*Scheme 5*).[75]



Scheme 5

However, inactive dienophiles in the Diels-Alder reaction can be transformed into reactive dienes such as **79** and **80**, and these provide a simple route to tetrahydroxanthone derivatives **81** and **82** when reacted with maleic anhydride **78** in boiling xylene (*Scheme 6*).

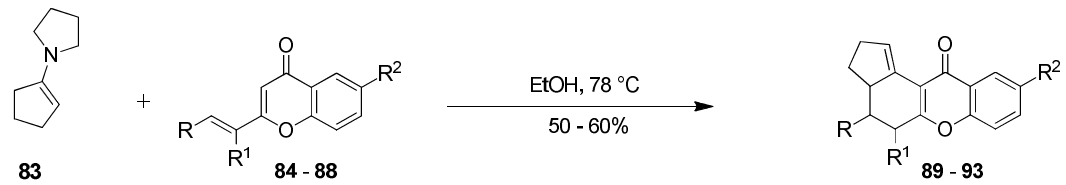


R = R' = OMe **79**
R = OMe, R' = H **80**

R = R' = OMe **81**
R = OMe, R' = H **82**

Scheme 6

Letcher and Yue conducted a favourable Diels-Alder reaction using an electron rich dienophile and electron deficient diene to obtain tetrahydroxanthone derivatives.[76] Equimolar amounts of the enamine **83** and a variety of (*E*)-2-vinylchromene-4-ones (**84-88**), gave tetrahydroxanthones (**89-93**) as Diels-Alder products in moderate yields (*Scheme 7*).

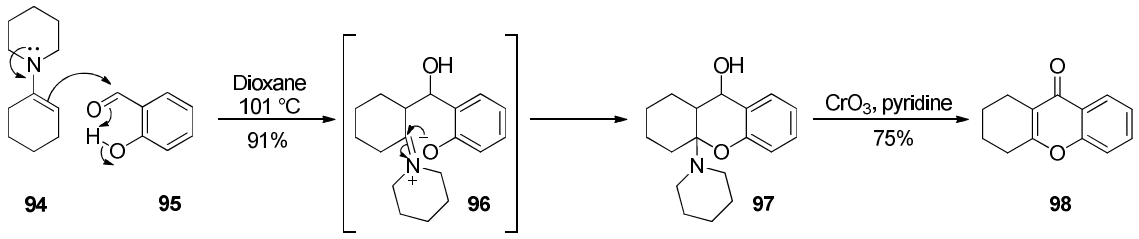


R = Ph, R^1 = Me, R^2 = H **84**
R = Ph, R^1 = R^2 = H **85**
R = Me, R^1 = R^2 = H **86**
R = 2-Methyl furan, R^1 = R^2 = H **87**
R = Ph, R^1 = H, R^2 = Br **88**

R = Ph, R^1 = Me, R^2 = H **89**
R = Ph, R^1 = R^2 = H **90**
R = Me, R^1 = R^2 = H **91**
R = 2-Methyl furan, R^1 = R^2 = H **92**
R = Ph, R^1 = H, R^2 = Br **93**

Scheme 7

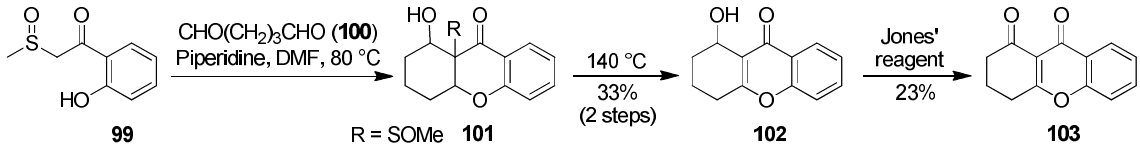
A decade later, Paquette reported a novel route for the synthesis of tetrahydroxanthones.[77] He treated enamine **94** with salicylaldehyde **95** in an inert solvent to promote intramolecular proton transfer driven by the difference in the basicities of alkoxy and phenoxy anions. Subsequent nucleophilic addition of the phenoxide ion to the iminium ion resulted in the formation of **97** in high yields. The structure of **97** was confirmed by Sarett oxidation to tetrahydroxanthone **98** (*Scheme 8*).



Scheme 8

The generality of this reaction and the mechanism of formation of the tetrahydroxanthone was detailed a year later when this chemistry was used in the synthesis of valuable tetrahydroxanthones, chromones, flavones and isoflavones.[78] Preliminary attempts to employ 2,5-dihydroxybenzaldehyde in this condensation reaction proved unsuccessful. However, 2-hydroxy-3-methoxybenzaldehyde gave high yields. Clearly, the presence of additional phenolic hydroxyl group interferes with the addition process, as may be expected from the proposed mechanistic pathway (*Scheme 8*).

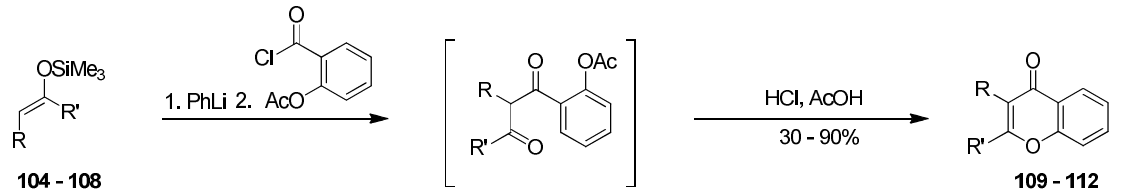
In 1975, Klutchko reported the synthesis of tetrahydroxanthone dione **103** from *β*-keto sulfoxide **99** through condensation with glutaraldehyde **100** and subsequent thermal elimination of methanesulfenic acid from **101** in poor yields (*Scheme 9*).[79]



Scheme 9

In 1977, Toshio *et al* described a novel synthesis of tetrahydroxanthones.[80] They were generated by treating the trimethylsilyl enol ether of various cyclic ketones with phenyl lithium to regenerate the lithium enolate followed by quenching with *O*-acetoxybenzoyl chloride at lower temperatures. The intermediate diketones without further purification

were cyclised in the presence of HCl and AcOH to obtain the corresponding tetrahydroxanthones (*Scheme 10*).



104 - 108

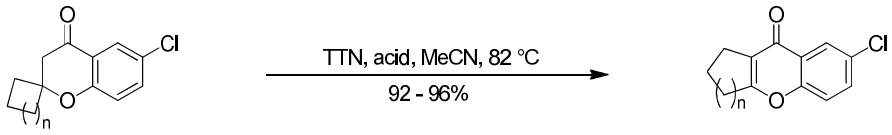
R = H, R' = Me **104**
R = Me, R' = Me **105**
R, R' = -$(CH_2)_3$- **106**
R, R' = -$(CH_2)_4$- **107**
R, R' = -$(CH_2)_5$- **108**

109 - 112

R = H, R' = Me **109**
R = Me, R' = Me **110**
R, R' = -$(CH_2)_3$- **111**
R, R' = -$(CH_2)_4$- **98**
R, R' = -$(CH_2)_5$- **112**

Scheme 10

In 1991, Singh *et al* disclosed a novel one step synthesis of tetrahydroxanthones in excellent yields exploiting a thallium (III) nitrate (TTN) oxidation of 2-spirochromones via 2,3-alkyl migration. The addition of Lewis or protic acids such as $BF.OEt_2$, *p*-TSA or $HClO_4$ reduced the consumption of TTN and shortened reaction times. The generality of this transformation was confirmed by treating several 2-substituted spirochromones with TTN under similar conditions (*Scheme 11*).[81]

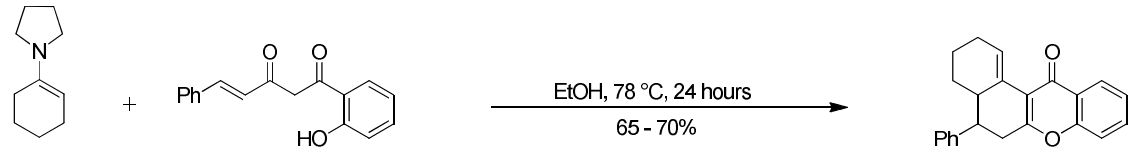


n = 0, **113**
n = 1, **114**
n = 2, **115**

n = 0, **116**
n = 1, **117**
n = 2, **98**

Scheme 11

A year later Letcher *et al* reported the reaction of enamine **118** with dione **119** leading to the formation of xanthone **120** in high yields (*scheme 12*).[82]

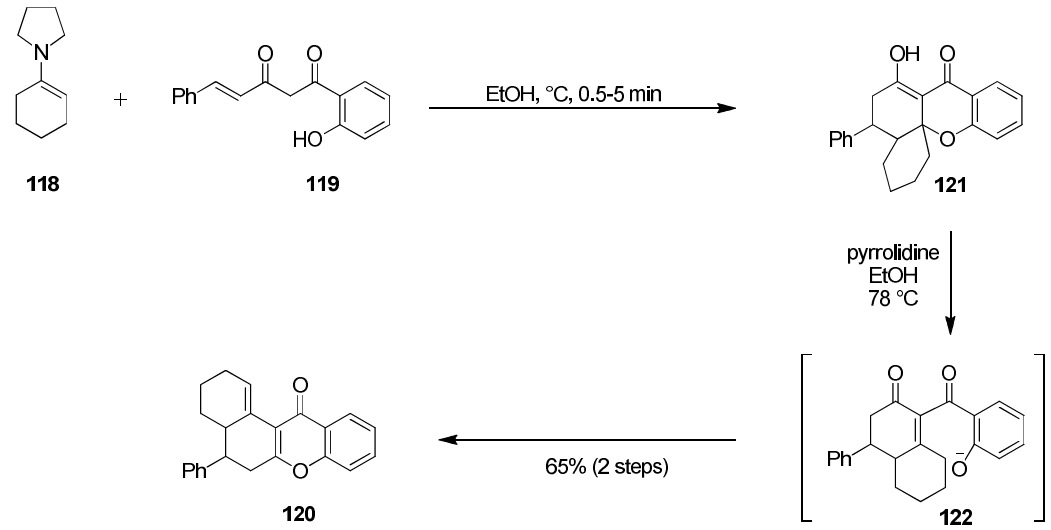


118 **119** **120**

Scheme 12

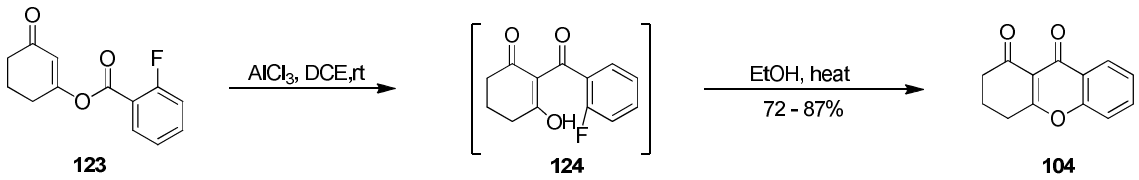
In an endeavour to investigate the mechanism of this transformation the reaction was monitored by TLC. It was observed that a new nitrogen free product, different from the final reported product **120**, formed rapidly within few minutes. The structure of the new

product was deduced by single X-ray crystallography to be **121**. That cycloalkanoxanthone **121** is an intermediate in the formation of **120** was confirmed by heating **121** in pyrrolidine, leading to hydroxanthone **120** in quantitative yield (*Scheme 13*).



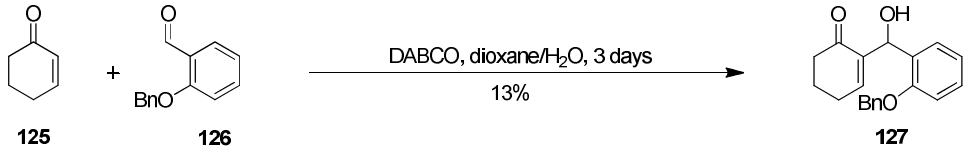
Scheme 13

In 1997, Luis *et al* reported a short and efficient synthesis of tetrahydroxanthone **104** by initiating Fries rearrangement of **123** with two equivalents of aluminium chloride to a mixture of the Fries rearranged product **124** and the cyclised product **104**. Complete cyclisation of **124** occurred during recrystallisation from ethanol with the loss of hydrogen fluoride in good yields (*Scheme 14*).[83]



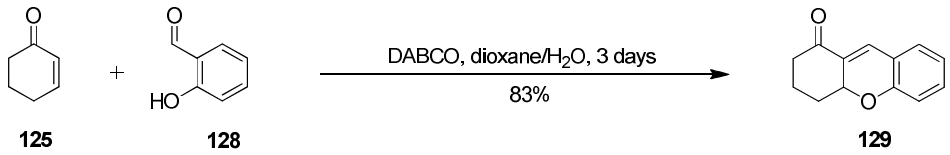
Scheme 14

In 2004, Brase *et al* conducted a Baylis-Hillman reaction of 2-cyclohexen-1-one (**125**) with *O*-benzylated salicylaldehyde **126** to obtain the desired allylic alcohol **127** in very poor yields (13%) (*Scheme 15*).[84]



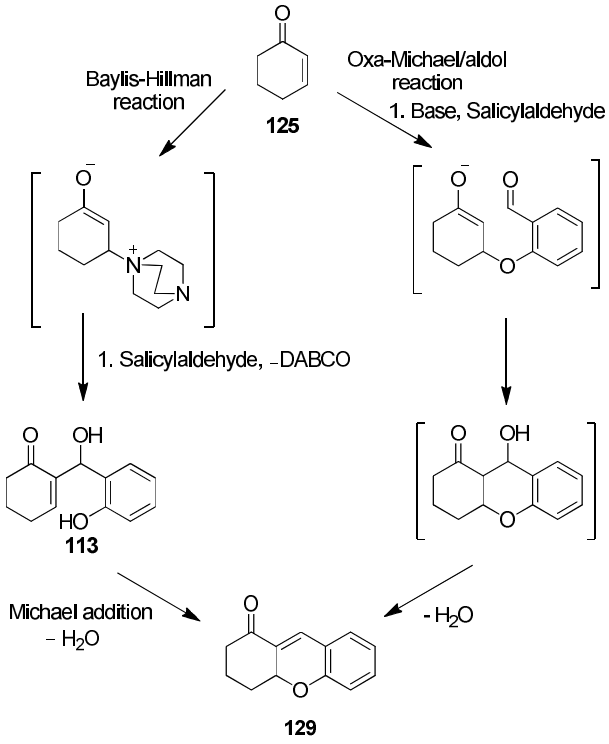
Scheme 15

In contrast the analogous reaction of unprotected salicylaldehyde **128** with cyclohexenone **125** did not result in the Baylis-Hillman adduct, but rather the xanthone **129** in good yields (*Scheme 16*).



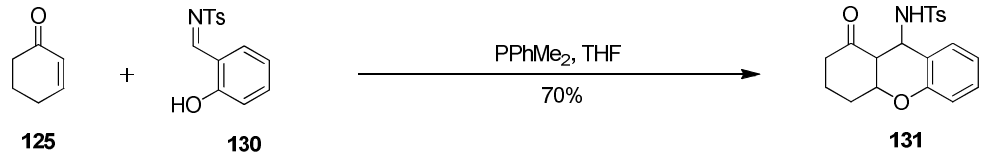
Scheme 16

Xanthone **129** may be formed by two different routes as formulated by Brase *et al*.[84] The first route starts with a Baylis-Hillamn reaction followed by an oxa-Michael addition and dehydration. In the second approach the reaction is initiated by the Michael addition of the phenol on the cyclohexenone followed by aldol condensation providing xanthone **129** (*Scheme 17*).



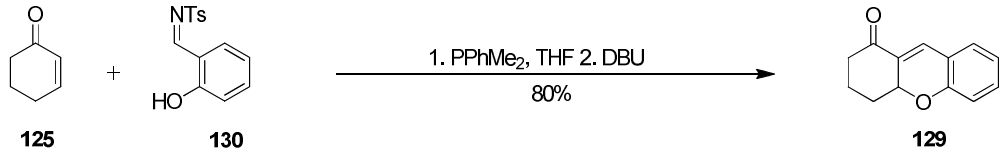
Scheme 17

A year later Shi *et al* reported a modification of the above reaction. They used salicyl *N*-tosylamine **130** to react with cyclohexenone **125** in the presence of catalytic dimethylphenyl phosphine to obtain the tricyclic compound **131** in good yield (*Scheme 18*).[85]



Scheme 18

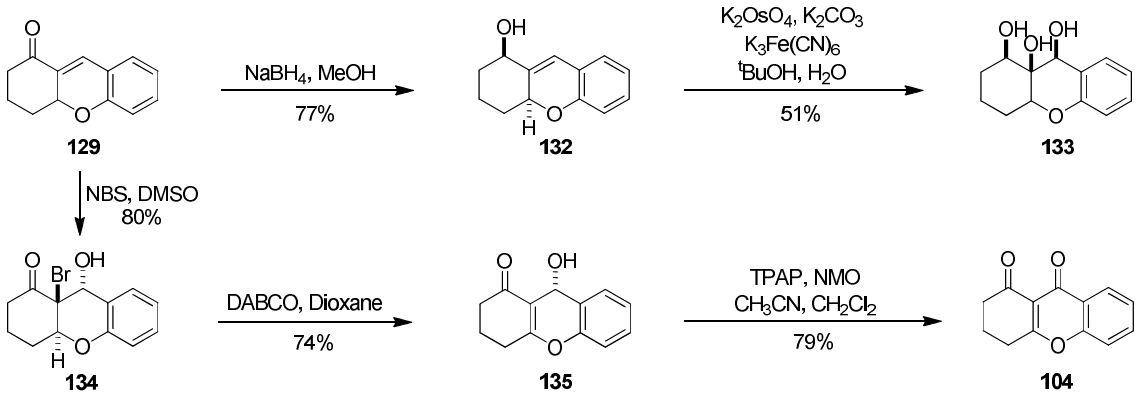
Shi further envisioned the conversion of **131** to tetrahydroxanthone **129** with the elimination of $TsNH_2$ using a strong base. In a one pot reaction, after the consumption of **130**, DBU was added to obtain **129** in very good yield (*Scheme 19*).



Scheme 19

In 2006, Brase *et al* examined the reactivity of easily accessible tetrahydroxanthones by oxa-Michael aldol condensation. The structure of tetrahydroxanthones offer various possibilities for further functionalisations, many of which might be performed with useful levels of diastereoselectivity hereby being of relevance to complex tetrahydroxanthone containing natural products.[86]

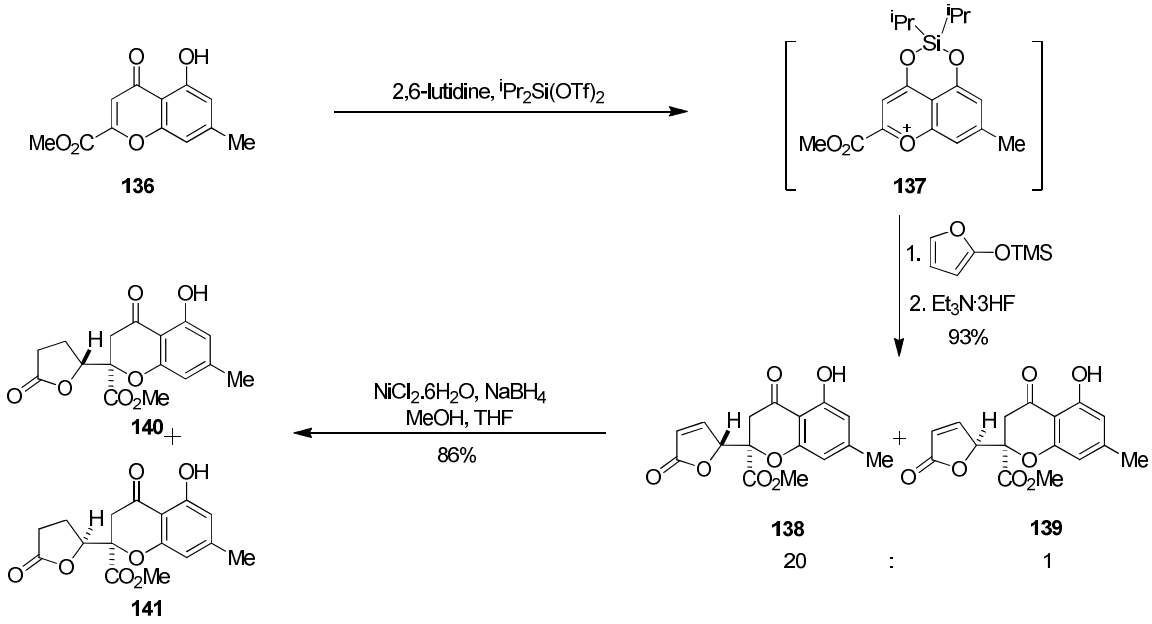
Tetrahydroxanthone **129** gave allylic alcohol **132** as a single diastereomer on reduction with sodium borohydride in good yield. The relative configuration of **132** was determined by X-ray crystallography. The allylic alcohol **132** was then transformed into the all *cis*-triol **133** by dihydroxylation. Tetrahydroxanthone **129** was also converted into its bromohydrin **134** to facilitate base induced elimination to obtain **135** which was then oxidised to tetrahydroxanthone dione **104** (*Scheme 20*).



Scheme 20

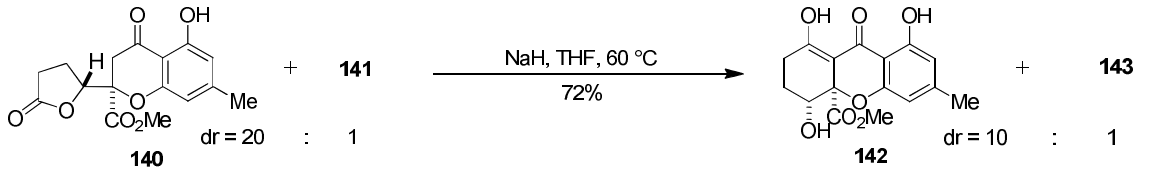
In 2011, Porco *et al* developed a concise approach to tetrahydroxanthone natural products employing a vinylogous addition of 2-trimethylsiloxyfuran to benzopyryllium **137** followed by a late-stage Dieckman cyclisation.[87]

The synthesis of benzopyrylium **137** was achieved by the treatment of **136** with diisopropylsilyl ditriflate in the presence of 2,6-lutidine.[88] Treatment of **137** with 2-trimethylsiloxyfuran at lower temperature and subsequent desilylation with triethylamine hydrogen fluoride led to the formation of chromone butenolides **138** and **139** (dr = 20:1). Conjugate reduction of the mixture using nickel boride gave access to chromone lactone **140** and **141** (dr = 20:1) (*Scheme 21*).



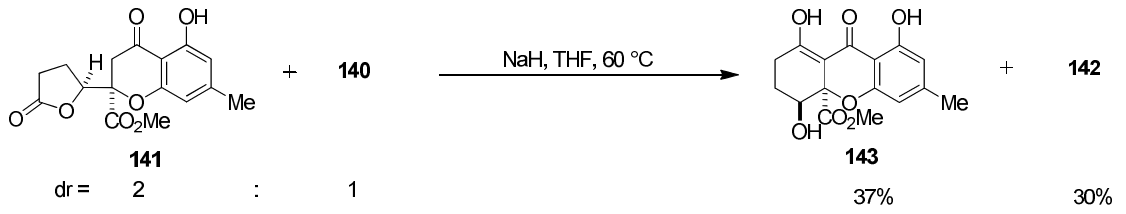
Scheme 21

Dieckman cyclisation of **140** using sodium hydride in refluxing THF gave the tetrahydroxanthone natural product *epi*-blenolide C **142** and blenolide C **143** in high diastereoselectivity and good yield (*Scheme 22*).



Scheme 22

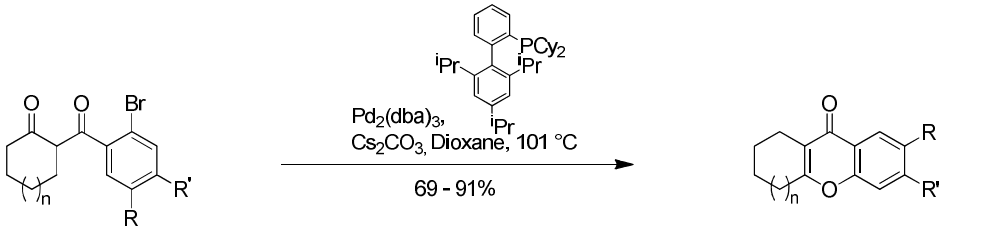
Similar transformations led to the formation of blenolide C **143** as the major product from a 1:2 mixture of lactones **140** and **141** (*Scheme 23*).



Scheme 23

The tetrahydroxanthones in the polycyclic natural products such as the actinoplanones, simaomicin *α*, kigamicins, kibdelones and isokibdelones are polyhydroxylated. This poses significant difficulties in relation to their synthesis due to facile aromatisation to the corresponding xanthones under strong acidic conditions. In our group, Penny Turner has recently developed a mild Pd(0) catalysed cyclisation method for the synthesis of tetrahydroxanthones in good yields.[89]

Diketones (**144-148**) were obtained via simple *C*-alkylation of the enolates derived from cyclic ketones with *ortho*-halo acid chlorides, then cyclised in the presence of $Pd_2(dba)_3$, Xphos and Cs_2CO_3 to produce tetrahydroxanthones (**149-153**) in excellent yields. The screening of a variety of phosphine ligands and solvent systems revealed Xphos and dioxane as the most effective system giving products in excellent yields (*Scheme 24*).

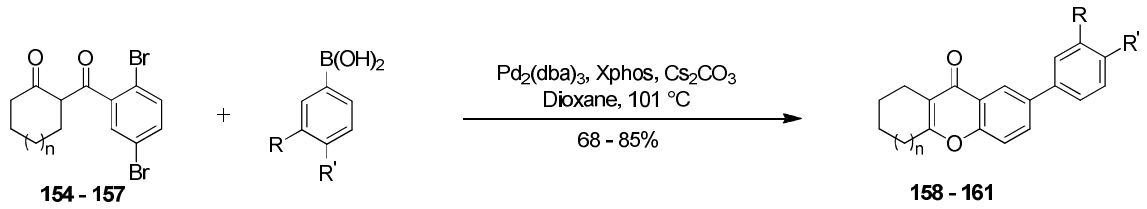


n = 1, R = Br, R' = H, **144**
n = 1, R = OMe, R' = H, **145**
n = 1, R = F, R' = F, **146**
n = 1, R = CF_3, R' = H, **147**
n = 2, R = H, R' = H,**148**

n = 1, R = Br, R' = H, **149**
n = 1, R = OMe, R' = H, **150**
n = 1, R = F, R' = F, **151**
n = 1, R = CF_3, R' = H, **152**
n = 2, R = H, R' = H, **153**

Scheme 24

When dibromides (**154-157**) were subjected to this Pd catalysed cyclisation in the presence of $ArB(OH)_2$, 7-aryl tetrahydroxanthones (**158-161**) were obtained by sequential C–O and C–C bond formation in very good yields (*Scheme 25*).



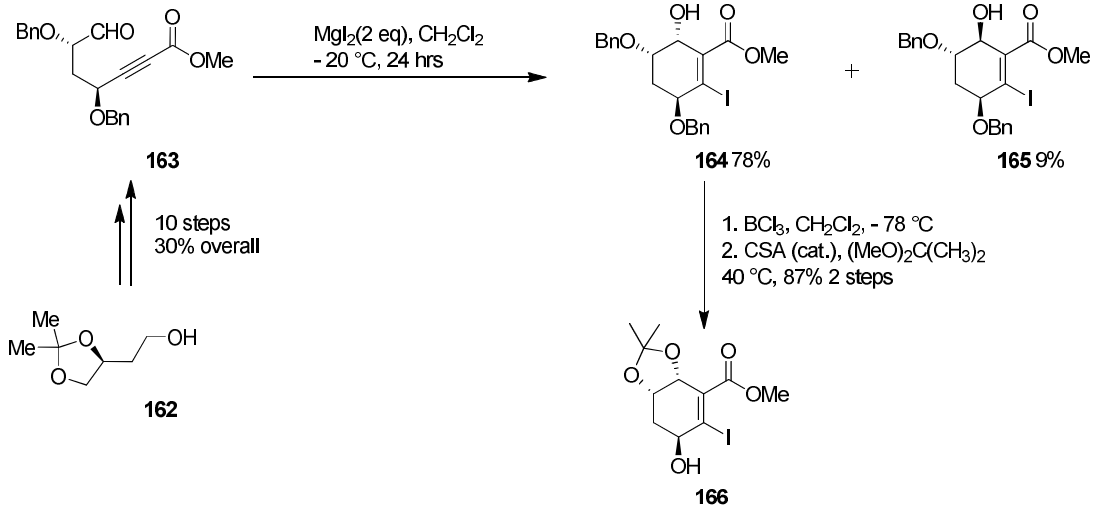
n = 1, R = H, R' = Me **154**
n = 1, R = CO_2Me, R' = H **155**
n = 2, R = H, R' = Me **156**
n = 2, R = CO_2Me, R' = H **157**

n = 1, R = H, R' = Me **158**
n = 1, R = CO_2Me, R' = H **159**
n = 2, R = H, R' = Me **160**
n = 2, R = CO_2Me, R' = H **161**

Scheme 25

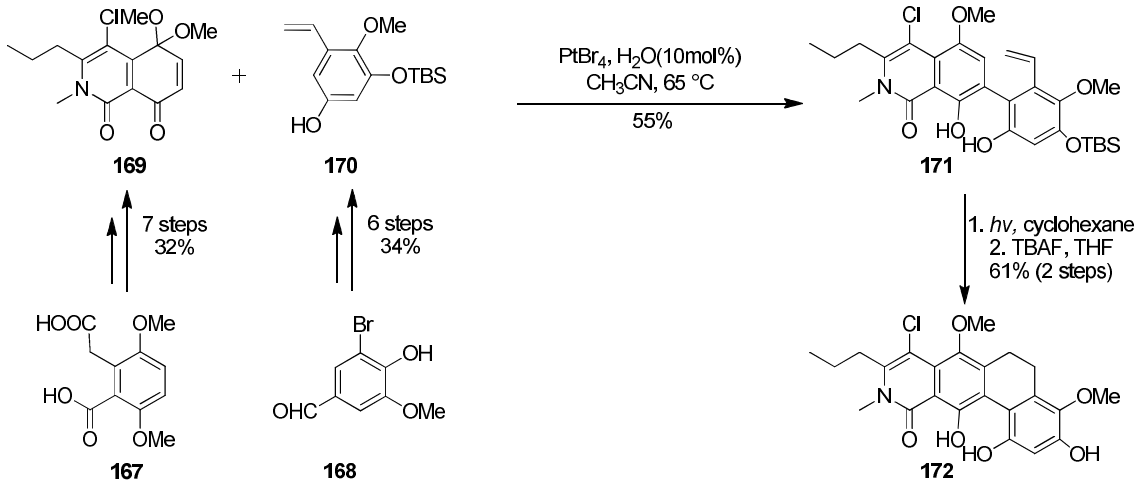
Synthetic efforts towards some polycyclic aromatic xanthones such as cervinomycins have been undertaken (*Figure 19*).[90] However, unsurprisingly there are few reports[91] on the synthesis of the most recently isolated hexacyclic tetrahydroxanthone natural products. In part this is due to the challenging saturated polyhydroxylated A-ring in these materials.

The first total synthesis of hexacyclic tetrahydroxanthone natural product kibdelone C **57** (*Figure 25*) was reported by Porco *et al* in 2011.[92] The synthesis of the chiral AB fragment was achieved by a diastereoselective, intramolecular halo-Michael aldol reaction of **163**, which was obtained in 30% yield over 10 steps starting from a commercially available enantiopure alcohol **162**. A further two step deprotection reprotection sequence provided **166** in very good yield (*Scheme 26*).



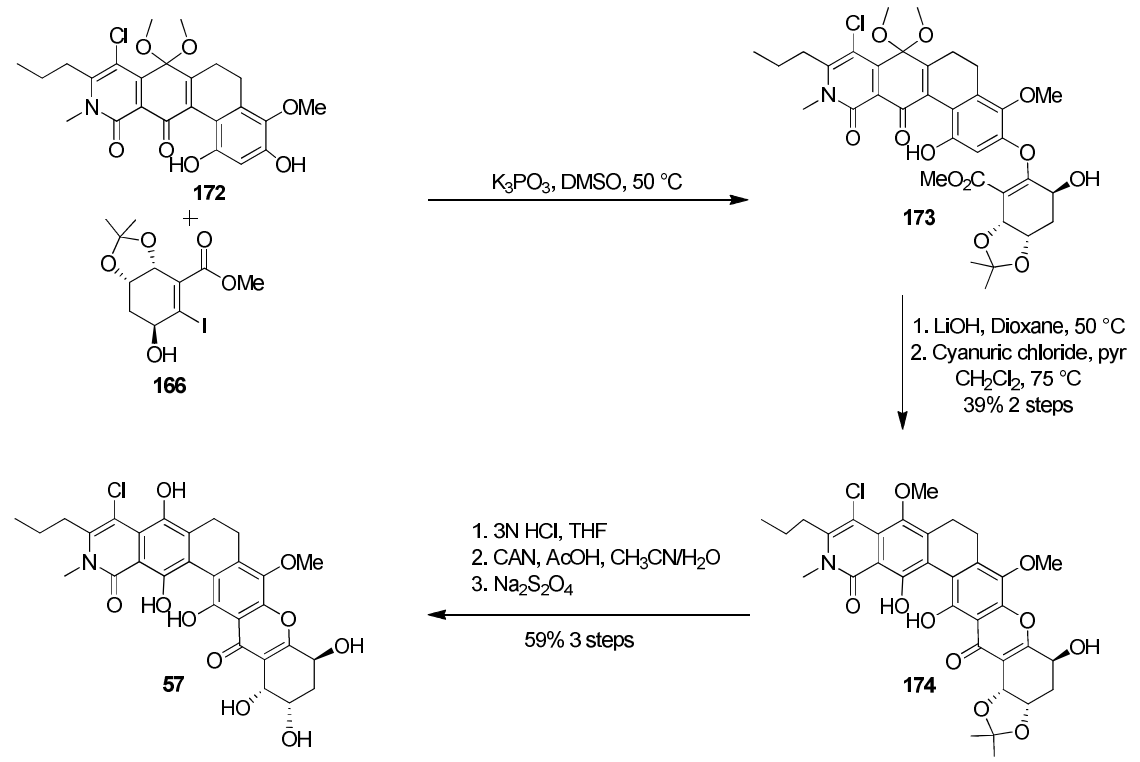
Scheme 26

Pt(IV) catalysed arylation of quinone monoketal **169** with hydroxystyrene **170** provided 2-vinylbiphenyl **171**, which on photoelectrocyclisation in cyclohexane yielded the CDEF dihydrophenanthrene fragment **172** (*Scheme 27*).[93]



Scheme 27

Regioselective *oxa*-Michael reaction of **166** and **172** afforded the sensitive vinylogous carbonate precursor **173**. Ester hydrolysis and a mild activation of derived carboxylic acid with cyanuric chloride provided the tetrahydroxanthone ring system **174**. Further two steps of selective deprotections furnished kibdelone C **57** (*Scheme 28*).

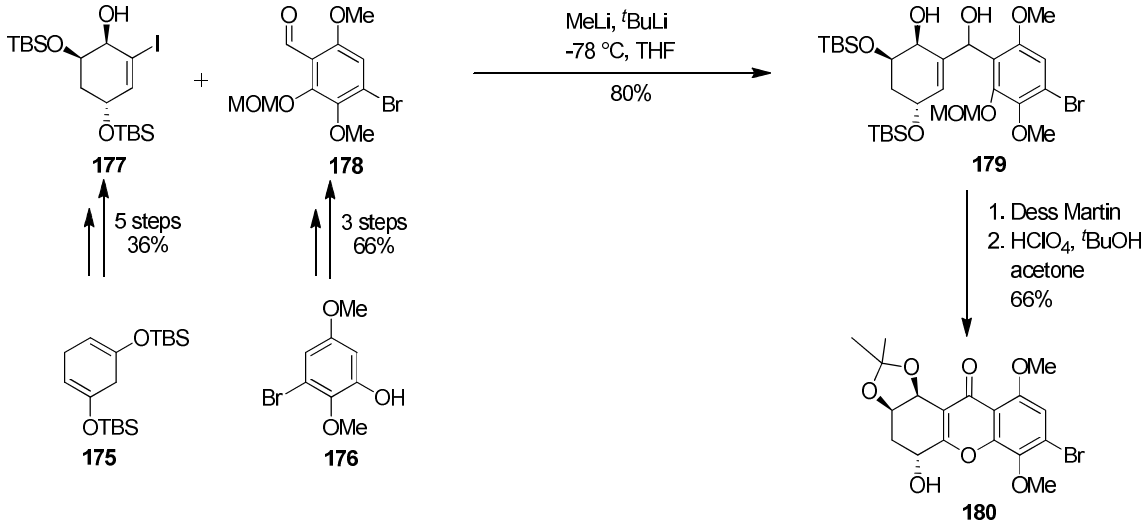


Scheme 28

In the same year, a second successful convergent enantioselective synthesis of (-) kibdelone C was reported by Joseph *et al* in the same issue of JACS.[94]

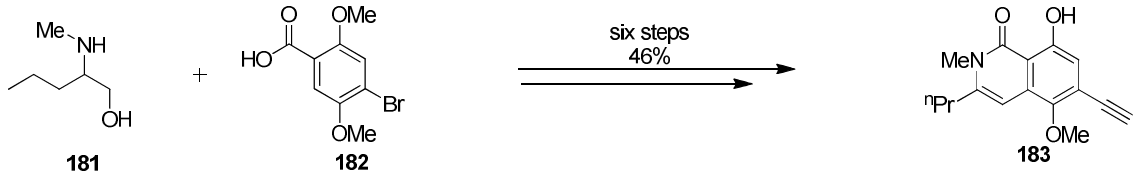
Joseph exploited the pseudo-C_2 symmetry within the saturated polyhydroxylated ring. Protected iodo-trihydroxy **177** was obtained as a single diastereomer and 95% enantioselectivity over five steps in 36 % yield. Aldehyde **178** was obtained in good

yield over three steps. Deprotonation and lithium iodine exchange of **177** with methyllithium and *tert*-butyllithium generated a reactive dianion which added to aldehyde **178** to give **179**. Dess Martin oxidation of **179** generated an enedione which on treatment with acidic acetone lost the methoxymethyl and silyl protecting groups and cyclised to tetrahydroxanthone **180** protected as an acetonide (*Scheme 29*).



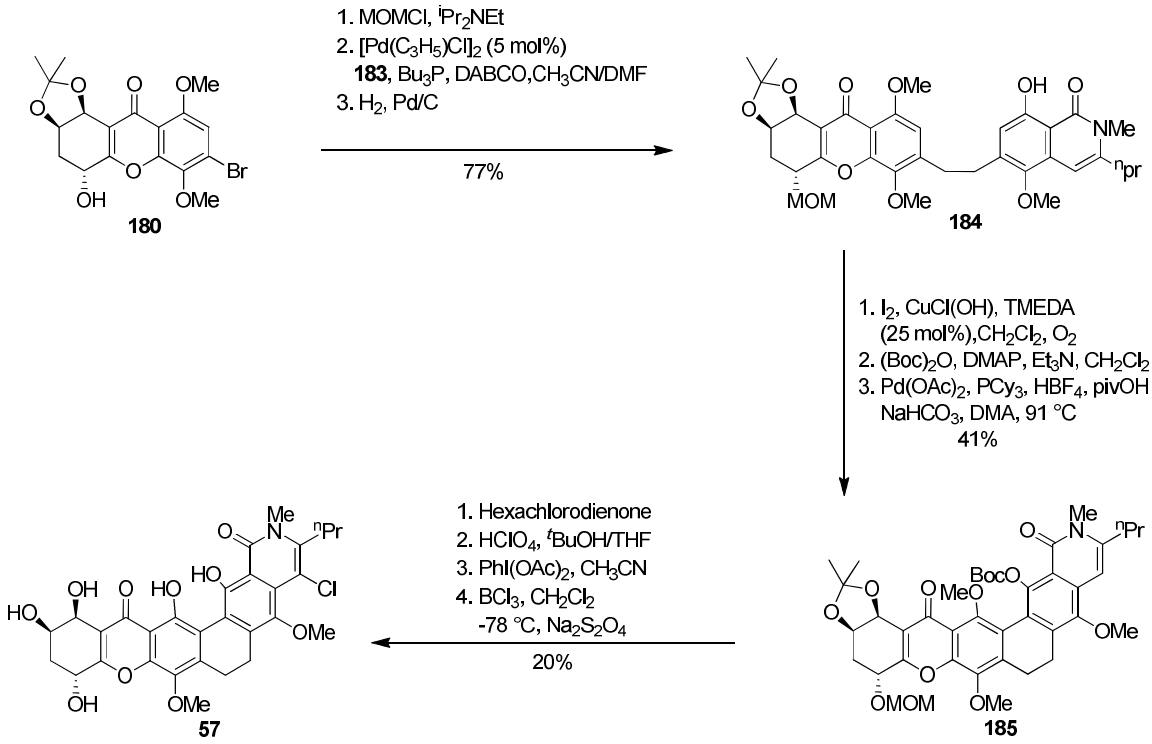
Scheme 29

Alkyne **183** was assembled in 46% yield over six steps starting from amino alcohol **181** (*Scheme 30*).



Scheme 30

Sonogashira coupling of alkyne **183** and the tetrahydroxanthone **180** led to a pentacyclic **184** containing all the carbons of kibdelones after palladium catalysed hydrogenation. Next, a Cu-catalysed iodination led to a substrate for C-H arylation *en route* to the C-ring of the kibdelones (*Scheme 31*)



Scheme 31

1.8 Comparative study of substitution pattern and stereochemistry of A-rings in the polycyclic natural products

One of the striking properties of all the polyketide assembled polycyclic xanthone natural products is the high degree of oxygenation of the A-ring (*Figure 31*). All the A-rings of the dihydro and tetrahydroxanthone containing polycyclic natural products are oxygenated at C-12 and C-15 while in kigamicins and actinoplanones additionally C-14 is oxygenated. The A-ring of kibdelones are oxygenated at C-13 instead of C-14. Simaomicins **43** and **44** are *trans* dihydroxylated at C-12 and C-15 while albofungin **42** is *cis* dihydroxylated at the same positions with the hydroxyl group at C-15 methylated (*Figure 29*).

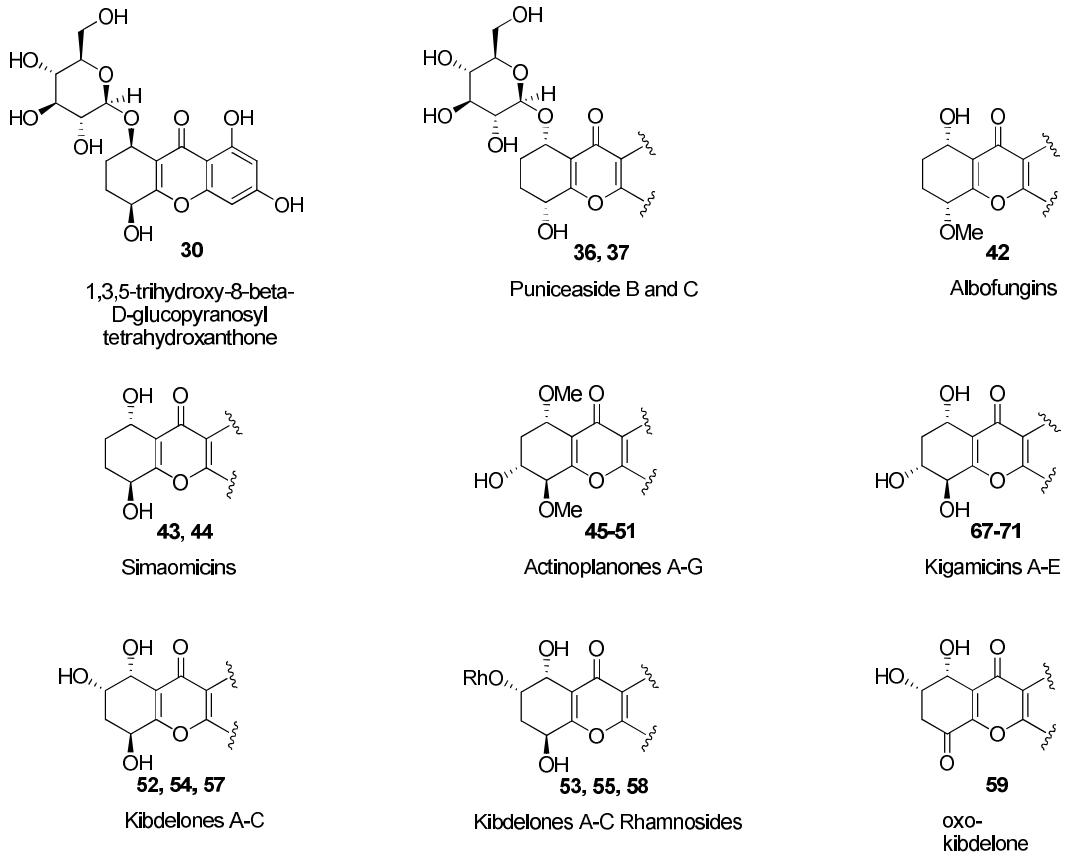


Figure 29. Stereochemistries of A-rings of polycyclic natural products

The tetrahydroxanthone glycoside **30** is the enantiomer of puniceaside B (**36**), and C (**37**) with respect to the stereochemistry of the hydroxyl groups in the A-ring. The spatial arrangement of hydroxyl groups in the A-ring of puniceasides B and C and albofungin **42**, is the same. The only difference being the methylation of the hydroxyl group at C-15 of albofungin **42** and glycosidation of hydroxyl groups of C-12 of puniceasides B and C respectively. The spatial arrangement of hydroxyl groups in the A-ring of actinoplanones and kigamicins are identical, and they differ only by the methylation of hydroxyl groups at C-12 and C-15 in actinoplanones and glycosidation of hydroxyl group at C-14 in kigamicins with D-amicetose (*Figure 31*). Clearly, it would be desirable to be able to devise general strategies for the assembly of these polyhydroxylated tetrahydroxanthones. From the work described in this chapter, it is clear that such general methods do not currently exist.

1.9 Conclusions

As we have seen, there are relatively few synthetic routes known for the synthesis of tetrahydroxanthones and even fewer suitable for the construction of those containing a polyhydroxylated A-ring. The research described in this thesis has focused on developing novel routes to such materials with the primary focus being on methods relevant for the construction of the kigamicin A-ring, but with broader applicability to other member of this important class of natural products.

Chapter 2:

Synthesis of Tetra- and Dihydroxanthones and their glycosides

2.1 Simple tetrahydroxanthone glycosides

The saturated A ring of kigamicin A (**67**) is highly functionalised and glycosidated. Through the synthesis of simple analogues such as **238** it was hoped to probe the importance of this ring system to the overall biological activity of these polycyclic natural products. Moreover, the synthesis of these simple tetrahydroxanthone analogues would help pave the way to the first total synthesis of the kigamicins themselves (*Figure 30*).

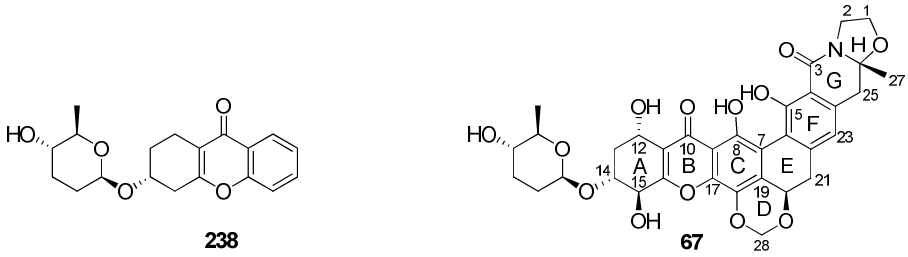
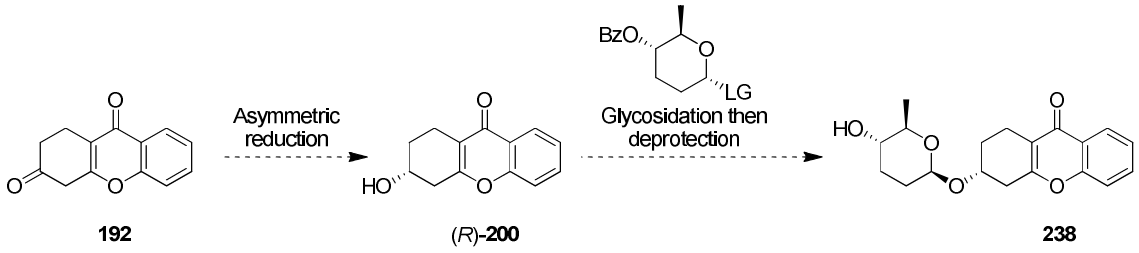


Figure 30

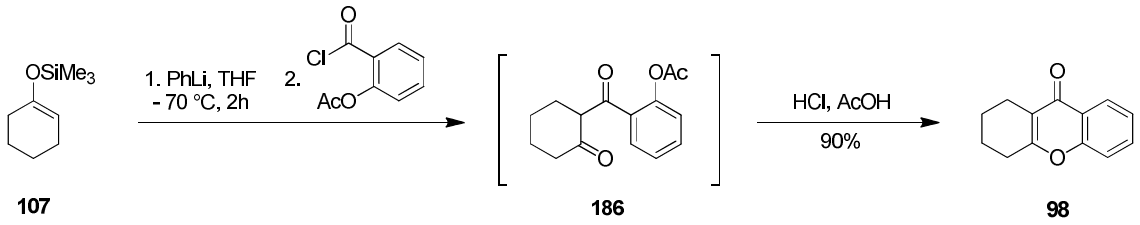
The synthesis of the simple tetrahydroxanthone glycoside was anticipated to be achieved by the chemoselective and enantioselective reduction of 3,9-diketo tetrahydroxanthone **192** followed by coupling with a sugar donor in a stereocontrolled fashion and final deprotection. Thus the first challenge was to develop a reliable and scaleable route to the 3,9-diketo tetrahydroxanthone **192** (*Scheme 32*).



Scheme 32

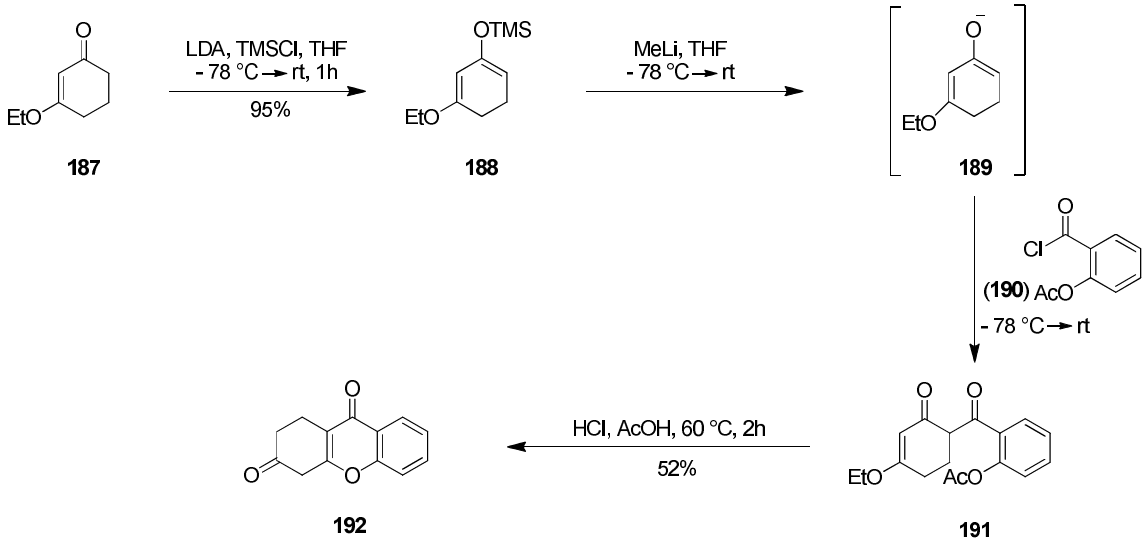
2.2 Synthesis of 3,9-diketotetrahydroxanthone 192

Toshio *et al* have successfully constructed simple tetrahydroxanthones by reacting lithium enolates of cyclohexanones generated from the trimethylsilylenol ethers, with acid chlorides to obtain *C*-alkylated intermediates which, without further purification, can be cyclised to the tetrahydroxanthones under acidic conditions (*Scheme 33*).[80]



Scheme 33

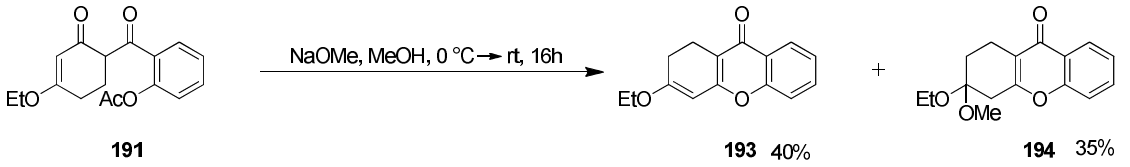
To explore the use of this approach to 3,9-diketoxanthone **192**, the trimethylsilylenol ether **188** was made from 3-ethoxy-2-cyclohexenone (**187**) by reaction with trimethylsilyl chloride and LDA in excellent yield.[95] On further treatment with methyllithium, the lithium enolate was regenerated which was reacted with 2-(chlorocarbonyl) phenyl acetate (**190**) to give diketone **191**. This intermediate without further purification, was cyclised to xanthone **192** in 22% yield by treatment with hydrochloric acid in acetic acid. Reasoning that the product **191** might quench enolate **189**, the reaction was repeated using a two-fold excess of the trimethylsilylenol ether in the acylation reaction. This resulted in a significant improvement in the yield from 22% to 52% (*Scheme 34*).



Scheme 34

To see if the reaction could be further improved, the cyclisation of **191** was also examined under basic conditions. Cyclisation of intermediates such as **191** under basic conditions are not reported in the literature. The intermediate **191** on treatment with sodium methoxide resulted in the formation of enol ether **193** alongside acetal **194** in good overall yield. Evidence for the structure of **194** was provided by ^{1}H NMR spectroscopy which revealed the appearance of OCH_3 peak and the disappearance of the alkene hydrogen. A characteristic quaternary acetal carbon at 99.1 ppm, suggesting the

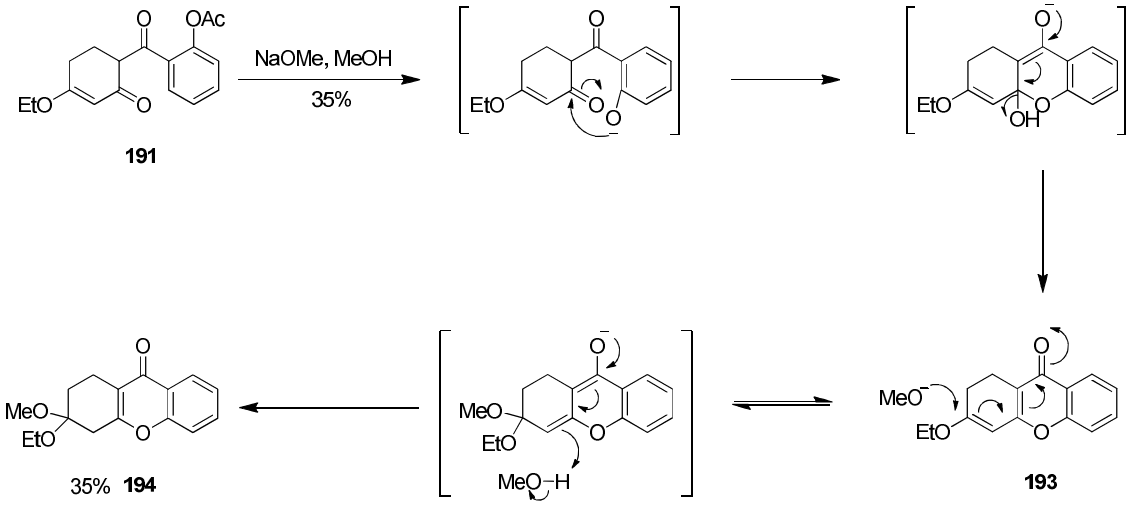
addition of MeOH across the alkene double bond, was seen in the ^{13}C NMR spectrum (*Scheme 35*).



