

BIOMIMETIC TOTAL SYNTHESIS OF MEROTERPENOID NATURAL PRODUCTS

A Thesis Submitted By

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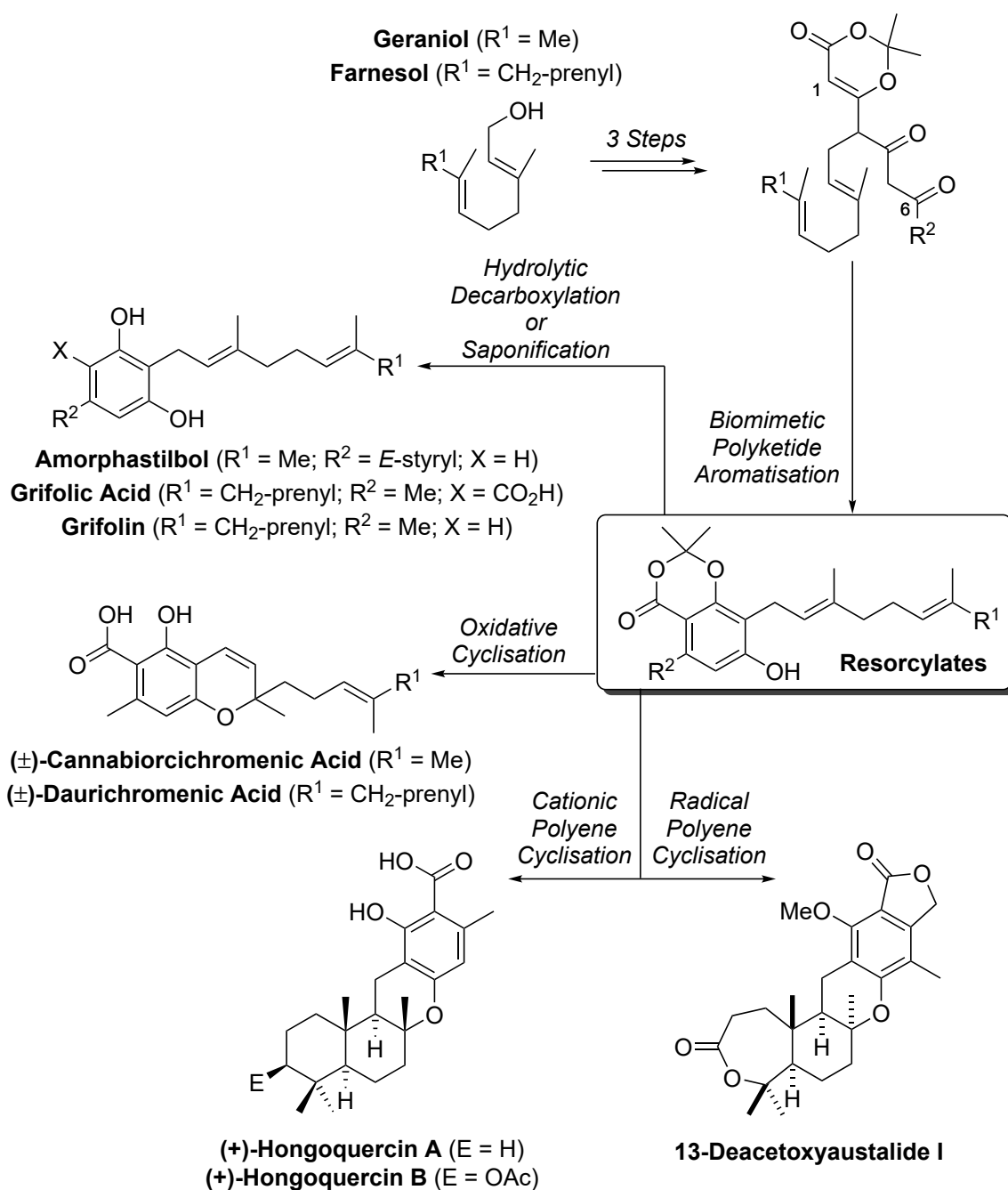
A thesis submitted to Imperial College London in partial
fulfilment of the requirements for the degree of DOCTOR OF
PHILOSOPHY in the Faculty of Natural Sciences.

April 2, 2019

ABSTRACT

Meroterpenoids belong to a class of natural products that are biosynthesised *via* a mixed polyketide-terpenoid pathway. Meroterpenoids are reported to have a range of promising antibiotic, anti-tumor, anti-HIV and anti-diabetic activities. To fully evaluate their therapeutic potential, a concise and flexible synthetic route is required to access these natural products and their analogues for parallel syntheses to assist future bioassay and structure-activity relationship (SAR) studies.

This thesis describes further developments and synthetic applications of the biomimetic polyketide aromatisation of β , δ -diketo dioxinones to produce resorcyates starting from commercially available terpene alcohols such as geraniol and *trans*, *trans*-farnesol. The resulting resorcyates are important intermediates which could be diversified into a selection of meroterpenoid natural products such as amorphastilbol, grifolic acid and grifolin *via* hydrolytic decarboxylation or saponification. Palladium catalysed oxidative cyclisation of resorcyates lead to the formation of chromene heterocycles to provide ($\pm$)-cannabiorcichromenic and ($\pm$)-daurichromenic acids. More complex polycyclic meroterpenoids such as the hongoquercins and the austalides could be accessed by subsequent cationic or radical anion polyene cyclisation (**Scheme 1**).



Scheme 1: Biomimetic synthesis of meroterpenoid natural products.

DEDICATION AND ACKNOWLEDGEMENTS

First of all, I would like express my sincere gratitude to Prof. Anthony G. M. Barrett for the challenging and rewarding research topic as well as his continuous support and advice throughout my Ph.D. Secondly, I would also like to thank Prof. Philip Parsons for all the additional advice and guidance. I must thank them for their patience, motivation, and immense knowledge. I would also like to thank Virginia for her constant assistance.

I would also like to take this opportunity to thank Prof. Chris Braddock, Prof. Alan Spivey and Prof. Donald Craig for their insightful comments and discussions which widen my knowledge from various perspectives. I would like to thank all the analytical staffs: Pete Haycock and Dick Sheppard for NMR spectroscopy, Dr. Andrew White for X-ray crystallography and Dr. Lisa Haigh for HRMS.

My special thanks are extended to everyone in the Barrett, Fuchter and Parsons group. Thank you everyone for the assistance, the knowledge they have passed on me as well as being wonderful labmates in the laboratory.

Last but not least, I would like to thank my family for their unconditional love and support. In particular, I must thank my fiancée Anny for her love and company in the past five years. Thank you Toffee and Mellow, the two amazing bichon frise, for accompanying us throughout this journey. This dissertation would not have been possible without their warm love, continued patience, and endless support.

One, remember to look up at the stars and not down at your feet. Two, never give up work. Work gives you meaning and purpose and life is empty without it. Three, if you are lucky enough to find love, remember it is there and don't throw it away.

— Stephen Hawking

AUTHOR'S DECLARATIONS

Declaration of Originality

I, Tsz Kan Ma, declare that the work in this thesis was carried out under the supervision of Professor Anthony G. M. Barrett. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the thesis are those of the author.

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TSZ KAN MA

APRIL 2, 2019

LIST OF ABBREVIATIONS

5-HT _{1A}	Serotonin 1A Receptor.
5-HT _{2A}	Serotonin 2A Receptor.
α_{2A}	Alpha-2A Adrenergic Receptor.
A ₁	Adenosine A ₁ Receptor.
Ac	Acetyl.
AIBN	2,2'-Azobis(2-methylpropionitrile).
Akt	Protein Kinase B.
Anal	Analysis.
ax	Axial.
β_1	Beta-1 Adrenergic Receptor.
β_2	Beta-2 Adrenergic Receptor.
BINOL	1,1'-Bi-2-naphthol.
Boc	<i>tert</i> -Butyloxycarbonyl.
brsm	Based on Recovered Starting Material.
BTK	Bruton's Tyrosine Kinase.
Bu	Butyl.
Calcd	Calculated.
CD	Circular Dichroism.
d	Doublet.
D2L	Dopamine Receptor (Longer).
DAPK	Death-Associated Protein Kinase.
dba	Dibenzylideneacetone.
DCC	<i>N, N'</i> -Dicyclohexylcarbodiimide.
dd	Doublet of Doublet.
ddd	Doublet of doublet of doublet.
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.
DMAP	4-Dimethylaminopyridine.
<i>dr</i>	Diastereomeric Ratio.
dt	Doublet of Triplet.
E	Electrophile.

LIST OF ABBREVIATIONS

EC ₅₀	Half Maximal Effective Concentration.
EDTA	Ethylenediaminetetraacetic Acid.
<i>ee</i>	Enantiomeric Excess.
EI	Electron Ionisation.
eq	Equatorial.
ERK	Extracellular Signal–Regulated Kinases.
ESI	Electrospray Ionisation.
Et	Ethyl.
FTMS	Fourier Transform Mass Spectrometry.
GPR	G Protein-Coupled Receptor.
H ₁	Histamine H ₁ Receptor.
Hep G2	Human Liver Cancer Cell Line.
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol.
HIV	Human Immunodeficiency Viruses.
HPLC	High Performance Liquid Chromatography.
HRMS	High Resolution Mass Spectrometry.
IC ₅₀	Half Maximal Inhibitory Concentration.
IR	Infrared.
<i>J</i>	Coupling Constant.
LD ₅₀	Median Lethal Dose.
m	Multiplet.
M ₂	Muscarinic Acetylcholine Receptor M ₂ .
Me	Methyl.
MIC	Minimum Inhibitory Concentration.
MOM	Methoxymethyl Ether.
Ms	Mesyl.
mTOR	Mammalian Target of Rapamycin.
NBS	<i>N</i> -Bromosuccinimide.
NMR	Nuclear Magnetic Resonance.
NOESY	Nuclear Overhauser Effect Spectroscopy.
<i>p</i>	Para.
PBMC	Peripheral Blood Mononuclear Cell.
Ph	Phenyl.
Phe	Phenylalanine.
Pim1	Proto-Oncogene Serine 1.
PPAR	Peroxisome Proliferator-Activated Receptor.
ppm	Parts Per Million.
PPTS	Pyridinium <i>p</i> -toluenesulfonate.

Pr	Propyl.
q	Quartet.
<i>S</i>	Sinister.
s	Singlet.
S6K	Ribosomal Protein S6 Kinase.
SEM	2-(Trimethylsilyl)ethoxymethyl.
SET	Single Electron Transfer.
t	Triplet.
TBAF	Tetra- <i>n</i> -butylammonium fluoride.
Tf	Triflyl.
TFA	Trifluoroacetic Acid.
THF	Tetrahydrofuran.
THP	Tetrahydropyran.
TLC	Thin Layer Chromatography.
TOF	Time of Flight.
tq	Triplet of Quartet.
Zap70	Zeta-Chain-Associated Protein Kinase 70.

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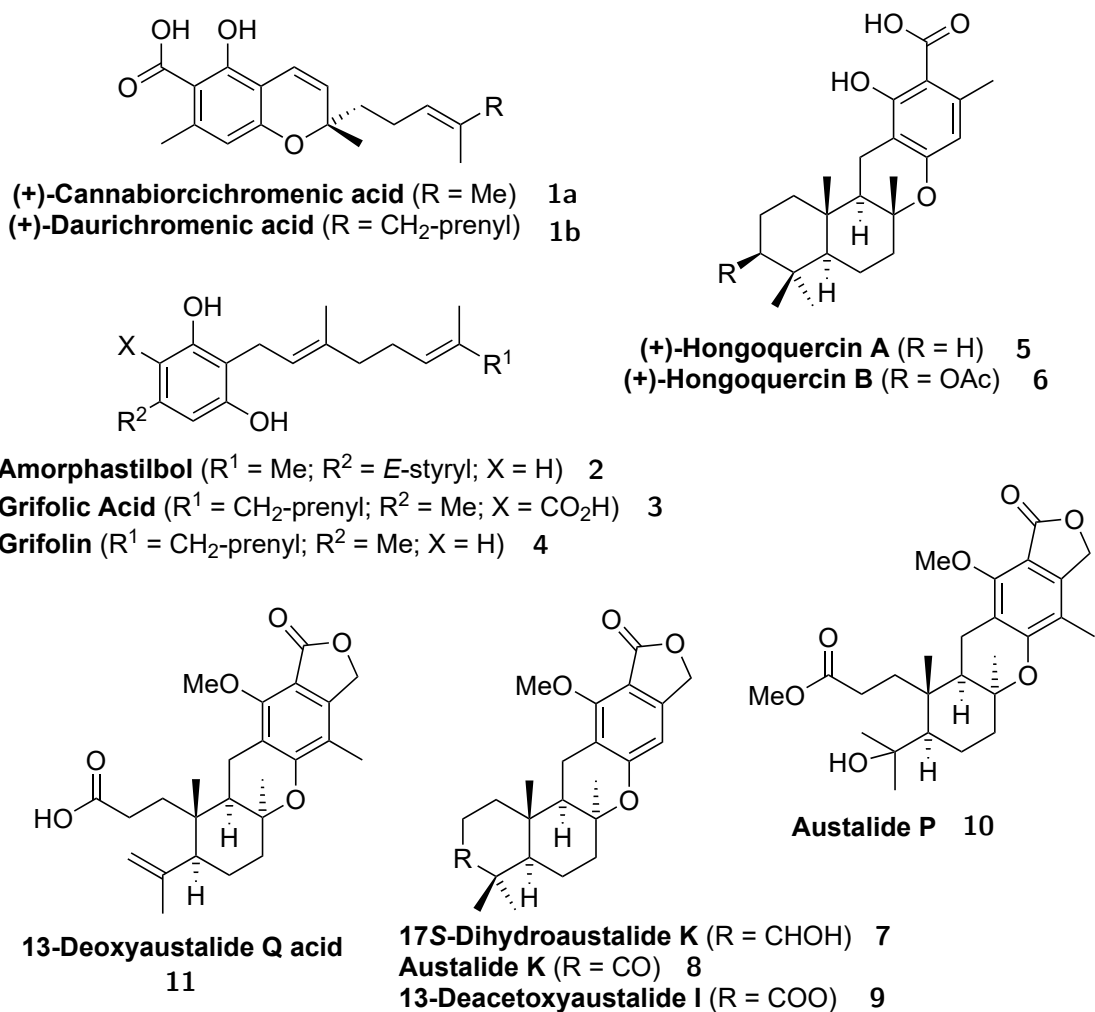
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GENERAL INTRODUCTION

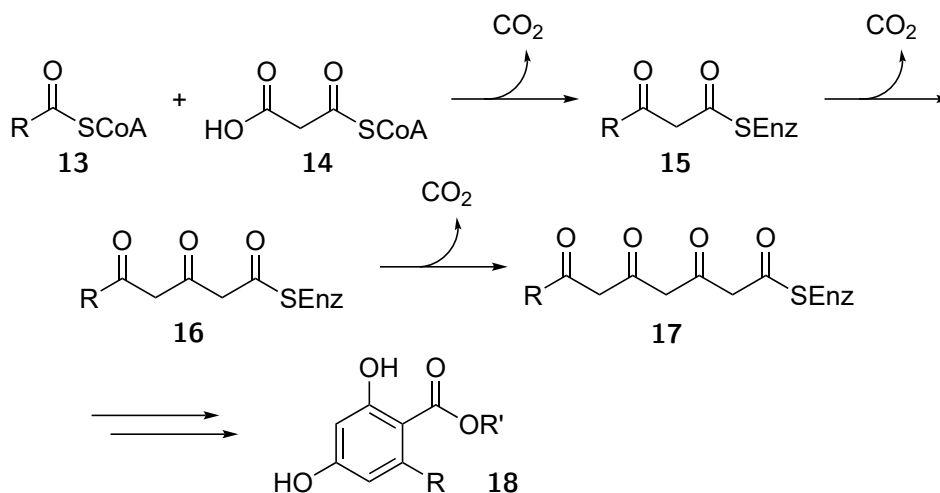
Meroterpenoids belong to a class of natural products that are biosynthesised *via* a mixed polyketide-terpenoid pathway and are isolated from a variety of fungus and medicinal plants (**Scheme 1.1**).^{1,2} For instance, cannabiorcichromenic acid (**1a**) and (+)-daurichromenic acid (**1b**) were found in *Cylindrocarpon olidum*, a parasitic fungi, and the dried leaves of a medicinal plant *Rhododendron dauricum*.^{3,4} It was found that they show significant biological activities such as anti-bacterial and anit-HIV properties. Amorphastilbol (**2**), grifolic acid (**3**) and grifolin (**4**) are meroterpenoids that contain a resorcinol core and were found in extracts of plants *Amorpha* and *Peperomia* and the secondary metabolite of fungi *Albatrellus*.^{5–8} Biological evaluation of these natural products revealed their promising bioactivities including anti-microbial, anti-diabetic and anti-cancer activities. Furthermore, structurally more complex polycyclic meroterpenoids including (+)-hongoquercin A (**5**) and B (**6**) as well as the austalides were recently isolated from the secondary metabolites of fungus LL-23G227, *Aspergillus* and *Penicillium*, which are known to show anti-bacterial, cytotoxic and glucanase inhibitory activities.^{9–14} Their unique structures with promising therapeutic activities encouraged numerous synthetic efforts from various research groups on these targets to explore their potential as novel lead compounds as well as showcasing innovative synthetic strategies and methodologies.



Scheme 1.1: Biologically active meroterpenoid natural products.

1.1 Biosynthesis of β -Resorcyates

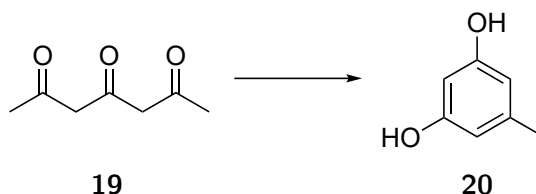
The hypothesised biosynthesis of polyketides was first described by Collie in 1907.^{1,2,15} The accepted proposal for the biosynthesis of β -resorcyates involves a series of decarboxylative Claisen condensation reactions between coenzyme A thioester **13** and malonyl coenzyme A ester **14** to give keto-thioester **15**. Further entropically favourable Claisen thioester condensations of keto-thioester **15** with malonyl coenzyme A ester **14** elongate the polyketide chain to produce linear polyketide chain **16** and **17** sequentially. Polyketide chain **17** would finally undergo an aldol-type cyclisation and aromatisation to assemble the resorcyate **18** core.



Scheme 1.2: Biosynthesis of β -resorcyates.

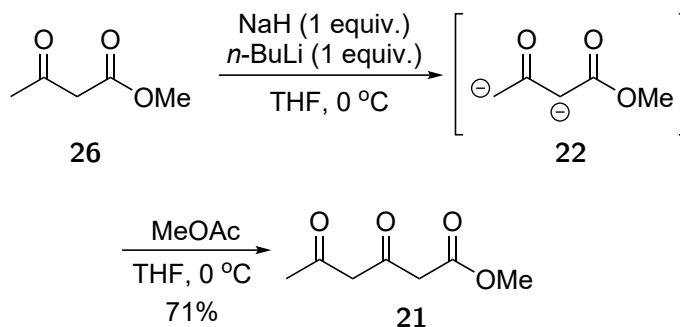
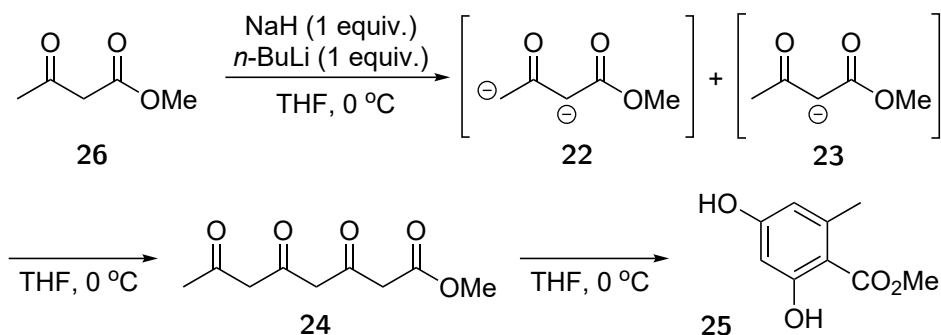
1.2 Biomimetic Polyketide Aromatisation

Inspired by the biosynthesis of β -resorcyate **18**, the synthetic challenges in synthesising β -polyketones to achieve the biomimetic synthesis of phenolic compounds simulated extensive synthetic studies. Pioneering research results that the β -polyketones such as 2,4,6-trione **19** are able to aromatise under laboratory conditions into orcinol **20** (**Scheme 1.3**).¹⁶

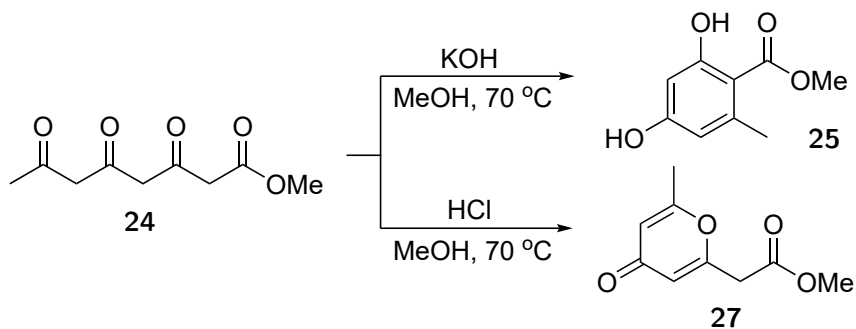


Scheme 1.3: Aromatisation of 2,4,6-trione **19**.

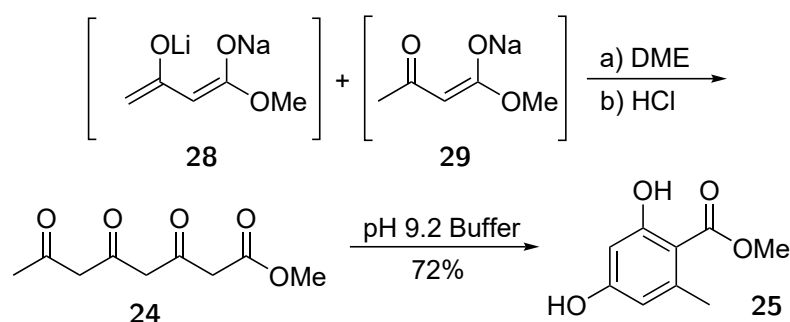
However, the major synthetic challenge is to be able to produce β -polyketones in good yield. In 1974, Weiler and co-workers disclosed an efficient method to synthesise β , δ -diketo ester **21** (71 %) by the acylation of the dianion of methyl acetoacetate **22** with methyl acetate (**Scheme 1.4**).¹⁷ Furthermore, they discovered that the dianion of methyl acetoacetate **22** could react with the monoanion of methyl acetoacetate **23** to produce a linear β , δ , γ -triketo ester chain **24** that would cyclise spontaneously and aromatise into methyl orsellinate **25** (**Scheme 1.5**).

**Scheme 1.4:** Weiler synthesis of β -keto ester **21**.**Scheme 1.5:** Weiler synthesis of methyl orsellinate **25**.

Following this pioneering work, Harris and co-workers conducted further studies on the biomimetic cyclisation of β -polyketones (**Scheme 1.6**).¹⁸ In particular, they discovered that β , δ , γ -triketo ester **24** underwent a facile aldol cyclisation and dehydration to form methyl orsellinate **25** under refluxing basic conditions. On the other hand, under acidic conditions, β , δ , γ -triketo ester **24** was cyclised into the corresponding pyrone **27**.

**Scheme 1.6:** Harris biomimetic cyclisation of β , δ , γ -triketo ester **24**.

In 1980, the synthesis of the β , δ , γ -triketo ester **24** was further optimised by Barton and co-workers. The key step involved the condensation of dienolate **28** with enolate **29** (**Scheme 1.7**).¹⁹ The resulting β , δ , γ -triketo ester **24** was subsequently converted into methyl orsellinate **25** (72%).

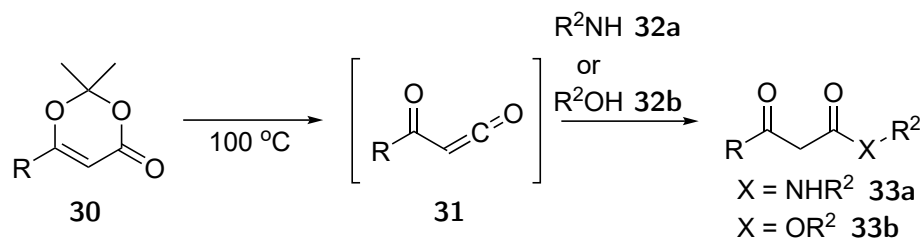


Scheme 1.7: Barton synthesis and biomimetic cyclisation of β , δ , γ -triketo ester **24**.

1.3 The Barrett Group Biomimetic Synthesis of Resorcylic Acid Lactones

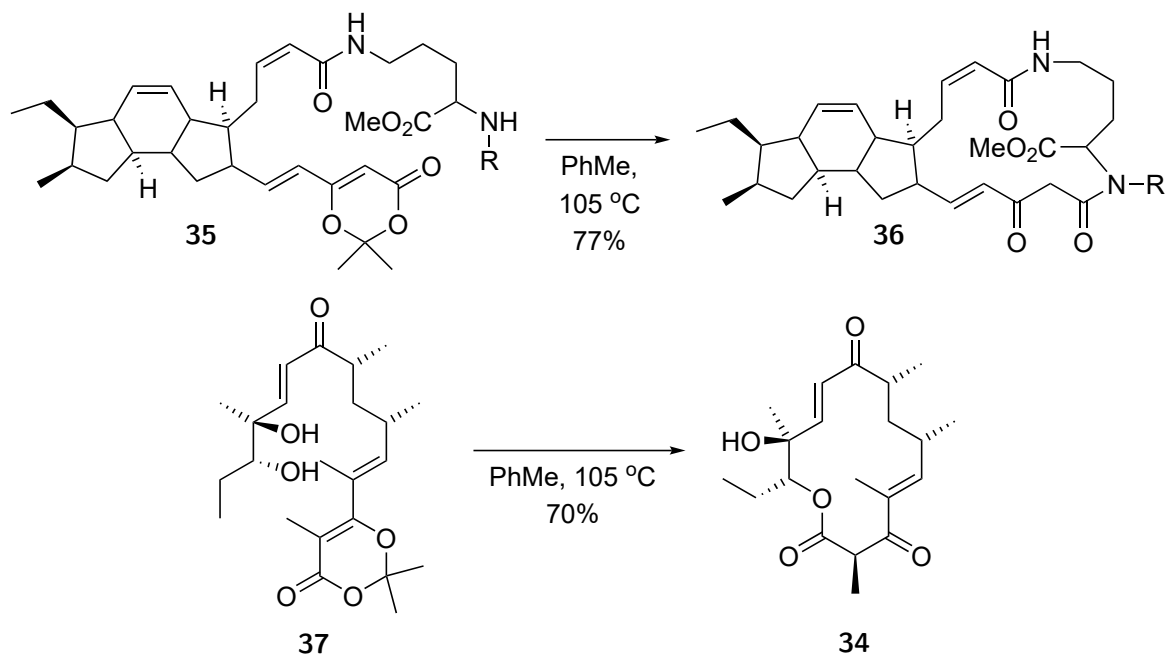
Although these pioneering studies demonstrated that simple β -resorcyates, such as methyl orsellinate **25**, could be synthesised biomimetically from the corresponding β , δ , γ -triketo ester **24**, all these methods required strongly basic conditions to generate the corresponding anions, having limited utility and functional group tolerance. In 1984, Hyatt and co-workers reported that thermolysis of 1,3-dioxin-4-ones **30** at 100 °C resulted in the formation of acyl ketenes **31** *via* a retro [4+2] cycloaddition reaction (**Scheme 1.8**).²⁰ The resulting acyl ketenes **31**, were highly electrophilic and reacted readily with a range of amines **32a** and alcohols **32b** to provide the corresponding β -keto-amines **33a** and esters **33b**.

Inspired by the work of Hyatt and co-workers, Boeckman and co-workers utilised 1,3-dioxin-4-ones to generate the corresponding acyl ketenes for intramolecular macrolactamisation and macrolactonisation reactions in the total syntheses of (+)-ikarugamycin and (-)-kromycin (**34**) (**Scheme 1.9**).^{21,22} In the synthesis of (+)-ikarugamycin, amine **35** was thermolysed in high dilution in PhMe and yielded the corresponding macrocyclic bis-amide **36** (77 %) *via* intramolecular



Scheme 1.8: Thermolysis of 1,3-dioxin-4-ones **30**.

trapping of the resulting highly electrophilic acyl ketene intermediate. The same strategy was applied to the synthesis of the 16-membered macrolide (-)-kromycin (**34**) (70 %) by trapping the resulting ketene generated from dioxolenone diol **37**.

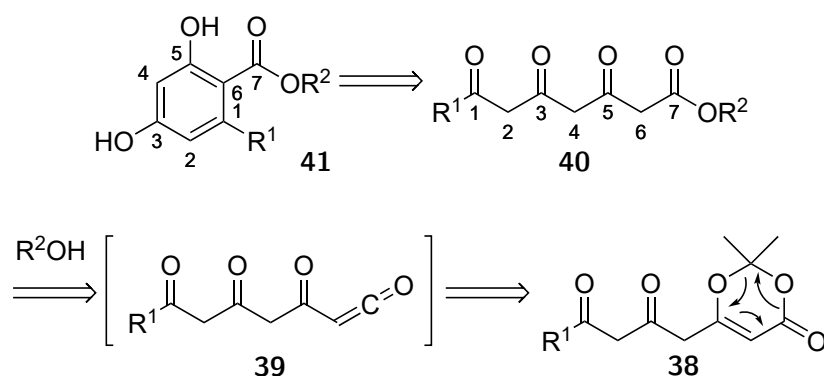


Scheme 1.9: Boeckman synthesis of (+)-ikarugamycin and (-)-kromycin (**34**).

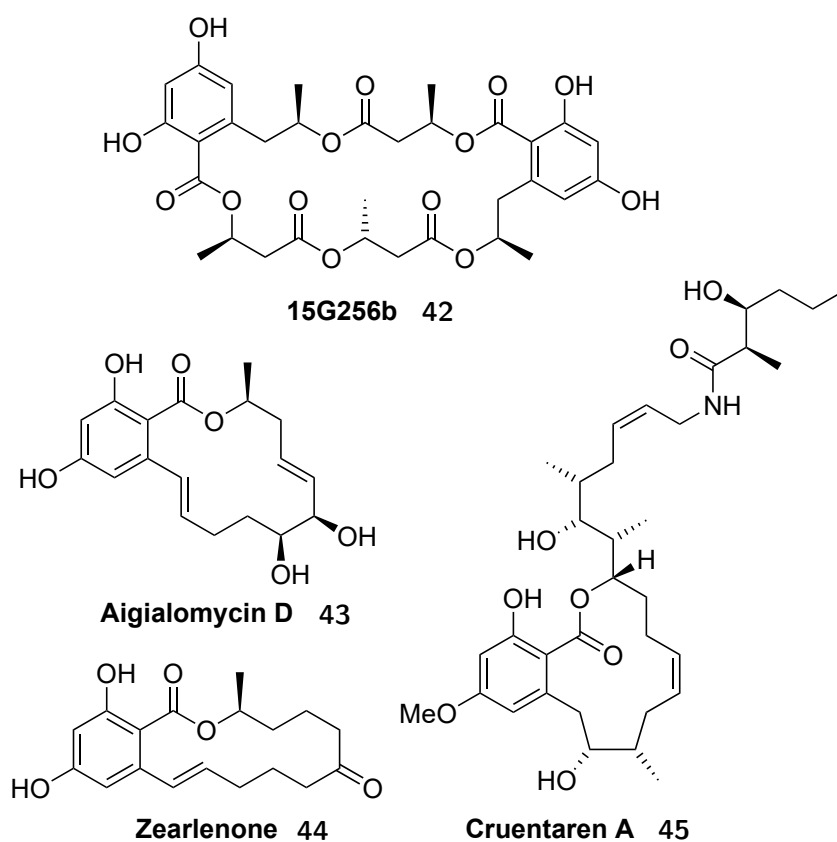
Inspired by the early works from Harris, Hyatt and Boeckman on biomimetic polyketide aromatisation, dioxinone thermolysis and its application in intramolecular macrolactamisation and macrolactonisation, the Barrett group has mainly focused on the synthesis and the retro-Diels-Alder reactions of β , δ -diketo-dioxinones **38** to generate α , γ , ϵ -triketo-ketenes **39** for inter- and intramolecular trapping with alcohols (**Scheme 1.10**). A variety of functionalised β , δ -diketo-dioxinones **38** could serve as more stable masked acyl ketene precursors to generate β ,

1.3. THE BARRETT GROUP BIOMIMETIC SYNTHESIS OF RESORCYLIC ACID LACTONES

δ , ζ -triketo-esters **40** *in situ* and aromatise into the corresponding β -resorcylates **41** for natural products total syntheses.²³ This general strategy was successfully utilised in the total syntheses of a variety of bioactive resorcylic acid lactones, including 15G256b (**42**), aigialomycin D (**43**), zearlenone (**44**) and cruentaren A (**45**) (**Scheme 1.11**).^{24–27}



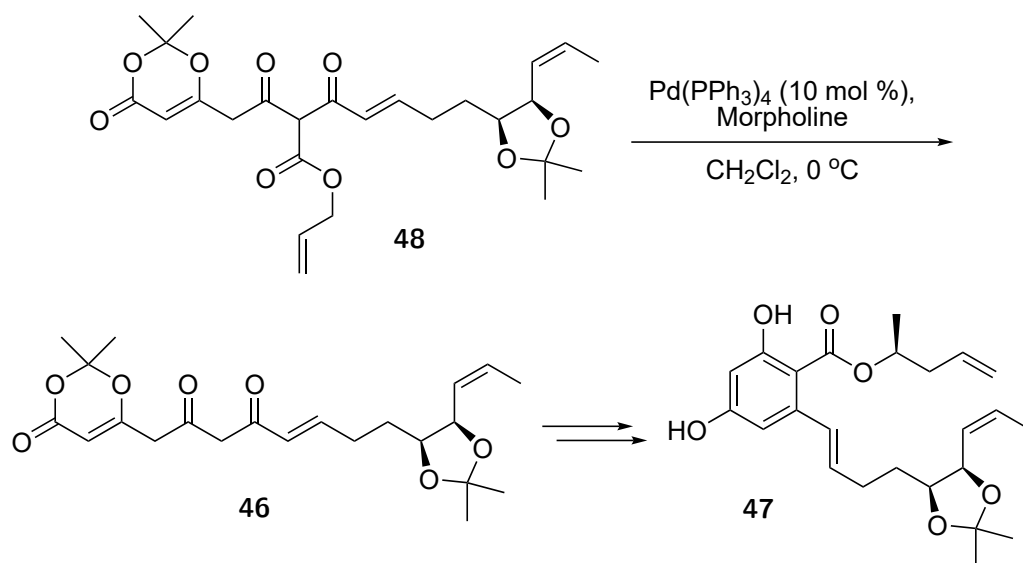
Scheme 1.10: Barrett synthesis of β , δ , ζ -triketo-esters **40**.



Scheme 1.11: Barrett synthesis of resorcylic acid lactones.

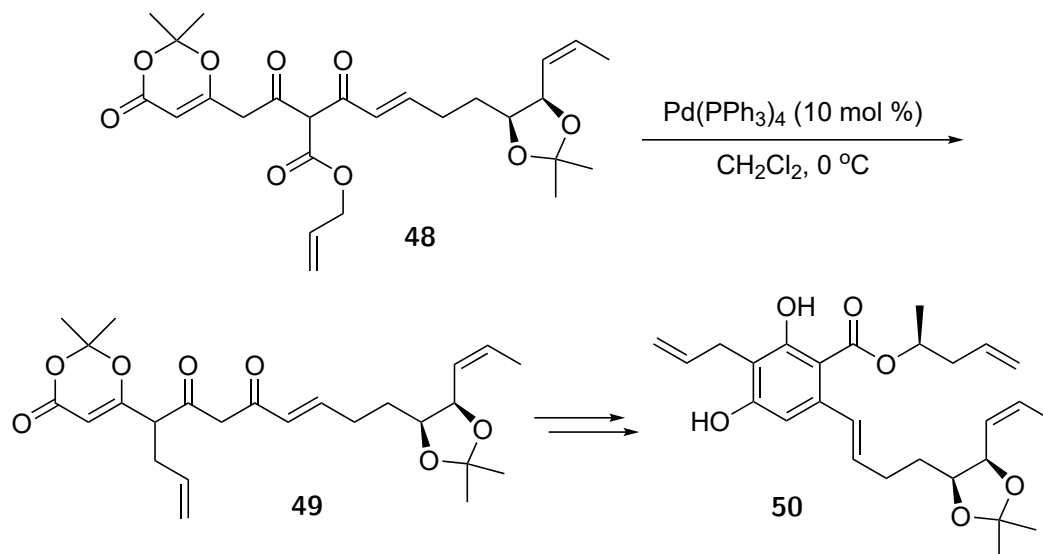
1.4 The Barrett Group Biomimetic Synthesis of Meroterpenoids

During the synthesis of aigialomycin D (**43**), a highly regioselective decarboxylative allylic rearrangement catalysed by palladium(0) was observed.²⁵ The key step in generating the desired β , δ -diketo-dioxinone **46**, which was subsequently aromatised to resorcyate **47**, involved a palladium(0) catalysed decarboxylative deallylation of β , δ -diketo-ester **48** (**Scheme 1.12**).



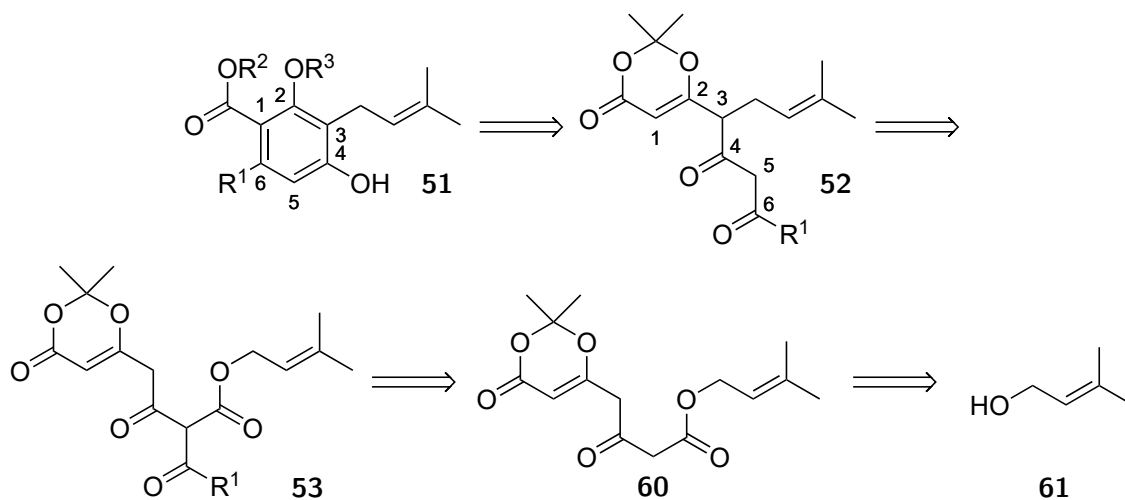
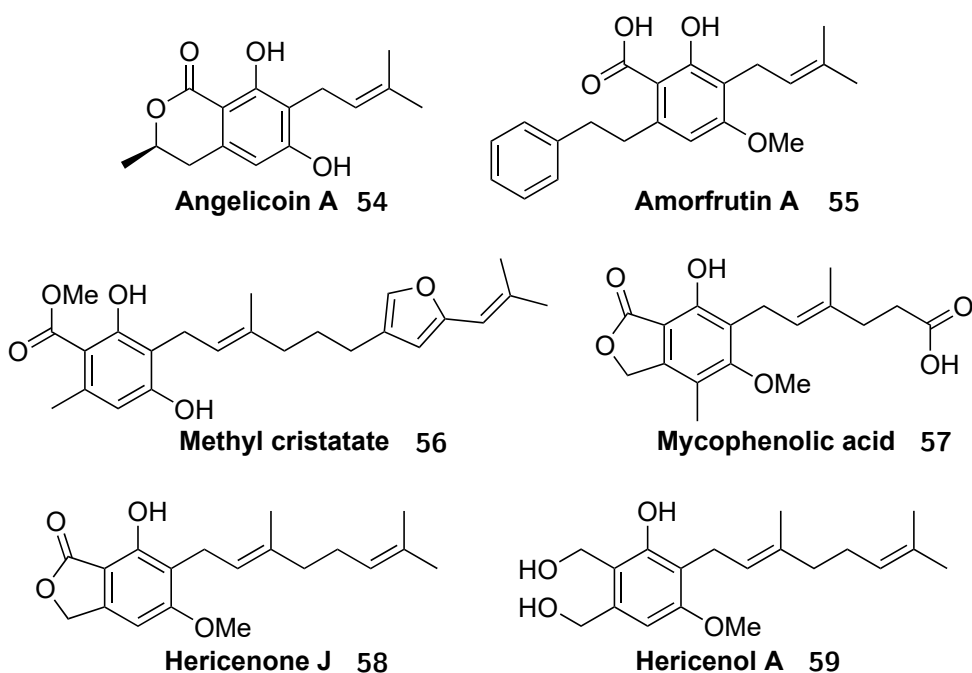
Scheme 1.12: Synthesis of resorcyate **47**.

In the presence of morpholine, acting as a palladium π -allyl cation scavenger, the reaction proceeded as expected to produce β , δ -diketo-dioxinone **46**. However, interestingly it was observed that a highly regioselective allylic rearrangement reaction occurred when morpholine was omitted from the conditions (**Scheme 1.13**). In the absence of the palladium π -allyl cation scavenger, β , δ -diketo-ester **48** underwent a modified Tsuji-Carroll transformation to give β , δ -diketo-dioxinone **49** and aromatised into the corresponding resorcyate **50**.²⁸



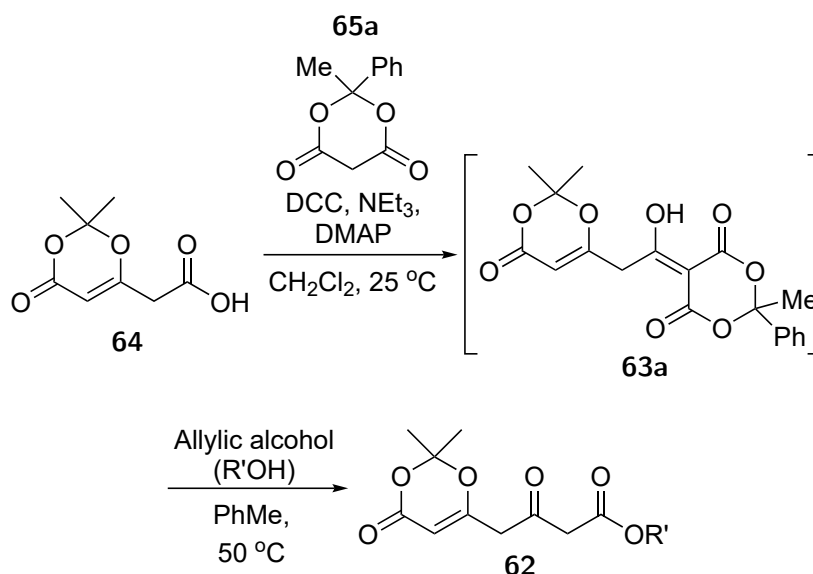
Scheme 1.13: Synthesis of resorcyate **50**.

Application of this fortuitous side reaction led to the development of a novel general approach to access meroterpenoids **51** with diverse substitution patterns (**Scheme 1.14**). The palladium(0)-induced regioselective allylic migration reaction was optimised and incorporated as the key step in generating β , δ -diketo-dioxinone **52** from β , δ -diketo-ester **53**. This general synthetic approach was proven to be very successful in the total syntheses of meroterpenoid natural products. Its synthetic utility has been demonstrated in the synthesis of a range of bioactive meroterpenoid natural products with valuable antimicrobial, antibiotic and immunosuppressing properties (**Scheme 1.15**). Examples of such meroterpenoids include angelicoic acid (**54**), amorfrutin A (**55**), hericenone J (**56**), methyl cristatate (**57**), mycophenolic acid (**58**) and hericenol A (**59**).^{29–32}

**Scheme 1.14:** Barrett synthetic approach to meroterpenoids.**Scheme 1.15:** Barrett synthesis of meroterpenoids.

More recently, an improved protocol for the synthesis of dioxinone β -keto esters **62** was developed in the Barrett group (**Scheme 1.16**). This methodology was based on the reaction of allylic alcohols with dioxinone-acyl-ketenes, generated from the selective mono-retro-Diels Alder reactions of dioxane-4,6-dione-keto-dioxinones **63a**.³³ Dioxane-4,6-dione-keto-dioxinones **63a** was prepared by a DCC mediated Steglich type coupling of dioxinone acid **64** and malonate **65a**. In

order to effect a monoketene generation reaction, the Meldrum's acid moiety was modified. It was observed that the thermally induced retro-Diels-Alder reaction of dioxane-4,6-dione-keto-dioxinones **63a** was regioselective. It selectively gave the key derived dioxinone acylketene reactive intermediate, presumably due to the phenyl ring π -delocalisation into the O-CO σ^* orbital during fragmentation.³⁴ The resulting dioxinone acylketene was trapped *in situ* with an allylic alcohol to give the corresponding dioxinone β -keto esters **62**.



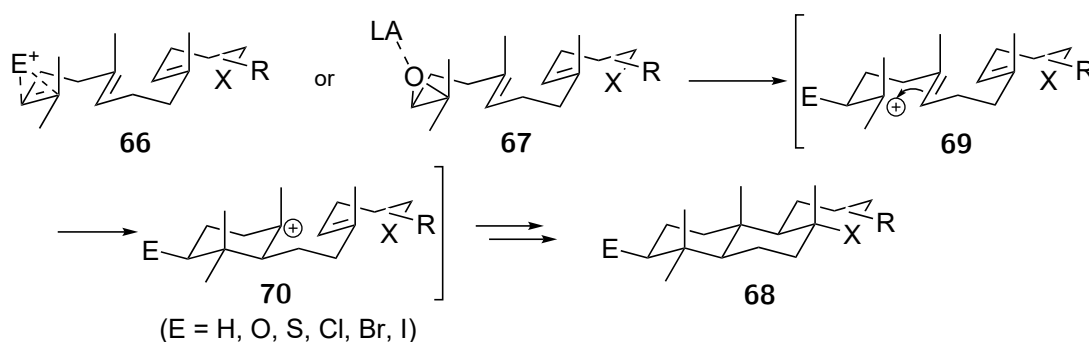
Scheme 1.16: Synthesis of dioxinone β -keto esters **62**.

1.5 Polyene Cyclisations

Biomimetic strategies are powerful methods in natural product synthesis since they can provide concise methods for the elaboration of structurally complex molecules from significantly simpler precursors. Polyene cyclisations are recognised as unique and efficient ways to build structural complexity from acyclic molecules *via* concerted and stereocontrolled C–C bond formations. In 1955, Stork and Eschenmoser independently published a hypothesis rationalising the stereo-electronic aspects that underpin the stereochemical outcomes of polyene cyclisations, which immediately encouraged further studies on these types of transformations.^{35–37} In 1968 and 1975, pioneering research on the biomimetic syntheses of steroids was reported by Johnson and

van Tamelen, both of whom demonstrated the profound synthetic power of polyene cyclisations in natural product total synthesis.^{38–42} Inspired by these revolutionary investigations into the use of polyene cyclisations in organic synthesis, considerable advancements were achieved in the past several decades on improving the efficiency of this biomimetic process, developing novel creative variants of the cyclisation processes, as well as inventing novel chiral reagents and catalysts to induce highly enantioselective and regioselective cyclisations, with comparable selectivity to the enzyme-controlled cyclisations in nature.^{43–52}

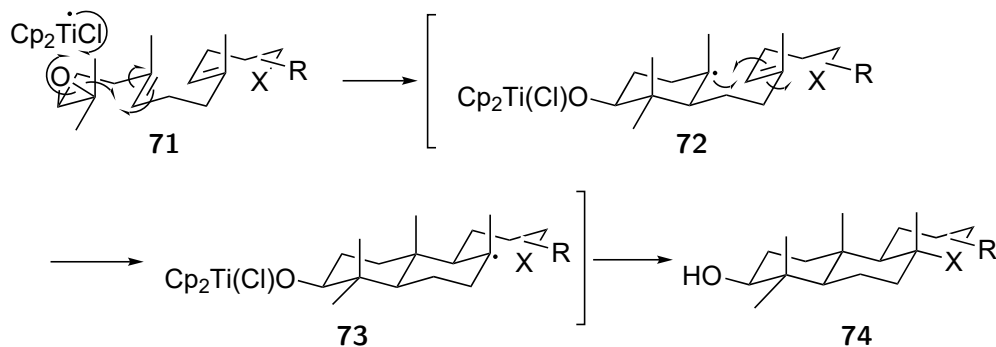
The underlying principle of all cationic cyclisation reactions is that the prearranged pseudo-chair-chair-(chair) conformation, seen in polyenes **66** and **67**, allows the efficient preparation of polycyclic compounds **68** with predefined relative configurations. This is based on the stereoelectronic arrangement of an alkene double bond in close proximity of the electrophilic carbocation center in intermediate **69**, with a subsequent nucleophilic attack by the alkene further down the terpene chain on intermediately formed carbocation centre (**Scheme 1.17**). As such, the *trans*-substitution of the polyene precursor sets the outcome for the observed *trans*-decalin stereoselectivity in the concerted cationic cyclisation through the given prearranged conformation according to the Stork-Eschenmoser hypothesis.^{35–37} In cases where the reactions are not proceeding in a concerted fashion, a mixture of products are formed.³⁵



Scheme 1.17: Cationic polyene cyclisations.

In addition to the Stork-Eschenmoser hypothesis, the origin of stereocontrol in radical polyene cyclisation reaction could be rationalised by the Beckwith-Houk rules (**Scheme 1.18**).⁵⁰ As an illustration, titanium(III)-mediated cyclisation of epoxide **71** would presumably proceed in a non-concerted fashion *via* radical intermediates **72** and **73** and favoured 6-*endo-trig*, *via* a chair

transition state being favoured over 5-*exo-trig* cyclisations to produce alcohol **74**, as a result of ring strain.



Scheme 1.18: Radical polyene cyclisations.

1.6 Aims and Objectives

The aim of this project was to expand the scope of the Barrett group biomimetic methodology in meroterpenoid syntheses. In particular, representative biomimetic total synthesis of meroterpenoids with different core structures and complexity would be explored. The prospect of this study was to develop a concise and facile route to various meroterpenoids with the minimal use of protecting groups. More importantly, the synthetic route needed to be amenable for analogues synthesis, enabling further biological evaluation and medicinal chemistry studies. All the synthetic meroterpenoids produced in the project were transferred to industrial collaborators for primary bioassays to identify new medicinal hit structures. It is important to note that β , δ -diketo-ester and diketo-dioxinones exist as mixtures of keto-enol tautomers but for simplicity they have been drawn solely as all keto-tautomers throughout the report.

CANNABIORCICHROMENIC AND DAURICHROMENIC ACID

In this chapter, the biomimetic five steps total syntheses of antibiotic ($\pm$)-cannabiorcichromenic acid and anti-HIV agent ($\pm$)-daurichromenic acid starting from geraniol and *trans, trans*-farnesol, respectively are reported.³³ Key steps involved *C*-acylation of dioxinone β -keto-esters, followed by palladium catalysed decarboxylative allylic rearrangement and biomimetic aromatisation to give the key resorcyate intermediate. Subsequent Pd(II)-catalysed Wacker-type oxidative cyclisation furnished the chromene core structure, which was then hydrolysed to yield the corresponding chromenic acids. The synthetic ($\pm$)-cannabiorcichromenic acid showed strong inhibition against the adenosine A₁ (IC₅₀ = 1.21 μ M) and the muscarinic acetylcholine M₂ (IC₅₀ = 2.98 μ M) receptors. On the other hand, ($\pm$)-daurichromenic acid was found to act as an antagonist on β_2 -adrenergic receptor (IC₅₀ = 3.39 μ M).

2.1 Isolation and Biological Evaluation of

Cannabiorcichromenic and Daurichromenic Acids

Cannabiorcichromenic acid (**1a**) and 8-chlorocannabiorcichromenic acid (**75**) were first isolated from *Cylindrocarpon olidum*, a parasitic fungi found at the root knot nematode *Meloidogyne incognita*, in 1994 by Coosemans and co-workers.³ They were isolated as an inseparable mixture (4 : 1) in which cannabiorcichromenic acid (**1a**) appeared as the major product. Their chemical

structures were fully characterised by ^1H , ^{13}C NMR and HRMS but the absolute configuration of the chiral centre of both natural products remained undetermined (**Figure 2.1**).

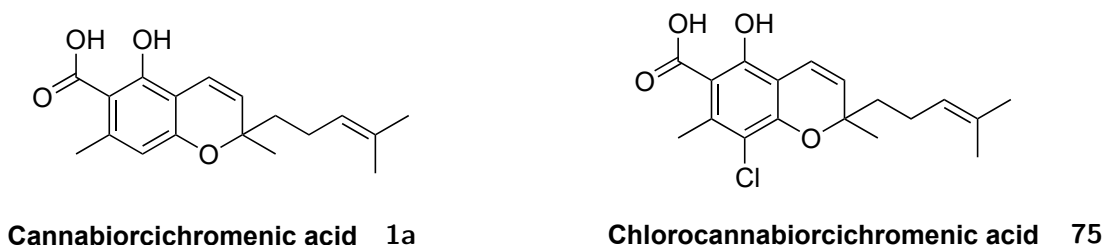


Figure 2.1: Structures of cannabiorcichromenic acid (**1a**) and 8-chlorocannabiorcichromenic acid (**75**).

Bioscreening of the natural products mixture showed that they exhibited antifungal and antibiotic properties.³ Their antibiotic activity was selective to all Gram-positive bacteria at concentrations of $5 - 10 \text{ mgL}^{-1}$ and it had no effect on Gram-negative bacteria. Additional testing have revealed their fungitoxicity. They were able to inhibit the growth of a broad spectrum of fungi such as *Fusarium oxysporum*, *Penicillium*, *Botrytis*, *Pythium* and *Verticillium* in the concentration range of $0 - 200 \text{ mgL}^{-1}$. Their toxicity was also tested with the nematode *Heterorhabditis* and 50 % mortality was observed at a concentration of 20 mgL^{-1} in H_2O . Furthermore, animal testing with house mouse, *Mus musculus*, demonstrated a very low toxicity for vertebrates with the LD_{50} value exceeded 500 mgL^{-1} .