191 **193** 40% **194** 35%

Scheme 35

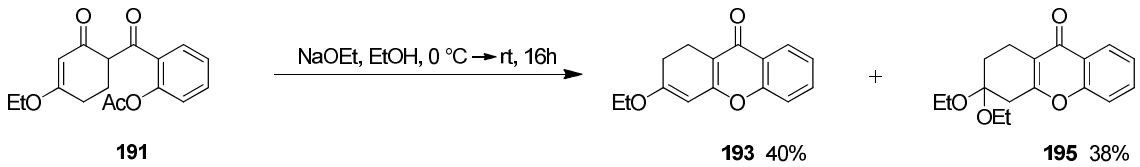
The formation of **193** and **194** presumably involves the formation of phenoxide ion which undergoes nucleophilic attack onto the ketone. Subsequent elimination of water yields **193** which on further conjugate addition of methoxide ion and quenching of the resulting enolate from the solvent results in the formation of **194** (*Scheme 36*).



191 35% **194** **193**

Scheme 36

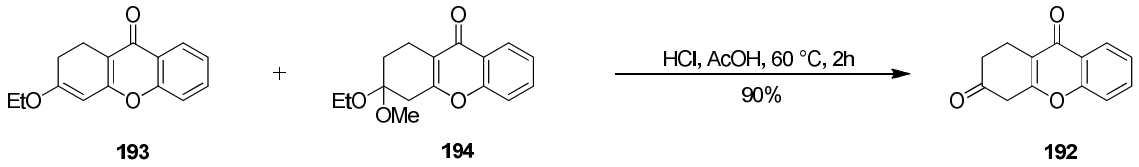
Additional evidence for this reaction course was obtained when the same process was carried out in ethanol. Under these conditions, diethyl acetal **195** was produced by the addition of EtOH across the double bond of alkene **193** (*Scheme 37*).



191 **193** 40% **195** 38%

Scheme 37

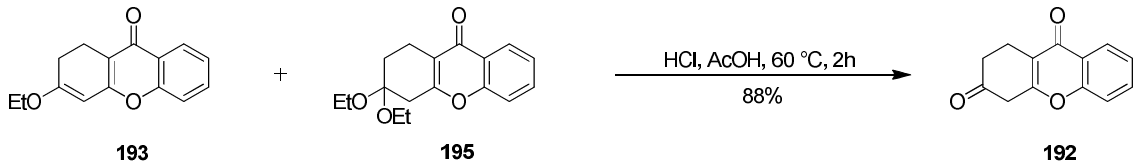
A mixture of alkene **193** and acetal **194** was smoothly hydrolysed to the 3,9-diketoxanthone **192** on heating in HCl and AcOH in excellent yield (*Scheme 38*).



193 194 192

Scheme 38

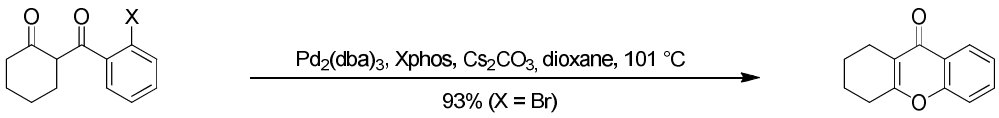
Separately, a mixture of alkene **193** and acetal **195** was hydrolysed to the 3,9-diketoxanthone **192** in 88% yield under the same conditions (*Scheme 39*). Using this base induced ring closure method, the overall yield of **192** could be improved from 52% to 70% overall.



193 195 192

Scheme 39

Within the Shipman group, Penny Turner has recently developed a mild Pd(0) catalysed method for the construction of tetrahydroxanthones via selective C–O bond formation from halo diketones.[89] These compounds are readily accessed by simple C-alkylation of *ortho*-halo acid chlorides by enolates derived from cyclic ketones. The key advantage of this method is that ring closure is achieved under very mild conditions (*Scheme 40*).



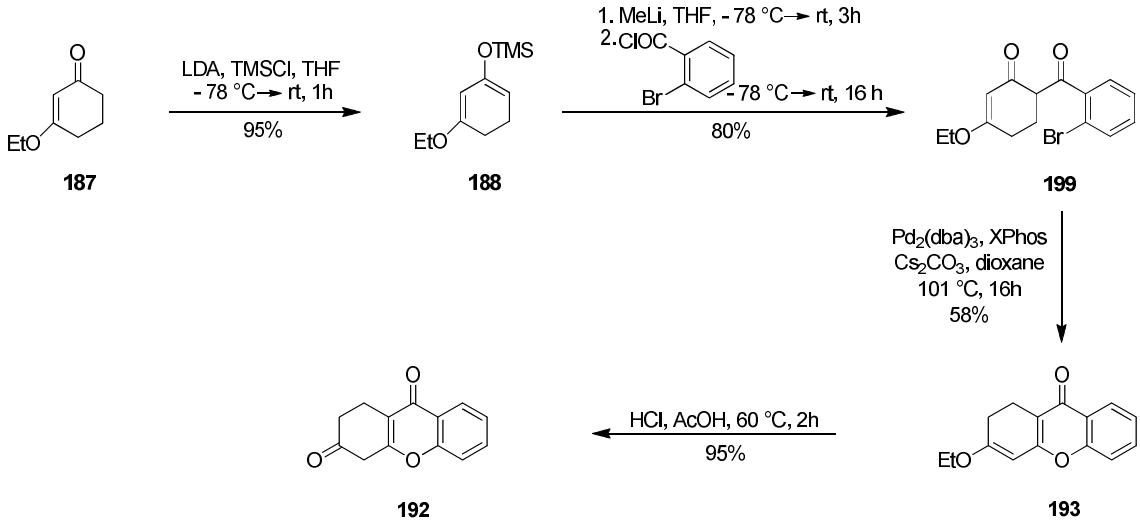
196 - 198

X = Cl **196**
X = Br **197**
X = I **198**

98

Scheme 40

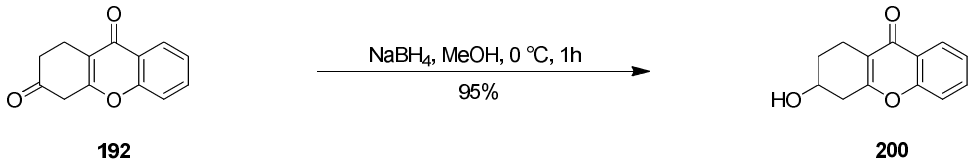
Encouraged by these results, it was decided to examine its use for the synthesis of diketo xanthone **192**. Treatment of trimethylsilylenol ether **188** with methyllithium then *O*-bromobenzoyl chloride produced *C*-alkylated ketone **199** in good yield. This intermediate was cyclised to alkene **193** containing a masked ketone using palladium catalysis in 58% yield. No efforts were made to further optimise the reaction conditions for this cyclisation. This new example of the metal mediated cyclisation nicely illustrates the fact that acid sensitive functional groups are well tolerated. Further acidic hydrolysis of **193** generated dicarbonyl **192** in excellent yield (*Scheme 41*).



Scheme 41

2.3 Chemo- and enantioselective reduction of 3,9-diketoxanthone 192

Having access to the multi-gram quantities of diketoxanthone **192** via acidic, basic and metal catalysed cyclisations, next it was set about establishing if chemoselective reductions of the ketone group could be achieved. Simple chemoselective reduction of **192** to alcohol **200** was realised by treatment with sodium borohydride in excellent yield (*Scheme 42*). The structure of alcohol **200** was unambiguously confirmed by single crystal X-ray diffraction on crystals grown from ethanol (*Figure 31*).



Scheme 42

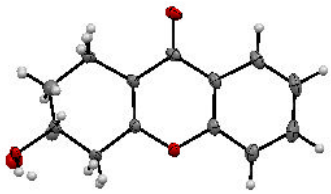
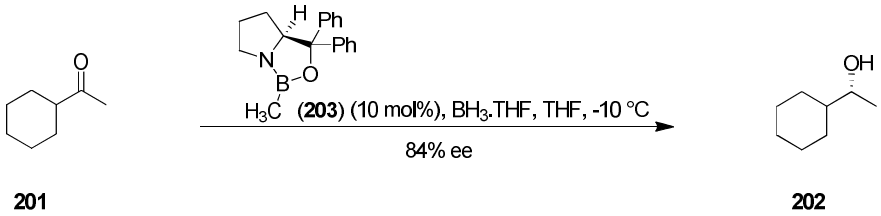


Figure 31 Single crystal X-ray diffraction structure of alcohol **200**

Having easily achieved the chemoselective reduction of **192** in excellent yield, next enantioselective reduction to this alcohol was examined.

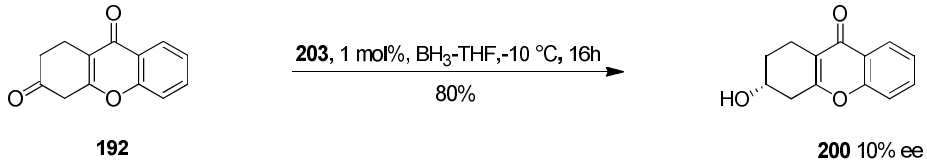
High asymmetric induction is achieved in the reduction of carbonyl compounds when the *Si* and *Re* faces of the carbonyl group offer different steric and/or electronic

environments. Typically this necessitates the use of ketones bearing rather different substituent patterns at the α-carbons. For example alkyl aryl ketones often undergo enantioselective reductions in high ee's.[96] A survey of the literature suggested that the stereocontrolled reduction of ketones having unsubstituted alpha methylene groups can be best achieved using either the Corey-Bukshi-Shibata (CBS) reduction or catalytic asymmetric transfer hydrogenation.[97, 98] The CBS stereoselective catalytic reduction of prochiral ketones to provide chiral alcohols has been extensively studied and excellent enantioselectivities have been achieved. Catalyst (*S*)-3,3-diphenyl-1-methylpyrrolidino[1,2-c]-1,2,3-oxazaborole (**203**) has been used to achieve over 80% enantioselectivities in the stereocontrolled reduction of challenging dialkyl ketones (*Scheme 43*).[99]



Scheme 43

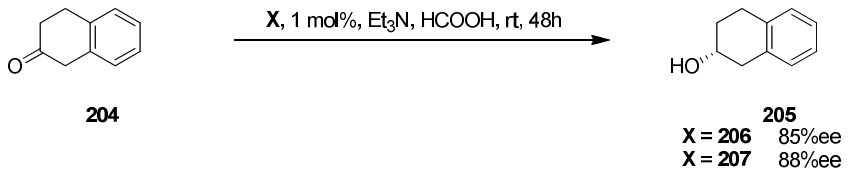
Therefore, **203** was used to explore the reduction of **192**. In this regard it was anticipated that the reduction of **192** might be very challenging as both the α- carbons are simple methylene groups. Indeed, the stereoselective reduction of xanthone **192** with catalytic (*S*)-**203** in 1M BH_3·THF solution at ambient temperature provided the chiral alcohol **200** in good yield but very poor enantioselectivity. The enantioselectivity of this and subsequent reduction was analysed by chiral HPLC using an ODH column (*Scheme 44*).



Scheme 44

The major enantiomer in this reaction was determined by HPLC retention times in conjuction with further derivatisation experiments (*vide infra*). Since the asymmetric reduction of **192** was very poor in the CBS catalysed enantioselective reduction, further attempts with similar catalysts were not explored. Within the department, the Wills group has extensive expertise in asymmetric transfer hydrogenation, and so it was

encouraging to explore the use of Noyori's catalyst **206** and Wills' catalyst **207** for asymmetric transfer hydrogenation of **192**. There is precedent for *β*- tetralone substrates such as **204** being reduced in high enantioselectivity (*Scheme 45*). [100]



204

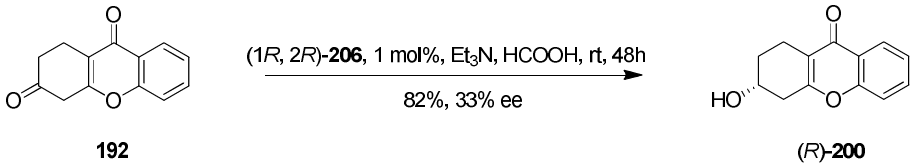
205
X = 206 85%ee
X = 207 88%ee

Scheme 45

(1*R*, 2*R*)-206 **(1*R*, 2*R*)-207**

Figure 32

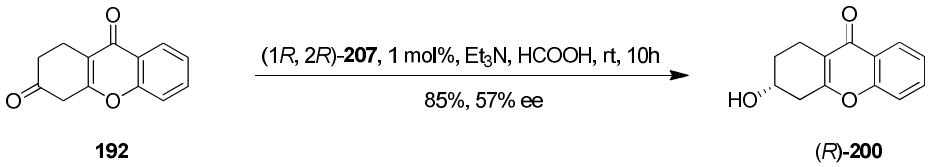
Encouraged by this precedent, the asymmetric transfer hydrogenation of dicarbonyl **192** was carried out using Noyori's catalyst (1*R*, 2*R*)-**206**, triethylamine and formic acid at ambient temperature over 2 days. This catalyst system provided alcohol **200** in very good yield, and 33% ee (*Scheme 46*).[101]



192 **(*R*)-200**

Scheme 46

Better enantiocontrol was achieved using the tethered ruthenium catalyst (1*R*, 2*R*)-**207** developed by Wills. Using this catalyst system, **200** was formed in 57% ee and 88% yield. Interestingly, this tethered ruthenium catalyst **207** not only improved the enantioselectivity, but also the rate of reduction was much faster as judged by the time for complete conversion into product (*Scheme 47*).

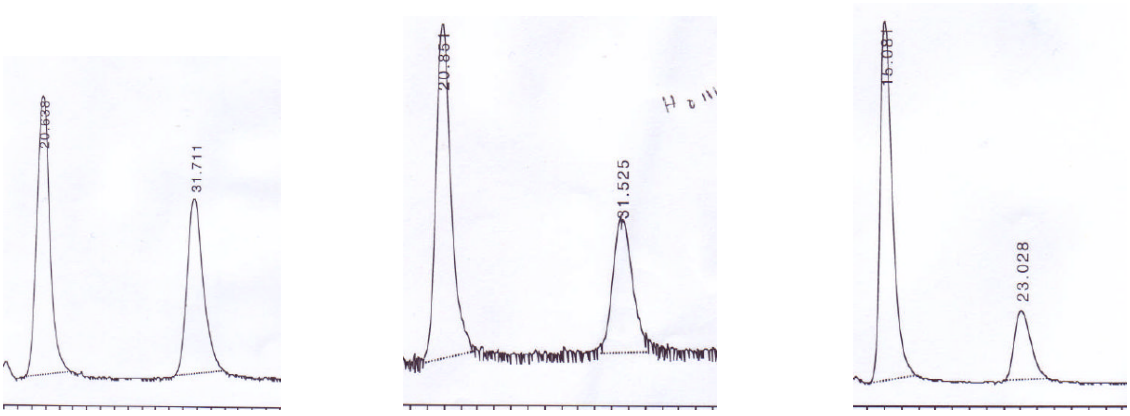


192 **(*R*)-200**

Scheme 47

Further efforts to enhance the ee of this reduction were not attempted at this juncture. It was reasoned that the ee of (*R*)-**200** could be further enriched through coupling to an enantiopure sugar donor and separation of the resulting diastereomers.

(i) (ii) (iii)



10% ee with **203** 33% ee with (1*R*, 2*R*)- **206** 57% ee with (1*R*, 2*R*)-**207**

Figure 33. HPLC traces of enantiomerically enriched **200** using ODH column (10% isopropanol in hexane) : (i) CBS reduction using (*S*)-3,3-diphenyl-1-methylpyrrolidino[1,2-c]-1,3,2-oxazaborole (**203**). (ii) Asymmetric transfer hydrogenation with *N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-amino]-4-methylbenzenesulfonamide (p-cymene) ruthenium chloride (**206**). (iii) Asymmetric transfer hydrogenation with *N*-[(1*R*,2*R*)-1,2-diphenyl2-3-(3-phenylpropylamino)-ethyl]-4-methylbenzenesulfonamide chloro ruthenium (**207**)

The absolute configuration of the major alcohol produced in these reductions is the same in all cases. By subsequent derivatisation, it was deduced that the (*R*)- enantiomer has formed as the major isomer. This sense of asymmetric induction is consistent with that seen in the reduction of *β*-tetralone. This can be understood if one imagines overlaying the benzene ring of *β*-tetralone over the central ring of the xanthone (*Figure 34*).[102]

(*R*)-**205** (*R*)-**200**

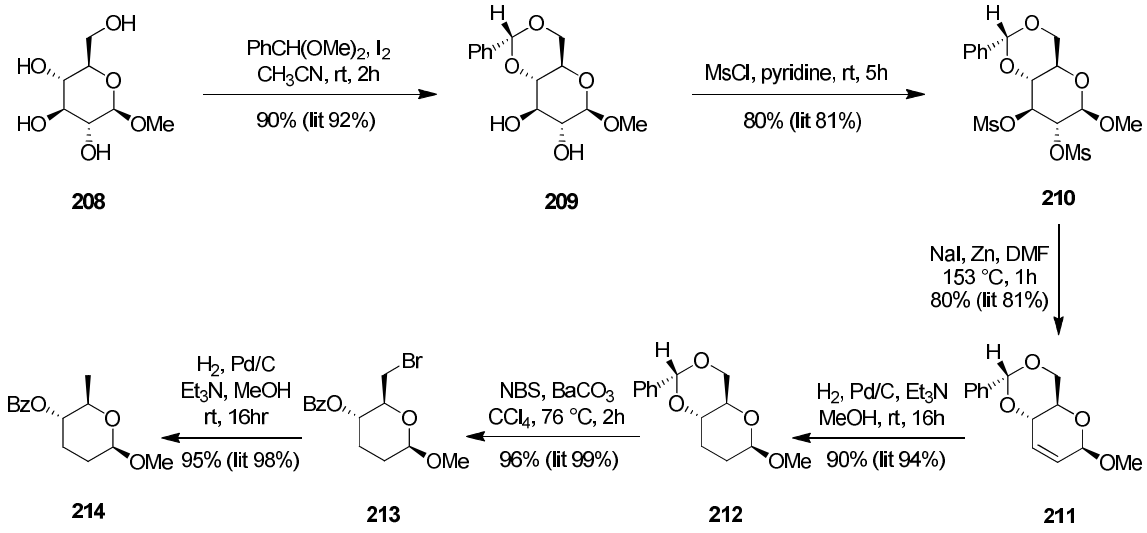
Figure 34

2.4 Synthesis of D-Amicetose 214

With alcohol **200** in enantiomerically enriched form, the next goal was to synthesise a suitable sugar donor to complete the synthesis of glycoside **238**. D-Amicetose derivative **214** has been made previously from the alkene **211** in 3 steps in 91% yield by Spohr *et al*.[103]

It was reasoned that **214** could be transformed into a variety of activated donors by subsequent hydrolysis of the anomeric ether followed by activation. Rather than devise new chemistry to **214** which might have been more direct, it was elected to repeat the published synthesis of this material as felt it would be more expedient.

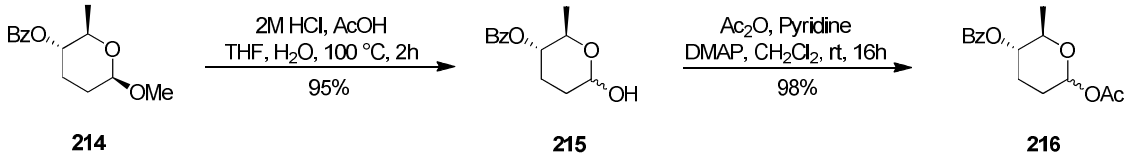
Commercially available *β*-methoxy D-glucose **208** was treated with dimethoxy benzylidene acetal in the presence of catalytic iodine to give benzylidene acetal **209** in excellent yield using the modified method developed by Rajib *et al*.[104] To deoxygenate **209**, it was converted to dimesylate **210**, using methanesulfonyl chloride and pyridine.[105] This dimesylate was treated with the Tipson-Cohen reagent to give alkene **211** in good yield,[106] which was hydrogenated in the presence of 5% palladium on carbon and triethylamine to give crystalline **212** in excellent yield. Oxidative cleavage of the benzylidene ring with NBS provided 6-bromo deoxysugar **213** in excellent yield. Further catalytic reduction of carbon-halogen bond of **213** with palladium on carbon in the presence of triethylamine gave *β*-methoxyamicetose **214** in 95% yield (*Scheme 48*).[103]



Scheme 48

β-Methoxyamicetose **214** was hydrolysed in excellent yield to a mixture of *α*- and *β*-hydroxyamicetose **215** in 1.4 : 1 ratio respectively, using a 1 : 2 : 3 mixture of hot 2M

HCl, AcOH and H_2O. The α- and β-hydroxyamicetose **215** were established on the basis of the chemical shift of the anomeric hydrogens. Fortunately the hydroxyl hydrogens of α- and β-hydroxyamicetose **215** were also visible in ^{1}H NMR spectrum at 2.91 ppm as a singlet and 3.45 ppm as a doublet with 5.9 Hz of coupling constant respectively. The mixture of α- and β- hydroxyamicetose **215** was further acetylated in excellent yield on treatment with acetic anhydride and pyridine in the presence of catalytic DMAP to obtain α- and β- acetoxyamicetose **216** in 1.4 : 1 ratio respectively (*Scheme 49*).[107]

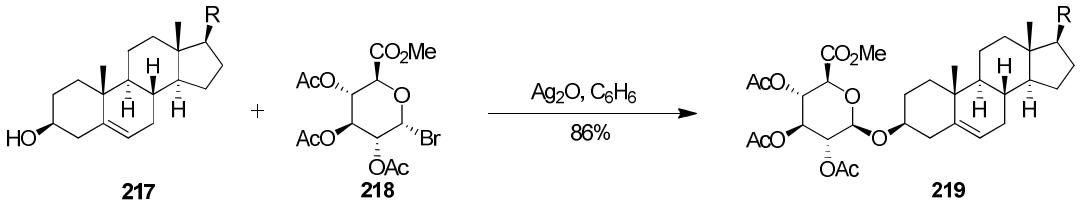


214 **215** **216**

Scheme 49

2.4.1 Synthesis of α-halogenated sugar donors

Most β-glycosidic bonds are constructed by S_N2 type reactions of α-sugar donors with the alcohol acceptor. Levels of stereocontrol also depend on the nature of the alcohol and the substitution pattern at the adjacent carbon (C-2). For example, the glycosidation of cholesterol **217** with α-bromo sugar **218** proceeds to give exclusively the β-glycosidic bond as reported by Schneider *et al* (*Scheme 50*).[108]



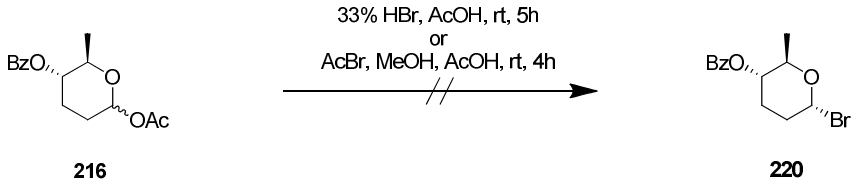
217 **218** **219**

R =CH_3 (CH)$(CH_2)_3$CH$(CH_3)_2$

Scheme 50

With this knowledge in hand, attempts were made to produce sugar donors with exclusively the α-configuration. To the best of our knowledge, no examples of exclusively α-halo sugar donors derived from 2,3,6-trideoxy sugars such as amicetose **216** have been reported. The synthesis of α-bromo anomer **220** from amicetose **216** was attempted by treating it with 33% HBr in AcOH. However the substrate was unstable to the strongly acidic conditions and this approach led only to degradation.

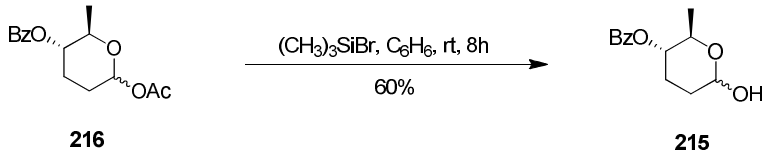
Generating HBr *in situ* by treating acetyl bromide with methanol in acetic acid, followed by the addition of **216** also gave a complex mixture of products (*Scheme 51*).[109]



216 **220**

Scheme 51

The synthesis of *α*-bromo sugar was also attempted under milder conditions by treating **216** with trimethylsilyl bromide in benzene at room temperature. The development of two closely running new spots was observed on thin layer chromatography. However, during the attempted isolation of **220** only *α*- and *β*-hydroxy amicetose **215** in 1.2 : 1 ratio respectively was recovered presumably as a result of hydrolysis of **220** (*Scheme 52*).[110]

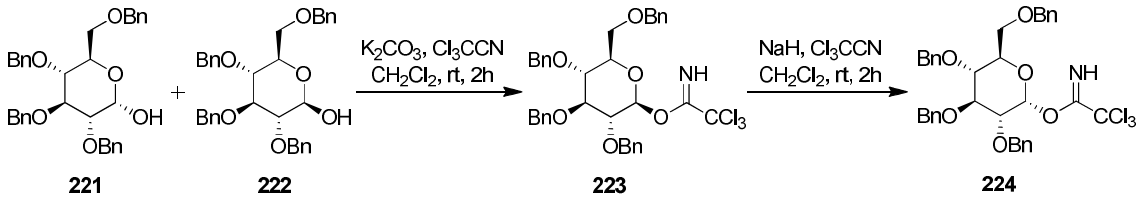


216 **215**

Scheme 52

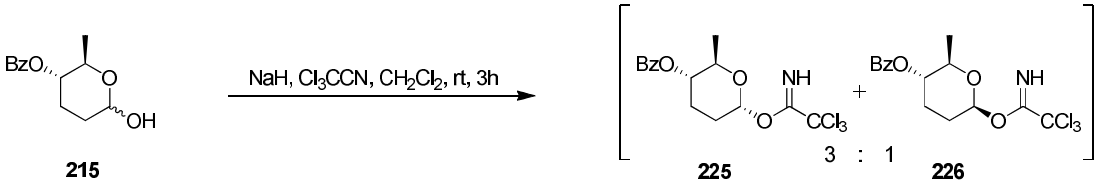
2.4.2 Synthesis of *α*-trichloroacetimidate donors

Since neither the *α*- or *β*-bromo derivatives of **220** could be produced, it was attempted to convert the anomeric hydroxyl group of **215** into trichloroacetimidate. When activated in the presence of Lewis acids, these are known to be excellent partners in the glycosidation reactions.[111] In a reversible activation step and with the help of kinetic and thermodynamic reaction control both the *α*- and *β*-anomers could potentially be accessed using this chemistry. The *β*-trichloroacetimidate **223** is generated from a mixture of *α*- **221** and *β*- **222** tetra-*O*-benzyl-D-glucose preferentially in a very rapid and reversible addition reaction using potassium carbonate in dichloromethane at room temperature (*Scheme 53*). However, this product can be anomerised in the presence of strong base such as sodium hydride through a retroreaction to form the thermodynamically more stable *α*-trichloroacetimidate sugar donor **224** exclusively (*Scheme 53*). [112]



Scheme 53

However, the synthesis of trichloroacetimidate derivatives of amicetose donors has not yet been reported. Treatment of the α- and β- mixture of amicetose **215** in 1.2 : 1 ratio respectively with excess trichloroacetonitile and catalytic sodium hydride (10mol%) produced both α-**225** and β-**226** trichloroacetimidates within 30 minutes as evidenced by thin layer chromatography. To shift the equilibrium to the thermodynamically more stable α-anomer, namely **225**, an excess of sodium hydride was added (*Scheme 54*). [113]

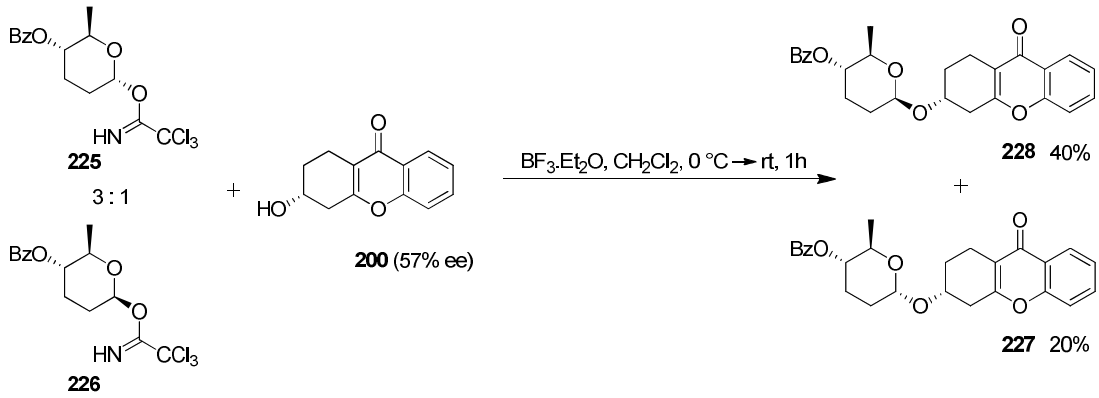


Scheme 54

Crude ^{1}H NMR analysis showed the presence of both the α-**225** and β-**226** trichloroacetimidate glycosyl donors in 3 : 1 ratio. This ratio of glycosyl donors remained unchanged when the reaction mixture was left for longer times, and varying amounts of sodium hydride were used. The major α-anomer was assigned on the basis of ^{1}H NMR chemical shifts and coupling constants of anomeric hydrogens. This mixture of trichloroacetimidates was used in further glycosidation reactions as they were unstable to storage or column chromatography on silica gel.

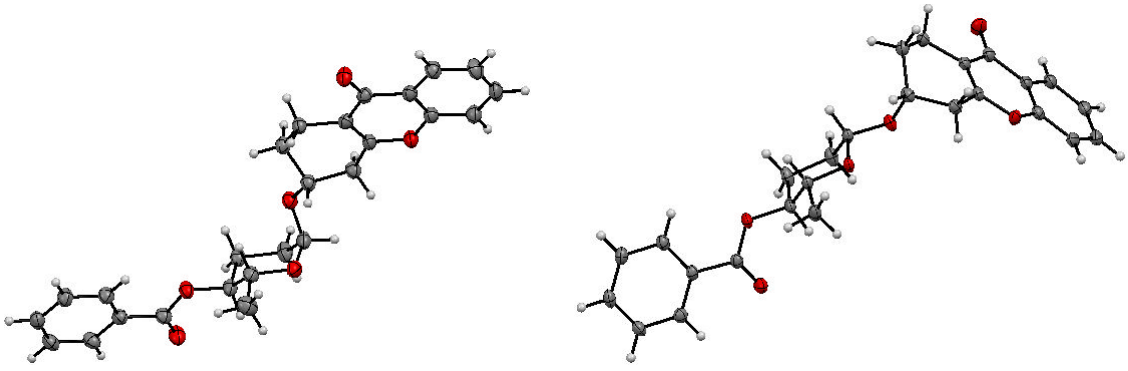
2.5 Glycosidations of alcohol 200

With both enantiomerically enriched alcohol **200** and a suitable activated sugar donor namely **225/226** in hand, I was in a position to construct amicetose substituted tetrahydroxanthones. Trichloroacetimidates **225**/**226** (3:1) were reacted with one equivalent of alcohol **200** (57% ee) in the presence of $BF_3.OEt_2$ in dichloromethane.[114] This reaction resulted in the formation of α-**130** and β-**131** anomeric glycosides in a combined 60% yield (*Scheme 62*). No products derived from the minor enantiomer of **200** were observed (*Scheme 55*).



Scheme 55

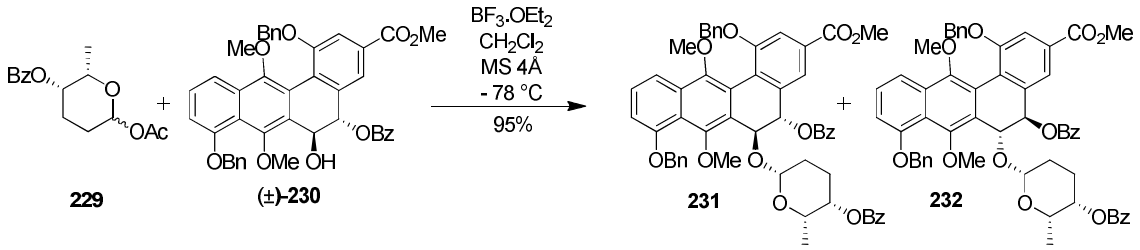
The stereochemistry at the anomeric positions of both the *α*-**227** and the *β*-**228** diastereomers was revealed by ^{1}H and ^{13}C NMR spectroscopy. The anomeric hydrogen of *α*-**227** is a multiplet at 5.05 ppm and the peak for anomeric carbon was at 95.0 ppm. Similarly, the anomeric hydrogen of *β*-**228** is a doublet of doublets at 4.76 ppm, with coupling constants of 1.8 and 9.4 Hz, while the peak for the anomeric carbon was at 99.6 ppm. Since the equatorial hydrogen in *α*-**227** is closer to the ring oxygen which causes deshielding of it, the assignments at this centre can be tentatively made based upon the ^{1}H chemical shifts. The stereochemistry at C-14 was unambiguously established by growing crystals of both the *α*-**227** and *β*-**228** diastereomers. Single crystal X-ray diffraction revealed that both the diastereomers possessed (*R*)-configuration at C-14 and are epimeric at the anomeric position (*Figure 35*). Since the combined yield is 60% and the enantiomeric ratio **200** is 78.5 : 21.5 this must mean that there is preferential reaction of the sugar donors with the major enantiomer of alcohol **200**. These observations also enabled us to conclude that the absolute configuration of the major enantiomer of alcohol **200** is (*R*).



α-**227** *β*-**228**

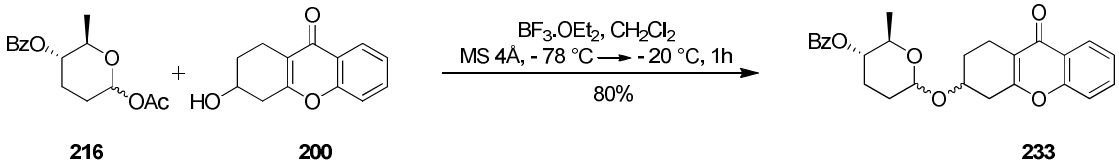
Figure 35 Single crystal X-ray structures of **227** and **228**.

Ohmori *et al* have successfully achieved exclusively α-anomers while coupling a mixture of α-and β-rhodinosyl acetate **229** (the diastereomer of amicetosyl acetate), with (±)-**230** at lower temperatures in the presence of $BF_3.OEt_2$ (*Scheme 56*).[107]



Scheme 56

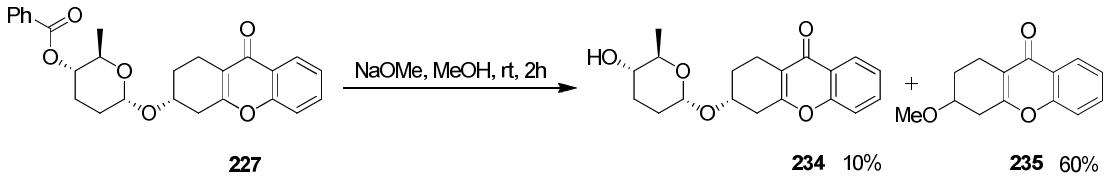
To exclusively obtain the anomer **227** and attempt the separation of the enantiomers of (±)-**200**, the acetoxy amicetose **216** was directly coupled with (±)-**200** following Ohmori's procedure. However, this gave a mixture of four inseparable diastereomers resulting from the coupling of both enantiomers of **200** and α- and the β- anomers of amicetosyl acetate **216** in good yield (*Scheme 57*).



Scheme 57

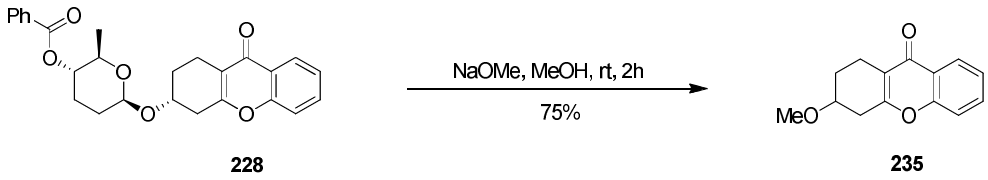
2.6 Deprotection

To complete the synthesis of the tetrahydroxanthone analogue, removal of the ester group was required. Deprotection of benzoyl group of α-**227** was conducted in methanolic sodium methoxide yielding **234** in 10% yield with the formation of methoxy tetrahydroxanthone **235** as a major product. The use of both catalytic and stoichiometric amounts of sodium methoxide did not have any appreciable effect on the product ratio (*Scheme 58*).



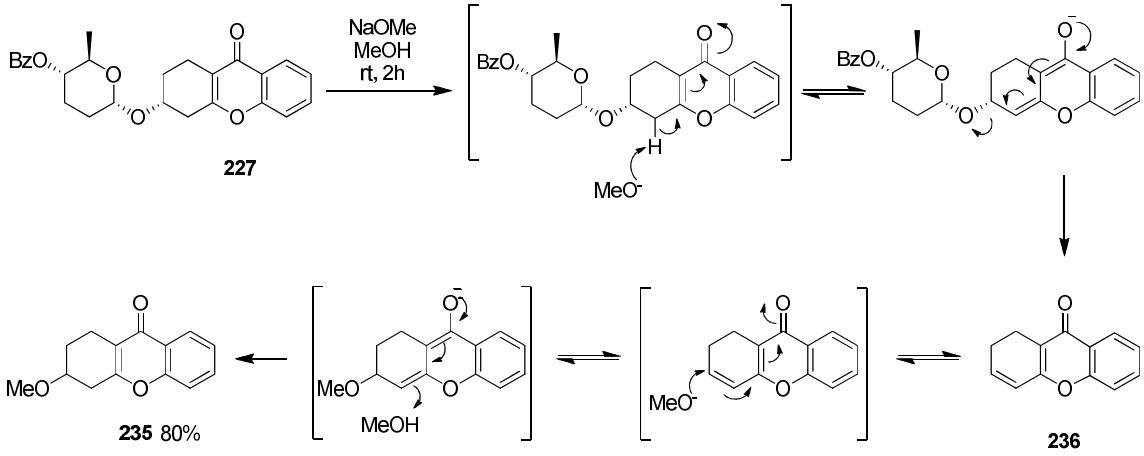
Scheme 58

The deprotection of benzoyl group of *β*-**228** was also conducted with methanolic sodium methoxide. In this case only methoxytetrahydroxanthone **235** was obtained (*Scheme 59*).



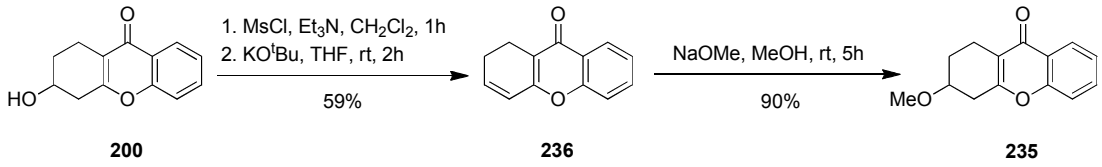
Scheme 59

Glycoside **227** has relatively acidic hydrogens at C-15 and could lead to the production of alkene **236** *via* an $E1_{CB}$-type mechanism (*Scheme 60*). Dihydroxanthone **236** presumably undergoes conjugate addition of methoxide to give methoxytetrahydroxanthone **235** in a manner analogous to that seen previously in the conversion of **193** into **194** (*Scheme 35*).



Scheme 60

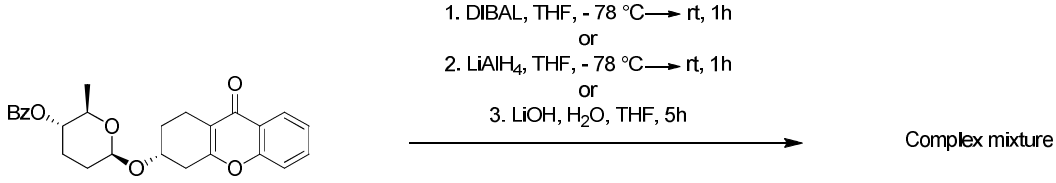
The formation of **235** was further investigated through the synthesis of the dihydroxanthone **236** from alcohol **200**. Activation of alcohol **200** as a mesylate was achieved by treating it with methanesulfonyl chloride in the presence of triethylamine.[115] Further treatment of this mesylate with KO^{t}Bu induced elimination to dihydroxanthone **236** in moderate yield over the two steps. Treatment of dihydroxanthone **236** with methanolic sodium methoxide resulted in the conjugate addition of MeOH to give methoxytetrahydroxanthone **235** (*Scheme 60*). This sequence adds credibility to the idea that **236** is an intermediate in the conversion of **227** and **228** into **235** (*Scheme 61*).



200 236 235

Scheme 61

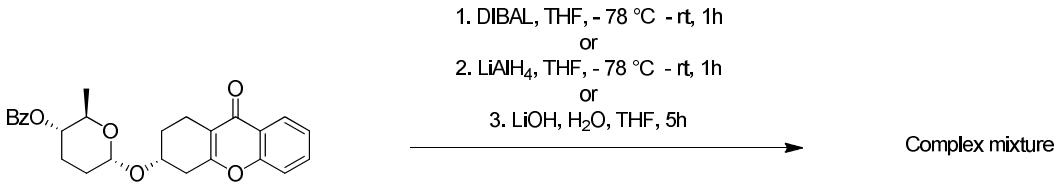
Attempts to remove the benzoyl group from **228** by reduction with DIBAL[116] or $LiAlH_4$[117] at low temperature gave only complex mixtures of products. The hydrolysis of **228** with aqueous LiOH in THF also resulted in a complex mixture of products (*Scheme 62*).



228

Scheme 62

The same reactions performed on glycoside **227** were also attempted. Again only complex mixtures were produced. Exhaustion of the limited supplies of **227** and **228** prevented exploration of alternative cleavage conditions (*Scheme 63*).



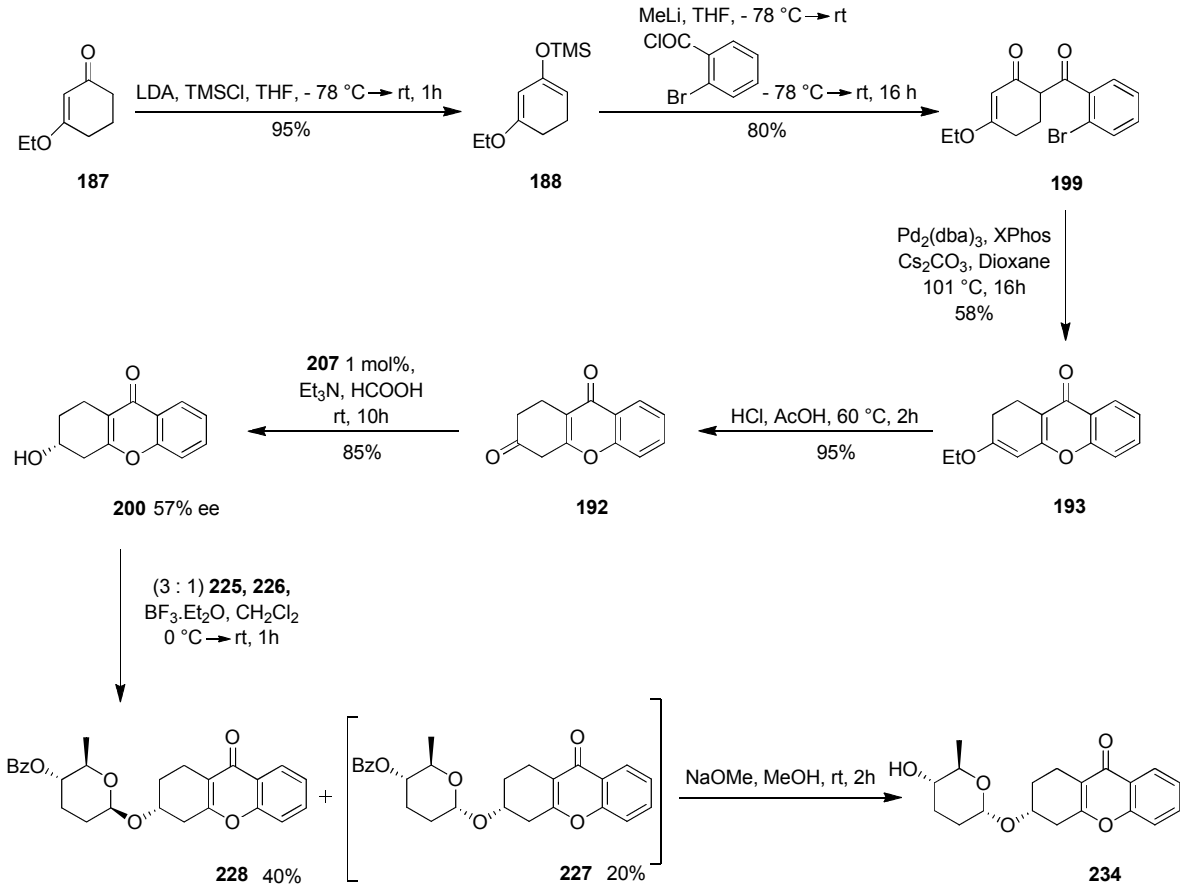
227

Scheme 63

2.7 Conclusions and Future work

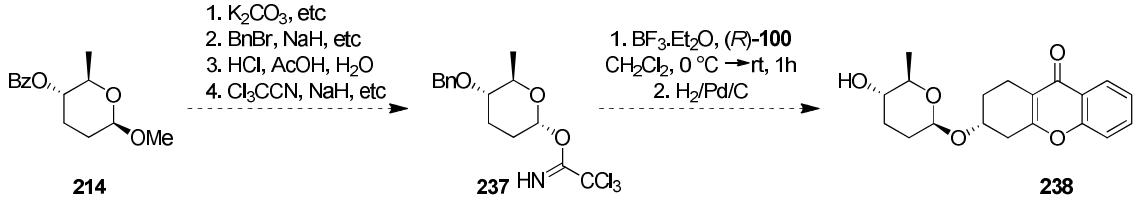
In this chapter an approach has been developed to amicetose substituted tetrahydroxanthones **228** in 3 linear steps and 32% overall yield from 3-ethoxy-1,2-dihydroxanthen-9-one (**193**). Key steps in the sequence include (i) palladium catalysed assembly of tetrahydroxanthone nucleus; (ii) enantiocontrolled reduction of the C=O group via asymmetric transfer hydrogenation; and (iii) stereoselective glycosidation using a novel trichloroacetimidate donor. The gross structure and stereochemistry of **228** were deduced by single crystal X-ray diffraction. Final deprotection to the free

amicetose systems proved problematic due to a competing elimination process (*Scheme 64*).



Scheme 64

Future work should focus on the use of more labile protecting groups in place of the benzoate group, and further efforts to improve the enantioselectivity of the asymmetric reduction. It was imagined that the alternative benzyl protected donor could be made in four steps from **214** (*scheme 65*).



Scheme 65

Further coupling and deprotection *via* catalytic hydrogenation could then yield the target amicetose substituted tetrahydroxanthones in good yields.

Chapter 3:
Polyhydroxylated A-Ring Tetrahydroxanthones

3.1 Introduction to di- and trihydroxy- tetrahydroxanthones

A variety of natural products including puniceasides B **36** and C **37**, albofungin, simaomicins, actinoplanones, kibdelones, isokibdelones and kigamicins, exist with various hydroxylation levels in the tetrahydroxanthone A-ring (*Figure 36*). In this chapter, new synthetic methods for the functionalisation of the A-ring of simple tetrahydroxanthones with a view to developing general strategies to these classes of natural products are reported.

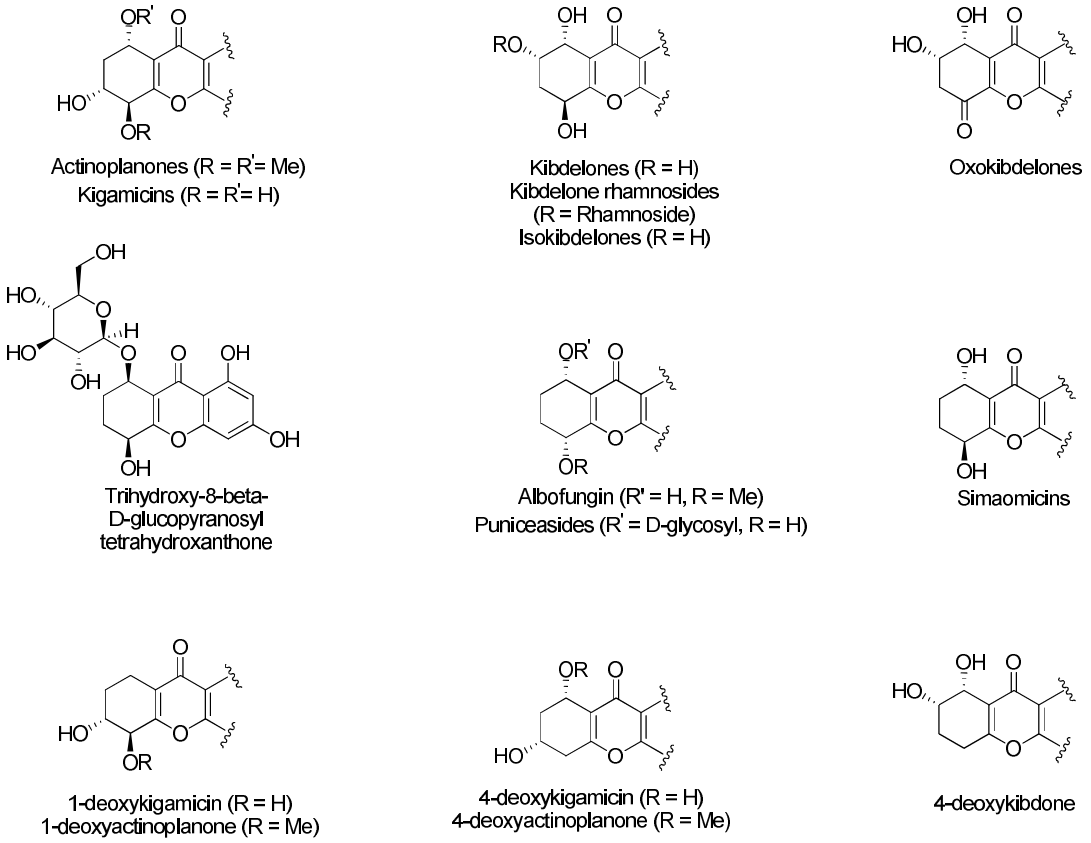


Figure 36

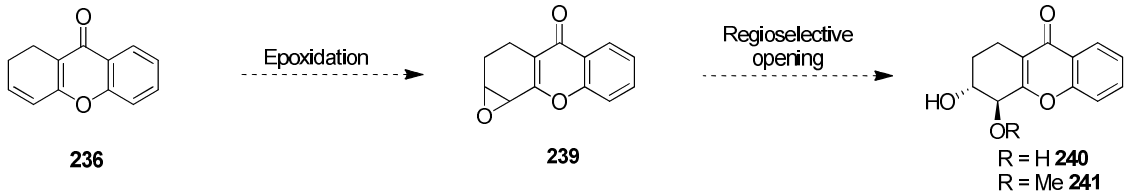
A range of deoxyderivatives were also targeted (e.g. 1-deoxy and 4-deoxy kigamicins, 4-deoxykibdelones) (*Figure 36*). It was anticipated that through screening of such analogues, new knowledge about how critical the extent of hydroxylation and the stereochemistry of such functional groups is to the biological activity of the various natural products could be obtained.

3.2 Dihydroxytetrahydroxanthones

3.2.1 Synthesis of 3,4-dihydroxylated tetrahydroxanthones

Having easy access to 3,9-diketoxanthone **192** (Chapter 2), further functionalisation of the A-ring to install the *trans*-hydroxyl groups at C-3 and C-4 was investigated. It was imagined that this might involve the reduction of the 3,9-diketoxanthone **192** followed

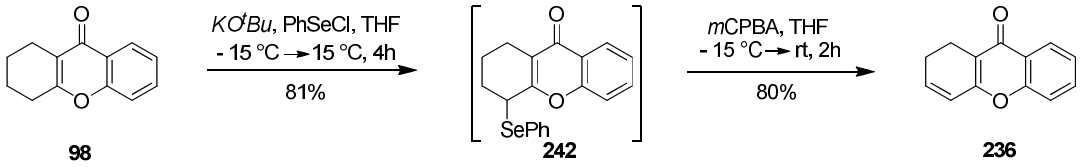
by elimination of the resulting alcohol to provide dihydroxanthone **236**, which could be further epoxidised and opened by water to yield diol **240**, or an alcohol nucleophile such as methanol to yield differentially protected diols e.g. **241** (*Scheme 66*).



236 **239**

Scheme 66

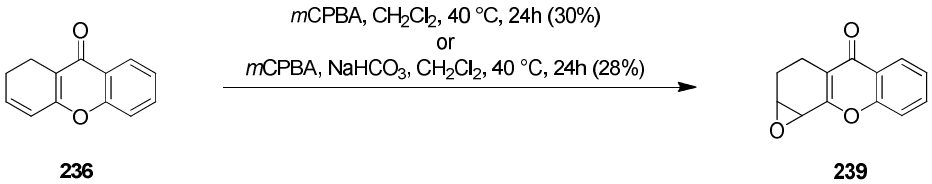
In Chapter 2, a simple route to alkene **236** from 3,9-diketone **192** by reduction and subsequent elimination was devised. Alternatively, tetrahydroxanthone **98** can be selectively deprotonated using KO^{t}Bu at –15 °C in THF and subsequently quenched with phenylselenyl chloride to give selenide **242** in good yield. This selenide upon oxidation with *m*CPBA undergoes spontaneous 2,3-sigmatropic rearrangement to give dihydroxanthone **236** in 80% yield (*Scheme 67*).



98 **242** **236**

Scheme 67

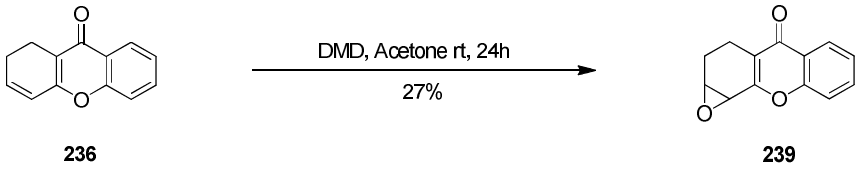
With dihydroxanthone **236**, accessible *via* two complementary routes, the epoxidation step was next explored. With *m*CPBA, the expected epoxide **239** was produced in poor yield. This epoxidation was also attempted with solution buffering in an attempt to minimise acid catalysed ring opening of the product. However, no appreciable improvement was observed when the reaction was performed in the presence of solid $NaHCO_3$ (*Scheme 68*).[118]



236 **239**

Scheme 68

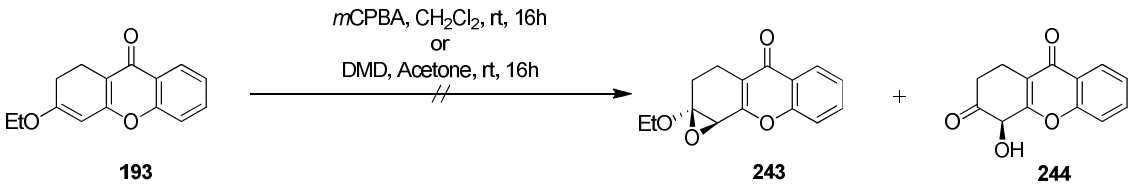
Further attempts to improve the yield of the epoxidation involved treatment of alkene **236** with the powerful, neutral oxidant dimethyldioxirane (DMDO).[119] This again led to the formation of epoxide **239** in low yield (*Scheme 69*).