The absolute configuration of cannabiorcichromenic acid (**1a**) was later determined in 2011 by Kitanaka and co-workers.⁵³ The chiral centre at C-2 was determined to be the *S* configuration based on its CD spectra (**Figure 2.2**).

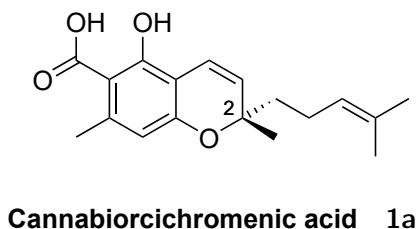


Figure 2.2: The absolute configuration of cannabiorcichromenic acid (**1a**).

On the other hand, (+)-daurichromenic acid (**1b**) received significantly greater attention than

2.1. ISOLATION AND BIOLOGICAL EVALUATION OF CANNABIORCICHROMENIC AND DAURICHROMENIC ACIDS

cannabiorcichromenic acid (**1a**) due to its promising anti-HIV property. (+)-Daurichromenic acid (**1b**) and two of its derivatives, rhodaurichromenic acids A (**76a**) and B (**76b**), were isolated from the dried leaves of *Rhododendron dauricum*, a medicinal plant which has been used as an expectorant and to treat acute chronic bronchitis in traditional Chinese medicine, by Kashiwada and co-workers in 2001 (**Figure 2.3**).⁴ The absolute configuration of these three compounds were unambiguously determined by X-ray crystallography based on the crystal structure of the *p*-bromophenacyl derivative of rhodaurichromenic acids A **77**.

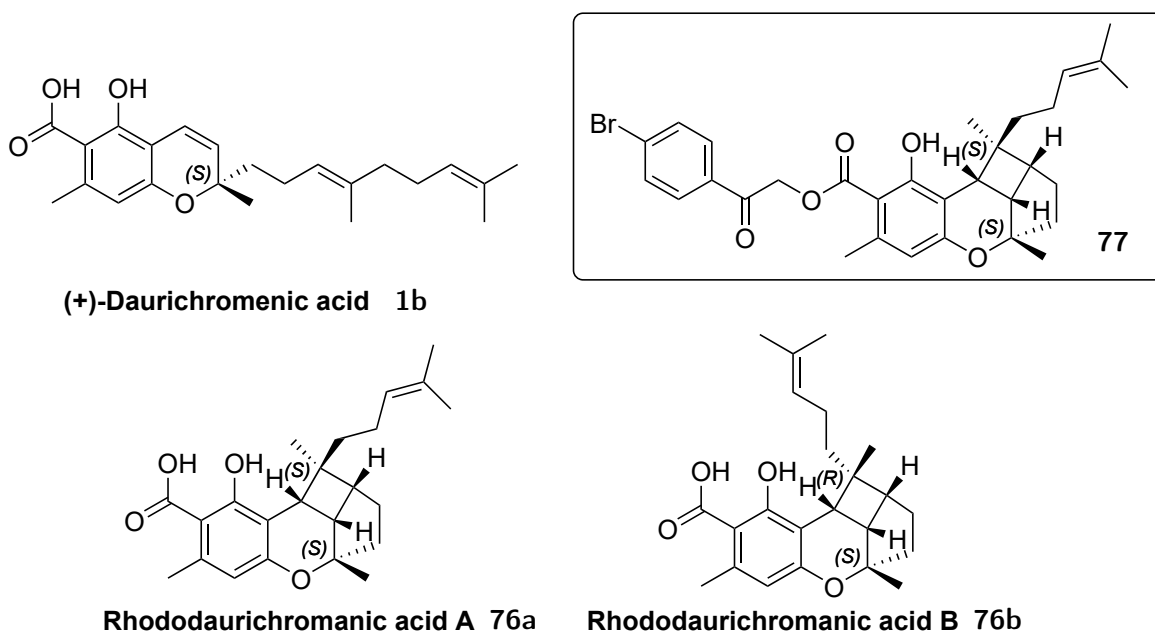
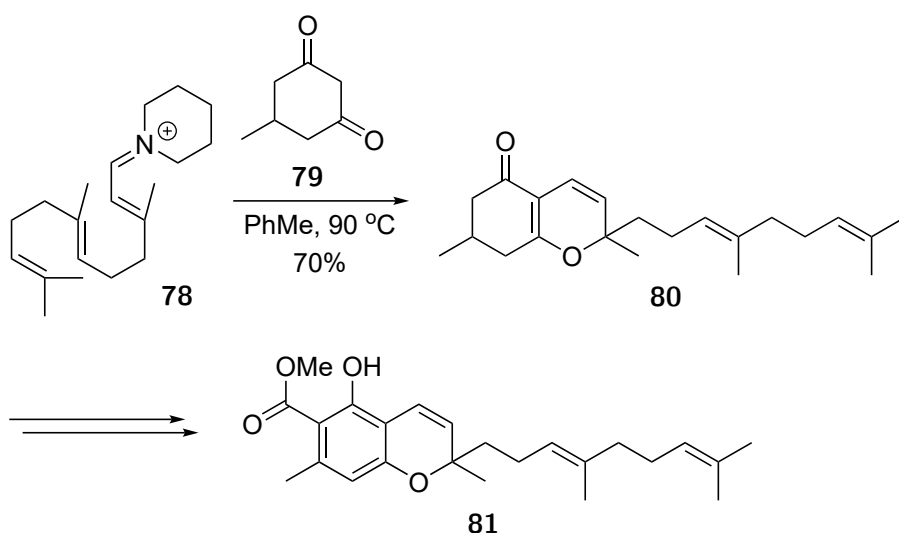


Figure 2.3: Structures of (+)-daurichromenic acid (**1b**), rhodaurichromenic acids A (**76a**) and B (**76b**).

In vitro studies conducted by Kashiwada and co-workers demonstrated that (+)-daurichromenic acid (**1b**) exhibit potent anti-HIV activity in acutely infected H9 human stem cells with an EC_{50} value of $0.00567 \mu\text{g mL}^{-1}$.⁴ It was found that uninfected H9 cells were also inhibited, with an IC_{50} value of $21.1 \mu\text{g mL}^{-1}$. Therefore, (+)-daurichromenic acid (**1b**) is more selective to infected H9 human stem cells, indicating its therapeutic potential to be considered as a new lead compound for the development of anti-HIV agents.

2.2 Previous Synthetic Approaches

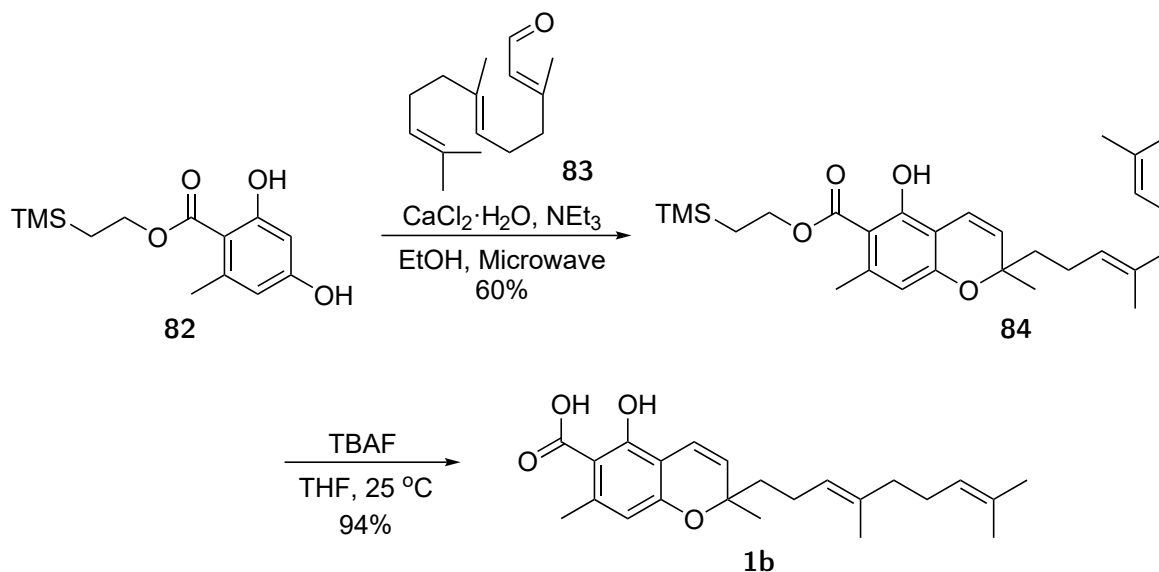
Due to the attractive bioactivity cannabiorcichromenic and daurichromenic acids (**1**) can offer, different approaches have been developed by various research groups. Wang and co-workers reported the first attempted total synthesis of ($\pm$)-daurichromenic acid (**1b**) in 2003 (**Scheme 2.1**).⁵⁴ Their approach featured a stepwise formal oxa-[3+3] cycloaddition of an α, β -unsaturated iminium salt **78** with 4-methyl-1,3-cyclohexanedione **79** to generate adduct **80** (70 %). Further derivatisation of adduct **80** furnished methyl ($\pm$)-daurichromenic ester **81**. However, the final saponification step was found to be challenging due to the occurrence of undesired decarboxylation.



Scheme 2.1: Wang synthesis of methyl ($\pm$)-daurichromenic ester (**81**).

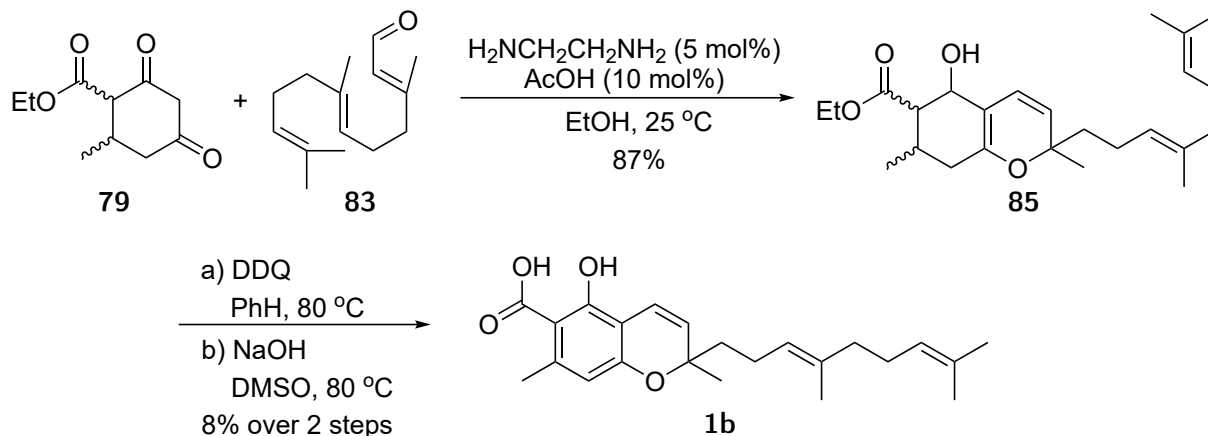
In the same year Jin and co-workers completed the first total synthesis of ($\pm$)-daurichromenic acid (**1b**) (**Scheme 2.2**).⁵⁵ The key steps involved a microwave-assisted condensation of resorcinol **82** with *trans, trans*-farnesal **83**, followed by intramolecular S_N2' -type cyclisation to furnish the 2*H*-benzopyran core structure of chromene **84** (60 %). Subsequent treatment with TBAF completed the total synthesis in five steps with 49 % overall yield.

In 2004, Wilson and co-workers completed a modular and concise four steps total synthesis of ($\pm$)-daurichromenic acid (**1b**) and its analogues (**Scheme 2.3**).⁵⁶ Tandem Knoevenagel condensation and electrocyclicalisation reaction of 1,3-cyclohexanedione **79** with *trans, trans*-farnesal **83** in the presence of a catalytic amount of 1,2-ethylenediammonium diacetate afforded 2*H*-pyran



Scheme 2.2: Jin synthesis of (±)-daurichromenic acid (**1b**).

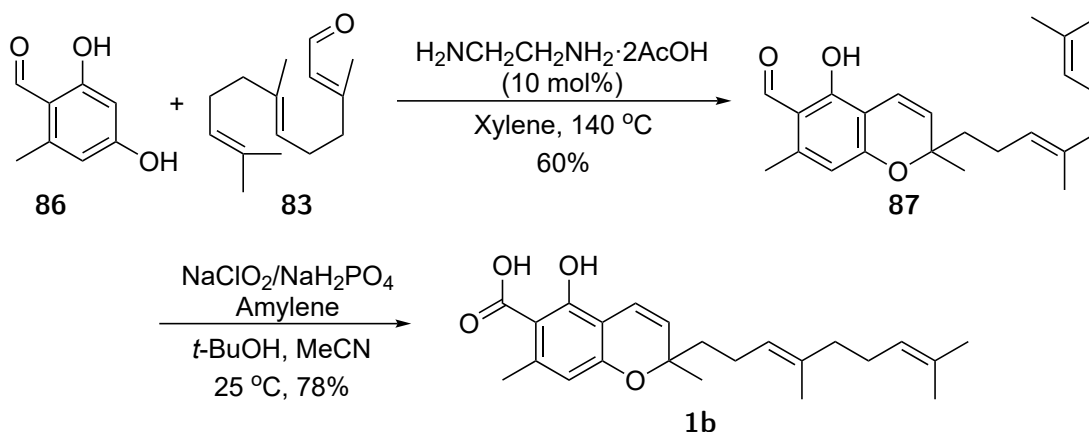
85 (87 %). Subsequent dehydrogenation reaction of the 2*H*-pyran **85** with DDQ, followed by saponification completed the synthesis of (±)-daurichromenic acid (**1b**) (8 % over 2 steps).



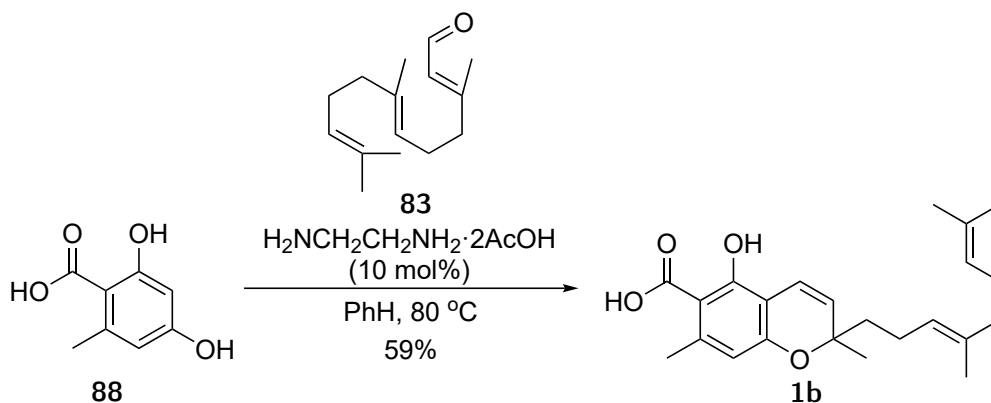
Scheme 2.3: Wilson synthesis of (±)-daurichromenic acid (**1b**).

Lee and co-workers reported the total synthesis of (±)-daurichromenic acid (**1b**) in 2005 (**Scheme 2.4**).^{57,58} Reaction of 2,4-dihydroxy-6-methylbenzaldehyde **86** with *trans,trans*-farnesal **83** in the presence of a catalytic amount of ethylenediamine diacetate in refluxing xylene produced chromene **87** (60 %). Oxidation of chromene **87** by sodium chlorite under buffered conditions yielded (±)-daurichromenic acid (**1b**) (78 %). Further optimisation of the reaction conditions

resulted in the second generation of the synthesis in one synthetic step (**Scheme 2.5**).⁵⁹ Ethylene-diamine diacetate catalysed reaction of acid **88** with *trans, trans*-farnesal **83** in refluxing benzene gave (±)-daurichromenic acid (**1b**) (59 %).



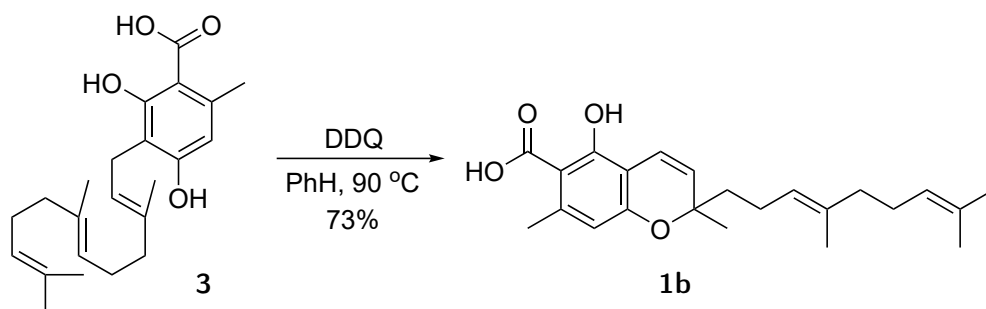
Scheme 2.4: Lee synthesis of (±)-daurichromenic acid (**1b**).



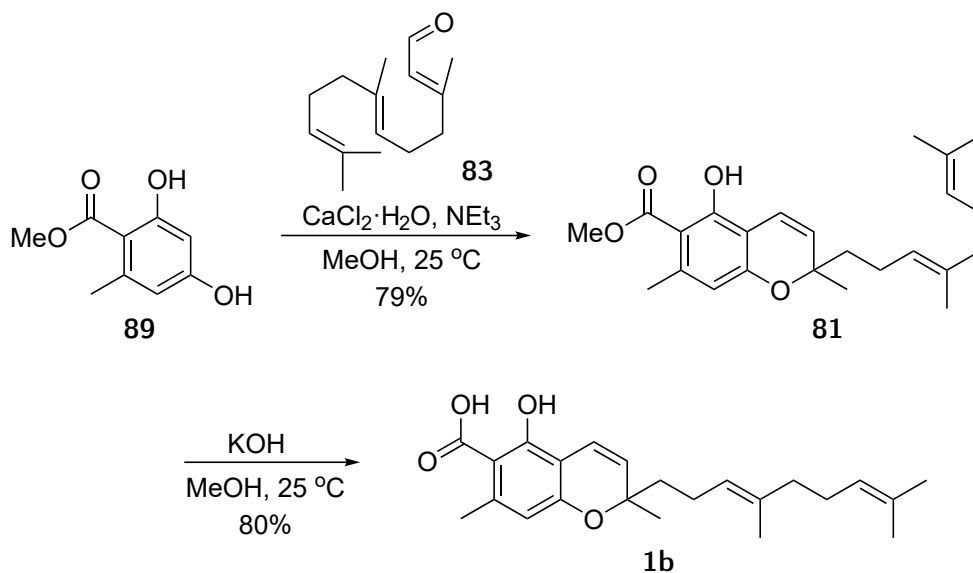
Scheme 2.5: Lee second generation synthesis of (±)-daurichromenic acid (**1b**).

In the same year, Asakawa and co-workers oxidised natural product grifolic acid **3** in the presence of DDQ in benzene to produce (±)-daurichromenic acid (**1b**) (73 %) (**Scheme 2.6**).⁶⁰

Argade and co-workers utilised a similar approach as Jin and co-workers in the synthesis of (±)-daurichromenic acid (**1b**) in 2007 (**Scheme 2.7**).⁶¹ Treatment of ester **89** with *trans, trans*-farnesal **83** in the presence of $\text{Ca}(\text{OH})_2$ gave methyl (±)-daurichromenic ester **81** (79 %). Subsequent saponification with KOH completed the synthesis of (±)-daurichromenic acid (**1b**) (80 %).

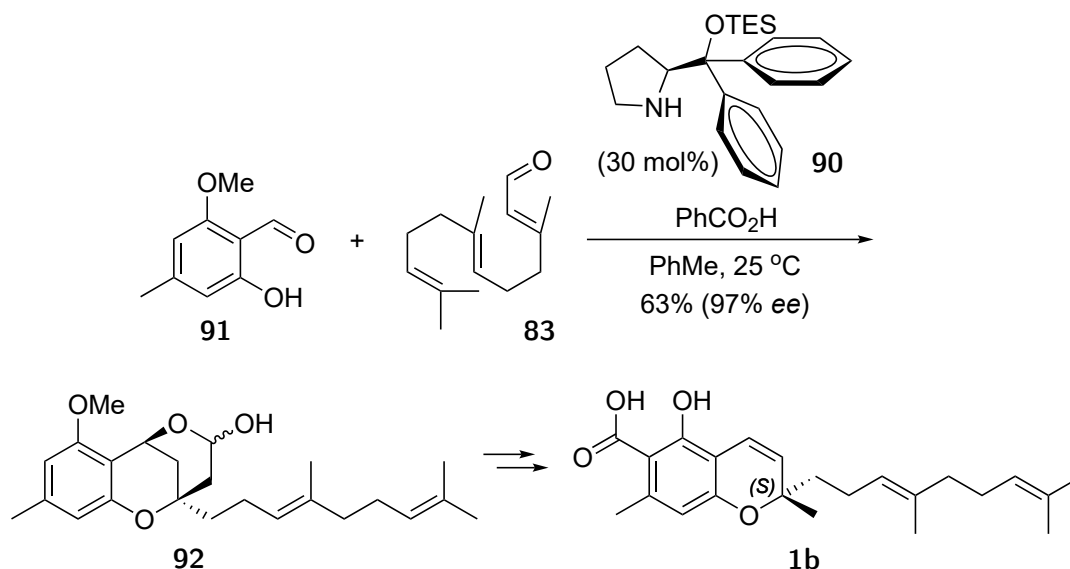


Scheme 2.6: Asakawa synthesis of (±)-daurichromenic acid (**1b**).



Scheme 2.7: Argade synthesis of (±)-daurichromenic acid (**1b**).

The first enantioselective total synthesis of (+)-daurichromenic acid (**1b**) was accomplished by Woggon and co-workers (**Scheme 2.8**).⁶² Their approach involved a proline-derived organocatalyst **90** to catalyse an aldol/oxa-Michael reaction of *trans, trans*-farnesal **83** with aldehyde **91** to give the key lactol **92** (63 %, 97 % *ee*). Further derivatisation of the lactol **92** completed (+)-daurichromenic acid (**1b**) in 12 steps with an overall yield of 0.05 %.

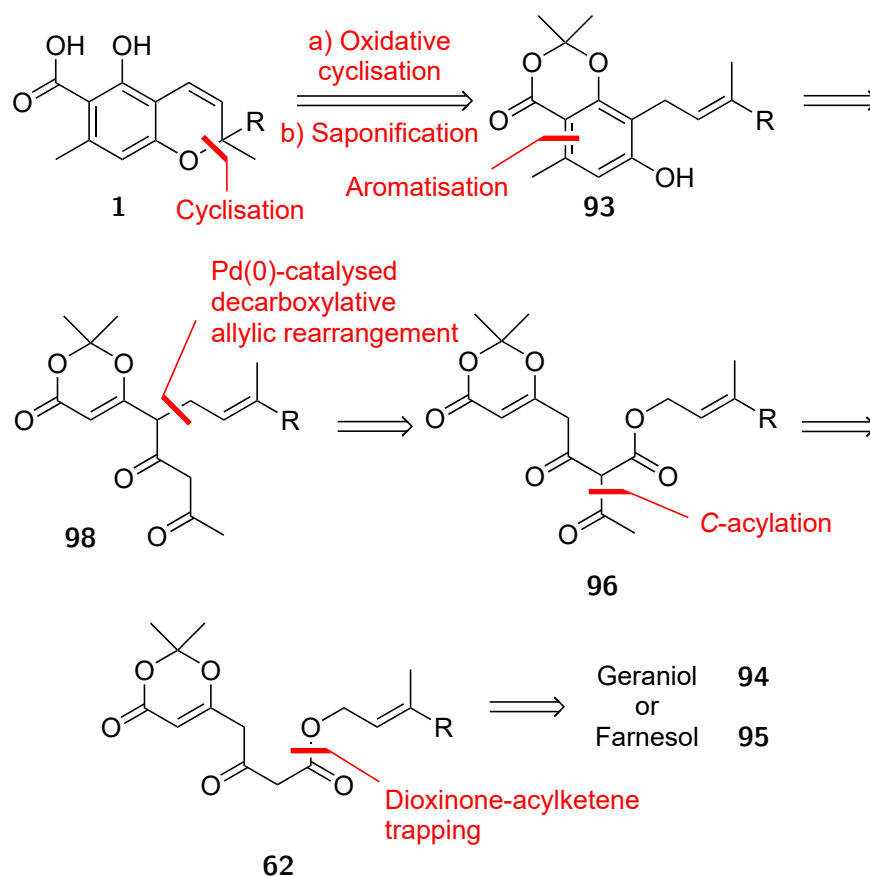


Scheme 2.8: Woggon synthesis of (+)-daurichromenic acid (**1b**).

2.3 Retrosynthetic Analysis of Cannabiorcichromenic and Daurichromenic Acids

It is envisioned that a concise and general route to access chromenic acids **1** would be possible utilising our recently developed protocol for the synthesis dioxinone β -keto-esters **62** to support the biomimetic synthesis of resorcyate **93** (Scheme 2.9).

Gentle warming of dioxane-4,6-dione-keto-dioxinone **63** results in selective fragmentation, generating a highly electrophilic dioxinone-acylketene **31** which can be trapped with either geraniol **94** or *trans, trans*-farnesol **95** to produce dioxinone β -keto-esters **62** in one step. Subsequent magnesium(II) mediated regioselective *C*-acylation of the dioxinone β -keto-esters **62** with acetyl chloride produces β , δ -diketo-ester **96**. Palladium(0) catalysed Tsuji-Carroll type decarboxylative allyl migration and base mediated biomimetic aromatisation of the β , δ -diketo-ester **96** should provide the resorcyate **93** in one pot. Finally, oxidative cyclisation of the resorcyate **93** should provide the corresponding chromene intermediate **97**, which is then hydrolysed to yield the desired chromenic acid **1** in five linear steps. This concise synthetic plan is general which should be capable for analogue syntheses.

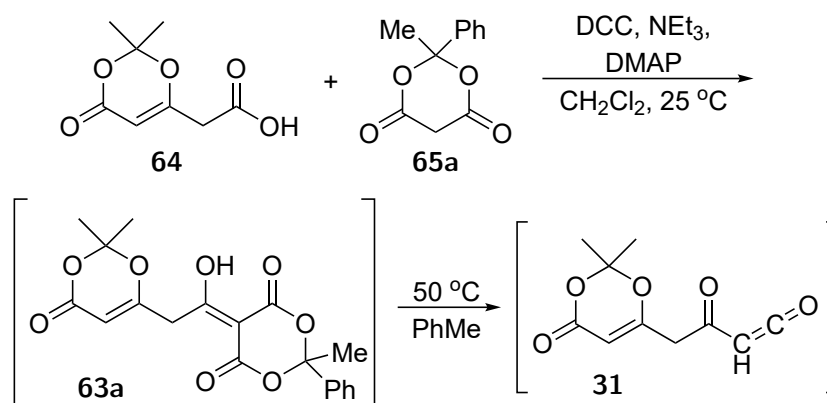


Scheme 2.9: Retrosynthetic analysis of the chromenic acids **1**.

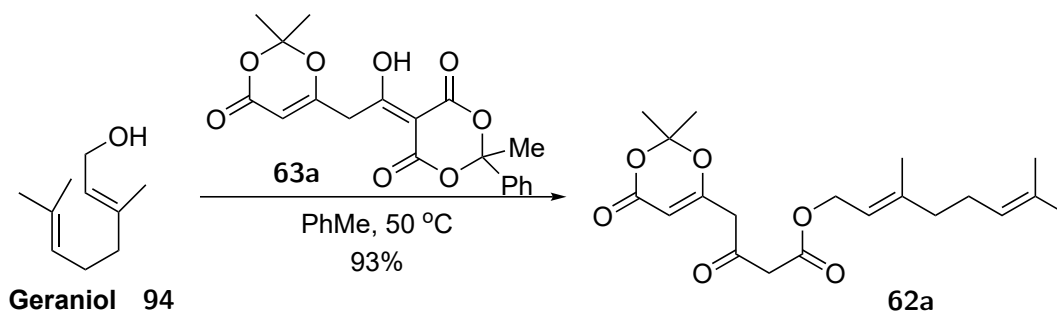
2.4 Total Synthesis of (±)-Cannabiorcichromenic Acid

The synthesis began with the thermolysis of dioxane-4,6-dione-keto-dioxinone **63a** (**Scheme 2.10**). The crude dioxane-4,6-dione-keto-dioxinone **63a**, prepared *via* DCC coupling of malonate **65a** with dioxinone acid **64**, was thermolysed selectively to produce a highly electrophilic dioxinone-acylketene **31** and trapped with geraniol **94** in one-pot to yield the corresponding dioxinone β -keto-ester **62a** (93 %) (**Scheme 2.11**).

The resulting dioxinone β -keto-ester **62a** was then converted into β , δ -diketo-ester **96a** *via* a regiospecific Claisen condensation and subsequently the resorcyate **93a** *via* decarboxylative Tsuji-Carroll rearrangement and base induced biomimetic aromatisation (**Scheme 2.12**). The regioselectivity of the Claisen condensation is presumably due to the enhanced acidity of the protons at the C-5 position after complexation of the carbonyl groups with magnesium(II) cation.



Scheme 2.10: Thermolysis of dioxane-4,6-dione-keto-dioxinone **63a**.



Scheme 2.11: Synthesis of dioxinone β -keto-ester **62a**.

As a result, selective deprotonation at the C-5 position over C-3 could be achieved with a weak base such as pyridine in this case. Treatment of the crude β , δ -diketo-ester **96a** with Pd_2dba_3 in the presence of $\text{P}(2\text{-furyl})_3$ as the ligand induced a decarboxylative Tsuji-Carroll type rearrangement, yielding β , δ -diketo-dioxinone **98a** that aromatised readily in the presence of CsOAc to give resorcyate **93a** (60 % over two steps from dioxinone β -keto-ester **62a**). The structure of resorcyate **93a** was unambiguously determined by X-ray crystallography (**Figure 2.4**).

Based on previous mechanistic studies conducted in the Barrett group with deuterium labelled experiments, the mechanism of the decarboxylative Tsuji-Carroll type rearrangement proceeded intermolecularly (**Scheme 2.13**).²⁸ The migrating allyl groups could originate from different molecules. In addition, the decarboxylative deallylation of β , δ -diketo-ester **96** could occur after (Pathway A) or before (Pathway B) allylation to form β , δ -diketo-ester **99** and β , δ -diketo-dioxinone **100**, respectively.¹ Furthermore, the regioselectivity of the allylation could be

¹ β , δ -diketo-ester and diketo-dioxinones exist as mixtures of keto-enol tautomers but for simplicity they have

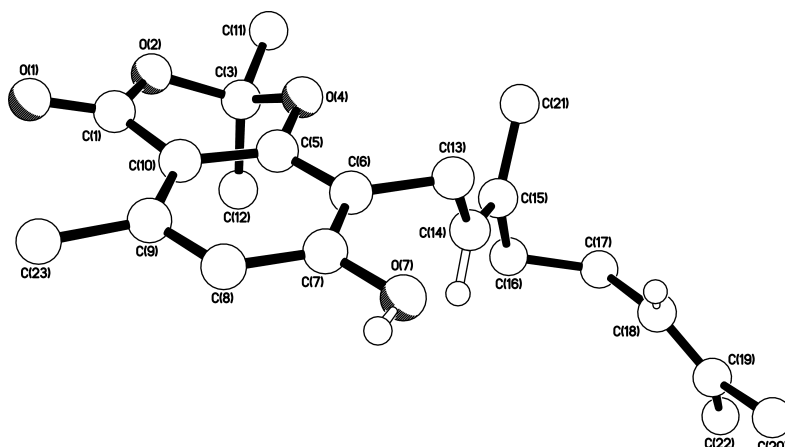
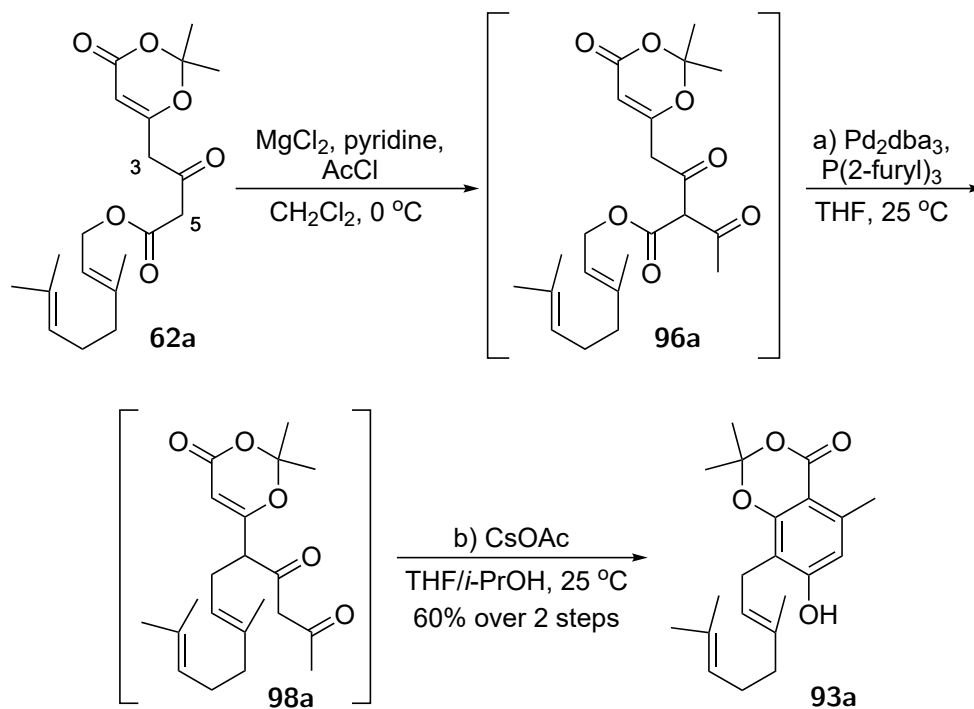


Figure 2.4: X-Ray crystal structure of resorcyate **93a**.

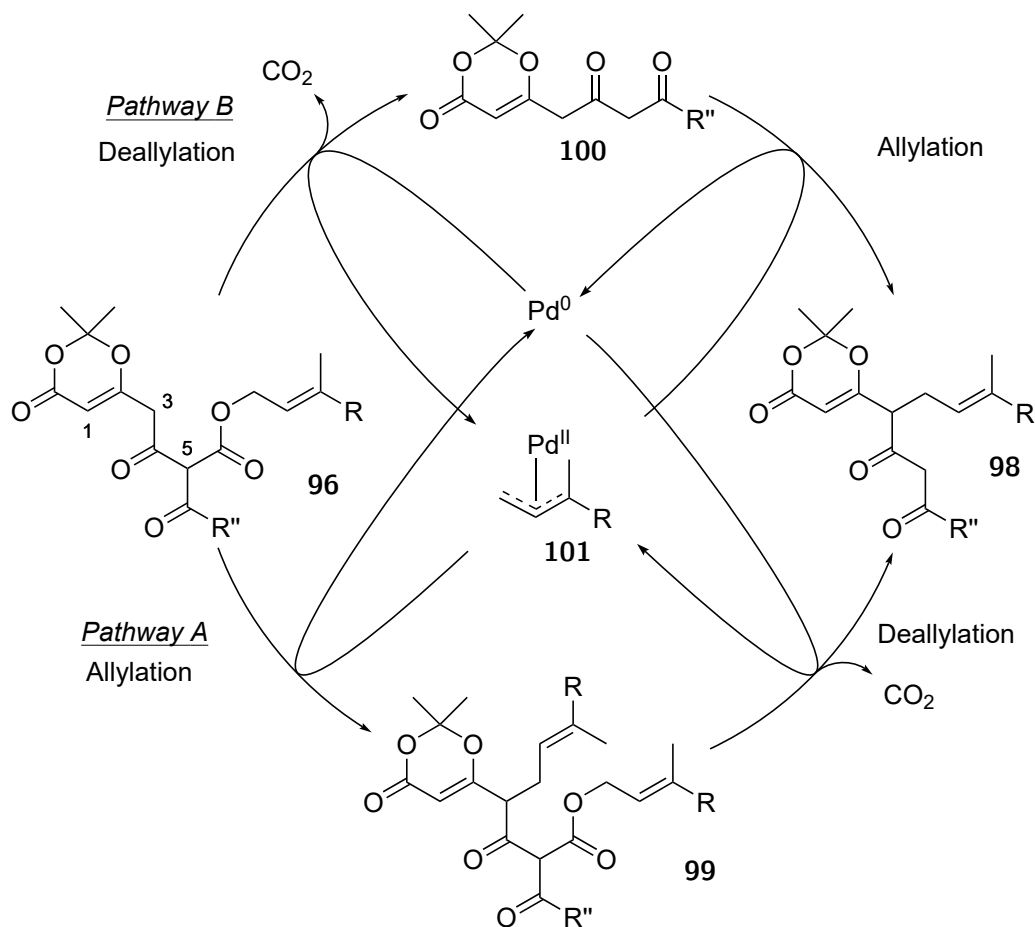


Scheme 2.12: Synthesis of resorcyate **93a**.

due to more acidic C-3 position, and better chelation and stabilisation for the Pd- π -allyl complex **101** at the C-3 position in comparison to C-5 or C-1 positions.

With the resorcyate **93a** in hand, conditions to achieve oxidative cyclisation to produce **97a** were examined (**Table 2.1**). It was observed that DDQ oxidation of resorcyate **93a** only gave

been drawn solely as all keto-tautomers.

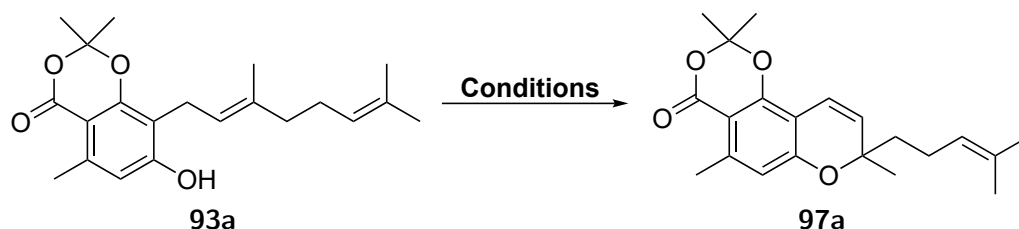


Scheme 2.13: Reaction mechanism of the palladium-catalysed decarboxylative Tsuji-Carroll type rearrangement.

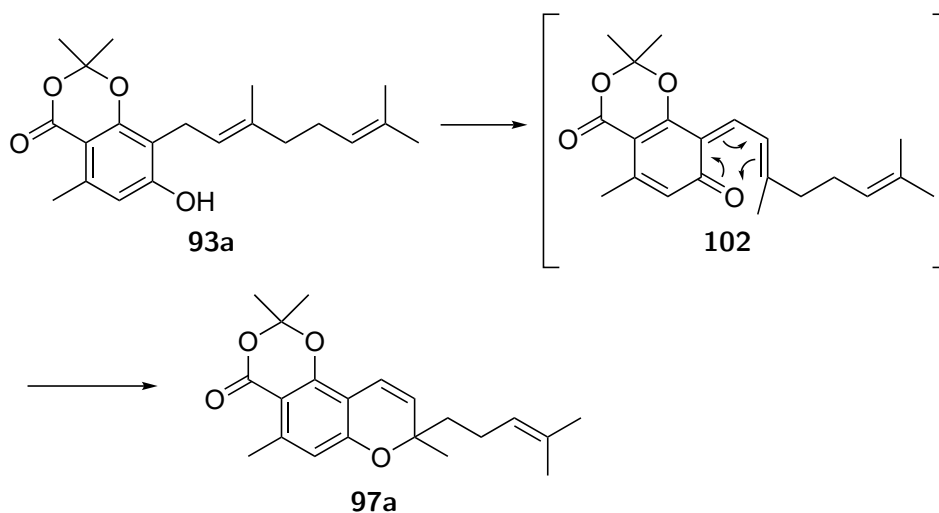
the desired product in 20 % yield (**Entry 1**). Reducing the equivalents of DDQ used (**Entry 2**) in the reaction have no effect on the isolated yield. On the other hand, employing other oxidative conditions, including dissolving dichromate in organic solvent with Adogen® 464 and DDQ oxidation in Et_2O (**Entry 3 – 4**) also did not result in a satisfactory transformation.⁶³ In all cases, incomplete conversion was observed and some unknown byproducts were formed. The low efficiency of the oxidative cyclisation could be rationalised from the reaction mechanism (**Scheme 2.14**). In the case with DDQ oxidation, the reaction first proceeded *via* hydrogen abstraction of the phenol of resorcyate **93a** *via* the SET pathway to give a highly reactive *o*-quinone methide intermediate **102**.⁶⁴ It would then undergo thermal electrocyclisation to form the desired chromene product **97a**. The highly reactive nature of the *o*-quinone methide intermediate

102 might have been decomposed into other side products *via* dimerisation or trimerisation, leading to a diminished yield of the desired product.⁶⁴

Table 2.1: Oxidative cyclisation of resorcyate **93a**.



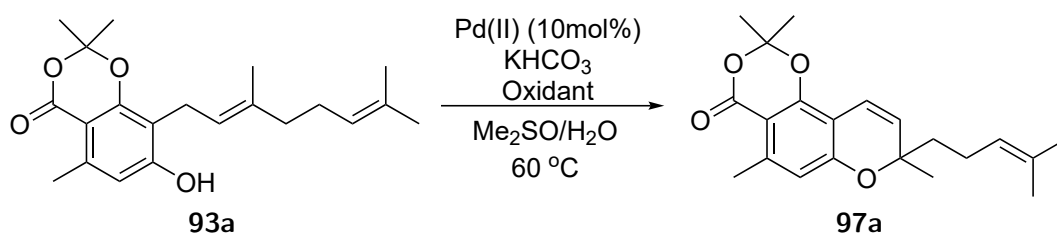
Entry	Conditions	Yield
1	3.0 equiv. DDQ, PhMe, 80 °C, 4 h	20 %
2	1.5 equiv. DDQ, PhMe, 80 °C, 23 h	20 %
3	1.1 equiv. DDQ, Et ₂ O, 25 °C	19 %
4	K ₂ Cr ₂ O ₇ , Adogen® 464, PhMe, 110 °C, 4.5 h	31 %



Scheme 2.14: Reaction mechanism of the oxidative cyclisation of resorcyate **93a**.

If the formation of the unstable *o*-quinone methide intermediate **102** was the cause of the low efficiency for this transformation, it is anticipated that avoiding its formation to yield chromene **97a** should overcome this issue. Therefore, the use of palladium(II)-catalysed oxidative cyclisation under aerobic conditions was investigated (**Table 2.2**).⁶⁵

By applying the optimal conditions reported by Larock and co-workers (**Entry 1**) to resorcyate

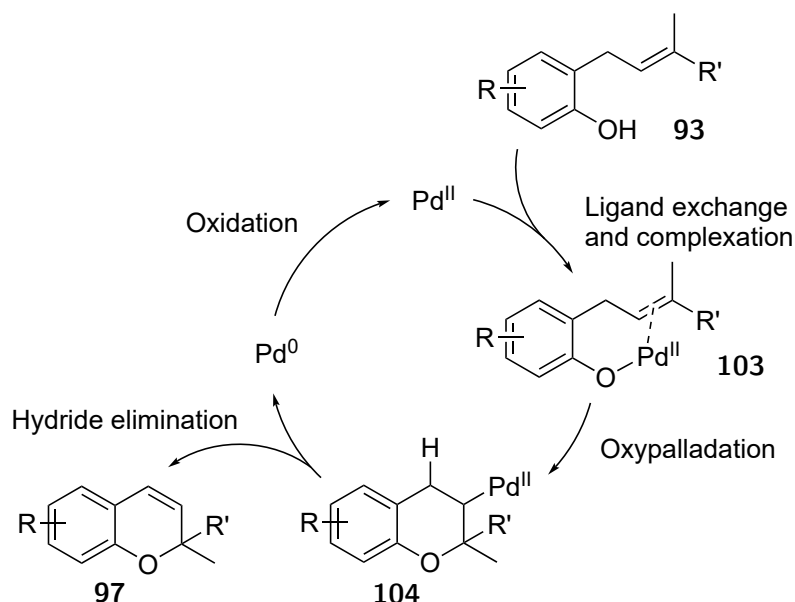
Table 2.2: Palladium-catalysed oxidative cyclisation of resorcyate **93a**.

Entry	Catalyst	Oxidant	Concentration	Reaction Time	Yield
1	Pd(OAc) ₂	Air	0.05 M	5 d	47 %
2	Pd(TFA) ₂	Air	0.05 M	7 d	Trace
3	Pd(OAc) ₂	Air	0.1 M	2 d	Trace
4	Pd(OAc) ₂	O ₂ (1 atm)	0.05 M	24 h	58 %
5 ^a	Pd(OAc) ₂	O ₂ (1 atm)	0.05 M	16.5 h	80 %
6 ^{a,b}	Pd(OAc) ₂	O ₂ (1 atm)	0.05 M	16 h	68 %

a) Solvent was saturated with molecular O₂ before use. b) Reaction was scaled up to 2 mmol of resorcyate **93a**.

93a, it was observed that 89 % conversion, determined by ¹H NMR spectroscopy, was achieved after 5 d to give the desired chromene **97a** (47 %).⁶⁵ The formation of palladium black was observed, suggesting that the slow reaction rate and incomplete conversion might be due to the decomposition of the palladium catalyst. To investigate whether the stability of the palladium catalyst was the cause of the incomplete conversion, another attempt was made using a more electrophilic Pd(TFA)₂ catalyst (**Entry 2**). Unfortunately, the ¹H NMR of the crude reaction mixture showed very low conversion and starting material was almost fully recovered. The formation of palladium black was still observed. Therefore, other condition parameters were varied to investigate their effect on the reaction outcome. By increasing the concentration (**Entry 3**), only trace amount of the desired product was detected from the ¹H NMR of the crude material after 2 d. Decomposition of the palladium catalyst was observed as before. Hence, the previous attempts suggested that the reaction might be inhibited by the decomposition of palladium(0) into palladium black, which was presumably caused by the inefficient reoxidation of palladium(0) back to the reactive palladium(II) catalyst. Therefore, modification was made by conducting the reaction under a positive pressure of molecular O₂ instead of air (**Entry 4**) and gratifying

after 24 h the desired chromene **97a** was formed (58 %) with no formation of palladium black. This encouraging result showed that air was not an efficient oxidant in this reaction and the use of molecular O₂ could promote the reoxidation step, leading to shorter reaction time and suppressing the undesired decomposition of palladium(0) to palladium black. By purging the solvent system with molecular O₂ for 15 min prior the reaction (**Entry 5**), it was observed that the reaction time was reduced further to 16.5 h and gave an improved yield of chromene **97a** (80 %). This result was also reproducible at a larger scale (**Entry 6**) (68 %). It is also noteworthy to mention that only the desired 6-*endo-trig* cyclised product was formed in this transformation.

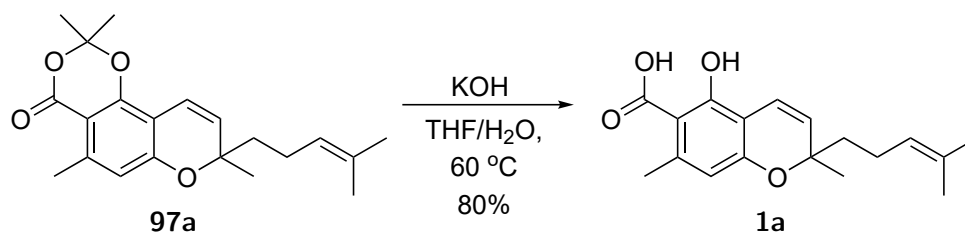


Scheme 2.15: Reaction mechanism of the palladium(II)-catalysed oxidative cyclisation.

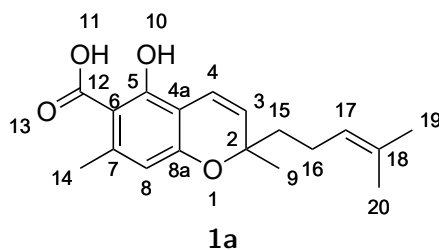
The reaction mechanism of the chromene **97** formation can be rationalised as a modified Tsuji-Wacker type oxidation (**Scheme 2.15**).⁶⁶ Firstly, deprotonation of the phenol of resorcyates **93** by KHCO₃ produces the corresponding potassium alkoxide, followed by the coordination of palladium catalyst with the alkene and oxygen atom to give intermediate **103**. After that, oxypalladation of intermediate **103** yields intermediate **104**. Finally, β -hydride elimination leads to the formation of the desired chromene **97** product and the resulting palladium(0) is oxidised back to palladium(II) to complete the catalytic cycle.

Finally, the acetonide of chromene **97a** was hydrolysed with aqueous KOH to yield (±)-

cannabiorcichromenic acid (**1a**) (80 %) (**Scheme 2.16**). The spectroscopic data were compared with the isolated natural product reported by Coosemans and co-workers and they were in excellent agreement (**Table 2.3**).³



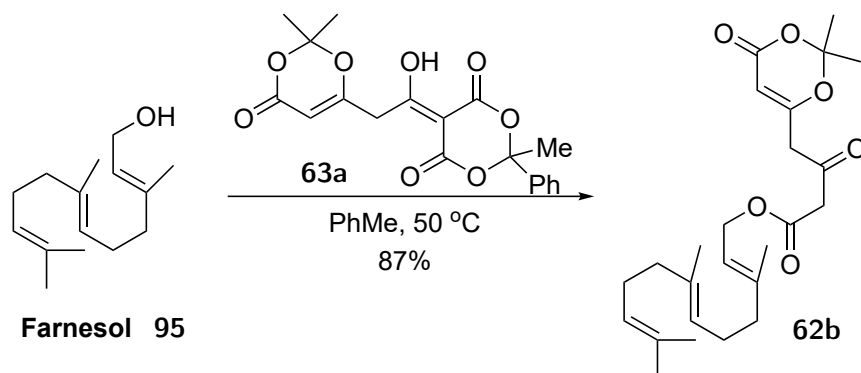
Scheme 2.16: Saponification of chromene **97a**.

Table 2.3: Comparison of ^1H and ^{13}C (±)-cannabiorcichromenic acid (**1a**) NMR data in CDCl_3 with literature.

Position	(±)-Cannabiorcichromenic acid (1a)		Literature data ³		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
2	80.1		80.0		+ 0.1	
3	126.3	5.48 (d, 10)	126.2	5.48 (d, 11)	+ 0.1	0
4	116.7	6.73 (d, 10)	116.8	6.74 (d, 11)	- 0.1	- 0.01
4a	107.0		107.1		- 0.1	
5	160.6		160.5		+ 0.1	
6	103.6		103.6		0	
7	144.5		144.4		+ 0.1	
8	112.2	6.24 (s)	112.1	6.23 (s)	+ 0.1	+ 0.01
8a	159.0		158.9		+ 0.1	
9	27.2	1.41 (s)	27.1	1.42 (s)	+ 0.1	- 0.01
10		11.25 – 12.00 (br)		10.0 – 12.5 (br)		
12	176.2		176.4		- 0.2	
14	24.5	2.54 (s)	24.3	2.55 (s)	+ 0.2	- 0.01
15	41.7	1.71 – 1.83 (m)	41.7	1.6 – 1.8 (m)	0	
16	22.7	2.09 (q, 8)	22.7	2.12 (q, 7)	0	- 0.03
17	123.9	5.09 (t, 7)	124.0	5.12 (t, br)	- 0.1	- 0.03
18	131.2		131.8		- 0.6	
19	25.6	1.66 (s)	25.6	1.68 (s)	0	- 0.02
20	17.6	1.58 (s)	17.6	1.60 (s)	0	- 0.02

2.5 Total Synthesis of (±)-Daurichromenic Acid

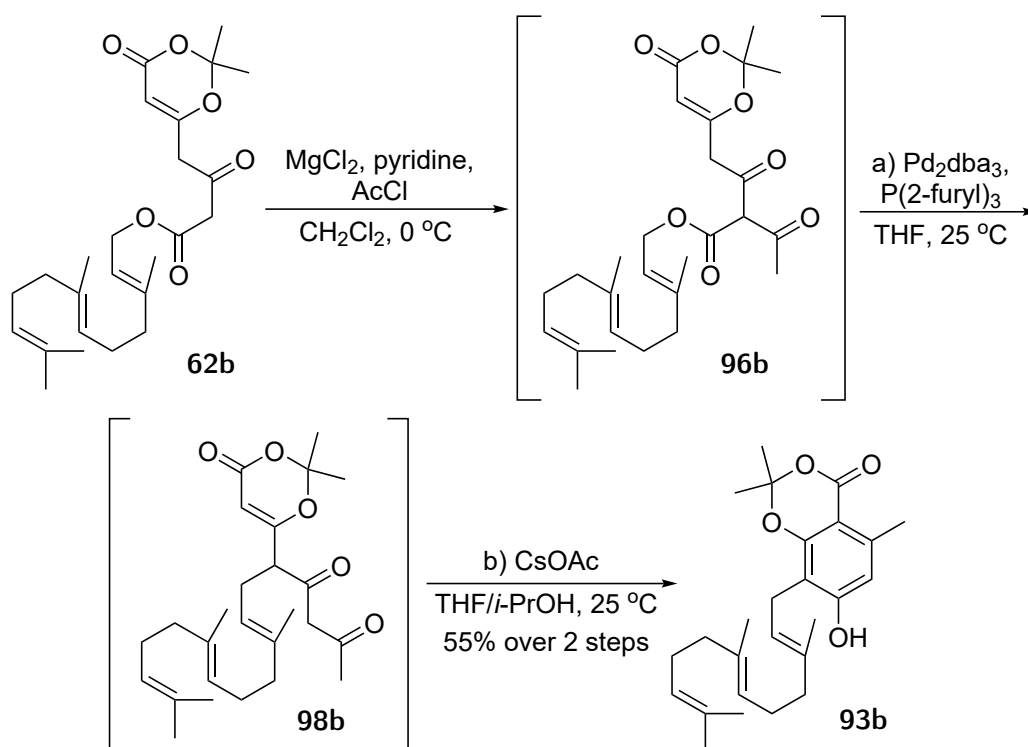
With the optimised synthetic route to ($\pm$)-cannabiorcichromenic acid (**1a**) established, the same approach was then applied to the synthesis of ($\pm$)-daurichromenic acid (**1b**) using *trans, trans*-farnesol **95** as the allylic alcohol. Starting from *trans, trans*-farnesol **95**, the corresponding dioxinone β -keto-ester **62b** (87 %) was synthesised by trapping the dioxinone-acylketene **31** generated from dioxane-4,6-dione-keto-dioxinone **63a** (Scheme 2.17).



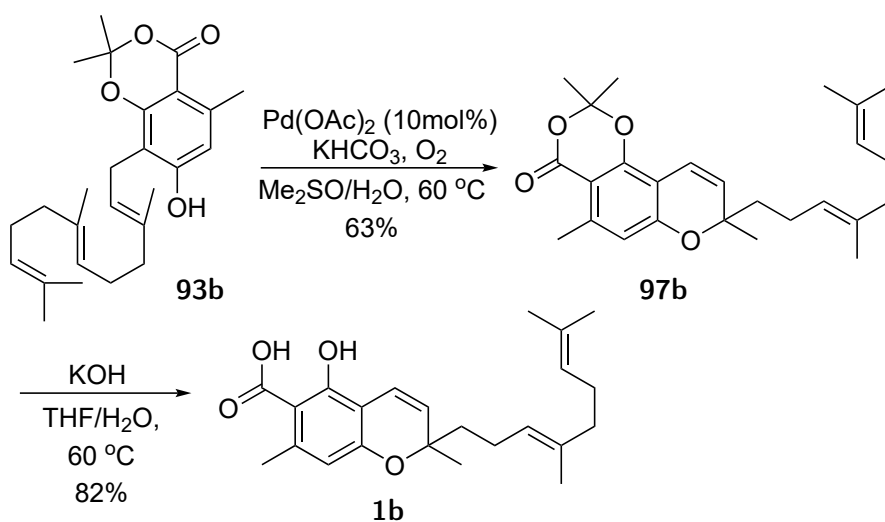
Scheme 2.17: Synthesis of dioxinone β -keto-ester **62b**.

Regioselective Claisen condensation of dioxinone β -keto-ester **62b** with acetyl chloride provided β , δ -diketo-ester **96b**, which was then treated with Pd₂dba₃ and P(2-furyl)₃ to give β , δ -diketo-dioxinone **98b** and cyclised *in-situ* in the presence of CsOAc in *i*-PrOH to afford resorcyate **93b** (55 % over two steps from dioxinone β -keto-ester **62b**) (**Scheme 2.18**). With the previously optimised reaction conditions, chromene **97b** was successfully prepared from resorcyate **93b** (63 %) as the sole product *via* palladium-catalysed aerobic Wacker-type oxidative cyclisation. Finally, saponification of the chromene **97b** with aqueous KOH furnished ($\pm$)-daurichromenic acid (**1b**) (82 %) with an overall yield of 25 % over five steps from *trans*, *trans*-farnesol **95** (**Scheme 2.19**). The spectroscopic data were compared with the isolated natural product reported by Kashiwada and co-workers and they were in full agreement (**Table 2.4**).⁴

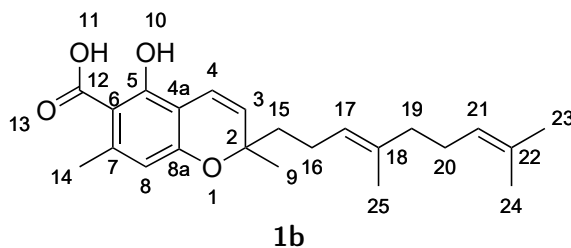
2.5. TOTAL SYNTHESIS OF (±)-DAURICHROMENIC ACID



Scheme 2.18: Synthesis of resorcyate **93b**.



Scheme 2.19: Synthesis of (±)-daurichromenic acid (**1b**).

Table 2.4: Comparison of ^1H and ^{13}C ($\pm$)-daurichromenic acid (**1b**) NMR data in CDCl_3 with literature.

Position	(±)-Daurichromenic acid (1b)		Literature data ⁴		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
2	80.1		80.1		0	
3	126.3	5.48 (d, 10)	126.3	5.48 (d, 11)	0	0
4	116.6	6.72 (d, 10)	116.7	6.73 (d, 11)	- 0.1	- 0.01
4a	107.0		107.1		- 0.1	
5	160.6		160.6		0	
6	103.5		103.5		0	
7	144.4		144.4		0	
8	112.1	6.23 (s)	112.2	6.24 (s)	- 0.1	- 0.01
8a	158.9		159.0		-0.1	
9	27.2	1.41 (s)	27.2	1.41 (s)	0	0
10		11.70 (s)		11.69 (s)		+ 0.01
12	175.9		175.9		0	
14	24.5	2.53 (s)	24.5	2.54 (s)	0	- 0.01
15	41.7	1.71 – 1.83 (m)	41.7	1.66 – 1.77 (m)	0	
16	22.6	2.00 – 2.16 (m)	22.6	2.04 – 2.12 (m)	0	
17	123.7	5.01 – 5.18 (m)	123.7	5.11 (t, 7)	0	
18	135.5		135.5		0	
19	39.6	1.92 – 2.00 (m)	39.7	1.95 (m)	- 0.1	
20	26.6	1.92 – 2.00 (m)	26.7	1.97 (m)	- 0.1	
21	124.3	5.01 – 5.18 (m)	124.3	5.08 (t, 7)	0	
22	131.4		133.3		+ 0.1	
23	25.7	1.67 (s)	25.7	1.67 (s)	0	0
24	17.7	1.59 (s)	17.7	1.59 (s)	0	0
25	16.0	1.57 (s)	16.0	1.57 (s)	0	0

2.6 Biological Activity of the Synthetic

(±)-Cannabiorcichromenic Acid and (±)-Daurichromenic Acid

In collaboration with AbbVie, the synthetic (±)-cannabiorcichromenic acid (**1a**) and (±)-daurichromenic acid (**1b**) were tested in different bioassays (**Table 2.5**). It was found that (±)-cannabiorcichromenic acid (**1a**) was able to act as an antagonist against several receptors. In particular, it showed strong inhibition against the adenosine A₁ receptor (IC₅₀ = 1.21 μM) and the muscarinic acetylcholine receptor M₂ (IC₅₀ = 2.98 μM). On the other hand, (±)-daurichromenic acid (**1b**) was found to act as an antagonist on β₂-adrenergic receptors (IC₅₀ = 3.39 μM).

Table 2.5: Biological profiling of (±)-cannabiorcichromenic acid (**1a**) and (±)-daurichromenic acid (**1b**).

	Assay	(±)-Cannabiorcichromenic acid (1a)	(±)-Daurichromenic acid (1b)
		IC ₅₀ (μM)	IC ₅₀ (μM)
Receptor Antagonist	5-HT _{1A}	5.77	>10
	A ₁	1.21	>10
	α _{2A}	4.13	>10
	β ₂	7.53	3.39
	β ₁	8.74	>10
	D2L	8.19	>10
	H ₁	7.21	>10
	M ₂	2.98	>10

2.7 Conclusion

In conclusion, the total syntheses of ($\pm$)-cannabiorcichromenic acid (**1a**) and ($\pm$)-daurichromenic acid (**1b**) were completed in five linear steps using a common reaction sequence starting from commercially available geraniol **94** or *trans, trans*-farnesol **95**. The key resorcyate intermediates **93** were biomimetically synthesised via a highly regioselective decarboxylative allylic rearrangement catalysed by palladium(0). To construct the chromene **97** core, two mechanistically distinct approaches involving DDQ oxidation and Pd(II)-Catalysed Wacker-type oxidative cyclisation of resorcyates **93** were investigated and it was found that DDQ oxidative cyclisation was less efficient, presumably due to the decomposition of the unstable *o*-quinone methide intermediate **102**.

2.8 Future Work

The current developed reaction sequence can be applied to the syntheses of other biologically active chromenic acid derivatives (**Figure 2.5**). For instance, salfredin B11 (**105**),⁶⁷ garcinisidone B (**106**),⁶⁸ brevipsidone A (**107**)⁶⁹ and (-)-deguelin (**108**)⁷⁰ were reported to have therapeutically useful activities. They are meroterpenoid natural products which contain a core chromene structure which should be accessible by adapting existing methodology.

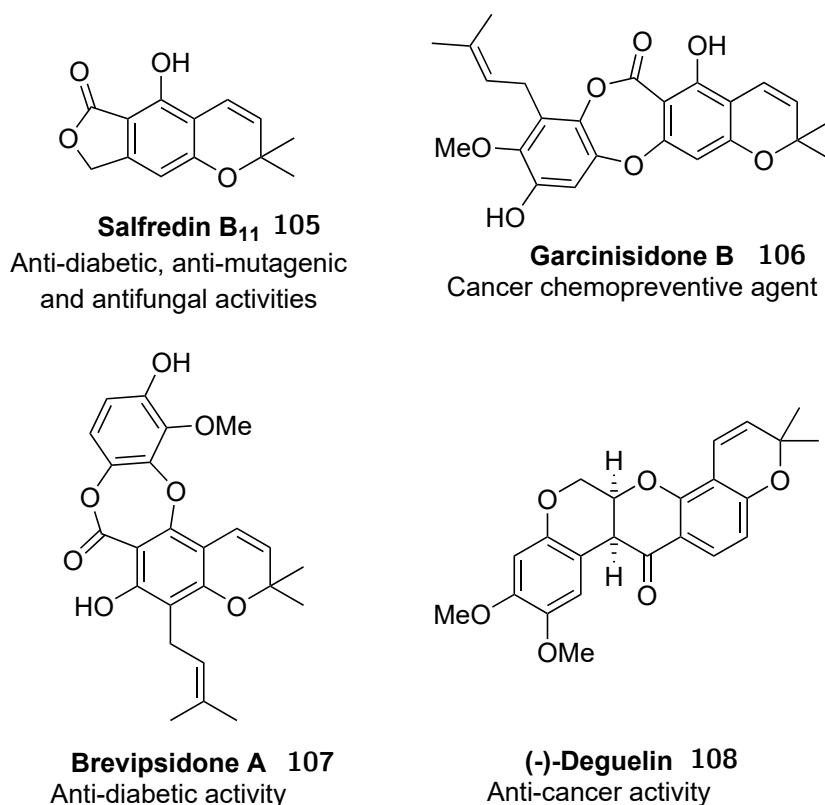


Figure 2.5: Potential targets of other chromenic acid natural products.

AMORPHASTILBOL, GRIFOLIN AND GRIFOLIC ACID

Biomimetic total syntheses of resorcinol natural products – amorphastilbol, grifolin and grifolic acid have been completed in five steps starting from geraniol and *trans, trans*-farnesol without the use of phenolic protection.⁷¹ The key steps involve *C*-acylation of dioxinone β -keto-ester, followed by palladium catalysed decarboxylative allylic rearrangement and biomimetic aromatisation. In addition, the recently developed protocol on the thermolysis of dioxane-4,6-dione-keto-dioxinone to generate dioxinone acyl ketene for the preparation of dioxinone β -keto esters has been reoptimised to produce more consistent results.

3.1 Isolation and Biological Evaluation of Amorphastilbol, Grifolin and Grifolic Acid

Meroterpenoids are hybrid natural products with mixed biosynthetic origin.^{72,73} Amorphastilbol (**2**), grifolic acid (**3**) and grifolin (**4**) are bioactive resorcinol meroterpenoids containing tetraketide-terpenoid moieties that are biosynthesised *via* polyketide and terpenoid pathways (**Figure 3.1**).

Amorphastilbol (**2**) was isolated from the extracts of *Amorpha fruticose*, *Amorpha nanna* and *Amorpha canescens*.^{5–7} In 1985, *in vitro* antimicrobial evaluation conducted by Mitscher and co-workers showed that it possesses moderately potent antimicrobial activity against *Staphylococcus aureus* and *Mycobacterium smegmatis*.⁶ Further *in vivo* investigation with mice model carried out

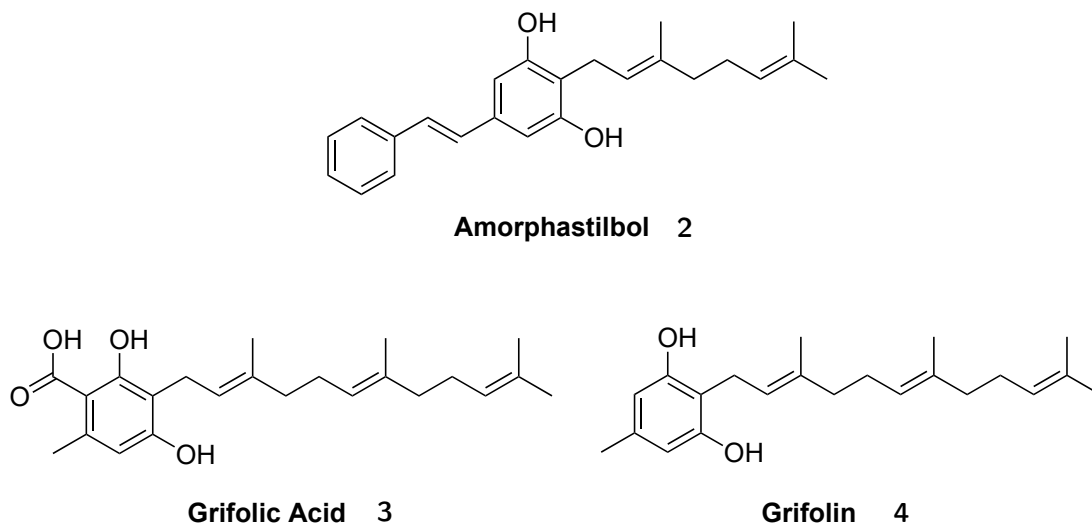


Figure 3.1: Structures of Amorphastilbol (2), grifolic acid (3) and grifolin (4).

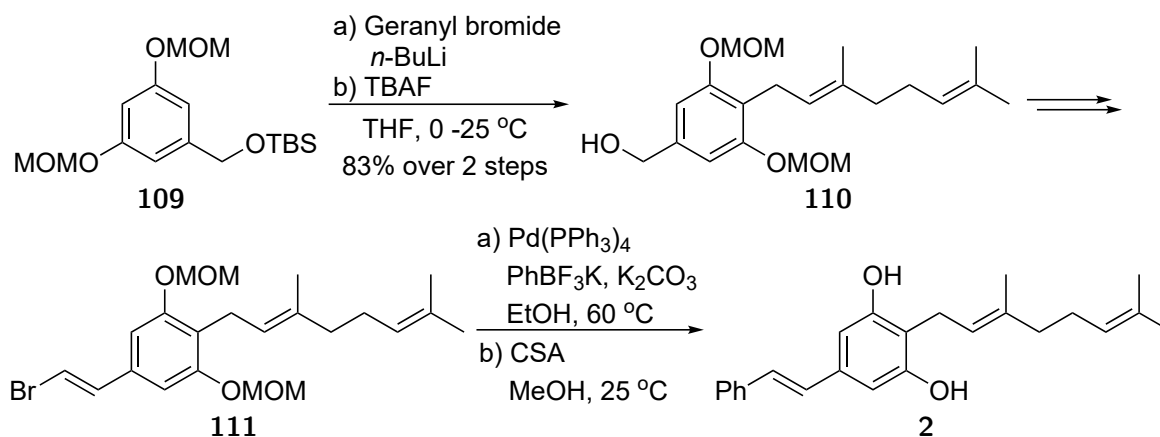
by Kim and co-workers revealed its anti-diabetic effect.⁷⁴ *In vivo* studies show that amorphastilbol (2) could selectively stimulate the transcriptional activities of both PPAR α and PPAR γ , enhancing fatty acid oxidation and glucose consumption. Experimental results suggest that it has valuable therapeutic application against type 2 diabetes and related metabolic disorders, such as obesity, by increasing glucose and lipid metabolism.

Grifolic acid (3) and grifolin (4) are structurally related resorcinols. Grifolin (4) was first isolated from *Grifola confluens* in 1963 by Hirata and co-workers.⁸ It was also found in *Albatrellus ovinus*, *Peperomia Galioides*, *Albatrellus Caeruleoporus* and inedible mushroom *Albatrellus Dispanus*.^{60,75–77} Early work by Cao and co-workers showed that grifolin (4) is able to inhibit the growth of various tumor cell lines *via* inducing apoptosis.⁷⁸ Further investigations concluded that grifolin (4) upregulates DAPK1 to act as an antitumor agent.^{79–81} Another study published by Jiang and co-workers showed that grifolin (4) induces autophagic cell death in human ovarian cancer by inhibiting the Akt/mTOR/S6K pathway.⁸² Moreover, Li and co-workers reported that grifolin (4) is capable of inducing apoptosis and suppressing the ERK1/2 pathway in order to inhibit the growth and invasion of gastric cancer cells.⁸³ All these studies indicated that grifolin (4) is a promising lead compound in developing a novel antitumor agent. Moreover, studies showed that grifolic acid (3) could act as free fatty acid receptor GPR120 agonist.^{84,85}

3.2 Previous Synthetic Approaches

Due to the fact that these natural products are potential lead molecules for infectious diseases and cancer, total syntheses and related studies of these resorcinols have been reported by various groups.

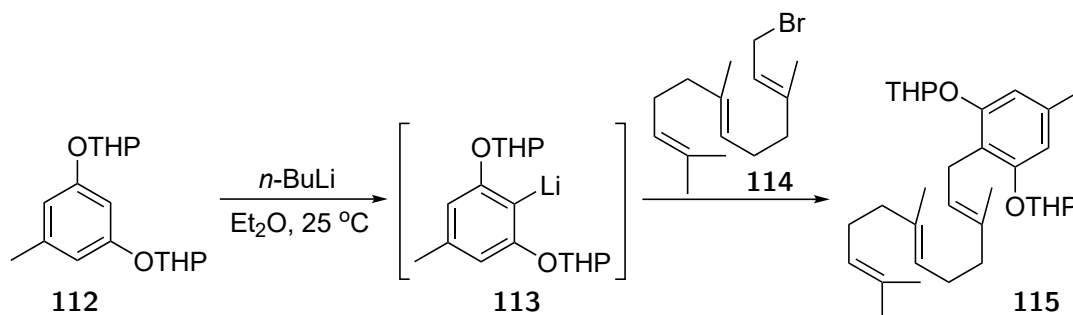
In 2012, Ham and co-workers disclosed the first total synthesis of amorphastilbol (**2**) (**Scheme 3.1**).⁸⁶ Geranylation of silyl ether **109** with *n*-BuLi and geranyl bromide provided alcohol **110** (83 % over 2 steps from silyl ether **109**) after subsequent treatment with TBAF. Further functionalisation of alcohol **110** provided styryl bromide **111**, which served as a common precursor for Suzuki-Miyaura cross-coupling to complete the ten steps synthesis of amorphastilbol (**2**) as well as related analogues.



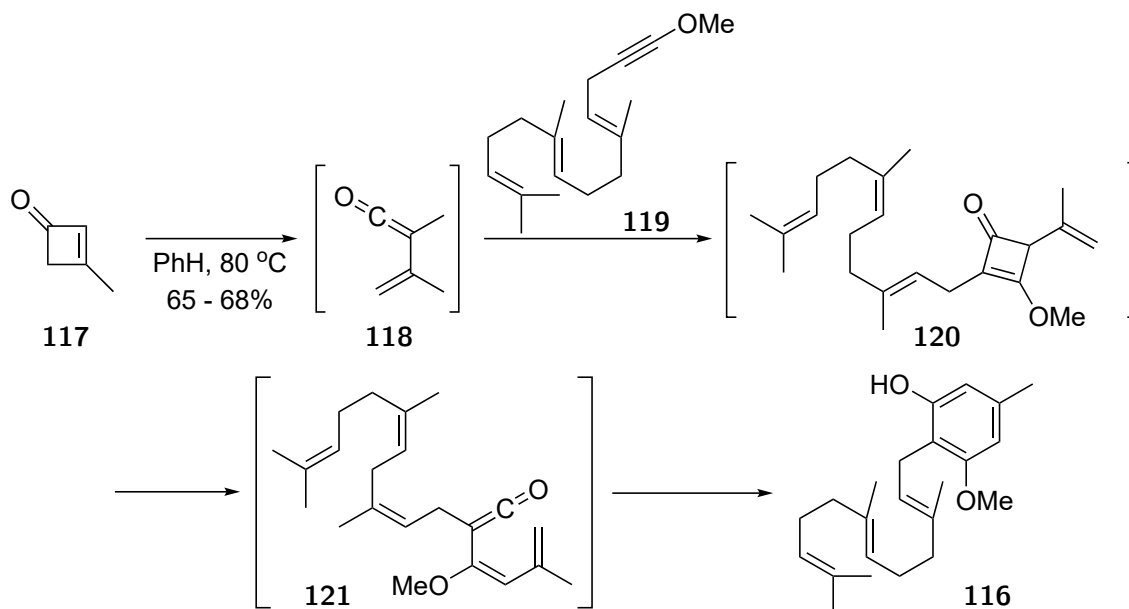
Scheme 3.1: Ham synthesis of amorphastilbol (**2**).

The first total synthesis of grifolin (**4**) was reported by Goto and co-workers (**Scheme 3.2**).⁸⁷ Lithiation of orcinol bis-tetrahydropyranyl ether **112** produced the corresponding lithio-compound **113**, which was then reacted with farnesyl bromide **114** to give grifolin bis-tetrahydropyranyl ether **115**. Subsequent THP deprotections with oxalic acid provided crude grifolin (**4**), which was then purified by repeated recrystallisations after converting it into the corresponding di-*p*-nitrobenzoate.

In 1984, Denheiser and co-workers utilised a regiocontrolled annulation approach to synthesise grifolin (**4**) (**Scheme 3.3**).⁸⁸ The key ether **116** was synthesised in one-step *via* a cascade of pericyclic reactions. Thermolysis of cyclobutenone **117** produced vinylketene **118**, by a reversible

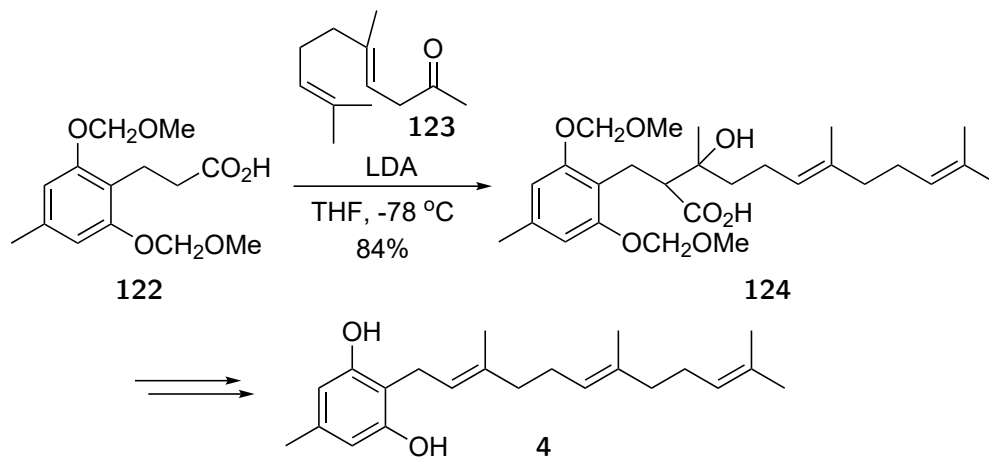
**Scheme 3.2:** Goto synthesis of grifolin **4**.

four-electron electrocyclic cleavage, which was reacted with a farnesyl derived acetylene **119** by [2+2] cycloaddition to give 2-vinylcyclobutenone **120** regioselectively. Reversible 4-electron electrocyclic cleave of 2-vinylcyclobutenone **120** gave dienylnkene **121**, which was then underwent 6-electron electrocyclisation and tautomerisation to form ether **116** (65 – 68 %). Subsequent hydrolysis of ether **116** yielded grifolin (**4**) with 21 – 43 % overall yield from *trans, trans*-farnesol **95**.

**Scheme 3.3:** Danheiser synthesis of grifolin **4**.

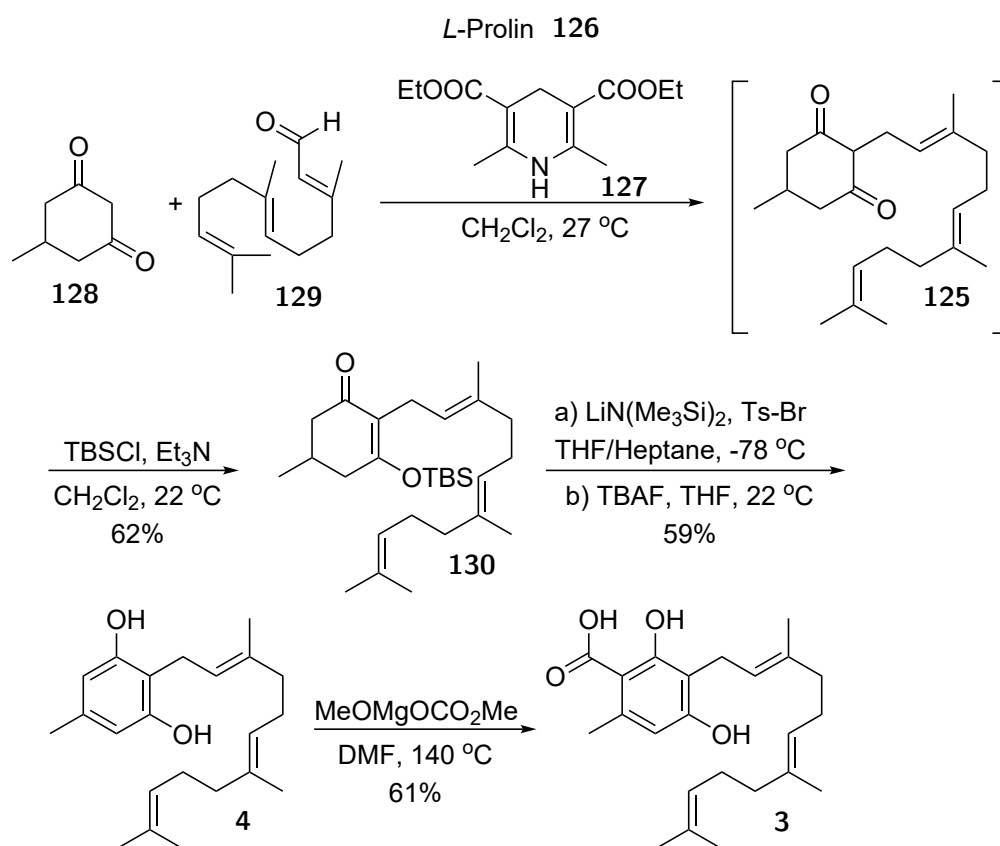
Ohta reported a seven steps total synthesis of grifolin (**4**) starting from orcinol in 1988 (**Scheme 3.4**).⁸⁹ The key step involved enolisation of phenylpropanoic acid **122** to give the corre-

sponding lithium enolate, which was reacted with geranylacetone **123** to yield hydroxypropionic acid **124** (84 %).



Scheme 3.4: Ohta synthesis of grifolin **4**.

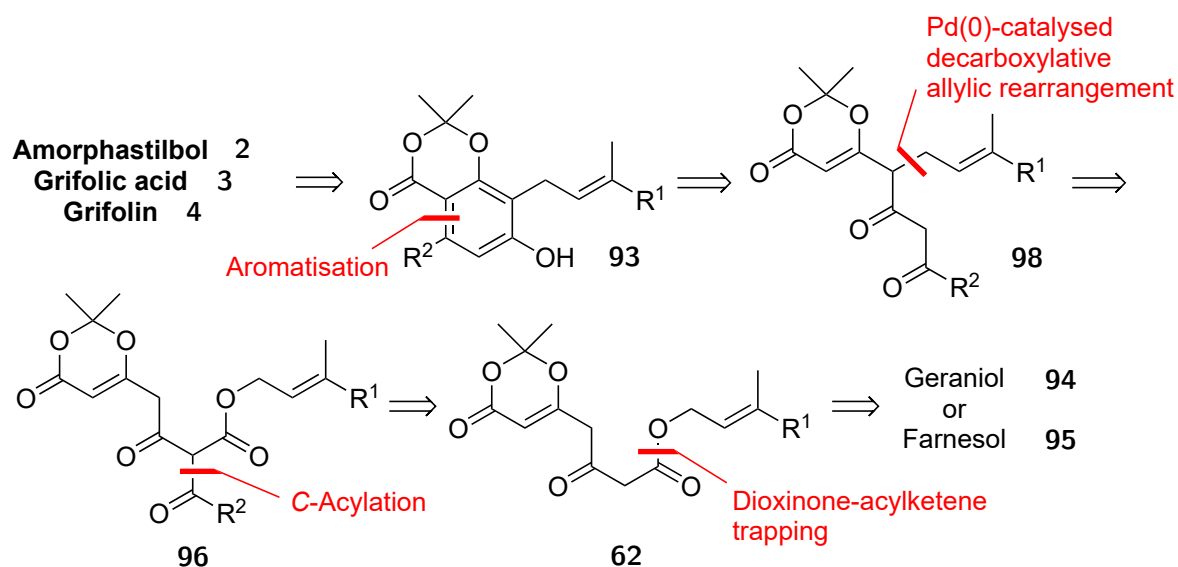
More recently in 2016, Mohr and co-workers disclosed a halogenative aromatisation approach for the synthesis for grifolin (**4**) and the first synthesis of grifolic acid (**3**) (**Scheme 3.5**).⁹⁰ Diketone **125** was synthesised from a cascade proline (**126**) catalysed direct aldol condensation and Hantzsch ester **127** mediated conjugate reduction from dione **128** and aldehyde **129**, which was then converted into the corresponding vinylogous silyl ester **130** (62 %). Halogenative aromatisation of vinylogous silyl ester **130** provided grifolin (**4**), which was further oxidised into grifolic acid (**3**) (61 %) by magnesium methyl carbonate in DMF.



Scheme 3.5: Mohr synthesis of grifolin (**4**) and grifolic acid (**3**).

3.3 Retrosynthetic Analysis of Amorphastilbol, Grifolin and Grifolic Acid

Since amorphastilbol (**2**), grifolic acid (**3**) and grifolin (**4**) share the same substitution pattern on the aromatic core, it is considered that they could be synthesised in five steps *via* a common reaction pathway (**Scheme 3.6**). The required diol or carboxylic acid moieties could be formed by selective manipulation of the 2,2-dimethyl-1,3-benzodioxan-4-one of resorcyates **93** *via* hydrolytic decarboxylation or saponification. Resorcyates **93** should be available *via* the cycloaromatization of β , δ -diketo dioxinones **98**, which could be synthesised *via* palladium(0)-catalysed decarboxylative allylic rearrangement of β , δ -diketo-ester **96**. β , δ -diketo-ester **96** is available *via* C-acylation of dioxinone β -keto-esters **62**, which in turn can be synthesised from geraniol **94** or *trans*, *trans*-farnesol **95**.

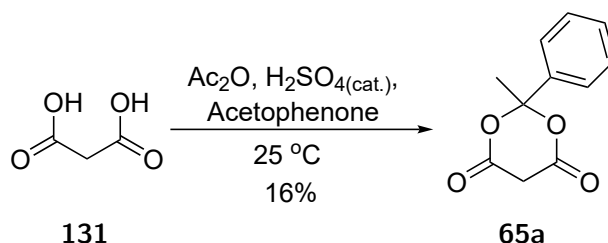


Scheme 3.6: Retrosynthetic analysis of the amorphastilbol (**2**), grifolic acid (**3**) and grifolin (**4**).

3.4 Optimisation of Dioxane-4,6-Dione-Keto-Dioxinones

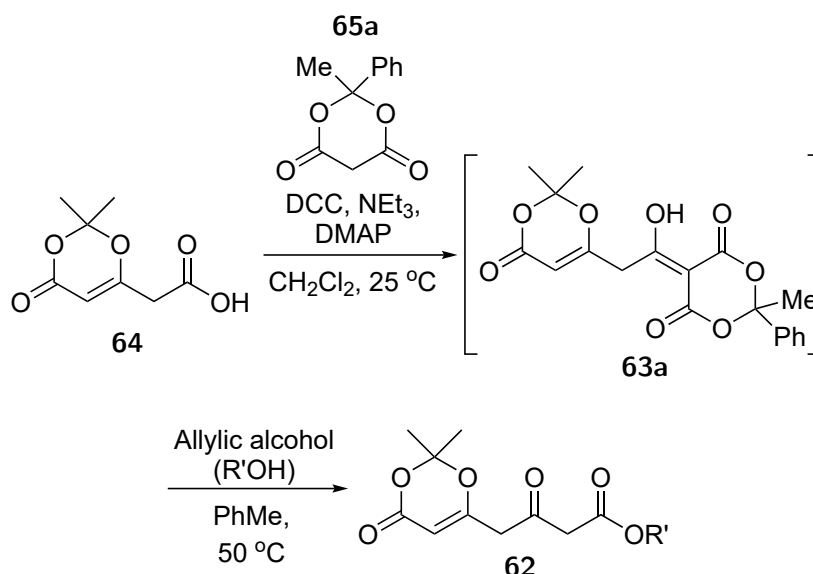
Thermolysis

Although the use of dioxane-4,6-dione-keto-dioxinone **63a** has been shown to be a more efficient protocol for the preparation of dioxinone β -keto-esters **62**, it is still unsuitable for large scale dioxinone β -keto-esters **62** production due to some limitations. First of all, the synthesis of malonate **65a** (16 %), *via* condensation of malonic acid **131** with acetophenone, was very low yielding (**Scheme 3.7**). Moreover, the thermal instability of dioxane-4,6-dione-keto-dioxinone **63a** sometimes led to undesired decomposition during the work up after the DCC mediated Steglich type coupling of dioxinone acid **64** and malonate **65a**. It was observed once that the decomposition of dioxane-4,6-dione-keto-dioxinone **63a** turned the crude material into a brown glue that was completely insoluble in common laboratory solvents and would not react with allylic alcohol in the next step. The decomposition of dioxane-4,6-dione-keto-dioxinone **63a**, therefore, has led to inconsistent yields of dioxinone β -keto-esters **62** (**Table 3.1**). As a result, the developed protocol required 2.5 equivalents of dioxane-4,6-dione-keto-dioxinone **63a** with respect to the allylic alcohol in order to achieve a full conversion.



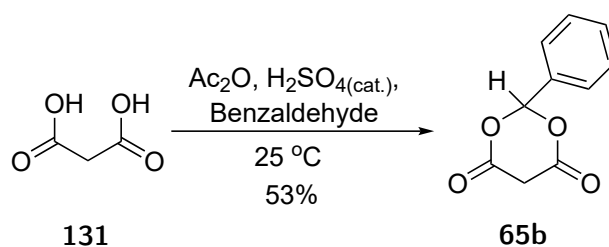
Scheme 3.7: Synthesis of malonate **65a**.

In order to overcome the current limitations on dioxinone β -keto-esters **62** syntheses, the use of a more readily available malonate **65b** was examined. It was more readily synthesised from malonic acid **131** and benzaldehyde and can be purified by simple crystallisation (**Scheme 3.8**). DCC mediated Steglich type coupling of dioxinone acid **64** and malonate **65b** provided dioxane-4,6-dione-keto-dioxinone **63b** (95 %) as a light yellow foam which is more stable than dioxane-4,6-dione-keto-dioxinone **63a** and storage at -20 °C for 2 d was possible without decomposition. To simplify the experimental procedure further, DMAP was used solely instead of a combination of

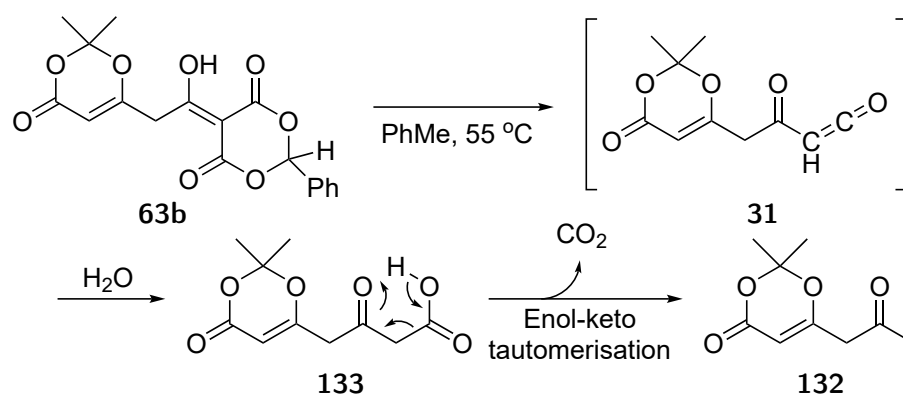
Table 3.1: Thermolysis of dioxane-4,6-dione-keto-dioxinone **63a** at different reaction scales.

Entry	Allylic alcohol	Scale (mmol)	Equiv. of 63a	Yield
1	Geraniol 94	6	2.5	93 %
2	<i>trans, trans</i> -Farnesol 95	6	2.5	87 %
3	<i>trans, trans</i> -Farnesol 95	18	2.5	69 %
4	<i>trans, trans</i> -Farnesol 95	27	2.5	72 %

DMAP and triethyl amine as DMAP ($pK_a = 9.6$) could have a dual role of deprotonating malonate **65b** ($pK_a \sim 5.0$) and acting as an acyl transfer reagent.⁹¹ More importantly, with heating at 55 °C, the thermally induced retro-Diels-Alder reaction of dioxane-4,6-dione-keto-dioxinone **63b** occurred similarly to that of dioxane-4,6-dione-keto-dioxinone **63a**. This provided the key derived dioxinone-acylketene **31** reactive intermediate, which was immediately trapped with *trans, trans*-farnesol **95**, yielding the corresponding dioxinone β -keto-esters **62** (62 %, **Entry 1, Table 3.2**).

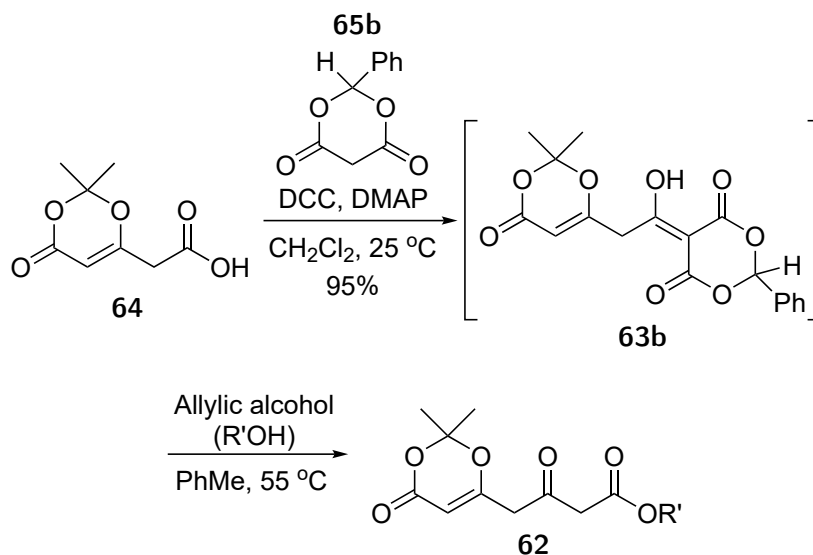
**Scheme 3.8:** Synthesis of malonate **65b**.

With the encouraging preliminary result showing that selective ketene generation of the malonate **65b** moiety of dioxane-4,6-dione-keto-dioxinone **63b** over the dioxinone moiety was possible, further investigations into optimising this reaction were carried out (**Table 3.2**). By varying the equivalents of dioxane-4,6-dione-keto-dioxinone **63b** used in the reaction, it was observed that 1.1 – 1.5 equiv. resulted in the formation of dioxinone β -keto-esters **62** in 54 – 72 % (**Entry 1 – 3**). The fluctuation in isolated yields was mainly due to incomplete conversion as well as some side reactions. For instance, the formation of β -keto dioxinone **132** was observed, presumably formed *via* reaction of dioxinone-acylketene **31** with H₂O to form β -keto acid **133**, which underwent spontaneous decarboxylation to yield β -keto dioxinone **132** (**Scheme 3.9**).



Scheme 3.9: Formation of β -keto dioxinone **132**.

Eventually, it was found that full conversion of *trans, trans*-farnesol **95** into the corresponding dioxinone β -keto-ester **62b** (78 %, **Entry 4**) was achieved when 1.8 equivalents of dioxane-4,6-dione-keto-dioxinone **63b** were used in this reaction. Similarly, geraniol **94** was converted into β -keto-ester **62a** (81 %) under the optimal conditions (**Entry 5**). The optimised conditions were also found to give consistent results at various scale (**Table 3.3**). Two additional runs with geraniol **94** at 20 mmol showed that this protocol could produce dioxinone β -keto-ester **62a** reproducibly (81 – 95 %, **Entry 1 – 2**). As a result, dioxinone β -keto-ester **62b** was successfully synthesised routinely in 78 – 96 % at 1 – 80 mmol scale (**Entry 3 – 7**).

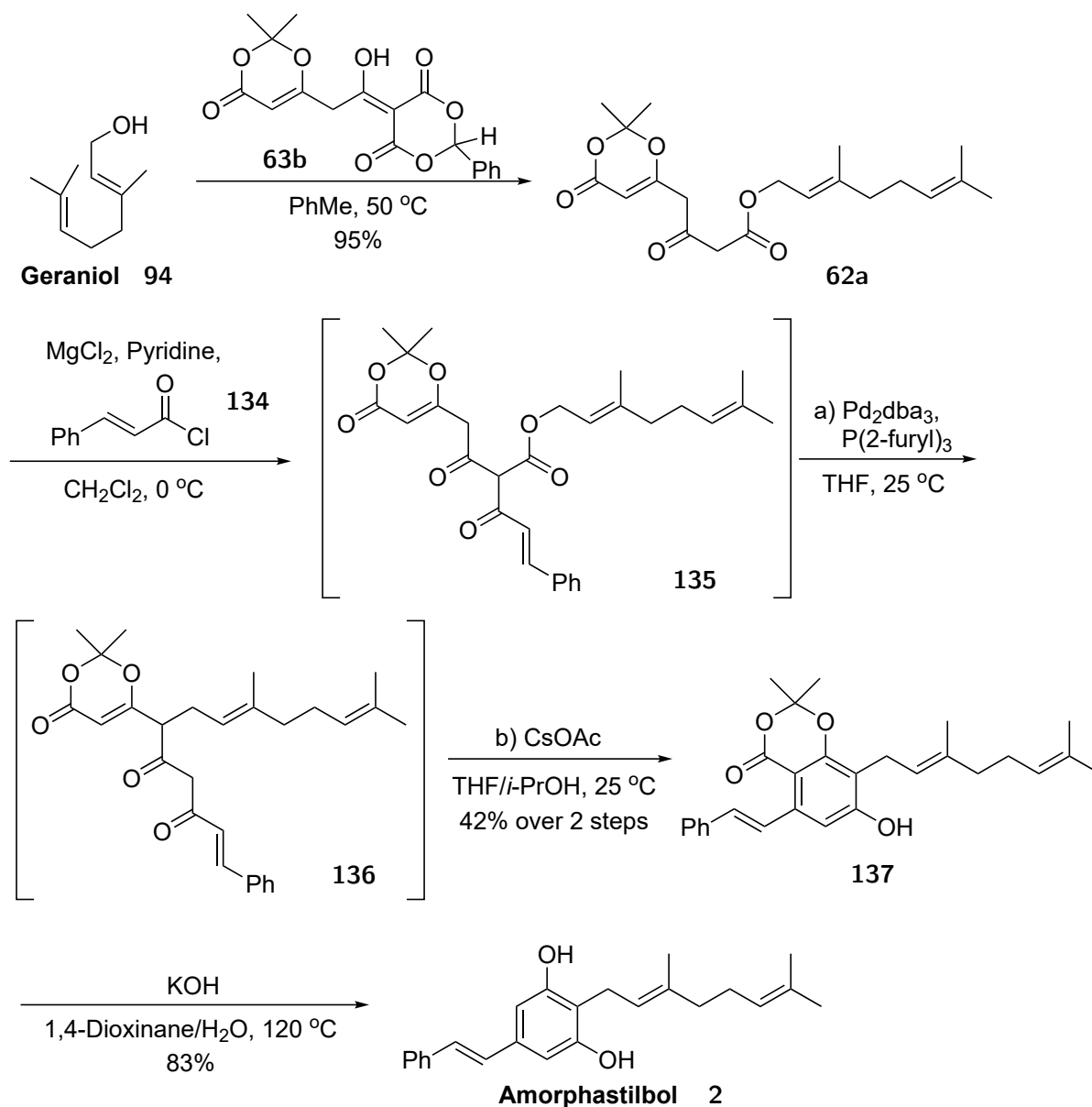
Table 3.2: Thermolysis of dioxane-4,6-dione-keto-dioxinone **63b**.

Entry ^a	Allylic alcohol	Equiv. of 63b	Time	Yield
1	<i>trans, trans</i> -Farnesol 95	1.1	6 h	62 %
2	<i>trans, trans</i> -Farnesol 95	1.3	3 h	54 %
3	<i>trans, trans</i> -Farnesol 95	1.5	3 h	72 %
4	<i>trans, trans</i> -Farnesol 95	1.8	4 h	78 %
5	Geraniol 94	1.8	4 h	81 %

a) Reactions were carried out with 1.00 mmol of allylic alcohol.

Table 3.3: Thermolysis of dioxane-4,6-dione-keto-dioxinone **63b** at different reaction scales.

Entry	Allylic alcohol	Scale (mmol)	Yield
1	Geraniol 94	20	87 %
2	Geraniol 94	20	95 %
3	<i>trans, trans</i> -Farnesol 95	20	79 %
4	<i>trans, trans</i> -Farnesol 95	20	89 %
5	<i>trans, trans</i> -Farnesol 95	20	88 %
6	<i>trans, trans</i> -Farnesol 95	41	96 %
7	<i>trans, trans</i> -Farnesol 95	80	87 %

Scheme 3.10: Total synthesis of amorphastilbol (**2**).

3.5 Total Synthesis of Amorphastilbol

Having established the optimal conditions for the synthesis of dioxinone β -keto-esters **62**, its application on the synthesis of amorphastilbol (**2**) was examined (Scheme 3.10). Geraniol **94** was trapped with the dioxinone-acylketene **31**, generated from dioxane-4,6-dione-keto-dioxinone **63b**, at 55 °C to yield dioxinone β -keto ester **62a** (95 %). Subsequent acylation with *trans*-cinnamoyl

chloride **134** in the presence of magnesium chloride and pyridine provided the dioxinone β , δ -diketo ester **135**. Direct reaction with Pd_2dba_3 and $\text{P}(2\text{-furyl})_3$ resulted in decarboxylative allylic rearrangement to give β , δ -diketo dioxinone **136**, which aromatised readily in the presence of caesium acetate in isopropanol to afford resorcyate **137** (42 % over two steps from dioxinone β -keto-ester **62a**). The expected regioselectivity of the palladium(0) catalysed allylic rearrangement reaction was confirmed by a single crystal X-ray structural determination of the resorcyate **137** (**Figure 3.2**). Subsequent hydrolytic decarboxylation under basic conditions at 120 °C gave amorphastilbol (**2**) (83 %) on gram scale with an overall yield of 33 % over four steps from geraniol **94**. The spectroscopic data were in full agreement with that reported for the isolated natural product (**Table 3.4**).⁵

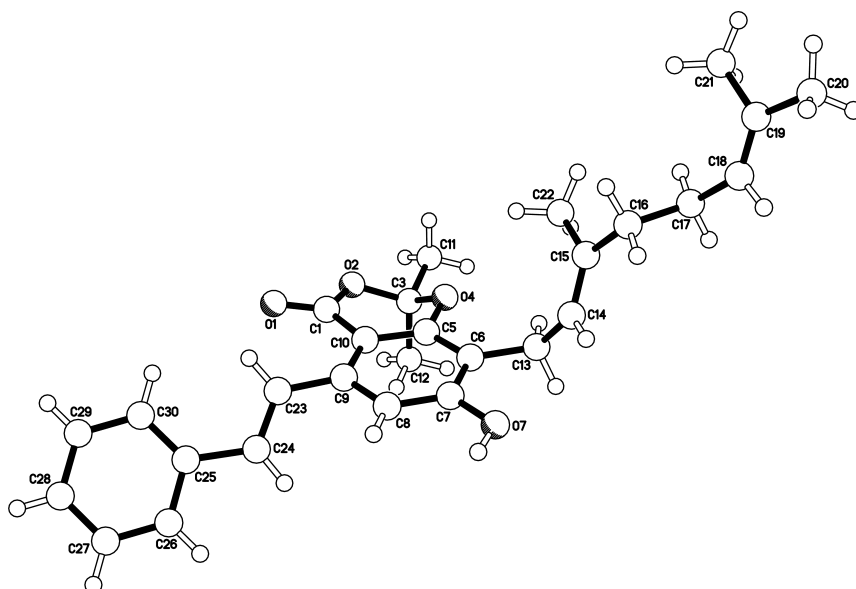
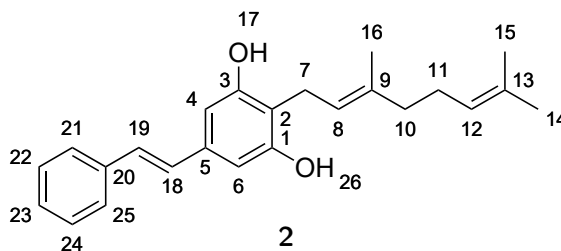


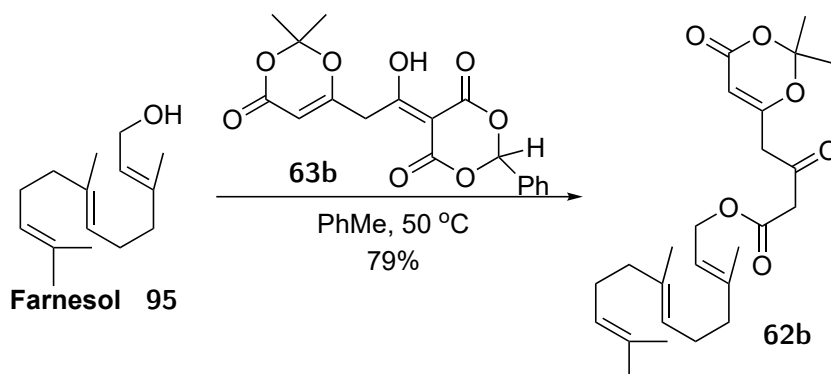
Figure 3.2: X-Ray crystal structure of resorcyate **137**.

Table 3.4: Comparison of ^1H and ^{13}C amorphastilbol (**2**) NMR data in CDCl_3 with literature.