236 **239**

Scheme 69

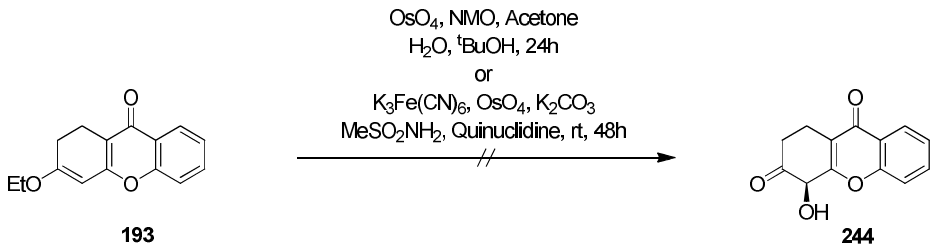
Next, attempts were made to epoxidise the more electron rich enol ether **193** produced in two steps as described in Chapter 2 (*Scheme 41*). Enol ether **193** was treated with *m*CPBA in dichloromethane, which surprisingly gave only starting material **193** after 24 hours. Using more reactive DMDO, a complex mixture of inseparable products was obtained (*Scheme 70*).



193 **243** **244**

Scheme 70

Dihydroxylation of enol ether **193** under Upjohn conditions was also attempted which revealed the inertness of this substrate with complete recovery of **193** after 48 hours.[120] Application of the Warren dihydroxylation conditions was also unsuccessful (*Scheme 71*).[121]

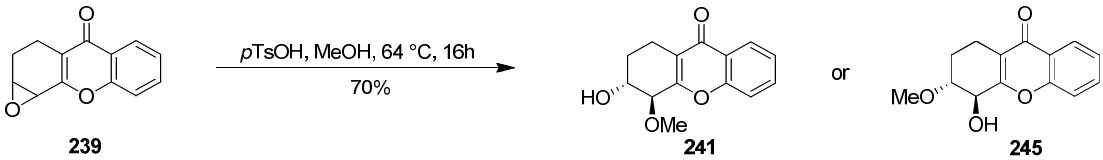


193 **244**

Scheme 71

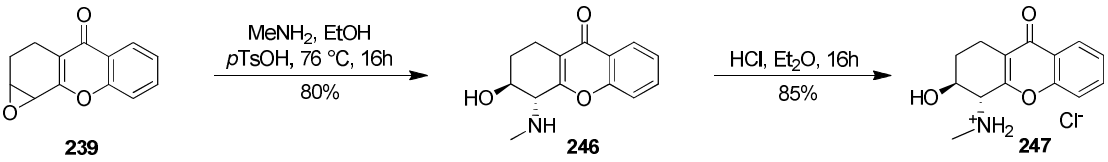
The installation of *trans*-hydroxyl groups at C-3 and C-4 was explored by heating epoxide **239** in methanol in the presence of *para*-toluenesulphonic acid. This resulted in the formation of a single regio- and stereoisomer. It was anticipated that the C-4 of the

epoxide should be more electrophilic due to the inductive effect of the carbonyl group and the fact that this carbon is allylic. Since the hydrogens at C-3 and C-4 in regioisomers **241** or **245** have nearly identical chemical shifts in the ^{1}H NMR spectrum, it was difficult to assign the regiochemical or indeed stereochemical outcome of this reaction (*Scheme 72*).

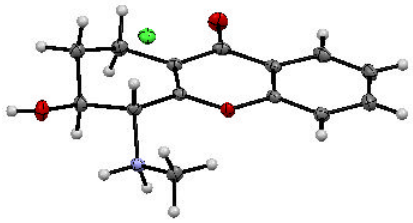


Scheme 72

To help resolve this problem, epoxide **239** was opened with an amine nucleophile, such that the hydrogen shifts at C-3 and C-4 would be less likely to be coincident in the resulting products. Epoxide **239** was reacted with methylamine leading to the formation of a single regioisomer **246** in 80% yield (*Scheme 73*). Analysis of ^{1}H NMR spectrum revealed an apparent doublet of triplets for H-3 at 3.90 ppm with coupling constants of 3.3 and 7.8 Hz, and a doublet of H-4 at 3.60 ppm with a coupling constant of 7.8 Hz consistent with the formation of **246** as product. This amine **246** was converted to its hydrochloride salt on stirring in 2M HCl in diethyl ether overnight. A single crystal X-ray structure was obtained on crystals grown from diethyl ether (*Figure 37*), which confirmed this regiochemical assignment. Moreover, it conclusively established the *trans*-configuration of substituents at C-3/C-4 (*Scheme 73*).



Scheme 73



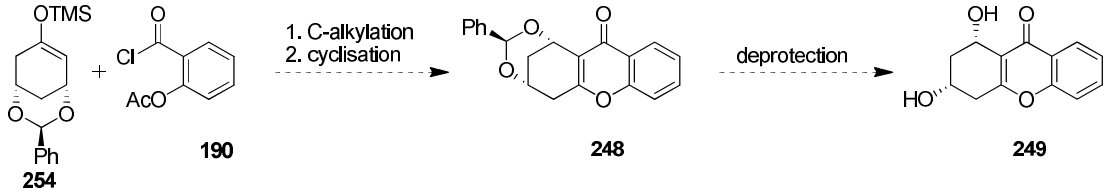
247

Figure 37 Single crystal X-ray structure of **247**

The use of the asymmetric epoxidations to control the absolute stereochemistry in these reactions is discussed in Section 3.3.1.1. Having identified a potential strategy for control of the stereochemistry at C-3 and C-4, our attention next turned to the introduction of the C-1 hydroxyl group.

3.2.2 Attempted synthesis of 1,3-dihydroxytetrahydroxanthones

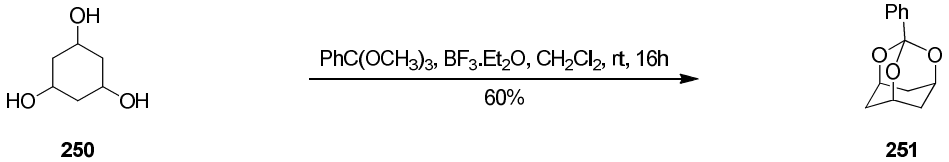
First, installation of *syn*-hydroxyl groups at C-1 and C-3 was investigated. The synthetic strategy initially selected involved coupling of a prefunctionalised A-ring containing the *syn* diols protected as a 1,3-benzylidene acetal with acid chloride **190** using enolate chemistry followed by condensation to form the tetrahydroxanthone nucleus (*Scheme 74*). Previously, it has been demonstrated that such cyclisations can be performed under either acidic or basic conditions (*Section 2.2*).



254 **190** **248** **249**

Scheme 74

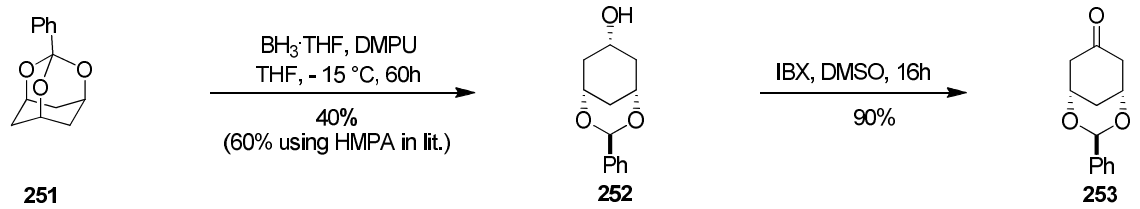
To obtain silylenol ether **254**, the synthesis of Honda *et al* was followed.[122] The reaction of commercially available *cis* and *trans* 1,3,5-trihydroxycyclohexane (**250**) with trimethyl *ortho*-benzoate in the presence of boron trifluoride diethyl etherate in dichloromethane at –15 °C provided the *ortho* ester **251** in moderate yield (*Scheme 75*).



250 **251**

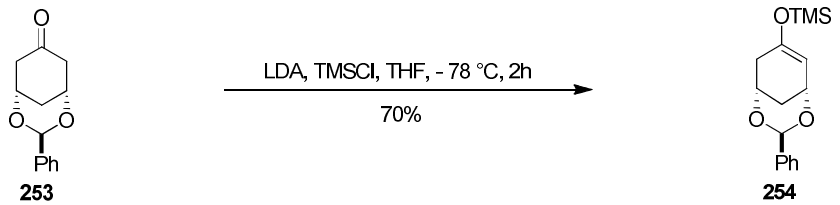
Scheme 75

Partial reduction of *ortho*-ester **251** was conducted with borane in the presence of DMPU. DMPU is less toxic then HMPA which was originally used in the literature for this step.[122] This provided the *cis*-3,5-*O*-benzylidenecyclohexanol **252** in 40% yield. Next, the *cis*-3,5-*O*-benzylidene cyclohexanol (**252**) was subjected to oxidation with IBX to provide ketone **253** in excellent yield (*Scheme 76*).



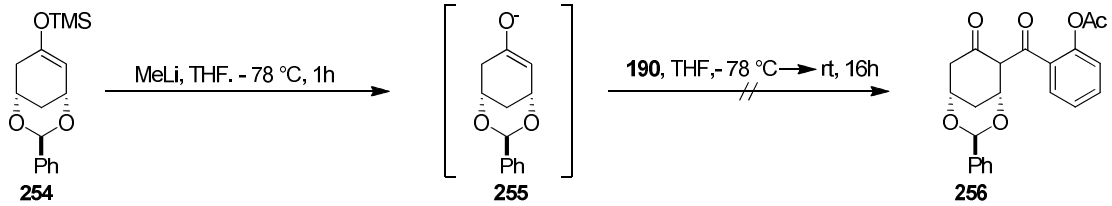
Scheme 76

The deprotonation of ketone **253** with LDA in THF generated the lithium enolate which on subsequent addition of trimethylsilyl chloride at low temperature gave silylenol ether **254** in good yield (*Scheme 77*).



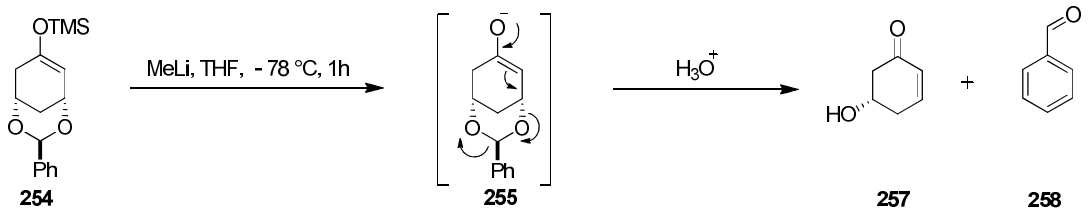
Scheme 77

With **254** in hand, next attention was turned to the key C–C bond construction. To this end, silylenol ether **254** was treated with MeLi at low temperature to regenerate the lithium enolate and quenched with 2-(chlorocarbonyl)phenyl acetate (**190**). Disappointingly, formation of the *C*-alkylated product was not detected. Further attempts performing the quench at elevated temperatures (– 60 °C, – 50 °C, – 30 °C, – 20 °C, – 10 °C, – 0 °C, and rt), were equally unsuccessful with no detected *C*-alkylated product (*Scheme 78*).



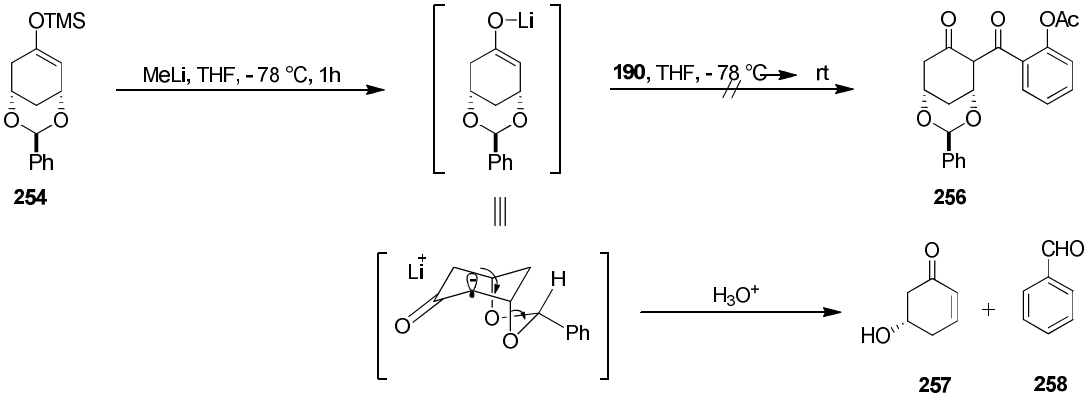
Scheme 78

However, the formation of 5-hydroxycyclo-2-enone (**257**), and benzaldehyde **258** *via* an intramolecular *β*-elimination of the enolate was observed in the ^{1}H NMR spectrum (*Scheme 79*). The assignment of **257** was based on comparison with literature data (*vide infra*).[123]



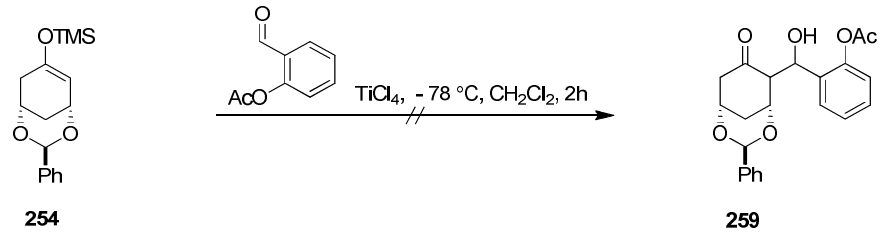
Scheme 79

Toshio *et al*[123] have previously shown that silylenol ether **254** can be used to generate enantiopure 5-hydroxy-2-cyclohexenone **257** along with benzaldehyde **258**. Since they have reported that the yield of formation of **257** was decreased from 77% to 33% when the temperature of the reaction was lowered from room temperature to – 78 °C, it was hoped that the lithium enolate generated from **254** could be successfully quenched with a highly reactive electrophile such as the acid chloride **190** at – 78 °C. However, this proved incorrect, the deprotonation of **254** at lower temperature and slow elevation of the temperature still resulted in the intramolecular elimination of **254** to form hydroxycyclohexenone **257** and benzaldehyde **258**. Presumably, this elimination is encouraged by the antiperiplanar orientation of the enolate anion with the adjacent C–O bond of the acetal (*Scheme 80*).



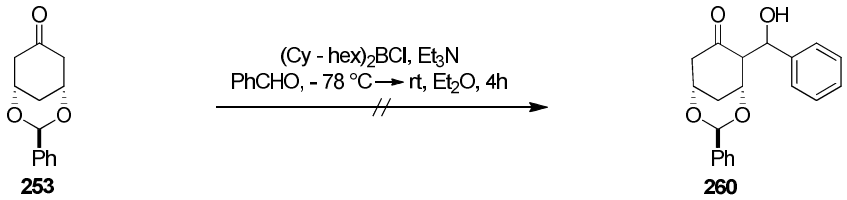
Scheme 80

To try to overcome these problems, a Mukaiyama aldol reaction of silylenol ether **254** with *o*-acetoxybenzaldehyde was attempted to make the *β*-hydroxy ketone **259** which could be further oxidised to the required ketone. Using titanium tetrachloride as activator, this reaction did not give the desired aldol products. To ensure the ester group was not interfering, the Mukaiyama aldol reaction was also attempted with benzaldehyde. A variety of Lewis acids were explored as promoters.[124] In no instances, could any of the desired products be detected (*Scheme 81*).



Scheme 81

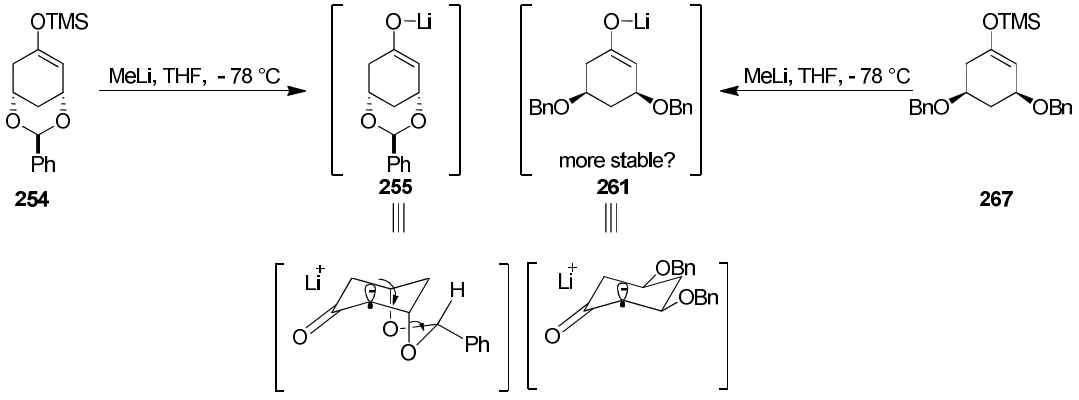
Attempts were also made to produce the boron enolate using triethylamine and dicyclohexylboron chloride.[125] However, further reaction with benzaldehyde to make the *β*-hydroxy ketone **260** led to no identifiable products (*Scheme 82*).



Scheme 82

3.2.2.1 Synthesis of 267

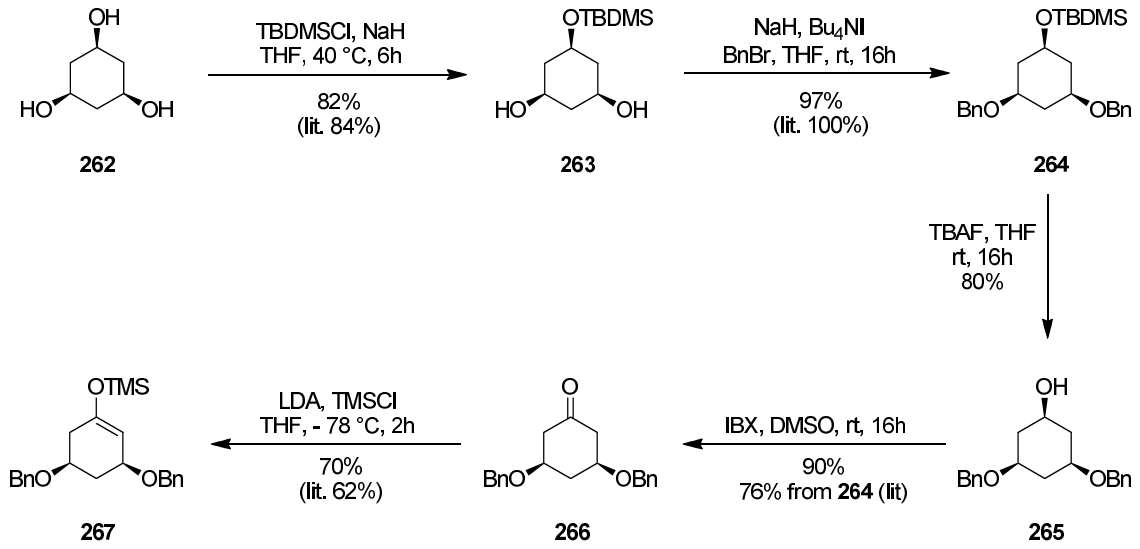
Silylenol ether **254** was very much prone to elimination due to the very well aligned orbitals of the generated lithium enolate. As an alternative, it was considered that the non-tethered *syn*-benzyloxy substituents in **267** might prove less prone to the unwanted *β*-elimination (*Scheme 83*).



Scheme 83

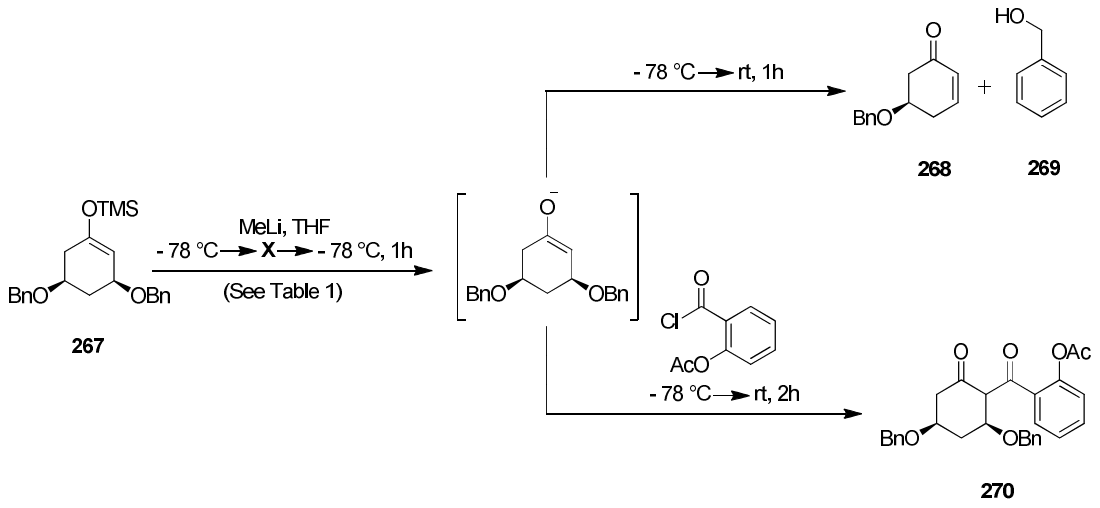
To obtain silylenol ether **267**, to test this idea, the synthesis of Honda *et al* was followed.[126] The mono sodium salt derived from the commercially available all- *cis* diastereomer of 1,3,5-trihydroxycyclohexane (**262**) on treatment with *tert*-butyldimethysilyl chloride in THF yielded mono silyl ether **263** in 82% yield. Diol **263**

was further alkylated with benzyl bromide in the presence of sodium hydride and tetrabutylammonium iodide to give dibenzyl ether **264** in 97% yield. The desilylation of monosilylated dibenzyl ether **264** was achieved with tetrabutylammonium fluoride in THF in 80% yield. Further oxidation of alcohol **265** with IBX gave crystalline ketone **266** in 90% yield. Dibenzyl ketone **266** was further converted into the corresponding silylenol ether in 70% yield. The temperature was carefully maintained at – 78 °C to avoid any *β*-elimination (*Scheme 84*).



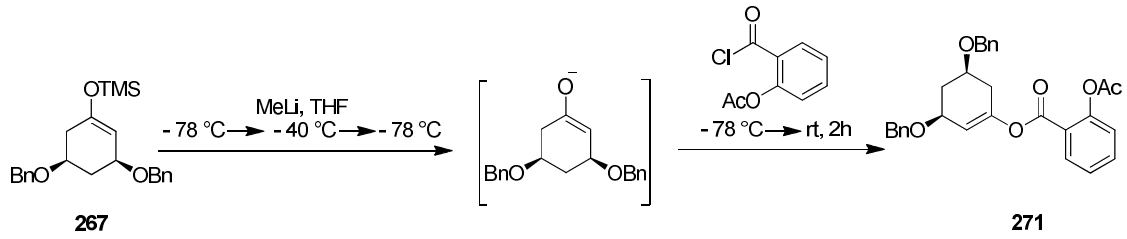
Scheme 84

The lithium enolate was regenerated from **267** on treatment with MeLi at –78 °C. Experiments were conducted at low temperatures to try to avoid elimination and favour the intermolecular C-acylation of the enolate (*Scheme 85*).



Scheme 85

The acylation of the silylenol ether of prefunctionalised A-ring **267** with the acid chloride **190** was conducted at various temperatures to encourage the formation of the C-C bond. Recovery of the dibenzyl ketone after conducting the reaction at –78 °C and even up to –45 °C encouraged us to conduct the reaction at higher temperatures and for longer periods of time. Although the molecular ion peak for **270** was clearly observed in the electrospray mass spectrum when the reaction was conducted at –40 °C, NMR analysis of crude product suggested isomeric ester **271** had been formed (*Scheme 86*)**.**



267 **271**

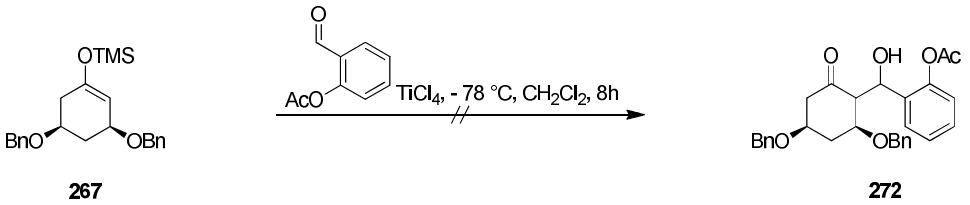
Scheme 86

The quantification of **271** was difficult by NMR. Unfortunately, the formation of the required C-C bond was again not achieved inspite of a number of changes to the reaction conditions (*Table 1*). These results suggest that this more hindered enolate prefers to react through oxygen rather than carbon.

Table 1. 1 eq of silylenol ether **267**, 1 eq of MeLi and 1 eq of acid chloride **190** was used in THF.

Entry	Temperature (-78 °C – X °C)	Time	Results by ES and NMR
1	-78 °C	30 min	**267**
2	-40 °C	40 min	**267**
3	-30 °C	10 min	**266** and **271**
4	-25 to -20 °C	30 min	**266** and **271**
5	-20 to -15 °C	30 min	**266** and **271**
6	-15 to -10 °C	30 min	**266** and **271**
7	-10 to -5 °C	30 min	**266** and **271**
8	rt (slowly)	30 min	**266** and **271**
9	rt (quickly)	30 min	**266**

Mukaiyama aldol reaction of the same silylenol ether was attempted using *o*-acetoxy benzaldehyde. However, in the presence of titanium tetrachloride, only a complex mixture of products was produced (*Scheme 87*).[127] Attempts with comparatively softer Lewis acid $ZnCl_2$, were also made but again only complex mixtures of products were produced.[124] Frustrated by our unsuccessful efforts to produce compounds containing *syn* hydroxyl groups at C-1 and C-3 we decided to turn our attention towards 1,4-dihydroxy tetrahydroxanthones instead.



Scheme 87

3.2.3 Synthesis of 1,4-dihydroxy tetrahydroxanthones

The 1,4-dihydroxy tetrahydroxanthone substitution pattern is found in the simaomicins and albofungin among others (*Figure 38*). Both *syn*- and *anti*-substitution patterns are known.

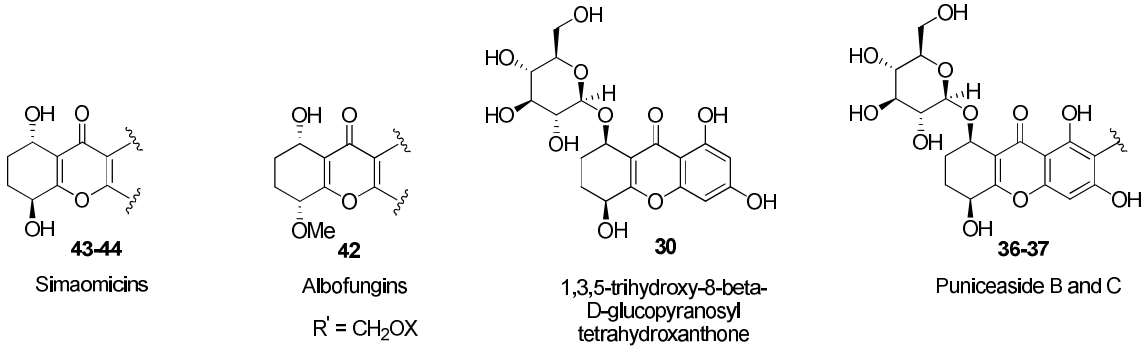
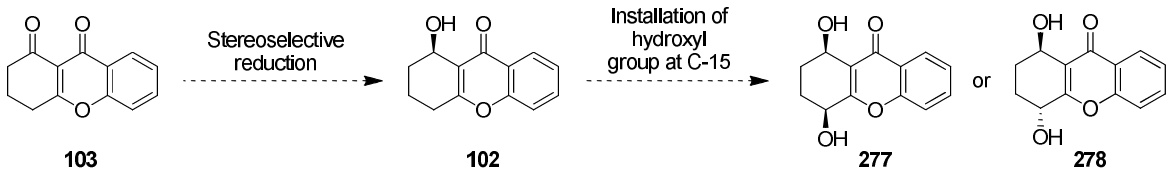


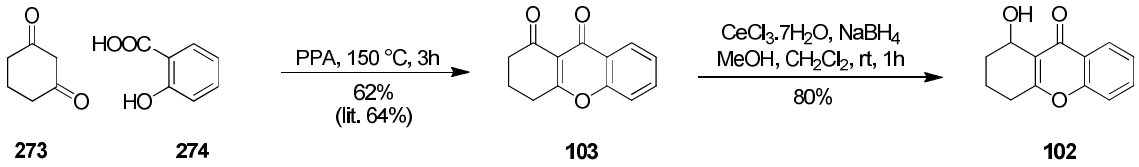
Figure 38

Our synthetic strategy for the installation of the *cis* and *trans* hydroxyl groups at C-1 and C-4 was based on using ketone **103** as the starting material. It was imagined that chemo- and enantioselective reduction would give alcohol **102**, which could be further deprotonated and quenched with an electrophilic oxygen source to form the 1,4-dihydroxytetrahydroxanthones **277** and/or **278**. I hoped that conditions might be found to control the facial selectivity of this process forming either **277** or **278** diastereoselectively (*Scheme 88*).



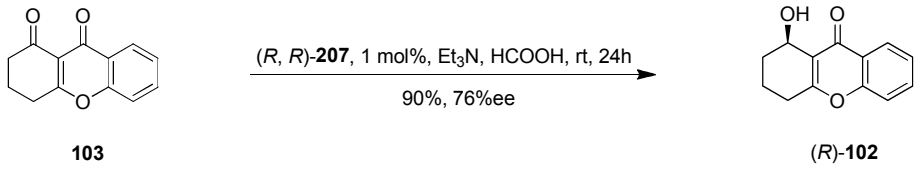
Scheme 88

Ketone **103** was obtained by the condensation of cyclohexadione (**273**) and salicylic acid (**274**) in the presence of polyphosphoric acid at high temperature in 62% yield.[128] Further chemoselective Luche reduction of **83** provided the racemic alcohol **102** in 80% yield (*Scheme 89*).[129]



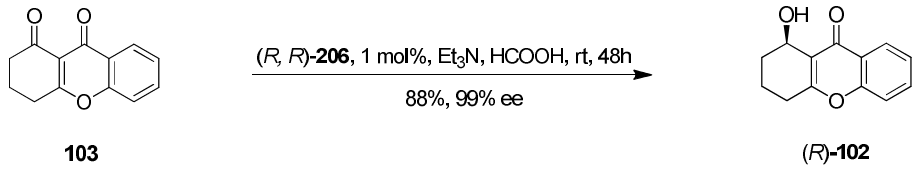
Scheme 89

Next, enantioselective reduction of **103** was explored to obtain alcohol **102** as a single enantiomer. Ketone **103** was subjected to asymmetric transfer hydrogenation with ruthenium tethered catalyst **207** (*Figure 32*), developed by Wills in the presence of triethylamine and formic acid to provide (*R*)-**102** in 90% yield and 76% enantioselectivity (*Scheme 90*).[130]



Scheme 90

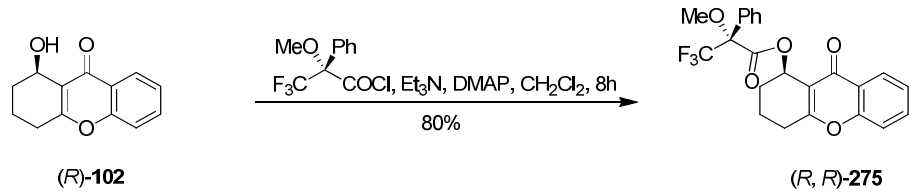
The major enantiomer in this reaction was determined by the chiral HPLC retention times, in conjunction with further derivatives experiments (*vide infra*). To further improve the enantioselectivity in the reduction, Noyori's ruthenium catalyst **206** (*Figure 32*), for asymmetric transfer hydrogenation was explored. The asymmetric transfer hydrogenation of ketone **103** was conducted with **206** in the presence of triethylamine and formic acid, and yielded alcohol (*R*)-**102** in excellent enantioselectivity and 88% yield (*Scheme 91*).



Scheme 91

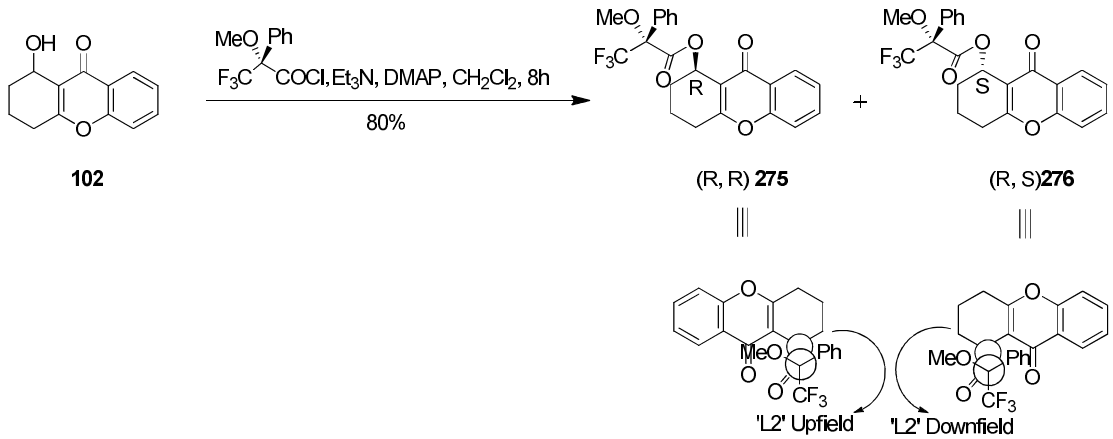
3.2.3.1 Determination of configuration of 102 by Mosher's method

The models and mechanistic studies of ketone reduction by ruthenium catalysts reveal that (*R*, *R*)- catalysts generally reduces the ketone to the *R*-alcohol. However, the absolute configuration of the alcohol (*R*)-**102** was determined by Mosher's method.[131] Treatment of the chiral alcohol (*R*)-**102** with (*S*)-(+)-MTPA-Cl (derived from the *R* acid, which gives the *R* configured ester) in the presence of triethylamine and catalytic DMAP produced (*R*, *R*)-**275** in good yield (*Scheme 92*).



Scheme 92

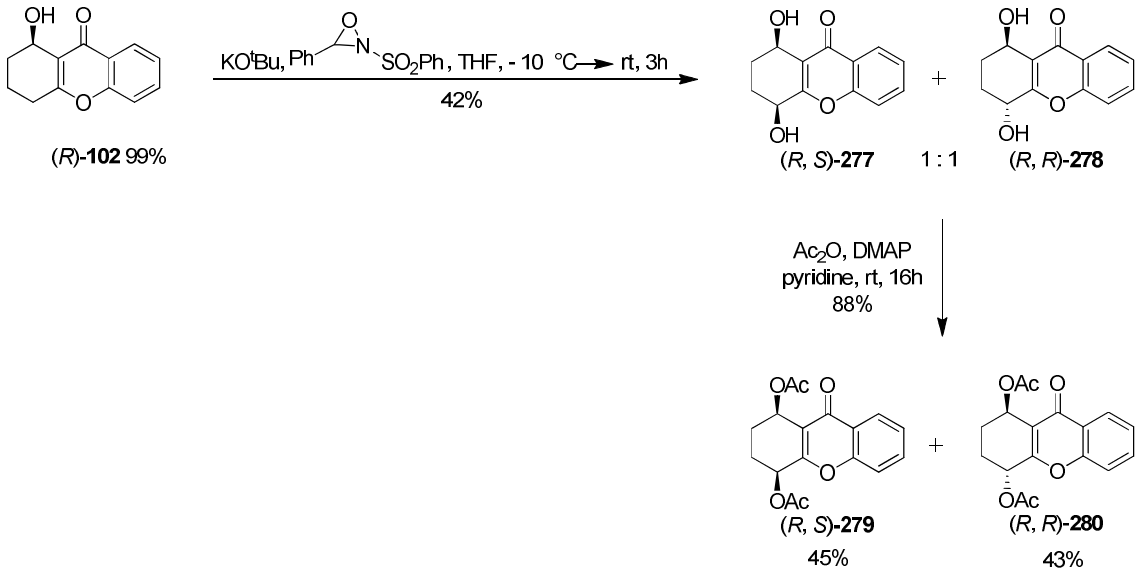
Using the notation from Mosher's paper, the protons at position 'L2' will be upfield in (*R*, *R*)-**275** compared to protons at position 'L2' in (*R*, *S*)-**276** (*Scheme 93*). The single enantiomer from the reduction gave the *R,R* Mosher ester. In order to compare the relative positions of the key peaks, the racemic alcohol was reacted with (*S*)-(+)-MTPA-Cl to give a mixture of isomers (*R*,*R*)-**275** and (*R*,*S*)-**276**. The Mosher model predicts that these isomers will adopt the conformations shown below (*Scheme 93*).



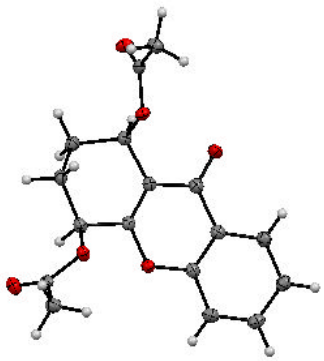
Scheme 93

Comparison of the ^{1}H NMR spectrum of (*R*,*R*)-**275** and a mixture of (*R*,*R*)-**275** and (*R*,*S*)-**276** confirmed the *R* configuration of the alcohol (*R*)-**102**.

Further installation of a hydroxyl group at C-4 was achieved by formation of the dianion of (*R*)-**102** and subsequent quench with the Davies oxaziridine[132] reagent. This provided an inseparable mixture of *cis* and *trans* diastereomers of 1,4-dihydroxy tetrahydroxanthones (*R*,*S*)-**277** and (*R*,*R*)-**278** in 1 : 1 ratio in 42% yield. Acetylation of the *cis* and *trans* diastereomeric mixture of (*R*,*S*)-**277** and (*R*,*R*)-**278** led to the separation of the diastereomers (*Scheme 94*). I was able to grow crystals of (*R*,*S*)-**279** to prove the relative stereochemistry of both diastereomers unambiguously (*Figure 39*).



Scheme 94



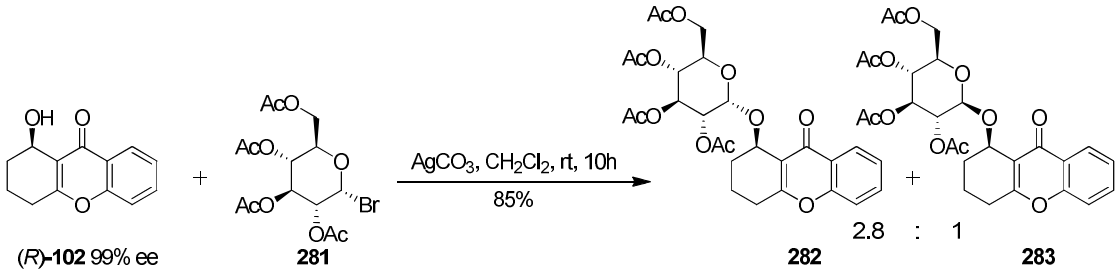
279

Figure 39 Single crystal X-ray structure of **279**

After the successful synthesis of (*R*,*S*)-**279** and (*R*,*R*)-**280** dihydroxy tetrahydroxanthones, it was decided to couple a glucose donor with the single enantiomer of alcohol (*R*)-**102**, then attempt the installation of the C-4 hydroxyl group using the above chemistry. In this way, I hoped to produce the fully functionalised A-ring fragment of puniceaside B **36** and C **37,** and natural product 1,3,5-trihydroxy-8-*β*-D-glucopyranosyl tetrahydroxanthone (**30**).

3.2.3.2 Glycosidation of alcohol (*R*)-102

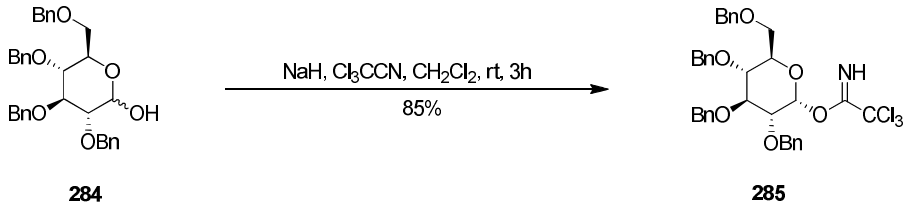
Puniceasides B and C contain a *β*-linked glucose to the C-1 hydroxyl group of the tetrahydroxanthone. Therefore, to construct the *β*-linkage between the D-glucose and alcohol (*R*)-**102**, glycosidation of the alcohol was carried out with the commercially available tetra-*O*-acetyl-*α*-D-glucopyransyl bromide **281** in the presence of silver carbonate at room temperature. Interestingly, this resulted in an inseparable 2.8:1 mixture of *α*– **282** and *β*– **283** glycosides in 85% yield (*Scheme 95*).



Scheme 95

The formation of the *β*-glycosidic bond does not only depend on the configuration of anomeric position of the sugar donor but also on the nature of the alcohol[133, 134, 135] and the glycosidation conditions.[136, 137] To further encourage *β*-glycosidic bond formation the glycosidation was repeated in the presence of silver triflate[138, 139] and silver oxide.[140] However, again no improved preference for the formation of the *β*-glycoside was observed. Since the synthesis of exclusively *β*-**283** was not achieved with tetra-*O*-acetyl-*α*-D-glucopyransyl bromide **281** as sugar donor, and further installation of the hydroxyl group at C-4 in the presence of acetate protection was problematic, the use of an alternative sugar donor was explored. A mixture of *α*- and *β*-hydroxy tetra-*O*-benzyl-D-glucose **284** and trichloroacetonitrile were stirred in the presence of catalytic sodium hydride, which quickly resulted in the appearance of two close running spots of *α*- and *β*- trichloroacetimidates observed on thin layer chromatography.[141] Addition of excess sodium hydride after 30 minutes initiated the retroreaction and allowed the formation of

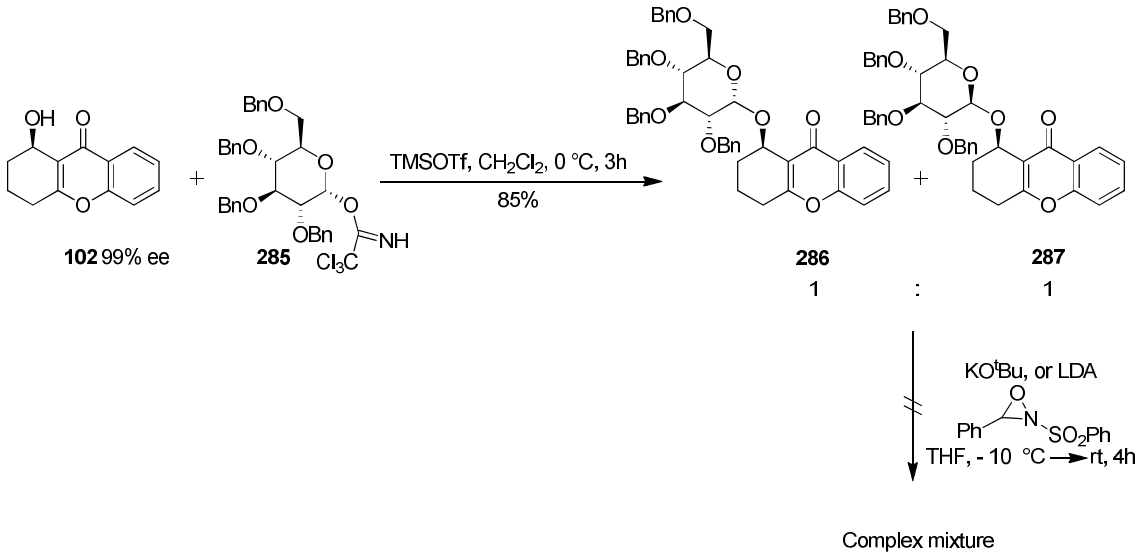
thermodynamically more stable α-trichloroacetimidate **285** in excellent yield (*Scheme 96*).[142]



284 **285**

Scheme 96

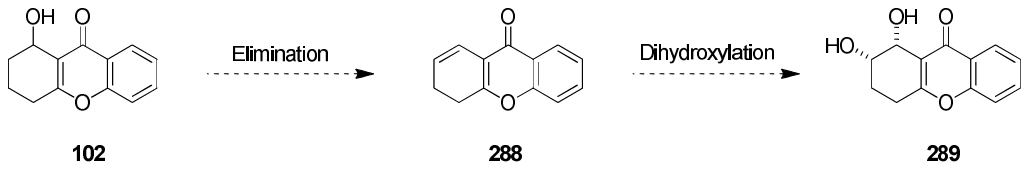
The α-trichloroacetimidate glycosyl donor **285** was quickly used in the glycosidation after purification through a short column of silica. Coupling of the alcohol (*R*)-**102** and the glycosyl donor **285** in the presence of TMSOTf resulted in an inseparable 1:1 mixture of the α-**286** and β-**287** glycosides.[143] Disappointingly, deprotonation of the α-**286** and β-**287** glycoside mixture at C-4 with 2 equivalents of KO^{t}Bu or LDA and subsequent quenching with the Davis reagent resulted in a complex mixture of products from which none of the desired alcohol could be isolated (*Scheme 97*).



Scheme 97

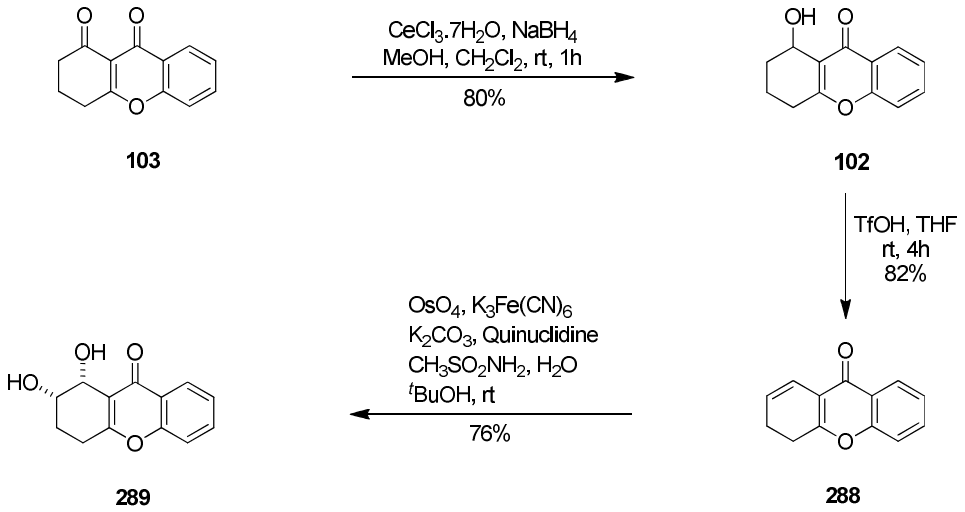
3.2.4 Synthesis of 1,2-dihydroxy tetrahydroxanthones

Our synthetic strategy to install the *cis* hydroxyl groups at C-1 and C-2 of the A-ring of kibdelones **52-59** (*Figure 24, 25 and 26*) was anticipated to involve elimination of alcohol **102** to obtain dihydroxanthone **288** which could be further dihydroxylated to synthesise diol **289** (*Scheme 98*).



Scheme 98

Alcohol **102** obtained *via* Luche reduction of ketone **103** on treatment with trifluoromethanesulfonic acid eliminated to give dihydroxanthone **288** in 82% yield. Dihydroxylation of the dihydroxanthone **288** under Upjohn condition gave the diol **289** in 70% yield. To further improve the yield, the reaction was repeated under the Warren conditions to obtain diol **289** in a slightly improved 76% yield (*Scheme 99*). No attempts were made to conduct this dihydroxylation in an enantioselective manner.



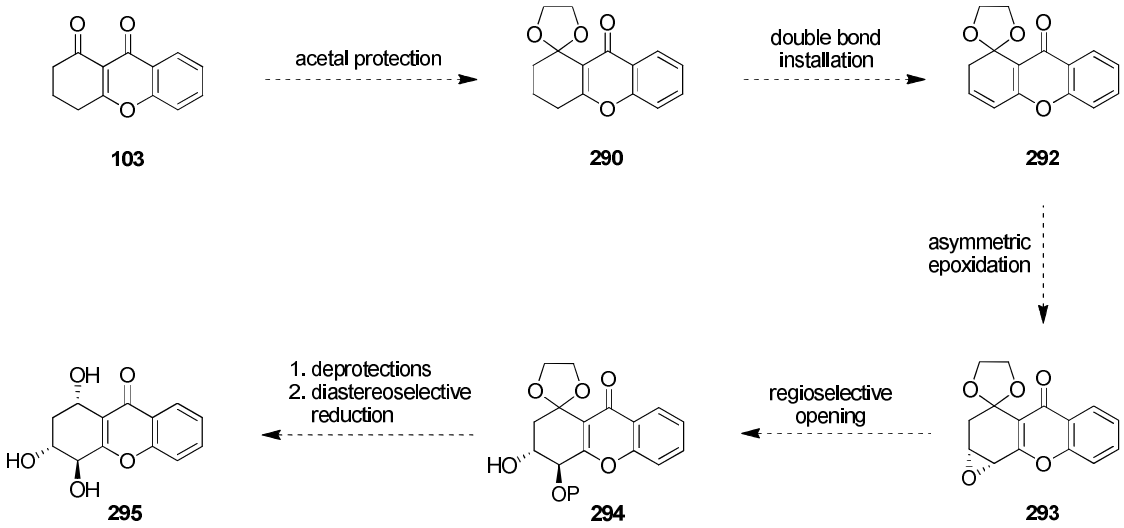
Scheme 99

3.3 Trihydroxy tetrahydroxanthones

Next, attention was turned towards the synthesis of trihydroxy tetrahydroxanthones found in the biologically active actinoplanones, kigamicins and kibdelones.

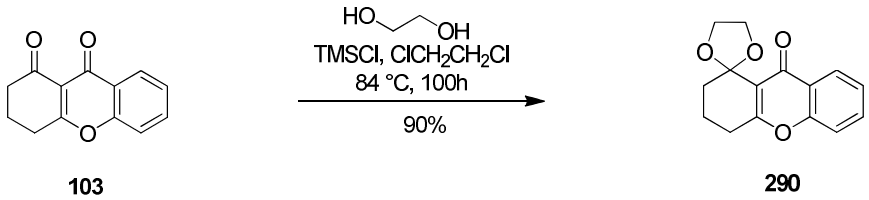
3.3.1 1,3,4-trisubstituted tetrahydroxanthones

To install the hydroxyl groups at C-1, C-3 and C-4 of the tetrahydroxanthones, a synthetic strategy based upon acetal **290** was devised. This acetal could be made by protection of ketone **103** followed by installation of double bond *via* oxidative [2-3]-sigmatropic rearrangement of the corresponding selenide. Alkene **292** could be further subjected to asymmetric epoxidation followed by regioselective opening, deprotection and hydroxyl directed reduction of the ketone to yield the fully functionalised A-ring of the kigamicins and actinoplanones (*Scheme 100*).



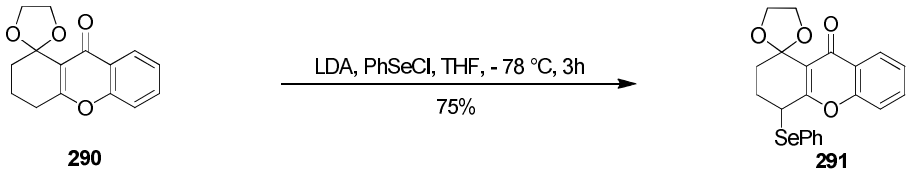
Scheme 100

Ketone **103** was protected with ethylene glycol in the presence of trimethylsilyl chloride in refluxing 1,2-dichloroethane in 90% yield (*Scheme 101*).[144]



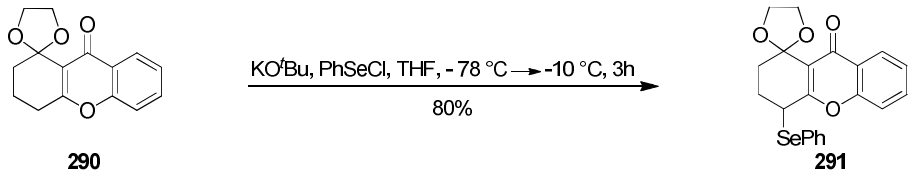
Scheme 101

Ketal **290** was deprotonated with lithium diisopropylamide at the *γ*-position to make an extended enolate which was quenched with phenylselenyl chloride to give selenide **291** in good yield (*Scheme 102*).



Scheme 102

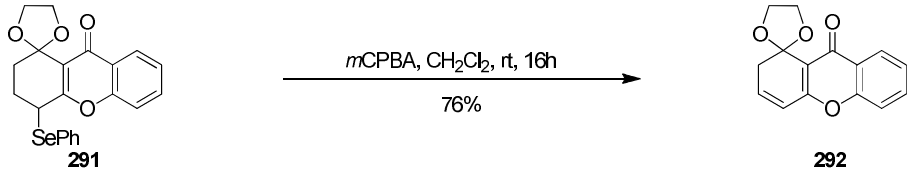
The yield of this selenide was further improved when lithium diisopropylamide was replaced with KO^{t}Bu and the temperature was warmed to – 10 °C before quenching with phenylselenyl chloride (*Scheme 103*).



290 **291**

Scheme 103

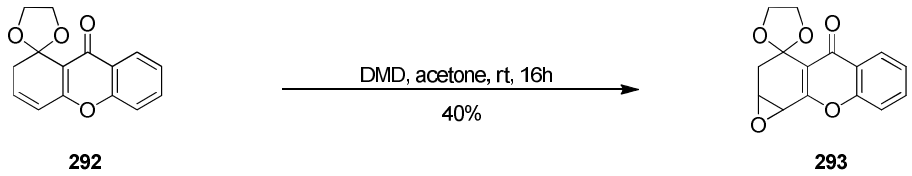
Oxidation of selenide **291** with *m*CPBA led to spontaneous [2-3]-sigmatropic rearrangement to yield alkene **292** in good yield (*Scheme 104*).



291 **292**

Scheme 104

However, the epoxidation of alkene **292** with *m*CPBA did not show any epoxide formation after 16 hours. Treatment with a more powerful oxidant dimethyldioxirane (DMDO) provided epoxide **293** in 40% yield (*Scheme 105*). No further attempts to improve this transformation were made, since we wished to achieve this conversion in an enantioselective manner.