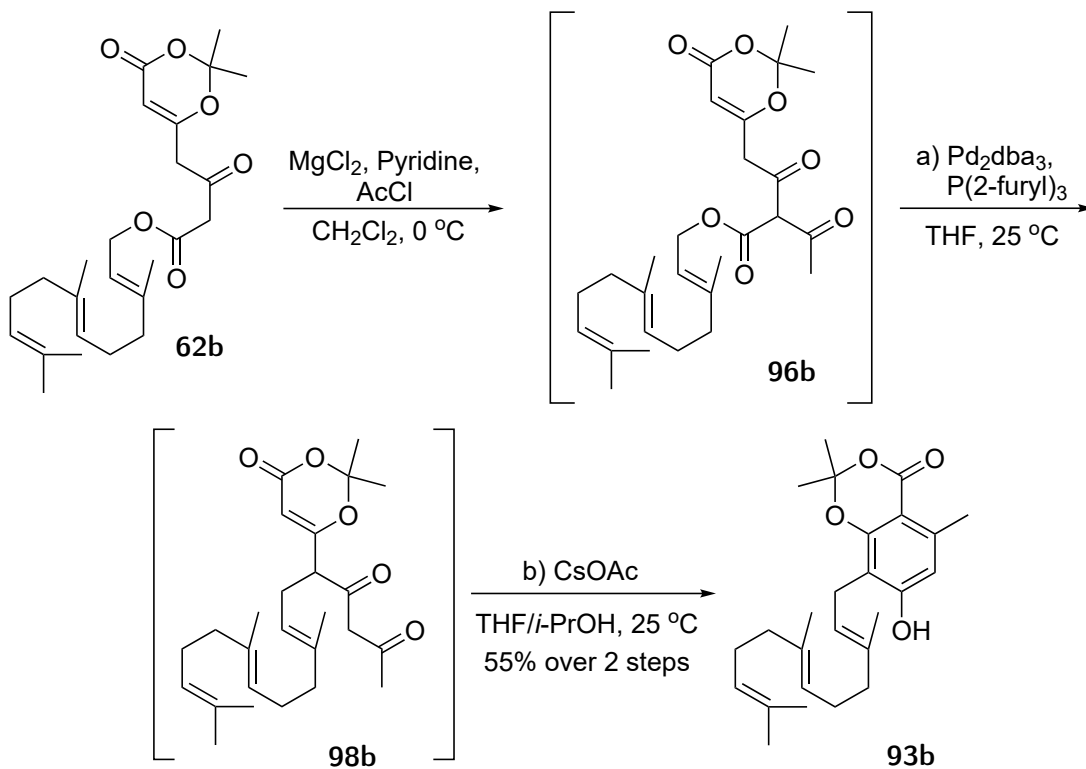
Position	Amorphastilbol (2)		Literature data ⁵		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	155.2		155.1		+ 0.1	
2	113.2		113.2		0	
3	155.2		155.1		+ 0.1	
4	106.6	6.59 (s)	106.5	6.55 (s)	+ 0.1	+ 0.04
5	136.9		136.8		+ 0.1	
6	106.6	6.59 (s)	106.5	6.55 (s)	+ 0.1	+ 0.04
7	22.5	3.44 (d, 7.1)	22.5	3.45 (d, 6)	0	- 0.01
8	123.7	5.28 (t, 7.1)	123.6	5.20 (t, 6)	+ 0.1	+ 0.08
9	139.5		139.4		+ 0.1	
10	39.7	2.25 – 2.03 (m)	39.7	2.03 (m)	0	
11	26.4	2.25 – 2.03 (m)	26.4	2.03 (m)	0	
12	121.2	5.09 – 5.01 (m)	121.2		0	
13	132.1		132.1		0	
14	25.7	1.69 (s)	25.6	1.68 (s)	+ 0.1	+ 0.01
15	17.7	1.60 (s)	17.7	1.62 (s)	0	- 0.02
16	16.2	1.83 (s)	16.2	1.76 (s)	0	+ 0.07
17		5.12 (s)		5.05 (s)		+ 0.07
18	128.0	6.93 (d, 16.3)	128.6	6.98 (s)	- 0.6	- 0.05
19	128.0	7.01 (d, 16.3)	128.0	6.98 (s)	0	+ 0.03
20	137.2		137.1		+ 0.1	
21	126.5	7.52 – 7.45 (m)	126.4	7.45 – 7.20 (m)	+ 0.1	
22	128.65	7.38 – 7.32 (m)	128.6	7.45 – 7.20 (m)	+ 0.05	
23	127.6	7.29 – 7.22 (m)	127.5	7.45 – 7.20 (m)	+ 0.1	
24	128.69	7.38 – 7.32 (m)	128.6	7.45 – 7.20 (m)	+ 0.09	
25	126.5	7.52 – 7.45 (m)	126.4	7.45 – 7.20 (m)	+ 0.1	
26		5.12 (s)		5.05 (s)		+ 0.07

3.6 Total Synthesis of Grifolin and Grifolic Acid

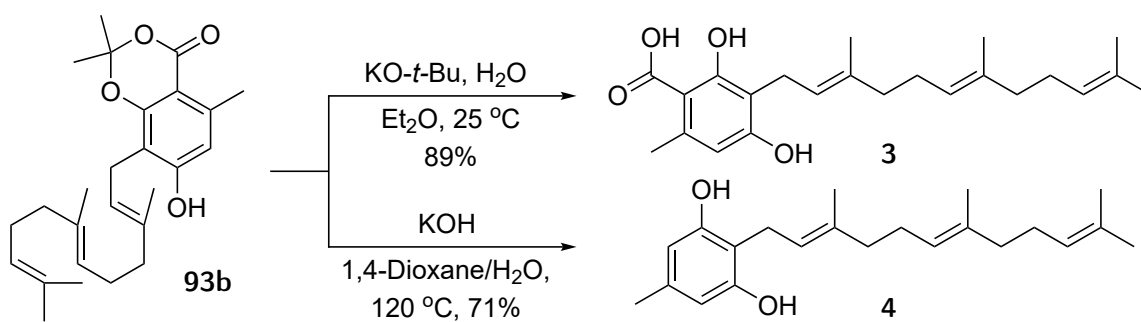
Encouraged by the results, the method was utilised for the syntheses of grifolic acid (**3**) and grifolin (**4**). Fragmentation of dioxane-4,6-dione-keto-dioxinone **63b** at 55 °C and ketene-trapping with *trans, trans*-farnesol **95** gave the dioxinone β -keto ester **62b** (79 %) (**Scheme 3.11**). This was directly converted into the corresponding resorcyate **93b** via Claisen condensation, palladium(0)-catalysed decarboxylative allylic rearrangement and base-mediated aromatisation (**Scheme 3.12**). Finally, saponification⁹² of resorcyate **93b** gave grifolic acid (**3**) (89 %) (**Table 3.5**) with an overall yield of 39 % while hydrolytic decarboxylation gave grifolin (**4**) (71 %) (**Table 3.6**) with an overall yield of 30 % (**Scheme 3.13**). The analytical data of the synthetic products were compared with data reported for the isolated natural products and were found to be in good agreement.⁷⁶



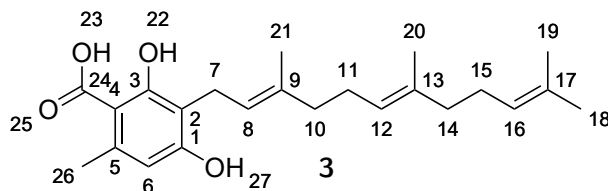
Scheme 3.11: Synthesis of dioxinone β -keto ester **62b**.



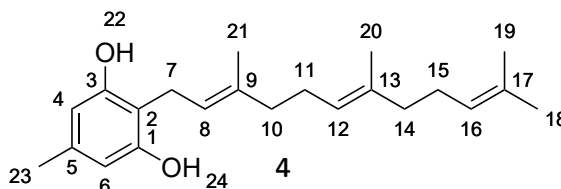
Scheme 3.12: Synthesis of resorcyate **93b**.



Scheme 3.13: Synthesis of grifolic acid (**3**) and grifolin (**4**).

Table 3.5: Comparison of ^1H and ^{13}C grifolic acid (**3**) NMR data in CD_3COCD_3 with literature.

Position	Grifolic Acid (3)		Literature data ⁷⁶		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	164.8		164.0		+ 0.8	
2	113.6		112.8		+ 0.8	
3	160.6		159.9		+ 0.7	
4	104.6		103.9		+ 0.7	
5	141.5		140.7		+ 0.8	
6	111.5	6.32 (s)	110.7	6.32 (s)	+ 0.8	0
7	22.5	3.32 (d, 7.2)	21.7	3.31 (d, 7)	+ 0.8	+ 0.01
8	123.6	5.30 – 5.22 (m)	122.9	5.25 (t, 7)	+ 0.7	
9	135.3		134.5		+ 0.8	
10	40.4	2.10 – 1.86 (m)	39.6	2.03 – 1.86 (m)	+ 0.8	
11	27.2	2.10 – 1.86 (m)	26.4	2.03 – 1.86 (m)	+ 0.8	
12	125.0	5.12 – 5.02 (m)	124.2	5.18 – 4.97 (m)	+ 0.8	
13	134.7		134.0		+ 0.7	
14	40.5	2.10 – 1.86 (m)	39.7	2.03 – 1.86 (m)	+ 0.8	
15	27.4	2.10 – 1.86 (m)	26.6	2.03 – 1.86 (m)	+ 0.8	
16	125.2	5.12 – 5.02 (m)	124.4	5.18 – 4.97 (m)	+ 0.8	
17	131.5		130.7		+ 0.8	
18	25.8	1.63 (s)	25.0	1.62	+ 0.8	+ 0.01
19	17.7	1.55 (s)	16.9	1.54	+ 0.8	+ 0.01
20	16.1	1.55 (s)	15.3	1.54	+ 0.8	+ 0.01
21	16.2	1.77 (s)	15.5	1.75	+ 0.7	+ 0.02
22		11.55 (s)				
23		12.49 (s)				
24	174.7		174.0		+ 0.7	
26	24.3	2.47 (s)	23.5	2.46	+ 0.7	
27		8.89 (s)				

Table 3.6: Comparison of ^1H and ^{13}C grifolin (4) NMR data in CD_3COCD_3 with literature.

Position	Grifolin (4)		Literature data ⁷⁶		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	156.7		156.0		+ 0.7	
2	112.6		112.0		+ 0.6	
3	156.7		156.0		+ 0.7	
4	108.4	6.19 (s)	107.8	6.19	+ 0.6	0
5	136.7		136.0		+ 0.7	
6	108.4	6.19 (s)	107.8	6.19	+ 0.6	0
7	22.7	3.31 (d, 7.1)	22.1	3.33 (d, 7)	+ 0.6	- 0.02
8	124.6	5.33 – 5.27 (m)	123.9	5.30 (t, 7)	+ 0.7	
9	135.3		134.6		+ 0.7	
10	40.4	2.08 – 1.89 (m)	39.8	2.07 – 1.87 (m)	+ 0.6	
11	27.38	2.08 – 1.89 (m)	26.8	2.07 – 1.87 (m)	+ 0.58	
12	125.1	5.14 – 5.04 (m)	124.5	5.09 – 5.06 (m)	+ 0.6	
13	134.1		133.7		+ 0.4	
14	40.6	2.08 – 1.89 (m)	40.0	2.07 – 1.87 (m)	+ 0.6	
15	27.35	2.08 – 1.89 (m)	26.8	2.07 – 1.87 (m)	+ 0.55	
16	125.2	5.14 – 5.04 (m)	124.6	5.09 – 5.06 (m)	+ 0.6	
17	131.5		130.8		+ 0.7	
18	25.8	1.64 (s)	25.4	1.63 (s)	+ 0.4	+ 0.01
19	17.7	1.57 (s)	17.3	1.56 (s)	+ 0.4	+ 0.01
20	16.0	1.57 (s)	15.6	1.56 (s)	+ 0.4	+ 0.01
21	16.2	1.76 (s)	15.8	1.76 (s)	+ 0.4	0
22		7.82 (s)		7.80 (s)		+ 0.02
23	21.2	2.09 (s)	20.8	2.10 (s)	+ 0.4	- 0.01
24		7.82 (s)		7.80 (s)		+ 0.02

3.7 Biological Activity of the Synthetic Amorphastilbol, Grifolin and Grifolic Acid

Biological evaluation of amorphastilbol (**2**) showed its cytotoxicity against peripheral blood mononuclear cell ($IC_{50} = 17.7 \mu M$) and human liver cancer cell line ($IC_{50} = 18.3 \mu M$). On the other hand, grifolic acid (**3**) showed selective inhibition against some kinases as well as receptors. In particular, it showed strong inhibition against histamine receptor H_1 ($IC_{50} = 5.89 \mu M$). Lastly, grifolin (**4**) has moderate cytotoxicity against PBMC ($IC_{50} = 23.9 \mu M$) and Hep G2 ($IC_{50} = 34.3 \mu M$).

Table 3.7: Biological profiling of amorphastilbol (**2**), grifolic acid (**3**) and grifolin (**4**).

	Assay	Amorphastilbol (2)	Grifolic acid (3)	Grifolin (4)
		$IC_{50} (\mu M)$	$IC_{50} (\mu M)$	$IC_{50} (\mu M)$
TR-FRET Kinome	BTK	>10	8.81	>10
	Pim1	>10	8.78	>10
	Zap70	>10	8.5	>10
Receptor Antagonist	5-HT _{1A}	>10	9.87	>10
	5-HT _{2A}	>10	9.77	>10
	A ₁	>10	9.78	>10
	β_2	>10	7.76	>10
	H ₁	>10	5.89	>10
Toxicity	PBMC	17.7	>40.0	23.9
	Hep G2	18.3	>40.0	34.3

3.8 Conclusion

In summary, experimental results have shown that thermolysis of dioxane-4,6-dione-keto-dioxinone **63b**, which was synthesised from dioxinone acid **64** and malonate **65b**, could generate dioxinone acyl ketene in a similar way as dioxane-4,6-dione-keto-dioxinone **63a** for the preparation of dioxinone β -keto esters. Application of the optimised conditions enabled efficient and concise total syntheses of amorphastilbol (**2**), grifolic acid (**3**) and grifolin (**4**) in five linear steps using a common reaction sequence starting from commercially available geraniol **94** or

trans, trans-farnesol **95**. The key resorcyate intermediates were biomimetically synthesised *via* a highly regioselective decarboxylative allylic rearrangement catalysed by palladium(0).

3.9 Future Work

This reaction sequence can be utilised in the syntheses of other biologically active resorcinol natural products such as albafuran B (**138**), cannabigerol (**139**), denticulatains A (**140**) and clusiparalicoline A (**141**) (**Figure 3.3**).^{93–96}

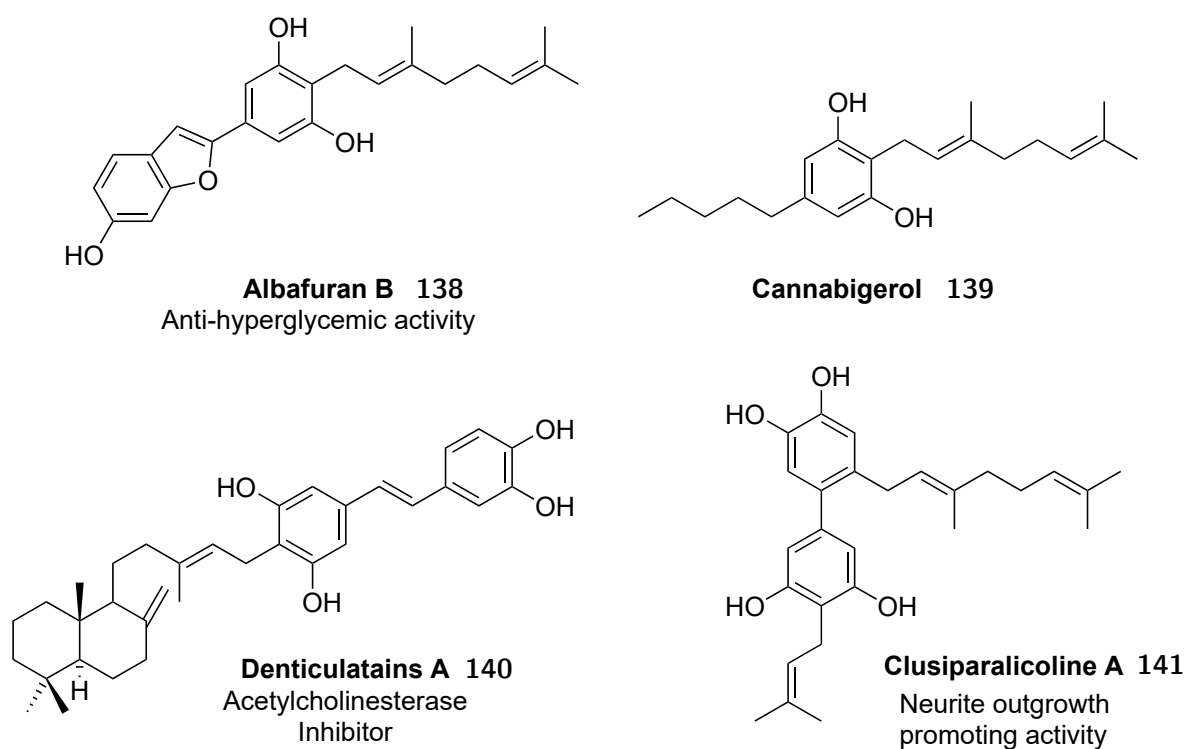


Figure 3.3: Potential targets of other resorcinol natural products.

HONGOQUERCIN A AND B

Hongoquercin A and B were synthesised in their enantiomerically pure forms from *trans, trans*-farnesol in six and eleven-steps respectively, using dual biomimetic strategies with polyketide aromatisation and subsequent polyene functionalisation from a common farnesyl-resorcyate intermediate.⁹⁷ Key steps involve Pd(0)-catalysed decarboxylative allylic rearrangement of a dioxinone β , δ -diketo-ester to a β , δ -diketo-dioxinone, which was readily aromatised into the corresponding resorcyate, and subsequent polyene cyclisation *via* enantioselective protonation or regioselective terminal alkene oxidation and cationic cyclisation of enantiomerically enriched epoxide to furnish the tetracyclic natural product cores. Analogues of the hongoquercins were synthesised *via* halonium-induced polyene cyclisations, and the meroterpenoids could be further functionalised *via* saponification, hydrolytic decarboxylation, reduction and amidation reactions.

4.1 Isolation and Biological Evaluation of (+)-Hongoquercin A and B

(+)-Hongoquercin A (**5**) and B (**6**) were isolated from the fermentation broths produced by an unidentified fungus LL-23G227 in 1998 by Roll and Abbanat (**Figure 4.1**).^{11,12} The antibacterial activity of the hongoquercins were examined. (+)-Hongoquercin A (**5**) showed moderate activity

against Gram-positive bacteria such as *Bacillus cereus* (MIC = 2 $\mu\text{g mL}^{-1}$), vancomycin-resistant *Enterococcus faecium* (MIC = 8 $\mu\text{g mL}^{-1}$) and methicillin-resistant *Staphylococcus aureus* (MIC = 4 ~8 $\mu\text{g mL}^{-1}$). However, it was inactive to Gram-negative organisms and *Candida albicans*. (+)-Hongoquercin B (**6**) was found to be inactive and only exhibited moderate activity against *Escherichia coli imp* (MIC = 16 $\mu\text{g mL}^{-1}$) and a strain of *Bacillus subtilis* (MIC = 32 $\mu\text{g mL}^{-1}$). These natural products are meroterpenoids which have a mixed biosynthetic origin involving polyketide and terpenoid pathways.

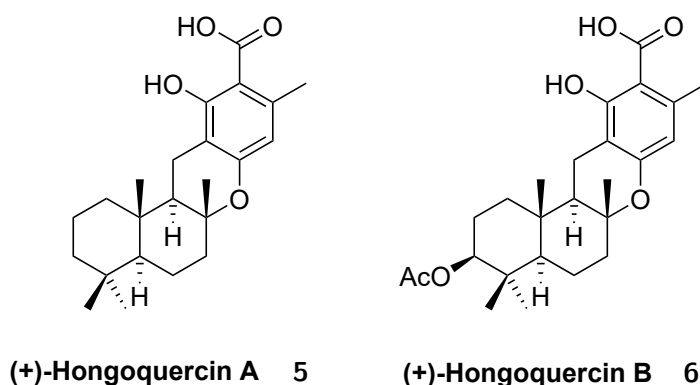
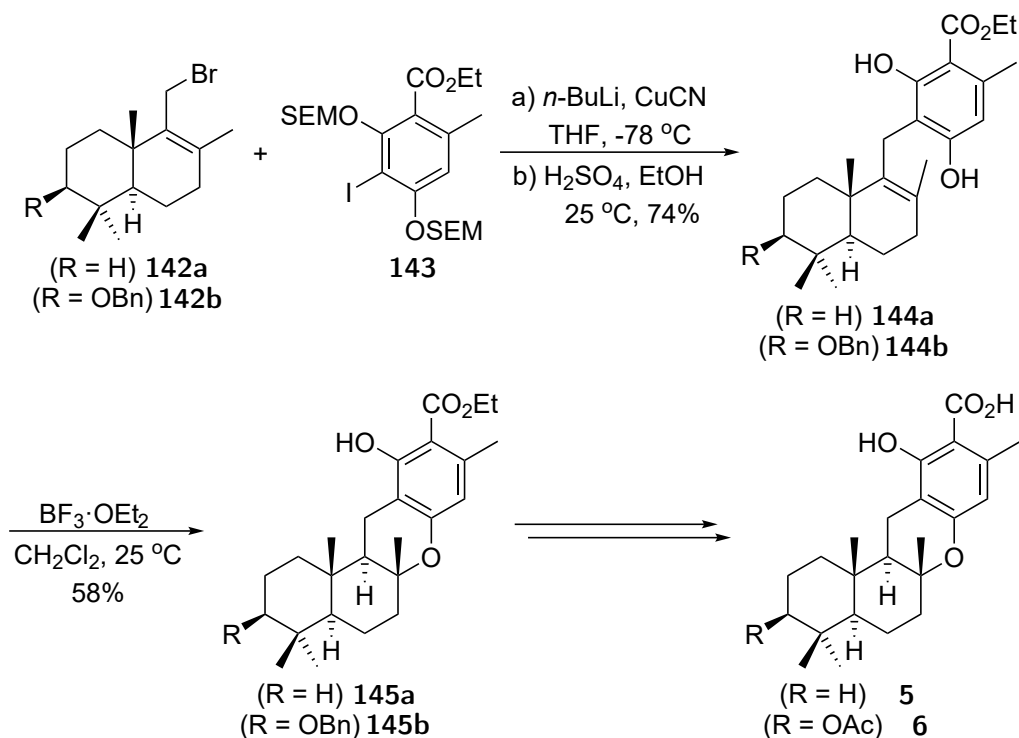


Figure 4.1: Structures of (+)-hongoquercin A (**5**) and B (**6**).

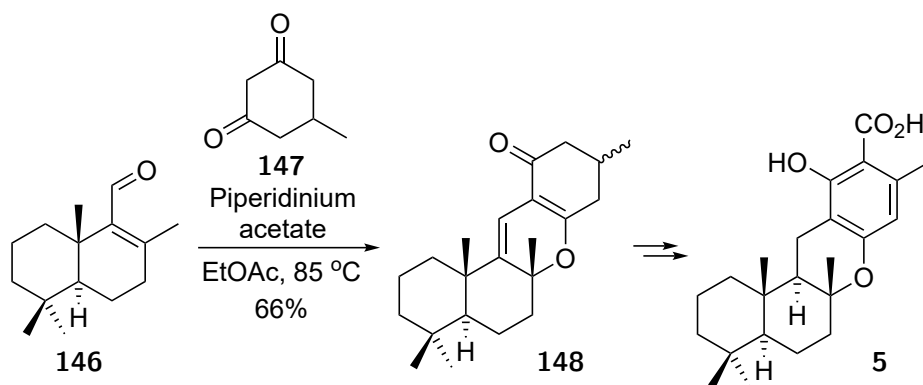
4.2 Previous Synthetic Approaches

Over the last two decades, several total syntheses of hongoquercins have been reported. The first total synthesis of (+)-hongoquercin A (**5**) and B (**6**) was reported by Mori and co-workers in a series of two publications (**Scheme 4.1**).^{98,99} The key step involved the coupling of an enantiopure drimene **142** with an orselinate derivative **143**. Lithiation of iodide **143** with *n*-BuLi produced the lithiated intermediate which was immediately reacted with copper(I) cyanide to provide the corresponding cuprate. The cuprate was then reacted with bromide **142** to produce phenol **144** (74% over 2 steps from iodide **143**) after subsequent SEM deprotection with sulfuric acid in ethanol. Treatment of the phenol **144** with boron trifluoride etherate induced the ring closure to provide the desired key meroterpenoid **145** along with some minor regioisomer as a 2 : 1 mixture. Further manipulation of meroterpenoids **145** furnished (+)-hongoquercin A (**5**) and B (**6**).



Scheme 4.1: Mori syntheses of (+)-hongoquercin A (**5**) and B (**6**).

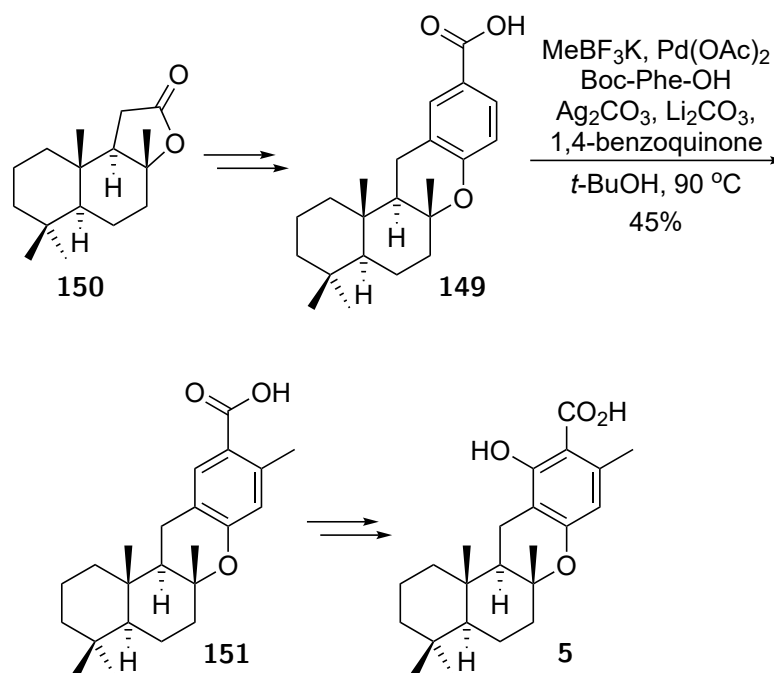
In 2006, Hsung and co-workers synthesised (+)-hongoquercin A (**5**) (**Scheme 4.2**).¹⁰⁰ The key step involved cycloaddition of enal **146** with dione **147** in the presence of piperidinium acetate to give cycloadduct **148**, furnishing the fused rings core structure. Further functionalisation and aromatisation of cycloadduct **148** completed the synthesis of (+)-hongoquercin A (**5**).



Scheme 4.2: Hsung synthesis of (+)-hongoquercin A (**5**).

Baran and co-workers featured a ligand accelerated C-H methylation approach in the synthe-

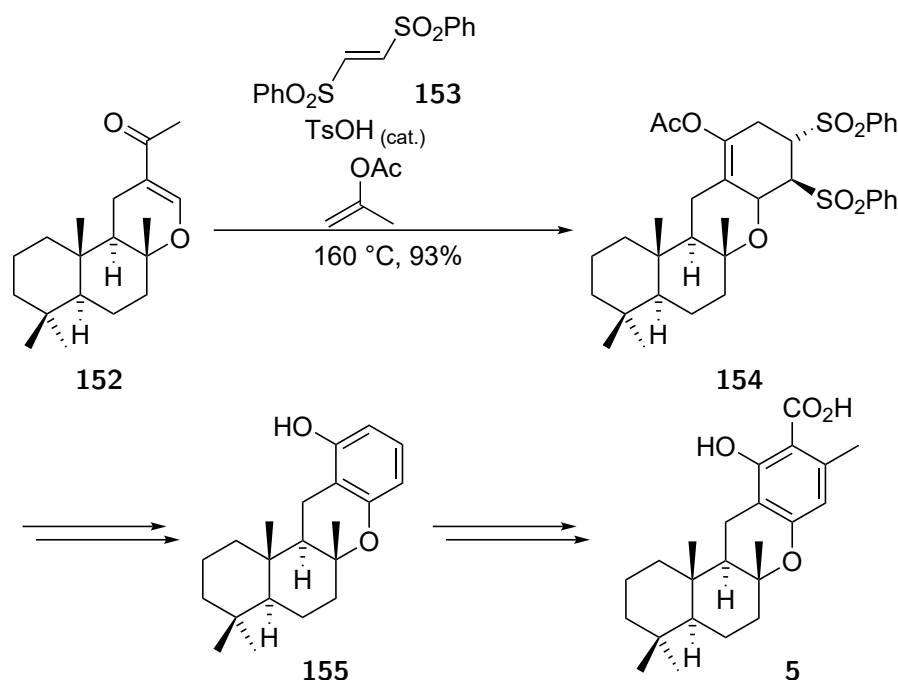
sis of (+)-hongoquercin A (**5**) (**Scheme 4.3**).¹⁰¹ The key acid **149**, synthesised from (+)-sclareolide (**150**) in eight steps, was methylated by Boc-Phe-OH accelerated C-H functionalisation to give the corresponding methylated carboxylic acid **151** (45 %). Carboxylic acid **151** was then further oxidised to furnish (+)-hongoquercin A (**5**).



Scheme 4.3: Baran synthesis of (+)-hongoquercin A (**5**).

Alvarez-Manzaneda and co-workers completed the synthesis of (+)-hongoquercin A (**5**) in 2014 by utilising a Diels-Alder cycloaddition as the key step (**Scheme 4.4**).¹⁰² (-)-Sclareol was first functionalised into tricyclic α , β -enone **152**, which was then reacted with ethylene **153** in isopropenyl acetate in the presence of catalytic amount of *p*-toluenesulfonic acid to generate the tetracyclic bis-sulphone **154** (93 %) as a mixture of two stereoisomers in a 1.2 : 1 ratio. The sulphone **154** was then further derivatised into phenol **155** and transformed into (+)-hongoquercin A (**5**).

In the same year the Barrett group achieved the synthesis of (+)-hongoquercin B ethyl ester **156** in nine steps starting from *trans,trans*-farnesyl acetate (**Scheme 4.5**) with a dual biomimetic approach.¹⁰³ (*S*)-Epoxyfarnesol **157**, prepared from enantioselective Sharpless dihydroxylation and epoxide formation, was transformed into the corresponding resorcyate **158**. The epoxy-

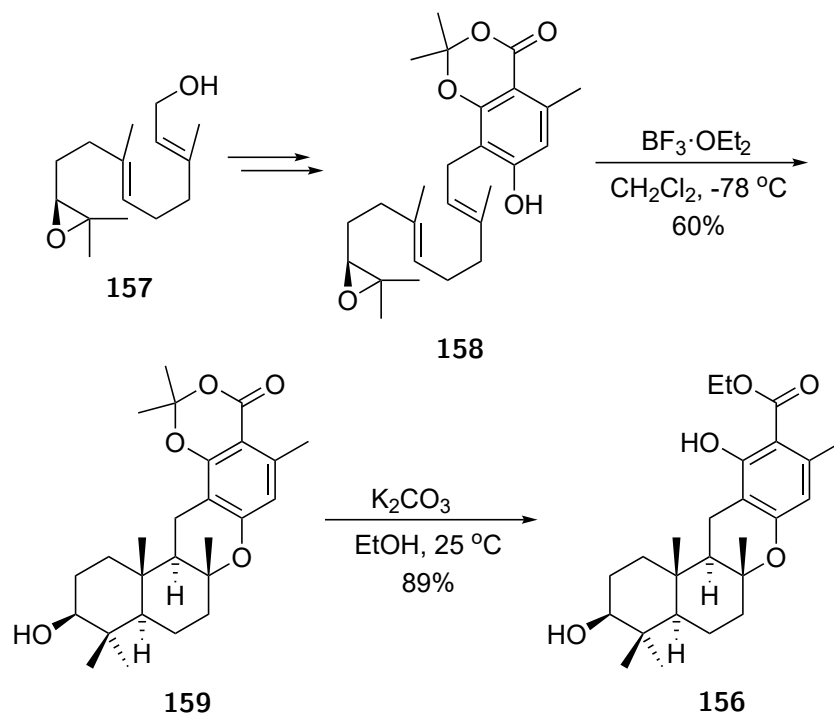


Scheme 4.4: Alvarez-Manzaneda synthesis of (+)-hongoquercin A (5).

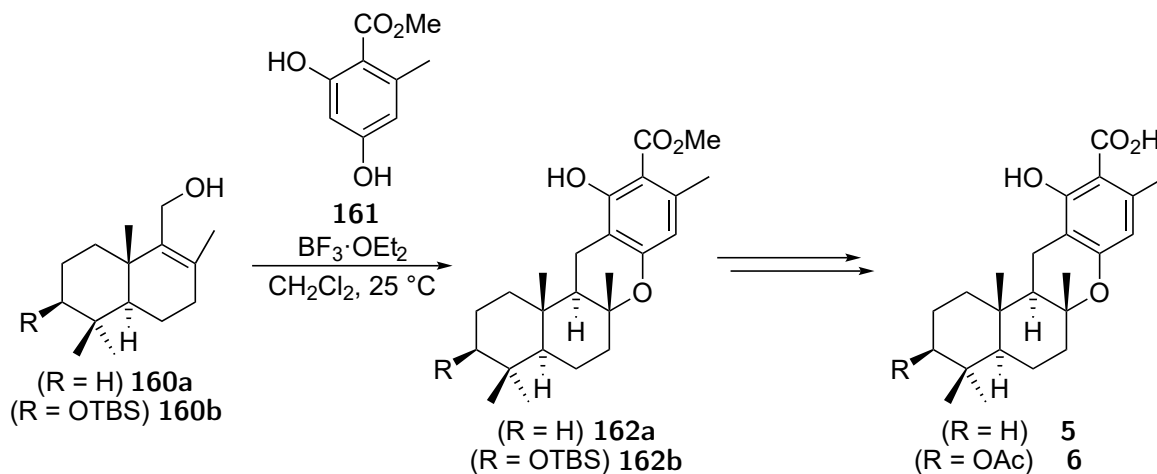
terpenoid resorcyate **158** was then cyclised into the tetracyclic alcohol **159** (60 %) upon treatment with the Lewis acidic boron trifluoride etherate. Subsequent transesterification of alcohol **159** gave (+)-hongoquercin B ethyl ester **156** (89 %).

More recently in 2017, Dethe and co-workers completed the enantiospecific syntheses of (+)-hongoquercin A (**5**) and B (**6**) (**Scheme 4.6**).¹⁰⁴ The enantiopure terpenoids **160**, prepared from (+)-sclareolide (**150**) and 1,3-cyclohexanedione, were reacted with resorcinol derivative **161** in a boron trifluoride etherate catalysed Friedel-Crafts alkylation to yield the corresponding esters **162**, which were further functionalised into the natural products.

Photoredox catalysis has been an emerging field over the past decade with many successful examples of synthetic transformations, and applications in natural product synthesis. One notable example of polyene cyclisation catalysed with Eosin Y (**163**) was published in 2017 by Luo and co-workers in the seven step synthesis of (±)-hongoquercin A (**5**) (**Scheme 4.7**).¹⁰⁵ Cyclisation of enolised di-ketone **164**, catalysed by Eosin Y (**163**), provided tetracyclic compound **165** (60 % by NMR), a key intermediate with the complete carbon framework of (±)-hongoquercin A (**5**).



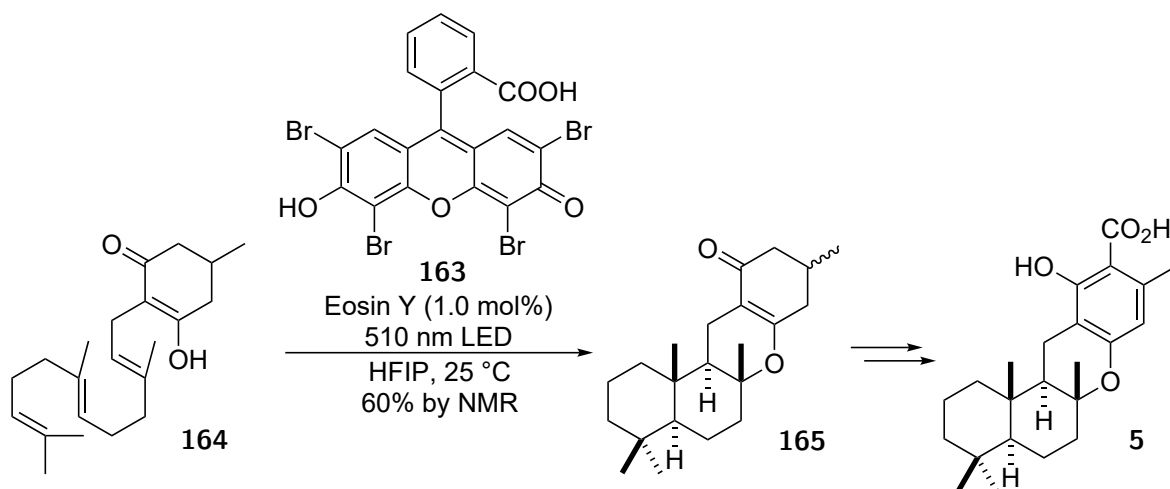
Scheme 4.5: Barrett synthesis of (+)-hongoquercin B ethyl ester **156**.



Scheme 4.6: Dethe syntheses of (+)-hongoquercin A (**5**) and B (**6**).

4.3 Retrosynthetic Analysis of (+)-Hongoquercin A and B

The common synthetic strategy in the literature involves the coupling of two synthons: an enantiopure synthesised drimene **166** coupled with a substituted resorcinol derivative **167** (**Scheme 4.8**). However, this conventional approach often requires extensive use of protecting

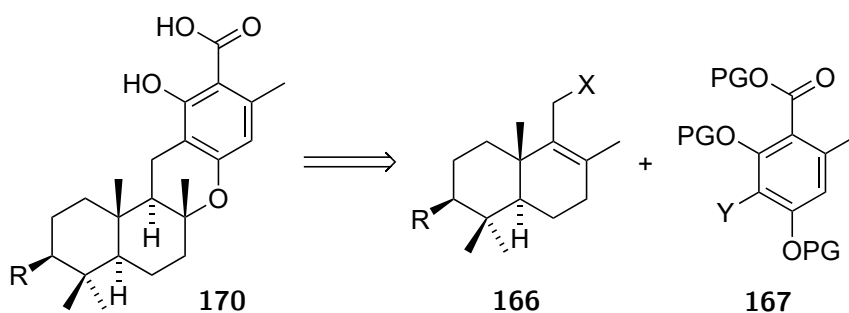


Scheme 4.7: Luo synthesis of (±)-hongoquercin A (**5**).

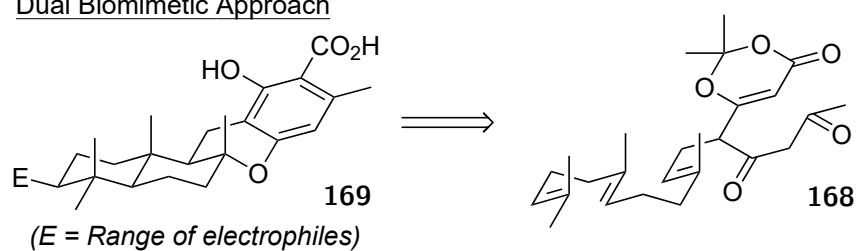
groups on the resorcinol unit **167** and multistep transformations for the synthesis of the precursor drimene **166** from another natural product. To overcome these problems, it is envisioned that a dual biomimetic approach for elaborating the arene ring and tricyclic terpenoid residues from acyclic precursor **168** sequentially *via* cascade cyclisations would simplify the syntheses of these natural products. Additionally, if the farnesyl residue was functionalised after aromatisation to construct the resorcyate entity, a diverse range of hongoquercin analogues **169** should be available by variation of the electrophilic reagents used in such derivatisations. This work is also based on the previous work published by the Barrett group in 2014.¹⁰³

It is considered that the key meroterpenoids **171** should be available using a polyene cyclisation from resorcyate **93b** by enantioselective electrophilic reactions with chiral Brønsted acids ($E = H$), epoxidation and subsequent reaction with a Lewis acid ($E = OH$) or halogenations with reagents that provide halonium ion intermediates ($E = Br$ and I) (**Scheme 4.9**). The common resorcyate intermediate **93b** should be available from the cycloaromatisation of β , δ -diketo dioxinone **98b**, which could be synthesised *via* palladium(0)-catalysed decarboxylative allylic rearrangement of dioxinone β , δ -diketo ester **96b**. Dioxinone β , δ -diketo ester **96b** in turn should be available *via* *C*-acylation of dioxinone β -keto ester **62b**, which in turn is available from trapping a dioxinone-acylketene with *trans*, *trans*-farnesol **95**.

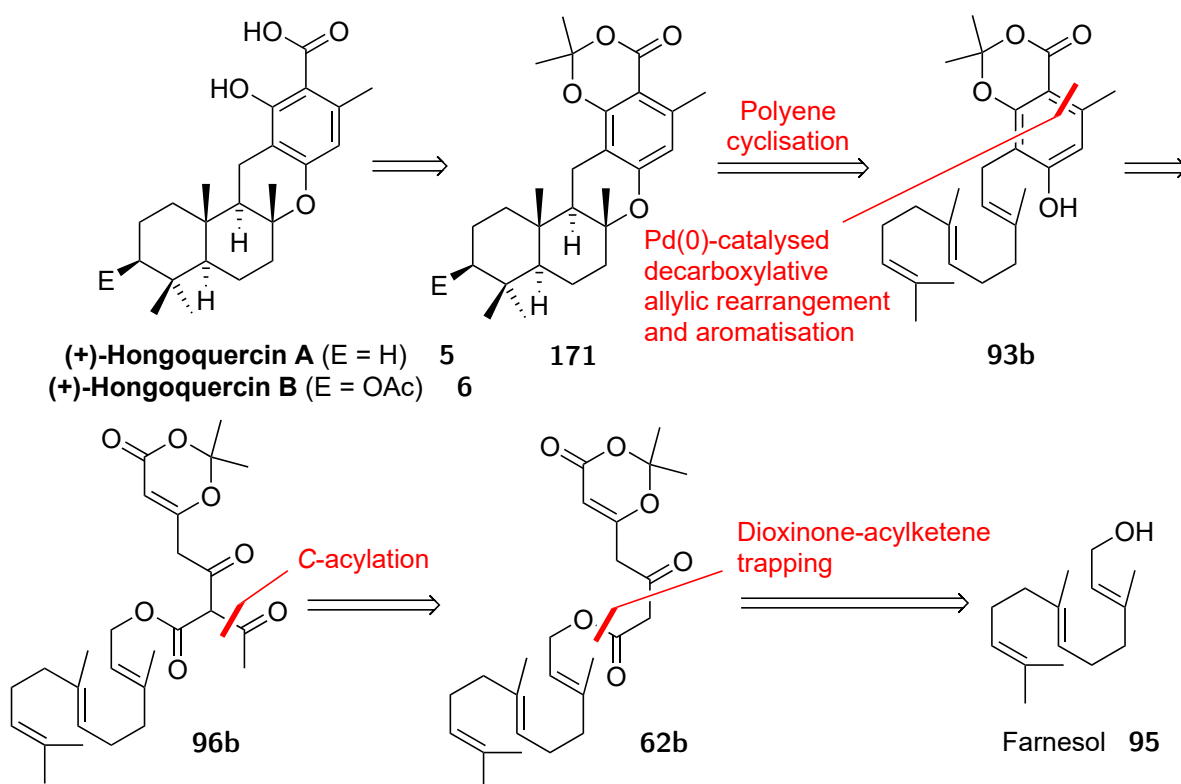
Conventional Approach



Dual Biomimetic Approach



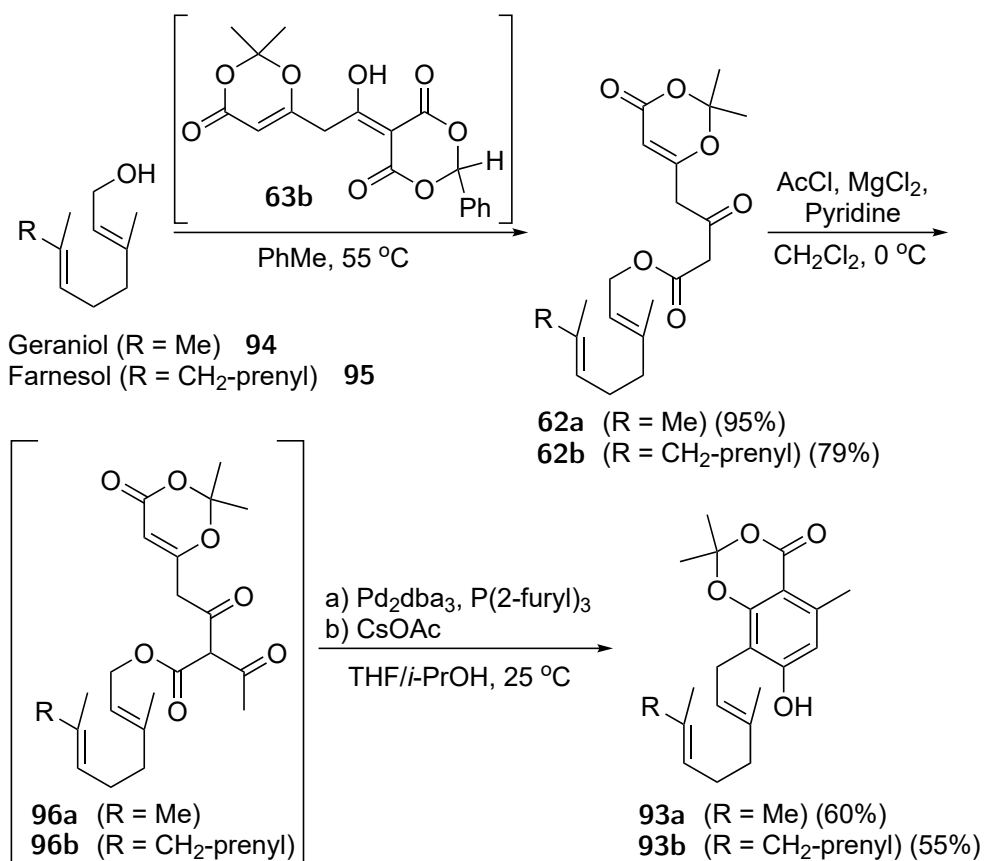
Scheme 4.8: Synthetic strategies of the hongoquercins.



Scheme 4.9: Retrosynthetic analyses of (+)-hongoquercins A (5) and B (6).

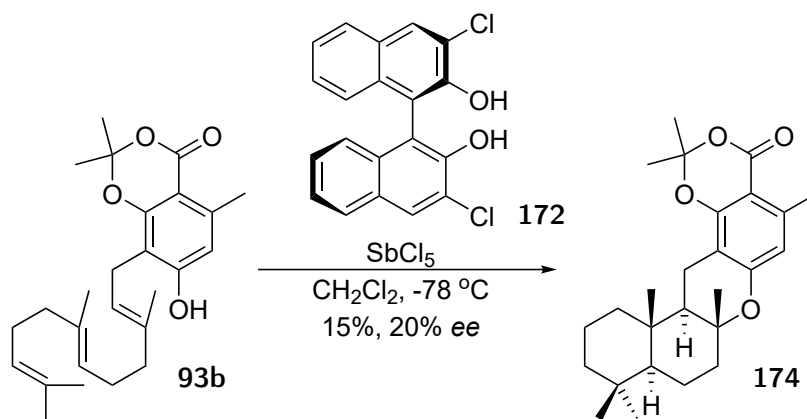
4.4 Total Synthesis of (+)-Hongoquercin A

Following the aforementioned protocol, thermolysis of dioxane-4,6-dione-keto-dioxanone **63b** at 55 °C generated the dioxinone acyl-ketene **31**, which was trapped with *trans, trans*-farnesol **95** to provide dioxinone β -keto ester **62b** (79 %) (**Scheme 4.10**). Magnesium chloride mediated regioselective *C*-acylation of dioxinone β -keto ester **62b** with acetyl chloride gave dioxinone β , δ -diketo ester **96b**, which on reaction with Pd₂(dba)₃ and tri(2-furyl)phosphine resulted in a highly regioselective decarboxylative allylic rearrangement giving the β , δ -diketo dioxinone **98b** and readily aromatised *in situ* to produce farnesyl resorcyate **93b** (55 % over two steps from dioxinone β -keto ester **62b**). A geranyl substituted analogue **93a** was also synthesised, using the same reaction sequence, from geraniol **94** in three steps with an overall yield of 57 %.



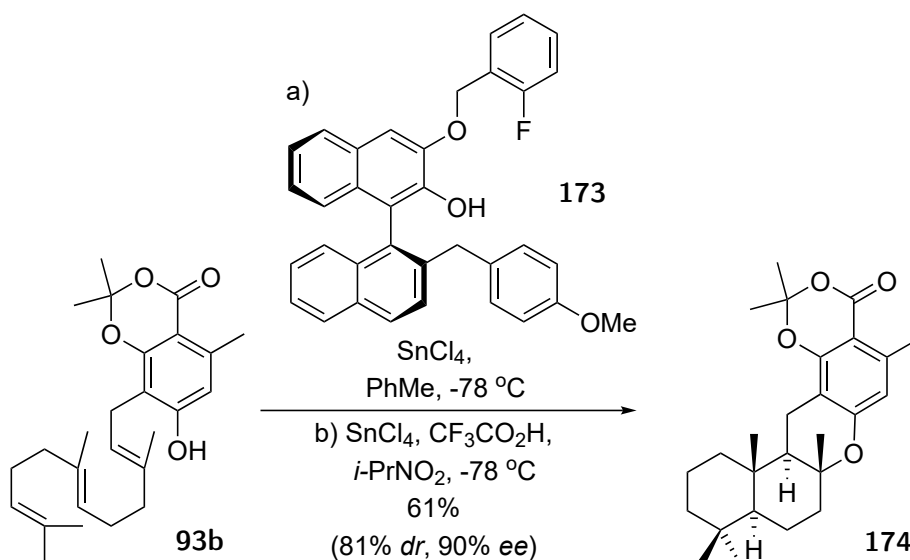
Scheme 4.10: Synthesis of the terpene resorcyates **93a** and **93b**.

The synthesis of (+)-hongoquercin A (**5**) was first investigated *via* enantioselective protonation of farnesyl resorcyate **93b** using the Lewis acid enhanced chiral Brønsted acids derived from antimony pentachloride with binol **172** and stannic chloride with binol **173** as introduced by Corey and co-workers¹⁰⁶ and Yamamoto and co-worker.¹⁰⁷ Enantioselective protonation with $\text{SbCl}_5 \cdot \mathbf{172}$ gave a mixture of partially cyclised products and the desired meroterpenoid **174** (15 %, 20 % *ee* as determined by chiral HPLC) (**Scheme 4.11**). On the other hand, the cyclisation using $\text{SnCl}_4 \cdot \mathbf{173}$ as the dual Brønsted and Lewis acids was highly enantioselective and gave the desired meroterpenoid **174** (61 %, 81 % *dr* and 90 % *ee* as determined by chiral HPLC) on sequential reaction with $\text{SnCl}_4 \cdot \mathbf{173}$ and SnCl_4 and trifluoroacetic acid (**Scheme 4.12**).



Scheme 4.11: Enantioselective protonation of resorcyate **93b** with $\text{SbCl}_5 \cdot \mathbf{172}$.

The observed enantioselectivity of this protonation could be rationalised by the two possible transition states **175** and **176** (**Figure 4.2**). After bidentate chelation of **173** with SnCl_4 , the activated O-H bond might be confined in the naphthoxy plane. As a result, the *re*-face of the terminal isoprenyl group of the farnesyl side chain would preferentially approach the activated proton perpendicularly during the initial protonation step which would be controlled by a linear OH/ π interaction.¹⁰⁷ Therefore, transition state **175** is favoured over transition state **176** due to less steric repulsion. The resulting tertiary carbocation would then trigger the polyene cyclisation to provide a mixture of cyclised products. Subsequent exposure of the reaction mixture to SnCl_4 and trifluoroacetic acid would promote a diastereoselective cyclisation of the partially cyclised products to yield meroterpenoid **174** as the major diastereoisomer which could be explained by



Scheme 4.12: Enantioselective protonation of resorcyate **93b** with $\text{SnCl}_4 \cdot \mathbf{173}$.

the Stork-Eschenmoser hypothesis.^{36,108}

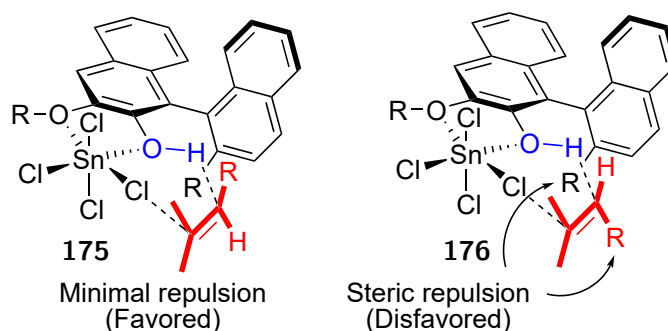
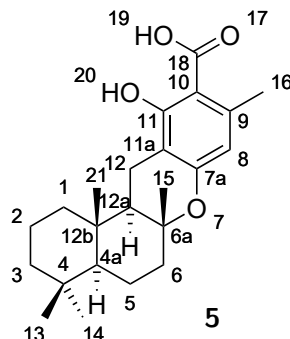


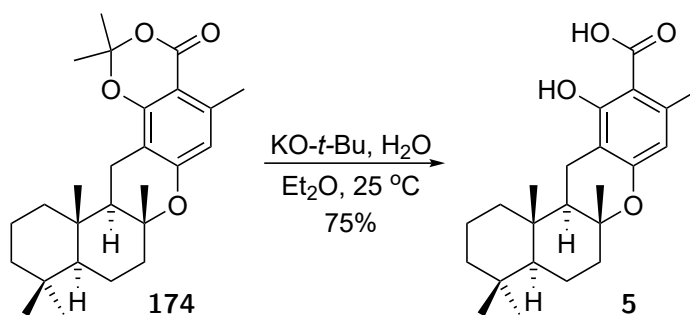
Figure 4.2: Plausible rationalisation for the stereoselectivity of $\text{SnCl}_4 \cdot \mathbf{173}$ mediated protonation.

Finally, saponification of meroterpenoid **174** gave (+)-hongoquercin A (**5**) (75 %) with an overall yield of 20 % over five steps from *trans, trans*-farnesol **95** (**Scheme 4.13**).⁹² The spectroscopic data were in full agreement with that reported for the isolated natural product (**Table 4.1**) and the structure was unambiguously confirmed by a single X-ray crystallography for the first time (**Figure 4.3**).

Table 4.1: Comparison of ^1H and ^{13}C (+)-hongoquercin A (**5**) NMR data in CD_3OD with literature.

Position	(+)–Hongoquercin A (5)		Literature data ¹¹		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	40.4	ax: 1.05 – 0.98 (m) eq: 1.81 – 1.76 (m)	40.5	ax: 1.00 (ddd, 13.1, 13.1, 3.5) eq: 1.77 (m, 13.1)	- 0.1	
2	19.6	ax: 1.50 – 1.40 (m) eq: 1.72 (dt, 13.7, 3.6)	19.6	ax: 1.47 (m, 13.7, 3.9, 3.6) eq: 1.69 (m, 13.7, 13.1, 3.9)	0	
3	43.0	ax: 1.26 – 1.21 (m, 1H) eq: 1.50 – 1.40 (m)	43.1	ax: 1.20 (ddd, 13.6, 13.5, 3.5) eq: 1.40 (m, 13.6, 2.6)	- 0.1	
4	34.2		34.1		+ 0.1	
4a	57.5	1.08 (dd, 12.2, 2.3)	57.6	1.05 (dd, 12.2, 1.8)	- 0.1	+ 0.03
5	20.8	ax: 1.81 – 1.76 (m) eq: 1.50 – 1.40 (m)	20.8	ax: 1.74 (m, 13.1, 12.2, 3.1) eq: 1.43 (m, 3.8, 3.0, 1.8)	0	
6	42.1	ax: 1.69 – 1.61 (m) eq: 2.05 (dt, 12.5, 3.2)	42.3	ax: 1.61 (ddd, 13.1, 12.4, 3.8) eq: 2.01 (ddd, 12.4, 3.0, 3.0)	- 0.2	+ 0.04
6a	79.0		78.1		+ 0.9	
7a	158.9		156.3		+ 2.6	
8	112.8	6.11 (s)	111.3	5.99 (s)	+ 1.5	+ 0.12
9	141.7		141.3		+ 0.4	
10	104.9		111.0		- 6.1	
11	164.5		163.1		+ 1.4	
11a	108.8		108.1		+ 0.7	
12	17.7	ax: 2.27 (dd, 16.7, 13.2) eq: 2.65 (dd, 16.9, 5.0)	18.0	ax: 2.26 (dd, 16.7, 13.2) eq: 2.61 (dd, 16.7, 5.0)	- 0.3	+ 0.01
12a	53.2	1.52 (dd, 13.2, 5.2)	53.6	1.52 (dd, 13.2, 5.1)	- 0.4	0
12b	38.1		38.1		0	
13	22.0	0.89 (s)	22.1	0.87 (s)	- 0.1	+ 0.02
14	33.9	0.92 (s)	33.9	0.91 (s)	0	+ 0.01
15	21.1	1.19 (s)	21.1	1.16 (s)	0	+ 0.03
16	24.2	2.46 (s)	23.7	2.50 (s)	+ 0.5	- 0.04
18	175.6		177.1		- 1.5	
21	15.4	0.96 (s)	15.4	0.94 (s)	0	+ 0.02

a) It was observed that the chemical shifts were affected by the concentration.