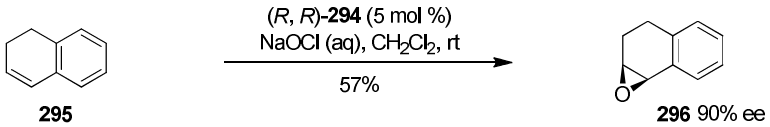


292 **293**

Scheme 105

3.3.1.1 Asymmetric epoxidations of dihydroxanthone 102 and alkene 161

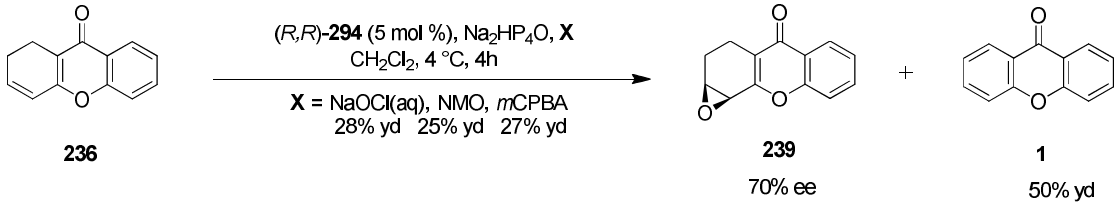
The enantioselective epoxidation of dihydroxanthone **236** and alkene **292** were investigated to find the best conditions in terms of chemical yields and enantioselectivities. Jacobsen's catalyst (*R*,*R*)-**294** has been extensively explored for the enantioselective epoxidation of alkenes (*Figure 40*).[145] For example, the enantioselective epoxidation of **295** with (*R*,*R*)-**294** is reported to give very good enantioselectivity in favour of the depicted enantiomer (*Scheme 106*).[146]



295 **296** 90% ee

Scheme 106

Epoxidation of dihydroxanthone **236** was conducted in the presence of Jacobsen's catalyst (*R,R*)-**294** under buffered conditions. The epoxidation of alkene **236** in the presence of Jacobsen's catalyst (*R,R*)-**294** using sodium hypochlorite as the stoichiometric reoxidant, gave epoxide **239** in low yield along with over oxidised xanthone **1**. The enantioselectivity of the reaction as determined by chiral HPLC, was quite good. Alternate stoichiometric reoxidants, namely NMO and *m*CPBA, were used in attempts to improve the yield and enantioselectivity. However, no substantial improvements were observed (*Scheme 107*).[147]



Scheme 107

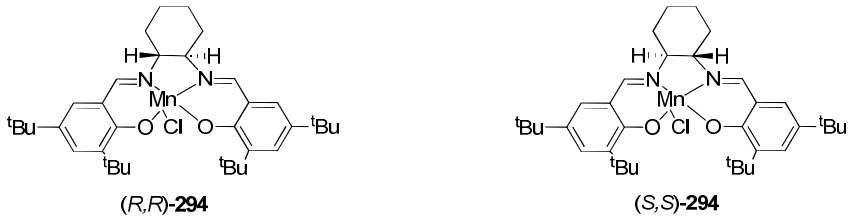
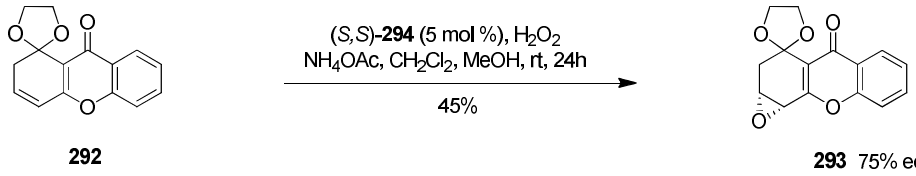


Figure 40

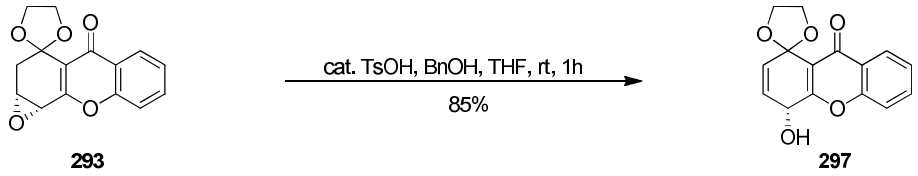
Next, we directed our attention towards the chiral epoxidation of alkene **292**. The use of ammonium acetate as a ligand in such enantioselective epoxidations is reported to decrease the Lewis acidity of the manganese leading to improvements in yields.[148] Treatment of alkene **292** with hydrogen peroxide and ammonium acetate in the presence of Jacobsen's catalyst **294** in a mixture of methanol and dichloromethane gave epoxide **293** in a more respectable 45% yield and good enantioselectivity (*Scheme 108*). The higher levels of conversion observed using this substrate may be because it can not undergo over oxidation to the xanthone **1**.



Scheme 108

3.3.1.2 Attempted regioselective opening of epoxide 293

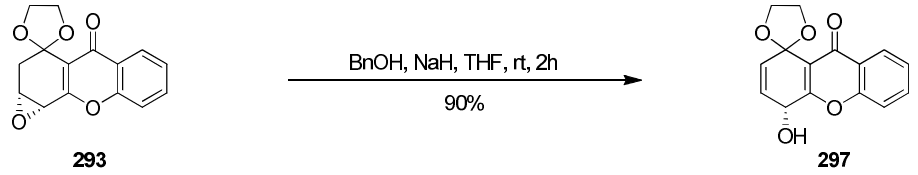
With the knowledge gained from the regioselectively opening of the epoxide **239** (*Scheme 50*), the opening of chiral epoxide **293** with benzyl alcohol was expected to be straightforward. However, under acidic conditions, rearrangement of the epoxide **293** to the allylic alcohol **297** was observed in 85% yield (*Scheme 109*).



293 **297**

Scheme 109

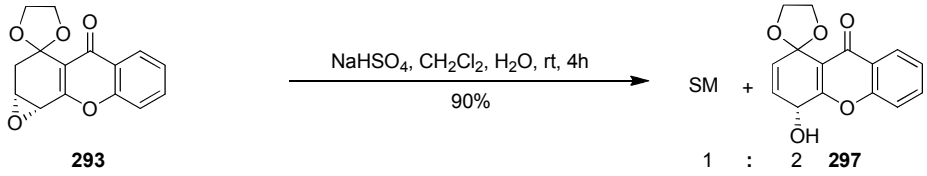
The opening of chiral epoxide **293** was also attempted under basic conditions. Reaction of the sodium salt of benzyl alcohol, derived from reaction of one equivalent of sodium hydride and benzyl alcohol in THF at 0 °C, with epoxide **293** again resulted in formation of allylic alcohol **297** (*Scheme 110*). Changing the nucleophile MeONa or EtONa did not show any change in the product formed.



293 **297**

Scheme 110

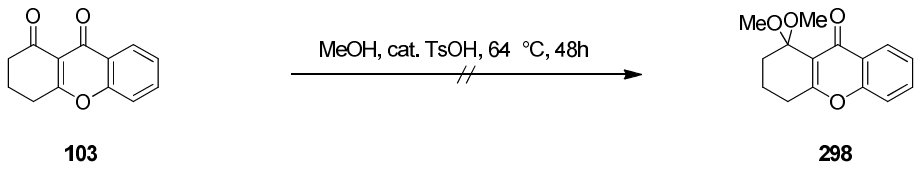
The opening of the chiral epoxide under more mildly basic aqueous conditions was also attempted.[149] However, the allylic alcohol **297** was still obtained with some starting material **293** recovered (*Scheme 111*).



293 **297**

Scheme 111

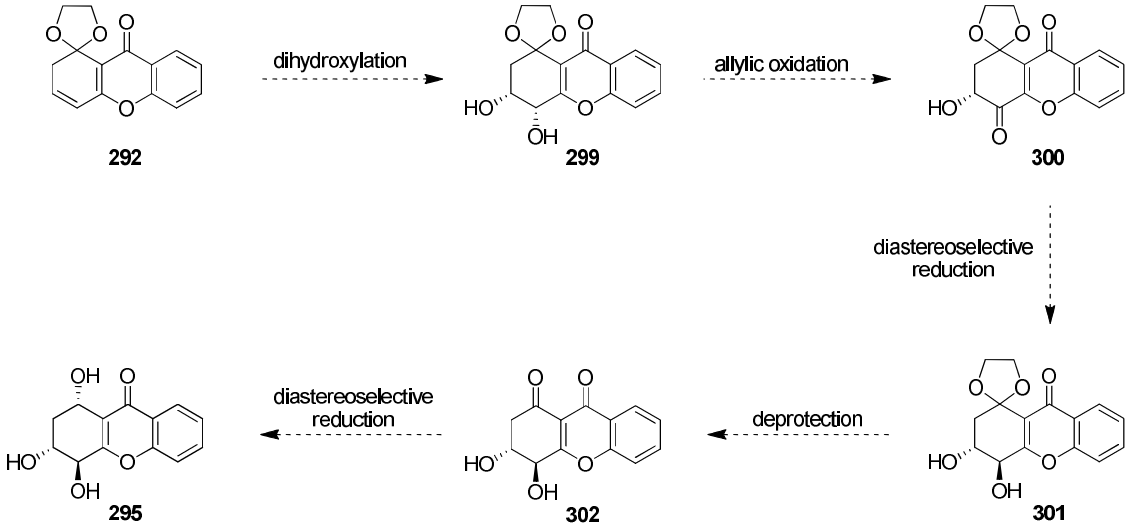
Since, the cyclic acetal group was rendering the adjacent methylene hydrogens acidic enough to trigger rearrangement of the allylic alcohol, attempts were made to change the acetal protecting group. Attempted protection of the ketone **103** as a dimethyl acetal using *p*-toluene sulphonic acid in methanol was investigated. However, only the starting material was recovered after 48 hours (*Scheme 112*).



103 298

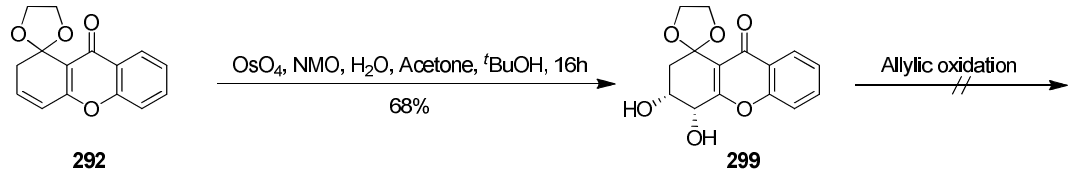
Scheme 112

Since replacement of the cyclic acetal was not achieved, a synthetic strategy was devised based upon dihydroxylation. After conversion to diol **299**, selective oxidation of the allylic alcohol followed by diastereocontrolled reduction to *trans*-diol was envisaged. Subsequent deprotection to **302** and further reduction would then provide the fully functionalised A-ring of the kigamicins and actinoplanones (*Scheme 113*). An additional feature of this strategy is that it could allow for selective introduction of the carbohydrate moiety at C-3 of intermediate **300**, in the context of kigamicin synthesis.



Scheme 113

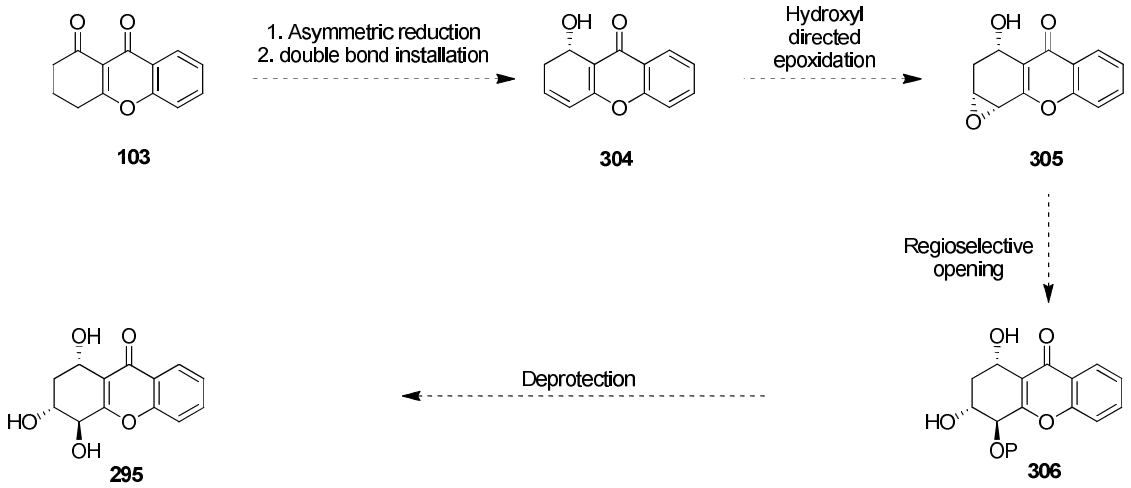
The dihydroxylation of the alkene **292** under Upjohn conditions gave the corresponding ketal diol **299** in 68% yield. However, special care was required during work up since this diol readily eliminates to give allylic alcohol **297** when 0.2N HCl acid is used (*Scheme 93*). To invert the stereochemistry of the allylic alcohol, the chemoselective oxidation of the allylic alcohol was required. Allylic alcohol oxidation was initially attempted with MnO_2 resulting only in the recovery of the starting material. Moreover, oxidation of this diol with Dess Martin periiodinane, IBX, or CrO_3 gave only a complex mixtures of products (*Scheme 114*).



Scheme 114

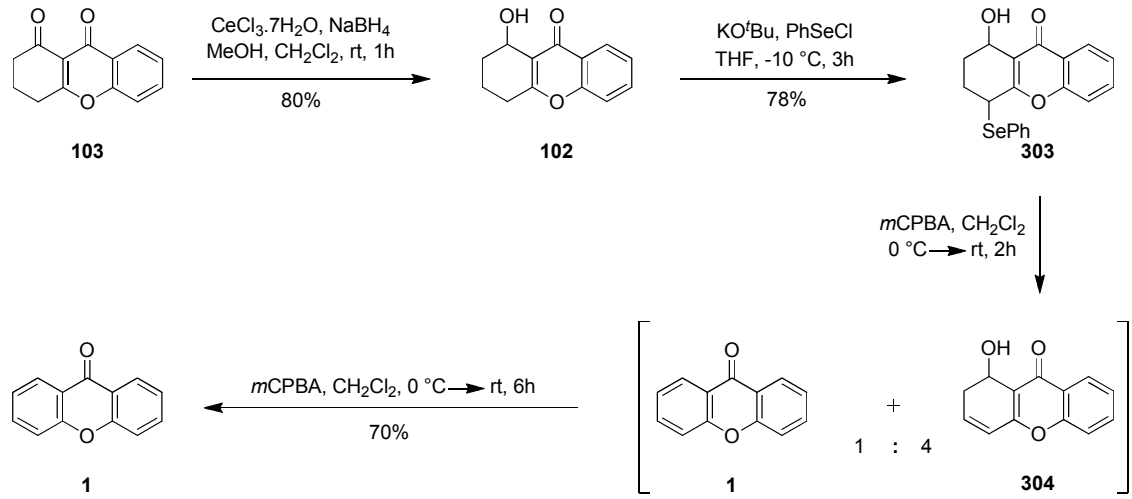
3.3.1.3 Functionalisation of A-ring via hydroxyl directed epoxidation

A slightly modified strategy was thus required. As it has been seen, ketone **103** can be reduced in excellent enantioselectivity to alcohol (*R*)-**102**. Installation of the double bond *via* well developed selenide chemistry, hydroxyl directed epoxidation followed by regioselective opening of the resultant enantiomer epoxide might yield a fully functionalised tetrahydroxanthone (*Scheme 115*).



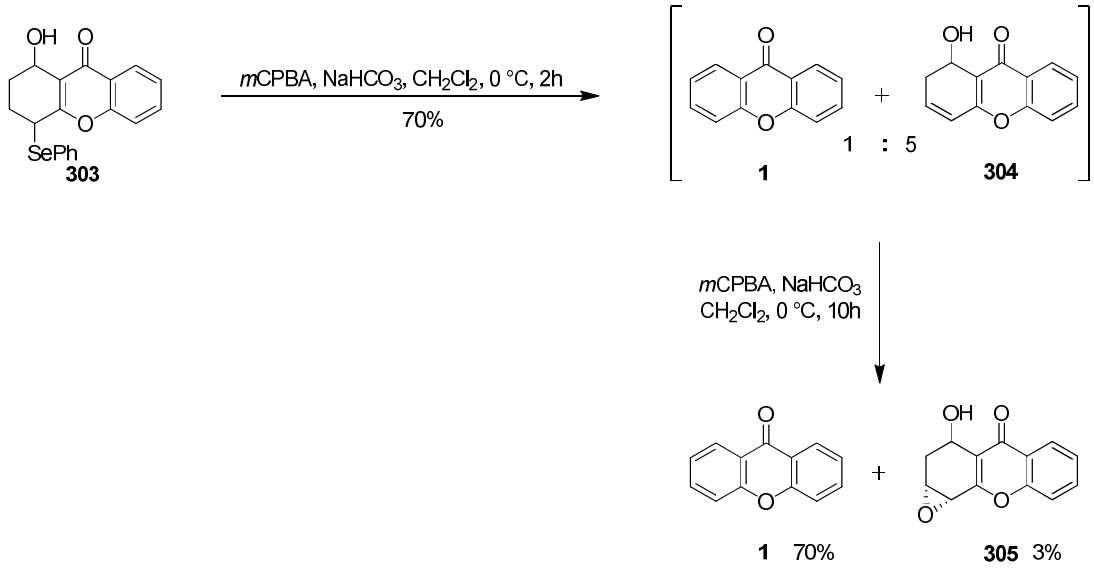
Scheme 115

For convenience, this synthesis was first tested with racemic alcohol **102** synthesised via the Luche reduction of ketone **103** in 82% yield. Di-deprotonation of alcohol **102** was achieved using just over two equivalents of KO^{t}Bu followed by electrophilic quench with a single equivalent of phenylselenyl chloride to obtain a 1 : 1 mixture of selenide diastereomers **303** in 78% yield. Further oxidation of the selenium atom to promote the [2,3]-sigmatropic rearrangement was carried out with *m*CPBA which resulted in the formation of alkene **304** alongside xanthone **1** in a disappointing 4 : 1 ratio. Epoxidation of unstable alkene **304** (used without purification) with *m*CPBA in dichloromethane resulted in the formation of xanthone **1** as the only product. It was perhaps not surprising that, this alkene was acid sensitive and underwent elimination of water under these acid oxidation conditions (*Scheme 116*).



Scheme 116

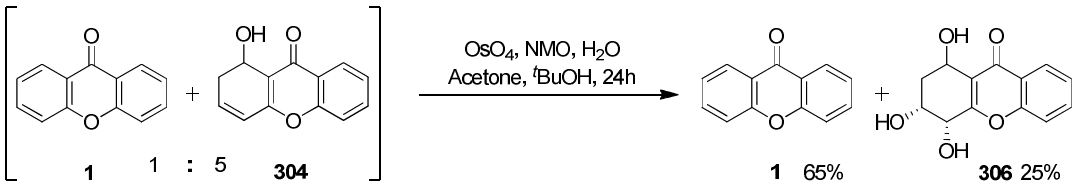
The oxidation of the selenides **303** with *m*CPBA was therefore performed under buffered conditions. Encouragingly, the crude ^{1}H NMR showed the formation of more alkene **304** relative to xanthone **1** under these conditions. The hydroxyl directed epoxidation of alkene **304** with buffered *m*CPBA gave a single diastereomer of the hydroxy epoxide **305** albeit in only 3% yield (*Scheme 117*). In view of the small amounts of **305** produced, I was unable to deduce its stereochemistry.



Scheme 117

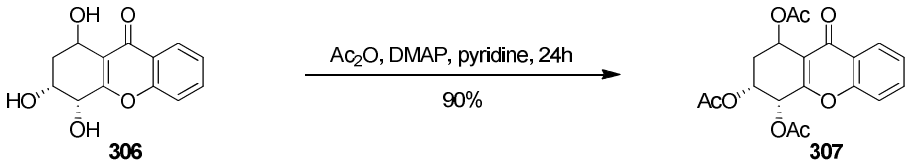
Since, alkene **304** was unstable to the epoxidation conditions, dihydroxylation of this alkene was investigated. Under Upjohn conditions, a single diastereomer of

trihydroxytetrahydroxanthone **306** was produced in 25% (over the 2 steps) (*Scheme 118*).



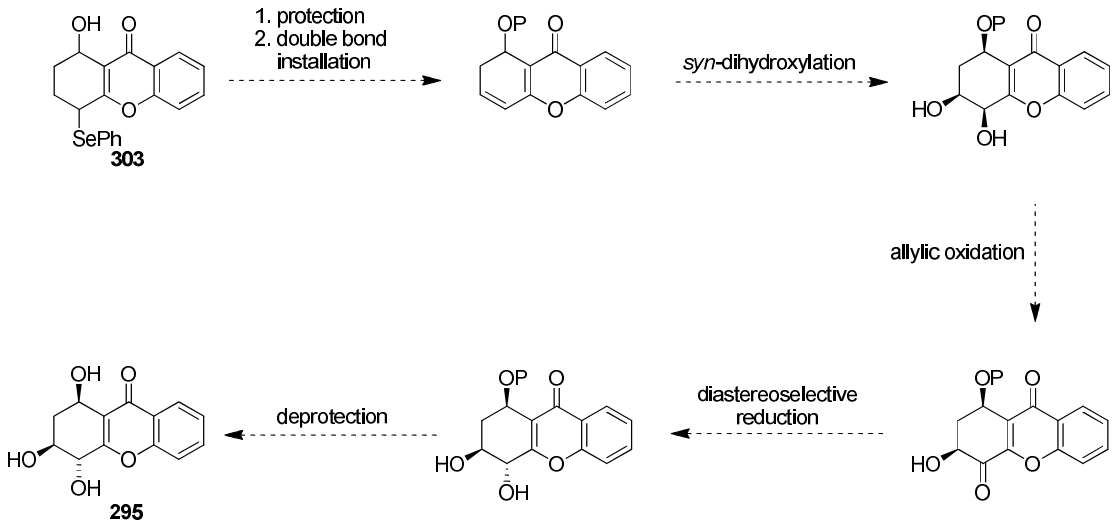
Scheme 118

The methylene hydrogens in tetrahydroxanthone **306** were multiplets in the ^{1}H NMR spectrum, making its stereochemical assignment using coupling constants difficult, leaving the stereochemistry unresolved. To elucidate its structure, it was triacetylated with acetic anhydride in the presence of catalytic DMAP and pyridine to obtain **307**. However, the methylene hydrogens of triacetoxy **307** were still multiplets, therefore, the stereochemistry could not be determined (*Scheme 119*).



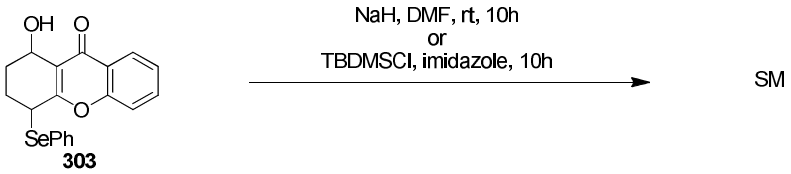
Scheme 119

Since the instability of alcohol **304** is due to rapid elimination of water to produce xanthone **1**, a revised strategy was devised to protect this alcohol before installation of double bond. It was anticipated that the protection of **102** could be achieved directly after the Luche reduction of **103**, or alternatively, after the formation of hydroxy selenide **303**. The same sequence of [2,3]-sigma tropic rearrangement, dihydroxylation, inversion of the allylic alcohol stereochemistry, and deprotection would provide triol **295** (*Scheme 120*). Clearly, a key use would be the diastereofacial selectivity of the dihydroxylation reaction with the all *syn* diastereomer being required.



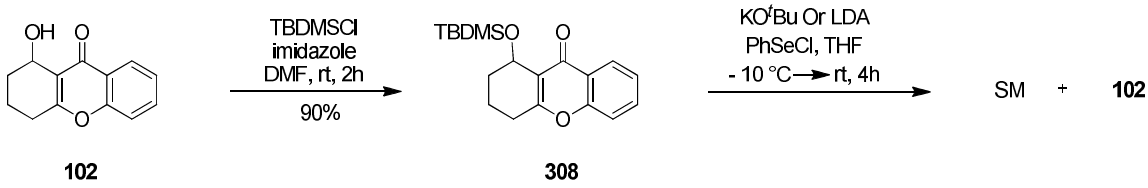
Scheme 120

Attempted protection of **303** with *tert*-butyldimethysilyl chloride in the presence of imidazole resulted only in the recovery of the starting material. Use of sodium hydride followed by the addition of *tert*-butyldimethysilyl chloride in DMF, also resulted in recovered starting material (*Scheme 121*).



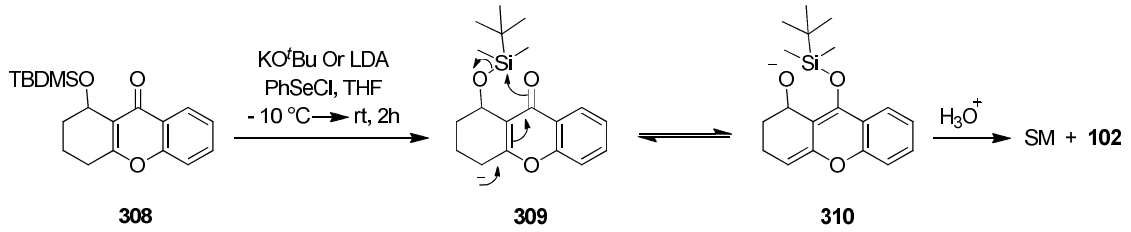
Scheme 121

In stark contrast, protection of alcohol **102** with *tert*-butyldimethysilyl chloride in the presence of imidazole proceeded smoothly in DMF to provide **308** in 90% yield.[150] Deprotonation of silyl protected **308** with KO^{t}Bu or LDA could be easily observed by a colour change from colourless to deep yellow upon addition of the base. However, the electrophilic quench with phenylselenyl chloride only resulted in the recovery of starting material **308** alongside quantities of alcohol **102** (*Scheme 122*).



Scheme 122

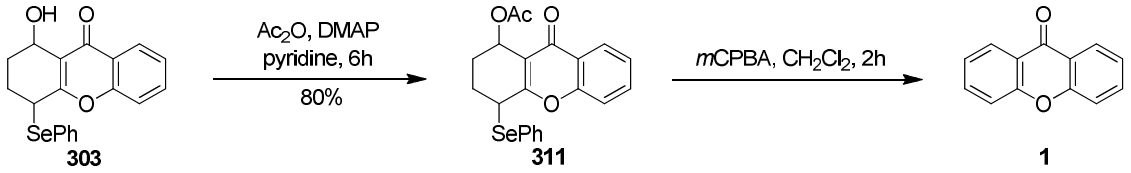
The enolate formed after deprotonation of **308** could trigger migration of the silyl protecting group, which after work up would account for the formation of alcohol **102** (*Scheme 123*).



308 **309** **310**

Scheme 123

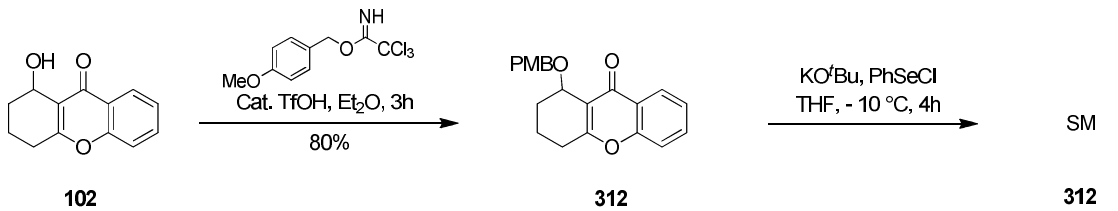
To avoid the migration of the silyl group, selenide **303** was treated with acetic anhydride in the presence of catalytic DMAP to obtain a diastereomeric mixture of acetoxy selenides **311** in good yield. Further oxidation of this selenide mixture with *m*CPBA resulted in the exclusive formation of xanthone **1** (*Scheme 124*).



303 **311** **1**

Scheme 124

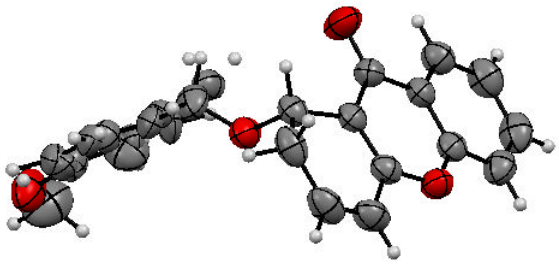
This result suggested a protecting group less prone to act as a good leaving group was required. Hence, a *p*-methoxybenzyl group was chosen to protect alcohol **102**. This protection was smoothly carried out using *p*-methoxy benzyl trichloroacetimidate in the presence of catalytic trifluoromethane sulfonic acid in diethyl ether.[151] However, further transformation of *p*-methoxybenzyl protected tetrahydroxanthone **312** into the corresponding selenide under the well developed conditions gave only the starting material back (*Scheme 125*).



102 **312** **312**

Scheme 125

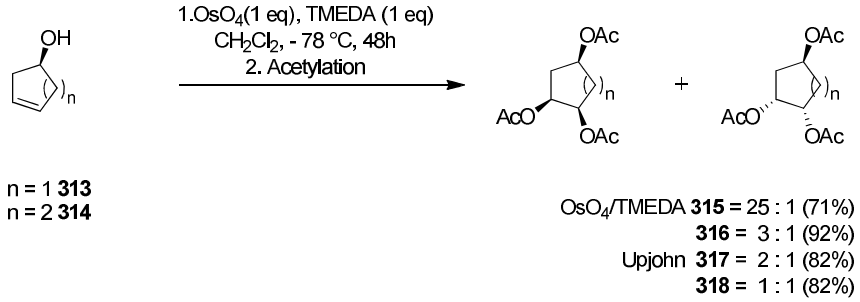
Alternatively, the protection of the diastereomeric mixture of selenides **303** was achieved by treating it with *para* methoxybenzyl trichloroacetimidate using the same proceedure. This selenide was oxidised with *m*CPBA to produce relatively stable alkene **321**. The slow evaporation of dichloromethane from a solution of **321** overnight left large crystals of the alkene whose structure was unambiguously deduced by X-ray crystallography (*Figure 41*) (*Scheme 127*).



321

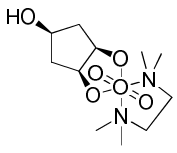
Figure 41 Single crystal X-ray structures of **321**

Donohoe *et al* have reported selective *syn* dihydroxylations of 5 and 6 membered rings of allylic and homo allylic alcohols in the presence of TMEDA and OsO_4 (*Scheme 126*).[152]



Scheme 126

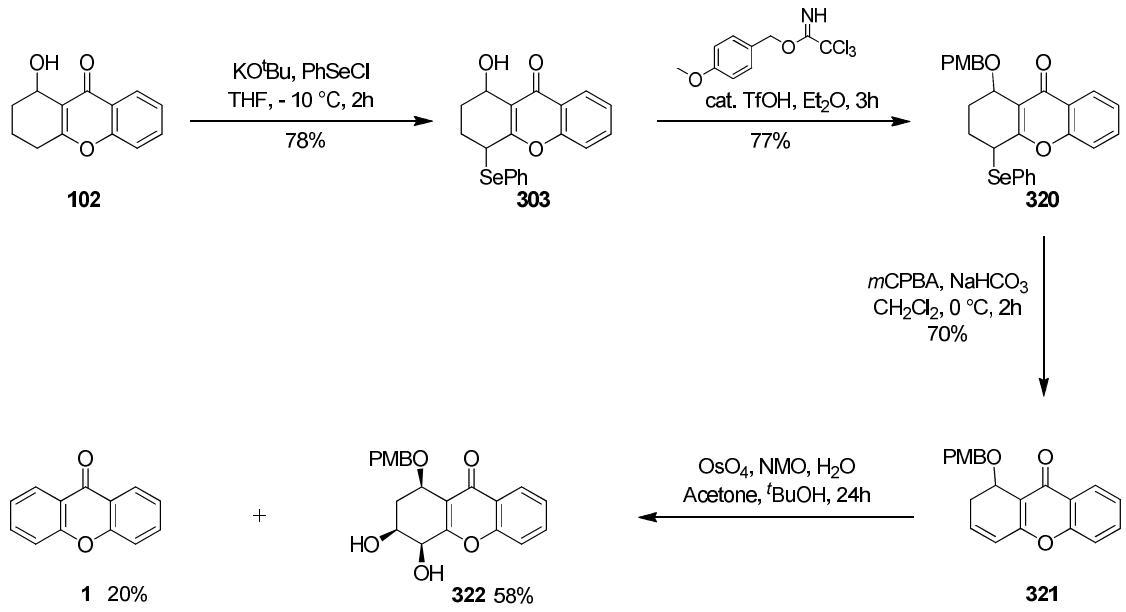
These workers obtained a single crystal structure of the osmate ester of **319** containing TMEDA and the intact osmate ester OsO_4. From the bond length seen in the complex, it has been proposed that there is a hydrogen bond between the alcohol and the bound TMEDA (*Figure 42*). Such H-bonding in the transition state, has been proposed to account for the facial selectivity of this reaction.[153, 154, 155]



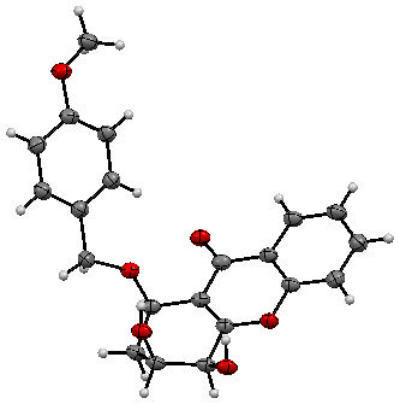
319

Figure 42

Interestingly, the dihydroxylation of alkene **321** under Upjohn conditions provided only a single diastereomer **322**. The structure of this diol was deduced to be all *syn* by single crystal X-ray diffraction (*Figure 43*). It was speculated that the *syn* selectivity could result from the hydrogen bonding provided by a water molecule between the PMB ether and the approaching OsO_4 complex (*Scheme 127*).



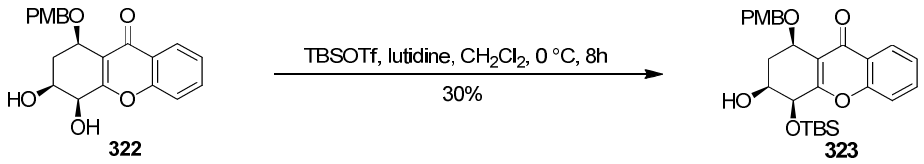
Scheme 127



322

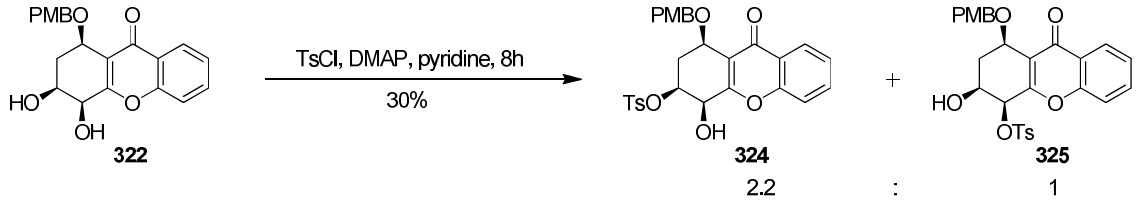
Figure 43 Single crystal X-ray structures of **322**

To invert the allylic hydroxyl stereocentre, selective protection of the hydroxyl group at C-3 of **322** was attempted. Treatment of diol **322** with one equivalent of *tert*-butyldimethylsilyl triflate in the presence of lutidine, resulted in protection of the wrong alcohol selectively in 30% yield (*Scheme 128*).[156] However, this reaction might be useful for the introduction of amicetose unit at this juncture.



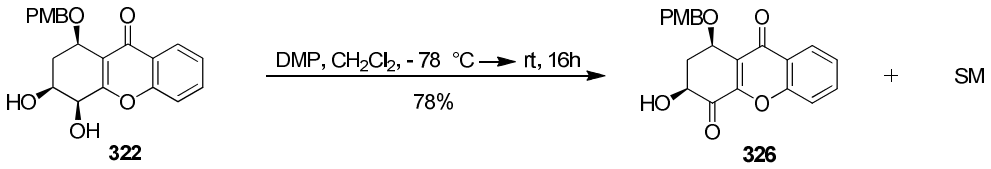
Scheme 128

Tosylation did not proceed in a selective manner rather **322** gave an inseparable mixture of **324** and **325** on treatment with one equivalent of *p*-toluenesulphonyl chloride in the presence of catalytic DMAP and pyridine in low yield (*Scheme 129*). The assignment of **324** as the major product was based on the downfield shift of the methine hydrogen at C-3.



Scheme 129

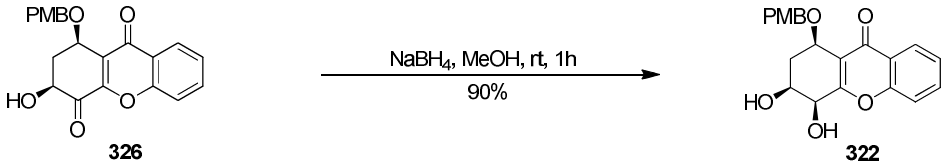
As selective protection of the secondary alcohol at C-3 of diol **322** was not achieved, it was decided to oxidise selectively the allylic alcohol instead. As before, use of manganese dioxide only resulted in recovery of the starting material. Use of one equivalent of Dess- Martin periodinane at room temperature gave a complex mixture of products.[157] Finally, the oxidation of **322** with half an equivalent of Dess Martin periodinane at –78 °C slowly warmed overnight gave the ketone **326** along with the recovery of the diol **322** in 78% yield based on recovered starting material (*Scheme 130*).



Scheme 130

It is known that α-hydroxy ketones can be reduced to *trans* diols with sodium borohydride by delivery of the hydride from the face of the hydroxyl group through complex formation.[158] However, when ketone **326** was reduced with sodium

borohydride both at low and ambient temperatures, only the *syn* diol **322** was obtained in 90% yield (*Scheme 131*).

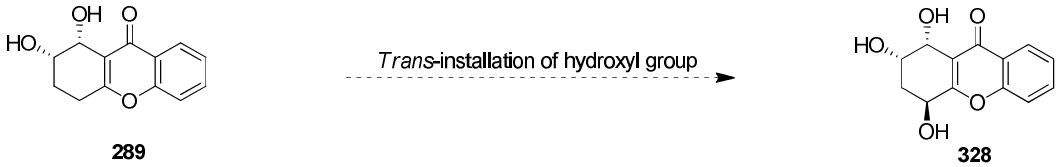


Scheme 131

Additional attempts to realise the required inversion with DIBAL and $LiAlH_4$ at low temperatures gave only complex mixture of products. Time and material constraints prohibited us from exploring other methods for this reduction.

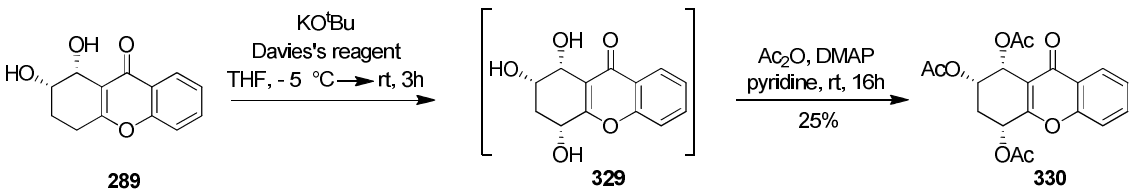
3.3.2 1,2,4-Trisubstituted tetrahydroxanthones

To make 1,2,4-trihydroxyl groups using the same general strategy, it was anticipated that diol **289** could be deprotonated to the trianion and quenched with a single equivalent of Davis reagent which would provide the fully functionalised A-ring of kibdelones (*Scheme 132*). Conditions for achieving stereoselectivity in favour of the desired diastereomer would need to be explored.



Scheme 132

Treatment of diol **289** with three equivalents of KO^{t}Bu at lower temperature, followed by slow warming up to 10 °C before quenching with Davis reagent provided a mixture of products which, without further purification, were subjected to acetylation by treatment with acetic anhydride in the presence of DMAP. This led to the isolation of **330** in 25% over the two steps. No other identifiable products were isolated (*Scheme 133*). The stereochemical assignment of **330** was deduced through NMR analysis.



Scheme 133

The structure of kibdelone C **57** is well established *via* the total syntheses by two independent research groups.[92, 94] Comparison of the coupling constants of the hydrogens of the A-ring of **330** with literatures values for kibdelone C, revealed substantial differences especially between H_{3a}/H_{3b} and H_4 (*Table 2*). This assignment was supported by consideration of the dihedral angles expected for **330** through application of the Karplus equation (*Table 2*).

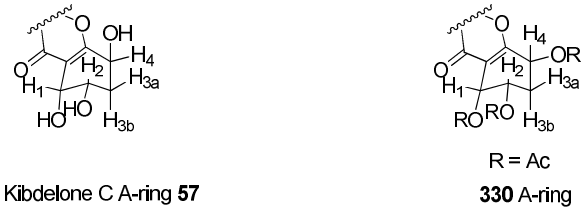
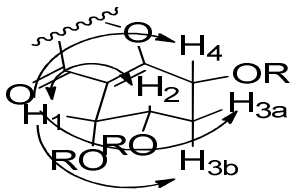


Figure 43

Table 2. Comparison of *J* values of A-ring hydrogens of Kibdelone C 57 and 330

57	*J* [Hz] (lit)	**188**	*J* [Hz]
J(1, 2)	3.9	*J*(1, 2)	3.6
J(1, 3b)	≤1.0	*J*(1, 3b)	
J(2, 3a)	12.0	*J*(2, 3a)	9.6
J(2, 3b)	3.0	*J*(2, 3b)	3.6
J(3a, 3b)	13.3	*J*(3a, 3b)	
J(3a, 4)	4.5	*J*(3a, 4)	9.6
J(3b, 4)	1.8	*J*(3b, 4)	

NOe studies were also conducted on **330**. Key NOe's are detailed in Table 3. Based on this **330** was tentatively assigned as all *syn*-triacetoxy tetrahydroxanthone. The tri-deprotonation of dihdydroxy tetrahydroxanthone **289** with three equivalents of KO^{t}Bu resulting in a trianion interacting with counter ions on the same face resembling to a metal surface followed by electrophilic quench could result in all the *syn*-selectivity.



R = Ac

330 A-ring

Figure 44

Table 3. NOe studies conducted on 330

Irradiated	1 (%)	2 (%)	3ab (%)	4 (%)
1	-	3.3	0.9	0.0
2	3.6	-	3.4	1.9
4	0.0	2.2	2.8	-

3.4 Biological evaluation of synthesised hydroxy tetrahydroxanthones

With a range of dihydroxy and trihydroxytetrahydroxanthones in hand, it was sought to test the biological activity of these compounds. I was especially interested in exploring their activity in anti-austerity assays, the biological screens used to discover the kigamicins themselves (Chapter 1).[68]

It was sought to understand the significance of the extent of unsaturation, oxygenation and stereochemistry of the A-ring of the tetrahydroxanthones in relation to this biological activity. The effects of all the dihydroxanthones, dihydroxy, and trihydroxy tetrahydroxanthones synthesised in the laboratory were evaluated against human pancreatic cancer cell line (PANC-1), grown separately in nutrient rich medium (NRM) and nutrient deprived medium (NDM). These assays were kindly conducted by a laboratory co-worker, Penny Turner at the Peninsula Medical School.

Previously, Turner *et al* have shown that **331** has considerable activity against PANC-1 cells[89] hence it was interested to ascertain if materials containing functionality in the A-ring, more closely resembling the structure of the kigamicins, might be more active. The data represent the results of testing in triplicate. Compounds were initially tested at three concentrations (in triplicate), to facilitate rapid screening. Retesting of actives being repeated at a wider range of concentrations.

A total of 9 compounds (**102**, **228**, **234**, **279**, **280**, **288**, **299**, **306**, **330**) produced in this thesis were evaluated. The key findings are detailed below. However, it is clear that these molecules at best display very weak activity.

Diol **299** when tested in nutrient rich medium (NRM) did not show any bioactivity against the pancreatic cancer cells (PANC-1). Interestingly, in the nutrient deprived medium (NDM) it selectively inhibited 10% of the pancreatic cancer (PANC-1) cells' survival at the highest concentration tested (*Figure 45*).

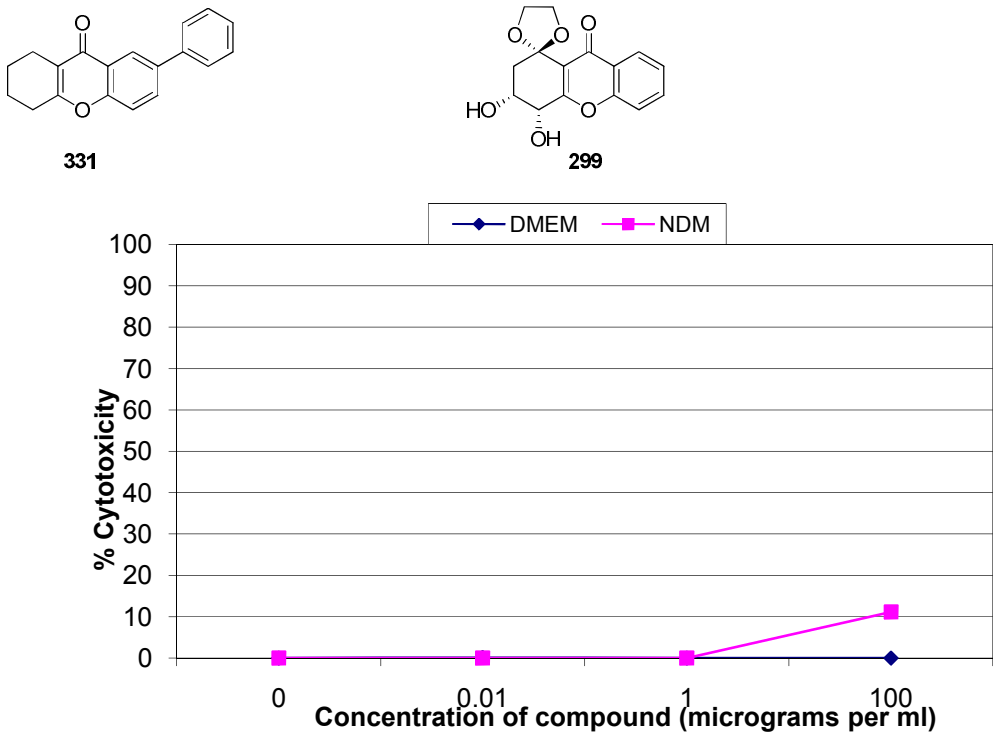


Figure 45

Trans and *cis* 1,4-diacetoxy tetrahydroxanthone showed very contrasting bioactivities against the pancreatic cancer cells (PANC-1) both in NRM and NDM. *Trans* (*R, R*)-1,4-diacetoxy tetrahydroxanthone **280** did not show any activity either in NRM and NDM against the pancreatic cancer cells (PANC-1) (*Figure 46*).

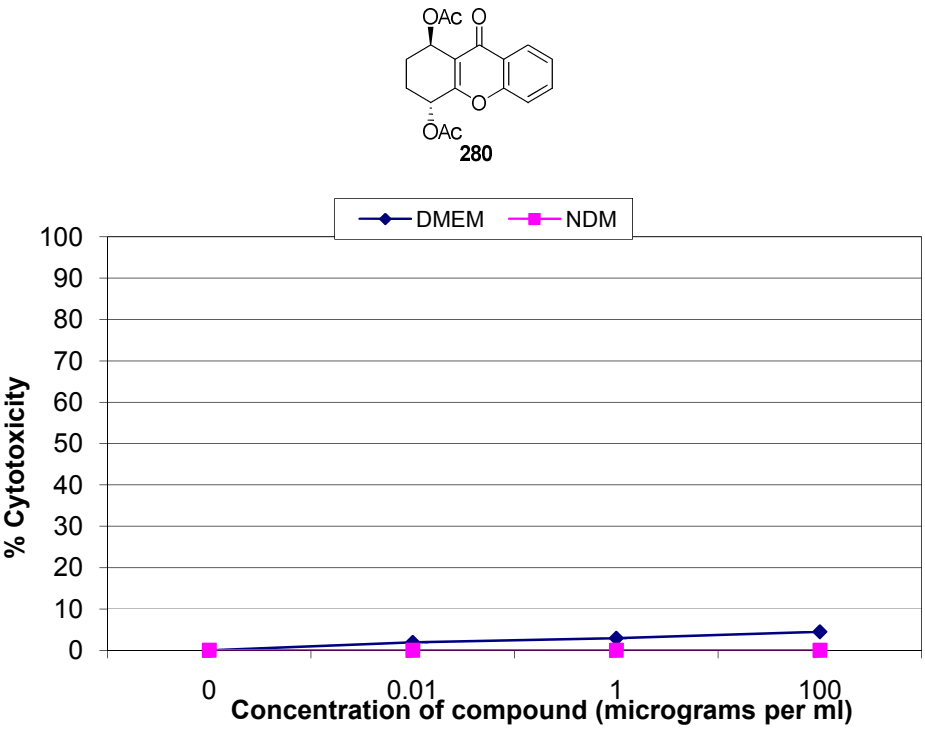


Figure 46

However, the *cis* (*R, S*)-1,4-diacetoxy tetrahydroxanthone **279** in contrast showed good selectivity, causing 36% cytotoxicity to pancreatic cancer cells (PANC-1) only in NDM and no biological activity was observed in the NRM (*Figure 47*).

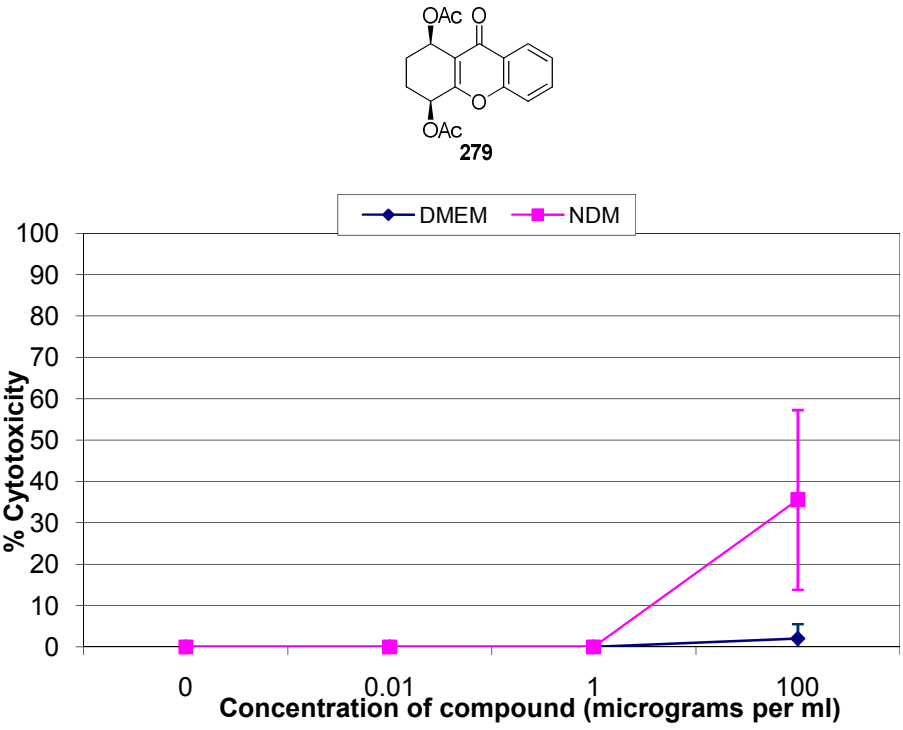


Figure 47

Dihydroxanthone **288** selectively killed PANC-1 cells under nutrient deprived conditions (NDM), and was inactive in the nutrient rich medium (NRM) (*Figure 48*).

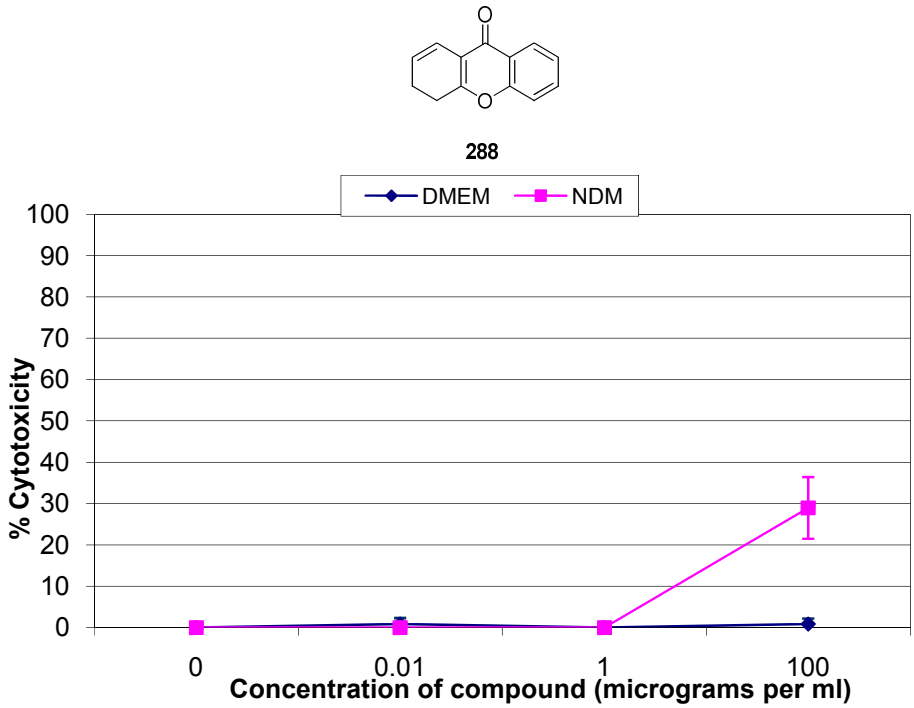


Figure 48

The inhibition of PANC-1 cells survival was enhanced to 85% when 1mg/mL of dihydroxanthone was used in the NDM. However, at such high concentration the inhibition of PANC-1 cells survival in NRM was also raised to 22%. From this plot an IC_{50} = 3.018 mM value was determined (*Figure 49*).

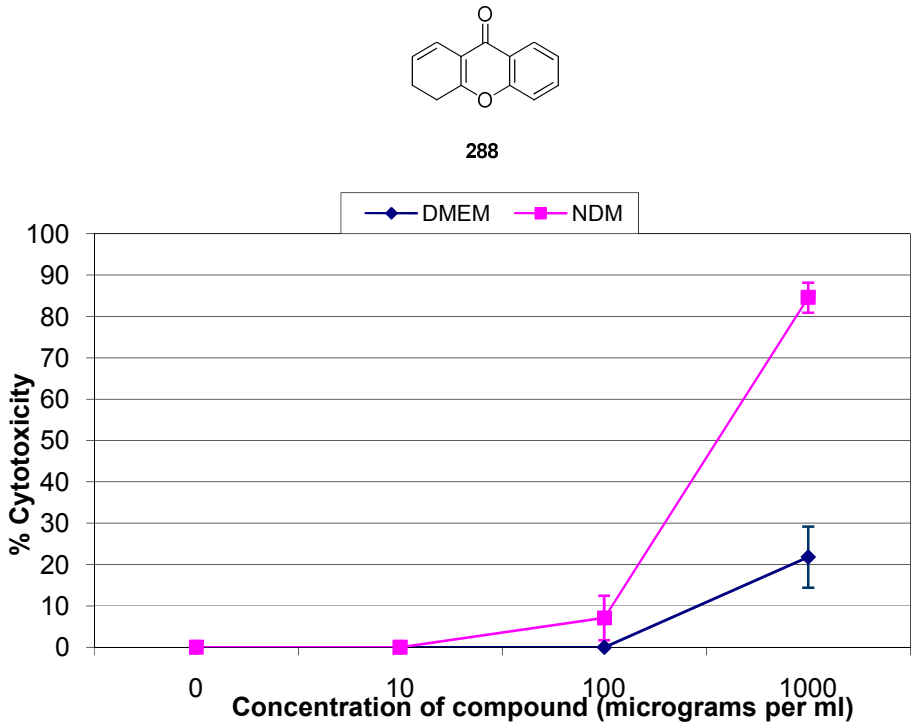
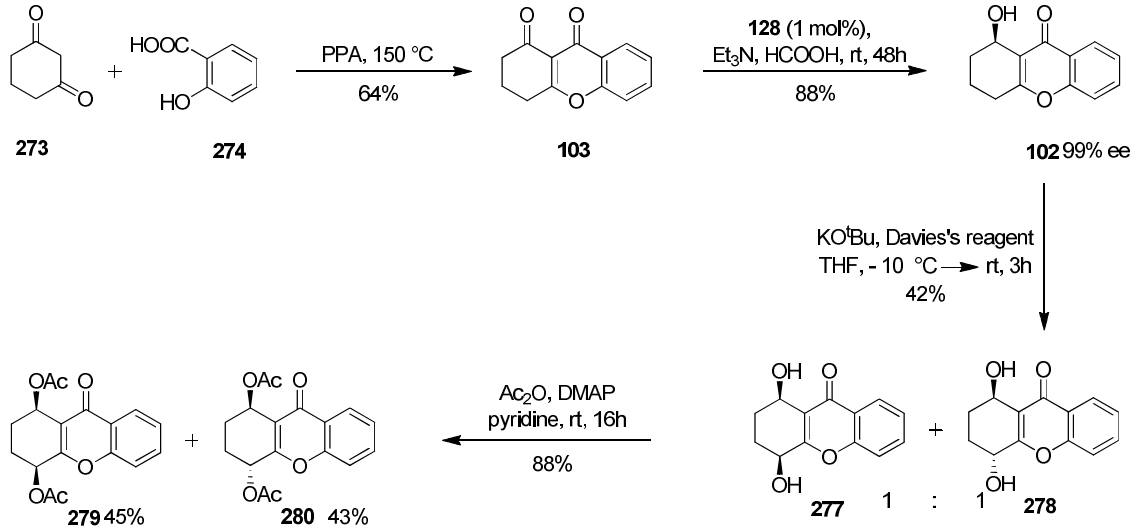


Figure 49

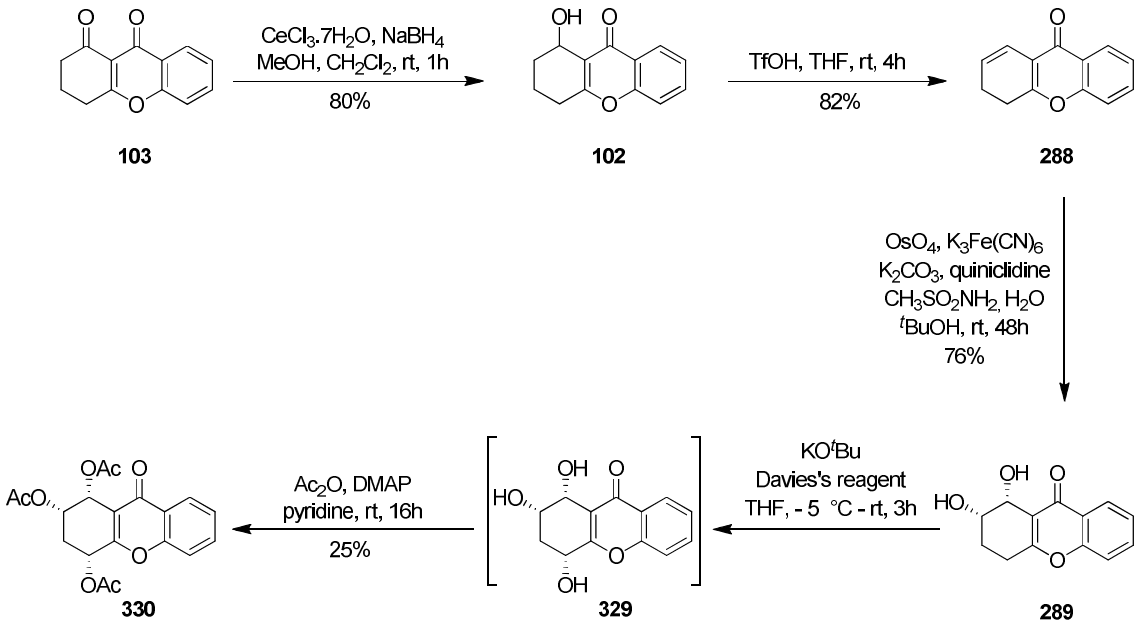
3.5 Conclusions and Future work

I have developed a short enantioselective route to *cis*-**277** and *trans*-**278** bearing the diol functionality found in the tetrahydroxanthone fragment of 1,3,5-trihydroxy-8-beta-D-glucopyranosyl, puniceaside B, puniceaside C, albofungins, and simaomicins in 3 linear steps from known ketone **103** and in 33% overall yield (*Scheme 134*). Excellent enantiocontrol was achieved in this sequence using an asymmetric ketone transfer hydrogenation as the key step. Improvements in the diastereoselectivity of the dihydroxyltion are still needed and could be a focus of future work. Interestingly, only **279** displays weak activity against PANC-1 cells grown under nutrient deprived conditions (*Figure 47*).



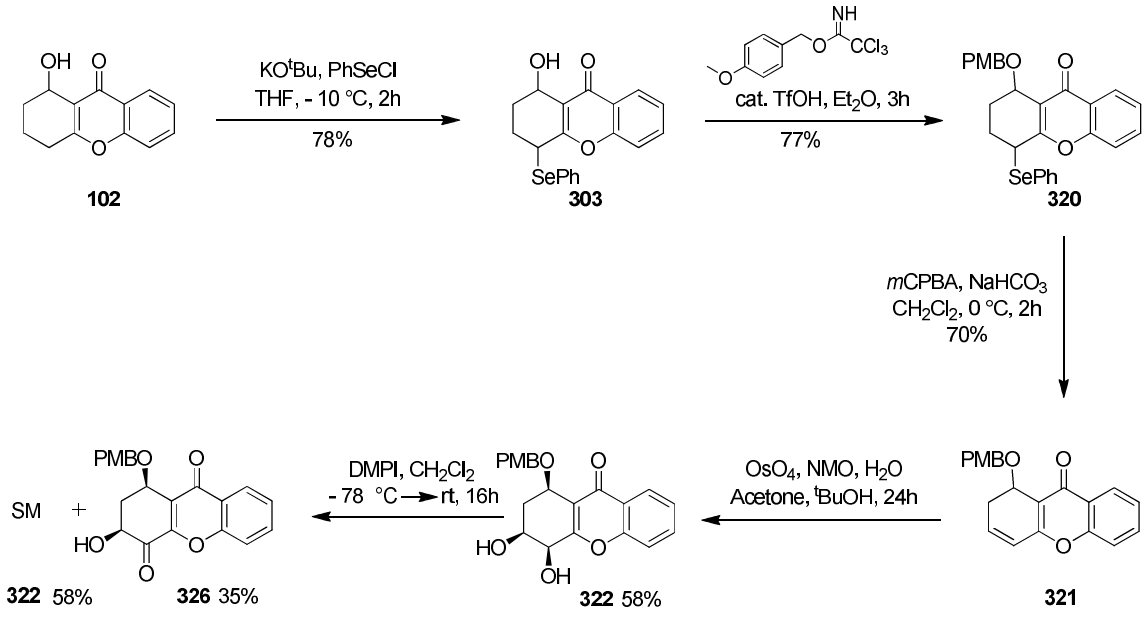
Scheme 134

A short route to the fully functionalised A-ring of the tetrahydroxanthone fragment of kibdelones and isokibdelones has been developed which again exploits enolate hydroxylation. However, in this instance, the wrong relative stereochemistry at C-4 was produced. Future work could focus on selective inversion of this stereocentre, after diol protection, or alternatively, diol protection before hydroxylation to overturn the facial bias of the enolate quench i.e from top face (*Scheme 135*).



Scheme 135

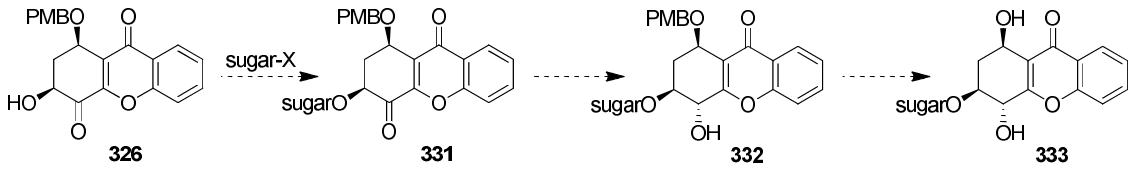
An attempt to develop a synthetic route to the fully functionalised A-ring of the tetrahydroxanthone fragments of actinoplanones and kigamicins has also been described. The use of PMB protecting group was essential for success in the sequence. Most interestingly, a *syn*-selective dihydroxylation of alkene **321** was observed. Ketone **326** is potentially a useful intermediate in the synthesis of kigamicin analogues (*Scheme 136*).



Scheme 136

Future work might involve the synthesis of a fully functionalised A-ring of kigamicins **67-71** through glycosidation of ketone **326** followed by diastereoselective reduction of

331 and deprotection. This chemistry might help pave the way to the total synthesis of kigamicins themseleves (*Scheme 137*).



Scheme 137

Based on the biological results it would be of interest to synthesise analogues of *syn* 1,4-diacetoxy tetrahydroxanthones such as **334** bearing an aryl group. This might lead to further improve the biological activities against PANC-1 cells grown under NDM conditions (*Figure 50*).

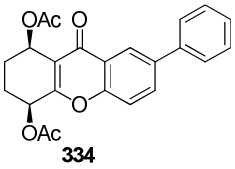


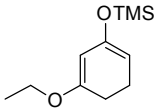
Figure 50

CHAPTER 4:
EXPERIMENTAL

GENERAL

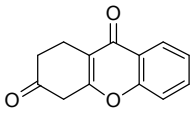
All reactions were performed under dry nitrogen atmosphere in flame dried glassware unless otherwise stated. Anhydrous solvent were purchased from Aigma-Aldrich in Sure/Seal^{TM} bottles. All the other solvents were used as received or purified by standard protocols. Petroleum ether refers to the fraction which boils in the range 40-60 °C. Commercially available starting materials were used without further purification. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}), visualised by $UV_{254\ nm}$ then stained with potassium permanganate or ceric ammonium molybdate solution. Flash chromatography was performed using Matrex silica 60. Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported as observed. Single crystal X-ray diffraction data were obtained using a Siemens SMART XRD system or an Oxford Diffraction Gemini XRD system. Optical rotations were measured with a AA1000 polarimeter and are quoted in 10^{-1} deg cm^2 g^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX (300, 400, 500 or 600 MHz) spectrometers. Chemical shifts are reported in parts per million relative to the standard tetramethylsilane for ^1H NMR and to the centre line of the chloroform triplet at 77.2 ppm for ^{13}C NMR. The peak multiplicities were specified as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint). Multipet coupling constants (*J*) are reported in Hertz. Low resolution mass spectra were recorded on an Esquire 2000 platform with electrospray ionisation. High resolution mass spectra were obtained using a Bruker MicroTOF spectrometer.

(5-Ethoxycyclohexa-1,5-dienyloxy)trimethylsilane (188)[95]



To a flask containing lithium diisopropylamide (3.00 mL, 6.00 mmol) in THF (15 mL) at – 78 °C was added 3-ethoxycyclohexenone (0.67 mL, 5 mmol). After 10 min, trimethysilyl chloride (0.75 mL, 6.00 mmol) was added and the reaction mixture was stirred at – 78 °C for 1 hour. The reaction mixture was then poured into a cold saturated solution of $NaHCO_3$ (10 mL), extracted with Et_2O (20 mL), washed with H_2O (3 × 10 mL) and brine (3 × 10 mL). The organic fraction was dried over $MgSO_4$ and concentrated *in vacuo* to give **188** (1.06 g, 100%) as a pale yellow oil used without further purification. IR (thin film) 2883, 1657, 1610, 1380, 1252, 1158 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.69 (1H, s, (=C*H*C(OEt)), 4.52 (1H, t, *J* = 1.7 Hz, C*H*CH_2), 3.76 (2H, q, *J* = 7.0 Hz, OC*H*$_2CH_3$), 2.19 (4H, m, C*H*$_2$C*H*$_2$), 1.31 (3H, t, *J* = 7.0 Hz, C*H*$_3CH_2O$), 0.18 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 160.2 (EtO*C*), 149 (TMSO*C*), 95.1 (*C*H=C(OTMS)), 94.3 (EtOC=*C*H), 62.8 (O*C*H_2CH_3), 27.5 (CH_2), 21.8 (CH_2), 14.4 (CH_2*C*H_3), 0.2 (3 × CH_3) ; MS (ES^+) *m/z* = 212 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{11}H_{21}O_2Si$ $[M+H]^+$: 212.1231; found: 212.1231. The data agree with that in literature.

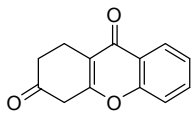
1,2-Dihydro-4*H*-xanthene-3,9-dione (192)



To a solution of **188** (1.11 g, 5.23 mmol) at –78 °C in THF (10 mL) was added methyllithium (3.26 mL, 5.23 mmol). The resulting solution was stirred a – 78 °C for 1 hour, and then allowed to warm to room temperature over 2 hours. The reaction was cooled again to –78 °C before the addition of *o*-acetoxybenzoyl chloride (490 mg, 2.61 mmol). The reaction mixture was stirred at –78 °C for 2 hours and then gradually warmed to room temperature overnight. Saturated NH_4Cl solution (10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic fractions were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. It was then dissolved in HCl and AcOH (1: 20, 18 mL) and heated to 60 °C for 1 hour. The mixture was poured into ice water and extracted with toluene (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 10 mL), brine (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain an orange solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **192** (279 mg, 52%) as a yellow solid. M.p. 159 – 160 °C; IR (thin film) 2954, 1715, 1629, 1462, 1154, 773 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 – 8.04 (1H, m, Ar), 7.52 – 7.47 (1H, m, Ar), 7.26 – 7.21 (2H, m, Ar), 3.38 (2H, s, CH_2CO), 2.81 (2H, t, *J* = 6.9 Hz, COC*H*$_2CH_2$), 2.48 (2H, t, *J* = 6.9 Hz,

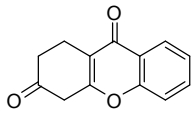
$COCH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 204 (CO), 176.4 (CO), 159.0 (C, Ar), 156.2 (C, Ar), 133.6 (CH, Ar), 125.9 (CH, Ar), 125.1 (CH, Ar), 123.0 (CH, Ar), 117.8 (C, Ar), 117.7 (C, Ar), 41.7 (CH_2), 38.2 (CH_2), 18.2 (CH_2) ; MS (ES^+) *m/z* = 215 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{13}H_{11}O_3$ $[M+H]^+$: 215.0708; found: 215.0705.

3,4-dihydro-2H-xanthene-1,9-dione from 194



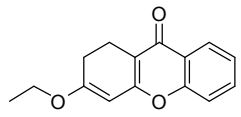
To a mixture of HCl (conc.) and glacial AcOH (1: 20, 5.40 mL), was added **194** (500 mg, 1.80 mmol). The reaction mixture was heated to 60 °C for 1 hour and the worked up as above (p 109) to give **192** (327 mg, 85%). Data as previously reported.

3,4-Dihydro-2H-xanthene-1,9-dione from 195



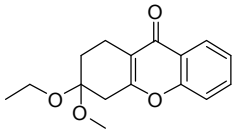
To a mixture of HCl (conc.) and glacial AcOH (1: 20, 3 mL), was added **195** (250 mg, 1.02 mmol). The reaction mixture was heated to 60 °C for 1 hour and then worked up and purified as above (p109) to give **192** (207 mg, 95%). Data as previously reported.

3-Ethoxy-1,2-dihydroxanthen-9-one (193) and 3-Ethoxy-1,2,3,4-tetrahydroxanthen-3-methoxy-9-one (194)



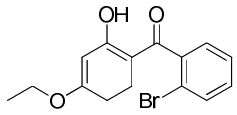
Sodium metal (15.2 mg, 0.65 mmol) was dissolved in methanol (5 mL) at room temperature. To this solution was added **191** (200 mg, 0.662 mmol) at 0 °C. The clear yellow solution slowly turned dark yellow and was stirred for 16 hours. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layers were washed with H_2O (3 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a thick yellow oil. Column chromatography (ethyl acetate : petroleum ether, 10 : 90) furnished **193** as a white solid (64 mg, 40%) and **194** as yellow solid (56 mg, 35%). (**193**) M.p. 105 – 106 °C; IR (thin film) 2977, 1653, 1595, 1420, 1178, 780 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.08 – 8.05 (1H, m, Ar), 7.47 – 7.40 (1H, m, Ar), 7.25 – 7.17 (2H, m, Ar), 5.20 (1H, s, =C*H*COEt), 3.87 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.77 (2H, t, *J* = 9.0 Hz, $EtOCCH_2$), 2.37 (2H, t, *J* = 9.0 Hz, $EtOCCH_2CH_2$), 1.28 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); δ_C (300 MHz, $CDCl_3$) 169.1 (CO), 162.2 (C, Ar), 154.9 (C, Ar),132.1 (CH, Ar), 125.1 (CH, Ar), 124.0 (CH, Ar), 123.0 (C, Ar), 117.8 (CH, Ar), 108.0 (C, Ar), 89.8 (CH=), 63.8 (OCH_2CH_3) 26.9 ($EtOCCH_2CH_2$), 17.9

(CH_2CH_2C=), 15.0 (OCH_2CH_3); MS (ES^+) *m/z* = 243 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1021; found: 243.1018.



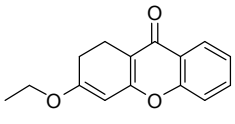
M.p. 110 – 111 °C; IR (thin film) 2954, 1610, 1466, 1096, 712 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.19 – 8.16 (1H, m, Ar), 7.61 – 7.56 (2H, m, Ar), 7.36 – 7.30 (1H, m, Ar), 3.54 (2H, m, OCH_2CH_3), 3.28 (3H, s, OCH_3), 2.93 (2H, s, (OEt)(OMe)CCH_2C=), 2.61 (2H, t, *J* = 7.2 Hz, (OEt)(OMe)CCH_2CH_2), 1.98 (2H, t, *J* = 7.2 Hz, CH_2CH_2C=), 1.19 (3H, m, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 177.4 (CO), 169.7 (C, Ar), 160.5 (C, Ar), 132.2 (CH, Ar), 125.6 (CH, Ar), 124.4 (CH, Ar), 123.1 (C, Ar), 117.6 (CH, Ar), 117.4 (C, Ar), 99.1 (C(OMe)(OEt)), 64.5 (OCH_2CH_3), 48.5 (OCH_3), 38.5 ((OEt)(OMe)CCH_2C=), 28.5 ((OEt)(OMe)CCH_2CH_2), 22.0 ((OEt)(OMe)CCH_2CH_2), 17.0 (OCH_2CH_3); MS (ES^+) *m/z* = 275 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1283; found: 275.1274.

5-(*o*-Bromobenzoyl)-3-ethoxycyclohexenone (199)



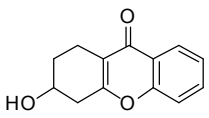
To a solution of **188** (7.72 mL, 36.4 mmol) in THF (15 mL) at - 78 °C was added methyllithium (1.6 M in THF), (22.7 mL, 36.4 mmol) dropwise over 5 minutes. The solution was warmed to room temperature over 2 hours and stirred for a further 2 hours before cooling to -78 °C. To the yellow solution was added the acid *o*-bromobenzoyl chloride (2.52 mL, 18.2 mmol) and the reaction mixture was warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution (5 mL), slowly poured into H_2O (25 mL), extracted with ethyl acetate (3 × 15 mL) and washed with brine (3 × 10 mL). This was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give yellow oil. Column chromatography (diethyl lether : petroleum ether, 20 : 80) furnished **199** (5.0 g, 80%) as a thick yellow oil. IR (thin film) 2991, 1593, 1377, 1198, 761 cm^{-1}; δ_H (400 MHz $CDCl_3$) 15.55 (1H, s, OH), 7.51 – 7.49 (1H, m, Ar), 7.28 – 7.24 (1H, m, Ar), 7.22 – 7.19 (1H, m, Ar), 7.16 – 7.10 (1H, m, Ar), 5.30 (1H, s, =C*H*CO), 3.86 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 2.25 – 2.16 (4H, m, 2 × CH_2), 1.21 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); δ_C (75 MHz) 192.7 (=CH*C*OCH), 176.4 (CH*C*OAr), 170.8 (C, Ar), 136.5 (C, Ar), 132.4 (CH, Ar), 131.2 (CH, Ar), 129.6 (CH, Ar), 127.4 (CH, Ar), 121.3 (C, Ar), 103.8 (EtOC=), 100.8 (CO*C*H=), 64.6 (OCH_2CH_3), 29.0 (=CCH_2CH_2), 22.6 (CH_2CH_2CH), 14.1 (OCH_2CH_3); MS (ES^+) *m/z* = 345 $[M(^{81}Br)+Na]^+$, 50%), 343 $[M(^{79}Br)+Na]^+$, 50%); HRMS (ES^+): calcd. for $C_{15}H_{15}O_3$ $^{79}BrNa$ $(M+Na)^+$: 345.0097; found 345.0103.

Synthesis of 3-Ethoxy-1,2-dihydroxanthen-9-one (193) using palladium catalysed process.



To a solution of **199** (500 mg, 1.50 mmol) in dioxane (7 mL) were added $Pd_2(dba)_3$ (34.0 mg, 0.03 mmol), Cs_2CO_3 (1.11 g, 3.30 mmol) and XPhos (44.0 mg, 0.09 mmol). The mixture was heated to reflux for 18 hours. After allowing the mixture to cool to room temperature, it was filtered through celite washing with dichloromethane (3 × 15 mL). The organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 10 : 90) furnished **193** (217 mg, 58%) as yellow solid. Data as previously described.

1,2,3,4-Tetrahydro-3-hydroxyxanthen-9-one (200)

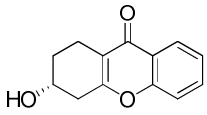


To a stirred solution of **192** (2.32 g, 10.8 mmol) in ethanol and dichloromethane (1:1, 20 mL) at 0 °C was added sodium borohydride (479 mg, 12.9 mmol). The reaction mixture was stirred for 1 hour and then diluted with saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with dichloromethane (3 × 10 mL), washed with brine (3 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a white crystalline solid that was purified by recrystallizations from methanol to yield **200** (2.20 g, 95%). M.p. 151 – 152 °C; IR (thin film) 3390, 2950, 1603, 1466, 1163, 761 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 – 8.05 (1H, m, Ar), 7.52 – 7.46 (1H, m, Ar), 7.26 – 7.26 (2H, m, Ar), 4.18 (1H, m, C*H*OH), 2.92 – 2.85 (1H, m, =CC*H*HCHOH), 2.72 – 2.44 (2H, m, C*H*HCH(OH)CH*H*), 2.08 (1H, d, *J* = 3.9 Hz, CH*H*CH(OH)CH_2), 1.89 – 1.67 (2H, m, CH_2CH_2C=); δ_C (150 MHz, $CDCl_3$) 177.3 (CO), 161.1 (C, Ar), 156.1 (C, Ar), 133.3 (CH, Ar), 125.7 (CH, Ar), 124.6 (CH, Ar), 123.0 (C, Ar), 117.6 (CH Ar), 117.5 (C, Ar), 65.5 ((OH)CH), 34.3 (OHCH*C*H_2C=), 29.7 (OHCH*C*H_2CH_2), 17.9 (CH_2CH_2C=); MS (ES^+) *m/z* = 239 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{12}H_{12}O_2Na$ $[M+Na]^+$: 239.0684; found: 239.0679.

Crystal Data. $C_{13}H_{12}O_3$, M = 216.23, triclinic, a = 7.1242(6) Å, b = 7.7029(5) Å, c = 9.8422(8) Å, α = 82.210(6)°, β = 72.540(7)°, γ = 79.158(6)°, V = 504.22(7) $Å^3$, T = 100(2), space group P-1 (no. 2), Z = 2, μ(MoKα) = 0.101, 6397 reflections measured, 3317 unique (R_{int} = 0.0368) which were used in all calculations. The final wR_2 was 0.1418 (all data) and R_1 was 0.0591 (>2sigma(I)).

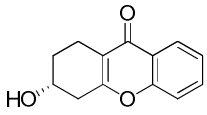
Asymmetric reduction of (*R*)-1,2,3,4-Tetrahydro-3-hydroxyxanthen-9-one (200)

Using Noyori's catalyst



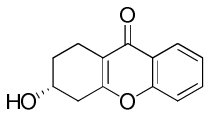
A solution of Noyori's catalyst monomer **206** (4 mg, 0.05 mmol) in formic acid and triethylamine 5 : 2 (0.25 mL), was stirred at 28 °C for 30 min. **193** (107 mg, 0.50 mmol) was added and the reaction mixture was stirred for 48 hours at the same temperature. The reaction mixture was filtered through silica, washed with ethyl acetate and hexane 1 : 1 (3 × 15 mL) and concentrated *in vacuo* to obtain a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **200** as a white solid. HPLC analysis on Chiracel OD+1 (90 : 10 hexane : isopropanol 1 mL/min) showed a major enantiomer at 20.3 min (66.9 A%) and the minor one at 31.5 min (33.1 A%) ee 33%; Data as previously reported.

Using Wills catalyst



A solution of catalyst **207** monomer (6.20 mg, 0.01 mmol) in formic acid and triethylamine 5 : 2 (0.50 mL) was stirred at 28 °C for 30 min. **193** (214 mg, 1.00 mmol) was added and the reaction mixture was stirred for 48 hours at the same temperature. The reaction mixture was filtered through silica, washed with ethyl acetate and hexane 1 : 1 (3 × 15 mL) and concentrated *in vacuo* to obtain a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **200** as a white solid. HPLC analysis on Chiracel OD+1 (90 : 10 hexane : isopropanol 1 mL/min) showed a major enantiomer at 15.0 min (78.51 A%) and the minor one at 23.0 min (21.49 A%) ee 57.6%; Data as previously reported.

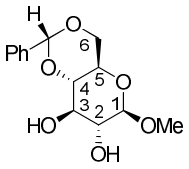
Using CBS reduction



To a stirred solution of **193** (511 mg, 1.05 mmol) in THF (5 mL) was added (*S*)-3,3-diphenyl-1-methylpyrrolidino[1,2-c]-1,2,3-oxazaborole (**203**) (792 µL, 0.792 mmol). The reaction mixture was cooled to – 15 °C followed by the addition of borane-dimethyl sulphide complex (528 µL, 1.05 mmol) dropwise. The reaction mixture was stirred for 3 hours before quenching with methanol at – 20 °C. The reaction mixture was then poured into ethyl acetate (15 mL) and washed with H_2O and HCl (2 : 1, 5 mL), H_2O (5 mL), saturated $NaHCO_3$ (5 mL) and saturated NaCl (10 mL). The organic fraction was dried over $MgSO_4$, and concentrated *in vacuo* to obtain a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **200** (136 mg, 60%) as a white solid. HPLC on Chiracel OD+1 (90 : 10 hexane : isopropanol, 1 mL/min) showed the major enantiomer

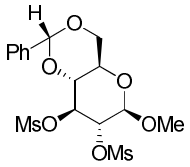
at 20.6 min (55.4 A%) and the minor one at 31.7 min (44.6 A%) ee 10%; Data as previously reported.

Methyl-4,6-*O*-benzylidene-β-D-erythro-hexopyranoside (209)[104]



To a solution of methyl-β-D-glucopyranoside (**208**) (5.00 g, 25.7 mmol) in dry acetonitrile (35 mL) was added benzaldehyde dimethylacetal (4.25 mL, 28.2 mmol) followed by iodine (652 mg, 2.57 mmol). The mixture was stirred for 1 hour before the evaporation of the solvent *in vacuo* to provide pure **209** (6.52 g, 90%), as white needle like crystals. IR (thin film) 2981, 1452, 1388, 1038, 694 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.88 – 7.61 (2H, m, Ar), 7.51 – 7.26 (3H, m, Ar), 5.55 (1H, s, C*H*Ph), 4.36 (1H, dd, *J* = 5.0, 10.5 Hz, H_{6a}), 4.33 (1H, d, *J* = 8.0 Hz, H_1), 3.82 (1H, t, *J* = 9.0 Hz, H_3), 3.80 (1H, t, *J* = 10.5 Hz, H_{6b}), 3.59 (3H, s, OCH_3), 3.48 – 3.42 (3H, m, H_2, H_4, H_5); δ_C (75 MHz) 137.5 (C, Ar), 129.2 (2 × CH, Ar), 128.2 (CH, Ar), 126.6 (2 × CH, Ar), 104.6 (Ph*C*H), 101.9 (*C*HOMe), 80.6 ((OH)*C*HCHOMe), 74.9 ((OH)*C*HCH(OH)), 73.6 (*C*HOCHPh), 68.9 (CH_2), 66.5 (CH_2*C*H), 57.4 (OCH_3). MS (ES^+) *m/z* = 305 $([M+Na])^+$, 100%). The data agree with that in literature.

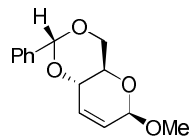
Methyl-4,6-*O*-benzylidene-2,3-dimethanesulfonate-β-D-erythro-pyranoside (210)[105]



To a solution of **209** (6.52 g, 23.1 mmol) in pyridine (20 mL) at 0 °C was added methanesulfonyl chloride (5.33 mL, 69.3 mmol) drop wise over 10 minutes. After stirring for 1 hour the solution was allowed to warm to room temperature and was stirred for further 1 hour before pouring into a separating funnel containing H_2O (50 mL) and then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 0.5N HCl (3 × 20 mL), H_2O (3 × 20 mL), saturated $NaHCO_3$ solution (3 × 20 mL) and brine (3 × 15 mL). The organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a white crystalline solid which was recrystallised from EtOH to provide **210** (7.34 gm, 85%). IR (thin film) 1593, 1372, 1094, 826 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.85 – 7.60 (2H, m, Ar), 7.49 – 7.23 (3H, m, Ar), 5.59 (1H, s, C*H*Ph), 5.15 (1H, d, *J* = 8.5 Hz, H_1), 4.97 (1H, t, *J* = 8.5 Hz, H_3), 4.94 (1H, t, *J* = 8.5, Hz, H_2), 4.45 (1H, dd, *J* = 5.0, 10.5 Hz, H_{6a}), 3.86 (1H, t, *J* = 8.5 Hz, H_4), 3.81 (1H, t, *J* = 10.5 Hz, H_{6b}), 3.67 – 3.65 (1H, m, H_5), 3.59 (3H, s, OCH_3), 3.24 (3H, s, SO_2CH_3), 3.09 (3H, s, SO_2CH_3); δ_C (75 MHz) 136.2 (C, Ar), 129.8 (2 × CH, Ar), 128.5 (CH, Ar), 126.0 (2 × CH, Ar), 101.7 (Ph*C*H), 99.6 (MeO*C*H), 80.6 ((MsO)*C*HCHOMe), 77.1 ((MsO)*C*HCH(OMs)), 76.7

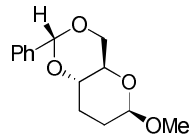
(*C*HOCHPh), 68.2 (CH_2), 66.0 (CH_2*C*H), 57.4 (OCH_3), 39.8 (SO_2CH_3), 39.2 (SO_2CH_3). MS (ES^+) *m/z* = 461 $([M+Na])^+$, 100%). The data agree with that in literature.

Methyl-4,6-*O*-benzylidene-β-D-erythro-hex-2-enopyranoside (211)[106]



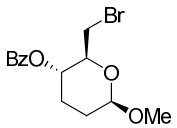
A mixture of **210** (7.34 g, 19.6 mmol), sodium iodide (29.4 g, 196 mmol) and zinc (12.7 g, 196 mmol) in DMF (100 mL) was heated to reflux for 5 minutes with stirring then diluted with H_2O (100 mL), chloroform (150 mL) and filtered. The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 × 50 mL), the combined organic layers were washed with H_2O (3 × 50 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a thick syrup which crystallised directly from MeOH to give **211** (3.83 g, 79%). IR (thin film) 2934, 1744, 1453, 1378, 1096, 693 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.87 – 7.61 (2H, m, Ar), 7.52 – 7.27 (3H, m, Ar), 6.15 (1H, br d, *J* = 10.5 Hz, H_2), 5.66 (1H, ddd, *J* = 1.5, 2.5 Hz, H_3), 5.59 (1H, s, C*H*Ph), 5.27 (1H, dt, *J* = 1.5, 3.0 Hz, H_1), 4.35 – 4.29 (2H, m, H_4, H_{6a}), 3.89 (1H, t, *J* = 10.0, Hz, H_{6b}), 3.87 (3H, s, OCH_3), 3.75 (1H, ddd, *J* = 8.0, 4.5 Hz, H_5); δ_C (75 MHz) 137.3 (C, Ar), 131.6 (CH, Ar), 129.1 (=*C*HCHOMe), 128.3 (2 × CH, Ar), 128.0 (=CHCHOCHPh), 126.6 (2 × CH, Ar), 102.1 (Ph*C*H), 99.3 (MeO*C*H), 75.0 (*C*HOCHPh), 70.4 (*C*HCH_2), 69.1 (CH_2), 55.0 (OCH_3). MS (ES^+) *m/z* = 271 $([M+Na])^+$, 100%). The data agree with that in literature.

Methyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-erythro-hexopyranoside (212)[103]



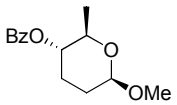
211 (3.83 gm, 15.4 mmol) was hydrogenated in the presence of 5% palladium on carbon (1.93 g) in MeOH (50 mL) containing triethylamine (20 mL) at room temperature in hydrogen atmosphere for 8 hours. Filtration and then evaporation *in vacuo* left a syrup which was dissolved in EtOAc (40 mL) and washed with H_2O (2 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided crystalline **212** (3.46 gm, 90%). IR (thin film) 2864, 1452, 1369, 1097, 915 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.88 – 7.61 (2H, m, Ar), 7.51 – 7.26 (3H, m, Ar), 5.55 (1H, s, C*H*Ph), 4.67 (1H, d, *J* = 2.5 Hz, H_1), 4.22 – 4.19 (1H, m, H_4), 3.70 – 3.44 (3H, m, H_5, H_{6a}, H_{6b}), 3.36 (3H, s, OCH_3), 2.12 – 1.64 (4H, m, H_{2ax}, H_{2eq}, H_{3ax}, H_{3eq}); δ_C (75 MHz) 137.7 (C, Ar), 131.6 (CH, Ar), 127.3 (CH, Ar), 127.0 (CH, Ar), 124.9 (CH, Ar), 101.6 (CH, Ar), 102.1 (Ph*C*H), 96.9 (MeO*C*H), 67.6 (*C*HOCHPh), 67.0 (*C*HCH_2), 64.0 (CH_2), 55.3 (OCH_3), 29.4 (*C*H_2CHOMe), 23.9 (PhCHOCH*C*H_2). MS (ES^+) *m/z* = 373 $([M+Na])^+$, 100%). The data agree with that in literature.

Methyl-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-D-erythro-hexopyranoside (213)[103]



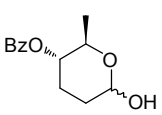
A mixture of **212** (3.46 g, 13.8 mmol), *N*-bromosuccinimide (2.97 g, 16.5 mmol) and barium carbonate (4.11 gm, 20.7 mmol) in carbon tetrachloride (70 mL) was heated to reflux for 30 minutes. The solvent was evaporated before diluting with dichloromethane (60 mL). The solution was washed with saturated $NaHCO_3$ solution (3 × 20 mL), H_2O (3 × 20 mL), dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a white crystalline solid which was recrystallised from MeOH to provide **213** (4.31 g, 95%). IR (thin film) 2944, 1718, 1446, 1360, 1062, 944 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.84 – 7.63 (2H, m, Ar), 7.57 – 7.39 (3H, m, Ar), 4.94 – 4.86 (1H, m, H_4), 4.54 (1H, dd, J = 2.4, 8.4 Hz, H_1), 3.87 – 3.71 (1H, m, H_5), 3.62 – 3.42 (2H, m, H_{6a}, H_{6b}), 3.39 (3H, s, OCH_3), 2.13 – 1.69 (4H, m, H_{2ax}, H_{2eq}, H_{3ax}, H_{3eq}); δ_C (75 MHz) 165.3 (CO), 133.2 (C, Ar), 129.7 (CH, Ar), 127.3 (2 × CH, Ar), 127.0 (CH, Ar), 124.9 (CH, Ar), 97.9 ($CH_3O\mathit{C}H$), 70.9 ($\mathit{C}HOC(O)Ph$), 70.0 ($\mathit{C}HCH_2$), 54.8 (OCH_3), 32.9 ($BrCH_2$), 28.7 ($\mathit{C}H_2CHOCH_3$), 24.1 ($PhC(O)OCH\mathit{C}H_2$). MS (ES^+) *m/z* = 351 $([M+Na])^+$, 50%) (^{79}Br). The data agree with that in literature.

Methyl-4-*O*-benzoyl-2,3,6-trideoxy-β-D-erythro-hexopyranoside (214)[103]



213 (4.31 gm, 13.1 mmol) was reduced by hydrogen in the presence of 5% palladium-on-carbon (2.23 g) in MeOH (70 mL) containing triethylamine (2.23 mL, 15.7 mmol) at room temperature under a hydrogen atmosphere for 8 hours. Filtration and evaporation *in vacuo* left a syrup, which was dissolved in EtOAc (40 mL) and washed with H_2O (3 × 30 mL). The organic layer was dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided syrup **214** (3.01 gm, 92%). IR (thin film) 2944, 1715, 1440, 1363, 1060, 615 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.04 – 7.44 (5H, m, Ar), 4.79 – 4.72 (1H, m, H_4), 4.47 (1H, dd, J = 2.2, 8.8 Hz, H_1), 3.87 – 3.71 (1H, m, H_5), 3.53 (3H, s, OCH_3), 2.33 – 1.69 (4H, m, H_{2ax}, H_{2eq}, H_{3ax}, H_{3eq}), 1.31 (3H, s, CH_3); δ_C (75 MHz) 165.3 (CO), 133.2 (C, Ar), 129.7 (CH, Ar), 127.3 (2 × CH, Ar), 127.0 (CH, Ar), 124.9 (CH, Ar), 97.9 ($CH_3O\mathit{C}H$), 70.9 ($\mathit{C}HOC(O)Ph$), 70.0 ($\mathit{C}HCH_2$), 54.8 (OCH_3), 28.7 ($\mathit{C}H_2CHOCH_3$), 24.1 ($PhC(O)OCH\mathit{C}H_2$), 20.1 (CH_3). MS (ES^+) *m/z* = 273 $([M+Na])^+$, 100%). The data agree with that in literature.

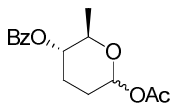
(2*R*,3*S*)-tetrahydro-6-hydroxy-2-methyl-2H-pyran-3-yl benzoate (215)



To a solution of **216** (357 mg, 1.02 mmol) in THF (5mL) and AcOH (5 mL) was added 2M HCl (0.12 mL, 5.10 mmol). The reaction was heated

at 74 °C for 4 hours before pouring into a separating funnel containing H_2O (10 mL), then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 10 mL), H_2O (3 × 10 mL) and brine (3 × 15 mL). The organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a colourless oil. Column chromatography (ethyl acetate : petroleum ether, 15 : 90) furnished a mixture of *α*- and *β*- anomers 1.4 : 1 ratio (339 mg, 95%) as colourless oil. IR (thin film) 2944, 1716, 1450, 1266, 1111, 1067, 996 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.98 – 7.93 (2H, m, Ar), 7.53 – 7.47 (1H, m, Ar), 7.38 (2H, t, *J* = 7.9 Hz, Ar), 5.23 – 5.22 (0.59H, m, C*H*(OH)), 4.83 – 4.80 (0.41, m, C*H*(OH)), 4.71 – 4.61 (1H, m, C*H*OBz), 4.18 (0.59, dq, *J* = 6.3, 9.4 Hz, C*H*CH_3), 3.78 (0.41, dq, *J* = 6.1, 9.2 Hz, C*H*CH_3), 3.45 (0.41, d, *J* = 5.9 Hz, CHO*H*), 2.91 (0.59H, s, CHO*H*), 2.04 – 1.80 (3H, m, BzOCHC*H*$_2$CH*H*), 1.66 – 1.58 (1H, m, BzOCHCH$_2$C*H*H), 1.21 (1.23H, d, *J* = 5.9 Hz, CH_3), 1.15 (1.77H, d, *J* = 5.9 Hz, CH_3); δ_C (100 MHz) 165.8 (2 × CO, major and minor), 133.1 (CH, Ar, minor), 133.0 (CH, Ar, major), 130.2 (C, Ar, minor), 130.1 (C, Ar, major), 129.66 (2 × CH, Ar, major and minor), 129.60 (2 × CH, Ar, major and minor), 128.44 (2 × CH, Ar, major and minor), 128.42 (2 × CH, Ar, major and minor), 95.9 (OCH(OH), minor), 90.9 (OCH(OH), major), 74.0 (BzOCH, minor), 73.6 (BzOCH, major), 73.2 (O*C*HCH_3, minor), 66.8 (O*C*HCH_3), 31.8 ((OH)CH*C*H$_2$, minor), 29.2 ((OH)CH*C*H$_2$, major), 27.5 (BzOCH*C*H$_2$, minor), 23.5 (BzOCH*C*H$_2$, major), 18.3 (CH_3, major), 18.2 (CH_3, minor); (ES^+) *m/z* = 359 ($[M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{13}H_{16}O_4Na$ [M+Na^+] : 359.0941; found: 359.0940.

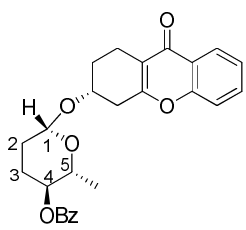
(2*R*,3*S*)-6-acetoxy-tetrahydro-2-methyl-2H-pyran-3-yl benzoate (216)



To a solution of **215** (500 mg, 1.48 mmol), was added acetic anhydride (1.90 mL, 14.8 mmol) and catalytic 4–dimethylaminopyridine (25.0 g, 0.21 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 16 hours before pouring into H_2O (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with 0.5N HCl (3 × 10 mL), H_2O (3 × 10 mL), saturated $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 15 mL). The organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* gave a colourless oil. Column chromatography (diethyl ether : petroleum ether, 10 : 90) furnished a mixture of α and β anomers 1.4 : 1 (578 mg, 98%) as colourless oil. IR (thin film) 2940, 1747, 1716, 1451, 1314, 1112, 1006, 945 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.96 (2H, t, *J* = 7.5 Hz, Ar), 7.53 – 7.49 (1H, m, Ar), 7.38 (2H, t, *J* = 7.5 Hz, Ar), 6.06 (0.59H, m, CHOAc), 5.74 – 5.72 (0.41H, m, CHOAc), 4.75 – 4.65 (1H, m,

CHOBz), 3.98 (0.59H, dq, *J* = 6.1, 9.3 Hz, C*H*CH_3), 3.78 (0.41H, dq, *J* = 6.1, 8.6 Hz, C*H*CH_3), 2.32 – 2.25 (0.41H, m, BzOCHCH_2C*H*H), 2.06 (1.77H, s, $OCOCH_3$), 2.05 (1.23H, s, $OCOCH_3$), 1.98 – 1.59 (3.59H, m, BzOCHC*H_2*CH*H*), 1.23 (1.23H, d, *J* = 6.1 Hz, CH_3), 1.14 (1.77H, d, *J* = 6.1 Hz, CH_3); δ_C (100 MHz) 190.2 (CO), 177.1 (2 × CO, Ar, major and minor), 133.2 (2 × C, Ar, major and minor), 133.1 (2 × CH, Ar, major and minor), 130.0 (2 × C, Ar, major and minor), 129.6 (4 × CH, Ar, major and minor), 128.4 (4 × CH, Ar, major and minor), 93.6 (CHOAc, minor), 90.9 (CHOAc, major), 74.2 (BzOCH, minor), 73.3 (BzOCH, major), 72.5 ($CHCH_3$, minor), 69.1 ($CHCH_3$, major), 28.5 (BzOCHCH_2*C*H_2, major), 28.1 (BzOCHCH_2*C*H_2, minor), 26.5 (BzOCH*C*H_2CH_2, minor), 23.9 (BzOCH*C*H_2CH_2, major), 21.2 (2 × (CO)CH_3, major and minor), 18.3 (CH_3, minor), 18.0 (CH_3, major); MS (ES^+) *m/z* = 301 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{15}H_{18}O_5Na$ [$M+Na^+$]: 301.1046; found: 301.1061.

(2*R*,3*S*,6*S*)-6-(*R*)-6,7,8,9-Tetrahydro-9-oxo-5H-xanthen-6-yloxy)-tetrahydro-2-methyl-pyran-3-yl benzoate (**228**)

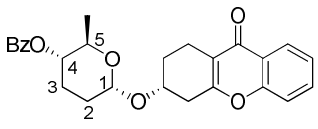


To a solution of **215** (60.0 mg, 0.25 mmol) in dichloromethane (4 mL) were added trichloroacetonitrile (0.10 mL, 1.00 mmol) and NaH (0.50 mg, 0.02 mmol). After 30 minutes tlc indicated the formation of both the *α* and *β* anomers. For anomerization and completion of the reaction further NaH (7.40 mg, 0.32 mmol) was added. After 2 hours, the mixture was filtered through celite quickly, and the solvent was concentrated *in vacuo* to provide **225** and **226**. A solution of **225** and **226** and **200** (54.0 mg, 0.25 mmol) in dichloromethane (5 mL), was stirred for 30 minutes at room temperature in the presence of molecular sieves (4Å, 100 mg). After cooling to 0 °C a solution of $BF_3.OEt_2$ (0.1 M solution in Et_2O (0.12 mL), CH_2Cl_2 (0.12 mL)), was added dropwise over 10 minutes. When the starting material was completely consumed as indicated by tlc in (30 minutes), saturated $NaHCO_3$ solution (63.0 mg, 0.75 mmol), was added and stirring continued for another 10 minutes. The reaction mixture was filtered and the solid was washed with further dichloromethane (3 × 10 mL). The solvent was evaporated *in vacuo* to leave a thick colourless oil. Column chromatography (diethyl ether : petroleum ether, 05 : 90) furnished a mixture of inseparable *α* and *β* anomers in 1 : 0.7 ratio respectively, as colourless thick oil. Trituration with Et_2O (5 mL), gave a solid which was recrystallised (diethylether, and petroleum ether) to give the *β* anomer (30 mg, 40%). The oil fraction on further trituration with cold Et_2O gave another portion of solid which was recrystallised from acetone and H_2O to give *α* anomer (32

mg, 20%). $[\alpha]_D^{30°}$ + 72.3° (*c* 0.1, $CHCl_3$) M.p. 194 – 195 °C; IR (thin film) 2914, 1728, 1471, 1175, 716 cm^{-1}; δ_H (700MHz $CDCl_3$) 8.21 – 8.20 (1H, m, Ar), 8.01 (2H, d, *J* = 7.5 Hz, Ar), 7.63 – 7.61 (1H, m, Ar), 7.59 (1H, t, *J* = 7.5 Hz, Ar), 7.46 (2H, t, *J* = 7.5 Hz, Ar), 7.41 (1H, d, *J* = 8.5 Hz, Ar), 7.37 – 7.35 (1H, t, *J* = 7.5 Hz, Ar), 4.76 (1H, dd, *J* = 1.8, 9.4 Hz, H_1), 4.73 (1H, td, *J* = 4.7, 10.4 Hz, H_4), 4.33 – 4.29 (1H, m, OC*H*$(CH_2)_2$), 3.74 – 3.70 (1H, m, H_5), 3.07 (1H, dd, *J* = 4.7, 18.9 Hz, OCHC*H*HC=), 2.91 (1H, dd, *J* = 6.6, 17.9 Hz, OCHCH*H*C=), 2.76 – 2.72 (1H, m, $OCHCH_2CH$*H*), 2.63 – 2.59 (1H, m, $OCHCH_2CH$*H*), 2.33 – 2.30 (1H, m, H_{3eq}), 1.98 – 1.90 (3H, m, H_{2eq},$OCHCH_2CH_2$), 1.78 – 1.73 (1H, m, H_{2ax}), 1.68 – 1.62 (1H, m, H_{3ax}), 1.31 (3H, d, *J* = 5.6 Hz, CH_3); δ_C (75 MHz) 177.3 (CO), 165.7 (CO), 161.3 (C, Ar), 156.1 (C, Ar), 133.1 (CH, Ar), 133.0 (CH, Ar), 130.1 (C, Ar), 129.5 (2 × CH, Ar), 128.4 (2 × CH, Ar), 125.7 (CH, Ar), 124.5 (CH, Ar), 123.1 (C, Ar), 117.7 (C, Ar), 117.6 (CH, Ar), 99.6 (OCHO), 73.5 (CHOBz), 73.3 (O*C*HCH_3), 71.1 (O*C*$H(CH_2)_2$), 35.5 (OCH*C*H_2C=), 30.5 (CH_3CHOCH*C*H2), 29.7 (BzOCH*C*H_2), 27.5 (OCH*C*H_2CH_2C=), 26.3 ($OCHCH_2$*C*H_2C=), 18.3 (CH_3); MS (ES^+) *m/z* = 457 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{26}H_{26}O_6Na$ [$M+Na^+$]: 457.1622; found: 457.1619.

Crystal Data. $C_{26}H_{26}O_6$, *M* =434.47, monoclinic, *a* = 13.7920(3) Å, *b* = 5.31169(13) Å, *c* = 14.3899(3) Å, *β* = 94.535(2)°, *V* = 1050.89(4) $Å^3$, *T* = 100(2), space group $P2_1$ (no. 4), *Z* = 2, μ(CuKα) = 0.795, 11589 reflections measured, 3869 unique (R_{int} = 0.0357) which were used in all calculations. The final wR_2 was 0.1029 (all data) and R_1 was 0.0383 (>2sigma(I)).

(2*R*,3*S*,6*S*)-6-((*R*)-6,7,8,9-Tetrahydro-9-oxo-5H-xanthen-6-yloxy)-tetrahydro-2-methyl-2H-pyran-3-yl benzoate (**227**)

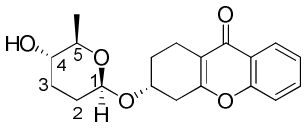


$[\alpha]_D^{30°}$ + 182° (*c* 0.2, $CHCl_3$); M.p. 156 – 157 °C; IR (thin film) 2914, 1728, 1471, 1175, 716 cm^{-1}; δ_H (500 MHz $CDCl_3$) 8.25 – 8.23 (1H, m, Ar), 8.08 – 8.06 (1H, m, Ar), 7.63 – 7.66 (1H, m, Ar), 7.58 – 7.61 (2H, m, Ar), 7.48 (2H, t, *J* = 8.1 Hz, Ar), 7.41 (1H, d, *J* = 8.1 Hz, Ar), 7.40 – 7.36 (1H, t, *J* = 6.9 Hz, Ar), 5.05 (1H, m, H_1), 4.81 – 4.76 (1H, m, H_4), 4.27 – 4.23 (1H, m, OC*H*$(CH_2)_2$), 4.09 (1H, dq, *J* = 6.2, 9.7 Hz, H_5), 3.00 (1H, dd, *J* = 4.4, 17.6 Hz, OCHC*H*HC=), 2.86 (1H, td, *J* = 6.6, 18.3 Hz, $OCHCH_2$C*H*HC=), 2.78 (1H, dd, *J* = 5.8, 18.3 Hz, OCHCH*H*C=), 2.69 (1H, td, *J* = 6.6, 17.6 Hz, $OCHCH_2CH$*H*C=), 2.10 – 1.86 (6H, m, BzOCHC$H_{2(3)}$C$H_{2(2)}$CHOCHCH_2CH_2C=), 1.26 (3H, d, *J* = 6.6 Hz, CH_3),; δ_C (75 MHz) 177.3 (CO), 165.8 (CO), 160.8 (C, Ar), 156.1 (C, Ar), 133.1 (CH, Ar), 130.1 (C, Ar), 129.6 (CH, Ar), 129.5 (CH, Ar), 128.4 (2 × CH,

Ar), 125.8 (CH, Ar), 124.5 (CH, Ar), 123.2 (C, Ar), 118.0 (C, Ar), 117.67 (CH, Ar), 117.60 (CH, Ar), 95.0 (OCHO), 73.9 (BzOCH), 69.9 ($OCHCH_3$), 67.3 ($OCH(CH_2)_2$), 33.8 ($OCHCH_2C$=), 29.6 ($CH_3CHOCHCH2$), 28.2 ($BzOCHCH_2$), 24.2 ($OCHCH_2CH_2C$=), 18.3 ($OCHCH_2CH_2C$=), 18.1 (CH_3); MS (ES^+) *m/z* = 457 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{26}H_{26}O_6Na$ $[M+Na^+]$:457.1622; found: 457.1619.

Crystal Data. $C_{26}H_{26}O_6$, M =434.47, orthorhombic, a = 7.11230(10) Å, b = 11.6173(2) Å, c = 26.2941(4) Å, V = 2172.57(6) $Å^3$, T = 100(2), space group $P2_12_12_1$ (no. 19), Z = 4, μ(CuKα) = 0.769, 23738 reflections measured, 4162 unique (R_{int} = 0.0516) which were used in all calculations. The final wR_2 was 0.1105 (all data) and R_1 was 0.0409 (>2sigma(I)).

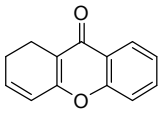
(*R*)-3-((2*S*,5*S*,6*R*)-Tetrahydro-5-hydroxy-6-methyl-2H-pyran-2-yloxy)-1,2,3,4-tetrahydroxanthen-9-one (234)



Sodium metal (0.50 mg, 0.02 mmol) was dissolved in methanol (5 mL) at 0 °C followed by the addition of **227** (100 mg, 0.23 mmol) and the transparent solution stirred at room temperature until tlc showed complete consumption of the starting material (16 hours). The reaction was quenched by the addition of saturated NH_4Cl solution (2 mL) and poured into a separating funnel containing H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (2 × 5 mL), dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 40 : 60) furnished **234** (9 mg, 11%) as a colourless oil and **235** (46 mg, 60%). $[\alpha]_D^{30°}$ + 117 (*c* 0.2, $CHCl_3$) IR (thin film) 2927, 1633, 1609, 1467, 1118, 1044, 759 cm^{-1}; δ_H (700 MHz $CDCl_3$) 8.21 – 8.20 (1H, m, Ar), 7.63 – 7.60 (1H, m, Ar), 7.39 – 7.35 (2H, m, Ar), 4.97 – 4.96 (1H, m, H_1), 4.28 – 4.17 (1H, m, $OCH(CH_2)_2$), 3.68 (1H, dq, J = 3.1, 5.7 Hz, H_5), 3.31 – 3.28 (1H, m, H_4), 2.97 – 2.93 (1H, dd, J = 5.7, 17.7 Hz, $OCHCHHC$=), 2.82 – 2.78 (1H, m, $OCHCH_2CHHC$=), 2.72 (1H, dd, J = 5.7, 17.7 Hz, $OCHCHHC$=), 2.64 – 2.62 (1H, m, $OCHCH_2CHHC$=), 2.25 – 1.98 (1H, m, $OCHCHHCH_2C$=), 1.95 – 1.90 (1H, m, $OCHCHHCH_2C$=), 1.89 – 1.75 (4H, m, $CH_{2(2)}CH_{2(3)}$), 1.29 – 1.28 (3H, d, J = 6.3 Hz, CH_3); δ_C (75 MHz) 177.3 (CO), 160.9 (C, Ar), 156.1 (C, Ar), 133.0 (CH, Ar), 125.7 (CH, Ar), 124.5 (CH, Ar), 123.1 (C, Ar), 118.0 (C, Ar), 117.6 (CH, Ar), 94.5 (OCHO), 72.1 ((OH)CH), 70.0 ($OCHCH_3$), 69.3 ($OCH(CH_2)_2$), 33.7 ($OCHCH_2C$=), 29.9 ($OCHCH_2CH_2CH(OH)$), 28.0

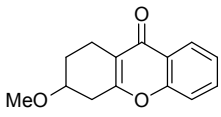
(OCH*C*H$_2$CH$_2$C=), 27.5 (OCHCH$_2$*C*H$_2$CH(OH)), 18.1 (OCHCH$_2$*C*H$_2$C=), 17.9 (CH$_3$); MS (ES$^+$) *m/z* = 353 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{19}H_{22}O_5Na$ [M+Na$^+$]: 353.1359; found: 353.1364.

7,8-Dihydroxanthen-9-one (**236**)



To a mixture of **242** (2.25 g, 7.60 mmol) in dichloromethane (25 mL) at 0 °C was added *m*CPBA (1.90 g, 8.69 mmol). The reaction mixture was allowed to warm up to room temperature slowly and was further stirred for an hour. The reaction mixture was diluted with H_2O (20 mL) and the solution was extracted with dichloromethane (3 × 30 mL). The organic layers were washed with saturated sodium thiosulfate solution (3 × 15 mL), brine (3 × 15 mL), dried over $MgSO_4$, filtered and evaporation of solvent *in vacuo* gave a white solid. Column chromatography (ethyl acetate : petroleum ether, 10 : 90) furnished **236** (1.3 g, 59%) as a white solid. M.p. 118 – 120 °C; IR (thin film) 2937, 1603, 1421, 1102, 899, 769 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 – 8.05 (1H, dd, *J* = 1.4, 8.1 Hz, Ar), 7.41 (1H, dt, *J* = 1.4, 8.1 Hz, Ar), 7.21 – 7.12 (2H, m, Ar), 6.38 – 6.32 (1H, m, CH$_2$CHC*H*), 6.10 (1H, td, *J* = 1.8, 2.1 Hz, CH$_2$C*H*CH), 2.68 – 2.61 (2H, m, CHC*H*$_2$CH$_2$), 2.42 – 2.25 (2H, m, CHCH$_2$C*H*$_2$); δ_C (75 MHz) 176.3 (CO), 158.3 (C, Ar), 154.7 (C, Ar), 139.5 (CH, Ar), 132.2 (CH, Ar), 125.9 (CH, Ar), 124.0 (CH, Ar), 123.4 (C, Ar), 121.1 (CH), 117.2 (CH), 113.4 (C, Ar), 23.2 (=CH*C*H$_2$), 22.2 (CH$_2$*C*H$_2$C=); MS (ES$^+$) *m/z* = 221 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{13}H_{10}O_2Na$ [M+Na]$^+$: 221.0578; found: 221.0573.