Scheme 4.13: Synthesis of (+)-hongoquercin A (**5**).

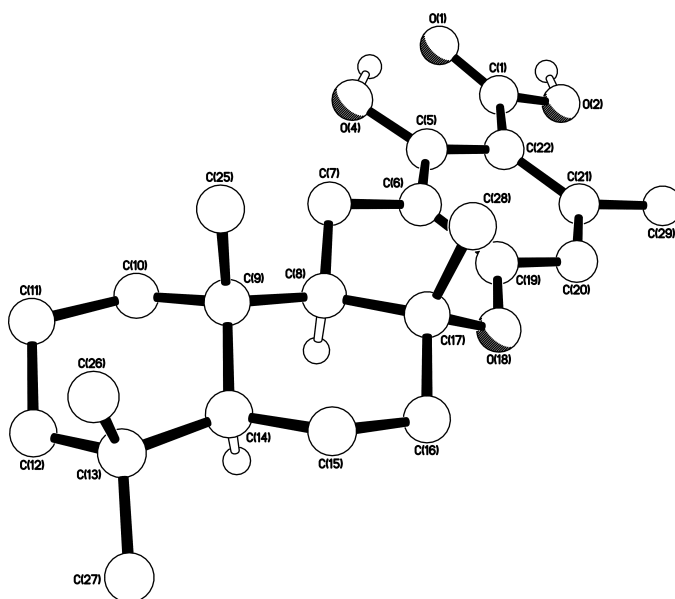
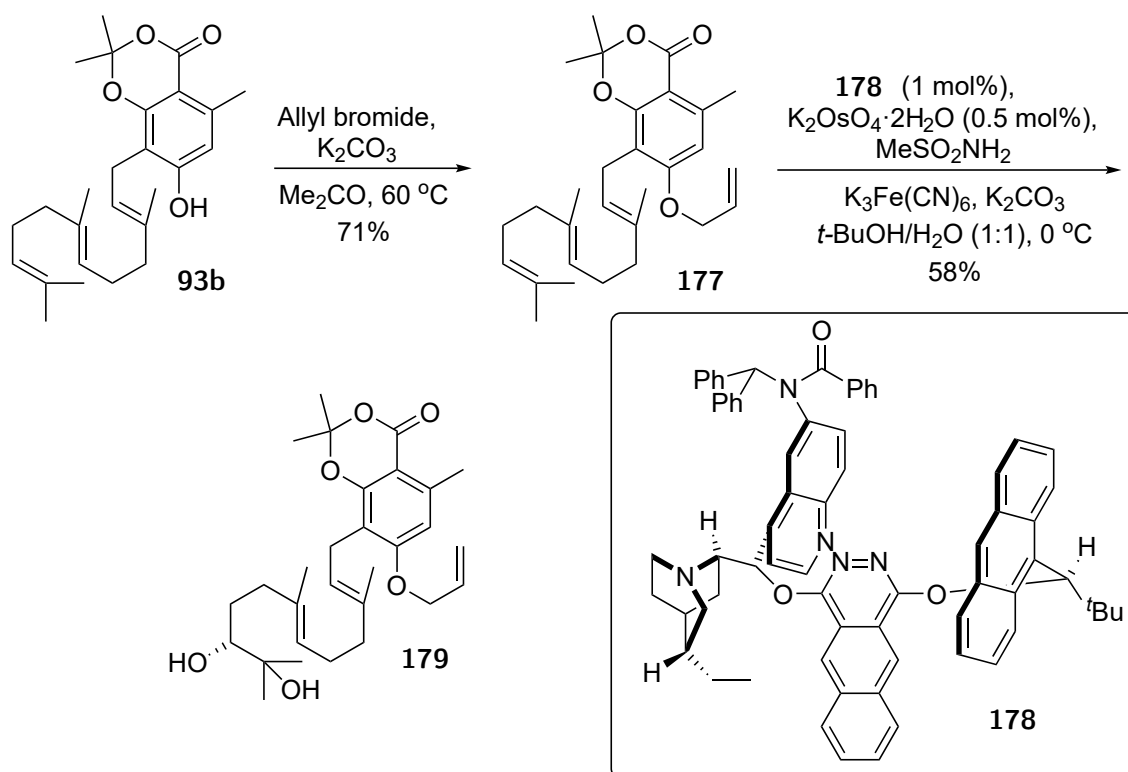


Figure 4.3: X-Ray crystal structure of (+)-hongoquercin A (**5**).

4.5 Total Synthesis of (+)-Hongoquercin B

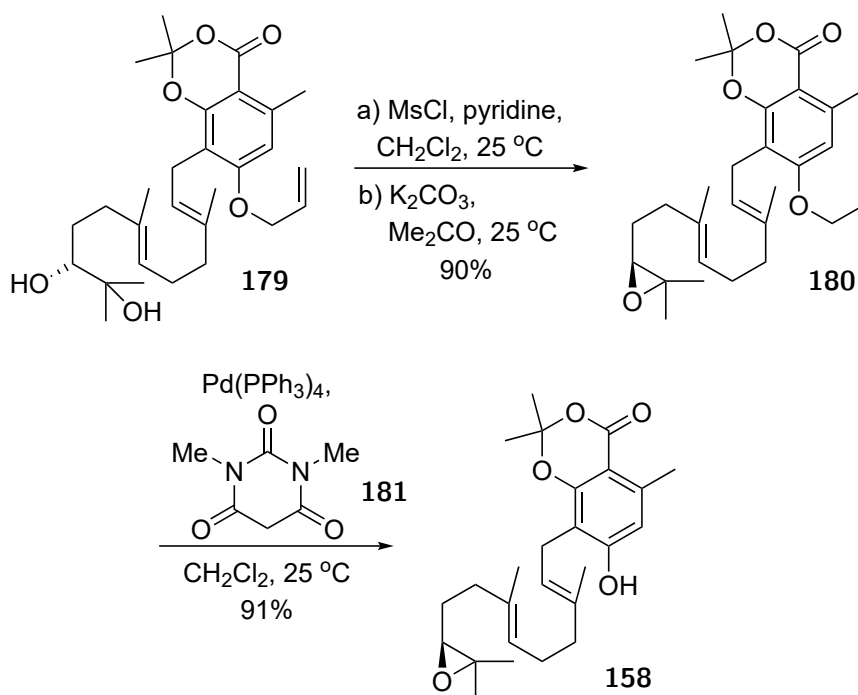
The synthesis of (+)-hongoquercin B (**6**), which utilised enantioselective epoxidation, was examined. Whilst previous work within the Barrett group had reported the synthesis of (+)-hongoquercin B ethyl ester **156** from the farnesyl derivative **158**,¹⁰³ the synthesis was reinvestigated with late-stage oxidation of the terminal alkene on the pendant farnesyl side chain, since this should greatly facilitate the synthesis and bioassay of a focused library of novel hongoquercin analogues with the late stage introduction of terpene structural diversity. In order to effect such electrophilic functionalisation of the terminal alkene unit, the phenol-directed oxidation has to be suppressed. It was envisioned that protection by phenol allylation would be suitable for this

purpose. One main advantage of the use of allyl protecting group is that the conditions during the deprotection step are mild and should not affect the reactive epoxide moiety.¹⁰⁹ Allylation of farnesyl resorcyate **93b** gave allyl ether **177** (71 %), which was subjected to dihydroxylation in the presence of the Corey dihydroquinidine ligand **178** thereby producing the (*R*)-diol **179** (58 %, 78 % brsm) (**Scheme 4.14**).¹¹⁰ Diol **179** was subsequently converted into the (*S*)-epoxide **180** (90 %) *via* mesylation and potassium carbonate mediated cyclisation. The allyl protecting group was selectively removed by reaction with dimethylbarbituric acid **181** catalysed by Pd(PPh₃)₄ to provide epoxide **158** (91 %) (**Scheme 4.15**).¹⁰⁹



Scheme 4.14: Synthesis of diol **179**.

Before the enantiomerically enriched epoxide **158** was carried forward in the synthesis, the key Lewis acid mediated polyene cyclisation was investigated with the racemic epoxide **158**, which was prepared by Dr. Daniel C. Elliott (**Table 4.2**). Exposure of epoxide **158** with BF₃·OEt₂ (**Entry 1**) resulted in polyene cyclisation to give meroterpenoid **159** (52 %), along with a mixture of other cyclised products including bicyclic ether **182** (7 %) and monocyclised products **183**

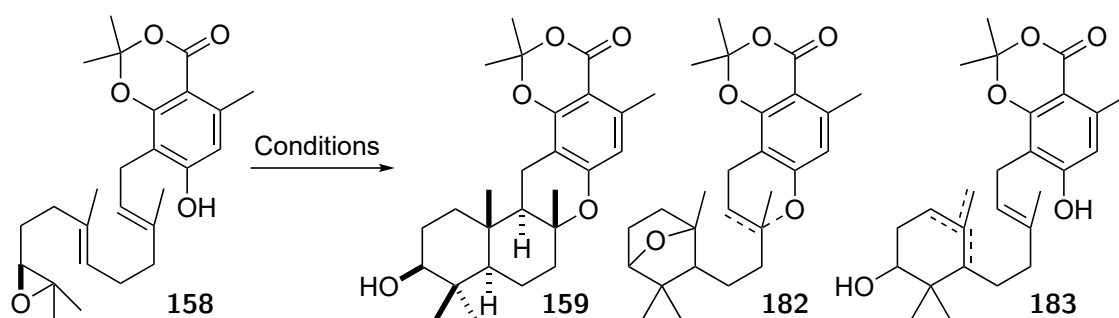


Scheme 4.15: Synthesis of epoxide **158**.

(13 %). However, the presence of other undesired products with similar R_f value complicated the purification process. As a result, the isolated yield was only 21 % after multiple purifications of the crude mixture by column chromatography. To circumvent this issue, the search for other Lewis acids as the initiator were further examined. It was found that the use of other promoters including SbCl₅, InBr₃, EtAlCl₂, SnCl₄ and FeBr₃ (**Entry 2 - 6**) only gave the meroterpenoid **159** in modest yields of 24 – 49 %. The major by-product in these experiments was found to be bicyclic ether **182** (6 – 38 %).

Further investigations with the use of other iron based Lewis acids showed more promising results. It was observed that the use of Fe(OTf)₃ provided the desired fully cyclised meroterpenoid **159** with an improved yield of 51 % with less formation of bicyclic ether **182** (19 %) and no monocyclised products **183** (**Entry 7**). Gratifyingly, the use of FeCl₃ and FeCl₃·6H₂O gave even better results, yielding meroterpenoid **159** (60 % and 65 % respectively), with only trace amount of bicyclic ether **182** (2 %) and no monocyclised products **183** (**Entry 8 - 9**).¹¹¹ It was proposed that FeCl₃·6H₂O could promote the cyclisation of epoxide **158** differently than traditional promoters *via* a combination of metal coordination and metal-mediated epoxide protonation.¹¹¹ Therefore,

After screening a variety of different Lewis acids with epoxide **158** and finding that ferric chloride hydrate was a superior Lewis acid catalyst to boron trifluoride etherate to provide meroterpenoid **159**, treatment of the enantiomerically enriched epoxide **158** with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ resulted in biomimetic cationic cyclisation to give meroterpenoid **159** (56 %, 92 % *ee* as determined by chiral HPLC) as a single diastereoisomer (**Scheme 4.16**). Saponification of meroterpenoid

Table 4.2: Conditions for Lewis acid initiated polyene cyclisation of epoxide **158**.

Entry	Lewis Acid ^a	Solvent	Temp (°C)	Time (min)	Yield ^b		
					159	182	183
1	BF ₃ ·OEt ₂	CH ₂ Cl ₂	-78	30	53 % ^c	7 %	11 %
2	SbCl ₅	CH ₂ Cl ₂	-78	20	49 %	38 %	6 %
3	InBr ₃	CH ₂ Cl ₂	25	30	24 %	13 %	2 %
4	EtAlCl ₂	CH ₂ Cl ₂	-78	20	27 %	26 %	0 %
5	SnCl ₄	CH ₂ Cl ₂	-78	30	34 %	6 %	0 %
6	FeBr ₃	CH ₂ Cl ₂	25	15	34 %	29 %	0 %
7	Fe(OTf) ₃	CH ₂ Cl ₂	25	15	51 %	19 %	0 %
8	FeCl ₃	CH ₂ Cl ₂	25	30	60 %	2 %	0 %
9	FeCl ₃ ·6H ₂ O	CH ₂ Cl ₂	25	15	65 %	2 %	0 %
10 ^d	FeCl ₃ ·6H ₂ O	CH ₂ Cl ₂	0	60	35 %	17 %	0 %
11	FeCl ₃ ·6H ₂ O	CH ₂ Cl ₂	-78	60	No reaction		
12	FeCl ₃ ·6H ₂ O	HFIP	25	15	50 %	0 %	0 %
13	FeCl ₃ ·6H ₂ O	CH ₃ NO ₂	25	15	65 % ^e	0 %	0 %

a) 3 Equivalents of Lewis acid was used in the reaction.

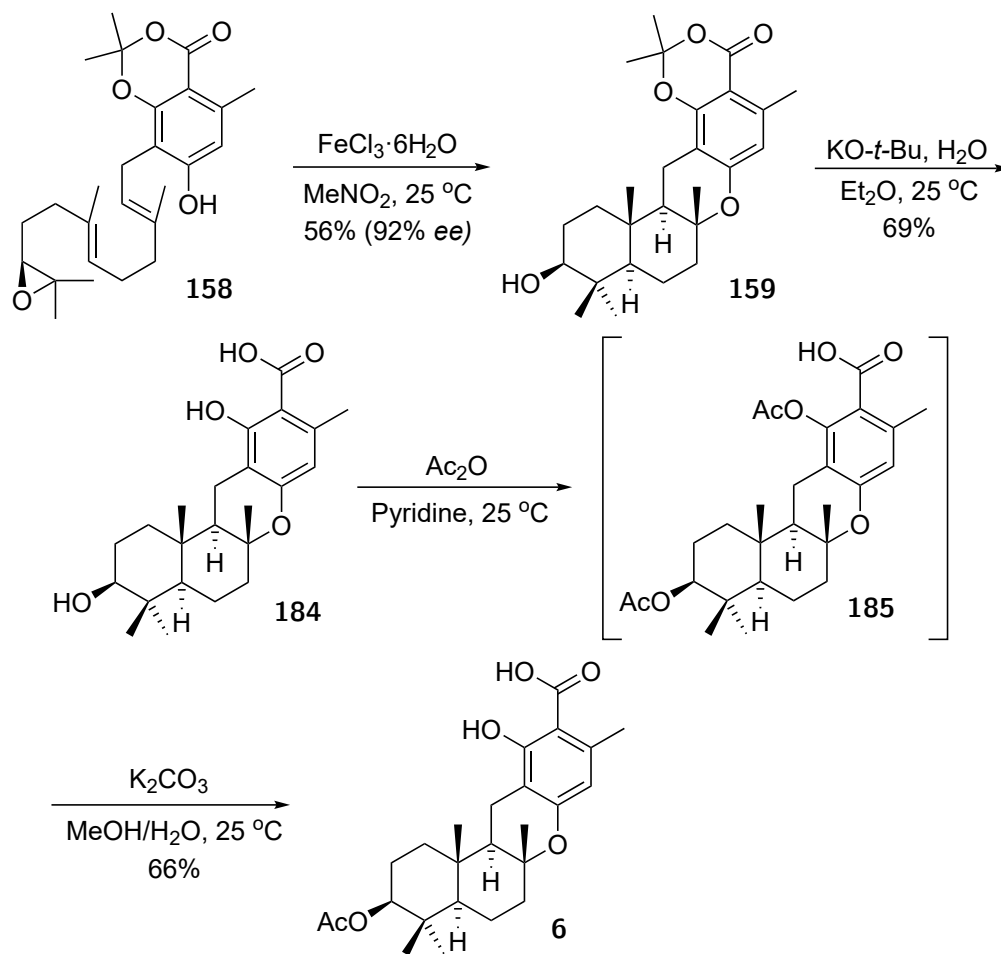
b) Determined by ¹H NMR spectroscopy using pentachloroethane (1 equiv.) as internal standard.

c) 21 % isolated yield after column chromatography.

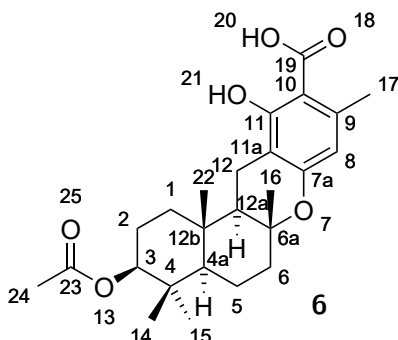
d) Incomplete conversion and 30 % of epoxide **158** was unconsumed.

e) 53 % isolated yield after column chromatography.

159 gave acid **184** (69 %),⁹² which was subjected to acetylation to provide diacetate **185**. Subsequent selective deacetylation of the phenolic acetate gave (+)-hongoquercin B (**6**) (66 %) with an overall yield of 4 % over eleven steps. The analytical data for this synthetic material were in full agreement with that reported for the isolated natural product (**Table 4.3**).¹¹



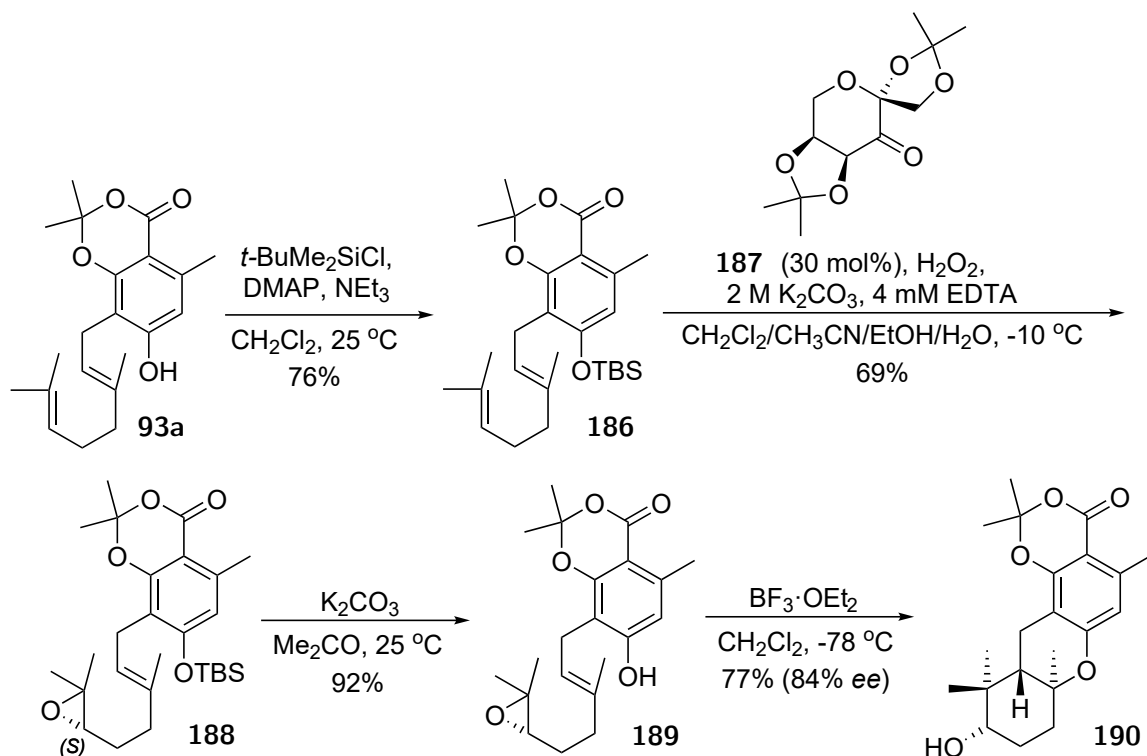
Scheme 4.16: Synthesis of (+)-hongoquercin B (**6**).

Table 4.3: Comparison of ^1H and ^{13}C (+)-hongoquercin B (**6**) NMR data in CDCl_3 with literature.

Position	(+)-Hongoquercin B (6)		Literature data ¹¹		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	37.1	ax: 1.24 – 1.18 (m) eq: 1.86 (dt, 13.3, 3.6)	37.1	ax: 1.19 (m, 13.1) eq: 1.86 (ddd, 13.1, 3.1, 3.1)	0	0
2	23.5	ax: 1.81 – 1.60 (m) eq: 1.81 – 1.60 (m)	23.5	ax: 1.65 (m) eq: 1.75 (m)	0	
3	80.4	4.52 (dd, 11.6, 4.7)	80.6	4.53 (dd, 11.2, 4.9)	- 0.2	
4	36.6		36.7		- 0.1	
4a	55.1	1.10 (dd, 12.1, 2.2)	55.2	1.10 (d, 11.6)	- 0.1	0
5	19.3	ax: 1.81 – 1.60 (m) eq: 1.47 – 1.42 (m)	19.3	ax: 1.79 (m, 11.6) eq: 1.43 (m, 3.4)	0	
6	40.6	ax: 1.81 – 1.60 (m) eq: 2.13 – 2.07 (m)	40.7	ax: 1.72 (m, 12.8) eq: 2.11 (m, 12.8, 3.4)	- 0.1	
6a	78.0		78.0		0	
7a	158.6		158.7		- 0.1	
8	112.6	6.21 (s)	112.7	6.21 (s)	- 0.1	0
9	141.6		141.6		0	
10	107.7		107.8		- 0.1	
11	163.8		163.9		- 0.1	
11a	102.7		102.7		0	
12	16.8	ax: 2.30 (dd, 16.8, 13.1) eq: 2.66 (dd, 16.8, 4.8)	16.8	ax: 2.30 (dd, 16.7, 12.9) eq: 2.66 (dd, 16.7, 4.3)	0	0
12a	51.3	1.53 (dd, 13.1, 5.0)	51.3	1.53 (dd, 12.9, 4.3)	0	0
12b	37.7		37.8		- 0.1	
14	16.7	0.90 (s)	16.7	0.90 (s)	0	0
15	28.1	0.91 (s)	28.1	0.91 (s)	0	0
16	20.7	1.20 (s)	20.7	1.20 (s)	0	0
17	24.1	2.52 (s)	24.1	2.52 (s)	0	0
19	175.9		176.0		- 0.1	
21		11.85 (s)		11.82 (s)		+ 0.03
22	15.0	0.96 (s)	15.0	0.96 (s)	0	0
23	171.0		171.1		- 0.1	
24	21.3	2.07 (s)	21.3	2.06 (s)	0	+ 0.01

4.6 Synthesis of the Hongoquercin Analogues

Additional meroterpenoids analogues were prepared *via* epoxidation and halogenations. Firstly, the geranyl-substituted resorcyate **93a** was protected as its silyl ether **186** (76 %) and epoxidised with the dioxirane derived from the Shi chiral ketone **187** to give epoxide **188** (69 %).^{112–114} Subsequent deprotection gave epoxide **189** (92 %), which was cyclised using boron trifluoride etherate to give meroterpenoid **190** (77 %, 84 % *ee* as determined by chiral HPLC) as a single diastereoisomer. The pure (*S*)-enantiomer of meroterpenoid **190** (98 % *ee* as determined by chiral HPLC) was obtained by recrystallisation from *n*-hexane to crystallise out the racemic crystals (**Scheme 4.17**). The structure was additionally characterised by X-ray crystallography (**Figure 4.5**).



Scheme 4.17: Synthesis of meroterpenoid **190**.

Secondly, the halonium-induced polyene cyclisation of the resorcyates to produce additional analogues was examined.¹¹⁵ Reaction of the geranyl resorcyate **93a** with the Snyder reagents $\text{Et}_2\text{SBr}\cdot\text{SbCl}_5\text{Br}$ (BDSB, **191**) and $(\text{Et}_2\text{SI})_2\text{Cl}\cdot\text{SbCl}_6$ (IDSI, **192**) resulted in bromo- and iodo-

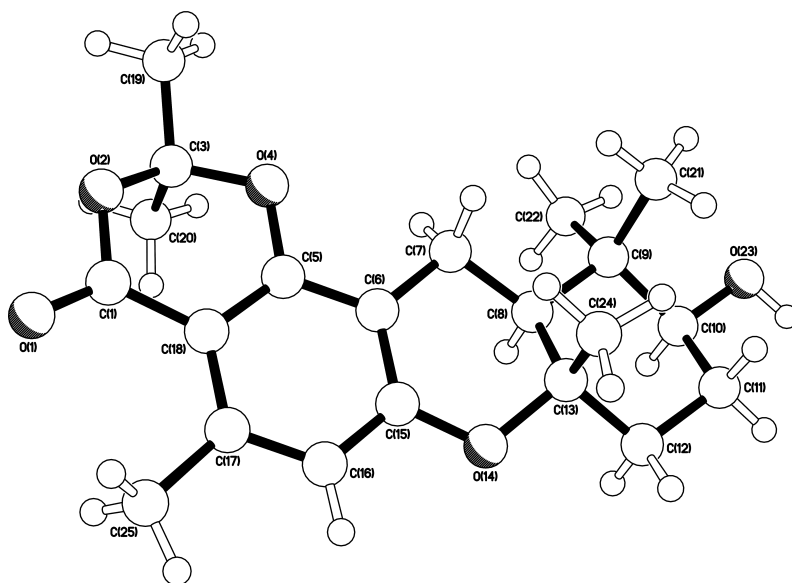


Figure 4.5: X-Ray crystal structure of meroterpenoid **190**.

cyclisations to produce the racemic bromo-meroterpenoid **193a** (64 %) (**Scheme 4.18**) and racemic iodo-meroterpenoid **194a** (88 %) (**Scheme 4.19**) as single diastereoisomers, respectively. Racemic bromide **193b** (45 %, 2 : 1 *dr*) and racemic iodide **194b** (54 %, 2 : 1 *dr*) were also successfully synthesised from farnesyl-substituted resorcyate **93b** using the BDSB **191** (**Scheme 4.18**) and IDSI **192** (**Scheme 4.19**) mediated halocyclisations. All the structures were unambiguously confirmed by single X-ray crystallography.

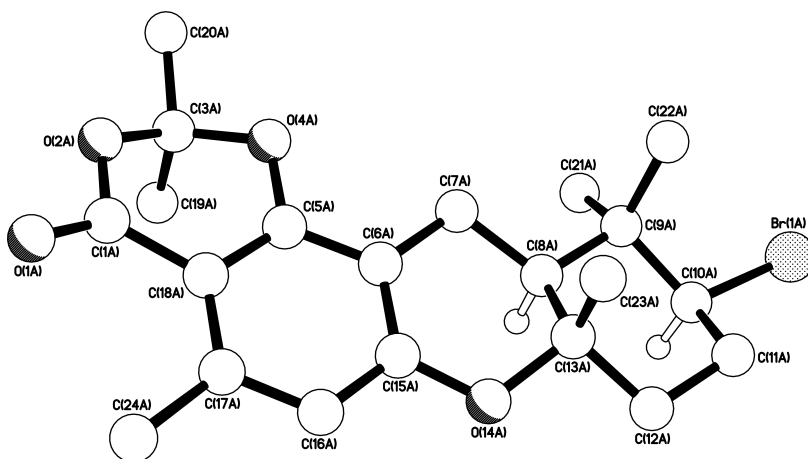


Figure 4.6: X-Ray crystal structure of bromide **193a**.

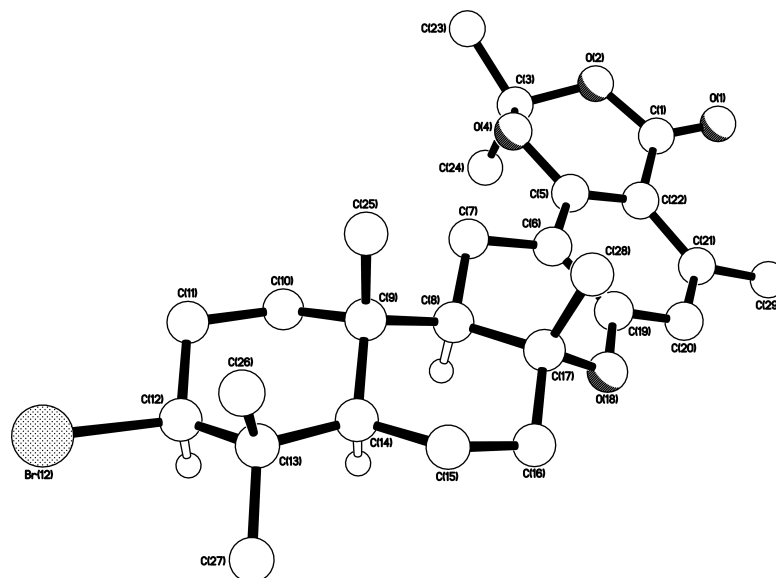


Figure 4.7: X-Ray crystal structure of bromide **193b**.

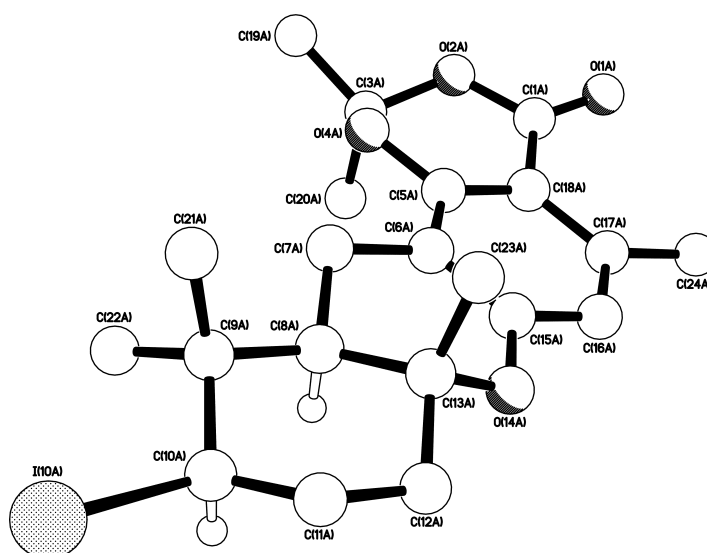
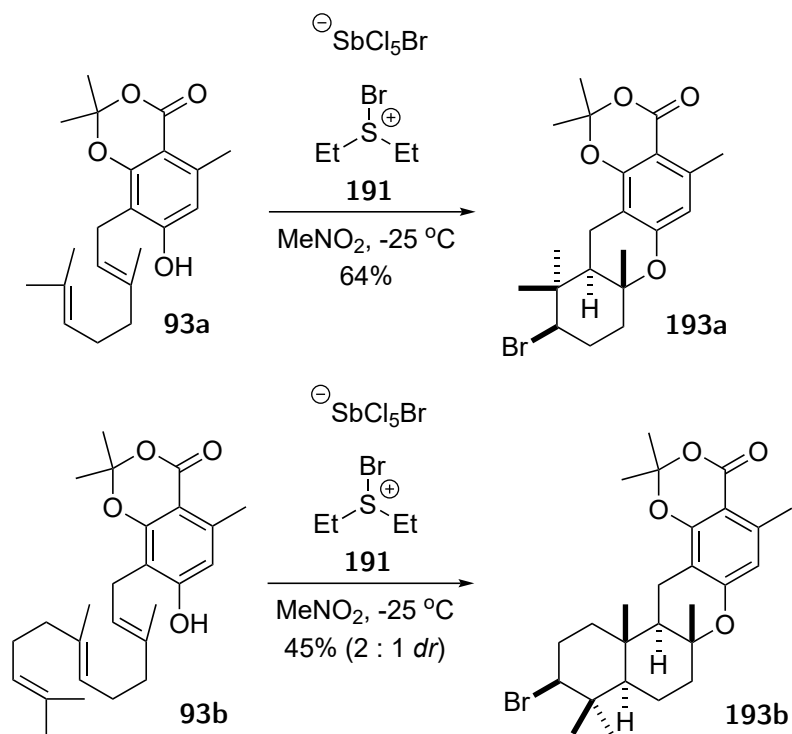
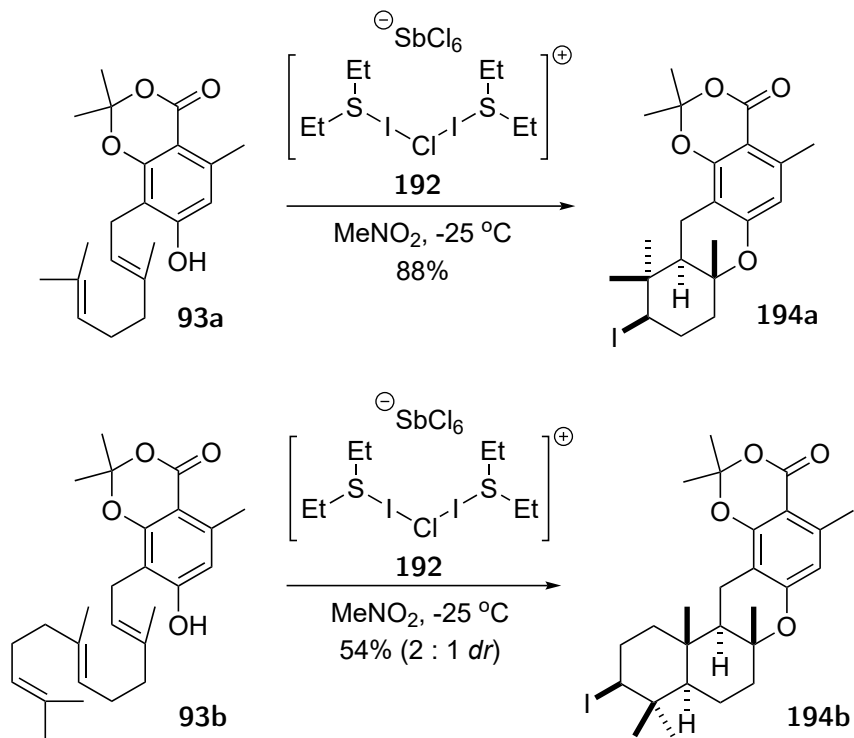


Figure 4.8: X-Ray crystal structure of iodide **194a**.

4.6. SYNTHESIS OF THE HONGOQUERCIN ANALOGUES



Scheme 4.18: Synthesis of bromo-meroterpenoids **193**.



Scheme 4.19: Synthesis of bromo-meroterpenoids **194**.

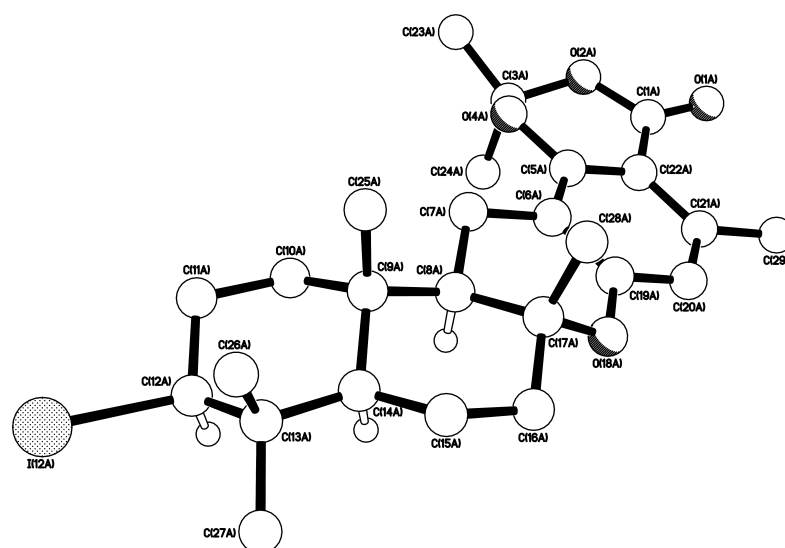
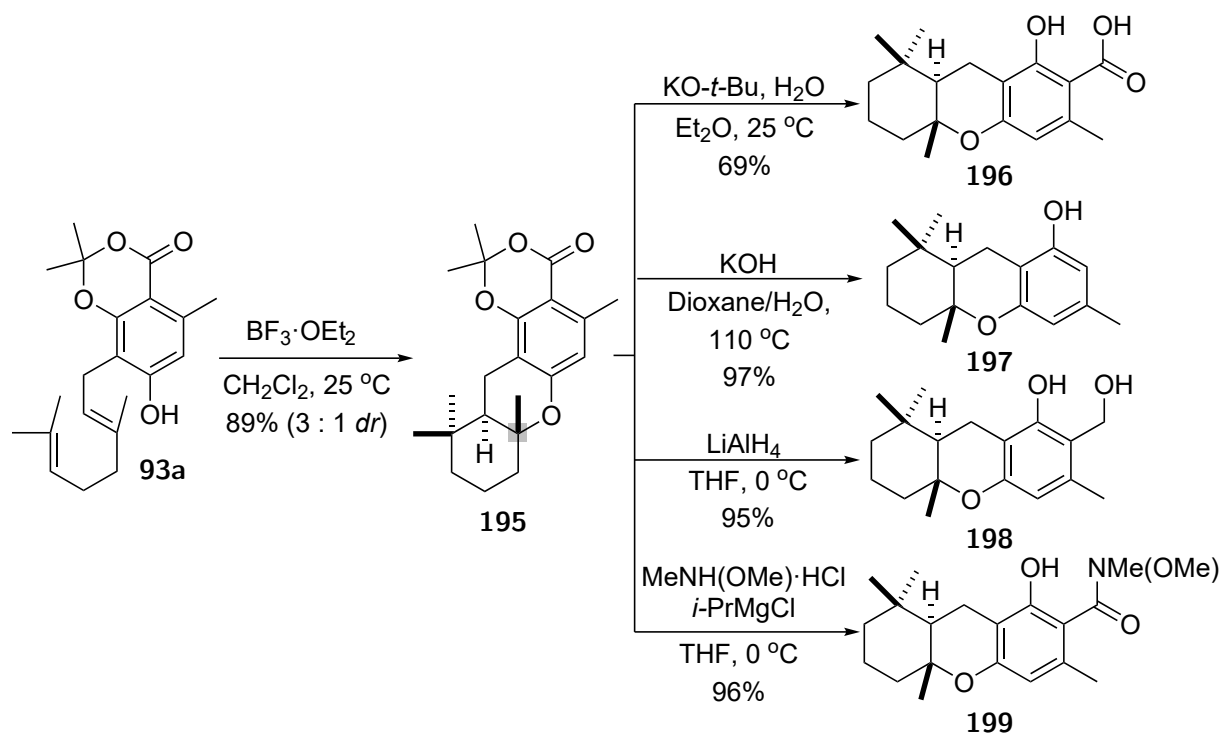


Figure 4.9: X-Ray crystal structure of iodide **194b**.

The 2,2-dimethyl-1,3-benzodioxan-4-one moiety of the meroterpenoids intermediates was also used in alternative derivatisation reactions (**Scheme 4.20**). Thus, reaction of the geranyl-substituted resorcyate **93a** with boron trifluoride etherate at 25 °C gave the racemic meroterpenoid **195** (89 %, 3 : 1 *dr*) and the desired pure *trans*-fused ring product was obtained by recrystallisation from *n*-hexane. The structure of meroterpenoid **195** was unambiguously determined by X-ray crystallography (**Figure 4.10**). Saponification of meroterpenoid **195** gave racemic carboxylic acid **196** (69 %) while hydrolytic decarboxylation gave racemic phenol **197** (97 %). Furthermore, reduction of meroterpenoid **195** with LiAlH_4 gave racemic diol **198** (95 %) and racemic Weinreb amide **199** (96 %) was obtained following Grignard reagent mediated amidation.¹¹⁶



Scheme 4.20: Synthesis and functionalisations of meroterpenoid **195**.

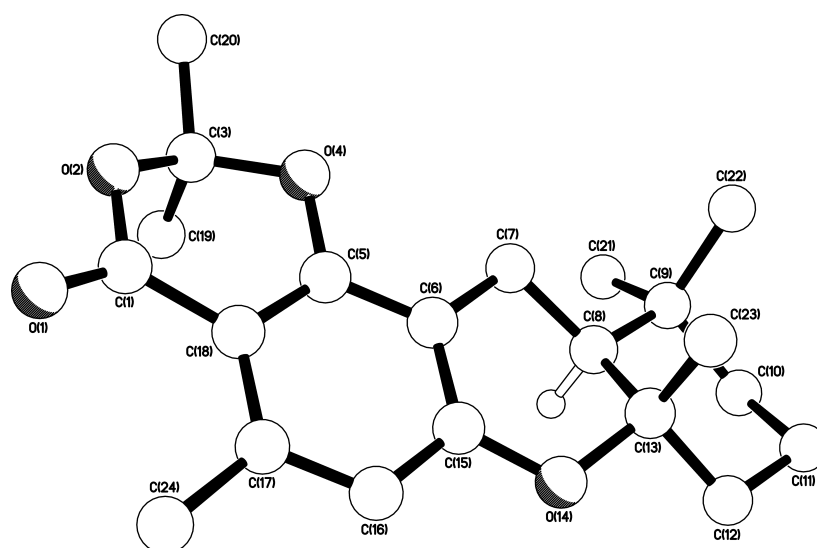


Figure 4.10: X-Ray crystal structure of meroterpenoid **195**.

4.7 Biological Activity of the Synthetic Meroterpenoids

Profiling of the synthetic meroterpenoids produced in this project revealed two biologically active compounds – carboxylic acid **196** and iodide **194b** (Table 4.4). It was found that carboxylic acid **196** could act as an antagonist against several receptors including 5-HT_{1A}, A₁, α_{2A} , β_2 , β_1 and M₂. In particular, it showed strong inhibition against A₁, β_1 and M₂ with an IC₅₀ value of 2.15, 1.08 and 2.23 μ M, respectively. On the other hand, iodide **194b** was found to be able to inhibit P38 (IC₅₀ = 4.93 μ M), a signaling pathway used in response to extracellular stimuli including heat, osmotic shock, inflammatory cytokines and UV light.¹¹⁷

Table 4.4: Biological profiling of meroterpenoids **196** and **194b**.

	Assay	Carboxylic acid 196	Iodide 194b
		IC ₅₀ (μ M)	IC ₅₀ (μ M)
TR-FRET Kinome	P38	>10	4.93
Receptor Antagonist	5-HT _{1A}	8.83	>10
	A ₁	2.15	>10
	α_{2A}	5.64	>10
	β_2	8.83	>10
	β_1	1.08	>10
	M ₂	2.23	>10

4.8 Conclusion

In conclusion, the total syntheses of (+)-hongoquercin A (**5**) and B (**6**) were completed in five and eleven steps respectively, with an overall yield of 20 % and 4 % *via* a dual biomimetic approach involving sequential polyketide and late stage electrophile mediated polyene cyclisations. Several analogues were synthesised by epoxidation or BDSB **191** and IDSI **192** mediated halocyclisations. The meroterpenoids were additionally functionalised using saponification, hydrolytic decarboxylation, reduction and Grignard reagent mediated amidation reactions.

AUSTALIDES

The first total synthesis of five austalide natural products ($\pm$)-17*S*-dihydroaustalide K, ($\pm$)-austalide K, ($\pm$)-13-deacetoxyaustalide I, ($\pm$)-austalide P and ($\pm$)-13-deoxyaustalide Q acid were accomplished *via* a series of biomimetic transformations. Key steps involved polyketide aromatisation of a *trans, trans*-farnesol derived β , δ -diketo-dioxinone into the corresponding β -resorcylate, followed by titanium(III)-mediated reductive radical cyclisation of an epoxide to furnish the drimene core. Subsequent phenyl-selenonium ion induced diastereoselective cyclisation of the drimene completed the essential carbon framework of the austalides to access ($\pm$)-17*S*-dihydroaustalide K, ($\pm$)-austalide K and ($\pm$)-13-deacetoxyaustalide I *via* sequential oxidations. Furthermore, ($\pm$)-13-deacetoxyaustalide I could serve as a common intermediate to be derivatised into other related natural products ($\pm$)-austalide P and ($\pm$)-13-deoxyaustalide Q acid by functionalising the cyclic lactone moiety.

5.1 Isolation, Biosynthesis and Biological Evaluation of the Austalides

The austalides (**Figure 5.1**) are a diverse group of meroterpenoid natural products featuring a *trans, transoid, cis*-fused ring system. The first twelve members were isolated from the whole maize cultures of *Aspergillus ustus*, strain MRC 1163 in the 1980s.^{9,10,118,119} Additional new

members were isolated recently from the metabolites of fungus *Aspergillus aureolatus*, *Penicillium thomii* and *Penicillium lividum*.^{13,14,120–122} Initial profiling of the isolated natural products showed them to possess a broad spectrum of bioactivity such as cytotoxic and, antibacterial properties as well as inhibiting *endo*-1,3- β -D-glucanase.

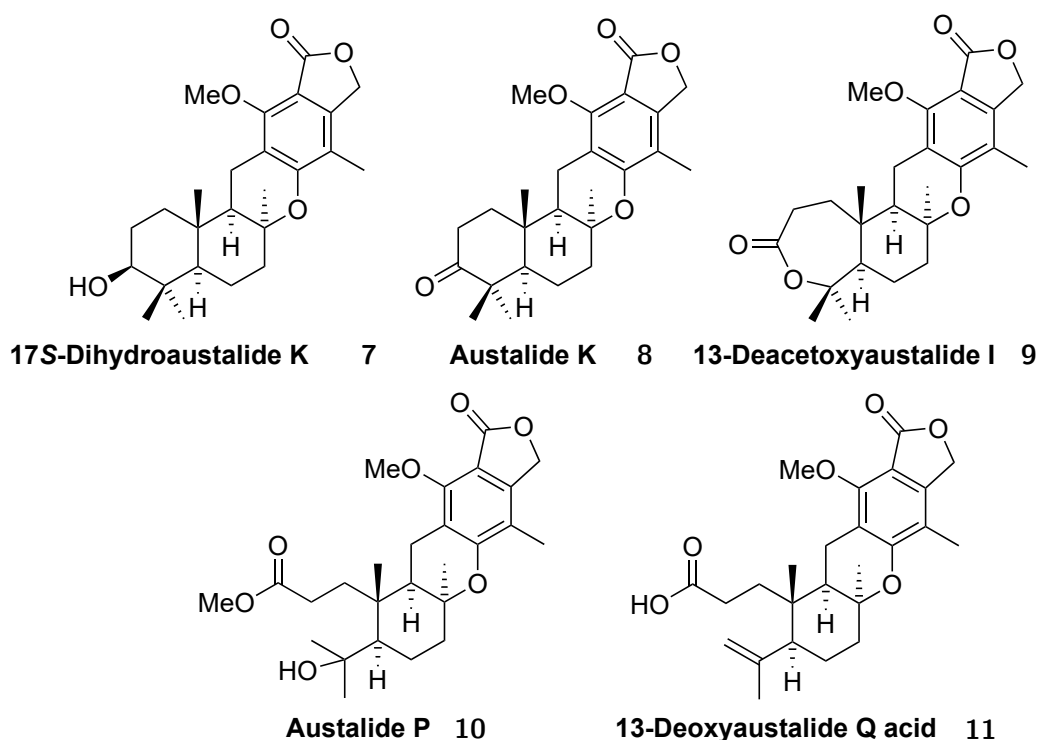
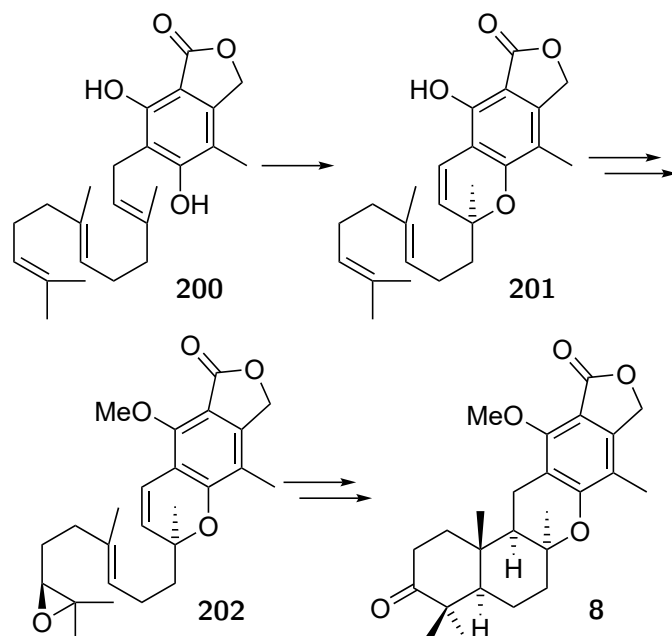


Figure 5.1: Representative austalide natural products.

The biosynthesis of austalide K (**8**) was first proposed in 1987.¹²³ It was postulated that 6-[(*2E,6E*)farnesyl]-5,7-dihydroxy-4-methylphthalide (**200**), a key intermediate in the biogenesis of mycophenolic acid, first undergoes cyclisation *via* a stereospecific attack of the phenol on the 11*si*, 21*si*-face of the alkene to provide chromene **201** (**Scheme 5.1**). Subsequent epoxidation of the terminal alkene gives epoxide **202**, which could undergo cationic polyene cyclisation to furnish the *trans*, *transoid*, *cis*-fused rings motif. However, further investigations on the fate of the hydrogen atom incorporation using of (¹³C, ²H)- and ²H-labelled mevalonolactones provided evidence to exclude the intermediacy of chromene **201**.¹²⁴ This has led to an alternative proposal on the biosynthesis of the austalides involving polyene cyclisation of epoxide **203** to generate carbocation intermediate **204**, followed by enzyme controlled stereospecific cyclisation of the

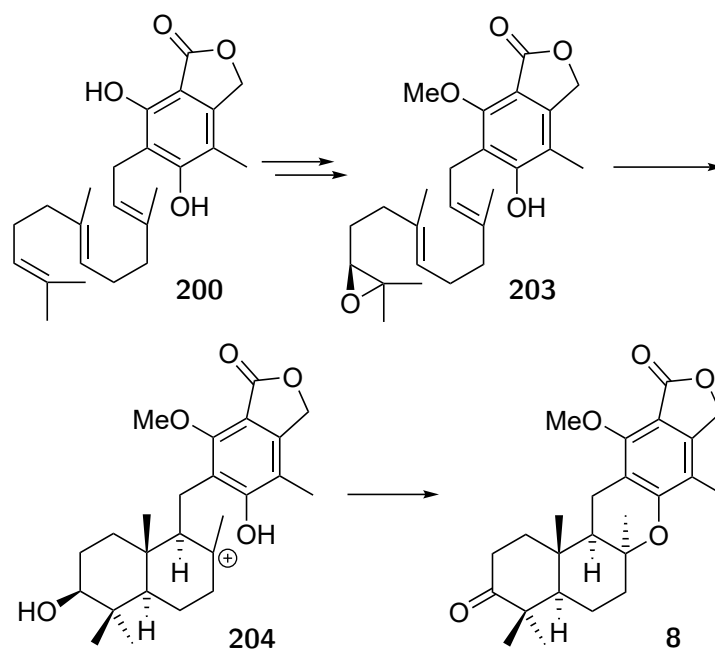
phenolic oxygen to furnish the chromane structure with the *cis*-fused ring (**Scheme 5.2**). It is important to note that concerted polyene cyclisation of epoxide **203** would lead to the formation of a stereoisomer of austalide K (**8**), featuring an all *trans*-fused ring systems.



Scheme 5.1: First proposed biosynthesis of austalides.