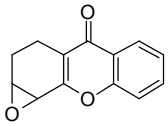
1,2,3,4-Tetrahydro-3-methoxyxanthen-9-one (**235**)



Sodium metal (5.00 mg, 0.21 mmol) was dissolved in methanol at 0 °C followed by the addition of **236** (47.0 mg, 0.23 mmol). The clean solution was allowed to stir at room temperature for 16 hours. The reaction was quenched by the addition of saturated NH_4Cl solution (1 mL) and poured into a separating funnel containing H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (2 × 5 mL), dried over $MgSO_4$, and concentration *in vacuo* gave a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 10 : 90) furnished **235** (47 mg, 92%) as a white solid. M.p. 63 – 64 °C; IR (thin film) 3286, 1661, 1402, 1206, 1009, 616 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.10 (1H, d, *J* = 8.0 Hz, Ar), 7.54 – 7.50 (1H, m, Ar), 7.30 – 7.26 (2H, m, Ar), 3.75 – 3.66 (1H, m, C*H*(OCH$_3$)), 3.30 (3H, s, OC*H*$_3$), 2.92 – 2.86 (1H, m, ((OCH$_3$)CHC*H*HC=) 2.68 – 2.60 (2H, m,

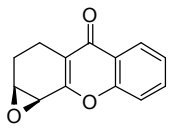
(C*H*H(OCH$_3$)CHCH*H*C=), 2.53 – 2.45 (1H, m, CH$_2$CH*H*CH(OCH$_3$)), 1.92 – 1.76 (2H, m, (OCH$_3$)CHCH$_2$C*H*$_2$); δ_C (75 MHz) 177.2 (CO), 161.0 (C, Ar), 156.1 (C, Ar), 133.0 (CH, Ar), 125.7 (CH, Ar), 124.5 (CH, Ar), 123.1 (C, Ar), 117.8 (C, Ar), 117.6 (CH, Ar), 74.0 (OCH$_3$), 56.1 (*C*H(OCH$_3$)), 34.1 ((OCH$_3$)CH*C*H$_2$C=), 25.8 ((OCH$_3$)CH*C*H$_2$CH$_2$), 17.7 (CH$_2$*C*H$_2$C=); MS (ES$^+$) *m/z* = 253 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for C$_{14}$H$_{14}$O$_3$Na [M+Na$^+$]: 253.0837; found: 253.0837.

(1*S,9*S**)-2,3-Dihydro-1-oxireno[2,3-c]xanthen-4(9)one (239)**



A solution of **236** (50.0 mg, 0.25 mmol) in CHCl$_3$ (5 mL) was charged with *m*CPBA (85.0 mg, 0.37 mmol) at 0 °C . The reaction mixture was stirred at 0 °C for 16 hours and then warmed upto room temperature. The mixture was washed with 10% aqueous sodium thiosulfate solution (2 × 5 mL) and saturated NaHCO$_3$ solution (3 × 10 mL). The organic fraction was dried over MgSO$_4$ and concentrated *in vacuo* to provide a pale yellow solid. Column chromatography (ethyl acetate : petroleum ether, 20 : 80) furnished **239** (16 mg, 30%) as a yellow solid. M.p. 150 – 151 °C; IR (thin film) 2930, 1608, 1466, 1148, 909, 697 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.91 (1H d, *J* = 8.1 Hz, Ar), 7.39 – 7.42 (1H, m, Ar), 7.22 (1H, d, *J* = 8.1 Hz, Ar), 7.14 (1H, t, *J* = 7.2 Hz, Ar), 3.57 – 3.55 (2H, m, C*H*C*H*), 2.71 (1H, dd, *J* = 6.3, 16.3 Hz, CHC*H*HCH$_2$), 2.22 (1H, dd, *J* = 7.2, 14.5 Hz, CHCH$_2$C*H*H), 1.96 – 1.84 (1H, m, CHCH*H*CH$_2$), 1.54 – 1.41 (1H, m, CHCH$_2$CH*H*); δ_C (75 MHz) 175.8 (CO), 158.1 (C, Ar), 155.4 (C, Ar), 132.7 (CH, Ar), 125.3 (CH, Ar), 124.4 (CH, Ar), 122.9 (C, Ar), 117.2 (CH, Ar), 116.7 (C, Ar), 55.5 (CH$_2$CHO*C*HC=), 48.2 (CH$_2$*C*HOCHC=), 20.2 (CH*C*H$_2$CH$_2$), 13.9 (CHCH$_2$*C*H$_2$); MS (ES$^+$) *m/z* = 237 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for C$_{13}$H$_{11}$O$_3$Na [M+Na]$^+$: 237.0528; found: 237.0518.

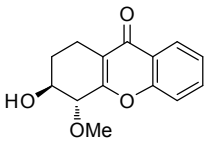
(1*S*, 9*S*)-2,3-dihydro-1-oxireno[2,3-c]xanthen-4(9)one (239)



Commercially available sodium hypochlorite (1 mL), was diluted to approximately 0.55 M in sodium hypochlorite with 0.05 M Na$_2$HPO$_4$ (30 mL). The pH of the resulting buffered solution was adjusted to 11.3 by addition of a 1M NaOH solution (few drops). To this solution was added a solution of Jacobsen's catalyst (5.00 mg, 0.08 mmol) and **236** (80.0 mg, 0.41 mmol) in dichloromethane (5 mL). The biphasic mixture was stirred at 4 °C and the reaction progress was monitored by tlc. After 16 hours, dichloromethane (2 mL) was added to the mixture and the brown organic phase was separated washed with H$_2$O (3 × 5 mL), brine (3 × 5 mL) and dried over Na$_2$SO$_4$. The organic fraction was concentrated *in*

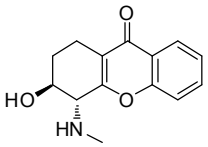
vacuo to obtain a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 20 : 80) furnished **239** (23 mg, 28%) as a yellow solid. M.p. 150 – 151 °C; HPLC analysis on Chiracel OD+1 (99 : 1 hexane : isopropanol, 1 mL/min) showed the minor enantiomer at 37.8 min (14.7 A%) and the minor one at 41.4 min (85.3 A%) ee 70%. IR (thin film) 2930, 1608, 1466, 1148, 909, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.91 (1H d, *J* = 8.1 Hz, Ar), 7.39 – 7.42 (1H, m, Ar), 7.22 (1H, d, *J* = 8.1 Hz, Ar), 7.14 (1H, t, *J* = 7.2 Hz, Ar), 3.57 – 3.55 (2H, m, C*H*C*H*), 2.71 (1H, dd, *J* = 6.3, 16.3 Hz, CHC*H*HCH$_2$), 2.22 (1H, dd, *J* = 7.2, 14.5 Hz, CHCH$_2$C*H*H), 1.96 – 1.84 (1H, m, CHCH*H*CH$_2$), 1.54 – 1.41 (1H, m, CHCH$_2$CH*H*); δ_C (75 MHz) 175.8 (CO), 158.1 (C, Ar), 155.4 (C, Ar), 132.7 (CH, Ar), 125.3 (CH, Ar), 124.4 (CH, Ar), 122.9 (C, Ar), 117.2 (CH, Ar), 116.7 (C, Ar), 55.5 (CH$_2$CHO*C*HC=), 48.2 (CH$_2$*C*HOCHC=), 20.2 (CH*C*H$_2$CH$_2$), 13.9 (CHCH$_2$*C*H$_2$); MS (ES^+) *m/z* = 237 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{13}H_{11}O_3Na$ $[M+Na]^+$: 237.0528; found: 237.0518.

(3*S,4*R**)-1,2,3,4-Tetrahydro-3-hydroxy-4-methoxyxanthen-9-one (241)**



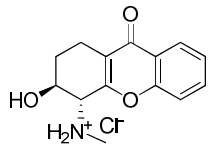
To a solution of **239** (23.0 mg, 0.10 mmol) in methanol (5mL) was added *para*-toluene sulfonic acid (10.0 mg, 0.05 mmol). The reaction mixture was heated at 65 °C for 16 hours and was then cooled down to room temperature, diluted with H_2O (5mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic fractions were collected washed with saturated $NaHCO_3$ solution (3 × 5 mL), H_2O (3 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **241** (27 mg, 60%) as a yellow solid. M.p. 151 – 152 °C; IR (thin film) 2930, 1608, 1466, 1148, 909, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39 (1H, dd, *J* = 1.7, 8.0 Hz, Ar), 7.42 (1H, td, *J* = 1.7, 8.6 Hz, Ar), 7.25 – 7.11 (2H, m, Ar), 3.93 – 3.91 (2H, m, (OH)C*H*C*H*OMe), 3.50 (3H, s, OC*H*$_3$), 2.98 – 2.90 (1H, m, (OH)CHC*H*HCH$_2$), 2.75 – 2.60 (1H, m, (OH)CHCH*H*CH$_2$), 1.91 – 1.83 (1H, m, CH$_2$C*H*HC=), 1.72 – 1.61 (1H, m, CH$_2$CH*H*C=); δ_C (75 MHz) 177.5 (CO), 159.4 (C, Ar), 155.8 (C, Ar), 133.1 (CH, Ar), 125.3 (CH, Ar), 124.5 (CH, Ar), 122.6 (C, Ar), 118.7 (C, Ar), 117.1 (CH, Ar), 80.1 (OCH$_3$), 68.6 (CHO*C*HC=), 59.8 (CH$_2$*C*HOCH), 25.1 ((OH)CH*C*H$_2$CH$_2$), 17.3 (CHCH$_2$*C*H$_2$C=); MS (ES^+) *m/z* = 269 $([M+Na])^+$, 100%); HRMS (ES^+): calcd.. for $C_{14}H_{14}O_4Na$ $[M+Na]^+$: 269.0779; found: 269.0784.

(3*S,4*R**)-1,2,3,4-Tetrahydro-3-hydroxy-4-(methylamino)xanthen-9-one (246)**



To the solution of **239** (200 mg, 0.93 mmol) in ethanol (5 mL) at room temperature was added *para*-toluene sulfonic acid (30.0 mg, 0.15 mmol). The reaction mixture was stirred for 5 minutes and then methylamine (288 mg, 9.30 mmol) was added. The reaction was heated to 76 °C and stirred for a further 16 hours. The reaction mixture was then cooled to room temterature, diluted with water (5 mL) and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic fractions were collected, washed with saturated $NaHCO_3$ solution (3 × 15 mL), H_2O (3 × 15 mL) and dried over $MgSO_4$ to obtain a pale yellow solid. Column chromatography (methanol : dichloromethane, 10 : 90) furnished **246** (136 mg, 60%) as a pale yellow solid; M.p. 155 – 156 °C; IR (thin film) 2930, 1608, 1466, 1148, 909, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.99 – 7.96 (1H, m, Ar), 7.46 – 7.40 (1H, m, Ar), 7.21- 7.13 (2H, m, Ar), 3.90 (1H, td, *J* = 3.3, 7.8 Hz, (OH)C*H*), 3.63 (1H, d, *J* = 7.8 Hz, C*H*NHMe), 2.92 – 2.81 (1H, dt, *J* = 4.6, 17.5 Hz, (OH)CHC*H*HCH$_2$), 2.51 – 2.42 (2H, m, (OH)CHCH*H*C*H*H), 2.53 (3H, s, NHCH_3), 2.25 – 2.19 (1H, m, NH), 1.80 – 1.48 (1H, m, (OH)CHCH*H*CH*H*); δ_C (300 MHz) 175.8 (CO), 158.1 (C, Ar), 155.4 (C, Ar), 132.7 (CH, Ar), 125.3 (CH, Ar), 124.4 (CH, Ar), 122.9 (C, Ar), 117.2 (CH, Ar), 116.7 (C, Ar), 55.5 ((OH)*C*HCHNHMe), 48.2 ((OH)CH*C*HNHMe), 32.3 (CH_3), 20.2 (CHCH$_2$*C*H$_2$), 13.9 (CH*C*H$_2$); MS (ES^+) *m/z* = 268 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{14}H_{15}O_3Na$ $[M+Na]^+$: 268.0950; found: 268.0954.

(3*S,4*R**)-1,2,3,4-Tetrahydro-3-hydroxy-4-(methylaminium) xanthene-9-one chloride (247)**

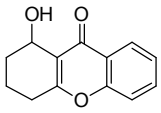


A 50 mL flask containing **246** (100 mg, 0.40 mmol) was charged with commercially available 1M HCl (5.00 mL, 5.00 mmol) in Et_2O. The reaction mixture was stirred for 16 hours before the solvent was evaporated *in vacuo* to obtain a yellow solid. The crude product was recrystallised from Et_2O to afford **247** (95 mg, 85%) as yellow crystals; M.p. 209 – 210 °C; IR (thin film) 2930, 1608, 1466, 1148, 909, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* = 8.1 Hz, Ar), 7.79 – 7.75 (1H, m, Ar), 7.53 (1H, d, *J* = 8.4 Hz, Ar), 7.47 – 7.43 (1H, m, Ar), 4.48 (1H, d, *J* = 8.4 Hz, (OH)C*H*), 4.28 – 4.22 (1H, m, C*H*NHMe), 2.79 (3H, s, NHCH_3), 2.70 – 2.66 (1H, m, (OH)CHC*H*HCH$_2$), 2.50 – 2.41 (1H, m, (OH)CHCH$_2$C*H*H), 2.21 – 2.18 (1H, m, (OH)CHCH*H*CH$_2$), 1.90 – 1.80 (1H, m, (OH)CHCH$_2$CH*H*); δ_C (100 MHz) 179.5 (CO), 155.8 (C, Ar), 153.9 (C, Ar), 135.2 (CH, Ar), 126.1 (CH, Ar), 124.9 (CH, Ar), 121.6 (C, Ar), 121.2 (CH, Ar), 118.0 (C, Ar), 65.0 (OH)*C*HCHNHMe), 60.8

((OH)CH*C*HNHMe), 30.1 (NHCH$_3$), 27.6 (CHCH$_2$*C*H$_2$), 18.4 (CH*C*H$_2$); MS (ES$^+$) *m/z* = 246 ([M+H])+, 100%); HRMS (ES$^+$): calcd. for $C_{14}H_{16}NO_3$ [M+H]$^+$: 246.1125; found: 246.1129

Crystal Data. $C_{14}H_{16}NO_3Cl$, M =281.73, orthorhombic, a = 13.1707(3) Å, b = 12.0072(2) Å, c = 16.8408(4) Å, V = 2663.25(9) Å^3, T = 100(2), space group Pbca (no. 61), Z = 8, μ(MoKα) = 0.290, 17479 reflections measured, 4554 unique (R_{int} = 0.0362) which were used in all calculations. The final wR_2 was 0.0906 (all data) and R_1 was 0.0386 (>2sigma(I)).

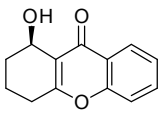
1,2,3,4-Tetrahydro-1-hydroxyxanthen-9-one (**102**)



To a solution of **103** (2.20 g, 10.2 mmol) in methanol and dichloromethane 5 : 1 (60 mL) was added cerium chloride heptahydrate (4.20 g, 11.3 mmol) in one portion followed by the slow addition of sodium borohydride (418 mg, 11.3 mmol) in 2 portions. The reaction mixture was stirred for 1 hour before the addition of saturated NH_4Cl solution (10 mL). The mixture was poured into a separating funnel containing 1.5 M HCl (40 mL) and extracted with dichloromethane (3 × 50 mL). The organic layers were washed with saturated $NaHCO_3$ solution (2 × 50 mL), brine (50 mL× 2), dried over $MgSO_4$, and concentration *in vacuo* provided a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **102** (1.71 g, 78%) as a white solid. M.p. 105 – 106 °C; IR (thin film) 2949, 1626, 1461, 1245, 1163, 1073, 848 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.05 (1H, d, J = 8.0 Hz, Ar), 7.56 – 7.53 (1H, m, Ar), 7.31 – 7.25 (2H, m, Ar), 4.97 – 4.94 (1H, m, C*H*(OH)), 4.1 (1H, brs, 1O*H*), 3.61 – 3.58 (1H, m, CH$_2$C*H*HC=), 2.68 – 2.50 (1H, m, CH$_2$CH*H*C=), 2.01 – 1.68 (4H, m, (OH)CHC*H*$_2$C*H*$_2$); δ_C (75 MHz) 178.8 (CO), 166.0 (C, Ar), 155.9 (C, Ar), 133.9 (CH, Ar), 125.4 (CH, Ar), 124.8 (CH, Ar), 123.3 (C, Ar), 120.0 (C, Ar), 117.5 (CH, Ar), 63.6 (CH(OH)), 29.6 (CH$_2$*C*H$_2$C=), 28.4 ((OH)CH*C*H$_2$), 17.9 (CH$_2$*C*H$_2$CH$_2$); MS (ES$^+$) *m/z* = 239 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{13}H_{12}O_3Na$ [M+Na$^+$]: 239.0679; found: 239.0678.

Enantioselective reductions

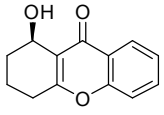
Using Noyori's catalyst



A solution of Noyori's catalyst **206** (43.0 mg, 0.07 mmol) in formic acid and triethylamine 5 : 2 (2.3 mL) was stirred at 28 °C for 30 min. **103** (1.00 g, 4.67 mmol) was added and the reaction mixture was stirred for 48 hours at the same temperature. The reaction mixture was filtered through silica,

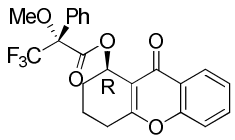
washed with ethyl acetate and hexane 1 : 1 (5 × 15 mL) and concentrated *in vacuo* to obtain a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **102** as white solid (806 mg, 80%). HPLC analysis on Chiracel OD+1 (90 : 10 hexane : isopropanol, 1 mL/min) showed only the major enantiomer at 17.2 min (100 A%) ee 99%; $[\alpha]_D^{30^\circ}$ – 117.5° (*c* 0.2, $CHCl_3$).

Using Wills catalyst



A solution of Wills catalyst **207** (38.0 mg, 0.06 mmol) in formic acid and triethylamine 5 : 2 (1.5 mL) was stirred at 28 °C for 30 min. **103** (850 mg, 3.97 mmol) was added and the reaction mixture was stirred for 48 hours at the same temperature. The reaction mixture was filtered through silica, washed with ethyl acetate and hexane 1 : 1 (5 × 15 mL) and concentrated *in vacuo* to obtain a yellow solid. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **102** as white solid (771 mg, 90%). HPLC analysis on Chiracel OD+1 (90 : 10 hexane : isopropanol, 1 mL/min) showed the major enantiomer at 16.0 min (88.8 A%) and the minor one at 23.0 min (11.2 A%), ee 76.4%;

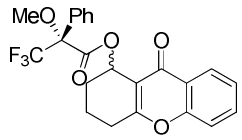
(2*R*)-(*R*)-6,7,8,9-Tetrahydro-9-oxo-5H-xanthen-8-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**275**)



To solution of **102** (20.0 mg, 0.09 mmol) triethylamine (10.0 mg, 0.10 mmol) and catalytic 4-dimethylamino pyridine (1 mg, 0.009 mmol) in dichloromethane was added (R) (+)-*α*-methoxy-*α*-trifluoromethylphenylacetyl chloride (25 mg, 0.10 mmol). The reaction mixture was stirred for 6 hours then poured into ice cold H_2O (2 mL), extracted with dichloromethane (2 × 5 mL), washed with NaCl (2 × 5 mL), dried over $MgSO_4$ and filtered and concentrated *in vacuo* to give colourless thick oil. Column chromatography (diethylether : petroleum ether, 25 : 75) furnished **275** (30 mg, 80%), as colourless oil. $[\alpha]_D^{26^\circ}$ – 54.6° (*c* 0.2, $CHCl_3$); IR (thin film) 2991, 1730, 1374, 1267, 1045, 752 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.13 – 8.10 (1H, m, Ar), 7.59 – 7.54 (1H, m, Ar), 7.51 – 7.48 (2H, m, Ar), 7.32 – 7.27 (5H, m, Ar), 6.36 – 6.34 (1H, m, C*H*OCO), 3.50 (3H, s, OCH_3), 2.58 – 2.55 (2H, m, CH_2C=), 2.18 – 2.14 (1H, m, OCOCHC*H*HCH$_2$) 1.77 – 1.55 (3H, m, OCOCHCH*H*CH_2); δ_C (100 MHz) 175.9 (CO), 168.1 (COO), 165.8 (C, Ar), 155.8 (C, Ar), 133.7 (CH, Ar), 132.7 (C, Ar), 129.4 (CH, Ar), 128.3 (2 × CH, Ar), 127.7 (CH, Ar), 127.4 (CH, Ar), 125.8 (CH, Ar), 125.1 (CH, Ar), 124.8 (CF_3), 123.6 (C, Ar), 122.0 (C, Ar), 117.7 (CH, Ar), 115.5 ((Ph)(CO)*C*(CF_3)(OCH_3)), 66.1 (*C*H(COO)), 55.7

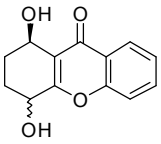
(OCH_3), 27.8 (CH_2CH_2C=), 27.1 ($CH_2CH_2CHOCOCO$), 16.4 ($CH_2CH_2CH_2C$=); MS (ES^+) *m/z* = 433 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{23}H_{20}F_3O_5$ [$M+H^+$]: 433.1257; found: 433.1256.

6,7,8,9-Tetrahydro-9-oxo-5H-xanthen-8-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**275, 276**)



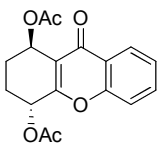
To a solution of **102** (20.0 mg, 0.09 mmol) Et_3N (14.0 mg, 0.10 mmol) and catalytic 4-dimethylaminopyridine (1.00 mg, 0.009 mmol) in dichloromethane was added (R) (+)-*α*-methoxy-*α*-trifluoromethylphenylacetyl chloride (25.0 mg, 0.10 mmol). The reaction mixture was stirred for 6 hours, before pouring slowly into ice cold H_2O (2 mL) and then extracted with dichloromethane (2 × 5 mL), washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a mixture of diastereomers. Column chromatography (diethylether : petroleum ether, 25 : 75) furnished a mixture of the diastereomers **275** and **276** (22 mg, 60%) in 1 : 3 as an oil. IR (thin film) 2991, 1730, 1374, 1267, 1045, 752 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.13 – 8.11 (0.75H, m, Ar), 8.09 – 8.06 (0.25H, m, Ar), 7.58 – 7.48 (3H, m, Ar), 7.32 – 7.27 (5H, m, Ar), 6.44 – 6.42 (0.25H, m, CH_2CHO(CO)), 6.36 – 6.35 (0.75H, m, CH_2CHO(CO)), 3.50 (2.25H, s, OCH_3), 3.45 (0.75H, s, OCH_3), 2.68 – 2.64 (0.5H, m, CH_2CH_2C=), 2.59 – 2.55 (1.5H, m, CH_2CH_2C=), 2.22 – 2.20 (0.25H, m, CH_2CHHCH_2C=), 2.15 – 2.14 (0.75H, m, CH_2CHHCH_2C=), 1.99 – 1.91 (2H, m, $CHHCHHCH_2C$=), 1.80 – 1.57 (1H, m, $CHHCH_2CH_2C$=),; δ_C (100 MHz) 175.9 (CO, Ar, major), 175.6 (CO, Ar, minor) 168.1 (CO, Ar, major), 167.7 (CO, Ar, minor), 165.8 (C, Ar, major), 165.5 (C, Ar, minor), 155.8 (2 × C, Ar, major and minor), 133.7 (CH, Ar, major), 133.6 (CH, Ar, minor), 132.6 (C, Ar, major), 132.2 (C, Ar, minor), 129.4 (CH, Ar, major), 129.3 (CH, Ar, minor), 128.5 (CH, Ar, minor), 128.3 (CH, Ar, major), 128.1 (CH, Ar, major), 128.0 (CH, Ar, minor), 127.4 (CH, Ar, major), 125.85 (CH, Ar, minor), 125.83 (CH, Ar, major), 125.1 (CH, Ar, major), 125.0 (CH, Ar, minor), 124.3 (C, Ar, major), 124.2 (C, Ar, minor), 123.6 (C, Ar, major), 123.5 (C, Ar, minor), 122.4 (C, Ar, major), 122.3 (C, Ar, minor), 120.5 (2 × C, Ar, major and minor), 117.77 (CH, Ar, major), 117.74 (CH, Ar, minor), 115.59 (C, Ar, minor), 115.51 (C, Ar, major), 66.1 (2 × CF_3), 55.7 (OCH_3, major), 55.4 (OCH3, minor), 29.7 (=CH_2, minor), 27.8 (=CH_2, major), 27.6 ($CHCH_2$, minor), 27.1 ($CHCH_2$, major), 16.9 (=$CH_2CH_2CH_2$, minor), 16.4 (=$CH_2CH_2CH_2$, major); MS (ES^+) *m/z* = 433 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{23}H_{20}F_3O_5$ [$M+H^+$]: 433.1257; found: 433.1256.

(*R*)-1,2,3,4-Tetrahydro-1,4-diacetoxyxanthen-9-one (277, 278)



To a solution of **102** (100 mg, 0.46 mmol) in THF 5 mL) at – 78 °C was added KO^{t}Bu (111 mg, 0.99 mmol) in 2 portions over 10 minutes. The reaction mixture was allowed to warm to 10 °C, and stirred for 1 hour at the same temperature. To the dark red solution was added Davies reagent (240 mg, 0.92 mmol) at the same temperature and warmed to room temperature to stir for a further 2 hours. The reaction was quenched with saturated NH_4Cl solution (2 mL) and poured slowly into a separating funnel containing H_2O (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (3 × 5 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a colourless oil. Column chromatography (methanol : dichloromethane, 2 : 98) furnished a 1 : 1 mixture of **277** and **278** (43 mg, 41%) as a colourless oil. IR (thin film) 2912, 2835, 16507, 1509, 1242, 786 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.02 (0.47H, dd, *J* = 1.5, 8.0 Hz, 1H, min), 7.97 (0.53H, dd, *J* = 1.2, 8.0 Hz, Ar), 7.51 – 7.57 (1H, m, Ar), 7.32 – 7.35 (1H, m, Ar), 7.20 – 7.29 (1H, m, Ar), 4.81 – 4.95 (1H, m, Ar), 4.60 – 4.63 (0.47H, m, (CO)C=C*H*(OH)), 4.54 – 4.57 (0.53H, m, (CO)C=C*H*(OH)), 4.43 (0.53H, brs, (CO)C=CH(O*H*)), 4.23 (0.47H, brs, (CO)C=CH(O*H*)), 3.76 (0.53H, m, (O)C=CH(O*H*)), 3.61 – 3.63 (0.47H, m, (O)C=CH(O*H*)), 2.20 – 1.68 (4H, m, 1H, CH_2CH_2); δ_C (100 MHz) 179.39 (CO), 179.34 (CO), 164.0 (C, Ar), 163.8 (C, Ar), 155.98 (C, Ar), 155.94 (C, Ar), 134.1 (2 × CH, Ar), 125.46 (CH, Ar), 125.42 (CH, Ar), 125.25 (CH, Ar), 125.23 (CH, Ar), 123.1 (C, Ar), 123.0 (C, Ar), 120.2 (C, Ar), 120.1 (C, Ar), 118.08 (CH, Ar), 118.04 (CH, Ar), 66.1 ((CO)*C*=CH(OH)), 65.8 ((CO)C=*C*H(OH)), 64.0 (CH(OH)), 63.6 (CH(OH)), 27.1 (CH_2), 27.0 (CH_2), 25.9 (CH_2), 25.6 (CH_2); MS (ES$^+$) *m/z* = 255 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{13}H_{12}O_5Na$ [M+Na$^+$]: 255.0628; found: 255.0630.

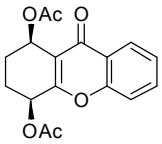
(1*R*,4*R*)-1,2,3,4-Tetrahydro-1,4-diacetoxyxanthen-9-one (280)



To a solution of **277**, and **278** (40.0 mg, 0.17 mmol) in pyridine (5 mL) was added acetic anhydride (0.16 mL, 1.70 mmol) and catalytic 4–dimethylamino pyridine (2.00 mg, 0.01 mmol). The reaction mixture was stirred for 24 hours before being poured into a separating funnel containing H_2O (10 mL) then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 0.5N HCl (3 × 10 mL), H_2O (3 × 10 mL), saturated $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 15 mL). The organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a thick colourless oil. Column

chromatography (diethyl ether : petroleum ether, 40 : 60) furnished **280** (25 mg, 47%) as a white solid and **279** (27 mg, 50%) as a white solid. $[\alpha]_D^{34°}$ + 94° (*c* 0.4, $CHCl_3$); M.p. 154 – 155 °C; IR (thin film) 2928, 1744, 1652, 1212, 1040, 727 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.12 (1H, dd, *J* = 1.6, 7.7 Hz, Ar), 7.63 – 7.59 (1H, m, Ar), 7.38 (1H, d, *J* = 8.5 Hz, Ar), 7.33 (1H, t, *J* = 7.1 Hz, Ar), 6.15 – 6.14 (1H, m, CHOAc), 5.82 – 5.81 (1H, m, CHOAc), 2.23 – 2.12 (1H, m, C*H*HCH_2), 2.07 (3H, s, CH*H*CH_2), 1.98 (3H, s, $OCOCH_3$), 1.90 – 2.00 (3H, m, $OCOCH_3$); δ_C (100 MHz) 176.3 (CO), 170.1 (CO), 169.9 (CO), 161.2 (C, Ar), 155.9 (C, Ar), 134.1 (CH, Ar), 125.9 (CH, Ar), 125.4 (CH, Ar), 123.7 (C, Ar), 118.7 (C, Ar), 118.2 (CH, Ar), 66.1 (CHOAc), 63.0 (CHOAc), 23.9 (CH_2), 23.0 (CH_2), 21.1 (CH_3), 21.0 (CH_3); MS (ES^+) *m/z* = 389 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{17}H_{16}O_6Na$ [$M+Na^+$]: 339.0841; found: 339.0839.

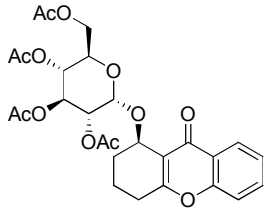
(1*R*,4*S*)-1,2,3,4-Tetrahydro-1,4-diacetoxyxanthen-9-one (279)



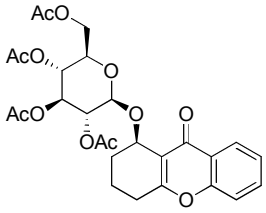
$[\alpha]_D^{34°}$ – 13.3° (*c* 0.3, $CHCl_3$); M.p. 147 – 148 °C; IR (thin film) 2937, 1742, 1648, 1468, 1220, 1017, 756 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.12 (1H, dd, *J* = 1.5, 8.2 Hz, Ar), 7.63 – 7.57 (1H, m, Ar), 7.35 – 7.31 (2H, m, Ar), 6.09 – 6.08 (1H, m, CHOAc), 5.87 (1H, dd, *J* = 5.8, 9.3 Hz, CHOAc), 2.15 (3H, s, CH_3), 2.14 – 2.04 (3H, m, CH*H*CH_2), 2.00 (3H, s, CH_3), 1.90 – 1.80 (1H, m, C*H*HCH_2); δ_C (100 MHz) 176.1 (CO), 170.2 (CO), 170.1 (CO), 162.4 (C, Ar), 155.7 (C, Ar), 134.0 (CH, Ar), 125.9 (CH, Ar), 125.4 (CH, Ar), 123.4 (C, Ar), 118.3 (C, Ar), 118.0 (CH, Ar), 67.1 (CHOAc), 63.3 (CHOAc), 25.4 (CH_2), 24.0 (CH_2), 21.1 (CH_3), 20.9 (CH_3); MS (ES^+) *m/z* = 389 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{17}H_{16}O_6Na$ [$M+Na^+$]: 339.0841; found: 339.0839.

Crystal Data. $C_{17}H_{16}O_6$, *M* =316.30, orthorhombic, *a* = 7.81730(10) Å, *b* = 11.96963(16) Å, *c* = 15.68901(18) Å, *V* = 1468.02(3) $Å^3$, *T* = 100(2), space group $P2_12_12_1$ (no. 19), *Z* = 4, μ(CuKα) = 0.916, 13875 reflections measured, 2810 unique (R_{int} = 0.0137) which were used in all calculations. The final wR_2 was 0.0696 (all data) and R_1 was 0.0270 (>2sigma(I)).

(*R*)-1-((2*S*,3*R*,4*S*,5*R*,6*R)-3,4,5-*Tris*(acetoxy)-6-(acetoxy)methyl)-tetrahydro-2*H*-pyran-2-yloxy)-1,2,3,4-tetrahydroxanthen-9-one (282) And (*R*)-1-((2*R*,3*R*,4*S*,5*R*,6*R**)-3,4,5-*Tris*(acetoxy)-6-(acetoxy)methyl)-tetrahydro-2*H*-pyran-2-yloxy)-1,2,3,4-tetrahydroxanthen-9-one (283)**



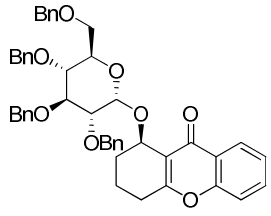
282



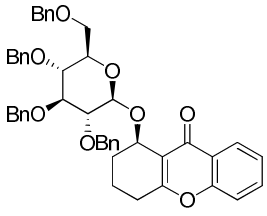
283

A solution of **102** (51.8 mg, 0.24 mmol) and tetra-*O*-acetyl-α-D-glucopyransyl bromide (**281**) (50.0 mg, 0.12 mmol) in dichloromethane (5 mL) was stirred at room temperature in the dark for 16 hours in the presence of Ag_2CO_3 (66.0 mg, 0.24 mmol). The mixture was filtered and the solvent evaporated *in vacuo* to obtain colourless oil. Column chromatography (ethyl acetate : petroleum ether, 15 : 85) furnished **282** and **283** (27 mg, 85%) as colourless oil in 2.8 : 1 respectively. IR (thin film) 2914, 1728, 1724, 1471, 1175, 716 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.14 – 8.12 (1H, m, Ar), 7.60 – 7.51 (1H, m, Ar), 7.35 – 7.25 (2H, m, Ar), 5.86 (0.65H, d, *J* = 5.2 Hz, H_1), 5.17 – 5.15 (1H, m, CH_2CHO), 5.13 – 5.10 (0.65H, m, H_3), 5.08 – 5.06 (0.35H, m, H_3), 5.00 – 4.94 (0.35H, m, H_1), 4.88 – 4.81 (1H, m, H_4), 4.33 (0.65H, dd, *J* = 5.1, 2.5 Hz H_2), 4.13 – 4.10 (2H, m, H_6), 4.07 – 4.03 (0.35H, m, H_2), 3.92 – 3.88 (0.65H, m, H_5), 3.60 – 3.54 (0.35H, m, H_5), 2.70 – 2.50 (4H, m, $OCHCH_2CH_2CH_2C$=), 2.27 – 1.63 (14H, m, 4 × (OCH_3), $OCHCH_2CH_2CH_2C$=); δ_C (100 MHz) 176.8 (CO), 176.4 (CO), 170.7 ($COCH_3$), 170.6 ($COCH_3$), 170.2 ($COCH_3$), 169.8 ($COCH_3$), 169.7 ($COCH_3$), 169.4 ($COCH_3$), 169.2 ($COCH_3$), 169.1 ($COCH_3$), 166.9 (C, Ar), 166.8 (C, Ar), 155.8 (2 × C, Ar), 133.6 (CH, Ar), 133.4 (CH, Ar), 125.8 (CH, Ar), 125.7 (CH, Ar), 124.9 (CH, Ar), 124.7 (2 × CH, Ar), 123.8 (C, Ar), 123.5 (C, Ar), 121.7 (C, Ar), 118.2 (C, Ar), 117.7 (CH, Ar), 117.6 (CH, Ar), 101.4 (OCHO, min), 97.2 (OCHO, maj), 73.3 ($AcOCH(CHOAc)_2$, min), 72.6 ($AcOCH(CHOAc)_2$, maj), 71.7 (AcO*C*HCHO, min), 70.1 (AcO*C*HCHO, maj), 70.0 (AcO*C*HCHCH_2, min), 68.38 (AcO*C*HCHCH_2, maj), 68.30 (AcOCH*C*HCH_2, min), 66.8 (AcOCH*C*HCH_2, maj), 63.8 (CH, min), 63.4 (CH, maj), 63.2 (OCH_2, maj), 61.5 (OCH_2, min), 29.6 (CH_2CH_2C=, min), 28.4 (CH_2CH_2C=, maj), 28.1 ($OCHCH_2CH_2$, min), 27.8 ($OCHCH_2CH_2$, maj), 20.88 ($COCH_3$), 20.85 ($COCH_3$), 22.7 ($COCH_3$), 22.66 ($COCH_3$), 22.60 ($COCH_3$), 22.56 ($COCH_3$), 16.2 ($OCHCH_2CH_2CH_2$, min), 16.2 ($OCHCH_2CH_2CH_2$, maj),; MS (ES^+) *m/z* = 457 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{27}H_{30}O_{12}Na$ [$M+Na^+$]:569.1635; found: 569.1639.

(*R*)-1-((2*S*,3*R*,4*S*,5*R*,6*R)-3,4,5-*Tris*(benzyloxy)-6-(benzyloxy)methyl)-tetrahydro-2*H*-pyran-2-yloxy)-1,2,3,4-tetrahydroxanthen-9-one (286) And (*R*)-1-((2*R*,3*R*,4*S*,5*R*,6*R**)-3,4,5-*tris*(benzyloxy)-6-(benzyloxy)methyl)-tetrahydro-2*H*-pyran-2-yloxy)-1,2,3,4-tetrahydroxanthen-9-one (287)**



286

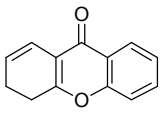


287

To a solution of trichloroacetimiate **285** (80 mg, 0.11 mmol) and the alcohol **102** (37.9 mg, 0.17 mmol) in dichloromethane (5 mL) were added molecular sieves (4 Å, 100 mgs) and stirred for 10 minutes at room temperature. Then TMSOTf (0.1M in dichloromethane, 2 mg, 0.01 mmol) was added dropwise over 10 minutes and stirred for an hour at 0 °C before treating with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was further extracted with dichloromethane (3 × 5 mL) and the organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a colourless oil. Column chromatography (ethyl acetate : petroleum ether, 20 : 80) furnished **286** and **287** (mg, 85%) in 1 : 1 ratio as colourless oil. IR (thin film) 2064, 1629, 1605, 1417, 1166, 754 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.15 – 8.13 (0.5H, m, Ar), 8.10 (0.5H, dd, *J* = 1.4, 7.9 Hz, Ar), 7.55 – 7.49 (1H, m, Ar), 7.30 – 7.11 (18H, m, Ar), 7.07 – 6.96 (4H, m, Ar), 5.86 (0.5H, d, *J* = 3.6 Hz, H_1), 5.19 – 5.16 (0.5H, m, CH), 5.05 – 5.01 (0.5H, m, CH), 4.86 (0.5H, d, *J* = 8.0 Hz, OC*H*HPh), 4.83 (1H, d, *J* = 7.1 Hz, OCH*H*Ph), 4.80 (0.5H, d, *J* = 9.3 Hz, H_1), 4.76 – 4.68 (1.5H, m, OCH_2Ph, OC*H*HPh), 4.66 (0.5H, d, *J* = 4.6 Hz, OCH*H*Ph), 4.63 (0.5H, d, *J* = 10.8 Hz, OC*H*HPh), 4.56 (0.5H, d, *J* = 12.1 Hz, OCH*H*Ph), 4.38 – 4.35 (2H, m, OCH_2Ph), 4.24 (0.5H, d, *J* = 12.4 Hz, OC*H*HPh), 3.96 (0.5H, d, *J* = 12.4 Hz, OCH*H*Ph), 3.87 – 3.83 (0.5H, m, H_3), 3.79 (0.5H, d, *J* = 9.3 Hz, H_3), 3.72 – 3.63 (1H, m, H_4), 3.59 – 3.45 (2.5H, m, H_2), 3.32 (0.5H, t, *J* = 8.3 Hz, H_2), 3.28 – 3.25 (0.5H, m, H_5), 3.18 – 3.15 (0.5H, m, H_5), 2.68 – 2.47 (2H, m, CH_2C=), 2.24 – 2.08 (2H, m, $OCHCH_2CH_2$), 1.77 – 1.74 (1H, m, OCHCH*H*CH_2), 1.59 – 1.40 (1H, m, OCHC*H*HCH_2),; δ_C (100 MHz) 177.0 (CO), 176.7 (CO), 166.7 (C, Ar), 166.4 (C, Ar), 156.0 (C, Ar), 155.9 (C, Ar), 139.0 (C, Ar), 138.7 (2 × C, Ar), 138.4 (C, Ar), 138.2 (C, Ar), 138.1 (2 × C, Ar), 138.0 (C, Ar), 133.5 (CH, Ar), 133.3 (CH, Ar), 128.6 – 125.8 (40 × CH, Ar), 124.7 (CH, Ar), 124.6 (CH, Ar), 123.9 (C, Ar), 123.8 (C, Ar), 119.1 (C, Ar), 119.0 (C, Ar), 117.8 (CH, Ar), 117.7 (CH, Ar), 103.0 (OCHO, *β*), 98.6 (OCHO, *α*), 85.0 (BnOCH$(CHOBn)_2$, *β*), 82.3 (BnOCHCHO, *β*), 81.8 (BnOCH$(CHOBn)_2$, *α*), 80.3 (BnOCHCHO, *α*), 78.0 (CH, *β*), 77.8 (CH, *α*), 75.6 (OCH_2, *β*), 75.5 (OCH_2, *α*), 75.3 ($PhCH_2O$, *β*), 74.8 ($PhCH_2O$, *α*), 74.7 ($PhCH_2O$, *β*), 74.5 ($BnOCHCHCH_2$, *β*), 73.6

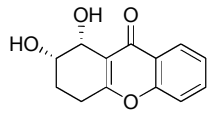
($PhCH_2O$, α), 73.2 ($PhCH_2O$, α), 72.4 ($PhCH_2O$, β), 70.8 ($BnOCHCHCH_2$, α), 69.4 ($BnOCHCHCH_2$, β), 68.8 ($PhCH_2O$, β), 68.3 ($BnOCHCHCH_2$, α), 68.2 ($PhCH_2O$, α), 29.2 ($CH_2CH_2C=$, β), 28.0 ($CH_2CH_2C=$, α), 27.9 ($OCHCH_2CH_2$, β), 27.8 ($OCHCH_2CH_2$, α), 16.8 ($OCHCH_2CH_2CH_2$, β), 16.3 ($OCHCH_2CH_2CH_2$, α),; MS (ES^+) *m/z* = 457 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{47}H_{46}O_8Na$ $[M+Na^+]$:761.3085; found: 761.3076.

5,6-Dihydroxanthen-9-one (**288**)



To a solution of **102** (1.00 g, 4.62 mmol) was added trifluoroacetic acid (0.7 mL, 9.2 mmol) dropwise in THF (15 mL). The reaction mixture was stirred for 1 hour and then poured into a separating funnel containing H_2O (15 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 15 mL). The organic layers were dried over $MgSO_4$, filtered and evaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (diethyl ether : petroleum ether, 10 : 90) furnished **288** (731 mg, 80%) as a yellow solid. M.p. 109 – 110 °C; IR (thin film) 1605, 1417, 1166, 894, 754 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.16 (1H, dd, *J* = 1.5, 7.9 Hz, Ar), 7.56 – 7.51 (1H, m, Ar), 7.35 – 7.28 (2H, m, Ar), 6.38 (1H, dt, *J* = 1.9, 9.8 Hz, CH_2CH=C*H*), 5.75 (1H, dt, *J* = 4.1, 9.8 Hz, CH_2CH=), 2.79 (2H, t, *J* = 9.1 Hz, $=CHCH_2CH_2$), 2.49 – 2.42 (2H, m, $=CHCH_2CH_2$); δ_C (100 MHz) 174.1 (CO), 164.2 (C, Ar), 159.2 (C, Ar), 132.9 (CH, Ar), 126.2 (CH, Ar), 124.9 (CH, Ar), 123.8 (C, Ar), 123.4 (=*C*HC), 119.2 ($=CHCH_2$), 117.8 (CH, Ar), 116 (C, Ar), 26.2 ($=CHCH_2CH_2$), 22.6 ($=CHCH_2CH_2$); MS (ES^+) *m/z* = 199 ([M+H])+, 100%); HRMS (ES^+): calcd. for $C_{13}H_{11}O_2$ $[M+H^+]$: 199.0754; found: 199.0753.

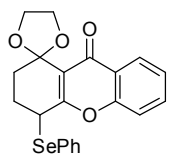
(1*R,2*S**)1,2,3,4-Tetrahydro-1,2-dihydroxyxanthen-9-one** (**289**)



Potassium carbonate (626 mg, 4.60 mmol), potassium ferricyanide (1.50 g, 4.55 mmol), OsO_4 (2.5 mg, 0.01 mmol), quinuclidine (31.0 mg, 0.27 mmol) and methanesulfonamide (143 mg, 1.50 mmol) were added to water (6 mL) and *tert*-butylalcohol (6 mL). The mixture was vigorously stirred until all the solids had dissolved. **288** (350 mg, 1.50 mmol) was added to the solution and a vigorous stirring of the solution was continued for 42 hours. Anhydrous sodium thiosulfate (567 mg, 4.50 mmol), was then added and the reaction mixture was stirred for a further hour before the addition of dichloromethane (15 mL). The layers were

separated and the aqueous phase was further extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with 2M KOH (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to obtain a colourless oil. Column chromatography (ethyl acetate : petroleum ether, 30 : 70) furnished **289** (245 mg, 70%) as a white solid. M.p. 139 – 140 °C; IR (thin film) 3357, 2919, 1627, 1465, 1105, 1061, 756 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.08 (1H, d, *J* = 8.3 Hz, Ar), 7.58 (1H, t, *J* = 7.7 Hz, Ar), 7.34 – 7.29 (2H, m, Ar), 5.11 (1H, brs, OH), 4.91 (1H, d, *J* = 3.8 Hz, $CH_2CH(OH)C\mathit{H}(OH)$), 4.06 – 4.01 (1H, m, $CH_2C\mathit{H}(OH)CH(OH)$), 3.09 (1H, brs, OH), 2.95 (1H, dt, *J* = 5.0, 18.3 Hz, $CH_2C\mathit{H}HC$=), 2.54 (1H, dt, *J* = 5.0, 18.3 Hz, ($C\mathit{H}HCH_2C$=), 2.21 – 2.13 (1H, m, $CH_2CH\mathit{H}C$=), 1.86 – 1.78 (1H, m, ($CH\mathit{H}CH_2C$=); δ_C (100 MHz) 179.5 (CO), 165.9 (C, Ar), 155.9 (C, Ar), 133.9 (CH, Ar), 125.4 (CH, Ar), 125.0 (CH, Ar), 123.0 (C, Ar), 117.8 (CH, Ar), 116.9 (C, Ar), 66.4 (OHCH), 66.2 (OHCH), 24.8 (CH_2), 24.6 (CH_2); MS (ES^+) *m/z* = 255 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{13}H_{12}O_4Na$ $[M+Na^+]$: 255.0628; found: 255.0630.

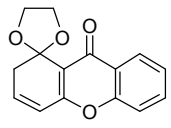
1,2,3,4-Tetrahydro-1-dioxa-spiro-4-(phenylselanyl)xanthen-9-one (**291**)



To a solution of **290** (2.09 g, 8.10 mmol) in THF (40 mL) at – 78 °C was added lithium diisopropylamide 2M in hexane (4.65 mL, 9.30 mmol) in a dropwise manner. The reaction mixture was stirred for 1 hour and phenylselenyl chloride (1.78 g, 9.30 mmol) was added to the yellow solution at the same temperature. The mixture was stirred for a further 2 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), diluted with H_2O (20 mL) and then allowed to warm up to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), the combined organic layers were washed with brine (3 × 15 mL), dried over $MgSO_4$ and evaporation of the solvent *in vacuo* gave yellow oil. The impure oil was purified by flash chromatography eluting with (ethyl acetate : petroleum ether, 40 : 60) to obtain a yellow oil (3.10 g, 90%). IR (thin film) 2954, 1617, 1463, 1393, 1023, 758 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.04 – 8.01 (1H, m, Ar), 7.61 – 7.58 (2H, m, Ar), 7.49 – 7.43 (1H, m, Ar), 7.26 – 7.18 (4H, m, Ar), 6.99 – 6.96 (1H, m, Ar), 4.51 – 4.49 (1H, m, $OC\mathit{H}HCH_2O$), 4.35 – 4.27 (2H, m, $OCH\mathit{H}CH\mathit{H}O$), 4.08 – 4.02 (1H, m, CHSePh), 3.97 – 3.90 (1H, m, $OCH_2C\mathit{H}HO$), 2.36 – 2.38 (1H, m, $CH_2C\mathit{H}HC(OCH_2CH_2O)$), 2.13 – 2.11 (1H, m, $CH_2CH\mathit{H}(OCH_2CH_2O)$), 2.09 – 2.00 (1H, m, $CH_2C\mathit{H}HCHSePh$), 1.89 – 1.83 (1H, m, $CH_2CH\mathit{H}CHSePh$); δ_C (75 Mz) 175.1 (CO), 166.3 (C, Ar), 154.3 (C, Ar), 135.2 (2 × CH, Ar), 132.7 (CH, Ar), 128.3 (CH, Ar), 128.1 (C, Ar), 128.0 (CH, Ar), 125.1 (CH, Ar), 124.3 (CH, Ar), 123.9 (CH, Ar), 123.7

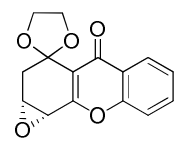
(C, Ar), 117.3 (C, Ar), 116.7 (CH, Ar), 106.2 (C), 66.0 (OCH_2), 65.6 (OCH_2), 40.4 (PhSeCH), 32.2 ((OCH$_2$CH$_2$O)C*C*H$_2$), 25.9 (PhSeCH*C*H$_2$); MS (ES^+) *m/z* = 437 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{21}H_{18}O_4SeNa$ $[M+Na]^+$: 437.0264; found: 437.0265.

1,2-Dihydro-1-dioxoa-spiro-xanthenes-9-one (**292**)



To a mixture of **291** (3.00 g, 7.22 mmol) and sodium hydrogen carbonate (1.20 g, 14.4 mmol) in dichloromethane (35 mL) at 0 °C was added *m*CPBA (1.90 g, 8.69 mmol). The reaction mixture was allowed to warm up to room temperature slowly and was further stirred for an hour. The reaction mixture was diluted with H_2O (20 mL) and the biphasic solution was extracted with dichloromethane (3 × 30 mL). The organic layers were washed with saturated sodium thiosulfate solution (3 × 15 mL), brine (3 × 15 mL), dried over $MgSO_4$, filtered and evaporation of solvent *in vacuo* gave a yellow oil. The crude oil was purified by flash chromatography eluting with (ethyl acetate : petroleum ether, 50 : 50) to obtain a white solid (1.48 g, 80%). M.p. 120 – 121 °C; IR (thin film) 2972, 1638, 1597, 1462, 1235, 1064, 759 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.19 – 8.17 (1H, d, *J* = 8.0 Hz, Ar), 7.63 – 7.59 (1H, t, *J* = 8.0 Hz, Ar), 7.38 – 7.34 (2H, m, Ar), 6.59 – 6.54 (1H, dt, *J* = 4.2, 9.8, Hz, CH$_2$C*H*CH), 6.39 – 6.36 (1H, m, CH$_2$CHC*H*), 4.47 – 4.43 (2H, m, OC*H*$_2$CH$_2$O), 4.11 – 4.08 (2H, m, OCH$_2$C*H*$_2$O), 2.87 – 2.85 (2H, m, C*H*$_2$); δ_C (100 MHz) 175.6 (CO), 161.6 (C, Ar), 154.8 (C, Ar), 137.3 (CH, Ar), 133.3 (CH, Ar), 125.8 (CH, Ar), 125.4 (C, Ar), 125.0 (CH, Ar), 120.9 (CH$_2$*C*HCHC=), 117.6 (CH$_2$CH*C*HC=), 115.0 (C, Ar), 107.4 (*C*(OCH$_2$CH$_2$O)), 66.3 (OCH_2), 60.4 (OCH_2), 38.9 (CH_2); MS (ES^+) *m/z* = 279 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{15}H_{12}O_4Na$ $[M+Na]^+$: 279.0628; found: 279.0621.

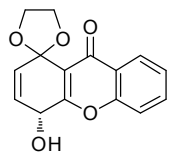
(1*R*, 9*R*)-2,3-Dihydro-3-dioxoa-spiro-1-oxireno[2,3-c]xanthen-4(9)-one (**293**)



To a solution of **292** (1.17 g, 4.57 mmol,), NH_4OAc (138 mg, 1.82 mmol) and **294** (114 mg, 0.18 mmol) in dichloromethane – methanol (1 : 1) (7.2 mL) was added precooled (0 °C) 30 % aqueous H_2O_2 (4.9 M, 2.18 mL, 13.8 mmol) in 4 portions over 40 minutes at 0 °C. The reaction was stirred at 0 °C for 1 hour and then allowed to warm upto room temperature and stirred for 48 hours. The reaction was diluted with dichloromethane (20 ml) and transferred into a separating funnel containing H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic

layers were washed with brine (3 × 15 mL), dried over $MgSO_4$, and evaporation of solvent *in vacuo* gave a yellow oil. The crude oil was purified by flash chromatography eluting with (ethyl acetate : petroleum ether, 1 : 1) to obtain a yellow oil (646 mg, 44%). $[\alpha]_D^{34°}$ – 21° (*c* 0.4, $CHCl_3$); HPLC analysis on Chiracel OD+1 (90 : 10 hexane : isopropanol, 1 mL/min) showed the major enantiomer at 19.5 min (87.5 A%) and the minor one at 23.2 min (12.5 A%) ee 75%; IR (thin film) 2963, 1645, 1464, 1334, 1151, 1007, 825 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.95 – 7.92 (1H, m, Ar), 7.46 – 7.40 (1H, m, Ar), 7.24 – 7.14 (2H, m, Ar), 4.39 – 4.30 (1H, m, OC*H*HCH_2O), 4.13 – 4.07 (1H, m, OCH_2CHHO), 3.93 – 3.80 (2H, m, OCH*H*CH*H*O), 3.69 – 3.68 (1H, m, OC*H*C=), 3.61 – 3.58 (1H, m, OC*H*CHC=), 2.50 – 2.44 (1H, m, C*H*HC($O(CH_2)_2O$), 2.17 – 2.08 (1H, m, CH*H*C($O(CH_2)O$); δ_C (75 MHz) 174.2 (CO), 162.0 (C, Ar), 154.6 (C, Ar), 133.0 (CH, Ar), 125.4 (CH, Ar), 124.9 (CH, Ar), 124.4 (CH, Ar), 117.9 (C, Ar), 117.0 (C, Ar), 103.7 (*C*($O(CH_2)_2O$), 66.0 (OCH_2CH_2O), 65.7 (OCH_2), 50.7 (O*C*HC=), 48.0 (OCH_2), 35.2 (CH_2), ; MS (ES^+) *m/z* = 295 ($[M+Na]$)$^+$, 100%); HRMS (ES^+): calcd. for $C_{15}H_{12}O_5Na$ $[M+Na]^+$: 295.0577; found: 295.0574.