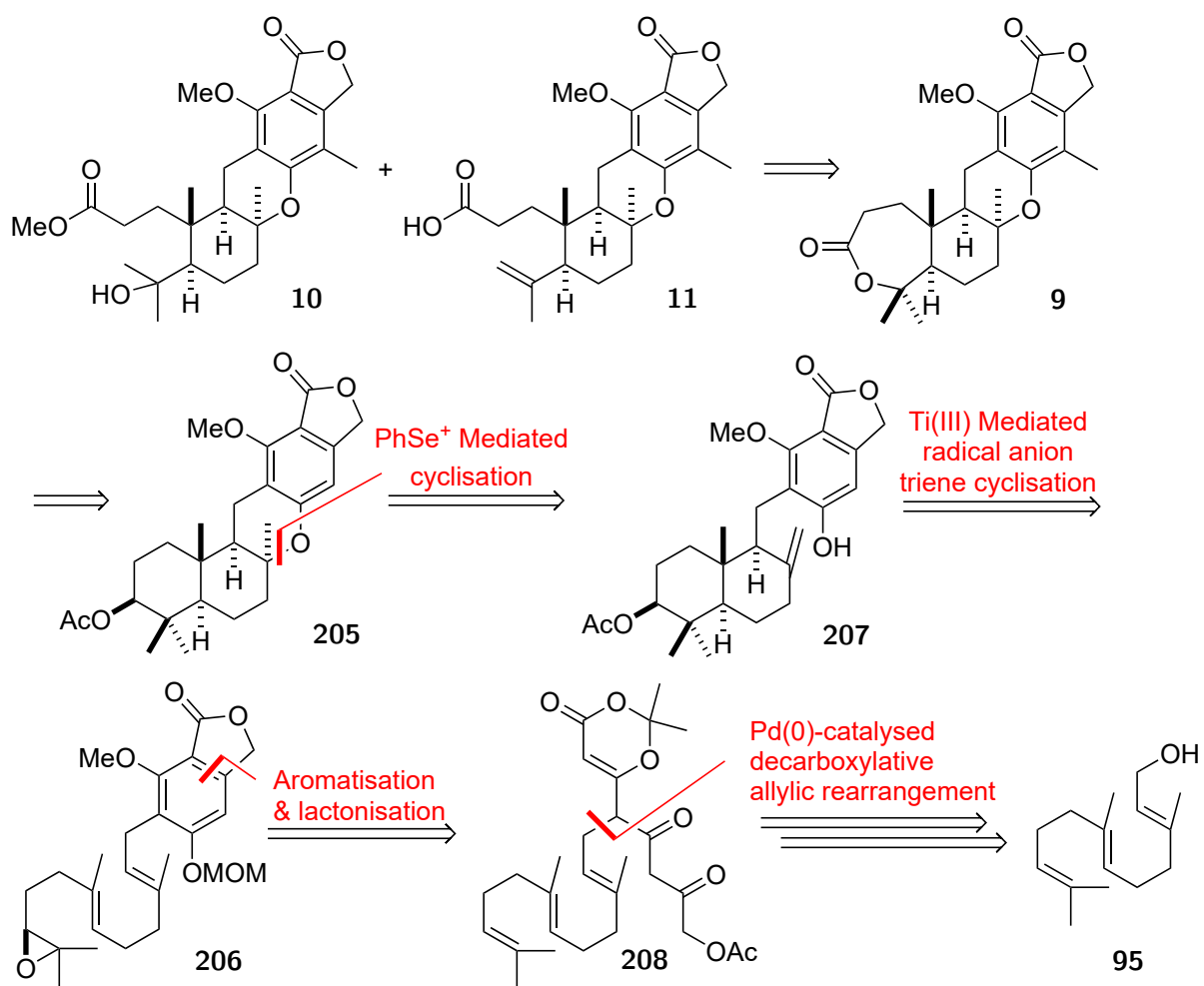
5.2 Retrosynthetic Analysis of the Austalides

To date, there is no reported total synthesis to the aforementioned austalide natural products. The only related synthetic study in the austalides was conducted by Paquette and co-workers on (-)-austalide B in 1994.^{125,126} Therefore, it is considered that austalide P (**10**) and 13-deoxyaustalide Q acid (**11**) could be derived from 13-deacetoxyaustalide I (**9**) by functionalising the cyclic lactone moiety (**Scheme 5.3**). Late stage arene methylation and deacetylation of acetate **205** would allow access to 17*S*-dihydroaustalide K (**7**), followed by sequential oxidations of the alcohol functionality to give austalide K (**8**) and 13-deacetoxyaustalide I (**9**). In order to construct the *trans*, *transoid*, *cis*-fused rings motif, it is anticipated that would be possible with the use of two sequential diastereoselective cyclisations. Firstly, a titanium(III)-mediated radical triene cyclisation of epoxide **206** would give drimene **207** to furnish the first *trans*-fused ring with an



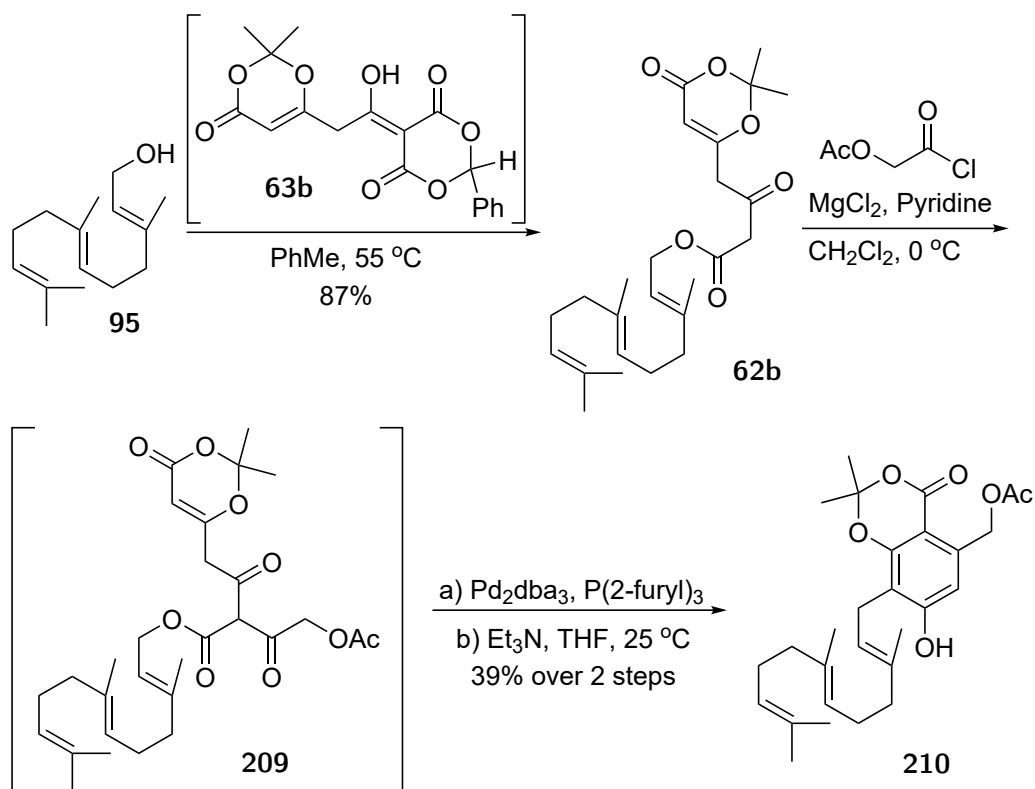
Scheme 5.2: Revised proposed biosynthesis of austalides.

exocyclic alkene, acting as an equivalent of carbocation **204**. Subsequent phenyl-selenonium ion-induced diastereoselective cyclisation of the drimene **207** should provide the desired *cis*-fused ring to complete the essential carbon framework. Epoxide **206** should be available from a farnesol derived β -resorcyate, which was accessible *via* sequential cycloaromatization and lactonization of β , δ -diketo dioxinone **208**. Dioxinone β , δ -diketo-ester **209**, synthesised *via* *C*-acylation of dioxinone β -keto-ester **62b**, should undergo palladium(0)-catalysed decarboxylative allylic rearrangement to provide β , δ -diketo-dioxinone **208**. Finally, dioxinone β -keto-ester **62b** is available from trapping a dioxinone-acylketene **31** with *trans, trans*-farnesol **95**.

**Scheme 5.3:** Retrosynthetic analysis of the austalides.

5.3 Total Synthesis of the Austalides

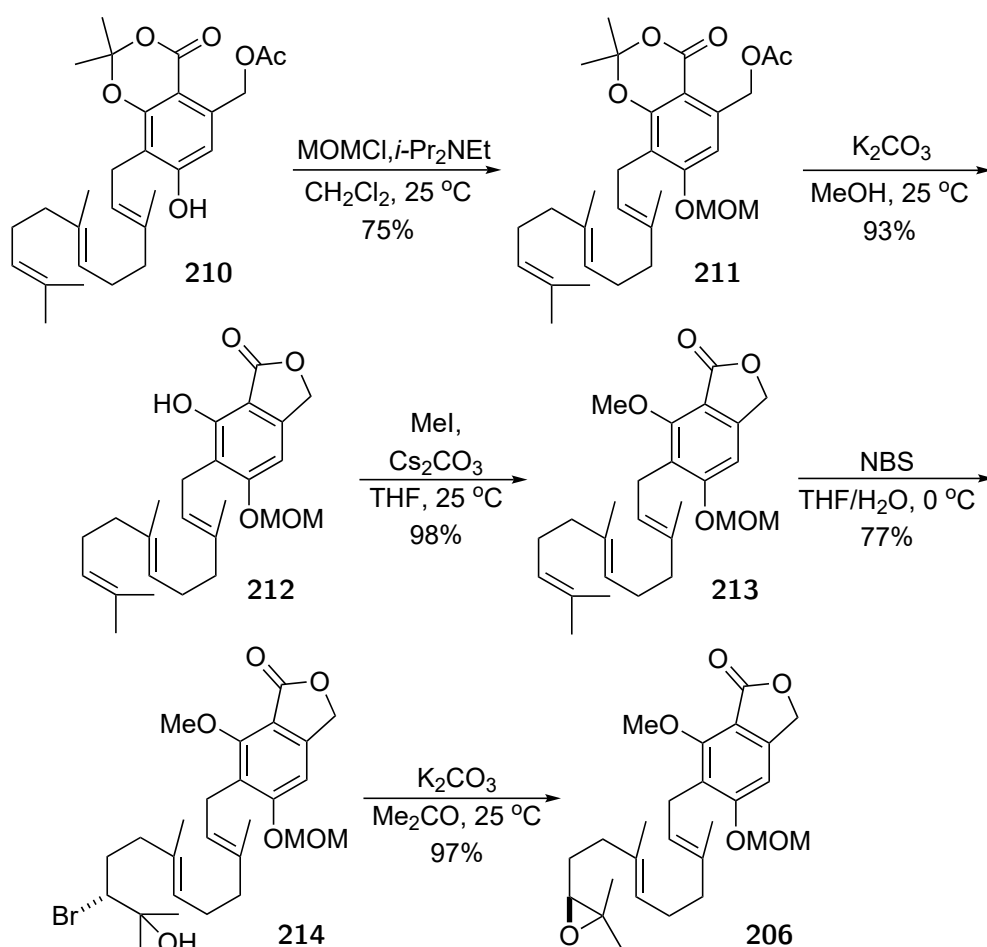
The synthesis of β -resorcyate **210** (Scheme 5.4) was undertaken by trapping dioxinone-acylketene **31**, generated *in situ* from 4,6-dione-keto-dioxanone **63b**, with *trans, trans*-farnesol **95** to provide dioxinone β -keto-ester **62b** (87 %). Subsequent magnesium chloride mediated regioselective *C*-acylation of the dioxinone β -keto-ester **62b** with acetoxyacetyl chloride gave dioxinone β , δ -diketo-ester **209**. The resulting dioxinone β , δ -diketo-ester **209** was allowed to react with a catalytic amount of $\text{Pd}_2(\text{dba})_3$ in the presence of tri-(2-furyl)phosphine to induce a decarboxylative allylic rearrangement to provide β , δ -diketo-dioxinone **208**, which was directly aromatised by treatment with triethyl amine to provide β -resorcyate **210** (39 % over 2 steps from dioxinone β -keto-ester **62b**).



Scheme 5.4: Synthesis of terpene resorcyate **210**.

With the β -resorcyate **210** in hand, attention was focused on the functionalisation of the aromatic core as well as installing the terminal epoxide for the triene cyclisation reaction (Scheme 5.5). The phenol group of β -resorcyate **210** was first protected as the MOM ether **211**

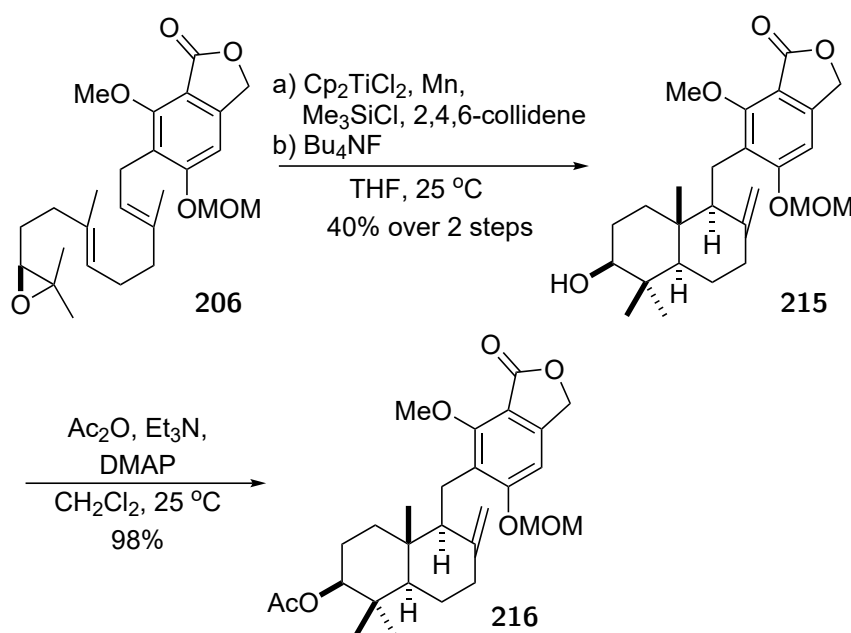
(75 %), followed by lactonisation under basic condition to give phthalide **212** (93 %). Methylation of the resulting phenol of phthalide **212** gave methyl ether **213** (98 %), which was allowed to react with *N*-bromosuccinimide with regioselective electrophilic addition at the terminal alkene of the terpene chain to form bromohydrin **214** (77 %). Subsequent potassium carbonate-mediated cyclisation of bromohydrin **214** gave the desired racemic epoxide **206** (97 %).



Scheme 5.5: Synthesis of epoxide **206**.

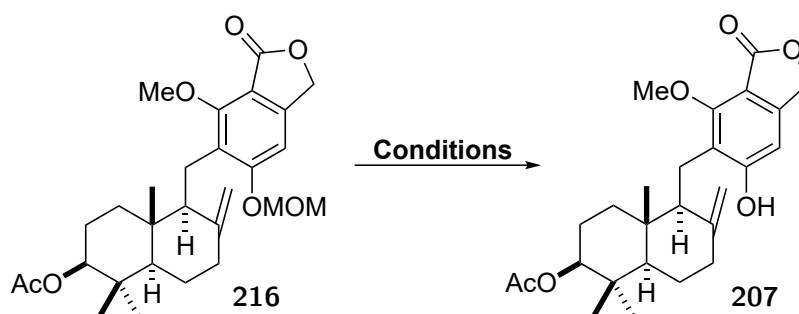
Next, the terpene side chain of epoxide **206** was functionalised (**Scheme 5.6**). Treatment of the epoxide **206** with a titanocene(III) catalyst, generated from titanocene(IV) dichloride, manganese, trimethylsilyl chloride and 2,4,6-collidine,¹²⁷ initiated a radical anion cascade cyclisation, thereby producing alcohol **215** (40 % over 2 steps) after desilylation with tetrabutylammonium fluoride. Acetylation of the alcohol **215** yielded acetate **216** (98 %), which was then subjected to various

conditions for the deprotection of the MOM group to produce the key phenol **207** (Table 5.1). It was found that p -TsOH·H₂O, acting as an acid catalyst, resulted in MOM deprotection and provide the desired phenol **207** (63 %) (Entry 1). However, another attempt under longer reaction time diminished the isolated yield of phenol **207** (45 %) as a result of an undesired cyclisation of phenol **207** into a diastereoisomer of meroterpenoid **205** (Entry 2). Therefore, other conditions were examined in the quest of minimising such side reaction to yield phenol **207** more consistently. The use of zinc bromide as a mild Lewis acid (Entry 3) and NaHSO₄·SiO₂ (Entry 4) both resulted in a complex mixture of unidentified cyclised products.^{128,129} Fortunately, the use of PPTS (pK_a ~5.21), a milder acid in comparison to p -TsOH·H₂O (pK_a ~-2.8), was able to selectively deprotect the phenolic MOM group to produce phenol **207** (86 % – 93 %) consistently without causing any subsequent cyclisation (Entry 5 – 7) even at prolonged reaction time and elevated temperature.



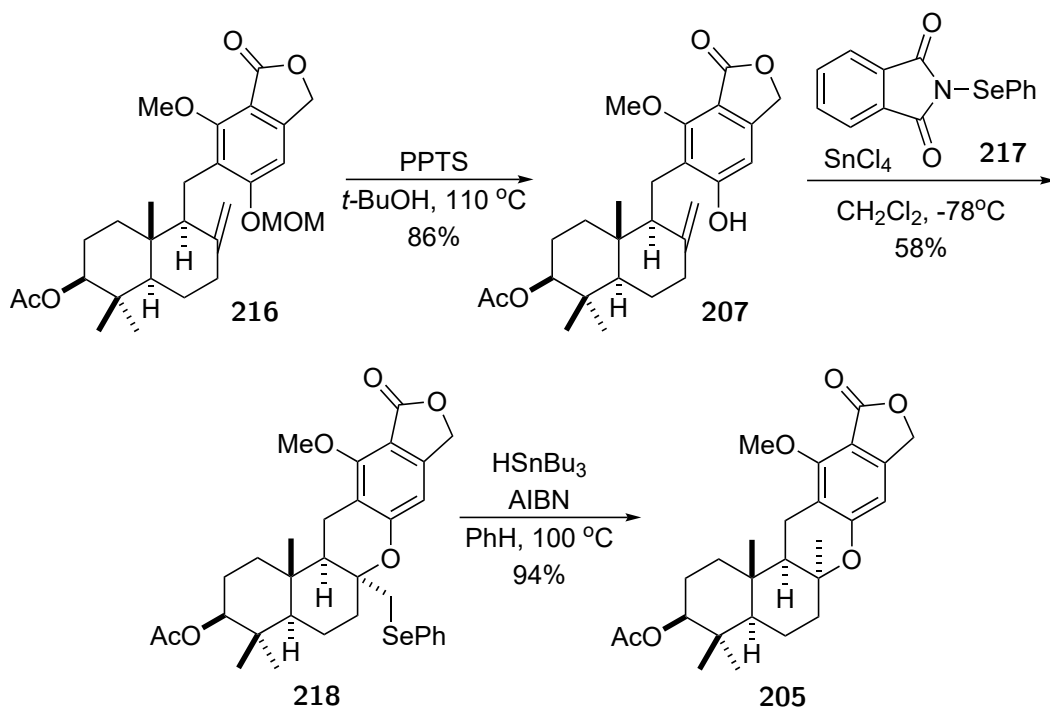
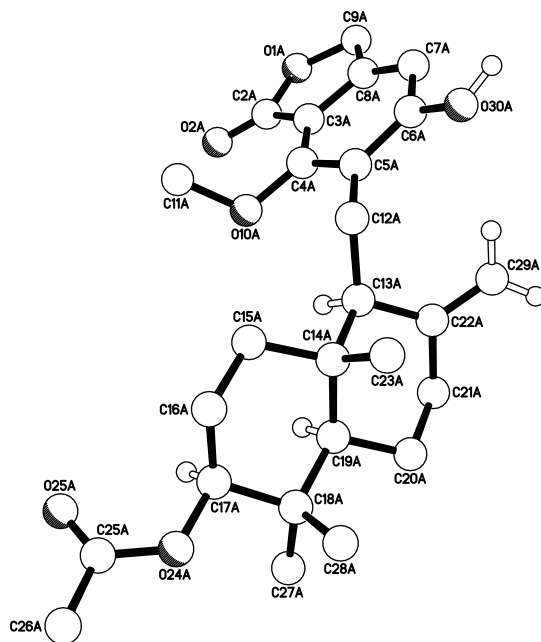
Scheme 5.6: Synthesis of acetate **216**.

Thus, PPTS and t -BuOH mediated phenolic MOM deprotection of acetate **216** furnished phenol **207** (86 %) (Scheme 5.7). The relative stereochemistry of phenol **207** was unambiguously determined by X-ray crystallography, confirming the formation of the *trans*-fused ring system (Figure 5.2). Reaction of N -(phenylseleno)phthalimide **217** and stannic chloride with phenol **207** resulted in the formation of a selenonium ion intermediate, which was intramolecularly

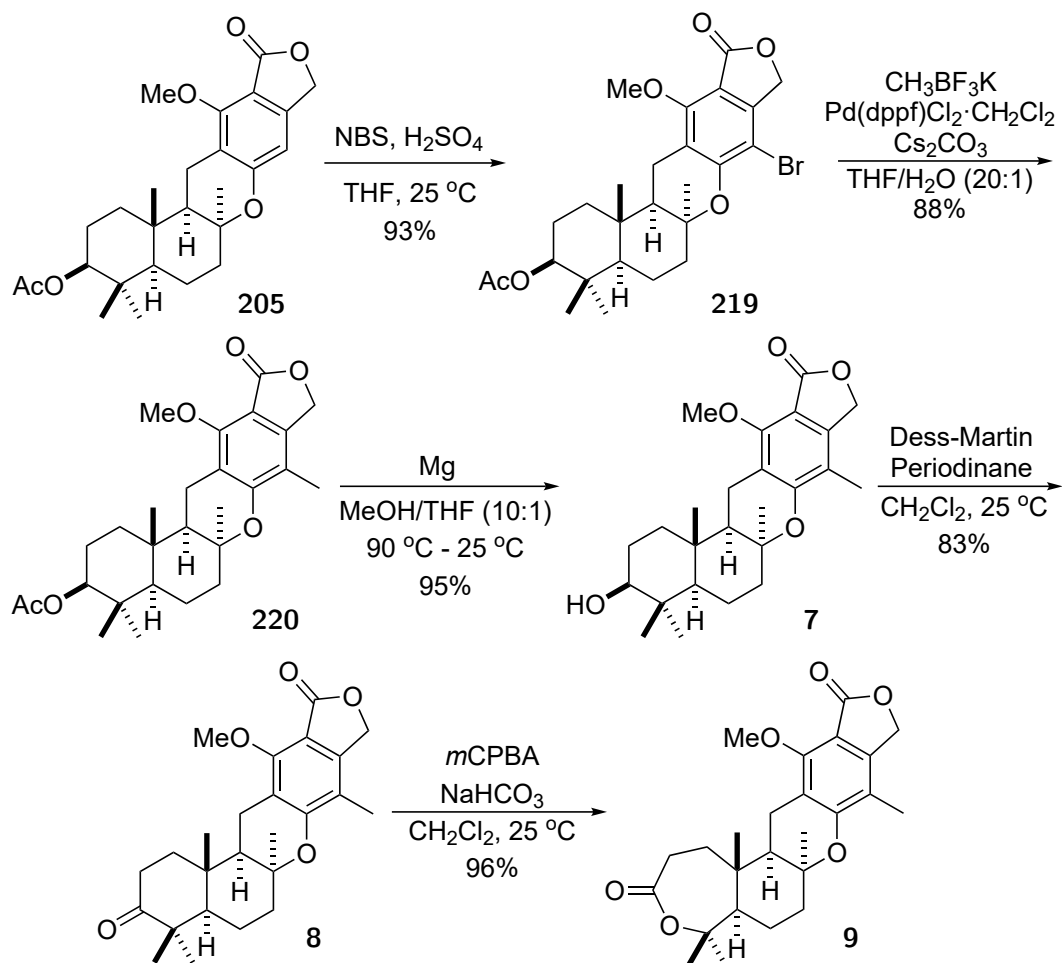
Table 5.1: MOM deprotection of acetate **216**.

Entry	Conditions	Yield
1	<i>p</i> -TsOH·H ₂ O, <i>t</i> -BuOH, 70 °C, 2 h	63 %
2	<i>p</i> -TsOH·H ₂ O, <i>t</i> -BuOH, 70 °C, 4 h	45 %
3	ZnBr ₂ , <i>n</i> -BuSH, CH ₂ Cl ₂ , 25 °C, 30 min	0 %
4	NaHSO ₄ ·SiO ₂ , CH ₂ Cl ₂ , 25 °C, 26 h	0 %
5	PPTS, <i>t</i> -BuOH, 70 °C, 26 h	93 %
6	PPTS, <i>t</i> -BuOH, 80 °C, 3 d	87 %
7	PPTS, <i>t</i> -BuOH, 110 °C, 36 h	86 %

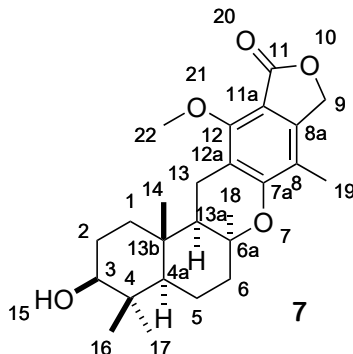
trapped by the phenolic group to provide the 6-*exo-trig* cyclised phenylselenide **218** (58 %).¹³⁰ After the removal of the phenylselenenyl group by reaction with tri-*n*-butylstannane in the presence of AIBN, meroterpenoid **205** (94 %) was isolated as a single diastereoisomer with the desired *trans*, *transoid*, *cis*-fused rings system, the relative stereochemistry of which was confirmed by additional NOESY experiments.

**Scheme 5.7:** Synthesis of meroterpenoid **205**.**Figure 5.2:** X-Ray crystal structure of phenol **207**.

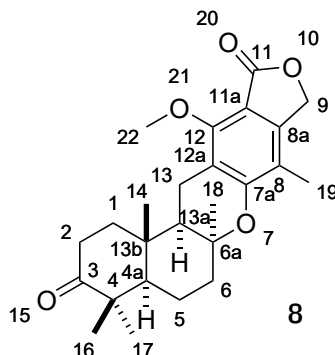
With the key meroterpenoid **205** in hand after establishing the correct relative stereochemistry, attention was directed to the arene methylation and sequential oxidation reactions to complete the synthesis of (±)-17*S*-dihydroaustalide K (**7**), (±)-austalide K (**8**) and (±)-13-deacetoxyaustalide I (**9**) (**Scheme 5.8**). Electrophilic aromatic substitution reaction of meroterpenoid **205** with *N*-bromosuccinimide gave bromide **219** (93 %), which was subjected to palladium-catalysed Suzuki-Miyaura cross-coupling reaction with potassium methyltrifluoroborate to furnish the hexa-substituted arene **220** (88 %).¹³¹ Finally, selective acetate deprotection with magnesium methoxide completed the synthesis of (±)-17*S*-dihydroaustalide K (**7**) (88 %).¹³² Furthermore, Dess–Martin periodinane-mediated oxidation of (±)-17*S*-dihydroaustalide K (**7**) gave (±)-austalide K (**8**) (83 %) and subsequent Baeyer-Villiger oxidation with *m*CPBA gave (±)-13-deacetoxyaustalide I (**9**) (96 %). The analytical data for these synthetic materials were in substantial agreement with those reported for the isolated natural product (**Table 5.2**, **Table 5.3** and **Table 5.4**).^{14,132}



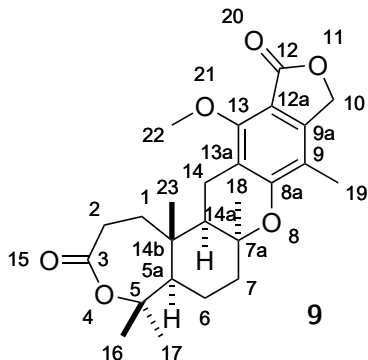
Scheme 5.8: Synthesis of (±)-17*S*-dihydroaustalide K (**7**), (±)-austalide K (**8**) and (±)-13-deacetoxyaustalide I (**9**).

Table 5.2: Comparison of ^1H and ^{13}C ($\pm$)-17*S*-dihydroaustalide K (**7**) NMR data in CDCl_3 with literature.

Position	(±)-17 <i>S</i> -Dihydroaustalide K (7)		Literature data ¹⁴		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	38.1	ax: 1.09 (td, 13.2, 3.8) eq: 1.89 (dt, 13.1, 3.5)	38.2	ax: 0.88 (m) eq: 1.91 (m)	- 0.1	+ 0.21 - 0.02
2	27.1	1.62 – 1.52 (m)	27.1	ax: 1.68 (m) eq: 1.57(m)	0	
3	78.8	3.24 (dd, 11.7, 4.5)	78.9	3.24 (dd, 11.7, 4.5)	- 0.1	0
4	38.8		38.8		0	
4a	54.1	0.93 (d, 11.5)	54.2	0.93 (d, 11.5)	- 0.1	0
5	17.9	1.62 – 1.52 (m)	17.9	ax: 1.60 (m) eq: 1.64 (m)	0	
6	40.3	ax: 1.62 – 1.52 (m) eq: 2.29 – 2.22 (m)	40.4	ax: 2.24 (m) eq: 2.27 (m)	- 0.1	
6a	76.4		76.5		- 0.1	
7a	158.9		158.9		0	
8	114.3		114.1		+ 0.2	
8a	145.3		145.4		- 0.1	
9	68.2	5.11 (s)	68.3	5.11 (s)	- 0.1	0
11	169.5		169.9		- 0.4	
11a	107.2		107.1		+ 0.1	
12	155.3		155.4		- 0.1	
12a	115.7		115.8		- 0.1	
13	18.0	ax: 2.73 (dd, 18.7, 8.2) eq: 2.91 (d, 18.6)	18.0	ax: 2.73 (dd, 18.6, 8.3) eq: 2.91 (d, 18.6)	0	0 0
13a	48.0	1.39 (d, 8.2)	48.1	1.39 (d, 8.8)	- 0.1	0
13b	38.0		38.1		- 0.1	
14	14.2	0.61 (s)	14.3	0.61 (s)	- 0.1	0
15		1.18 (d, 6.2)				
16	15.7	0.78 (s)	15.7	0.78 (s)	0	0
17	28.5	1.03 (s)	28.5	1.03 (s)	0	0
18	27.3	1.15 (s)	27.3	1.16 (s)	0	- 0.01
19	10.7	2.03 (s)	10.7	2.03 (s)	0	0
22	61.9	4.09 (s)	61.8	4.10 (s)	+ 0.1	- 0.01

Table 5.3: Comparison of ^1H and ^{13}C ($\pm$)-austalide K (**8**) NMR data in CDCl_3 with literature.

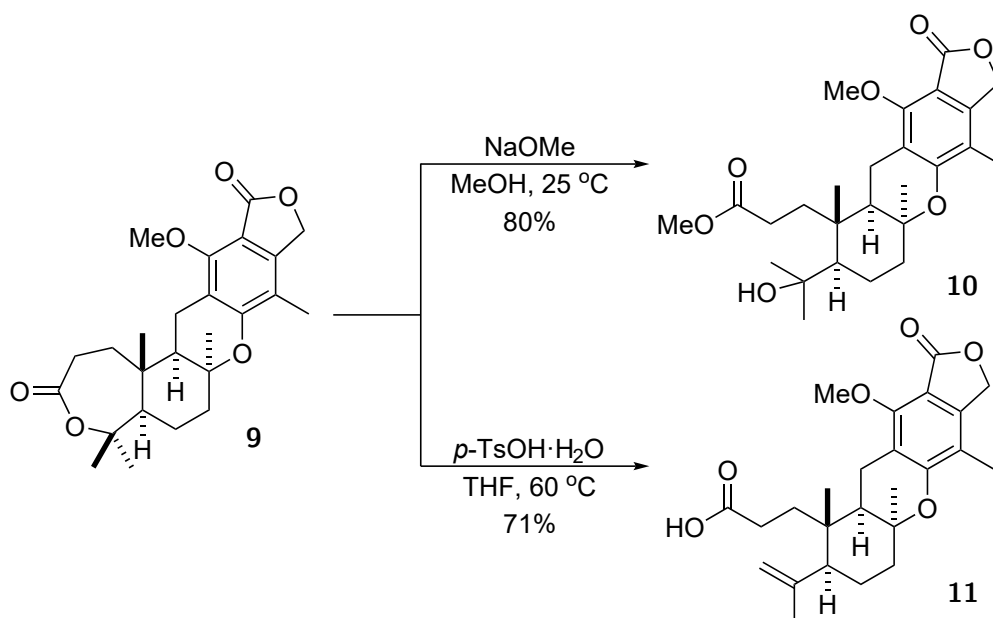
Position	($\pm$)-Austalide K (8)		Literature data ^{9,10}		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	38.4	ax: 1.57 – 1.47 (m) eq: 2.11 (ddd, 13.4, 6.9, 3.8)	39.6	ax: 1.52 – 1.46 (m) eq: 2.07 (ddd, 13.3, 6.9, 3.8)	- 1.2	+ 0.4
2	34.1	ax: 2.47 – 2.36 eq: 2.54 (ddd, 16.1, 11.7, 7.0)	33.9	ax: 2.37 (ddd, 16.1, 6.5, 3.8) eq: 2.49 (ddd, 16.1, 11.6, 6.9)	+ 0.2	
3	216.6		216.2		+ 0.4	
4	47.3		47.1		+ 0.2	
4a	54.2	1.57 – 1.47 (m)	54.1	1.52 – 1.46 (m)	+ 0.1	
5	19.1	ax: 1.57 – 1.47 (m) eq: 1.88 – 1.74 (m)	21.5	ax: 1.52 – 1.46 (m) eq: 1.79 (dddd, 13.9, 13.9, 13.9, 3.0)	- 2.4	
6	39.7	ax: 1.72 – 1.60 (m) eq: 2.31 – 2.25 (m)	38.2	ax: 1.62 (ddd, 13.9, 13.9, 4.2) eq: 2.26 (ddd, 13.9, 3.0, 3.0)	+ 1.5	
6a	76.2		76.2		0	
7a	158.6		158.5		+ 0.1	
8	114.4		114.3		+ 0.1	
8a	145.5		145.4		+ 0.1	
9	68.2	5.12 (s)	68.1	5.09 (s)	+ 0.1	+ 0.03
11	169.4		169.2		+ 0.2	
11a	107.3		107.2		+ 0.1	
12	155.4		155.2		+ 0.2	
12a	115.3		115.1		+ 0.2	
13	18.3	ax: 2.81 (dd, 18.6, 8.2) eq: 2.93 (d, 18.5)	18.2	ax: 2.79 (dd, 18.5, 8.0) eq: 2.91 (d, 18.5)	+ 0.1	+ 0.02 + 0.02
13a	47.1	1.57 – 1.47 (m)	47.0	1.52 – 1.46 (m)	+ 0.1	
13b	37.6		37.5		+ 0.1	
14	14.2	0.73 (s)	14.1	0.70 (s)	+ 0.1	+ 0.03
16	21.7	1.03 (s)	26.6	1.00 (s)	- 4.9	+ 0.03
17	26.7	1.12 (s)	27.0	1.09 (s)	- 0.3	+ 0.03
18	27.1	1.19 (s)	29.5	1.17 (s)	- 2.4	+ 0.02
19	10.7	2.05 (s)	10.5	2.02 (s)	+ 0.2	+ 0.03
22	62.0	4.11 (s)	61.8	4.08 (s)	+ 0.2	+ 0.03

Table 5.4: Comparison of ^1H and ^{13}C ($\pm$)-13-deacetoxyaustalide I (**9**) NMR data in CDCl_3 with literature.

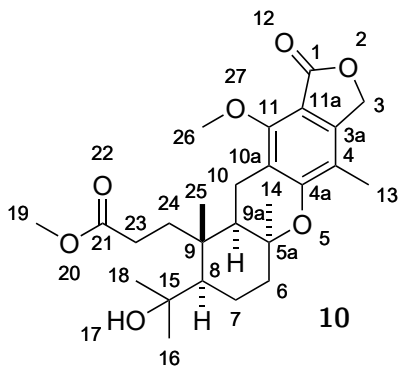
Position	(±)-13-Deacetoxyaustalide I (9)		Literature data ¹⁴	
	δ_C	δ_H (mult, J in Hz)	δ_C	$\Delta\delta$
1	37.3	ax: 1.75 – 1.62 (m) eq: 2.02 – 1.84 (m)	37.4	- 0.1
2	31.8	ax: 2.60 (ddd, 15.6, 8.3, 2.7) eq: 2.69 (ddd, 15.6, 11.2, 3.1)	31.8	0
3	175.1		175.2	- 0.1
5	85.8		85.9	- 0.1
5a	53.6	2.02 – 1.84 (m)	54.0	- 0.4
6	22.1	ax: 1.54 – 1.53 (m) eq: 2.02 – 1.84 (m)	22.3	- 0.2
7	39.3	ax: 1.75 – 1.62 (m) eq: 2.25 (dt, 14.2, 3.1)	39.5	- 0.2
7a	76.0		76.1	- 0.1
8a	158.3		158.4	- 0.1
9	114.3		114.2	+ 0.1
9a	145.6		145.9	- 0.3
10	68.2	5.14 (s)	68.3	- 0.1
12	169.3		169.7	- 0.4
12a	107.4		107.6	- 0.2
13	155.3		155.5	- 0.2
13a	115.1		115.3	- 0.2
14	18.7	ax: 2.84 (dd, 18.7, 8.1) eq: 2.96 (d, 18.6)	18.7	0
14a	47.3	1.56 (d, 7.8)	47.5	- 0.2
14b	40.4		40.6	- 0.2
16	25.8	1.42 (s)	25.8	0
17	32.5	1.52 (s)	32.5	0
18	27.1	1.21 (s)	27.3	- 0.2
19	10.6	2.06 (s)	10.7	- 0.1
22	62.0	4.13 (s)	62.2	- 0.2
23	16.7	0.83 (s)	16.8	- 0.1

a) ^1H NMR data is not available from the isolation publication.

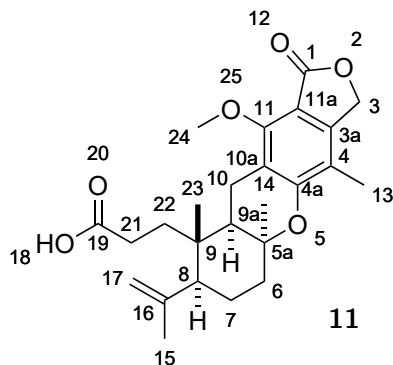
($\pm$)-13-Deacetoxyaustalide I (**9**) was also used in alternative derivatisation reactions for the synthesis of additional austalide natural products (**Scheme 5.9**). Reaction of ($\pm$)-13-Deacetoxyaustalide I (**9**) with sodium methoxide resulted in transesterification to provide ($\pm$)-austalide P (**10**) (80 %).¹³³ Under acidic conditions at elevated temperature, the cyclic lactone moiety of ($\pm$)-13-deacetoxyaustalide I (**9**) was hydrolysed accompanied with elimination of the resulting tertiary alcohol to give ($\pm$)-13-deoxyaustalide Q acid (**11**) (71 %).¹³⁴ The analytical data of the synthetic products were compared with those reported for the isolated natural products and were found to be in substantial agreement (**Table 5.5** and **Table 5.6**).^{13,14}



Scheme 5.9: Synthesis of ($\pm$)-austalide P (**10**) and ($\pm$)-13-deoxyaustalide Q acid (**11**).

Table 5.5: Comparison of ^1H and ^{13}C ($\pm$)-austalide P (**10**) NMR data in CD_3OD with literature.

Position	($\pm$)-Austalide P (10)		Literature data ¹³		$\Delta\delta$	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)	$\Delta\delta_C$	$\Delta\delta_H$
1	171.8		172.1		- 0.3	
3	69.8	5.20 (s)	69.8	5.21 (s)	0	- 0.01
3a	147.5		148.0		- 0.5	
4	115.8		117.3		- 1.5	
4a	160.4		160.0		+ 0.4	
5a	78.3		78.3		0	
6	40.5	ax: 1.66 – 1.57 (m) eq: 2.15 – 2.10 (m)	40.2	1.61 (dt, 14.3, 3.8)	+ 0.3	
7	22.6	ax: 1.57 – 1.48 (m) eq: 1.88 – 1.75 (m)	22.4	ax: 1.52 (t, 10.7) eq: 1.83 (m)	+ 0.2	
8	52.0	1.57 – 1.48 (m)	40.1	2.14 (dd, 13.7, 3.4)	+ 11.9	
9	41.4		41.6		- 0.2	
9a	42.8	1.68 (d, 8.0)	41.2	1.70 (d, 8.1)	+ 1.6	- 0.02
10	18.8	ax: 2.76 (dd, 18.6, 7.9) eq: 3.01 (d, 18.6)	18.5	ax: 2.78 (dd, 18.5, 8.1) eq: 3.03 (d, 18.6)	+ 0.3	- 0.02
10a	117.3		118.0		- 0.7	
11	156.6		158.1		- 1.5	
11a	108.2		108.0		+ 0.2	
13	10.6	2.05 (s)	10.6	2.08 (s)	0	- 0.03
14	27.7	1.20 (s)	27.9	1.20 (s)	- 0.2	0
15	75.7		75.7		0	
16	28.1	1.19 (s)	28.0	1.19 (s)	+ 0.1	0
18	33.2	1.27 (s)	33.2	1.27 (s)	0	0
19	52.1	3.67 (s)	52.0	3.68 (s)	+ 0.1	- 0.01
21	176.9		177.7		- 0.8	
23	30.1	2.65 – 2.55 (m), 2.37 – 2.27 (m)	30.0	2.60 (m), 2.32 (m)	+ 0.1	
24	34.9	2.42 (tdd, 11.5, 4.8, 2.5), 1.88 – 1.75 (m)	34.9	2.42 (m), 1.80 (m)	0	
25	19.5	0.70 (s)	19.5	0.70 (s)	0	0
26	62.2	4.04 (s)	62.1	4.04 (s)	+ 0.1	0

Table 5.6: Comparison of ^1H and ^{13}C ($\pm$)-13-deoxyaustalide Q acid (**11**) NMR data in CDCl_3 with literature.

Position	(±)-13-Deoxyaustalide Q acid (11)		Literature data ¹⁴	$\Delta\delta$
	δ_C	δ_H (mult, J in Hz)	δ_C	$\Delta\delta_C$
1	169.5		169.5	0
3	68.3	5.12 (s)	68.2	+ 0.1
3a	145.5		145.5	0
4	114.4		114.4	0
4a	158.6		158.6	0
5a	76.5		76.5	0
6	39.0	ax: 1.68 – 1.61 (m) eq: 2.23 – 2.06 (m)	39.1	- 0.1
7	23.8	ax: 1.49 – 1.44 (m) eq: 2.23 – 2.06 (m)	23.8	0
8	50.1	2.23 – 2.06 (m)	50.2	- 0.1
9	40.0		40.1	- 0.1
9a	39.6	1.57 (d, 7.8)	39.6	0
10	18.1	ax: 2.77 (dd, 18.4, 7.8) eq: 2.89 (d, 18.5)	18.1	0
10a	115.2		115.3	- 0.1
11	155.5		155.5	0
11a	107.3		107.3	0
13	10.7	2.04 (s)	10.7	0
14	27.4	1.20 (s)	27.4	0
15	23.6	1.74 (s)	23.5	+ 0.1
16	146.7		146.7	0
17	114.2	4.69 (s), 4.90 (s)	114.2	0
19	179.1		178.2	+ 0.9
21	28.5	2.52 – 2.26 (m)	28.3	+ 0.2
22	32.9	1.74 – 1.70 (m)	33.0	- 0.1
23	18.1	0.60 (s)	18.1	0
24	62.0	4.11 (s)	62.0	0

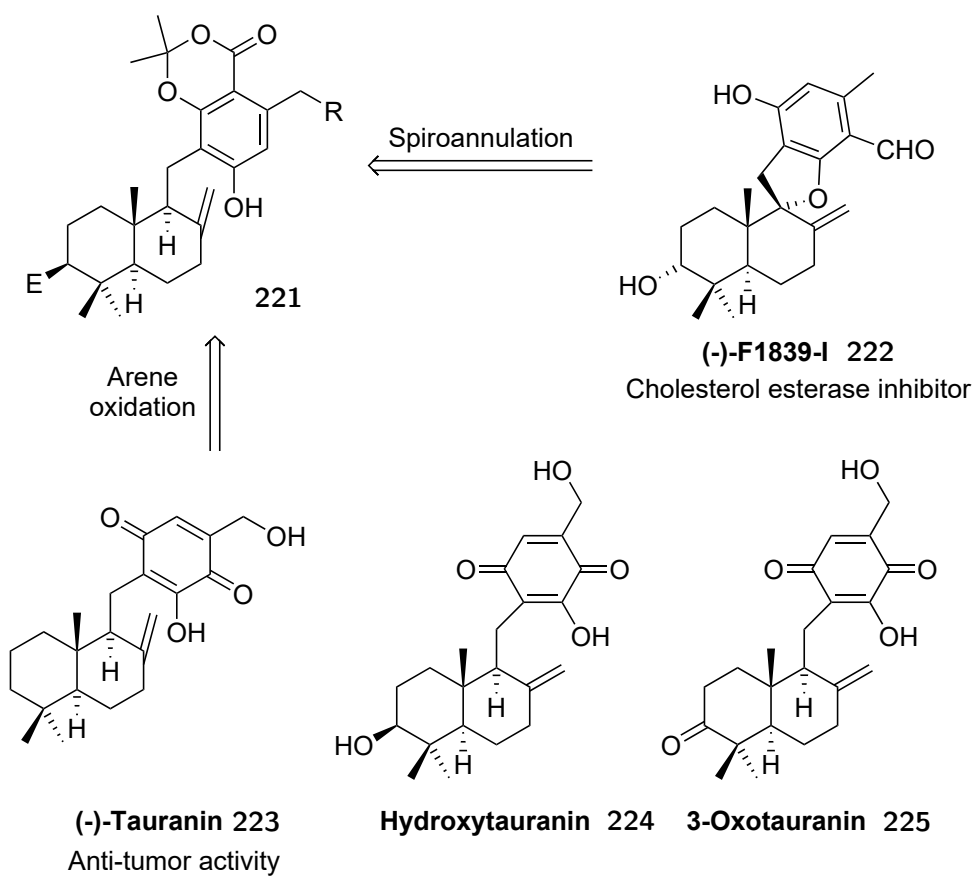
a) ^1H NMR data is not available from the isolation publication.

5.4 Conclusion

In conclusion, the first total syntheses of five austalide natural products ($\pm$)-17*S*-dihydroaustalide **7**, ($\pm$)-austalide **8**, ($\pm$)-13-deacetoxyaustalide **9**, ($\pm$)-austalide **10** and ($\pm$)-13-deoxyaustalide **11** were completed in seventeen to twenty steps. A series of biomimetic transformations were employed to construct the carbon skeleton of these natural products. The aromatic core was synthesised by biomimetic polyketide aromatisation while the fused-rings motif was constructed by sequential reductive radical anion triene cyclisation of an epoxide, followed by phenylselenium-mediated diastereoselective cyclisation reaction.

5.5 Future Work

The use of the sequential biomimetic aromatisation and radical triene cyclisation provided a synthetically useful intermediate **221** which would be suitable to be further functionalised into other natural meroterpenoids (**Scheme 5.10**). For instance, F1839-I (**222**), a pancreatic cholesterol esterase inhibitor, would be accessible by sequential alkene isomerisation and spiroannulation of meroterpenoid **221**.¹³⁵ On the other hand, (-)-tauranin (**223**), β -hydroxytauranin (**224**) and 3-oxotauranin (**225**) are biosynthetically related meroterpenoids which should be accessible with current strategy by further decarboxylation and arene oxidation of meroterpenoid **221**.^{136,137}



Scheme 5.10: Potential synthesis of other meroterpenoids.

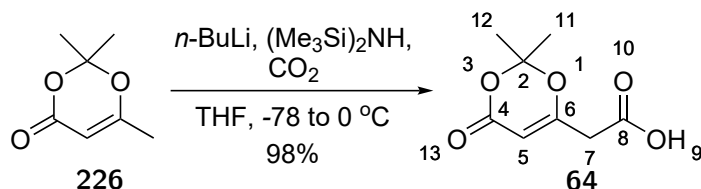
EXPERIMENTAL

General Experimental Procedures

All reagents and solvents were used directly without further purification unless otherwise stated. BINOLs **172** and **173** were prepared respectively according to the procedures reported by Corey and co-workers,¹⁰⁶ and Yamamoto and co-workers,¹⁰⁷ respectively. Dihydroquinidine ligand **178** was prepared according to Corey and co-workers.¹¹⁰ Et₂SBr·SbCl₅Br (BDSB, **191**) and (Et₂SI)₂Cl·SbCl₆ (IDSI, **192**) were prepared according to the method published by Snyder and co-workers.¹¹⁵ The chiral ketone **187** was prepared from *L*-fructose according to the established method by Shi and co-workers.¹¹³ All solvents were purified and dried by distillation under an atmosphere of N₂ before use. Et₂O and THF were redistilled from Na-Ph₂CO. CH₂Cl₂, Et₃N, MeOH, *i*-PrNO₂, MeNO₂ and pyridine were redistilled from CaH₂ and PhMe was redistilled from Na. Me₂CO and *t*-BuOH were dried over 4 Å activated molecular sieves under N₂ for 24 h. Alternatively, these solvents were obtained from the Grubbs apparatus. All air- and moisture-sensitive reactions were carried out under an atmosphere of N₂ using standard Schlenk techniques in oven-dried glassware equipped with a magnetic stirring bar. The progress of reactions was monitored by analytical TLC on silica gel coated aluminum oxide F254 plates. Developed TLC were visualised under UV light and stained with acidic vanillin solution. Flash column chromatography was performed employing silica gel 60 Å, particle size 40 – 63 µm. The

enantiomeric excesses of the compounds were determined by chiral HPLC analysis on Chiralpak® IE column with *n*-hexane and *i*-PrOH as the mobile phase. All ^1H and proton-decoupled ^{13}C NMR spectra were recorded at 400 or 500 MHz and 100 MHz respectively at ambient temperature in deuterated solvent as noted. NMR spectra were referenced to residual solvent peaks (CDCl_3 : $\delta = 7.26$ for ^1H NMR and $\delta = 77.0$ for ^{13}C NMR; CD_3OD $\delta = 3.31$ and 4.87 for ^1H NMR and $\delta = 49.0$ for ^{13}C NMR; $(\text{CD}_3)_2\text{CO}$: $\delta = 2.05$ for ^1H NMR and $\delta = 29.8$ for ^{13}C NMR) and chemical shifts were reported in ppm. IR spectra are reported in cm^{-1} . Optical rotations were recorded with a polarimeter with the specified concentration and temperature. Mass spectra were obtained from the Imperial College Mass Spectrometry Service with the use of TOF and magnetic analysers for ESI and EI techniques, respectively. Melting points were uncorrected. X-ray diffraction data were recorded by the Imperial College X-ray Crystallography Facility. Elemental analyses were carried out by London Metropolitan University.

2-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid



$n\text{-BuLi}$ in hexane (2.5 M; 100 mL, 250 mmol) was added dropwise via a cannula to $(\text{Me}_3\text{Si})_2\text{NH}$ (52.4 mL, 250 mmol) in THF (200 mL) at -78°C , and the resulting mixture was allowed to warm to 0°C for 30 min and cooled back to -78°C . Dioxinone **226** (30.2 mL, 227 mmol) was added dropwise with stirring at -78°C . After 1 h, CO_2 gas was bubbled through the solution for 20 min and the resulting mixture was allowed to warm to 0°C for over 2 h. Aqueous HCl (4 M) was added to pH ~ 1 and the mixture diluted with EtOAc (200 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (5×150 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and recrystallised from EtOH to provide dioxinone acid **64** (41.3 g, 222 mmol, 98 %) as colourless plates.

R_f 0.16 (Pentane : EtOAc 1 : 1).

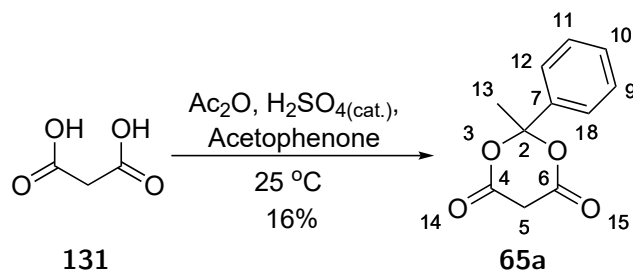
Melting Point $104.1 - 104.2^\circ\text{C}$.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.54 (s, 1H, H_9), 5.45 (s, 1H, H_5), 3.31 (s, 2H, H_7), 1.70 (s, 6H, H_{11-12}).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 172.2 (C_8), 163.3 (C_6), 161.2 (C_4), 107.5 (C_2), 96.6 (C_5), 39.0 (C_7), 24.8 (C_{11-12}).

IR ν_{max} (neat) 3111, 1701, 1646 cm^{-1} .

Elemental Analysis Anal. Calcd for $\text{C}_8\text{H}_{10}\text{O}_5$: C, 51.61; H, 5.41; Found: C, 51.52; H, 5.49.

2-Methyl-2-phenyl-1,3-dioxane-4,6-dione

Malonate **65b** was prepared according a modified procedure of Davidson and co-worker.¹³⁸ Concentrated H_2SO_4 (0.5 mL) was added to a suspension of malonic acid **131** (62.5 g, 0.600 mol) in Ac_2O (222 mL, 2.34 mol) and the resulting mixture was stirred overnight. Excess AcOH and Ac_2O were removed under reduced pressure below $45\text{ }^\circ\text{C}$ and PhAc (140 mL, 1.20 mol) was added. The resulting mixture was stirred for 1 h and chromatographed to give the malonate **65a** (19.7 g, 93.1 mmol, 16 %) as white powder.

R_f 0.48 (Pentane : EtOAc 4 : 1).

Melting Point $96.9 - 97.0\text{ }^\circ\text{C}$.

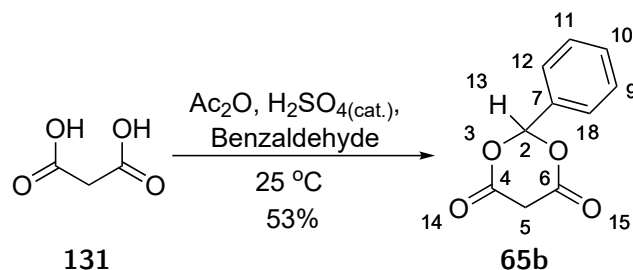
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.52 – 7.38 (m, 5H, H_{8-12}), 3.43 (d, $J = 19.6\text{ Hz}$, 1H, H_{5eq}), 2.99 (d, $J = 19.6\text{ Hz}$, 1H, H_{5ax}), 1.98 (s, 3H, H_{13}).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.5 ($\text{C}_{4,6}$), 139.6 (C_7), 130.2 (C_{10}), 129.6 ($\text{C}_{9,11}$), 124.7 ($\text{C}_{8,12}$), 106.5 (C_2), 38.6 (C_5), 30.1 (C_{13}).

IR ν_{max} (neat) 2995, 2913, 1783, 1759, 1154, 1055 cm^{-1} .

Elemental Analysis Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_4$: C, 64.08; H, 4.89; Found: C, 64.04; H, 5.02.

2-Phenyl-1,3-dioxane-4,6-dione



Malonate **65b** was prepared according a modified procedure of Michael and Weiner.¹³⁹ Concentrated H_2SO_4 (0.5 mL) was added to a suspension of malonic acid **131** (52.0 g, 500 mmol) in Ac_2O (142 mL, 1.50 M) and the resulting mixture was stirred overnight. The reaction mixture was cooled to $25\text{ }^\circ\text{C}$ and PhCHO (51.0 mL, 502 mmol) was added dropwise. After standing at $5\text{ }^\circ\text{C}$ overnight, PhMe (150 mL) was added and the excess AcOH and Ac_2O were removed under reduced pressure below $40\text{ }^\circ\text{C}$ to give the crude product as a brown white solid. The solid was filtered off and washed with H_2O (300 mL) and Et_2O (30 mL). The crude product was purified by dissolving in Me_2CO (400 mL), followed by addition of ice water (600 mL) and stirred for 15 min. The precipitate was filtered off, washed with H_2O (200 mL) and dried to give the malonate **65b** (50.7 g, 264 mmol, 53 %) as white powder.

R_f 0.20 (Pentane : EtOAc 4 : 1).

Melting Point $143.1\text{ }^\circ\text{C}$ (lit. $148\text{ }^\circ\text{C}$).