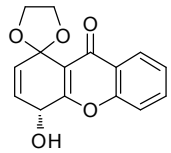
1-Dioxoa-spiro-4-hydroxy-4H-xanthene-9-one (**297**)



To a solution of benzyl alcohol (0.03 mL, 0.30 mmol) in THF (5 mL) at 0 °C was added sodium hydride 60 % (8.00 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 30 minutes. To the cloudy solution was added **293** (55.0 mg, 0.20 mmol) and the stirring was continued for 6 hours. The reaction was slowly quenched with saturated NH_4Cl solution (5 mL). The reaction mixture was transferred to a separating funnel containing H_2O (5 mL) and was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a yellow solid. The crude material was purified by flash chromatography eluting with (dichloromethane : methanol, 98 : 2) to furnish **297** (47 mg, 85 %) as a yellow solid. M.p. 120 – 121 °C; IR (thin film) 2918, 1652, 1599, 1464, 1279, 1072, 756 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.24 – 8.21 (1H, m, Ar), 7.82 – 7.76 (1H, m, Ar), 7.62 – 7.59 (1H, d, *J* = 8.3 Hz, Ar), 7.44 – 7.39 (1H, t, *J* = 8.3 Hz, Ar), 7.26 – 7.23 (1H, d, *J* = 9.2 Hz, CH=C*H*CH(OH)), 6.88 – 6.85 (1H, d, *J* = 8.8 Hz, C*H*=CHCH(OH)), 4.17 – 4.14 (2H, m, OCH_2CH_2O), 3.95 – 3.92 (2H, m, OCH_2CH_2O), 3.33 – 3.31 (1H, m, =CHC*H*(OH)); δ_C (75 MHz) 181.4 (CO), 156.4 (C, Ar), 153.3 (C, Ar), 141.5 (C, Ar), 136.1 (CH, Ar), 127.3 (CH, Ar), 125.3 (CH, Ar), 123.5 (C, Ar), 122.1 (=CH=*C*HCH(OH)), 118.8 (CH), 109.6 (=*C*H=CHCH(OH)), 103.3 (C), 83 (*C*H(OH)),

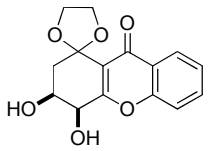
73.6 (O*C*H_2), 61.6 (O*C*H_2); MS (ES^+) *m/z* = 295 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{15}H_{12}O_5Na$ $[M+Na]^+$: 295.0577; found: 295.0574.

1-Dioxoa-spiro-4-hydroxy-4H-xanthene-9-one (**297**)



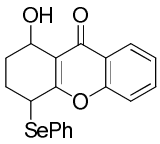
To a solution of **293** (50.0 mg, 0.19 mmol) in THF (5 mL) at 0 °C was added benzyl alcohol (0.03 mL, 0.30 mmol) and *para*-toluenesulfonic acid dihydrate (2.50 mg, 0.10 mmol). The reaction mixture was stirred for 1 hour. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* gave a yellow solid. The crude material was purified by flash chromatography eluting with (dichloromethane : methanol, 2 : 98) to furnish **297** (45 mg, 90 %) as a yellow solid. Data as previously reported.

(3*S,4*S**)1-(1,3-dioxalane)-3,4-Dihydro-3,4-dihydroxy-2H-xanthene-9-one** (**299**)

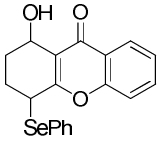


To a stirred solution of **293** (1.20 g, 4.68 mmol) in a mixture of acetone (6.00 mL), H_2O (6.00 mL) and ^{t}BuOH (2.40 mL) at room temperature was added *N*-methylmorpholine-*N*-oxide monohydrate (759 mg, 5.61 mmol) and a catalytic amount of OsO_4 (20 µL, 0.02 gm/mL, ^{t}BuOH). The reaction mixture was stirred for 48 hours, and then treated with sodium metabisulfite (1.06 g, 5.61 mmol). The reaction mixture was stirred for 1 hour and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 1N HCl (20 mL), H_2O (3 × 30 mL), brine (3 × 15 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (methanol : dichloromethane, 2 : 98) furnished **299** (720 mg, 60%) as a yellow solid. M.p. 230 – 231 °C; IR (thin film) 2928, 1628, 1536, 1160, 764 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.93 – 7.90 (1H, m, Ar), 7.44 – 7.38 (1H, m, Ar), 7.24 – 7.21 (1H, m, Ar), 7.14 – 7.11 (1H, m, Ar), 4.30 (1H, d, *J* = 4.0 Hz, (OH)C*H*C=), 4.35 – 4.23 (2H, m, OC*H*$_2$CH_2O), 4.05 – 4.00 (1H, m, OHC*H*CH_2), 3.95 – 3.82 (2H, m, OCH_2C*H*$_2$O), 2.11 (1H, dd, *J* = 8.1, 13.9 Hz, C*H*H), 1.90 (1H, dd, *J* = 2.7, 13.9 Hz, CH*H*); δ_C (75 MHz) 175.0 (CO), 162.8 (C, Ar), 155.0 (C, Ar), 133.2 (CH, Ar), 125.2 (CH, Ar), 124.7 (CH, Ar), 123.7 (C, Ar), 117.7 (C, Ar), 117.2 (CH, Ar), 105.7 (C, Ar), 67.9 (O*C*H_2), 66.0 ((OH)CH), 65.8 ((OH)CH), 65.7 (O*C*H_2), 37.5 (CH_2); MS (ES^+) *m/z* = 313 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{15}H_{12}O_6Na$ $[M+Na^+]$:313.0683; found: 313.0675.

(1*R,4*S**) 1,2,3,4-Tetrahydro-1-hydroxy-4-(phenylselanyl)xanthen-9-one and (1*R**, 4*R**)1,2,3,4-Tetrahydro-1-hydroxy-4-(phenylselanyl)xanthen-9-one (303)**

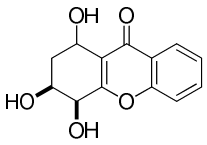


To a solution of **102** (1.00 g, 4.62 mmol) in THF (25 mL) at – 78 °C was added KO^{t}Bu (1.10 g, 9.70 mmol) in two portions over 10 minutes. The reaction mixture was allowed to warm up to 10 °C, and stirred for 1 hour at the same temperature. To the dark red solution was added phenylselenyl chloride (1.06 g, 5.08 mmol), at the same temperature and warmed to room temperature to stir for a further 2 hours. The reaction was slowly quenched with saturated NH_4Cl solution (5 mL) and poured into a separating funnel containing H_2O (15 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL), washed with brine (3 × 15 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 15 : 85) furnishedthe cis and trans diastereomers of **303** (660 mg, 38%), and (710 mg, 41%) as yellow oils. IR (thin film) 3456, 2918, 1620, 1463, 1223, 1044, 759 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.16 – 8.14 (1H, d, *J* = 8.0 Hz, Ar), 7.70 – 7.68 (2H, d, *J* = 7.4 Hz, Ar), 7.64 – 7.62 (1H, m, Ar), 7.40 – 7.30 (4H, m, Ar), 7.22 – 7.20 (1H, d, *J* = 8.6 Hz, Ar), 5.12 – 5.08 (1H, m, C*H*(OH)), 4.81 (1H, brs, O*H*), 4.34 – 4.33 (1H, m, C*H*SePh), 2.30 – 2.07 (4H, m, CHCH_2CH_2CH); δ_C (100 MHz) 179.3 (CO), 164.7 (C, Ar), 155.7 (C, Ar), 137.5 (CH, Ar), 137.4 (CH, Ar), 135.7 (CH, Ar), 129.2 (CH, Ar), 129.0 (CH, Ar), 128.6 (C, Ar), 127.7 (CH, Ar), 125.4 (CH, Ar), 125.1 (CH, Ar), 123.1 (C, Ar), 119.6 (C, Ar), 117.8 (CH, Ar), 65.3 (CH(OH)), 40.7 (PhSeCH), 27.0 (CH_2), 26.8 (CH_2); MS (ES$^+$) *m/z* = 395 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{21}H_{18}O_3SeNa$ [M+Na$^+$]: 395.0158; found: 395.0173.



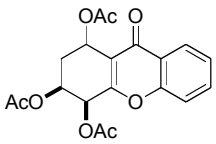
IR (thin film) cm^{-1} 3456, 2918, 1620, 1463, 1223, 1044, 759 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.16 – 8.14 (1H, d, *J* = 8.0 Hz, Ar), 7.68 – 7.66 (2H, d, *J* = 7.4 Hz, Ar), 7.64 – 7.60 (1H, t, *J* = 8.0 Hz, Ar), 7.38 – 7.29 (4H, m, Ar), 7.20 – 7.18 (1H, d, *J* = 8.6 Hz, Ar), 5.05 (1H, m, C*H*(OH)), 4.3 (1H, m, PhSeC*H*), 3.66 (1H, brs, O*H*), 2.57 – 2.51 (1H, m, PhSeCHC*H*HCH$_2$), 2.09 – 2.00 (3H, m, PhSeCHCH*H*C*H*$_2$); δ_C (100 MHz) 178.6 (CO), 165.0 (C, Ar), 155.6 (C, Ar), 135.8 (CH, Ar), 135.5 (CH, Ar), 133.8 (CH, Ar), 129.2 (C, Ar), 128.9 (2 × CH, Ar), 127.7 (CH, Ar), 125.5 (CH, Ar), 125.0 (CH, Ar), 123.3 (C, Ar), 119.3 (C, Ar), 117.8 (CH, Ar), 61.1 ((OH)CH), 40.6 (PhSe*C*H), 26.5 (CH_2), 24.9 (CH_2); MS (ES$^+$) *m/z* = 395 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{19}H_{18}O_3SeNa$ [M+Na$^+$]: 395.0158; found: 395.0173.

(3*S,4*S**)-1,2,3,4-Tetrahydro-1,3,4-trihydroxyxanthen-9-one (306)**



To a stirred solution of crude **304** (500 mg, 2.33 mmol) in a mixture of acetone (4.16 mL), H_2O (4.16 mL) and ^{t}BuOH (1.68 mL) at room temperature was added *N*-methylmorpholine-*N*-oxide monohydrate (377 mg, 2.79 mmol) and a catalytic amount of OsO_4 (20 μL, 0.02 gm/mL, ^{t}BuOH). The reaction mixture was stirred for 48 hours, then it was treated with sodium metabisufite (105 mg, 0.55 mmol). The reaction mixture was stirred for 1 hour and then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 1 N HCl (15 mL), H_2O (3 × 30 mL), brine (3 × 15 mL) and dried over $MgSO_4$ and evaporation of solvent *in vacuo* gave a yellow oil. Column chromatography (methanol : dichloromethane, 5 : 95) furnished **306** (173 mg, 30%) as a colourless oil. IR (thin film) 3334, 2918, 1629, 1466, 1096, 1095, 762 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.11 – 8.13 (1H, m, Ar), 7.67 – 7.62 (1H, m, Ar), 7.50 (1H, d, *J* = 8.2 Hz, Ar), 7.38 – 7.34 (1H, m, Ar), 5.03 (1H, t, *J* = 4.1 Hz, CH_2CHOH), 4.52 (1H, d, *J* = 4.1 Hz, $CH_2HOCHCHOH$), 4.20 – 4.00 (1H, m, $CH_2HOCHCHOH$), 2.44 – 2.41 (1H, m, C*H*H), 1.99 – 191 (1H, m, CH*H*); δ_C (75 MHz) 178.2 (CO), 161.8 (C, Ar), 156.5 (C, Ar), 134.1 (CH, Ar), 129.7 (CH, Ar), 125.5 (CH, Ar), 123.2 (C, Ar), 119.3 (C, Ar), 118.3 (CH, Ar), 68.9 ($CH_2(OH)CH$), 67.5 ($CH_2CH(OH)CH(OH)$), 62.9 ($CH_2CH(OH)CH(OH)$), 32.1 (CH_2); MS (ES^+) *m/z* = 271 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{13}H_{12}O_5Na$ [$M+Na^+$]: 271.0577; found: 271.0575.

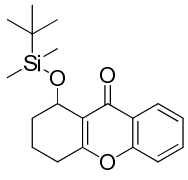
(3*S,4*S**)-1,2,3,4-Tetrahydro-1,3,4-triacetoxyxanthen-9-one (307)**



To a solution of **306** (25.0 mg, 0.10 mmol) was added acetic anhydride (0.10 mL, 1.00 mmol) and catalytic 4–dimethylamino pyridine (1.20 mg, 0.01 mmol) in pyridine (2 mL). The reaction mixture was stirred for 48 hours before pouring into a separating funnel containing H_2O (5 mL) and then extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with 0.5N HCl (3 × 5 mL), H_2O (3 × 5 mL), saturated $NaHCO_3$ solution (3 × 5 mL) and brine (3 × 5 mL). The organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* gave a colourless oil. Column chromatography (diethyl ether : petroleum ether, 10 : 90) furnished **307** (35.0 mg, 94%) as white solid. M.p. 158 – 160 °C; IR (thin film) 3068, 2358, 1737, 1646, 1366, 1042, 759 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.00 – 7.97 (1H, m, Ar), 7.53 – 7.48 (1H, m, Ar), 7.25 (2H, d, *J* = 7.7 Hz, Ar), 6.05 (1H, t, *J* = 5.8 Hz, $AcOCHCH_2$), 5.92 (1H, d, *J* = 3.8 Hz, $AcOCHCHOAcC$=), 5.07 – 5.00 (1H, m, $CH_2AcOCHCHOAcC$=), 2.25 – 2.12 (2H, m, CH_2), 2.05 (3H, s,

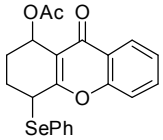
$OCOCH_3$), 1.90 (3H, s, $OCOCH_3$), 1.87 (3H, s, $OCOCH_3$); δ_C (125 MHz) 175.1 (CO), 169.4 (CO), 169.3 (CO), 169.2 (CO), 158.0 (C, Ar), 155.1 (C, Ar), 133.5 (CH, Ar), 125.3 (CH, Ar), 125.0 (CH, Ar), 122.9 (C, Ar), 117.6 (C, Ar), 117.4 (CH, Ar), 65.9 (AcO*C*HCH$_2$), 65.5 (CH$_2$AcOCH*C*HOAc), 61.9 (CH$_2$AcO*C*HCHOAc), 28.3 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 20.0 (CH_3); MS (ES^+) *m/z* = 397 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{19}H_{18}O_8Na$ [$M+Na^+$]: 397.0894; found: 397.0896.

1-*Tert*-butyldimethylsilyloxy-1,2,3,4-tetrahydroxanthen-9-one (308)



To a solution of **102** (1.00 g, 4.62 mmol) in DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (900 mg, 6.00 mmol) followed by the addition of imidazole (409 mg, 6.00 mmol). The reaction mixture was stirred for 2 hours and then poured into H_2O (20 mL). The biphasic solution was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with H_2O (3 × 15 mL), brine (3 × 15 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (diethyl ether : petroleum, ether 5 : 95) furnished **308** (1.45 g, 96%) as a white solid. M.p. 126 – 127 °C; IR (thin film) 2950, 1635, 1468, 1244, 1022, 775 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.06 (1H, dd, *J* = 1.4, 8.1 Hz, Ar), 7.49 – 7.43 (1H, m, Ar), 7.24 – 7.17 (2H, m, Ar), 4.90 (1H, t, *J* = 4.6 Hz, C*H*(OTBS)), 2.62 – 2.41 (2H, m, CH$_2$C*H*$_2$C=), 2.17 – 2.01 (1H, m, C*H*HCH$_2$CH(OTBS)), 1.77 – 1.75 (1H, m, CH*H*CH$_2$CH(OTBS)), 1.73 – 1.66 (1H, m, C*H*HCH(OTBS)), 1.46 – 1.35 (1H, m, CH*H*CH(OTBS)), 0.74 (9H, s, C(CH_3)$_3$), 0.12 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); δ_C (75 MHz) 176.5 (CO), 165.9 (C, Ar), 155.9 (C, Ar), 133.0 (CH, Ar), 125.8 (CH, Ar), 124.5 (CH, Ar), 124.0 (C, Ar), 120.5 (C, Ar), 117.6 (CH, Ar), 60.9 (CH(OTBS)), 31.0 (CH$_2$*C*H$_2$CH(OTBS)), 28.0 (CH$_2$*C*H$_2$C=), 25.9 (3 × CH_3), 18.1 (C(CH_3)), 15.9 (CH$_2$*C*H$_2$CH$_2$), -4.3 ($SiCH_3$), -5.2 ($SiCH_3$); MS (ES^+) *m/z* = 353 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{19}H_{26}O_3SiNa$ [$M+Na^+$]: 353.1543; found: 353.1542.

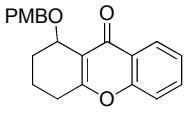
1,2,3,4-Tetrahydro-1-acetoxy-4-(phenylselanyl)xanthen-9-one (311)



To a solution of **303** (770 mg, 2.06 mmol) in pyridine (10 mL) was added acetic anhydride (0.60 mL, 6.20 mmol) and catalytic 4-dimethylamino pyridine (25.0 mg, 0.20 mmol). The reaction mixture was stirred for 16 hours before pouring into a separating funnel containing H_2O (10 mL) and extracting with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1M HCl (3 × 10 mL), H_2O (3 × 10 mL), $NaHCO_3$ (3 × 10 mL) and brine (3 × 15 mL). The

organic layers were dried over $MgSO_4$, filtered, and evaporation of solvent *in vacuo* gave a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 15 : 85) furnished **311** (539 mg, 70%) as a yellow oil. IR (thin film) 2922, 2338, 1634, 1465, 1236, 949, 738 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.11 (0.16H, dd, *J* = 1.2, 6.6 Hz, Ar), 8.08 (0.84H, dd, *J* = 1.7, 7.9 Hz, Ar), 7.57 – 7.59 (2H, m, Ar), 7.50 – 7.53 (1H, m, Ar), 7.19 – 7.33 (4H, m, Ar), 7.16 (0.16H, d, *J* = 8.6 Hz, Ar), 7.08 (0.84H, d, *J* = 8.4 Hz, Ar), 6.13 (0.16H, t, *J* = 3.1 Hz, C*H*OAc), 6.07 – 6.09 (0.84H, m, C*H*OAc), 4.33 – 4.34 (0.84H, m, C*H*SePh), 4.25 (0.16H, dd, *J* = 2.3, 6.3 Hz, C*H*OSePh), 1.9 (0.48H, s, CH_3), 2.33 – 2.43 (1H, m, PhSeCHC*H*HCH$_2$CHOAc), 2.01 – 2.12 (3H, m, PhSeCHCH*H*C*H*$_2$CHOAc), 1.9 (2.52H, s, CH_3); δ_C (100 MHz) 176.2 (2 × CO, Ar, major and minor), 170.0 (2 × CO, major and minor), 166.4 (2 × C, Ar, major and minor), 155.5 (2 × C, Ar, major and minor), 136.0 (2 × CH, Ar, major and minor), 135.9 (CH, Ar), 133.7 (2 × CH, Ar, major and minor), 129.2 (2 × CH, Ar, major and minor), 129.1 (CH, Ar), 128.8 (CH, Ar), 128.6 (CH, Ar), 128. (C, Ar), 125.8 (2 × CH, Ar, major and minor), 125.1 (2 × CH, Ar, major and minor), 123.5 (C, Ar), 117.7 (2 × CH, Ar, major and minor), 115.6 (C, Ar), 64.0 (CHOAc, minor), 63.2 (CHOAc, major), 40.2 (PhSeCH, major), 39.0 (PhSeCH, minor), 24.8 (CH_2, minor), 24.6 (CH_2, major), 21.1 (2 × CH_3, major and minor); MS (ES^+) *m/z* = 437 $([M+Na])^+$, 100%); HRMS (ES^+): calcd. for $C_{21}H_{18}O_4SeNa$ [$M+Na^+$]: 437.0267; found: 437.0264.

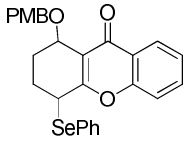
1-(4-Methoxybenzyloxy)-1,2,3,4-Tetrahydroxanthen-9-one (312)



To a solution of **102** (490 mg, 2.26 mmol) in Et_2O (10 mL) was added *para*-methoxybenzyl trichloroacetimidate (0.93 mL, 4.53 mmol) followed by the addition of trifluoroacetic acid (1 mg, 0.006 mmol). The cloudy reaction mixture was stirred for 2 hours. To drive the reaction to completion a further 3 drops of trifluoroacetic acid was added and the reaction mixture was filtered before evaporating the solvent *in vacuo* to provide a thick yellow oil. Column chromatography (ethyl acetate : petroleum ether, 15 : 85) furnished **312** (625 mg, 77%) as a yellow oil. IR (thin film) 2989, 1962, 1634, 1464, 1240, 1069, 756 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.10 – 8.06 (1H, m, Ar), 7.49 – 7.43 (1H, m, Ar), 7.24 – 7.18 (4H, m, Ar), 6.75 – 6.70 (2H, m, Ar), 4.78 (1H, t, *J* = 2.2 Hz, C*H*(OCH_2)), 4.61 – 4.53 (2H, m, OC*H*$_2$), 3.63 (3H, s, OCH_3), 2.60 – 2.42 (2H, m, CH_2CH_2C=), 2.07 – 1.99 (2H, m, C*H*HC*H*HCH), 1.76 – 1.68 (1H, m, CH*H*CH), 1.41 – 1.29 (1H, m, CH*H*CH_2CH); δ_C (75 MHz) 176.4 (CO), 166.1 (C, Ar), 158.4 (C, Ar), 155.2 (C, Ar), 132.7 (CH, Ar), 130.5 (C, Ar), 128.9 (CH, Ar), 128.5 (CH, Ar), 125.2 (CH, Ar), 124.0 (CH, Ar), 123.2

(C, Ar), 118.3 (C, Ar), 117.0 (CH, Ar), 113.5 (CH, Ar), 113.0 (CH, Ar), 71.4 (CHOPMB), 67.3 ($CH_2OC_6H_4OMe$), 54.6 ($PhOCH_3$), 27.3 (CH_2C=), 26.2 (CH_2CH), 15.7 ($CH_2CH_2CH_2$); MS (ES^+) *m/z* = 359 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{21}H_{20}O_4Na$ [$M+Na^+$]: 359.1254; found: 359.1264.

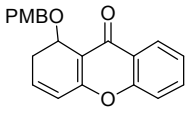
1-(4-Methoxybenzyloxy)-1,2,3,4-Tetrahydro-4-(phenylselanyl)xanthen-9-one (320)



To a solution of **303** (3.00 g, 8.06 mmol) in Et_2O (20 mL) was added *para*-methoxybenzyl trichloroacetimidate (3.34 mL, 16.1 mmol) followed by the addition of catalytic trifluoroacetic acid (3.60 mg, 0.02 mmol, 0.3 mol %). The dark red reaction mixture was stirred for 3 hours, followed by the addition of further 3 drops of triflouroaceict acid to drive the reaction to completion and then poured into a separating funnel containing H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over $MgSO_4$ and evaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 25 : 75) furnished a mixture of diastereomers in 1 : 3 (3 g, 76%) as a yellow oil. IR (thin film) 3456, 2918, 1620, 1463, 1223, 1044, 759 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.21 (1H, d, *J* = 7.9 Hz, Ar), 7.72 – 7.58 (3H, m, Ar), 7.40 – 7.29 (6H, m, Ar), 7.17 (0.25H, d, *J* = 8.3 Hz, Ar), 7.14 (0.75H, d, *J* = 8.3 Hz, Ar), 6.89 – 6.85 (2H, m, Ar), 4.95 (0.25H, m, CHOPMB), 4.83 (0.75H, m, CHOPMB), 4.77 – 4.68 (1.5H, m, $CH_2C_6H_4OMe$), 4.67 – 4.61 (0.5H, m, $CH_2C_6H_4OMe$), 4.40 (0.75H, d, *J* = 4.3 Hz, PhSeCH), 4.37 – 4.32 (0.25H, m, PhSeCH), 3.81 (0.75H, s, OCH_3), 3.70 (2.25H, s, OCH_3), 2.72 – 2.63 (0.75H, m, PMBOCHC*H*H), 2.48 – 2.38 (0.25, m, PMBOCHC*H*H), 2.48 – 2.22 (0.25H, m, PMBOCHOCH*H*), 2.14 – 2.09 (1.75H, m, PMOCHCH*H*C*H*H), 1.99 – 1.89 (0.75H, m, PhSeCH*H*), 1.65 – 1.56 (0.25H, m, PhSeCH*H*); δ_C (100 MHz) 177.1 (2 × CO, Ar, major and minor), 165.4 (2 × C, Ar, major and minor), 159.1 (2 × C, Ar, major and minor), 155.5 (2 × C, Ar, major and minor), 135.9 (2 × CH, Ar, major and minor), 135.5 (CH, Ar, minor), 133.5 (CH, Ar, minor), 133.4 (CH, Ar, major), 131.7 (C, Ar, minor), 130.9 (C, Ar, major), 129.7 (2 × CH, Ar, major and minor), 129.3 (CH, Ar, major), 129.1 (2 × CH, Ar, major and minor), 129.0 (CH, Ar, minor), 128.9 (C, Ar, minor), 128.6 (2 × CH, Ar, major and minor), 128.3 (CH, Ar, minor), 125.9 (CH, Ar, minor), 125.8 (2 × CH, Ar, major and minor), 124.9 (CH, Ar, major), 124.8 (2 × CH, Ar, major and minor), 123.8 (C, Ar, minor), 118.0 (C, Ar, major), 117.7 (2 × CH, Ar, major and minor), 113.7 (2 × CH, Ar, major and minor), 113.6 (CH, Ar, major), 72.4 ($OCH_2C_6H_4OMe$, major), 71.4 ($OCH_2C_6H_4OMe$, minor), 67.8 (CHOPMB, major), 67.4

(CHOPMB, minor), 55.2 (2 × OCH_3, major and minor), 40.9 (CHSePh, major), 39.1 (CHSePh, minor), 28.2 (PMBOCH*C*H_2, major), 25.4 (PMBOCH*C*H_2, minor), 24.6 (PhSeCH*C*H_2, major), 23.9 (PhSeCH*C*H_2, minor); MS (ES^+) *m/z* = 515 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{27}H_{24}O_4SeNa$ [$M+Na^+$]: 515.0734; found: 515.0733.

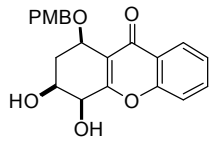
1-(4-Methoxybenzyloxy)-1,2-Dihydroxanthen-9-one (**321**)



To a solution of **320** (2.00 g, 4.06 mmol) in dichloromethane (20 mL) at – 15 °C was added $NaHCO_3$ (341 mg, 4.06 mmol) and *m*CPBA (77%) (1.06 g, 4.87 mmol) over 2 minutes. The reaction mixture was allowed to warm upto room temperature and stirring continued for 2 hours until tlc showed the complete consumption of the starting material. The cloudy reaction mixture was poured into a separating funnel containing H_2O (20 mL) and extracted with dichloromethane (3 × 15 mL). The organic layers were washed with saturated sodium thiosulfate solution (20 mL), brine (15 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain a thick yellow oil, which on washing with petroleum ether (40 mL) left a white solid that was quickly used in the next reaction. IR (thin film) 2836, 1609, 1426, 1245, 1026, 760 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.22 (1H, dd, *J* = 1.7, 7.8 Hz, Ar), 7.61 – 7.58 (1H, m, Ar), 7.42 – 7.34 (2H, m, Ar), 7.26 – 7.24 (2H, m, Ar), 6.81 – 6.78 (2H, m, Ar), 6.59 – 6.54 (1H, m, CH_2CH=CH), 6.38 (1H, dd, *J* = 3.0, 9.7 Hz, CH_2CH=C*H*), 5.07 (1H, dt, *J* = 1.3, 6.1 Hz, C*H*OPMB), 4.59 (1H, d, *J* = 11.4 Hz, OC*H*H), 4.51 (1H, d, *J* = 11.4 Hz, OCH*H*), 3.71 (3H, s, OCH_3), 2.81 – 2.89 (1H, m, =CHC*H*HCH), 2.44 – 2.54 (1H, m, =CHCH*H*CH); δ_C (75 MHz) 176.3 (CO), 160.2 (C, Ar), 158.4 (C, Ar), 154.7 (C, Ar), 138.4 (CH_2CH), 132.7 (CH, Ar), 130.4 (C, Ar), 128.9 (2 × CH, Ar), 125.3 (CH, Ar), 124.3 (CH, Ar), 124.0 (C), 120.2 (CH=*C*HC=), 117.4 (CH, Ar), 113.5 (C, Ar), 113.0 (2 × CH), 70.3 ($MeOPhOCH_2$), 64.9 (PMBOCH), 54.6 (OCH_3), 30.5 (CH_2); MS (ES^+) *m/z* = 357 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{21}H_{20}O_4Na$ [$M+Na^+$]: 357.1097; found 357.1095.

Crystal Data. $C_{21}H_{18}O_4$, *M* =334.35, monoclinic, *a* = 8.5842(2) Å, *b* = 8.4818(2) Å, *c* = 23.5350(6) Å, *β* = 99.773(3)°, *V* = 1688.70(8) $Å^3$, *T* = 296(2), space group $P2_1/c$ (no. 14), *Z* = 4, μ(MoKα) = 0.091, 13335 reflections measured, 4135 unique (R_{int} = 0.0180) which were used in all calculations. The final wR_2 was 0.1184 (all data) and R_1 was 0.0426 (>2sigma(I)).

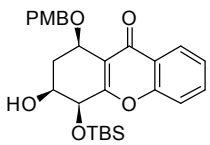
(1*R,3*S**,4*S**)-1-(4-Methoxybenzyloxy)-1,2,3,4-Tetrahydro-3,4-dihydroxyxanthene-9-one (322)**



To a stirred solution of **321** (1.20 g, 3.61 mmol) in a mixture of $(CH_3)_2CO$ (6.00 mL), H_2O (6.00 mL) and ^tBuOH (2.40 mL), at room temperature was added *N*-methylmorpholine-*N*-oxide monohydrate (583 mg, 4.33 mmol) and OsO_4 (20 μL, 0.02 gm/mL, ^tBuOH). The reaction mixture was stirred for 48 hours, and then treated with sodium metabisulfite (820 mg, 4.31 mmol). The reaction mixture was stirred for 1 hour then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 1N HCl (20 mL), H_2O (3 × 30 mL), brine (3 × 15 mL), dried over $MgSO_4$ and vaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 60 :40) furnished **322** (648 mg, 76%) as a yellow solid. M.p. 129 – 131 °C; IR (thin film) 2967, 1608, 1462, 1248, 1095, 755 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.10 (1H, dd, *J* = 1.3, 8.0 Hz, Ar), 7.64 – 7.59 (1H, m, Ar), 7.40 (1H, d, *J* = 8.0 Hz, Ar), 7.37 – 7.32 (1H, m, Ar), 7.26 – 7.24 (2H, m, Ar), 6.82 – 6.76 (2H, m, Ar), 5.03 (1H, m, C*H*OPMB), 4.69 (1H, d, *J* = 10.5 Hz, OC*H*H), 4.65 (1H, d, *J* = 10.5 Hz, OCH*H*), 4.60 – 4.57 (1H, br s, =CCHO*H*), 4.41 (1H, d, *J* = 4.5 Hz, (OH)CH(OH)C*H*C=), 4.21 – 4.11 (1H, m, (OH)C*H*CH_2), 3.70 (3H, s, OCH_3), 3.52 (1H, br s, CH_2CHOH), 2.52 – 2.59 (1H, m, C*H*H), 1.77 – 1.83 (1H, m, CH*H*); δ_C (75 MHz) 176.1 (CO), 162.3 (C, Ar), 158.8 (C, Ar), 155.6 (C, Ar), 133.1 (CH, Ar), 129.05 (2 × CH, Ar), 129.01 (C, Ar), 124.6 (2 × CH, Ar), 124.4 (CH, Ar), 123.1 (C, Ar), 117.6 (CH, Ar), 117.5 (C, Ar), 113.2 (CH, Ar), 71.9 (OCH_2), 68.5 ($PMBCH_2OCH$), 68.2 ((OH)CHC=), 67.2 (CH_2 (OH)*C*H), 54.6 (OCH_3), 30.0 (CH_2); MS (ES^+) *m/z* = 391 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{21}H_{20}O_6Na$ [$M+Na^+$]:391.1152; found: 391.1155.

Crystal Data. $C_{21}H_{20}O_6$, *M* =368.37, orthorhombic, *a* = 8.23140(10) Å, *b* = 8.81910(10) Å, *c* = 24.2007(2) Å, *V* = 1756.81(3) $Å^3$, *T* = 100(2), space group $Pna2_1$ (no. 33), *Z* = 4, μ(CuKα) = 0.848, 10917 reflections measured, 1665 unique (R_{int} = 0.0469) which were used in all calculations. The final wR_2 was 0.1013 (all data) and R_1 was 0.0369 (>2sigma(I)).

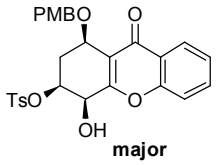
(1*R,3*S**,4*S**)-1-(4-Methoxybenzyloxy)-2,3,4,9-tetrahydro-3-*tert*-butyldimethysilyloxy-4-hydroxy-9-oxo-1H-xanthen (323)**



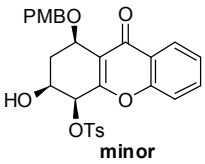
Tert-butyldimethylsilyl trifluoromethanesulfonate (0.04 mL, 0.17 mmol) was added to a solution of **322** (64.0 mg, 0.17 mmol) and 2,6-lutidine (0.06 mL, 0.52 mmol) in dichloromethane (5 mL) at 0 °C and

the mixture was stirred for 1 hour. Saturated $NaHCO_3$ solution (5 mL) was added and the aqueous phase extracted with dichloromethane (3 × 5 mL). The combined organic phase was dried over $MgSO_4$, and evaporation of solvent *in vacuo* gave a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 20 : 80) furnished **323** (15 mg, 30%) as a white solid. M.p.138 – 140 °C; IR (thin film) 2361, 1440, 1230, 1081, 620 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.07 – 8.04 (1H, dd, *J* = 1.6, 8.0 Hz, Ar), 7.53 – 7.48 (1H, m, Ar), 7.33 (1H, d, *J* = 7.7 Hz, Ar), 7.26 – 7.24 (1H, m, Ar), 7.22 (2H, d, *J* = 8.6 Hz, Ar), 6.71 (2H, d, *J* = 8.6 Hz, Ar), 4.68 (1H, t, *J* = 6.6 Hz, CHOPMB), 4.64 – 4.56 (2H, m, OCH_2), 4.33 (1H, br s, CHOTBS), 3.81 (1H, dt, *J* = 3.8, 8.0 Hz, C*H*(OH)), 3.64 (3H, s, OCH_3), 2.81 (1H, br s, OH), 2.10 – 2.00 (1H, m, C*H*H), 1.93 – 1.85 (1H, m, CH*H*), 0.75 (9H, s, $C(CH_3)_3$), 0.04 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); δ_C (75 MHz) 176.7 (CO), 160.7 (C, Ar), 158.5 (C, Ar), 155.5 (C, Ar), 133.0 (CH, Ar), 130.2 (C, Ar), 129.3 (2 × CH, Ar), 125.2 (CH, Ar), 124.4 (CH, Ar), 123.4 (C, Ar), 119.3 (C, Ar), 117.4 (CH, Ar), 113.0 (2 × CH, Ar), 71.8 (OCH_2), 68.3 (CHOPMB), 68.2 (OCH), 67.0 (OCH), 54.6 (OCH_3), 31.6 (CH_2), 25.1 (3 × CH_3), 17.5 ($C(CH_3)_3$), -5.1 ($SiCH_3$), -5.5 ($SiCH_3$); MS (ES^+) *m/z* = 505 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{27}H_{34}O_6SiNa$ $[M+Na^+]$: 505.2017; found: 505.2033.

(1*R,3*S**,4*S**)-1-(4-Methoxybenzyloxy)-2,3,4,9-Tetrhydro-4-hydroxy-9-oxo-1H-xanthen-3-yl-4-methylbenzensulfonate (324) and (1*R**,3*S**,4*S**)-1-(4-Methoxybenzyloxy)-2,3,4,9-Tetrhydro-3-hydroxy-9-oxo-1H-xanthen-4-yl-4-methylbenzensulfonate (325)**



major

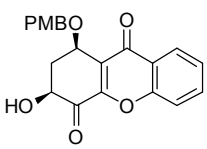


minor

To a solution of **322** (75.0 mg, 0.20 mmol) in pyridine (5 mL) were added *p*-toluenesulfonyl chloride (38.0 mg, 0.20 mmol) and 4–dimethylamino pyridine (2.00 mg, 0.01 mmol). The reaction mixture was stirred for 24 hours before pouring into a separating funnel containing H_2O (10 mL) and then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 0.5N HCl (3 × 10 mL), H_2O (3 × 10 mL), saturated $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 15 mL). The organic layers were dried over $MgSO_4$, evaporation of solvent *in vacuo* provided a thick oil. Column chromatography (ethyl acetate : petroleum ether, 40 : 60) furnished an inseparable mixture of regioisomers (35 mg, 47%) as a colourless oil in 2.2 : 1 ratio. IR (thin film) 2931, 1640, 1465, 1173, 1032, 728 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.09 – 8.07 (1H, d, *J* = 7.7 Hz, Ar), 7.87 – 7.85 (0.68H, d, *J* = 7.7 Hz, Ar), 7.70 (1.32H, d, *J* = 8.1 Hz, Ar), 7.57

– 7.53 (1H, m, Ar), 7.35 – 7.32 (0.68H, d, *J* = 8.5 Hz, Ar), 7.31 – 7.28 (1.68H, m, Ar), 7.20 (3.36H, dd, *J* = 8.5, 20.8 Hz, Ar), 7.07 (.32H, d, *J* = 8.5 Hz, Ar), 6.75 (2H, d, *J* = 8.1 Hz, Ar), 5.45 (0.32H, d, *J* = 3.2 Hz, TsOC*H*C=), 4.90 (0.32H, m, CHOPMB), 4.82 – 4.77 (1.36H, m, TsOC*H*CHCH$_2$C*H*OPMB), 4.65 – 4.55 (2.68H, m, (OH)C*H*CH(TsO)CH$_2$CHOC*H*$_2$PhOMe), 4.19 (0.32H, m, (OH)C*H*CH$_2$), 3.69 (3H, s, OCH$_3$), 2.46 – 2.40 (1H, m, CHC*H*HCH), 2.38 (0.96H, s, SO$_2$PhCH$_3$), 2.33 (2.04H, s, SO$_2$PhCH$_3$), 2.05 – 1.99 (1H, m, CHCH*H*CH); δ_C (75 MHz) 176.7 (CO, Ar, major), 176.4 (CO, Ar, minor), 160.6 (C, Ar, major), 159.2 (C, Ar, minor), 159.0 (C, Ar, major), 156.8 (C, Ar, minor), 155.8 (C, Ar, minor),145.1 (C, Ar, major), 134.1 (CH, Ar, minor), 133.9 (CH, Ar, major), 133. (C, Ar, major), 130.3 (C, Ar, major), 129.94 (2 × CH, Ar, major), 129.91 (2 × CH, Ar, minor), 129.8 (2 × C, Ar, major and minor), 128.0 (CH, Ar, minor), 127.9 (CH, Ar, major), 125.9 (CH, Ar, major), 125.5 (CH, Ar, minor), 125.4 (CH, Ar, minor), 123.8 (C, Ar, major), 123.4 (C, Ar, minor), 120.0 (C, Ar, major), 119.3 (C, Ar, major), 118.0 (2 × CH, Ar, major and minor), 113.8 (CH, Ar, minor), 113.6 (CH, Ar, major), 75.9 (CH(OTs), minor), 73.2 (MeOPhOCH$_2$, minor), 73.2 (MeOPhOCH$_2$, major), 68.4 (CHOPMB, minor), 67.6 (CHOPMB, major), 67.5 (CH(OTs), major), 67.0 (CH(OH), major), 55.2 (2 × PMBOCH$_3$ major and minor), 31.0 (*C*H$_2$CHOPMB, minor), 29.6 (*C*H$_2$CHOPMB, major), 21.6 (2 × CH$_3$, major and minor); MS (ES$^+$) *m/z* = 523 ([M+Na])$^+$, 100%); HRMS (ES$^+$): calcd. for $C_{28}H_{27}O_8SNa$ [M+H$^+$]: 523.1421; found: 523.1423.

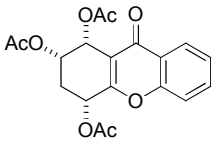
(1*R,3*S**)-1-(4-Methoxybenzyloxy)-2,3-Dihydro-3-hydroxy-1H-xanthene-4,9-dione (326)**



To a solution of **322** (100 mg, 0.27 mmol) in dichloromethane (5 mL) at – 78 °C was added Dess Martin periodinane (57.0 mg, 0.13 mmol) and the reaction mixture was allowed to warm to room temperature overnight. To the yellow solution was added sodium thiosulfate (16.0 mg, 0.13 mmol). The reaction mixture was stirred for 1 hour before pouring in H_2O (10 mL) and extracting with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over $MgSO_4$, filtered, and evaporation of solvent *in vacuo* provided a yellow oil. Column chromatography (ethyl acetate : petroleum ether, 50 : 50) furnished **326** (35 mg, 35%) as a yellow oil and **322** (45 mg, 45%) as a yellow oil. IR (thin film) 2934, 1717, 1644, 1611, 1464, 1245, 1051, 973 cm^{-1}; δ_H (300 MHz $CDCl_3$) 8.59 – 8.56 (1H, dd, *J* = 1.6, 7.8 Hz, Ar), 8.14 – 8.09 (1H, m, Ar), 7.98 – 7.96 (1H, m, Ar), 7.84 – 7.79 (1H, m, Ar), 7.70 – 7.67 (2H, d, *J* = 8.9 Hz, Ar), 7.24 – 7.21

(2H, d, J = 8.9 Hz, Ar), 5.54 – 5.51 (1H, t, J = 4.6 Hz, CHOPMB), 5.19 (2H, s, OCH_2), 4.68 – 4.67 (1H, m, C*H*OH), 4.10 (3H, s, OCH_3), 2.82 – 2.80 (2H, d, J = 4.6 Hz, CH_2); δ_C (75 MHz) 191.9 (CO), 178.0 (CO), 159.5 (C, Ar), 155.4 (C, Ar), 150.1 (C, Ar), 135.2 (CH, Ar), 130.6 (CH, Ar), 130.0 (CH, Ar), 129.8 (C, Ar), 129.4 (C, Ar), 128.0 (CH, Ar), 125.9 (CH, Ar), 124.2 (C, Ar), 118.9 (CH, Ar), 113.9 (CH, Ar), 113.7 (CH, Ar), 73.5 (OCH_2), 71.3 (CHOPMB), 68.1 (HOCH), 55.2 (OCH_3), 34.1 (CH_2); MS (ES^+) *m/z* = 389 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{21}H_{18}O_6Na$, $[M+Na^+]$:389.0996; found: 389.0997.

(1*R,2*S**, 4*R**)1,2,3,4-Tetrahydro-1,2,4-triacetoxyxanthen-9-one (330)**



To a solution of impure **329** (20.0 mg, 0.08 mmol) were added acetic anhydride (0.08 mL, 0.80 mmol) and 4–dimethylamino pyridine (1.00 mg, 0.008 mmol) in pyridine (2 mL). The reaction mixture was stirred for 48 hours before pouring into a separating funnel containing H_2O (5 mL) and then extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with 0.5N HCl (3 × 5 mL), H_2O (3 × 5 mL), saturated $NaHCO_3$ solution (3 × 5 mL) and brine (3 × 5 mL). The organic layers were dried over $MgSO_4$, and evaporation of solvent *in vacuo* provided a colourless oil. Column chromatography (diethyl ether : petroleum ether, 10 : 90) furnished **330** (27 mg, 93%) as a colourless oil. IR (thin film) 2924, 1744, 1651, 1365, 1040, 727 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.12 – 8.09 (1H, m, Ar), 7.64 – 7.54 (1H, m, Ar), 7.36 – 7.33 (2H, m, Ar), 6.45 (1H, d, J = 2.7 Hz, (AcO)C*H*CH(OAc)CH_2), 6.00 (1H, t, J = 8.6 Hz, CH_2(AcO)C*H*C=), 5.11 – 5.01 (1H, m, (AcO)CHC*H*(OAc)CH_2), 2.33 (2H, t, J = 2.3 Hz, CH_2), 2.16 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.98 (3H, s, CH_3); δ_C (100 MHz) 175.6 (CO), 169.8 (CH_3*C*O), 169.6 (CH_3*C*O), 169.2 (CH_3*C*O), 158.0 (C, Ar), 155.1 (C, Ar), 134.3 (CH, Ar), 126.0 (CH, Ar), 125.7 (CH, Ar), 123.2 (C, Ar), 118.1 (C, Ar), 116.2 (CH, Ar), 65.98 (CH_2CH(OAc)*C*H(OAc)), 65.94 (CH_2*C*H(OAc)), 62.1 (CH_2*C*H(OAc)CH(OAc)), 28.7 (CH_2), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3); MS (ES^+) *m/z* = 397 ($[M+Na]^+$, 100%); HRMS (ES^+): calcd. for $C_{19}H_{18}O_8Na$ $[M+Na^+]$: 397.0894; found: 397.0896.

Cytotoxicity Assays (Performed by Penny Turner at the University of Exeter)

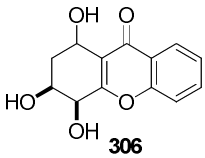
Cell culture

PANC-1 cells were obtained from the European Collection of Cell Cultures (Porton Down, UK) and maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 20% (v/v) foetal bovine serum, 2mM glutamine and 0.1% gentamicin. The medium was routinely changed every 3 days and cells were passaged by trypsinisation at approximately 80% confluence. Nutrient deprived medium (NDM) was prepared as follows: $CaCl_2$ (1M) (0.6 ml), $Fe(NO_3)_3.9H_2O$ (0.5 mg), KCl (200 mg), $MgSO_4.7H_2O$ (100 mg), NaCl (3.2 g), $NaHCO_3$ (350 mg), NaH_2PO_4 (62.5 mg), phenol red (7.5mg), 1M HEPES buffer (12.5 ml) and MEM vitamin solution (5 ml) (Lonza UK) were dissolved in ddH_2O (final volume 500 ml). pH was adjusted to 7.4 using $NaHCO_3$ (saturated solution). NDM was sterile filtered and stored at –4°C.

Lactate Dehydrogenase assay (LDH)

Cell death was assayed by determination of cellular release of LDH using assay kits from Roche Diagnostics Ltd (Burgess Hill, UK). LDH is rapidly lost from dying cells into the culture medium upon damage of the plasma membrane and can be quantified by colourimetric changes in added assay reagent. Assays were performed according to the manufacturer's instructions.

Briefly, cells were seeded in 96 well plates (3×10^4 per well) and incubated in fresh DMEM for 24 h at 37°C under 5% CO_2 / 95% air atmosphere. Serial dilutions of the relevant compound in both DMEM and NDM were prepared at 0.001, 0.01, 0.1, 5, 10, 50 and 100µg/ml. Blank controls (containing only media), low controls (containing untreated cells) and high controls (containing cells lysed with 2% Triton X to determine maximum cellular LDH levels) were included on each plate. DMEM was removed from the wells and the cells were washed with warm phosphate buffered saline (PBS) before adding the serial dilutions (100µl per well) of the compound. Each concentration was assayed in triplicate. After 24 h incubation at 37 °C under a 5% CO_2 / 95% air atmosphere, the plate was centrifuged and 80 µl of supernatant from each well was transferred to a new 96 well plate. The LDH assay catalyst (diaphorase and NAD+) and dye solution (iodotetrazolium chloride and sodium lactate) were combined and 80 µl of this reagent mix was added to each well. After 30 minutes at room temperature in the dark to allow colour development, absorbance was measured at 490 nm. All experiments were carried out in triplicate.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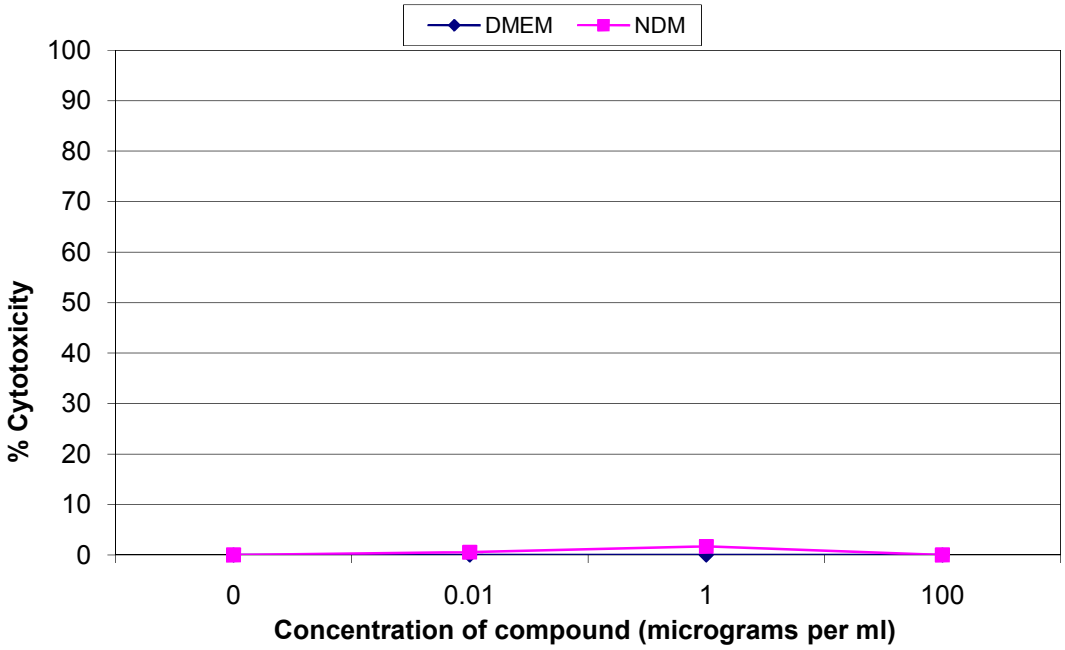
O
OH

306


DMEM
NDM
100
90
80
70
60
50
40
30
20
10
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% Cytotoxicity
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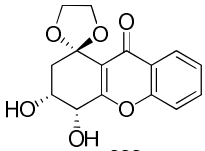
0.01
1
100
Concentration of compound (micrograms per ml)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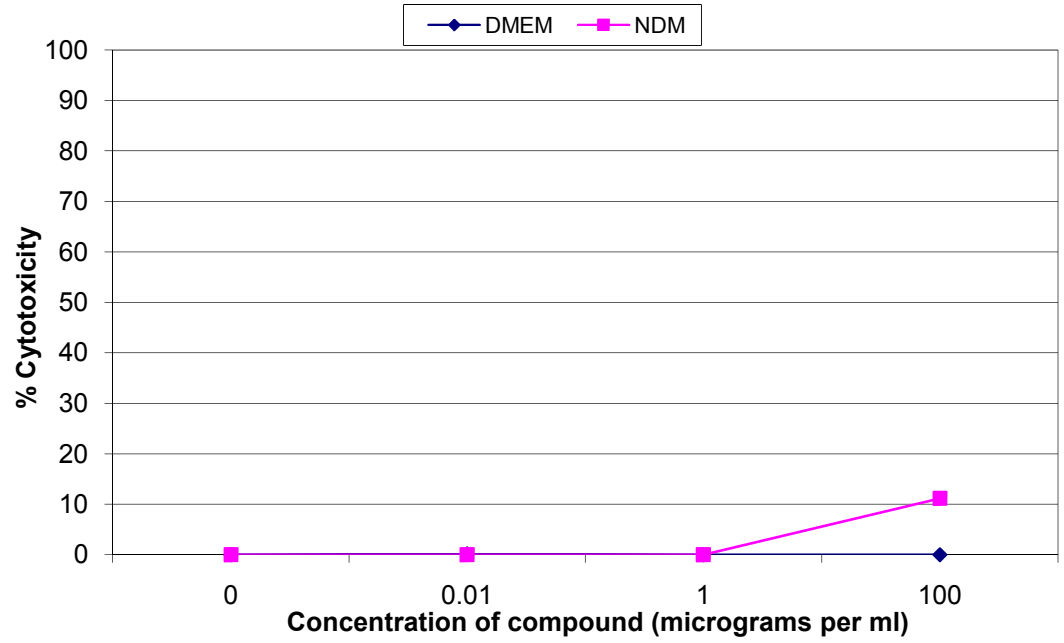
HO
O
OH

299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80
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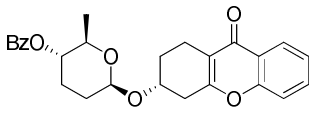
50
40
30
20
10
0
% Cytotoxicity
0
0.01
1
100
Concentration of compound (micrograms per ml)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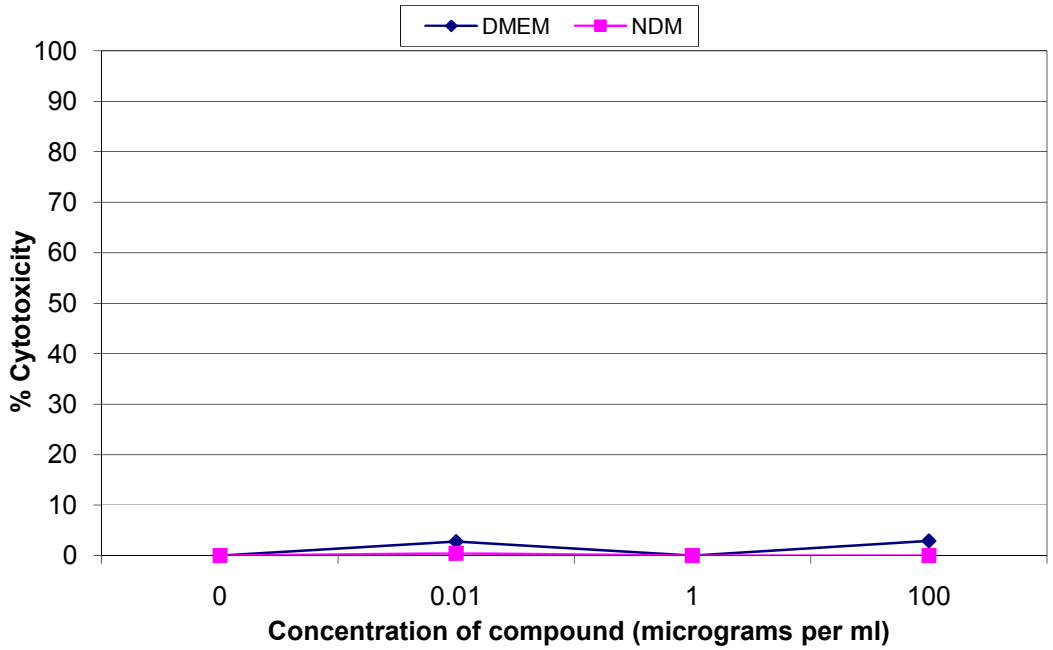
O
O
O

228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% Cytotoxicity
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0.01
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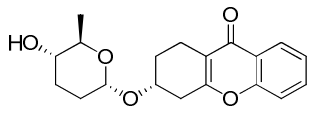
100
Concentration of compound (micrograms per ml)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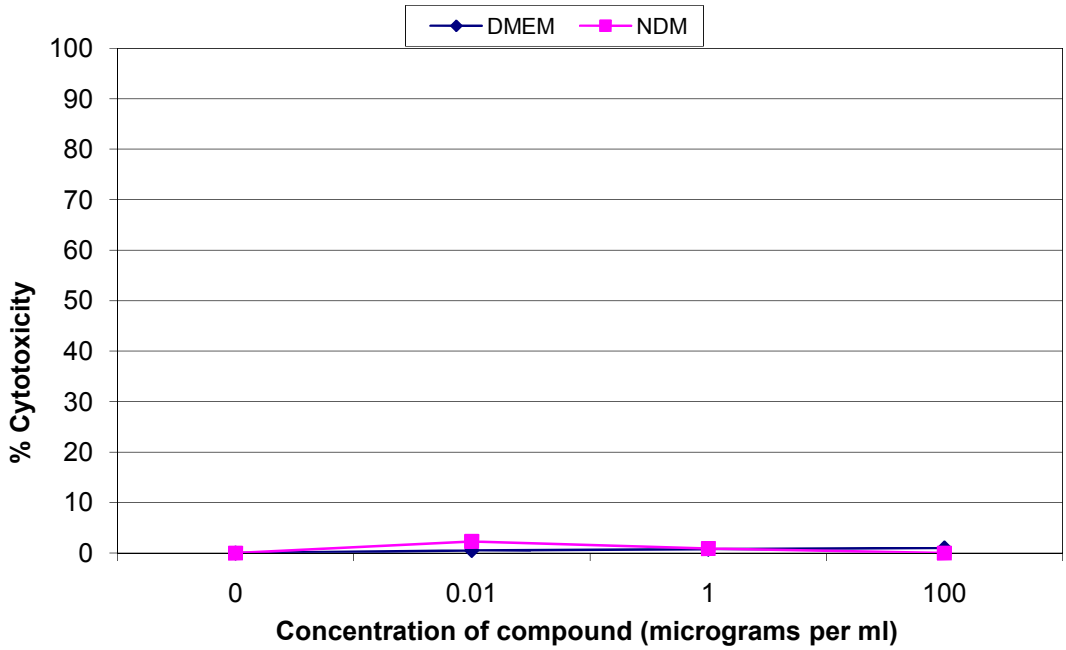
O
O
O