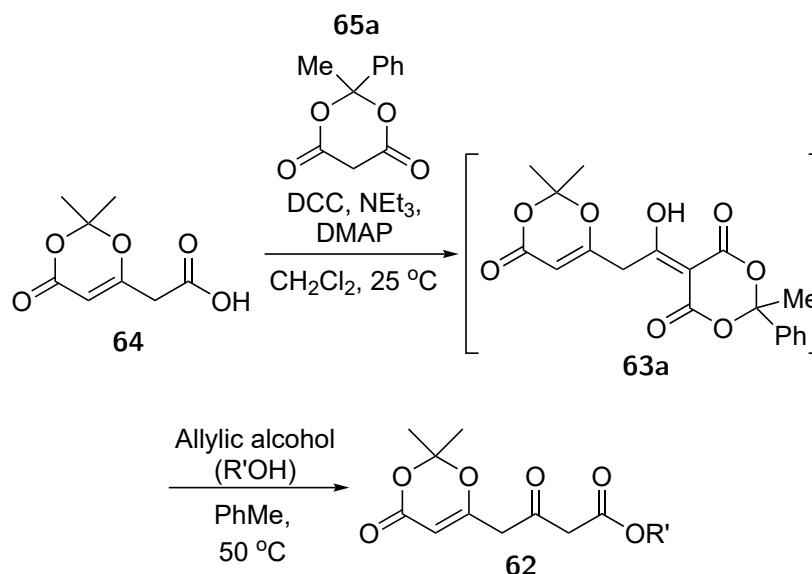
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67 – 7.38 (m, 5H, H_{8-12}), 6.80 (s, 1H, H_{13}), 3.83 (d, $J = 18.8\text{ Hz}$, 1H, H_{5eq}), 3.66 (d, $J = 18.8\text{ Hz}$, 1H, H_{5ax}).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.0 ($\text{C}_{4,6}$), 132.2 (C_7), 131.0 (C_{10}), 129.0 ($\text{C}_{9,11}$), 126.3 ($\text{C}_{8,12}$), 98.0 (C_2), 39.1 (C_5).

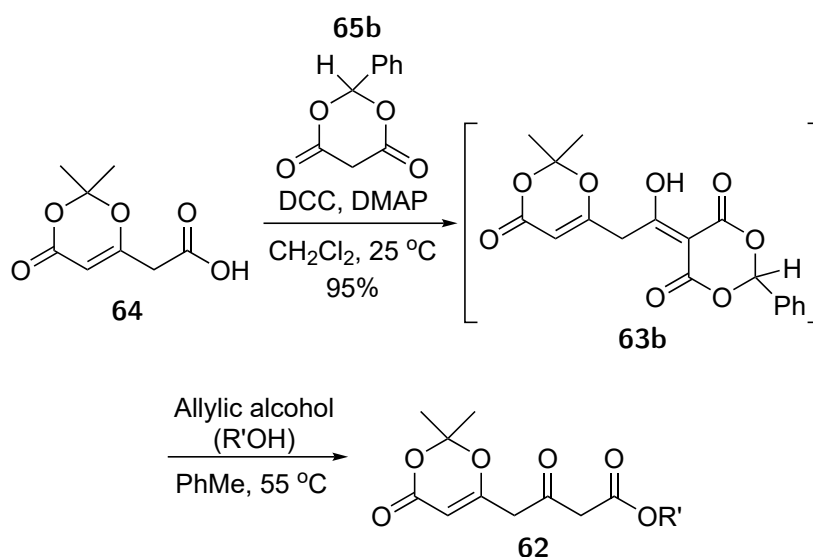
IR ν_{max} (neat) 1760, 1464, 1409, 1326, 958, 761, 698 cm^{-1} .

General Procedures for the Synthesis of Dioxinone β -Keto

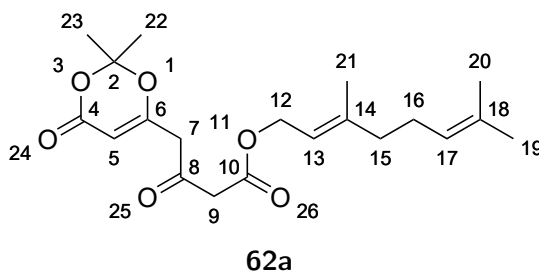
Esters



Method A: Malonate **65a** (3.09 g, 15.0 mmol), DCC (5.32 g, 25.8 mmol), Et_3N (3.60 mL, 25.8 mmol) and DMAP (34 mg, 0.300 mmol) were dissolved in CH_2Cl_2 (70 mL) and the resulting mixture was stirred for 5 min at 25°C . Dioxinone acid **64** (4.80 g, 25.8 mmol) in THF (70 mL) was added to the reaction mixture and stirred for 18 h. The reaction mixture was concentrated and subsequently diluted with Et_2O (20 mL) and H_2O (20 mL). The insoluble solid was filtered and washed with Et_2O (3×20 mL) and H_2O (3×20 mL). The phases were separated and the organic layer was extracted with H_2O (5×30 mL). The combined aqueous layers were cooled to 0°C and acidified to pH ~ 1 with solid citric acid. The aqueous layer was then extracted with CHCl_3 (5×30 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give the crude dioxane-4,6-dione-keto-dioxinone **63a** as a brown oil. Crude dioxane-4,6-dione-keto-dioxinone **63a** in PhMe (25 mL) was added to the solution of allylic alcohol (6.00 mmol) in PhMe (25 mL) at 50°C dropwise and the resulting mixture was stirred at 50°C for 45 min. The reaction mixture was concentrated under reduced pressure and the brown residue was purified by chromatography (pentane : EtOAc 9 : 1 to 4 : 1) to provide dioxinone β -keto-esters **62**.



Method B: Malonate **65b** (6.91 g, 36.0 mmol), DCC (7.43 g, 36.0 mmol) and DMAP (4.40 g, 36.0 mmol) were dissolved in CH_2Cl_2 (300 mL) and the resulting mixture was stirred for 5 min at 25°C . Dioxinone acid **64** (6.70 g, 36.0 mmol) was added with stirring at 25°C . After 18 h, the mixture was cooled to 0°C and the insoluble solid was filtered off and washed with CH_2Cl_2 (15 mL). The filtrate was washed with aqueous HCl (1 M; 2×200 mL) and the two phases were separated and the organic layer was dried (MgSO_4), filtered, and concentrated under reduced pressure to give the crude dioxane-4,6-dione-keto-dioxinone **63b** as yellow foam, which was used directly. Crude dioxane-4,6-dione-keto-dioxinone **63b** and allylic alcohol (20.0 mmol) were dissolved in PhMe (150 mL) and stirred at 55°C for 4 h. The reaction mixture was concentrated under reduced pressure and the brown residue chromatographed (pentane : EtOAc 9 : 1 to 4 : 1) to provide dioxinone β -keto esters **62**.

(E)-3,7-Dimethylocta-2,6-dienyl**4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate**

Method A: Dioxinone β -keto-ester **62a** (2.02 g, 5.55 mmol, 93 %), prepared from geraniol **94** (1.04 mL, 6.00 mmol), was obtained as a pale yellow oil.

Method B: Dioxinone β -keto-ester **62a** (6.92 g, 19.0 mmol, 95 %), prepared from geraniol **94** (3.47 mL, 20.0 mmol), was obtained as a pale yellow oil.

R_f 0.20 (Pentane : EtOAc 4 : 1).

¹H NMR (400 MHz, CDCl₃) δ 5.36 (s, 1H, H₅), 5.34 – 5.30 (m, 1H, H₁₃), 5.09 – 5.04 (m, 1H, H₁₇), 4.67 (d, J = 7.2 Hz, 2H, H₁₂), 3.51 (s, 2H, H₉), 3.50 (s, 2H, H₇), 2.14 – 2.01 (m, 4H, H_{15–16}), 1.71 (s, 6H, H_{22–23}), 1.68 (s, 3H, H₂₁), 1.67 (s, 3H, H₁₉), 1.59 (s, 3H, H₂₀).

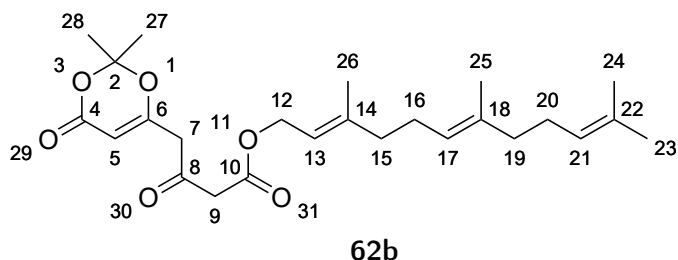
¹³C NMR (100 MHz, CDCl₃) δ 195.6 (C₈), 166.3 (C₁₀), 163.5 (C₄), 160.4 (C₆), 143.6 (C₁₄), 132.0 (C₁₈), 123.5 (C₁₇), 117.3 (C₁₃), 107.3 (C₂), 97.1 (C₅), 62.6 (C₁₂), 49.1 (C₉), 46.9 (C₇), 39.4 (C₁₅), 26.2 (C₁₆), 25.7 (C₁₉), 25.0 (C_{22–23}), 17.7 (C₂₀), 16.5 (C₂₁).

IR ν_{max} (neat) 1720, 1375, 1272, 1201, 1015 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₀H₂₉O₆ 365.1964; Found 365.1977.

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

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



Method A: Dioxinone β -keto-ester **62b** (2.27 g, 5.24 mmol, 87 %), prepared from *trans, trans*-farnesol **95** (1.50 mL, 6.00 mmol), was obtained as a pale yellow oil.

Method B: Dioxinone β -keto-ester **62b** (6.81 g, 15.7 mmol, 79 %), prepared from *trans, trans*-farnesol **95** (5.02 mL, 20.0 mmol), was obtained as a pale yellow oil.

R_f 0.36 (Pentane : Et₂O 1 : 1).

¹H NMR (400 MHz, CDCl₃) δ 5.34 (s, 1H, H₅), 5.33 – 5.28 (m, 1H, H₁₃), 5.11 – 5.02 (m, 2H, H_{17,21}), 4.65 (d, *J* = 7.2 Hz, 2H, H₁₂), 3.49 (s, 2H, H₉), 3.48 (s, 2H, H₇), 2.13 – 1.99 (m, 6H, H_{15–16,20}), 1.99 – 1.91 (m, 2H, H₁₉), 1.69 (s, 6H, H_{27–28}), 1.66 (s, 3H, H₂₆), 1.65 (s, 3H, H₂₃), 1.57 (s, 6H, H_{24–25}).

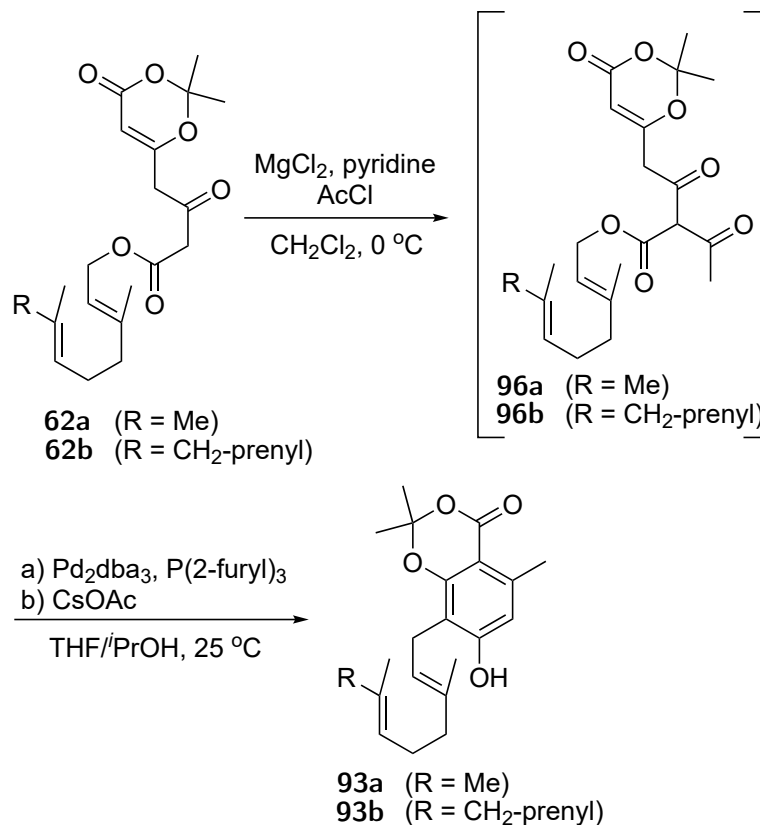
¹³C NMR (100 MHz, CDCl₃) δ 195.6 (C₈), 166.3 (C₁₀), 163.5 (C₄), 160.4 (C₆), 143.5 (C₁₄), 135.5 (C₁₈), 131.2 (C₂₂), 124.2 (C₁₇), 123.4 (C₂₁), 117.3 (C₁₃), 107.2 (C₂), 97.0 (C₅), 62.5 (C₁₂), 49.0 (C₉), 46.9 (C₇), 39.6 (C₁₉), 39.4 (C₁₅), 26.6 (C₁₆), 26.1 (C₂₀), 25.6 (C₂₃), 24.9 (C_{27–28}), 17.6 (C₂₄), 16.4 (C₂₆), 15.9 (C₂₅).

IR ν_{max} (neat) 2922, 1722, 1639, 1375, 1272, 1202, 1015, 901, 806 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₅H₃₇O₆ 433.2590; Found 433.2598.

Elemental Analysis Anal. Calcd for C₂₅H₃₆O₆: C, 69.42; H, 8.39; Found: C, 69.49; H, 8.24.

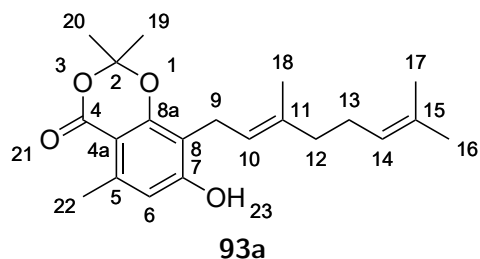
General Procedure for the Synthesis of Resorcylates



MgCl_2 (476 mg, 5.00 mmol) and pyridine (0.810 mL, 10.0 mmol) were added with stirring to β -keto-ester **62** (5.00 mmol) in CH_2Cl_2 (25 mL) at $0\text{ }^\circ\text{C}$. After 15 min, acetyl chloride (0.540 mL, 7.50 mmol) was added dropwise and the reaction mixture was further stirred for 1 h at $0\text{ }^\circ\text{C}$. Reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the pH was adjusted to ~ 2 with aqueous HCl (1 M). The two phases were separated and the aqueous layer was extracted with EtOAc ($3 \times 50\text{ mL}$). The combined organic layers were dried (MgSO_4), filtered, and concentrated under reduced pressure to give the crude β, δ -diketo-ester **96**. P(2-furyl)_3 (232 mg, 1.00 mmol) and Pd_2dba_3 (229 mg, 0.250 mmol) were added sequentially with stirring to this crude material in THF (30 mL) at $25\text{ }^\circ\text{C}$. After 1 h, CsOAc (2.88 g, 15.0 mmol) in *i*-PrOH (30 mL) was added and the resulting mixture was stirred for additional 1.5 h. Reaction was quenched with aqueous HCl (1 M; 30 mL) and the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 ($3 \times 50\text{ mL}$). The combined organic layers were dried (MgSO_4), filtered, concentrated un-

der reduced pressure and chromatographed (pentane : EtOAc 19 : 1 to 10 : 1) to give resorcyate **93**.

(*E*)-8-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



Resorcyate **93a** (1.03 g, 3.02 mmol, 60 % over 2 steps), prepared from dioxinone β -keto-ester **62a** (1.83 g, 5.00 mmol), was obtained as a white solid. An analytically pure sample was obtained by recrystallisation from MeNO₂.

R_f 0.37 (Pentane : EtOAc 4 : 1).

Melting Point 102.9 – 103.0 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.42 (s, 1H, H₆), 6.06 (s, 1H, H₂₃), 5.19 (t, J = 7.4 Hz, 1H, H₁₀), 5.04 (t, J = 6.3 Hz, 1H, H₁₄), 3.33 (d, J = 7.2 Hz, 2H, H₉), 2.59 (s, 3H, H₂₂), 2.14 – 1.98 (m, 4H, H_{12–13}), 1.79 (s, 3H, H₁₈), 1.69 (s, 6H, H_{19–20}), 1.67 (s, 3H, H₁₆), 1.59 (s, 3H, H₁₇).

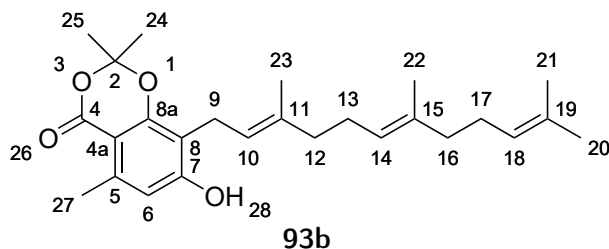
¹³C NMR (100 MHz, CDCl₃) δ 161.2 (C₄), 160.2 (C₇), 156.0 (C_{8a}), 142.8 (C_{4a}), 138.5 (C₁₁), 132.0 (C₁₅), 123.7 (C₁₄), 120.8 (C₁₀), 113.7 (C₆), 112.8 (C₈), 105.3 (C₅), 104.8 (C₂), 39.7 (C₁₂), 26.4 (C₁₃), 25.7 (C_{19–20}), 25.6 (C₁₆), 22.0 (C₂₂), 21.9 (C₉), 17.7 (C₁₇), 16.2 (C₁₈).

IR ν_{max} (neat) 3199, 1694, 1608, 1300, 1282, 1210, 1177, 1106, 1045, 754 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₁H₂₉O₄ 345.2066; Found 345.2067.

Elemental Analysis Anal. Calcd for C₂₁H₂₈O₄: C, 73.32; H, 8.19; Found: C, 73.35; H, 8.31.

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



Resorcyate **93b** (1.14 g, 2.75 mmol, 55 % over 2 steps), prepared from dioxinone β -keto-ester **62b** (2.17 g, 5.00 mmol), was obtained as a yellow oil which solidified upon standing.

R_f 0.24 (Pentane : EtOAc 9 : 1).

Melting Point 72.2 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.41 (s, 1H, H₆), 6.15 (s, 1H, H₂₈), 5.19 (t, J = 6.7 Hz, 1H, H₁₀), 5.13 – 5.00 (m, 2H, H_{14,18}), 3.32 (d, J = 7.2 Hz, H₉), 2.58 (s, 3H, H₂₇), 2.14 – 1.90 (m, 8H, H_{12–13,16–17}), 1.79 (s, 3H, H₂₃), 1.68 (s, 6H, H_{24–25}), 1.67 (s, 3H, H₂₀), 1.58 (s, 6H, H_{21–22}).

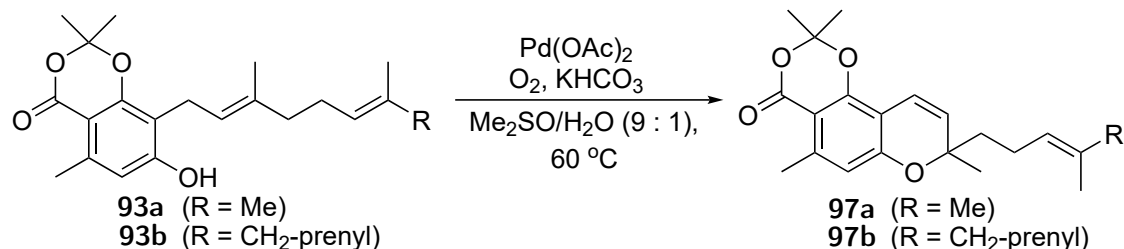
¹³C NMR (100 MHz, CDCl₃) δ 161.0 (C₄), 160.1 (C₇), 156.0 (C_{8a}), 142.8 (C_{4a}), 138.6 (C₁₁), 135.6 (C₁₅), 131.3 (C₁₉), 124.3 (C₁₄), 123.5 (C₁₈), 120.8 (C₁₀), 113.6 (C₆), 112.7 (C₈), 105.3 (C₅), 104.8 (C₂), 39.7 (C₁₆), 39.6 (C₁₂), 26.7 (C₁₇), 26.3 (C₁₃), 25.7 (C_{24–25}), 25.7 (C₂₀), 22.0 (C₂₇), 21.9 (C₉), 17.7 (C₂₁), 16.2 (C₂₂), 16.0 (C₂₃).

IR ν_{max} (neat) 3209, 2971, 2926, 1738, 1704, 1964, 1606, 1590, 1376, 1284, 1217, 1170, 1107, 1046, 858, 751 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₆H₃₇O₄ 413.2692; Found 413.2680.

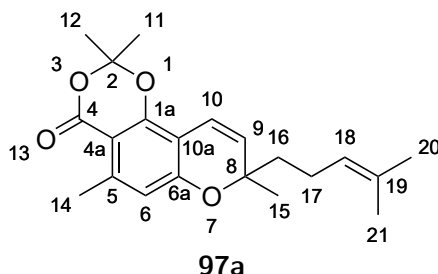
Elemental Analysis Anal. Calcd for C₂₆H₃₆O₄: C, 75.69; H, 8.80; Found: C, 75.56; H, 8.96.

General Procedure for the Synthesis of Chromenes



Resorcylate **93** (2.00 mmol), KHCO₃ (220 mg, 2.20 mmol) and Pd(OAc)₂ (49 mg, 0.200 mmol) were dissolved in O₂ saturated Me₂SO (45 mL) and H₂O (5 mL) and the resulting mixture was heated to 60 °C with stirring for 16 h under O₂ (1 atm). The reaction mixture was diluted with CH₂Cl₂ (20 mL) and aqueous HCl (1 M) was added until pH ~2. The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with H₂O (5 × 50 mL), dried over MgSO₄, filtered, concentrated and chromatographed (pentane : Et₂O 9 : 1) to give chromene **97**.

2,2,5,8-Tetramethyl-8-(4-methylpent-3-enyl)-[1,3]dioxino[4,5-*f*]chromen-4(8*H*)-one



Chromene **97a** (465 mg, 1.35 mmol, 68 %), prepared from resorcyate **93a** (689 mg, 2.00 mmol), was obtained as colourless oil.

R_f 0.32 (Pentane : Et₂O 9 : 1).

¹H NMR (400 MHz, CDCl₃) δ 6.54 (d, J = 10.1 Hz, 1H, H₁₀), 6.35 (d, J = 1.0 Hz, 1H, H₆), 5.52 (d, J = 10.1 Hz, 1H, H₉), 5.12 – 5.04 (m, 1H, H₁₈), 2.59 (s, 3H, H₁₄), 2.17 – 2.00 (m, 2H, H₁₇), 1.81 – 1.72 (m, 1H, H₁₆), 1.70 (s, 6H, H_{11–12}), 1.66 (s, 3H, H₂₀), 1.65 – 1.60 (m, 1H, H₁₆), 1.57 (s, 3H, H₂₁), 1.40 (s, 3H, H₁₅).

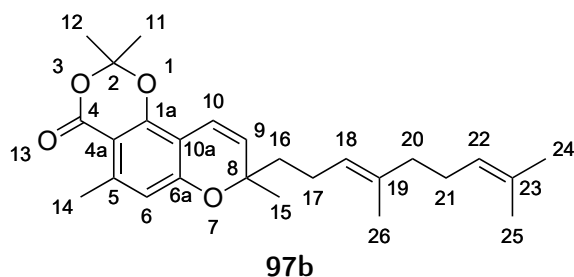
¹³C NMR (100 MHz, CDCl₃) δ 160.6 (C₄), 158.6 (C_{6a}), 152.8 (C_{1a}), 144.8 (C₅), 132.0 (C₁₉), 127.8 (C₉), 123.7 (C₁₈), 115.8 (C₁₀), 113.8 (C₆), 107.4 (C_{10a}), 105.0 (C_{4a}), 104.8 (C₂), 80.1 (C₈), 41.6 (C₁₆), 27.0 (C₁₅), 25.8 (C₁₁), 25.7 (C₁₂), 25.6 (C₂₀), 22.6 (C₁₇), 22.3 (C₁₄), 17.6 (C₂₁).

IR ν_{max} (neat) 2970, 2927, 1726, 1612, 1565, 1452, 1388, 1375, 1280, 1152, 1068, 1039, 896, 764 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₁H₂₇O₄ 343.1909; Found 343.1920.

Elemental Analysis Anal. Calcd for C₂₁H₂₆O₄: C, 73.66; H, 7.65; Found: C, 73.55; H, 7.79.

(E)-8-(4,8-Dimethylnona-3,7-dienyl)-2,2,5,8-tetramethyl-[1,3]dioxino[4,5-*f*]chromen-4(8*H*)-one



Chromene **97b** (522 mg, 1.27 mmol, 63 %), prepared from resorcyate **93b** (827 mg, 2.00 mmol), was obtained as colourless oil.

R_f 0.32 (Pentane : Et₂O 9 : 1).

¹H NMR (400 MHz, CDCl₃) δ 6.51 (d, *J* = 10.1 Hz, 1H, H₁₀), 6.32 (s, 1H, H₆), 5.50 (d, *J* = 10.1 Hz, 1H, H₉), 5.13 – 4.96 (m, 2H, H_{18,22}), 2.56 (s, 3H, H₁₄), 2.13 – 1.96 (m, 4H, H_{20–21}), 1.96 – 1.87 (m, 2H, H₁₇), 1.79 – 1.69 (m, 2H, H₁₆), 1.67 (s, 6H, H_{11–12}), 1.63 (s, 3H, H₂₄), 1.55 (s, 3H, H₂₅), 1.53 (s, 3H, H₂₆), 1.37 (s, 3H, H₁₅).

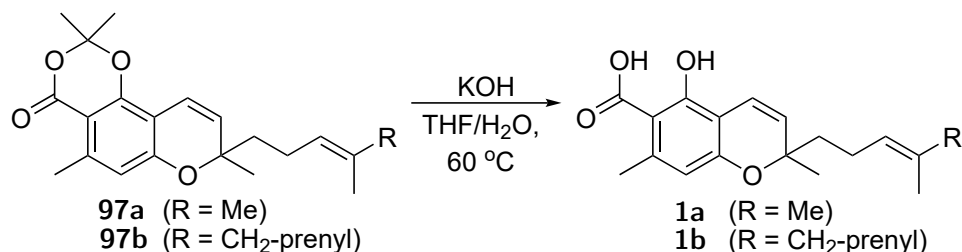
¹³C NMR (100 MHz, CDCl₃) δ 160.3 (C₄), 158.5 (C_{6a}), 152.7 (C_{1a}), 144.5 (C₅), 135.4 (C₁₉), 131.1 (C₂₃), 127.6 (C₉), 124.1 (C₂₂), 123.4 (C₁₈), 115.6 (C₁₀), 113.7 (C₆), 107.2 (C_{10a}), 104.8 (C_{4a}), 104.6 (C₂), 80.0 (C₈), 41.5 (C₁₆), 39.5 (C₂₀), 26.9 (C₁₅), 26.5 (C₂₁), 25.6 (C₂₄), 25.6 (C_{11–12}), 22.4 (C₁₇), 22.2 (C₁₄), 17.5 (C₂₅), 15.8 (C₂₆).

IR ν_{max} (neat) 2969, 2926, 1729, 1612, 1566, 1452, 1388, 1375, 1281, 1151, 1039, 897, 764 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₅O₄ 411.2535; Found 411.2540.

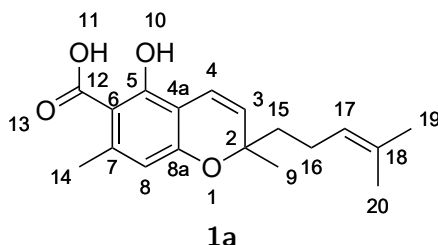
Elemental Analysis Anal. Calcd for C₂₆H₃₄O₄: C, 76.06; H, 8.35; Found: C, 75.88; H, 8.27.

General Procedure for the Synthesis of Chromenic Acids



Aqueous KOH (5 M, 6.5 mL) was added with stirring to chromene **97** (1.00 mmol) in THF (6.5 mL). The resulting mixture was heated at 60 °C for 42 h. The reaction mixture was cooled to 25 °C and diluted with Et₂O (10 mL) and H₂O (10 mL). Phases were separated and the organic layer was extracted with H₂O (5 × 10 mL). The combined aqueous layer was acidified with aqueous HCl (1 M) to pH ~1 and extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated and chromatographed (pentane : EtOAc : AcOH 9 : 1 : 0.01) to obtain chromenic acid **1**.

5-Hydroxy-2,7-dimethyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromene-6-carboxylic acid



(±)-Cannabiorcichromenic acid **1a** (242 mg, 0.801 mmol, 80 %), prepared from chromene **97a** (343 mg, 1.00 mmol), was obtained as white solid.

R_f 0.36 (Pentane : EtOAc 17 : 3).

Melting Point 131.5 – 134.8 °C.

¹H NMR (400 MHz, CDCl₃) δ 11.68 (s, 1H, H₁₀), 6.73 (d, *J* = 10.1 Hz, 1H, H₄), 6.23 (s, 1H, H₈), 5.48 (d, *J* = 10.1 Hz, 1H, H₃), 5.09 (t, *J* = 6.7 Hz, 1H, H₁₇), 2.54 (s, 3H, H₁₄), 2.09 (q, *J* = 8.0 Hz, 2H, H₁₆), 1.83 – 1.71 (m, 1H, H₁₅), 1.66 (s, 3H, H₁₉), 1.64 – 1.59 (m, 1H, H₁₅), 1.57 (s, 3H, H₂₀), 1.40 (s, 3H, H₉).

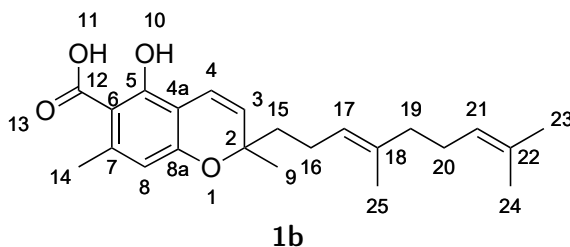
¹³C NMR (100 MHz, CDCl₃) δ 176.1 (C₁₂), 160.6 (C₅), 159.0 (C_{8a}), 144.4 (C₇), 131.8 (C₁₈), 126.3 (C₃), 123.8 (C₁₇), 116.6 (C₄), 112.2 (C₈), 107.0 (C_{4a}), 103.5 (C₆), 80.1 (C₂), 41.7 (C₁₅), 27.2 (C₉), 25.6 (C₁₉), 24.5 (C₁₄), 22.7 (C₁₆), 17.6 (C₂₀).

IR ν_{max} (neat) 3392 (br), 2969, 2924, 1625, 1579, 1451, 1397, 1375, 1294, 1183, 1144, 1085, 1059, 991, 754, 714 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₁₈H₂₃O₄ 303.1596; Found 303.1597.

Elemental Analysis Anal. Calcd for C₁₈H₂₂O₄: C, 71.50; H, 7.33; Found: C, 71.41; H, 7.42.

(*E*)-2-(4,8-Dimethylnona-3,7-dienyl)-5-hydroxy-2,7-dimethyl-2*H*-chromene-6-carboxylic acid



(±)-Daurichromenic acid **1b** (305 mg, 0.822 mmol, 82 %), prepared from chromene **97b** (411 mg, 1.00 mmol), was obtained as yellow oil which solidified upon standing.

R_f 0.17 (Pentane : EtOAc 9 : 1).

¹H NMR (400 MHz, CDCl₃) δ 11.71 (s, 1H, H₁₀), 6.73 (d, J = 10.1 Hz, 1H, H₄), 6.23 (s, 1H, H₈), 5.48 (d, J = 10.1 Hz, 1H, H₃), 5.19 – 4.99 (m, 2H, H_{17,21}), 2.54 (s, 3H, H₁₄), 2.15 – 2.00 (m, 4H, H_{16,20}), 1.99 – 1.91 (m, 2H, H₁₉), 1.83 – 1.70 (m, 1H, H₁₅), 1.67 (s, 3H, H₂₃), 1.66 – 1.62 (m, 1H, H₁₅), 1.59 (s, 3H, H₂₄), 1.57 (s, 3H, H₂₅), 1.41 (s, 3H, H₉).

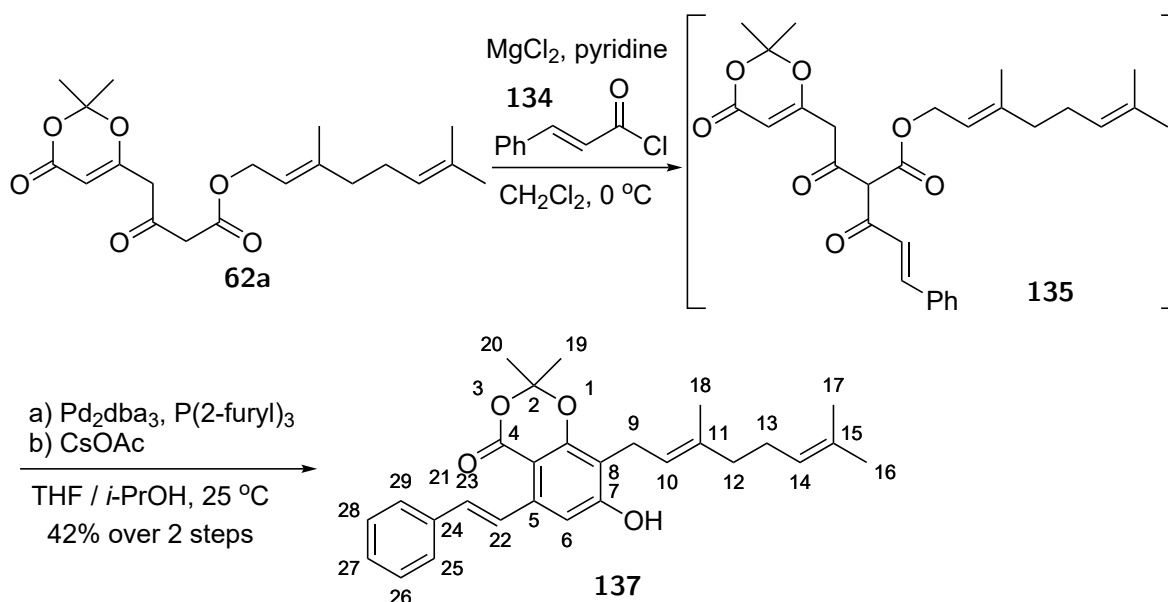
¹³C NMR (100 MHz, CDCl₃) δ 175.8 (C₁₂), 160.6 (C₅), 158.9 (C_{8a}), 144.4 (C₇), 135.5 (C₁₈), 131.3 (C₂₂), 126.3 (C₃), 124.3 (C₂₁), 123.7 (C₁₇), 116.6 (C₄), 112.1 (C₈), 107.0 (C_{4a}), 103.6 (C₆), 80.1 (C₂), 41.7 (C₁₅), 39.7 (C₁₉), 27.2 (C₉), 26.7 (C₂₀), 25.7 (C₂₃), 24.5 (C₁₄), 22.6 (C₁₆), 17.7 (C₂₄), 16.0 (C₂₅).

IR ν_{max} (neat) 2969, 1618, 1455, 1268, 1177 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₃H₃₁O₄ 371.2222; Found 371.2213.

Elemental Analysis Anal. Calcd for C₂₃H₃₀O₄: C, 74.56; H, 8.16; Found: C, 74.56; H, 8.25.

8-((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2-dimethyl-5-((*E*)-styryl)-4*H*-benzo[*d*][1,3]dioxin-4-one



MgCl₂ (1.43 g, 15.0 mmol) and pyridine (2.42 mL, 30.0 mmol) were added to dioxinone β -keto ester **62a** (5.47 g, 15.0 mmol) in CH₂Cl₂ (100 mL) and the mixture was cooled to 0 °C. *trans*-Cinnamoyl chloride **134** (3.75 g, 22.5 mmol) was added with stirring at 0 °C. After 1.5 h, saturated aqueous NH₄Cl (50 mL) was added and the mixture acidified with aqueous HCl (1 M) to pH ~2. The two phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 100 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated to provide crude dioxinone β,δ -diketo ester **135**. The crude ester **135** was dissolved in THF (90 mL), and P(2-furyl)₃ (697 mg, 3.00 mmol) and Pd₂dba₃ (687 mg, 0.750 mmol) were sequentially added with stirring at 25 °C. After 1.5 h, CsOAc (8.64 g, 45.0 mmol) in *i*-Pr-OH (90 mL) was added and the mixture stirred for 1.5 h at 25 °C. Aqueous HCl (1 M) was added to pH ~1 and phases were separated. The aqueous layer was extracted with CH₂Cl₂ (4 $\times$ 150 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 19 : 1 to 10 : 1) to provide resorcylate **137** (2.70 g, 6.23 mmol, 42 % over 2 steps) as an off-white powder. An analytical sample was prepared by recrystallisation from *n*-hexane.

R_f 0.32 (Pentane : EtOAc 10 : 1).

Melting Point 123.7 – 124.1 °C.

¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, J = 16.2 Hz, 1H, H₂₂), 7.63 – 7.49 (m, 2H, H_{25,29}), 7.38 – 7.32 (m, 2H, H_{16,28}), 7.31 – 7.22 (m, 1H, H₂₇), 7.01 (d, J = 16.2 Hz, 1H, H₂₃), 6.89 (s, 1H, H₆), 5.93 (s, 1H, H₃₀), 5.29 – 5.16 (m, 1H, H₁₀), 5.12 – 4.99 (m, 1H, H₁₄), 3.38 (d, J = 7.2 Hz, 2H, H₉), 2.18 – 2.01 (m, 4H, H_{12–13}), 1.81 (s, 3H, H₁₈), 1.72 (s, 6H, H_{19–20}), 1.68 (s, 3H, H₁₆), 1.60 (s, 3H, H₁₇).

¹³C NMR (100 MHz, CDCl₃) δ 160.7 (C₄), 160.2 (C₇), 155.8 (C_{8a}), 141.2 (C₂₄), 139.4 (C₁₁), 137.1 (C₅), 132.2 (C₁₅), 132.0 (C₂₃), 128.6 (C_{26,28}), 128.0 (C₂₇), 127.1 (C_{25,29}), 126.8 (C₂₂), 123.6 (C₁₄), 120.4 (C₁₀), 114.2 (C₈), 108.8 (C₆), 104.8 (C₂), 104.3 (C_{4a}), 39.7 (C₁₂), 26.3 (C₁₃), 25.7 (C_{19–20}), 22.1 (C₉), 17.7 (C₁₇), 16.25 (C₁₈).

IR ν_{max} (neat) 3295, 2925, 1686, 1583, 1297, 1279, 1062, 751 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₈H₃₃O₄ 433.2373; Found 433.2366.

diol



83 %) as white crystals.

R_f 0.30 (Pentane : EtOAc 11 : 1).

Melting Point 94.8 – 95.6 °C.

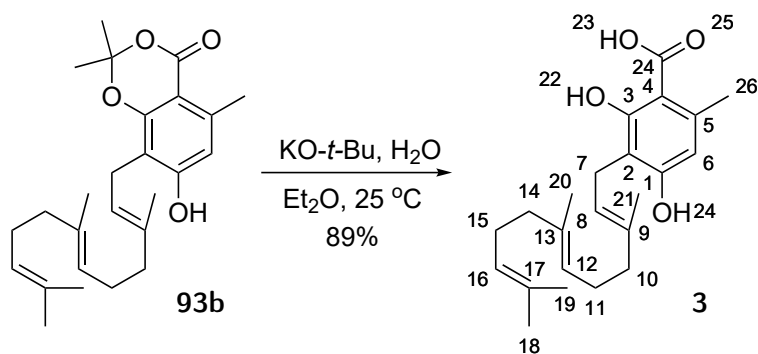
¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.45 (m, 2H, H_{21,25}), 7.38 – 7.32 (m, 2H, H_{22,24}), 7.29 – 7.22 (m, 1H, H₂₃), 7.01 (d, *J* = 16.3 Hz, 1H, H₁₉), 6.93 (d, *J* = 16.3 Hz, 1H, H₁₈), 6.59 (s, 2H, H_{4,6}), 5.28 (t, *J* = 7.1 Hz, 1H, H₈), 5.12 (s, 2H, H_{17,26}), 5.09 – 5.01 (m, 1H, H₁₂), 3.44 (d, *J* = 7.1 Hz, 2H, H₇), 2.25 – 2.03 (m, 4H, H_{10–11}), 1.83 (s, 3H, H₁₆), 1.69 (s, 3H, H₁₄), 1.60 (s, 3H, H₁₅).

¹³C NMR (100 MHz, CDCl₃) δ 155.2 (C_{1,3}), 139.5 (C₉), 137.2 (C₂₀), 136.9 (C₅), 132.1 (C₁₃), 128.69 (C₂₄), 128.65 (C₂₂), 128.0 (C_{18,19}), 127.6 (C₂₃), 126.5 (C_{21,25}), 123.7 (C₈), 121.2 (C₁₂), 113.2 (C₂), 106.6 (C_{4,6}), 39.7 (C₁₀), 26.4 (C₁₁), 25.7 (C₁₄), 22.5 (C₇), 17.7 (C₁₅), 16.2 (C₁₆).

IR ν_{max} (neat) 3376, 2922, 2587, 1582, 1449, 1425, 1166, 1042, 960, 821, 750, 692 cm^{-1} .

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₄H₂₈O₂ 349.2168; Found 349.2196.

2,4-Dihydroxy-6-methyl-3-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoic acid



H₂O (72 μ L, 4.00 mmol) was added dropwise with stirring to KO-*t*-Bu (898 mg, 8.00 mmol) in Et₂O (10 mL) at 0 °C. Subsequently, resorcyate **93b** (413 mg, 1.00 mmol) was added and the slurry was stirred at 25 °C for 3 d. Ice was added until the two phases separated and the organic layer was extracted with H₂O (5 $\times$ 10 mL). The combined aqueous layers were acidified with HCl (4 M) to pH $\sim$ 1 and subsequently extracted with CH₂Cl₂ (5 $\times$ 10 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc : AcOH 9 : 1 : 0.01) to give grifolic acid **3** (333 mg, 0.894 mmol, 89 %) as a white solid.

R_f 0.21 (Pentane : EtOAc : AcOH 9 : 1 : 0.01).

Melting Point 95.8 – 96.2 °C.

¹H NMR (400 MHz, CDCl₃) δ 11.83 (s, 1H, H₂₃), 6.27 (s, 1H, H₆), 5.92 (s, 1H, H₂₂), 5.28 (t, *J* = 6.8 Hz, 1H, H₈), 5.12 – 5.04 (m, 2H, H_{12,16}), 3.43 (d, *J* = 7.2 Hz, 2H, H₇), 2.53 (s, 3H, H₂₆), 2.14 (s, 1H, H₂₇), 2.14 – 1.93 (m, 8H, H_{10–11,14–15}), 1.82 (s, 3H, H₂₁), 1.67 (s, 3H, H₁₈), 1.59 (s, 6H, H_{19–20}).

¹H NMR (400 MHz, CD₃COCD₃) δ 12.49 (s, 1H), 11.55 (s, 1H), 8.89 (s, 1H), 6.32 (s, 1H), 5.30 – 5.22 (m, 1H), 5.12 – 5.02 (m, 2H), 3.32 (d, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.10 – 1.86 (m, 8H), 1.77 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 176.0 (C₂₄), 163.6 (C₁), 160.5 (C₃), 142.5 (C₅), 139.3 (C₉), 135.6

(C₁₃), 131.3 (C₁₇), 124.4 (C₁₆), 123.5 (C₁₂), 121.2 (C₈), 111.9 (C₂), 111.5 (C₆), 103.8 (C₄), 39.70 (C₁₀), 39.65 (C₁₄), 26.7 (C₁₅), 26.3 (C₁₁), 25.7 (C₁₈), 24.2 (C₂₆), 22.0 (C₇), 17.7 (C₁₉), 16.3 (C₂₁), 16.1 (C₂₀).

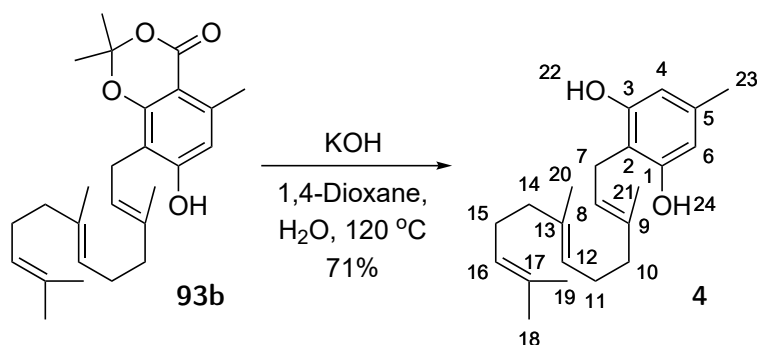
¹³C NMR (100 MHz, CD₃COCD₃) δ 174.7, 164.8, 160.6, 141.5, 135.3, 134.7, 131.5, 125.2, 125.0, 123.6, 113.6, 111.5, 104.6, 40.5, 40.4, 27.4, 27.2, 25.8, 24.3, 22.5, 17.7, 16.2, 16.1.

IR ν_{max} (neat) 3416, 2968, 2910, 2854, 1617, 1456, 1382, 1257 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₃H₃₁O₄ 371.2222; Found 371.2213.

Elemental Analysis Anal. Calcd for C₂₃H₃₂O₄: C, 74.16; H, 8.66; Found: C, 74.22; H, 8.61.

5-Methyl-2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene-1,3-diol



KOH (5 M; 4 mL) was added to resorcyate **93b** (413 mg, 1.00 mmol) in 1,4-dioxane (8 mL) and the resulting mixture was heated to 120 °C for 24 h. After cooling to 25 °C, aqueous HCl (4 M) was added to pH ~1 and the two phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 3 : 1) to give grifolin **4** (234 mg, 0.712 mmol, 71 %) as an orange oil which solidified upon standing.

R_f 0.45 (Pentane : Et₂O 3 : 1).

Melting Point 41.0 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.24 (s, 2H, H_{4,6}), 5.32 – 5.22 (m, 1H, H₈), 5.13 – 5.06 (m, 2H, H_{12,16}), 5.05 (s, 2H, H_{22,24}), 3.39 (d, *J* = 7.1 Hz, 2H, H₇), 2.21 (s, 3H, H₂₃), 2.17 – 1.92 (m, 8H, H_{10–11,14–15}), 1.82 (s, 3H, H₂₁), 1.68 (s, 3H, H₁₈), 1.60 (s, 3H, H₂₀), 1.59 (s, 3H, H₁₉).

¹H NMR (400 MHz, CD₃COCD₃) δ 7.82 (s, 2H), 6.19 (s, 2H), 5.33 – 5.27 (m, 1H), 5.14 – 5.04 (m, 2H), 3.31 (d, *J* = 7.1 Hz, 2H), 2.09 (s, 3H), 2.08 – 1.89 (m, 8H), 1.76 (s, 3H), 1.64 (s, 3H), 1.57 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 154.8 (C_{1,3}), 139.0 (C₅), 137.5 (C₉), 135.6 (C₁₃), 131.3 (C₁₇), 124.4 (C₁₂), 123.6 (C₁₆), 121.6 (C₈), 110.4 (C₂), 109.0 (C_{4,6}), 39.68 (C₁₀), 39.65 (C₁₄), 26.7 (C₁₁), 26.4 (C₁₅), 25.7 (C₁₈), 22.2 (C₇), 21.0 (C₂₃), 17.7 (C₁₉), 16.2 (C₂₁), 16.0 (C₂₀).

¹³C NMR (100 MHz, CD₃COCD₃) δ 156.7, 136.7, 135.3, 134.1, 131.5, 125.2, 125.1, 124.6, 112.6,

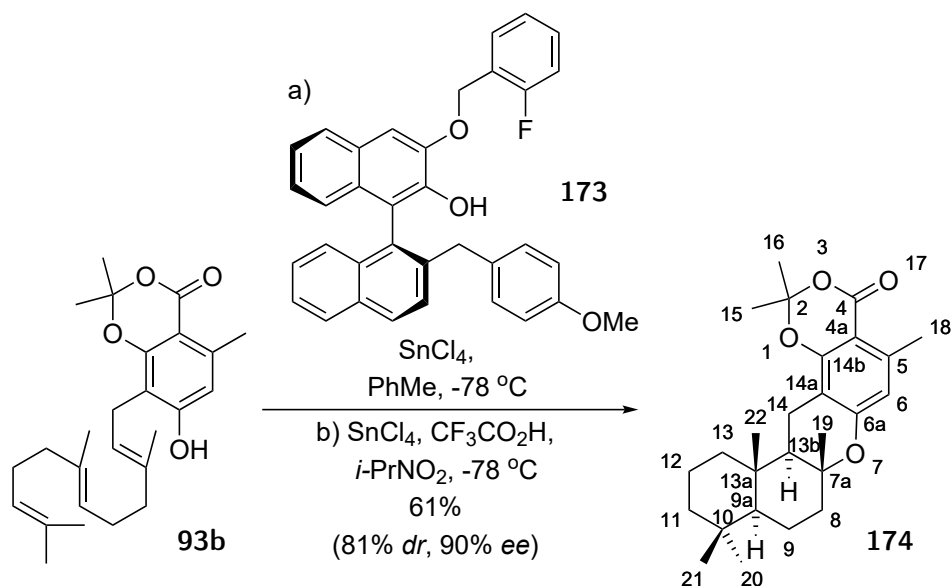
108.4, 40.6, 40.4, 27.38, 27.35, 25.8, 22.7, 21.2, 17.7, 16.2, 16.0.

IR ν_{max} (neat) 3430, 2966, 2918, 2855, 1631, 1590, 1444, 1041 cm^{-1} .

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{32}\text{O}_2$ 328.2402; Found 328.2406.

Elemental Analysis Anal. Calcd for $\text{C}_{22}\text{H}_{32}\text{O}_2$: C, 80.44; H, 9.82; Found: C, 80.32; H, 9.73.

**(7a*R*,9a*S*,13a*S*,13b*R*)-2,2,5,7a,10,10,13a-Heptamethyl-
7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-
benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one**



SnCl_4 in heptane (1 M; 0.750 mL, 0.750 mmol) was added with stirring to binol **173** (463 mg, 0.900 mmol) in PhMe (9 mL) at 25°C . After 10 min, the mixture was cooled to -78°C , when resorcyate **93b** (124 mg, 0.300 mmol) in PhMe (1.5 mL) was added dropwise and the reaction mixture was further stirred for 48 h at -78°C . Reaction was quenched with NaHCO_3 (15 mL) and the mixture diluted with Et_2O (10 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4×15 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O 9 : 1 to PhMe : Et_2O 12 : 1) to recover the binol **173**. The crude mixture of products was then dissolved in $i\text{-PrNO}_2$ (6 mL) and cooled to -78°C . SnCl_4 in heptane (1 M; 0.750 mL, 0.750 mmol) and CF_3COOH (0.230 mL, 3.00 mmol) were sequentially added dropwise with stirring at -78°C . After 24 h, reaction was quenched with saturated aqueous NaHCO_3 (10 mL) and diluted with Et_2O (10 mL). The two phases were separated, and the aqueous layer was extracted with Et_2O (4×15 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O 9 : 1) to

provide meroterpenoid **174** (78 mg, 0.189 mmol, 63 %, 80 % *dr*, 90 % *ee*, measured by chiral HPLC, Chiralpak® IE column, *n*-hexane : *i*-PrOH 19 : 1, 5 mL/min, t_R = 15.9 [(+)-enantiomer], 14.9 [(-)-enantiomer] min) as a colourless oil containing a mixture of diastereoisomers. An analytical sample was purified by preparative chiral HPLC.

R_f 0.75 (Pentane : EtOAc 3 : 1).

Specific Rotation $[\alpha]_D^{20} + 80.3^\circ$ (*c* 0.57, MeOH).

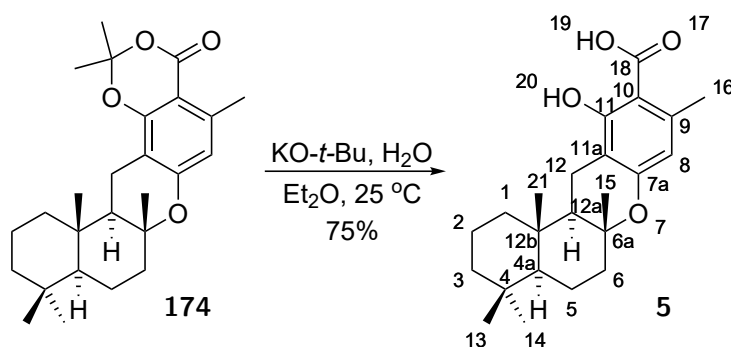
¹H NMR (500 MHz, CDCl₃) δ 6.33 (s, 1H, H₆), 2.57 (s, 3H, H₁₈), 2.53 (dd, 1H, H_{14eq}), 2.24 (dd, *J* = 16.8, 13.2 Hz, 1H, H_{14ax}), 2.08 (dt, *J* = 12.5, 3.2 Hz, 1H, H_{8eq}), 1.82 – 1.77 (m, 1H, H_{9eq}), 1.77 – 1.74 (m, 1H, H_{13eq}), 1.72 (s, 3H, H₁₆), 1.69 (s, 3H, H₁₅), 1.68 – 1.65 (m, 1H, H_{8ax}), 1.65 – 1.62 (m, 1H, H_{12eq}), 1.53 (d, *J* = 5.3 Hz, 1H, H_{13b}), 1.52 – 1.45 (m, 1H, H_{12ax}), 1.45 – 1.39 (m, 1H, H_{11eq}), 1.39 – 1.34 (m, 1H, H_{9ax}), 1.19 (s, 3H, H₁₉), 1.16 (dd, *J* = 13.5, 4.3 Hz, 1H, H_{11ax}), 1.02 (dd, *J* = 12.2, 2.3 Hz, 1H, H_{9a}), 0.98 (dd, *J* = 12.8, 3.8 Hz, 1H, H_{13ax}), 0.91 (s, 6H, H_{20,22}), 0.85 (s, 3H, H₂₁).

¹³C NMR (100 MHz, CDCl₃) δ 160.9 (C₄), 158.7 (C_{14a}), 156.1 (C_{14b}), 142.0 (C_{4a}), 114.3 (C₆), 108.3 (C_{6a}), 104.8 (C₂), 103.9 (C₅), 78.4 (C_{7a}), 56.1 (C_{9a}), 51.3 (C_{13b}), 41.8 (C₁₁), 40.8 (C₈), 39.2 (C₁₃), 36.9 (C_{13a}), 33.4 (C₂₀), 33.2 (C₁₀), 26.2 (C₁₆), 25.5 (C₁₅), 22.0 (C₁₈), 21.6 (C₂₁), 20.7 (C₁₉), 19.7 (C₉), 18.5 (C₁₂), 16.5 (C₁₄), 14.9 (C₂₂).

IR ν_{max} (neat) 2928, 2867, 1728, 1616, 1575, 1452, 1388, 1285, 1127 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₇O₄ 413.2696; Found 413.2698.