234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NDM
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60
50
40
30
20
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0
% Cytotoxicity
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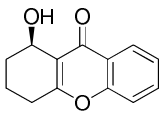
0.01
1
100
Concentration of compound (micrograms per ml)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O

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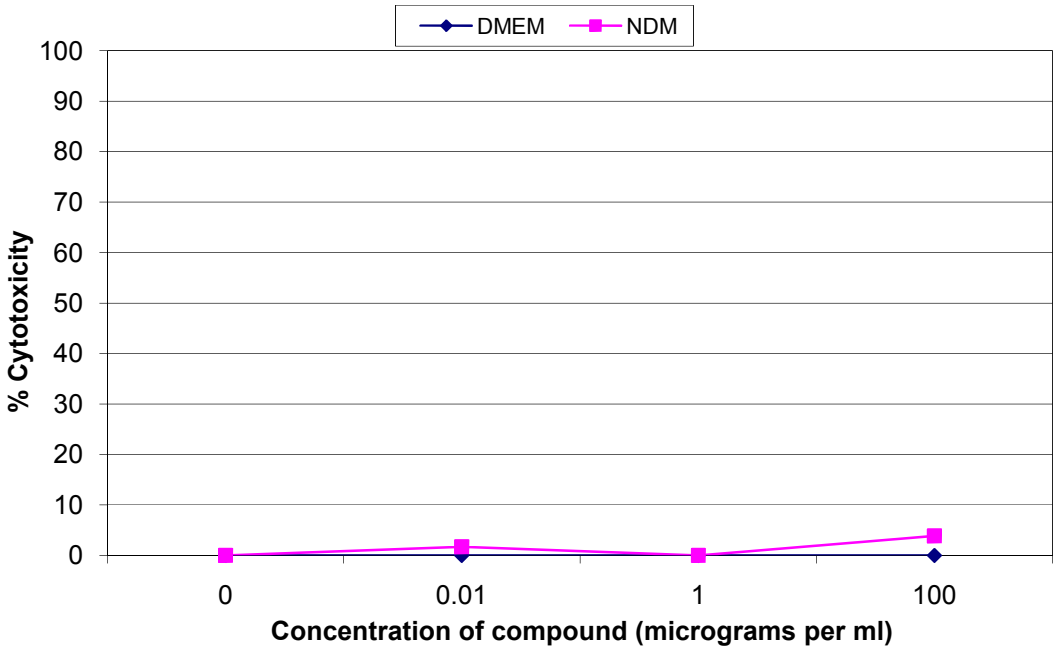
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80
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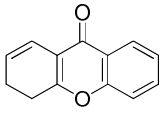
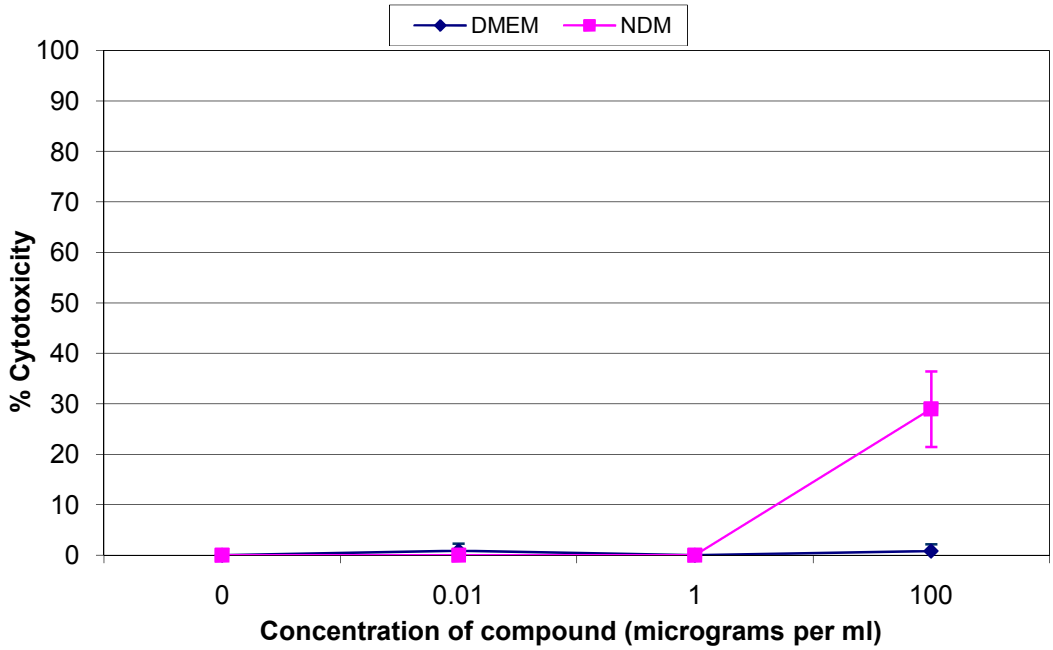
60
50
40
30
20
10
0
% Cytotoxicity
0
0.01
1
100
Concentration of compound (micrograms per ml)


O
O

288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20
10
0
% Cytotoxicity
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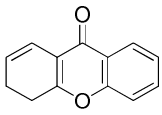
0.01
1
100
Concentration of compound (micrograms per ml)



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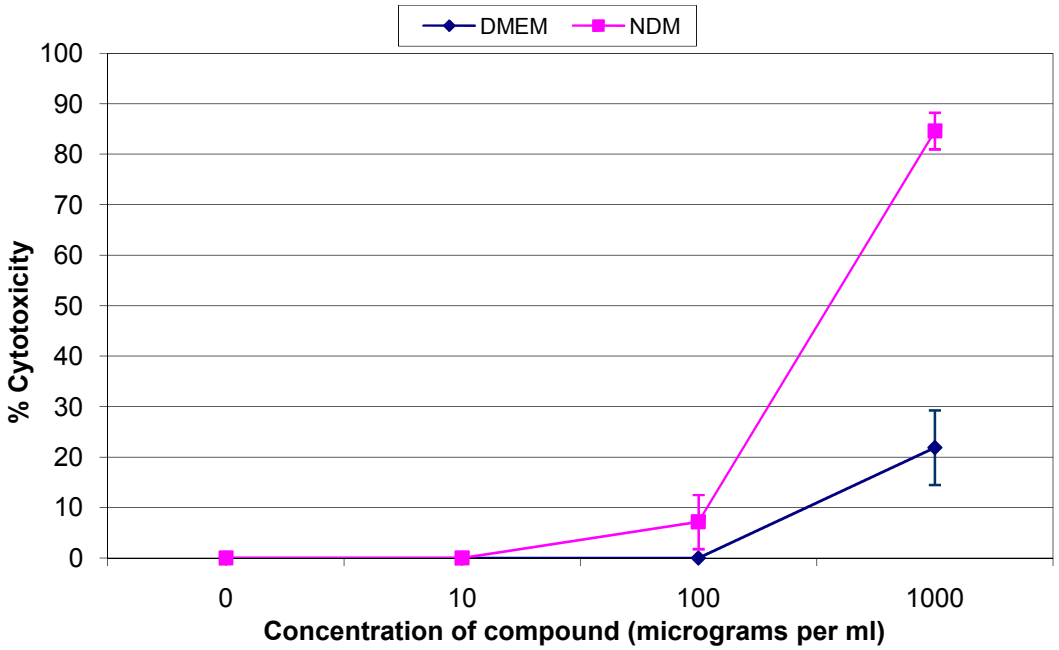
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NDM
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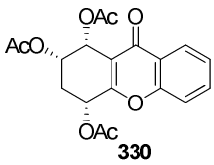
10
100
1000
Concentration of compound (micrograms per ml)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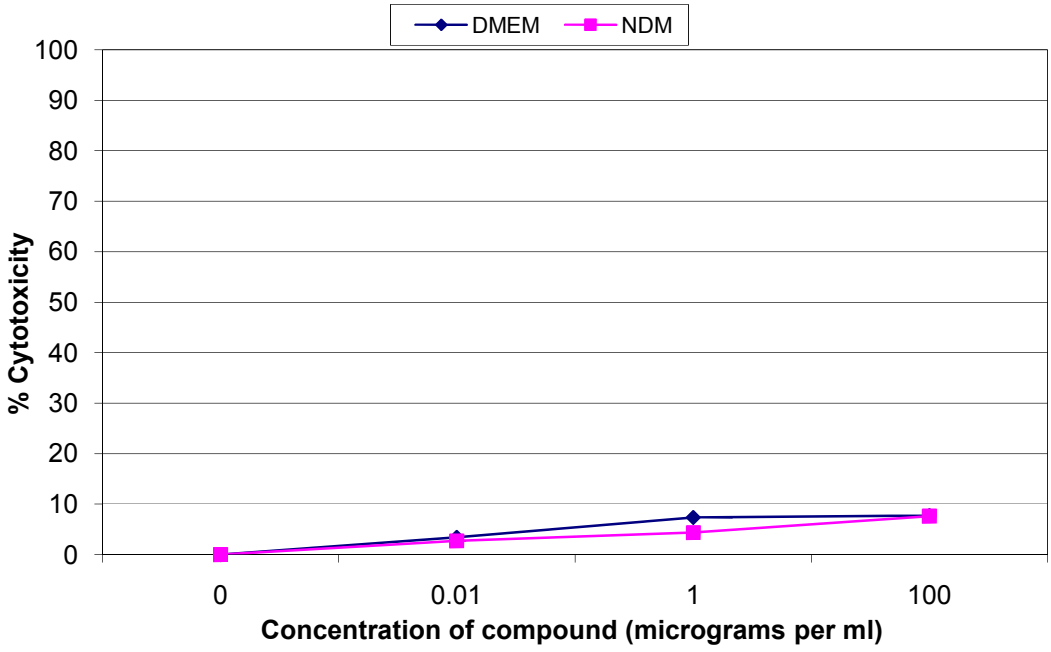
AcO
O
OAc

330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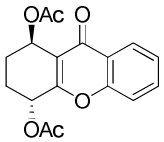
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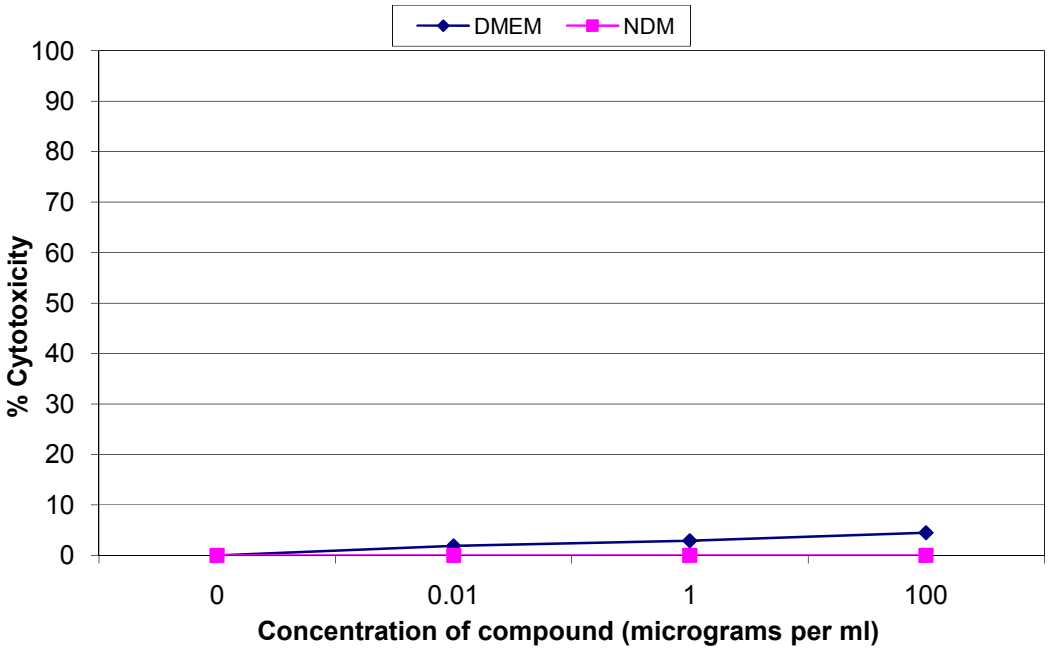
280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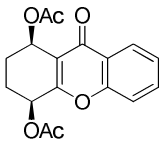
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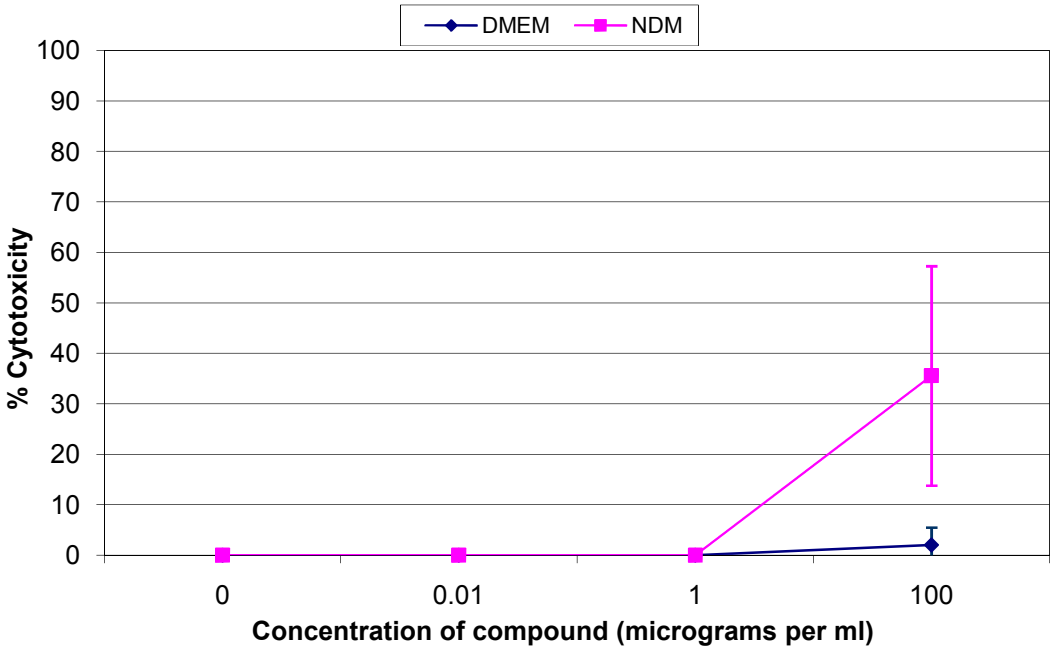
279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100
Concentration of compound (micrograms per ml)

References

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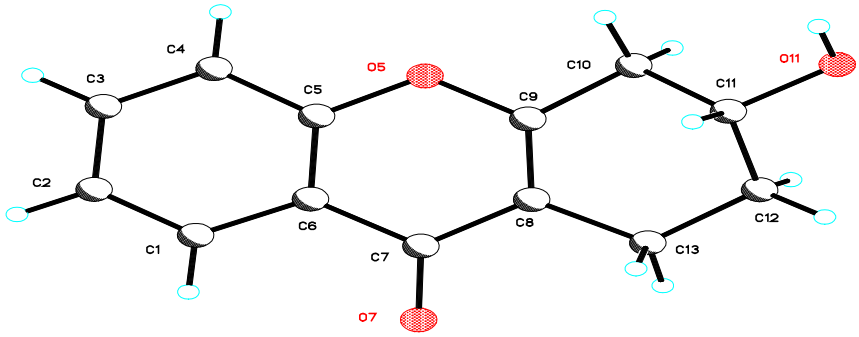
Appendix

X-Ray data for 200

Crystal Data. $C_{13}H_{12}O_3$, M =216.23, triclinic, a = 7.1242(6) Å, b = 7.7029(5) Å, c = 9.8422(8) Å, α = 82.210(6)°, β = 72.540(7)°, γ = 79.158(6)°, V = 504.22(7) Å^3, T = 100(2), space group P-1 (no. 2), Z = 2, μ(MoKα) = 0.101, 6397 reflections measured, 3317 unique (R_{int} = 0.0368) which were used in all calculations. The final wR_2 was 0.1418 (all data) and R_1 was 0.0591 (>2sigma(I)).

Solid state structure of **200** showing atom numbering.



200

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for sam1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	8311(2)	2515(2)	5445.2(19)	24(1)
C(2)	8093(2)	2348(2)	6891.5(19)	28(1)
C(3)	7399(2)	3828(2)	7676.7(19)	28(1)
C(4)	6925(2)	5482(2)	7025.5(17)	23(1)
O(5)	6695.0(14)	7311.3(13)	4940.8(11)	19(1)
C(5)	7155(2)	5631.5(19)	5555.2(16)	19(1)
C(6)	7831(2)	4180.8(19)	4743.2(17)	19(1)
C(7)	8041.7(19)	4409.6(18)	3201.1(17)	18(1)
O(7)	8633.9(15)	3145.9(13)	2451.2(12)	25(1)
C(8)	7537(2)	6221.3(18)	2629.4(15)	16(1)

C(9)	6934(2)	7551.2(18)	3500.3(15)	16(1)
C(10)	6519(2)	9462.3(18)	3008.3(16)	20(1)
O(11)	7002(4)	11536(2)	867(2)	21(1)
C(11)	7593(3)	9758(2)	1394(2)	17(1)
C(12)	7069(4)	8482(2)	583(2)	19(1)
C(13)	7823(2)	590.9(19)	1043.7(16)	19(1)
C(10A)	6519(2)	9462.3(18)	3008.3(16)	20(1)
C(11A)	6267(11)	9778(9)	1510(7)	18(2)
O(11A)	6282(11)	11636(11)	983(9)	30(2)
C(12A)	7978(13)	8610(10)	583(9)	22(2)
C(13A)	7823(2)	6590.9(19)	1043.7(16)	19(1)

Table 2. Bond lengths [A] and angles [deg] for **200**.

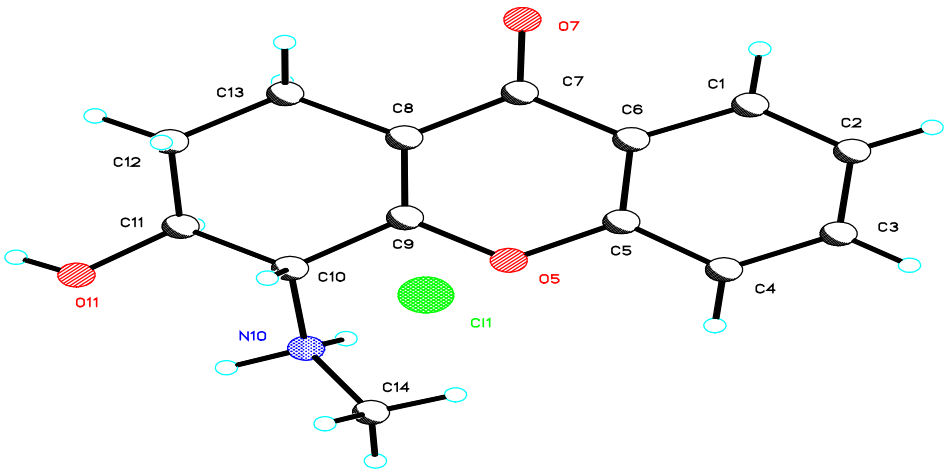
C(1)-C(2)	1.376(2)	C(7)-O(7)	1.2344(18)
C(1)-C(6)	1.406(2)	C(7)-C(8)	1.454(2)
C(1)-H(1A)	0.9500	C(8)-C(9)	1.349(2)
C(2)-C(3)	1.392(3)	C(8)-C(13)	1.506(2)
C(2)-H(2A)	0.9500	C(9)-C(10)	1.489(2)
C(3)-C(4)	1.377(2)	C(10)-C(11)	1.549(2)
C(3)-H(3A)	0.9500	C(10)-H(10A)	0.9900
C(4)-C(5)	1.398(2)	C(10)-H(10B)	0.9900
C(4)-H(4A)	0.9500	O(11)-C(11)	1.430(2)
O(5)-C(9)	1.3671(17)	O(11)-H(11)	0.837(16)
O(5)-C(5)	1.3765(17)	O(11)-H(11C)	0.81(6)
C(5)-C(6)	1.388(2)	C(11)-C(12)	1.507(3)
C(6)-C(7)	1.469(2)	C(11)-H(11A)	1.0000

C(12)-C(13)	1.513(2)	C(11A)-C(12A)	1.507(10)
C(12)-H(12A)	0.9900	C(11A)-H(11B)	1.0000
C(12)-H(12B)	0.9900	O(11A)-H(11)	1.144(19)
C(13)-H(13A)	0.9900	O(11A)-H(11C)	0.84(2)
C(13)-H(13B)	0.9900	C(12A)-H(12C)	0.9900
C(11A)-O(11A)	1.455(11)	C(12A)-H(12D)	0.9900

X-ray data for 247

Crystal Data. $C_{14}H_{16}NO_3Cl$, M =281.73, orthorhombic, a = 13.1707(3) Å, b = 12.0072(2) Å, c = 16.8408(4) Å, V = 2663.25(9) Å^3, T = 100(2), space group Pbca (no. 61), Z = 8, μ(MoKα) = 0.290, 17479 reflections measured, 4554 unique (R_{int} = 0.0362) which were used in all calculations. The final wR_2 was 0.0906 (all data) and R_1 was 0.0386 (>2sigma(I)).

Solid state structure of **247** with atom labelling.



247

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **247**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	1236.9(2)	6302.7(2)	2630.1(2)	18(1)
C(1)	4730.9(11)	8675.1(10)	5507.1(7)	19(1)
C(2)	5618.3(10)	8117.2(10)	5354.3(8)	20(1)
C(3)	5802.3(10)	7679.6(10)	4595.0(8)	20(1)
C(4)	5108.5(10)	7815.1(9)	3992.7(8)	17(1)
O(5)	3542.9(7)	8498.8(6)	3536.9(5)	14(1)
C(5)	4213.0(10)	8386.6(9)	4157.8(7)	14(1)
C(6)	4001.3(10)	8822.6(9)	4907.5(7)	14(1)
O(7)	2811.6(8)	9821.3(8)	5691.4(5)	23(1)
C(7)	3046.8(10)	9420.3(10)	5039.0(7)	16(1)
C(8)	2380.2(10)	9513.5(9)	4353.8(7)	14(1)
C(9)	2659.6(9)	9058.7(9)	3651.8(7)	13(1)
N(10)	2561.5(8)	9240.5(8)	2164.5(6)	14(1)
C(10)	1997.1(9)	9039.2(10)	2928.4(7)	13(1)
O(11)	499.4(7)	9639.8(8)	2335.1(6)	21(1)
C(11)	1147.5(10)	9893.8(10)	2982.4(7)	15(1)
C(12)	633.2(10)	9816.2(10)	3787.0(7)	18(1)
C(13)	1381.0(10)	10113.6(10)	4443.4(8)	18(1)
C(14)	3146.5(10)	8292.6(10)	1818.7(8)	18(1)

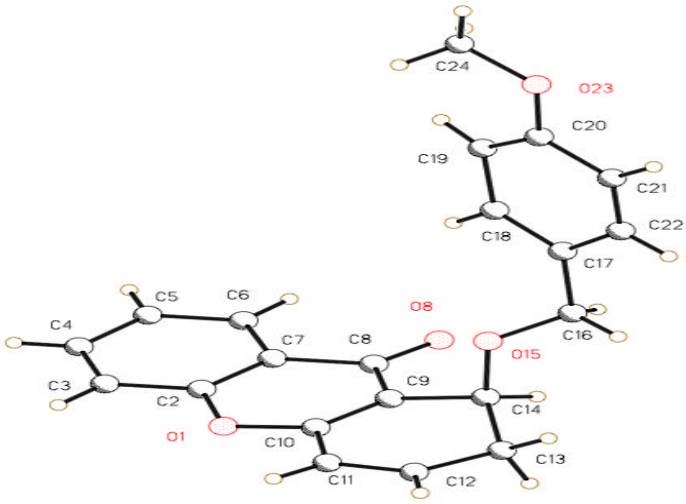
Table 2. Bond lengths [A] and angles [deg] for **247**.

C(1)-C(2)	1.3715(19)	N(10)-C(14)	1.4928(15)
C(1)-C(6)	1.4051(17)	N(10)-C(10)	1.5053(15)
C(1)-H(1A)	0.9500	N(10)-H(10B)	0.935(7)
C(2)-C(3)	1.4035(19)	N(10)-H(10C)	0.949(7)
C(2)-H(2A)	0.9500	C(10)-C(11)	1.5210(17)
C(3)-C(4)	1.3750(18)	C(10)-H(10A)	1.0000
C(3)-H(3A)	0.9500	O(11)-C(11)	1.4177(15)
C(4)-C(5)	1.3926(17)	O(11)-H(11)	0.815(18)
C(4)-H(4A)	0.9500	C(11)-C(12)	1.5178(17)
O(5)-C(9)	1.3575(14)	C(11)-H(11A)	1.0000
O(5)-C(5)	1.3750(14)	C(12)-C(13)	1.5230(18)
C(5)-C(6)	1.3948(17)	C(12)-H(12A)	0.9900
C(6)-C(7)	1.4644(17)	C(12)-H(12B)	0.9900
O(7)-C(7)	1.2390(14)	C(13)-H(13A)	0.9900
C(7)-C(8)	1.4543(17)	C(13)-H(13B)	0.9900
C(8)-C(9)	1.3533(16)	C(14)-H(14A)	0.9800
C(8)-C(13)	1.5079(18)	C(14)-H(14B)	0.9800
C(9)-C(10)	1.4986(17)	C(14)-H(14C)	0.9800

X-ray data for 321

Crystal Data. $C_{21}H_{18}O_4$, M =334.35, monoclinic, a = 8.5842(2) Å, b = 8.4818(2) Å, c = 23.5350(6) Å, β = 99.773(3)°, V = 1688.70(8) Å^3, T = 296(2), space group $P2_1/c$ (no. 14), Z = 4, μ(MoKα) = 0.091, 13335 reflections measured, 4135 unique (R_{int} = 0.0180) which were used in all calculations. The final wR_2 was 0.1184 (all data) and R_1 was 0.0426 (>2sigma(I)).

Solid state structure of **321** with atom numbering.



321

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **321**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	2538.9(10)	8592.7(9)	215.9(3)	53(1)
C(2)	3150.6(13)	10087.3(13)	296.4(5)	47(1)
C(3)	4319.9(15)	10307.8(17)	773.5(6)	60(1)
C(4)	4986.3(15)	11772.2(19)	869.5(6)	66(1)
C(5)	4506.0(16)	13008.9(17)	497.3(6)	65(1)
C(6)	3347.8(15)	12778.7(14)	24.8(6)	56(1)
C(7)	2638.4(13)	11300.1(13)	-83.9(5)	44(1)
C(8)	1426.4(14)	11003.8(13)	-593.0(5)	47(1)
O(8)	876.6(12)	12065.3(11)	-923.0(4)	72(1)
C(9)	968.6(12)	9368.5(13)	-679.0(5)	43(1)
C(10)	1524.5(13)	8270.7(13)	-280.0(5)	47(1)
C(11)	1109.3(17)	6620.3(15)	-342.3(6)	61(1)
C(12)	34.7(18)	6151.7(15)	-781.2(6)	65(1)

C(13)	-827.1(15)	7270.8(16)	-1199.0(6)	62(1)
C(14)	17.0(14)	8840.0(14)	-1240.9(5)	49(1)
O(15)	1124.1(10)	8691.0(10)	-1635.9(3)	56(1)
C(16)	592(3)	9136(7)	-2174.6(11)	65(1)
C(17)	1911(8)	9176(7)	-2521(3)	50(1)
C(18)	3299(11)	9995(9)	-2332(3)	64(2)
C(19)	4622(11)	10140(12)	-2654(3)	62(2)
C(20)	4418(9)	9226(9)	-3138(3)	52(2)
C(21)	2960(15)	8436(14)	-3344(5)	48(1)
C(22)	1823(12)	8430(13)	-3047(4)	53(1)
C(16A)	1077(8)	9972(7)	-2053(2)	57(2)
C(17A)	2253(12)	9658(10)	-2444(5)	44(2)
C(18A)	3679(18)	10425(11)	-2345(5)	58(2)
C(19A)	4697(19)	9930(20)	-2674(7)	87(5)
C(20A)	4459(17)	9105(16)	-3175(6)	60(4)
C(21A)	3110(30)	8380(20)	-3271(9)	70(5)
C(22A)	1894(16)	8637(19)	-2899(5)	50(3)
O(23)	5537.8(13)	8967.3(15)	-3499.5(4)	84(1)
C(24)	7085(2)	9536(3)	-3299.4(9)	110(1)

Table 2. Bond lengths [A] and angles [deg] for **321**.

O(1)-C(10)	1.3601(14)	C(3)-C(4)	1.370(2)
O(1)-C(2)	1.3730(14)	C(3)-H(3A)	0.9300
C(2)-C(7)	1.3853(16)	C(4)-C(5)	1.384(2)
C(2)-C(3)	1.3859(18)	C(4)-H(4A)	0.9300

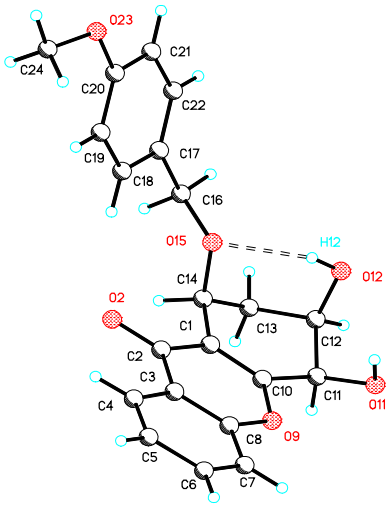
C(5)-C(6)	1.3740(19)	C(18)-C(19)	1.473(14)
C(5)-H(5A)	0.9300	C(18)-H(18A)	0.9300
C(6)-C(7)	1.3986(16)	C(19)-C(20)	1.366(13)
C(6)-H(6A)	0.9300	C(19)-H(19A)	0.9300
C(7)-C(8)	1.4691(16)	C(20)-O(23)	1.404(7)
C(8)-O(8)	1.2295(14)	C(20)-C(21)	1.430(14)
C(8)-C(9)	1.4464(16)	C(21)-C(22)	1.293(16)
C(9)-C(10)	1.3506(16)	C(21)-H(21A)	0.9300
C(9)-C(14)	1.5002(16)	C(22)-H(22A)	0.9300
C(10)-C(11)	1.4458(17)	C(16A)-C(17A)	1.501(11)
C(11)-C(12)	1.324(2)	C(16A)-H(16C)	0.9700
C(11)-H(11A)	0.9300	C(16A)-H(16D)	0.9700
C(12)-C(13)	1.472(2)	C(17A)-C(22A)	1.370(12)
C(12)-H(12A)	0.9300	C(17A)-C(18A)	1.371(11)
C(13)-C(14)	1.5266(17)	C(18A)-C(19A)	1.33(3)
C(13)-H(13A)	0.9700	C(18A)-H(18B)	0.9300
C(13)-H(13B)	0.9700	C(19A)-C(20A)	1.36(2)
C(14)-O(15)	1.4432(13)	C(19A)-H(19B)	0.9300
C(14)-H(14A)	0.9800	C(20A)-C(21A)	1.29(3)
O(15)-C(16)	1.328(3)	C(20A)-O(23)	1.302(13)
O(15)-C(16A)	1.460(4)	C(21A)-C(22A)	1.49(3)
C(16)-C(17)	1.504(8)	C(21A)-H(21B)	0.9300
C(16)-H(16A)	0.9700	C(22A)-H(22B)	0.9300
C(16)-H(16B)	0.9700	O(23)-C(24)	1.416(2)
C(17)-C(22)	1.383(8)	C(24)-H(24A)	0.9600
C(17)-C(18)	1.385(6)	C(24)-H(24B)	0.9600

C(24)-H(24C) 0.9600

X-ray data for 322

Crystal Data. $C_{21}H_{20}O_6$, M =368.37, orthorhombic, a = 8.23140(10) Å, b = 8.81910(10) Å, c = 24.2007(2) Å, V = 1756.81(3) Å^3, T = 100(2), space group Pna2$_1$ (no. 33), Z = 4, μ(CuKα) = 0.848, 10917 reflections measured, 1665 unique (R_{int} = 0.0469) which were used in all calculations. The final wR_2 was 0.1013 (all data) and R_1 was 0.0369 (>2sigma(I)).

Solid state structure of **322** with atom numbering showing the internal H bond.



322

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **322**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	3857(3)	8321(3)	4442.4(11)	27(1)
O(2)	4545(2)	5734(2)	4561.7(8)	31(1)
C(2)	3808(3)	6717(3)	4291.5(11)	27(1)

C(3)	2799(3)	6353(3)	3817.0(11)	27(1)
C(4)	2523(4)	4847(3)	3641.7(11)	31(1)
C(5)	1530(4)	4544(3)	3204.9(12)	35(1)
C(6)	788(4)	5733(3)	2916.3(12)	34(1)
C(7)	1032(3)	7222(3)	3072.0(11)	30(1)
C(8)	2028(3)	7511(3)	3521.9(10)	27(1)
O(9)	2217(2)	9009.0(19)	3667.5(8)	29(1)
C(10)	3062(3)	9356(3)	4130.4(11)	26(1)
O(11)	1449(2)	11642(2)	4130.5(8)	31(1)
C(11)	3002(3)	11040(3)	4254.3(12)	29(1)
O(12)	2218(2)	11077(2)	5225.4(9)	31(1)
C(12)	3516(3)	11371(3)	4850.5(12)	29(1)
C(13)	5047(3)	10486(3)	4988.0(11)	30(1)
C(14)	4761(3)	8768(3)	4955.7(11)	28(1)
O(15)	3782(2)	8237(2)	5409.1(8)	28(1)
C(16)	4695(4)	7945(3)	5904.0(11)	33(1)
C(17)	3948(3)	6604(3)	6198.1(12)	30(1)
C(18)	3712(3)	5260(3)	5908.0(12)	30(1)
C(19)	3038(3)	3994(3)	6164.4(12)	30(1)
C(20)	2613(3)	4066(3)	6714.8(12)	30(1)
C(21)	2854(3)	5403(3)	7015.3(12)	34(1)
C(22)	3516(4)	6657(3)	6751.7(13)	32(1)
O(23)	1923(3)	2887(2)	7003.7(8)	37(1)
C(24)	2008(4)	1421(3)	6750.8(14)	38(1)

Table 2. Bond lengths [A] and angles [deg] for **322**.

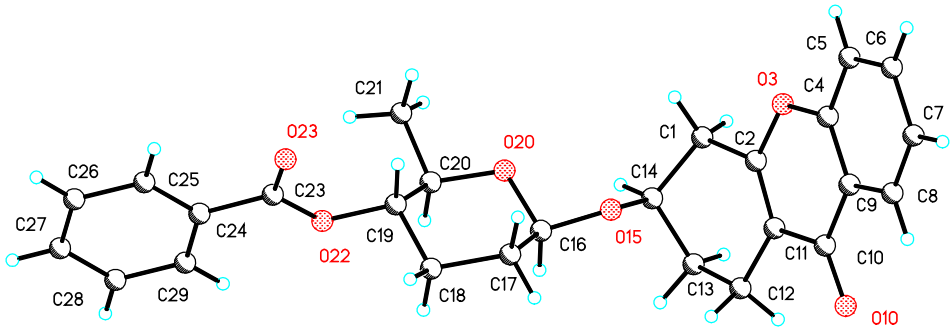
C(1)-C(10)	1.354(4)	C(12)-C(13)	1.520(4)
C(1)-C(2)	1.462(3)	C(12)-H(12A)	1.0000
C(1)-C(14)	1.501(4)	C(13)-C(14)	1.535(3)
O(2)-C(2)	1.244(3)	C(13)-H(13A)	0.9900
C(2)-C(3)	1.453(4)	C(13)-H(13B)	0.9900
C(3)-C(8)	1.398(4)	C(14)-O(15)	1.440(3)
C(3)-C(4)	1.413(4)	C(14)-H(14A)	1.0000
C(4)-C(5)	1.363(4)	O(15)-C(16)	1.437(3)
C(4)-H(4A)	0.9500	C(16)-C(17)	1.511(4)
C(5)-C(6)	1.400(4)	C(16)-H(16A)	0.9900
C(5)-H(5A)	0.9500	C(16)-H(16B)	0.9900
C(6)-C(7)	1.382(4)	C(17)-C(22)	1.387(4)
C(6)-H(6A)	0.9500	C(17)-C(18)	1.392(4)
C(7)-C(8)	1.387(4)	C(18)-C(19)	1.393(4)
C(7)-H(7A)	0.9500	C(18)-H(18A)	0.9500
C(8)-O(9)	1.376(3)	C(19)-C(20)	1.379(4)
O(9)-C(10)	1.354(3)	C(19)-H(19A)	0.9500
C(10)-C(11)	1.515(3)	C(20)-O(23)	1.376(3)
O(11)-C(11)	1.416(3)	C(20)-C(21)	1.399(4)
O(11)-H(11)	0.86(2)	C(21)-C(22)	1.389(4)
C(11)-C(12)	1.532(4)	C(21)-H(21A)	0.9500
C(11)-H(11A)	1.0000	C(22)-H(22A)	0.9500
O(12)-C(12)	1.425(3)	O(23)-C(24)	1.432(4)
O(12)-H(12)	0.84(2)	C(24)-H(24A)	0.9800

C(24)-H(24B)	0.9800	C(24)-H(24C)	0.9800

X-ray data for 228

Crystal Data. $C_{26}H_{26}O_6$, M =434.47, monoclinic, a = 13.7920(3) Å, b = 5.31169(13) Å, c = 14.3899(3) Å, β = 94.535(2)°, V = 1050.89(4) Å^3, T = 100(2), space group $P2_1$ (no. 4), Z = 2, μ(CuKα) = 0.795, 11589 reflections measured, 3869 unique (R_{int} = 0.0357) which were used in all calculations. The final wR_2 was 0.1029 (all data) and R_1 was 0.0383 (>2sigma(I)).

Solid state structure of **228** with atom labelling.



228

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **228** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	2327.4(12)	10902(4)	3192.9(11)	22(1)
C(2)	1442.3(12)	9432(4)	2861.4(11)	20(1)
O(3)	1632.3(8)	7865(3)	2140.9(8)	22(1)
C(4)	928.9(12)	6204(4)	1811.0(11)	21(1)
C(5)	1186.3(13)	4519(4)	1125.5(12)	24(1)
C(6)	518.5(14)	2728(4)	800.3(12)	26(1)

C(7)	-401.7(13)	2608(4)	1144.1(12)	26(1)
C(8)	-650.0(12)	4313(4)	1810.8(12)	24(1)
C(9)	11.2(12)	6143(4)	2152.4(11)	21(1)
O(10)	-1043.1(9)	8059(3)	3165.6(9)	29(1)
C(10)	-228.2(12)	7964(4)	2877.9(11)	22(1)
C(11)	574.9(12)	9564(4)	3226.3(11)	20(1)
C(12)	427.1(12)	11269(4)	4048.4(11)	22(1)
C(13)	1281.5(12)	13045(4)	4300.1(12)	23(1)
C(14)	2250.6(12)	11763(4)	4197.1(12)	21(1)
O(15)	2325.2(8)	9504(3)	4753.1(8)	22(1)
C(16)	2800.7(11)	9810(4)	5641.3(11)	19(1)
C(17)	2645.6(13)	7458(4)	6189.1(13)	27(1)
C(18)	3259.9(14)	7537(4)	7120.5(12)	27(1)
C(19)	4308.0(13)	8027(4)	6937.5(12)	22(1)
O(20)	3806.2(8)	10151(2)	5509.5(8)	20(1)
C(20)	4413.3(12)	10402(4)	6361.5(11)	20(1)
C(21)	5441.6(12)	10762(4)	6081.1(12)	28(1)
O(22)	4871.5(9)	8424(3)	7824.8(8)	24(1)
O(23)	5523.9(10)	4561(3)	7753.5(9)	31(1)
C(23)	5452.3(12)	6551(4)	8142.8(11)	20(1)
C(24)	6012.5(12)	7180(4)	9045.1(11)	19(1)
C(25)	6716.1(12)	5471(4)	9376.7(12)	23(1)
C(26)	7242.5(13)	5894(4)	10230.2(12)	25(1)
C(27)	7058.3(13)	8015(4)	10745.2(12)	26(1)
C(28)	6350.3(13)	9726(4)	10415.5(12)	24(1)
C(29)	5828.2(12)	9326(4)	9560.2(12)	23(1)

Table 2. Bond lengths [A] and angles [deg] for **228**.

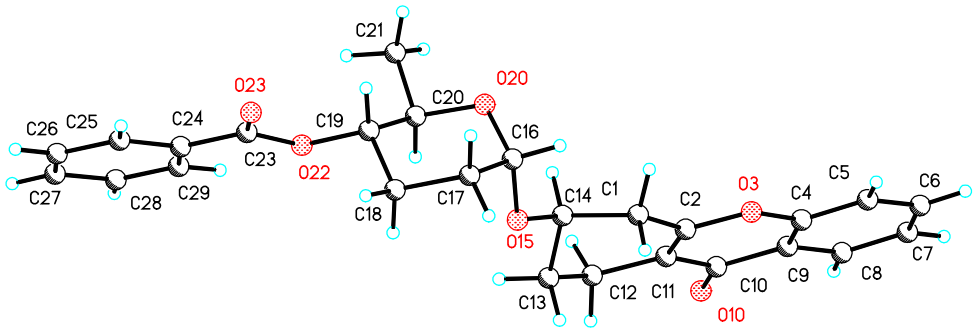
C(1)-C(2)	1.495(2)	C(12)-H(12B)	0.9900
C(1)-C(14)	1.527(2)	C(13)-C(14)	1.518(2)
C(1)-H(1A)	0.9900	C(13)-H(13A)	0.9900
C(1)-H(1B)	0.9900	C(13)-H(13B)	0.9900
C(2)-C(11)	1.346(2)	C(14)-O(15)	1.441(2)
C(2)-O(3)	1.371(2)	C(14)-H(14A)	1.0000
O(3)-C(4)	1.368(2)	O(15)-C(16)	1.3992(19)
C(4)-C(9)	1.394(2)	C(16)-O(20)	1.4260(19)
C(4)-C(5)	1.398(3)	C(16)-C(17)	1.502(3)
C(5)-C(6)	1.380(3)	C(16)-H(16A)	1.0000
C(5)-H(5A)	0.9500	C(17)-C(18)	1.529(2)
C(6)-C(7)	1.400(3)	C(17)-H(17A)	0.9900
C(6)-H(6A)	0.9500	C(17)-H(17B)	0.9900
C(7)-C(8)	1.382(3)	C(18)-C(19)	1.512(2)
C(7)-H(7A)	0.9500	C(18)-H(18A)	0.9900
C(8)-C(9)	1.395(3)	C(18)-H(18B)	0.9900
C(8)-H(8A)	0.9500	C(19)-O(22)	1.4566(19)
C(9)-C(10)	1.479(2)	C(19)-C(20)	1.523(3)
O(10)-C(10)	1.229(2)	C(19)-H(19A)	1.0000
C(10)-C(11)	1.454(2)	O(20)-C(20)	1.4351(19)
C(11)-C(12)	1.516(2)	C(20)-C(21)	1.517(2)
C(12)-C(13)	1.530(2)	C(20)-H(20A)	1.0000
C(12)-H(12A)	0.9900	C(21)-H(21A)	0.9800

C(21)-H(21B)	0.9800	C(25)-H(25A)	0.9500
C(21)-H(21C)	0.9800	C(26)-C(27)	1.383(3)
O(22)-C(23)	1.335(2)	C(26)-H(26A)	0.9500
O(23)-C(23)	1.204(2)	C(27)-C(28)	1.390(3)
C(23)-C(24)	1.495(2)	C(27)-H(27A)	0.9500
C(24)-C(25)	1.386(2)	C(28)-C(29)	1.392(2)
C(24)-C(29)	1.394(3)	C(28)-H(28A)	0.9500
C(25)-C(26)	1.395(2)	C(29)-H(29A)	0.9500

X-ray data for 227

Crystal Data. $C_{26}H_{26}O_6$, M =434.47, orthorhombic, a = 7.11230(10) Å, b = 11.6173(2) Å, c = 26.2941(4) Å, V = 2172.57(6) Å^3, T = 100(2), space group $P2_12_12_1$ (no. 19), Z = 4, μ(CuKα) = 0.769, 23738 reflections measured, 4162 unique (R_{int} = 0.0516) which were used in all calculations. The final wR_2 was 0.1105 (all data) and R_1 was 0.0409 (>2sigma(I)).

Solid state structure of **227**.



227

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **227**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	4512(3)	2213.4(14)	1383.8(6)	31(1)
C(2)	4329(2)	1357.3(14)	964.6(6)	28(1)
O(3)	4205.1(18)	270.0(10)	1149.7(4)	31(1)
C(4)	4081(2)	-631.0(14)	815.9(6)	29(1)
C(5)	4000(3)	-1722.5(16)	1029.9(7)	35(1)
C(6)	3903(3)	-2663.3(15)	714.1(8)	38(1)
C(7)	3858(3)	-2522.2(16)	186.9(7)	39(1)
C(8)	3925(3)	-1437.1(16)	-21.4(7)	35(1)
C(9)	4051(2)	-465.2(14)	291.9(6)	29(1)
C(10)	4149(2)	711.8(14)	83.9(6)	28(1)
O(10)	4116(2)	911.6(11)	-375.2(4)	36(1)
C(11)	4284(2)	1617.9(14)	463.3(6)	27(1)
C(12)	4406(3)	2847.7(14)	283.8(6)	30(1)
C(13)	4082(3)	3715.4(14)	712.4(6)	32(1)
C(14)	5186(3)	3382.2(14)	1182.3(6)	30(1)
O(15)	4886.6(18)	4263.7(10)	1552.4(4)	32(1)
C(16)	6125(3)	4227.8(14)	1971.6(6)	33(1)
C(17)	5474(3)	5127.8(15)	2348.4(6)	36(1)
C(18)	5775(3)	6332.4(14)	2124.4(6)	31(1)
C(19)	7797(3)	6446.8(14)	1961.9(6)	30(1)
O(20)	8005.6(18)	4401.6(10)	1823.4(4)	33(1)
C(20)	8364(3)	5498.4(15)	1592.1(6)	32(1)
C(21)	10427(3)	5516.3(18)	1462.1(8)	43(1)
O(22)	8105(2)	7515.0(10)	1689.8(4)	31(1)

O(23)	8440(2)	8458.8(11)	2430.3(5)	40(1)
C(23)	8455(2)	8454.5(14)	1973.4(6)	30(1)
C(24)	8830(2)	9489.3(15)	1652.8(6)	29(1)
C(25)	9091(3)	10540.3(15)	1893.6(6)	34(1)
C(26)	9415(3)	11527.2(15)	1615.3(7)	35(1)
C(27)	9492(3)	11464.1(15)	1086.6(7)	34(1)
C(28)	9255(3)	10414.1(16)	845.3(7)	35(1)
C(29)	8927(3)	9425.0(15)	1124.1(6)	32(1)

Table 2. Bond lengths [A] and angles [deg] for **227**.

C(1)-C(2)	1.490(2)	C(8)-C(9)	1.401(2)
C(1)-C(14)	1.534(2)	C(8)-H(8A)	0.9500
C(1)-H(1A)	0.9900	C(9)-C(10)	1.474(2)
C(1)-H(1B)	0.9900	C(10)-O(10)	1.229(2)
C(2)-C(11)	1.353(2)	C(10)-C(11)	1.453(2)
C(2)-O(3)	1.357(2)	C(11)-C(12)	1.507(2)
O(3)-C(4)	1.369(2)	C(12)-C(13)	1.530(2)
C(4)-C(5)	1.389(2)	C(12)-H(12A)	0.9900
C(4)-C(9)	1.391(2)	C(12)-H(12B)	0.9900
C(5)-C(6)	1.374(3)	C(13)-C(14)	1.514(2)
C(5)-H(5A)	0.9500	C(13)-H(13A)	0.9900
C(6)-C(7)	1.396(3)	C(13)-H(13B)	0.9900
C(6)-H(6A)	0.9500	C(14)-O(15)	1.4286(19)
C(7)-C(8)	1.375(3)	C(14)-H(14A)	1.0000
C(7)-H(7A)	0.9500	O(15)-C(16)	1.412(2)

C(16)-O(20)	1.408(2)	C(21)-H(21B)	0.9800
C(16)-C(17)	1.513(2)	C(21)-H(21C)	0.9800
C(16)-H(16A)	1.0000	O(22)-C(23)	1.3452(19)
C(17)-C(18)	1.533(2)	O(23)-C(23)	1.201(2)
C(17)-H(17A)	0.9900	C(23)-C(24)	1.492(2)
C(17)-H(17B)	0.9900	C(24)-C(25)	1.388(2)
C(18)-C(19)	1.506(3)	C(24)-C(29)	1.394(2)
C(18)-H(18A)	0.9900	C(25)-C(26)	1.379(3)
C(18)-H(18B)	0.9900	C(25)-H(25A)	0.9500
C(19)-O(22)	1.4490(19)	C(26)-C(27)	1.393(3)
C(19)-C(20)	1.524(2)	C(26)-H(26A)	0.9500
C(19)-H(19A)	1.0000	C(27)-C(28)	1.385(3)
O(20)-C(20)	1.435(2)	C(27)-H(27A)	0.9500
C(20)-C(21)	1.507(3)	C(28)-C(29)	1.383(2)
C(20)-H(20A)	1.0000	C(28)-H(28A)	0.9500
C(21)-H(21A)	0.9800	C(29)-H(29A)	0.9500

X-ray data for 279

Crystal Data. $C_{17}H_{16}O_6$, M=316.30, orthorhombic, a = 7.81730(10) Å, b = 11.96963(16) Å, c = 15.68901(18) Å, V = 1468.02(3) Å^3, T = 100(2), space group $P2_12_12_1$ (no. 19), Z = 4, μ(CuKα) = 0.916, 13875 reflections measured, 2810 unique (R_{int} = 0.0137) which were used in all calculations. The final wR_2 was 0.0696 (all data) and R_1 was 0.0270 (>2sigma(I)).

Solid state structure of **279** with atom numbering.

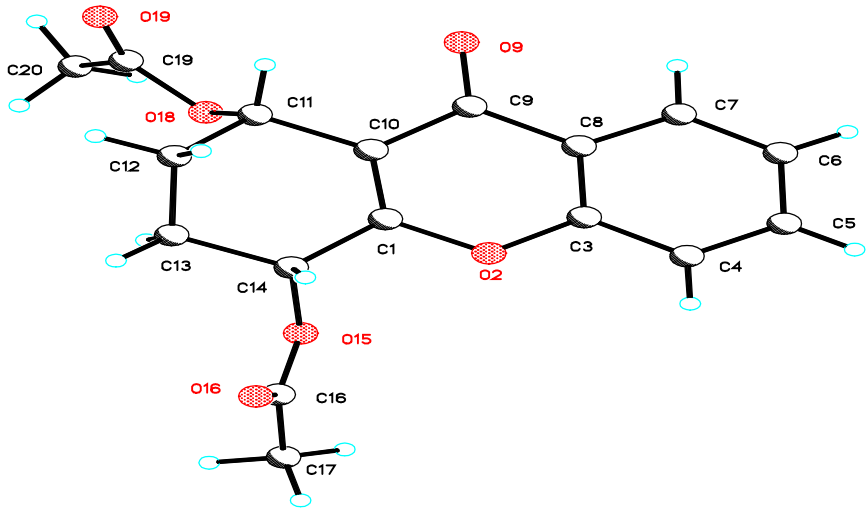


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Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **279**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	1924.2(15)	5439.4(10)	8802.6(7)	16(1)
O(2)	359.2(11)	5721.8(7)	9106.8(5)	17(1)
C(3)	-199.5(16)	6803.1(10)	9011.0(7)	16(1)
C(4)	-1835.9(16)	7029.5(11)	9312.9(8)	19(1)
C(5)	-2502.2(16)	8087.9(11)	9191.2(8)	21(1)
C(6)	-1535.3(17)	8917.4(10)	8788.6(8)	22(1)
C(7)	112.3(16)	8691.1(10)	8523.6(8)	20(1)
C(8)	806.3(16)	7624.3(10)	8635.6(7)	17(1)

O(9)	3568.6(12)	8055.3(7)	8093.8(6)	22(1)
C(9)	2566.7(16)	7353.6(10)	8368.5(7)	17(1)
C(10)	3028.5(16)	6169.6(10)	8453.7(7)	16(1)
C(11)	4780.1(16)	5805.6(10)	8178.8(7)	17(1)
C(12)	5313.5(16)	4708.0(10)	8593.6(8)	20(1)
C(13)	3907.0(17)	3833.9(10)	8500.5(8)	20(1)
C(14)	2297.1(15)	4220.6(10)	8954.3(8)	18(1)
O(15)	821.4(12)	3613.1(7)	8652.5(5)	19(1)
O(16)	1069.0(13)	2399.8(7)	9741.5(5)	24(1)
C(16)	362.5(16)	2695.8(9)	9098.5(7)	18(1)
C(17)	-1104.3(17)	2117.5(11)	8678.8(8)	23(1)
O(18)	4702.4(10)	5661.1(7)	7253.3(5)	17(1)
O(19)	7538.7(11)	5996.7(8)	7187.1(6)	23(1)
C(19)	6215.0(15)	5755.9(10)	6842.2(8)	18(1)
C(20)	6006.1(16)	5512.3(11)	5913.0(8)	22(1)

Table 2. Bond lengths [A] and angles [deg] for **279**.

C(1)-C(2)	1.490(2)	C(1)-H(1A)	0.9900
C(1)-C(14)	1.534(2)	C(1)-H(1B)	0.9900

C(2)-C(11)	1.353(2)	C(12)-H(12B)	0.9900
C(2)-O(3)	1.357(2)	C(13)-C(14)	1.514(2)
O(3)-C(4)	1.369(2)	C(13)-H(13A)	0.9900
C(4)-C(5)	1.389(2)	C(13)-H(13B)	0.9900
C(4)-C(9)	1.391(2)	C(14)-O(15)	1.4286(19)
C(5)-C(6)	1.374(3)	C(14)-H(14A)	1.0000
C(5)-H(5A)	0.9500	O(15)-C(16)	1.412(2)
C(6)-C(7)	1.396(3)	C(16)-O(20)	1.408(2)
C(6)-H(6A)	0.9500	C(16)-C(17)	1.513(2)
C(7)-C(8)	1.375(3)	C(16)-H(16A)	1.0000
C(7)-H(7A)	0.9500	C(17)-C(18)	1.533(2)
C(8)-C(9)	1.401(2)	C(17)-H(17A)	0.9900
C(8)-H(8A)	0.9500	C(17)-H(17B)	0.9900
C(9)-C(10)	1.474(2)	C(18)-C(19)	1.506(3)
C(10)-O(10)	1.229(2)	C(18)-H(18A)	0.9900
C(10)-C(11)	1.453(2)	C(18)-H(18B)	0.9900
C(11)-C(12)	1.507(2)	C(19)-O(22)	1.4490(19)
C(12)-C(13)	1.530(2)	C(19)-C(20)	1.524(2)
C(12)-H(12A)	0.9900	C(19)-H(19A)	1.0000

O(20)-C(20)	1.435(2)	C(24)-C(29)	1.394(2)
C(20)-C(21)	1.507(3)	C(25)-C(26)	1.379(3)
C(20)-H(20A)	1.0000	C(25)-H(25A)	0.9500
C(21)-H(21A)	0.9800	C(26)-C(27)	1.393(3)
C(21)-H(21B)	0.9800	C(26)-H(26A)	0.9500
C(21)-H(21C)	0.9800	C(27)-C(28)	1.385(3)
O(22)-C(23)	1.3452(19)	C(27)-H(27A)	0.9500
O(23)-C(23)	1.201(2)	C(28)-C(29)	1.383(2)
C(23)-C(24)	1.492(2)	C(28)-H(28A)	0.9500
C(24)-C(25)	1.388(2)	C(29)-H(29A)	0.9500