(4a*S*,6a*R*,12a*R*,12b*S*)-11-Hydroxy-4,4,6a,9,12b-pentamethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid



H₂O (7 µL, 0.383 mmol) was added with stirring to a suspension of meroterpenoid **174** (79 mg, 0.191 mmol) and KO-*t*-Bu (172 mg, 1.53 mmol) in Et₂O (3 mL) at 25 °C. After 2 h, ice was added until two layers were formed and the two phases were separated. The organic layer was extracted with H₂O (5 × 5 mL) and the combined aqueous layers were acidified with HCl (4 M) to pH ~1. The two phases were separated and the aqueous layer was extracted with Et₂O (5 × 5 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc : AcOH 9 : 1 : 0.01) to afford (+)-hongoquercin A (**5**) (53 mg, 0.142 mmol, 75 %) as white solid. An analytical sample was prepared by recrystallisation (pentane : CH₂Cl₂).

R_f 0.25 (pentane : EtOAc : AcOH 9 : 1 : 0.01).

Melting Point 146.1 – 148.5 °C.

Specific Rotation [α]_D²⁴ + 90.5° (c 0.57, MeOH).

¹H NMR (400 MHz, CDCl₃) δ 11.86 (s, 1H, H₂₀), 6.21 (s, 1H, H₈), 2.69 (dd, *J* = 16.9, 5.0 Hz, 1H, H_{12eq}), 2.51 (s, 3H, H₁₆), 2.29 (dd, *J* = 16.9, 13.2 Hz, 1H, H_{12ax}), 2.08 (dt, *J* = 12.5, 3.1 Hz, 1H, H_{6eq}), 1.86 – 1.72 (m, 2H, H_{1eq,5ax}), 1.69 (dd, *J* = 13.1, 4.8 Hz, 1H, H_{6ax}), 1.66 – 1.58 (m, 1H, H_{2eq}), 1.55 (dd, *J* = 13.1, 5.0 Hz, 1H, H_{12a}), 1.52 – 1.45 (m, 1H, H_{2ax}), 1.44 – 1.42 (m, 1H, H_{3eq}),

1.42 – 1.34 (m, 1H, H_{5eq}), 1.20 (s, 3H, H₁₅), 1.15 (dd, $J = 13.4, 4.0$ Hz, 1H, H_{3ax}), 1.03 (dd, $J = 12.2, 2.2$ Hz, 1H, H_{4a}), 1.00 – 0.94 (m, 1H, H_{1ax}), 0.92 (s, 3H, H₂₁), 0.91 (s, 3H, H₁₃), 0.85 (s, 3H, H₁₄).

¹H NMR (500 MHz, CD₃OD) δ 6.11 (s, 1H), 2.65 (dd, $J = 16.9, 5.0$ Hz, 1H), 2.46 (s, 3H), 2.27 (dd, $J = 16.7, 13.2$ Hz, 1H), 2.05 (dt, $J = 12.5, 3.2$ Hz, 1H), 1.81 – 1.76 (m, 2H), 1.72 (dt, $J = 13.7, 3.6$ Hz, 1H), 1.69 – 1.61 (m, 1H), 1.52 (dd, $J = 13.2, 5.2$ Hz, 1H), 1.50 – 1.40 (m, 3H), 1.26 – 1.21 (m, 1H), 1.19 (s, 3H), 1.08 (dd, $J = 12.2, 2.3$ Hz, 1H), 1.05 – 0.98 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 175.3 (C₁₈), 163.9 (C₁₁), 158.8 (C_{7a}), 141.3 (C₉), 112.6 (C₈), 108.1 (C_{11a}), 102.4 (C₁₀), 78.4 (C_{6a}), 56.1 (C_{4a}), 51.5 (C_{12a}), 41.8 (C₃), 40.8 (C₆), 39.2 (C₁), 37.0 (C_{12b}), 33.4 (C₁₃), 33.2 (C₄), 24.1 (C₁₆), 21.6 (C₁₄), 20.8 (C₁₅), 19.7 (C₅), 18.5 (C₂), 16.7 (C₁₂), 14.9 (C₂₁).

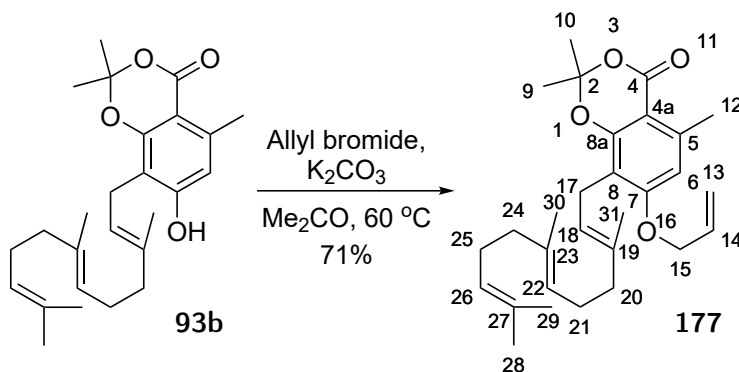
¹³C NMR (126 MHz, CD₃OD) δ 175.6, 164.5, 158.9, 141.7, 112.8, 108.8, 104.9, 79.0, 57.5, 53.2, 43.0, 42.1, 40.4, 38.1, 34.2, 33.9, 24.2, 22.0, 21.1, 20.8, 19.6, 17.7, 15.4.

IR ν_{max} (neat) 2927, 1621, 1574, 1454, 1378, 1262, 1126 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₃H₃₃O₄ 373.2383; Found 373.2379.

Elemental Analysis Anal. Calcd for C₂₃H₃₂O₄: C, 74.16; H, 8.66; Found: C, 74.22; H, 8.78.

7-(Allyloxy)-2,2,5-trimethyl-8-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one



Allyl bromide (0.65 mL, 7.50 mmol) was added with stirring to a suspension of K_2CO_3 (1.38 g, 10.0 mmol) and resorcyate **93b** (2.06 g, 5.00 mmol) in Me_2CO (50 mL). The resulting suspension was heated to 60 °C with stirring for 18 h, when the mixture was concentrated and diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 9 : 1) to provide allyl ether **177** (1.61 g, 3.56 mmol, 71 %) as a pale yellow oil.

R_f 0.33 (Pentane : Et_2O 9 : 1).

^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H, H_6), 6.04 (ddt, J = 17.3, 10.3, 5.1 Hz, 1H, H_{14}), 5.42 (dd, J = 17.3, 1.6 Hz, 1H, H_{13}), 5.30 (dd, J = 10.6, 1.4 Hz, 1H, H_{13}), 5.13 (tq, J = 7.3, 1.3 Hz, 1H, H_{18}), 5.07 (tdd, J = 6.9, 3.1, 1.4 Hz, 2H, $H_{22,26}$), 4.60 (dt, J = 5.1, 1.6 Hz, 2H, H_{15}), 3.29 (d, J = 7.3 Hz, 2H, H_{17}), 2.63 (s, 3H, H_{12}), 2.10 – 1.89 (m, 8H, $H_{20,21,24,25}$), 1.75 (s, 3H, H_{31}), 1.68 – 1.66 (m, 9H, $H_{9,10,28}$), 1.58 (s, 3H, H_{29}), 1.56 (s, 3H, H_{30}).

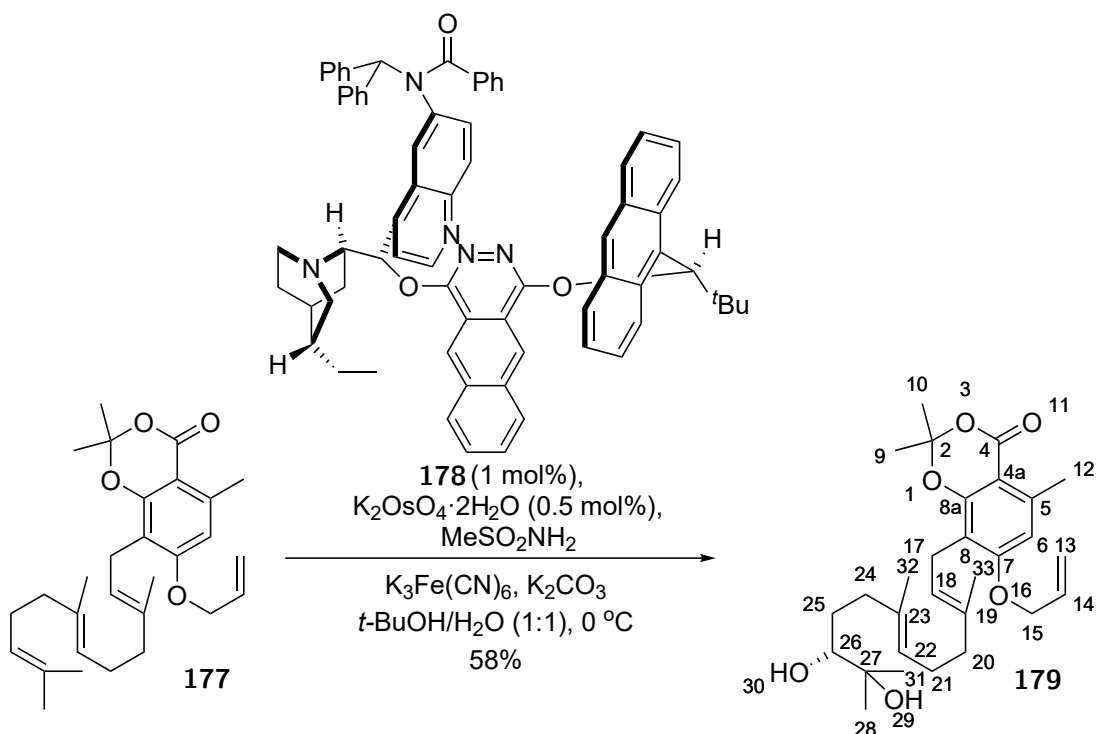
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 ($C_{4,7}$), 155.6 (C_{8a}), 142.5 (C_{4a}), 135.2 (C_{19}), 134.9 (C_{23}), 132.6 (C_{14}), 131.2 (C_{27}), 124.3 (C_{22}), 124.1 (C_{26}), 121.6 (C_{18}), 117.6 (C_{13}), 116.0 (C_8), 109.3 (C_6), 105.7 (C_5), 104.7 (C_2), 68.9 (C_{15}), 39.74 (C_{20}), 39.66 (C_{24}), 26.7 (C_{21}), 26.5 (C_{25}), 25.73 ($C_{9,10}$), 25.66 (C_{28}), 22.5 (C_{12}), 21.8 (C_{17}), 17.6 (C_{29}), 16.1 (C_{30}), 16.0 (C_{31}).

IR ν_{max} (neat) 2969, 3925, 2856, 1729, 1606, 1575, 1376, 1278, 1207, 1169, 1115, 1046, 980, 908 cm^{-1} .

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{29}\text{H}_{41}\text{O}_4$ 453.3005; Found 453.2983.

Elemental Analysis Anal. Calcd for $\text{C}_{29}\text{H}_{40}\text{O}_4$: C, 76.95; H, 8.91; Found: C, 76.84; H, 8.87.

7-(Allyloxy)-8-((*R*,2*E*,6*E*)-10,11-dihydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



Allyl ether **177** (1.53 g, 3.38 mmol) was dissolved in *t*-BuOH (17 mL) and H_2O (17 mL) and cooled to 0°C . Ligand **178** (35 mg, 33.8 μmol), MeSO_4NH_2 (322 mg, 3.39 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (3.34 g, 10.1 mmol), K_2CO_3 (1.40 g, 10.1 mmol) and $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (6.3 mg, 17.1 μmol) were added sequentially with stirring at 0°C . After 24 h, solid Na_2SO_3 (3.00 g) was added and the mixture was further stirred for 30 min. The reaction mixture was diluted with H_2O (25 mL) and EtOAc (25 mL), the two phases were separated, and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : EtOAc 4 : 1 to 1 : 1 to EtOAc : EtOH 4 : 1) to afford unreacted allyl ether **177** (400 mg, 0.88 mmol, 26 %), tetraol (204 mg, 0.392 mmol, 12 %), ligand **178** (33 mg, 32.3 μmol , 96 % recovered) and diol **179** (956 mg, 1.96 mmol, 58 %, 78 % corrected for recovered allyl ether **177**) as a colourless oil.

R_f 0.36 (Pentane : EtOAc 1 : 1).

Specific Rotation $[\alpha]_{\text{D}}^{23} + 10.4^{\circ}$ (*c* 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 6.42 (s, 1H, H₆), 6.05 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1H, H₁₄), 5.42 (dd, *J* = 17.3, 1.6 Hz, 1H, H₁₃), 5.30 (dd, *J* = 10.6, 1.4 Hz, 1H, H₁₃), 5.19 – 5.10 (m, 2H, H_{18,22}), 4.61 (dt, *J* = 5.1, 1.6 Hz, 2H, H₁₅), 3.33 (dd, *J* = 10.5, 2.0 Hz, 1H, H₂₆), 3.29 (d, *J* = 7.4 Hz, 2H, H₁₇), 2.63 (s, 3H, H₁₂), 2.25 – 1.92 (m, 6H, H_{20,21,24}), 1.75 (s, 3H, H₃₃), 1.71 (s, 2H, H_{29,30}), 1.67 (s, 6H, H_{9,10}), 1.59 (s, 3H, H₃₂), 1.56 – 1.45 (m, 1H, H₂₅), 1.46 – 1.32 (m, 1H, H₂₅), 1.18 (s, 3H, H₃₁), 1.14 (s, 3H, H₂₈).

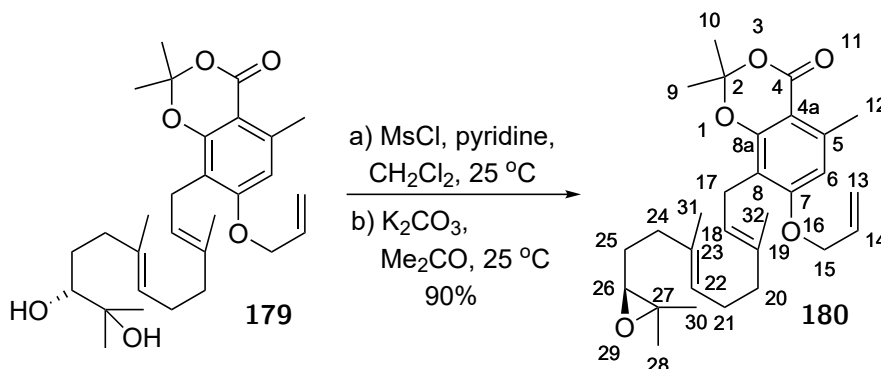
¹³C NMR (100 MHz, CDCl₃) δ 161.14 (C₄), 161.08 (C₇), 155.7 (C_{8a}), 142.7 (C_{4a}), 135.2 (C₁₉), 135.1 (C₂₃), 132.8 (C₁₄), 125.1 (C₂₂), 121.9 (C₁₈), 117.9 (C₁₃), 116.1 (C₈), 109.5 (C₆), 105.9 (C₅), 104.9 (C₂), 78.4 (C₂₆), 73.1 (C₂₇), 69.1 (C₁₅), 39.9 (C₂₀), 36.9 (C₂₄), 29.8 (C₂₅), 26.7 (C₂₁), 26.6 (C₂₈), 25.9 (2C, C_{9,10}), 23.4 (C₃₁), 22.6 (C₁₂), 21.9 (C₁₇), 16.2 (C₃₂), 16.0 (C₃₃).

IR ν_{max} (neat) 3443, 2931, 2972, 1729, 1606, 1576, 1451, 1377, 1329, 1281, 1209, 1170, 1117 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₉H₄₃O₆ 487.3060; Found 487.3051.

Elemental Analysis Anal. Calcd for C₂₉H₄₂O₆: C, 71.57; H, 8.70; Found: C, 71.69; H, 8.73.

7-(Allyloxy)-8-((2*E*,6*E*)-9-((*S*)-3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



Pyridine (2.20 mL, 27.3 mmol) and MsCl (0.28 mL, 3.62 mmol) were added sequentially with stirring at 25 °C to diol **179** in CH₂Cl₂ (20 mL). After 15 h, the mixture was diluted with Me₂CO (50 mL) and K₂CO₃ (20.0 g, 0.145 mmol) was added and stirring continued for 24 h at 25 °C. H₂O (30 mL) was added and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 19 : 1 to 5 : 1) to give epoxide **180** (767 mg, 1.64 mmol, 90 %) as colorless oil.

R_f 0.25 (Pentane : EtOAc 19 : 1).

Specific Rotation [α]_D²⁵ - 1.8° (c 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 6.41 (s, 1H, H₆), 6.16 – 5.90 (m, 1H, H₁₄), 5.46 – 5.36 (m, 1H, H₁₃), 5.32 – 5.26 (m, 1H, H₁₃), 5.17 – 5.05 (m, 2H, H_{18,22}), 4.60 (d, *J* = 5.0 Hz, 2H, H₁₅), 3.28 (d, *J* = 7.3 Hz, 2H, H₁₇), 2.66 (t, *J* = 6.3 Hz, 1H, H₂₆), 2.62 (s, 3H, H₁₂), 2.17 – 1.91 (m, 6H, H_{20,21,24}), 1.74 (s, 3H, H₃₂), 1.66 (s, 6H, H_{9,10}), 1.57 (s, 3H, H₃₁), 1.67 – 1.48 (m, 2H, H₂₅), 1.28 (s, 3H, H₃₀), 1.23 (s, 3H, H₂₈).

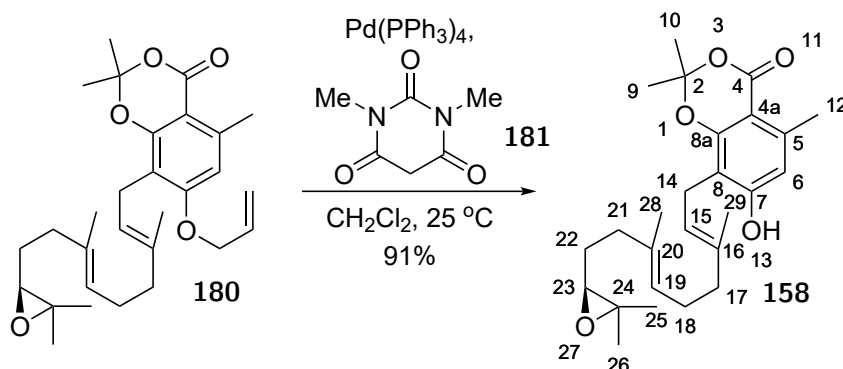
¹³C NMR (100 MHz, CDCl₃) δ 160.9 (2C, C_{4,7}), 155.5 (C_{8a}), 142.5 (C_{4a}), 135.0 (C₁₉), 134.0 (C₂₃), 132.6 (C₁₄), 124.7 (C₂₂), 121.7 (C₁₈), 117.6 (C₁₃), 115.9 (C₈), 109.3 (C₆), 105.7 (C₅), 104.6 (C₂),

68.9 (C₁₅), 64.1 (C₂₆), 58.2 (C₂₇), 39.7 (C₂₀), 36.2 (C₂₄), 27.4 (C₂₅), 26.5 (C₂₁), 25.7 (2C, C_{9,10}), 24.9 (C₃₀), 22.4 (C₁₂), 21.8 (C₁₇), 18.7 (C₂₈), 16.1 (C₃₂), 15.9 (C₃₁).

IR ν_{max} (neat) 2961, 2923, 1727, 1606, 1575, 1450, 1376, 1327, 1279, 1207, 1169, 1115 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₉H₄₁O₅ 469.2954; Found 469.2960.

8-((2*E*,6*E*)-9-((*S*)-3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



Dimethylbarbituric acid **181** (217 mg, 1.39 mmol) and $\text{Pd(PPh}_3)_4$ (29 mg, 0.0251 mmol) were added sequentially with stirring to epoxide **180** (589 mg, 1.26 mmol) in CH_2Cl_2 (10 mL). After 1 h at 25 °C, the reaction mixture was concentrated and purified by chromatography (pentane : EtOAc 4 : 1) to afford epoxide **158** (491 mg, 1.15 mmol, 91 %) as a colourless oil.

R_f 0.30 (Pentane : EtOAc 4 : 1).

Specific Rotation $[\alpha]_D^{26} + 13.8^\circ$ (c 1.0, CHCl_3).

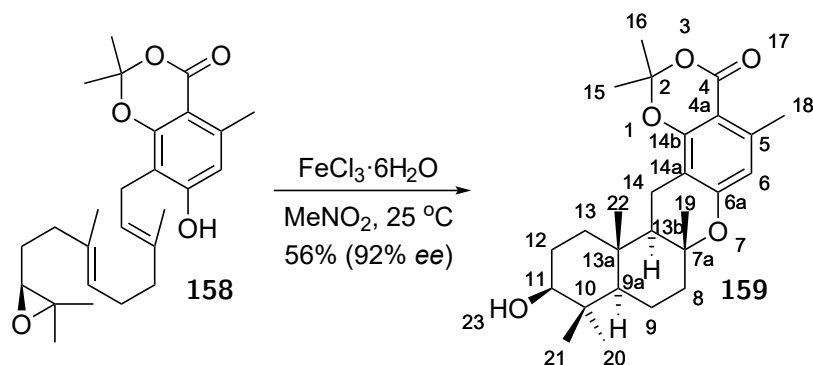
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.90 (s, 1H, H_{13}), 6.42 (s, 1H, H_6), 5.19 – 5.13 (m, 1H, H_{15}), 5.12 – 5.05 (m, 1H, H_{19}), 3.29 (d, $J = 7.3$ Hz, 2H, H_{14}), 2.77 (dd, $J = 7.4, 4.9$ Hz, 1H, H_{23}), 2.58 (s, 3H, H_{12}), 2.19 – 1.98 (m, 6H, $\text{H}_{17,18,21}$), 1.74 (s, 3H, H_{29}), 1.73 – 1.69 (m, 1H, H_{22}), 1.68 (s, 6H, $\text{H}_{9,10}$), 1.57 (s, 3H, H_{28}), 1.56 – 1.49 (m, 1H, H_{22}), 1.33 (s, 3H, H_{26}), 1.29 (s, 3H, H_{25}).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 161.1 (C_4), 160.4 (C_7), 155.9 (C_{8a}), 142.6 (C_{4a}), 136.8 (C_{16}), 134.0 (C_{20}), 124.5 (C_{19}), 121.9 (C_{15}), 113.5 (C_6), 113.2 (C_8), 105.0 (C_5), 104.7 (C_2), 64.6 (C_{23}), 59.5 (C_{24}), 39.3 (C_{17}), 36.2 (C_{21}), 27.0 (C_{22}), 25.74 (2C, $\text{C}_{9,10}$), 25.66 (C_{18}), 24.9 (C_{26}), 22.0 (C_{12}), 21.8 (C_{14}), 18.7 (C_{25}), 16.0 (2C, $\text{C}_{28,29}$).

IR ν_{max} (neat) 3258, 2964, 2927, 1727, 1693, 1609, 1514, 1452, 1377, 1327, 1276, 1210, 1107 cm^{-1} .

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₆H₃₇O₅ 429.2641; Found 429.2645.

(7a*R*,9a*R*,11*S*,13a*S*,13b*R*)-11-Hydroxy-2,2,5,7a,10,10,13a-heptamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one



$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (892 mg, 3.30 mmol) was added with stirring to epoxide **158** (470 mg, 1.10 mmol) in MeNO_2 (220 mL) and the resulting mixture was further stirred at 25 °C for 15 min. Saturated aqueous NaHCO_3 (150 mL) was added and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 50 mL) and the combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : EtOAc 3 : 1) to give meroterpenoid **159** (263 mg, 0.614 mmol, 56 %, 92 % *ee*, measured by chiral HPLC, Chiralpak® IE column, *n*-hexane : *i*-PrOH 17 : 3, 5 mL/min, t_R = 18.9 [(-)-enantiomer], 25.8 [(+)-enantiomer] min) as a white foam.

R_f 0.19 (Pentane : EtOAc 3 : 1).

Specific Rotation $[\alpha]_D^{24} + 52.2^\circ$ (c 1.0, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 6.33 (s, 1H, H_6), 3.26 (dt, J = 11.0, 5.3 Hz, 1H, H_{11}), 2.56 (s, 3H, H_{18}), 2.56 – 2.49 (m, 1H, H_{14eq}), 2.25 (dd, J = 16.7, 13.1 Hz, 1H, H_{14ax}), 2.10 (dt, J = 12.5, 3.2 Hz, 1H, H_{8eq}), 1.86 – 1.76 (m, 2H, $\text{H}_{9eq,13eq}$), 1.72 (s, 3H, H_{16}), 1.68 (s, 3H, H_{15}), 1.73 – 1.60 (m, 3H, $\text{H}_{8ax,12}$), 1.52 (dd, J = 13.1, 5.0 Hz, 1H, H_{13b}), 1.47 – 1.41 (m, 1H, H_{9ax}), 1.40 (d, J = 5.9 Hz, 1H, H_{23}), 1.19 (s, 3H, H_{19}), 1.12 (td, J = 13.0, 4.3 Hz, 1H, H_{13ax}), 1.03 (s, 3H, H_{20}), 1.02 – 0.98 (m, 1H, H_{9a}), 0.92 (s, 3H, H_{21}), 0.82 (s, 3H, H_{22}).

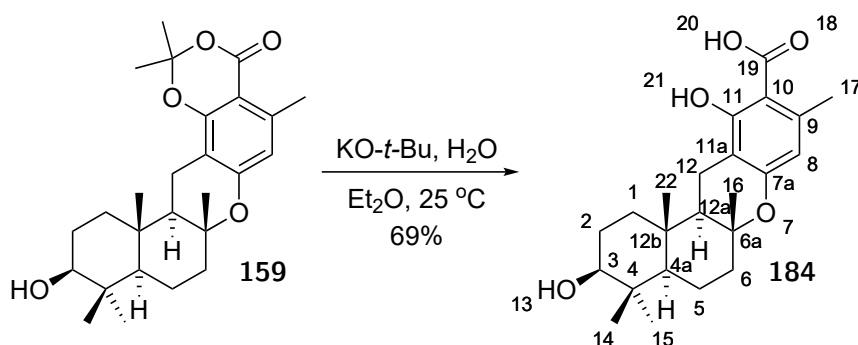
^{13}C NMR (101 MHz, CDCl_3) δ 160.8 (C_4), 158.6 (C_{14a}), 156.1 (C_{14b}), 142.1 (C_{4a}), 114.3 (C_6), 108.0

(C_{6a}), 104.8 (C₂), 104.0 (C₅), 78.6 (C₁₁), 78.1 (C_{7a}), 55.0 (C_{9a}), 51.1 (C_{13b}), 40.7 (C₈), 38.8 (C₁₀), 37.4 (C₁₃), 36.7 (C_{13a}), 28.1 (C₂₀), 27.1 (C₁₂), 26.1 (C₁₆), 25.5 (C₁₅), 22.0 (C₁₈), 20.7 (C₁₉), 19.4 (C₉), 16.5 (C₁₄), 15.5 (C₂₂), 15.0 (C₂₁).

IR ν_{max} (neat) 3440, 2930, 2867, 1713, 1616, 1574, 1452, 1388, 1286, 1207, 1126, 1043 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₆H₃₇O₅ 429.2641; Found 429.2646.

**(3*S*,4*aR*,6*aR*,12*aR*,12*bS*)-3,11-Dihydroxy-4,4,6*a*,9,12*b*-
pentamethyl-1,3,4,4*a*,5,6,6*a*,12,12*a*,12*b*-decahydro-2*H*-
benzo[*a*]xanthene-10-carboxylic
acid**



H₂O (10 μ L, 0.552 mmol) was added to a suspension of KO-*t*-Bu (124 mg, 1.10 mmol) in Et₂O (1 mL) at 0 °C and stirred for 5 min. Meroterpenoid **159** (59 mg, 0.138 mmol) in Et₂O (1 mL) was added with stirring at 25 °C. After 3 h, ice was added until two layers were formed and the two phases were separated and diluted with Et₂O (2 mL). The pH was adjusted to ~1 with aqueous HCl (4 M). The two phases were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 2 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc : AcOH 3 : 1 : 0.01) to give the carboxylic acid **184** (37 mg, 0.0952 mmol, 69 %) as a white solid.

R_f 0.14 (Pentane : EtOAc : AcOH 4 : 1 : 0.01).

Melting Point 153 – 155 °C.

Specific Rotation $[\alpha]_{\text{D}}^{24} + 104.3^\circ (c\ 0.3, \text{CH}_3\text{OH})$.

¹H NMR (400 MHz, CD₃OD) δ 6.08 (s, 1H, H₈), 3.18 (dd, $J = 11.3, 5.0$ Hz, 1H, H₃), 2.61 (dd, $J = 16.8, 5.0$ Hz, 1H, H_{12eq}), 2.45 (s, 3H, H₁₇), 2.26 (dd, $J = 16.7, 13.0$ Hz, 1H, H_{12ax}), 2.03 (dt, $J = 12.4, 3.2$ Hz, 1H, H_{6eq}), 1.84 – 1.73 (m, 2H, H_{1eq,5eq}), 1.72 – 1.59 (m, 3H, H_{2,6ax}), 1.54 – 1.41 (m, 2H, H_{5ax,12a}), 1.16 (s, 3H, H₁₆), 1.15 – 1.08 (m, 1H, H_{1ax}), 1.04 – 1.01 (m, 1H, H_{4a}), 1.00 (s, 3H,

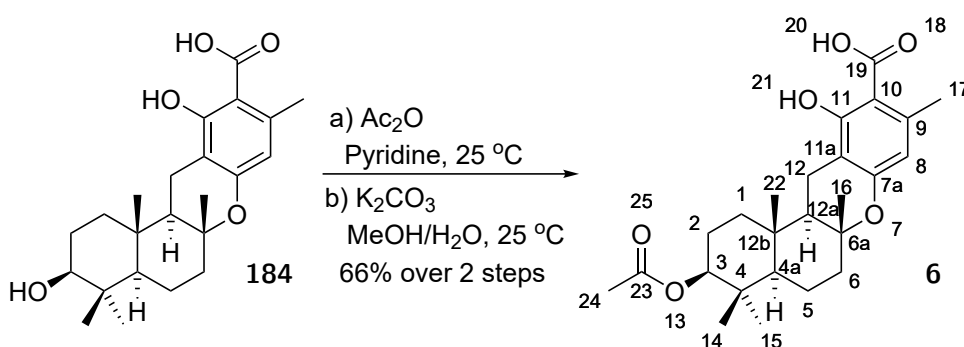
H₁₅), 0.94 (s, 3H, H₂₂), 0.81 (s, 3H, H₁₄).

¹³C NMR (101 MHz, CD₃OD) δ 175.6 (C₁₉), 164.4 (C₁₁), 158.7 (C_{7a}), 141.7 (C₉), 112.7 (C₈), 108.6 (C₁₀), 105.2 (C_{11a}), 79.4 (C₃), 78.7 (C_{6a}), 56.5 (C_{4a}), 52.9 (C_{12a}), 42.1 (C₆), 39.9 (C_{12b}), 38.8 (C₁), 37.8 (C₄), 28.7 (C₁₅), 27.9 (C₂), 24.2 (C₁₇), 21.0 (C₁₆), 20.5 (C₅), 17.8 (C₁₂), 16.2 (C₁₄), 15.5 (C₂₂).

IR ν_{max} (neat) 3445, 2972, 2934, 2865, 1621, 1579, 1453, 1379, 1265, 1178, 1126, 1038 cm⁻¹.

HRMS (ESI) m/z: [M - H]⁻ Calcd for C₂₃H₃₁O₅ 387.2171; Found 387.2180.

(3*S*,4*aR*,6*aR*,12*aR*,12*bS*)-3-Acetoxy-11-hydroxy-4,4,6*a*,9,12*b*-pentamethyl-1,3,4,4*a*,5,6,6*a*,12,12*a*,12*b*-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid



Ac_2O (63 μL , 0.666 mmol) was added with stirring to carboxylic acid **184** (37 mg, 0.0952 mmol) in pyridine (0.5 mL) at 25 °C. After 24 h, CH_2Cl_2 (2 mL) was added and the pH was adjusted to ~1 with aqueous HCl (4 M). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 2 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated to give diacetate. Crude diacetate was dissolved in MeOH (2 mL) and H_2O (0.2 mL) and K_2CO_3 (20 mg, 0.143 mmol) were added at 25 °C. The resulting mixture was stirred for 5 h, when CH_2Cl_2 (2 mL) was added and the pH was adjusted to ~1 with aqueous HCl (4 M). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 1 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated and chromatographed (pentane : EtOAc : AcOH 3 : 1 : 0.01) to give (+)-hongoquercin B **6** (27 mg, 0.0627 mmol, 66 % over 2 steps from carboxylic acid **184**) as white solid.

R_f 0.29 (Pentane : EtOAc : AcOH 3 : 1 : 0.01).

Melting Point 155 – 157 °C.

Specific Rotation $[\alpha]_D^{30} + 91.0^\circ (c\ 0.52, \text{CH}_3\text{OH})$.

^1H NMR (400 MHz, CDCl_3) δ 11.85 (s, 1H, H_{21}), 6.21 (s, 1H, H_8), 4.52 (dd, $J = 11.6, 4.7$ Hz, 1H,

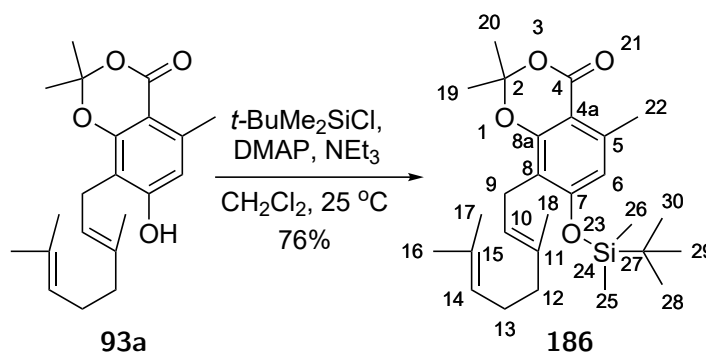
H₃), 2.66 (dd, $J = 16.8, 4.8$ Hz, 1H, H_{12eq}), 2.52 (s, 3H, H₁₇), 2.30 (dd, $J = 16.8, 13.1$ Hz, 1H, H_{12ax}), 2.13 – 2.07 (m, 1H, H_{6eq}), 2.07 (s, 3H, H₂₄), 1.86 (dt, $J = 13.3, 3.6$ Hz, 1H, H_{1eq}), 1.81 – 1.60 (m, 4H, H_{2,5ax,6ax}), 1.53 (dd, $J = 13.1, 5.0$ Hz, 1H, H_{12a}), 1.47 – 1.42 (m, 1H, H_{5eq}), 1.24 – 1.18 (m, 1H, H_{1ax}), 1.20 (s, 3H, H₁₆), 1.10 (dd, $J = 12.1, 2.2$ Hz, 1H, H_{4a}), 0.96 (s, 3H, H₂₂), 0.91 (s, 3H, H₁₅), 0.90 (s, 3H, H₁₄).

¹³C NMR (126 MHz, CDCl₃) δ 175.9 (C₁₉), 171.0 (C₂₃), 163.8 (C₁₁), 158.6 (C_{7a}), 141.6 (C₉), 112.6 (C₈), 107.7 (C₁₀), 102.7 (C_{11a}), 80.4 (C₃), 78.0 (C_{6a}), 55.1 (C_{4a}), 51.3 (C_{12a}), 40.6 (C₆), 37.7 (C_{12b}), 37.1 (C₁), 36.6 (C₄), 28.1 (C₁₅), 24.1 (C₁₇), 23.5 (C₂), 21.3 (C₂₄), 20.7 (C₁₆), 19.3 (C₅), 16.8 (C₁₂), 16.7 (C₁₄), 15.0 (C₂₂).

IR ν_{max} (neat) 3063, 2972, 2941, 1731, 1623, 1580, 1454, 1371, 1263, 1178, 1126, 1035, 1007 cm⁻¹.

HRMS (ESI) m/z : [M - H]⁻ Calcd for C₂₅H₃₃O₆ 429.2277; Found 429.2284.

(*E*)-7-(Tert-butyldimethylsilyloxy)-8-(3,7-dimethylocta-2,6-dienyl)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



NEt₃ (1.08 mL, 7.72 mmol) was added with stirring to resorcyate **93a** (806 mg, 2.34 mmol) in CH₂Cl₂ (50 mL) at 25 °C, when *t*-BuMe₂SiCl (1.16 g, 7.72 mmol) and DMAP (5.7 mg, 0.0468 mmol) were added. The resulting mixture was stirred for 2 h, when 10 % aqueous citric acid (30 mL) and CH₂Cl₂ (20 mL) were added. The two phases were separated and the organic layer was washed with 10 % citric acid solution (2 × 30 mL), H₂O (30 mL) and brine (30 mL). The organic layer was dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 19 : 1) to give silyl ether **186** (815 mg, 1.78 mmol, 76 %) as a colorless oil.

R_f 0.59 (Pentane : Et₂O 10 : 1).

¹H NMR (400 MHz, CDCl₃) δ 6.36 (s, 1H, H₆), 5.13 – 5.00 (m, 2H, H_{10,14}), 3.24 (d, *J* = 7.0 Hz, 2H, H₉), 2.58 (s, 3H, H₂₂), 2.07 – 1.99 (m, 2H, H₁₃), 1.98 – 1.90 (m, 2H, H₁₂), 1.73 (s, 3H, H₁₈), 1.65 (s, 6H, H_{19,20}), 1.63 (s, 3H, H₁₆), 1.55 (s, 3H, H₁₇), 1.01 (s, 9H, H_{28–30}), 0.28 (s, 6H, H_{25–26}).

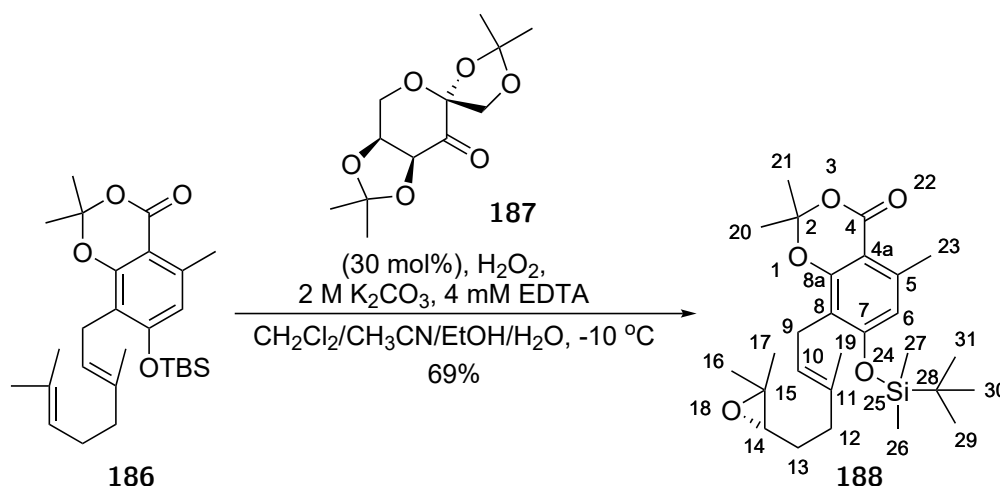
¹³C NMR (100 MHz, CDCl₃) δ 160.9 (C₄), 158.9 (C₇), 156.4 (C_{8a}), 141.7 (C_{4a}), 134.9 (C₁₁), 131.3 (C₁₅), 124.1 (C₁₄), 121.8 (C₁₀), 118.4 (C₈), 116.1 (C₆), 105.9 (C₅), 104.6 (C₂), 39.6 (C₁₂), 26.5 (C₁₃), 25.7 (2C, C_{19–20}), 25.6 (4C, C_{16,28–30}), 22.2 (C₉), 22.1 (C₂₂), 18.2 (C₂₇), 17.6 (C₁₇), 16.2 (C₁₈), -4.1 (2C, C_{25–26}).

IR **v**_{max} (neat) 2930, 2859, 1733, 1606, 1569, 1292, 1209, 1169, 1044, 841, 782 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₇H₄₃O₄Si 459.2931; Found 459.2938.

Elemental Analysis Anal. Calcd for C₂₇H₄₂O₄Si: C, 70.70; H, 9.23; Found: C, 70.52; H, 9.10.

(*S,E*)-7-((Tert-butyltrimethylsilyl)oxy)-8-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



Silyl ether **186** (334 mg, 0.75 mmol) and the chiral ketone **187** (58 mg, 0.225 mmol) were dissolved in CH₂Cl₂ (6 mL), CH₃CN (3 mL), EtOH (3 mL) and aqueous buffer (2 M K₂CO₃; 4 mM EDTA; 6 mL) and cooled to 0 °C. H₂O₂ (0.42 mL) was added dropwise with stirring. After 15 h, Na₂SO₃ (200 mg) was added and the phases were separated. The aqueous layer was extracted with Et₂O (3 × 15 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 10: 1) to afford epoxide **188** (244 mg, 0.514 mmol, 69 %) as a colorless oil.

R_f 0.22 (Pentane : EtOAc 19 : 1).

Specific Rotation [α]_D²³ + 2.8° (c 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 6.35 (s, 1H, H₆), 5.12 (tq, *J* = 7.1, 1.3 Hz, 1H, H₁₀), 3.24 (d, *J* = 7.0 Hz, 2H, H₉), 2.65 (t, *J* = 6.2 Hz, 1H, H₁₄), 2.58 (s, 3H, H₂₃), 2.20 – 1.98 (m, 2H, H₁₂), 1.74 (s, 3H, H₁₉), 1.65 (s, 6H, H_{20–21}), 1.61 – 1.53 (m, 2H, H₁₃), 1.24 (s, 3H, H₁₆), 1.21 (s, 3H, H₁₇), 1.00 (s, 9H, H_{29–31}), 0.28 (s, 6H, H_{26–27}).

¹³C NMR (100 MHz, CDCl₃) δ 160.8 (C₄), 158.9 (C₇), 156.3 (C_{8a}), 141.9 (C_{4a}), 134.1 (C₁₁), 122.5

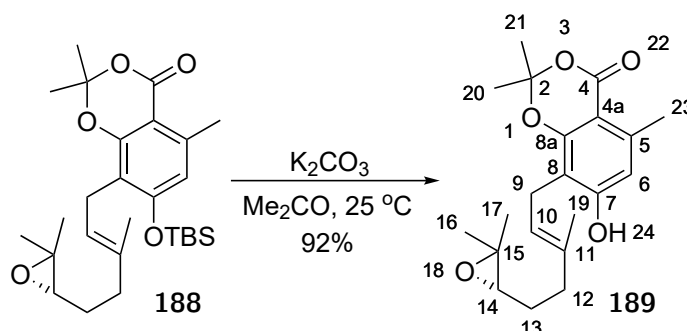
(C₁₀), 118.1 (C₈), 116.1 (C₆), 105.9 (C₅), 104.6 (C₂), 64.0 (C₁₄), 58.2 (C₁₅), 36.2 (C₁₂), 27.3 (C₁₂), 25.8 (2C, C₂₀₋₂₁), 25.6 (3C, C₂₉₋₃₁), 24.8 (C₁₆), 22.2 (C₉), 22.1 (C₂₃), 18.6 (C₁₇), 18.3 (C₂₈), 16.2 (C₁₉), -4.0 (2C, C₂₆₋₂₇).

IR ν_{max} (neat) 2959, 2930, 2859, 1732, 1605, 1570, 1279, 842 cm⁻¹.

HRMS (FTMS) m/z: [M + H]⁺ Calcd for C₂₇H₄₃O₅Si 475.2874; Found 475.2870.

Elemental Analysis Anal. Calcd for C₂₇H₄₂O₅Si: C, 68.31; H, 8.92; Found: C, 68.21; H, 9.03.

(*S,E*)-8-(5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



K_2CO_3 (2.33 g, 16.9 mmol) was added with stirring to epoxide **188** (160 mg, 0.337 mmol) in Me_2CO (20 mL) at 25 °C. After 2 h, CH_2Cl_2 (30 mL) and H_2O (50 mL) were added and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 20 mL) and the combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : EtOAc 5 : 1) to give epoxide **189** (112 mg, 0.311 mmol, 92 %) as colorless oil.

R_f 0.29 (Pentane : EtOAc 5 : 1).

Specific Rotation $[\alpha]_{\text{D}}^{24}$ - 9.4° (c 1.0, CHCl_3).

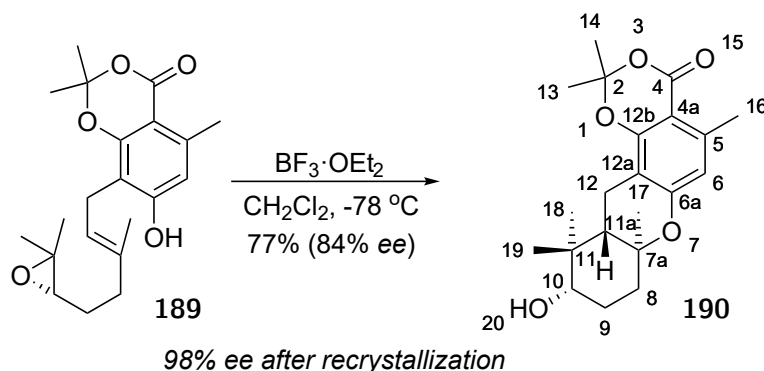
^1H NMR (400 MHz, CDCl_3) δ 6.40 (s, 1H, H_6), 6.17 (s, 1H, H_{24}), 5.30 – 5.15 (m, 1H, H_{10}), 3.31 (dd, J = 7.0, 2.1 Hz, 2H, H_9), 2.69 (dd, J = 6.8, 5.6 Hz, 1H, H_{14}), 2.58 (s, 3H, H_{23}), 2.26 – 2.07 (m, 2H, H_{12}), 1.80 (s, 3H, H_{19}), 1.68 (s, 6H, H_{20-21}), 1.69 – 1.55 (m, 2H, H_{13}), 1.28 (s, 3H, H_{16}), 1.25 (s, 3H, H_{17}).

^{13}C NMR (100 MHz, CDCl_3) δ 160.9 (C_4), 159.8 (C_7), 156.0 (C_{8a}), 142.8 (C_{4a}), 136.8 (C_{11}), 121.7 (C_{10}), 113.6 (C_6), 113.0 (C_8), 105.4 (C_5), 104.8 (C_2), 64.2 (C_{14}), 58.6 (C_{15}), 36.5 (C_{12}), 27.2 (C_{13}), 25.8 (C_{20}), 25.7 (C_{21}), 24.8 (C_{16}), 22.0 (C_{23}), 21.8 (C_9), 18.7 (C_{17}), 16.2 (C_{19}).

IR ν_{max} (neat) 3235, 2928, 1727, 1696, 1609, 1277 cm^{-1} .

HRMS (FTMS) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{29}\text{O}_5$ 361.2010; Found 361.2016.

(7a*S*,10*S*,11a*S*)-10-Hydroxy-2,2,5,7a,11,11-hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-[1,3]dioxino[4,5-*a*]xanthen-4-one



BF_3OEt_2 (0.2 mL, 0.139 mmol) was added with stirring to epoxide **189** (110 mg, 0.305 mmol) in CH_2Cl_2 (30 mL) at -78°C . After 5 min, Et_3N (5 mL) and H_2O (20 mL) were added, the mixture was allowed to warm up to 25°C and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried (MgSO_4), filtered, concentrated and purified by chromatography (pentane : EtOAc 5 : 2) to give the meroterpenoid **190** (85 mg, 0.236 mmol, 77 %, 84 % ee, measured by chiral HPLC, Chiralpak® IE column, *n*-hexane : *i*-PrOH 9 : 1, 5 mL/min, $t_R = 22.0$ [(-)-enantiomer], 26.6 [(+)-enantiomer] min) as white foam.

R_f 0.29 (Pentane : EtOAc 5 : 2).

Specific Rotation $[\alpha]_D^{24} - 71.0$ (c 1.0, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 6.33 (s, 1H, H_6), 3.41 (dd, $J = 11.4, 4.2$ Hz, 1H, H_{10}), 2.63 (dd, $J = 16.8, 4.9$ Hz, 1H, H_{12eq}), 2.56 (s, 3H, H_{16}), 2.31 (dd, $J = 16.9, 13.2$ Hz, 1H, H_{12ax}), 2.00 (dt, $J = 12.5, 3.3$ Hz, 1H, H_{8eq}), 1.91 – 1.81 (m, 1H, H_{9eq}), 1.78 – 1.74 (m, 1H, H_{8ax}), 1.73 (s, 3H, H_{13}), 1.69 (s, 3H, H_{14}), 1.64 – 1.52 (m, 2H, $\text{H}_{9ax,11a}$), 1.20 (s, 3H, H_{17}), 1.12 (s, 3H, H_{18}), 0.89 (s, 3H, H_{19}).

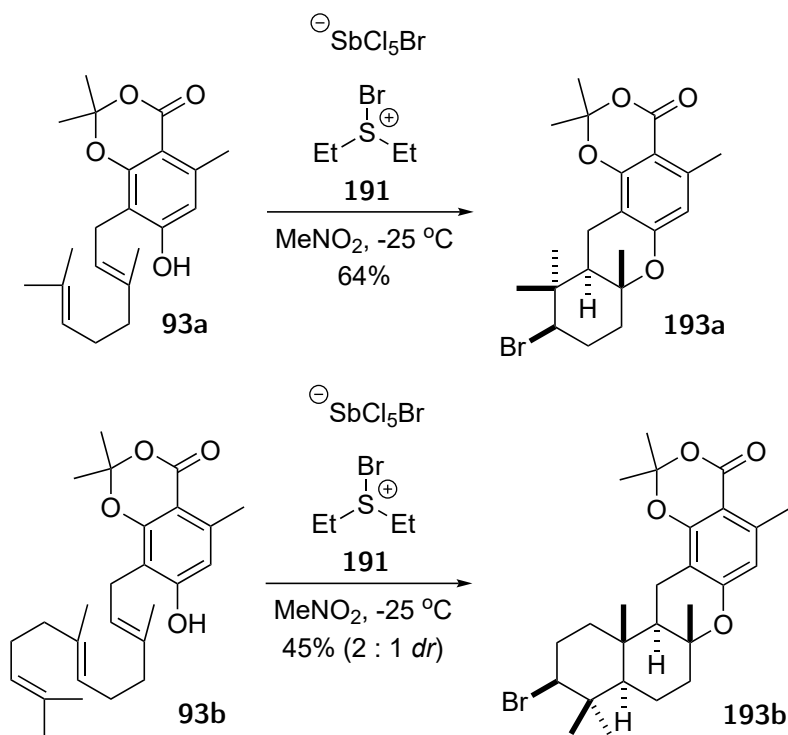
^{13}C NMR (100 MHz, CDCl_3) δ 160.8 (C_4), 158.6 (C_{6a}), 156.0 (C_{12b}), 142.2 (C_5), 114.3 (C_6), 107.9

(C_{12a}), 104.8 (C₂), 104.1 (C_{4a}), 77.8 (C₁₀), 77.6 (C_{7a}), 46.1 (C_{11a}), 38.5 (C₁₁), 37.4 (C₈), 28.1 (C₉), 27.3 (C₁₈), 26.1 (C₁₃), 25.4 (C₁₄), 21.9 (C₁₆), 19.8 (C₁₇), 17.2 (C₁₂), 14.3 (C₁₉).

IR ν_{max} (neat) 3433, 2942, 1708, 1617, 1573, 1287, 1128 cm⁻¹.

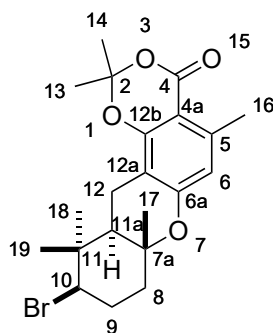
HRMS (ESI) m/z: [M - H]⁻ Calcd for C₂₁H₂₇O₅ 359.1858; Found 359.1853.

Elemental Analysis Anal. Calcd for C₂₁H₂₈O₅: C, 69.98; H, 7.83; Found: C, 69.86; H, 7.94.

General Procedure for BDSB Induced Halocyclisation

BDSB (**191**) (604 mg, 1.10 mmol) was added with stirring to resorcyate **93a** or **93b** (1.00 mmol) in MeNO_2 (50 mL) at -25°C . After 10 min, saturated aqueous NaHCO_3 (15 mL) and aqueous Na_2SO_3 (0.5 M; 5 mL) were added and stirring was continued for 15 min. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O 9 : 1) to give the bromo-meroterpenoid **193a** or **193b**.

10-Bromo-2,2,5,7a,11,11-hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-[1,3]dioxino[4,5-*a*]xanthen-4-one



193a

Bromide **193a** (272 mg, 0.642 mmol, 64 %), prepared from resorcyate **93a** (344 mg, 1.00 mmol), was obtained as a white solid.

R_f 0.29 (Pentane : Et₂O 9 : 1).

Melting Point 225.3 – 225.7 °C.

¹H NMR (400 MHz, (CD₃)₂CO) δ 6.36 (s, 1H, H₆), 4.26 (dd, *J* = 11.8, 4.8 Hz, 1H, H₁₀), 2.80 – 2.77 (m, 1H, H_{12eq}), 2.52 (s, 3H, H₁₆), 2.50 – 2.43 (m, 1H, H_{12ax}), 2.30 – 2.13 (m, 2H, H₉), 2.00 (dt, *J* = 13.0, 3.5 Hz, 1H, H_{8eq}), 1.90 – 1.79 (m, 2H, H_{8ax,11}), 1.70 (s, 3H, H₁₃), 1.67 (s, 3H, H₁₄), 1.27 (s, 3H, H₁₇), 1.19 (s, 3H, H₁₈), 1.06 (s, 3H, H₁₉).

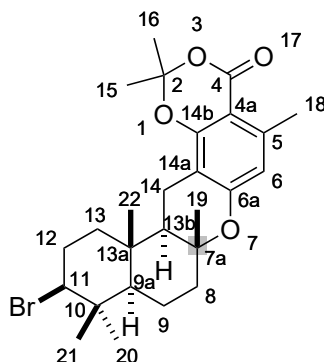
¹³C NMR (100 MHz, (CD₃)₂CO) δ 160.7 (C₄), 159.1 (C_{6a}), 157.0 (C_{12b}), 142.6 (C₅), 115.1 (C₆), 109.3 (C_{12a}), 105.8 (C₂), 105.4 (C_{4a}), 78.2 (C_{7a}), 66.9 (C₁₀), 47.9 (C_{11a}), 41.0 (C₈), 40.1 (C₁₁), 32.3 (C₉), 29.9 (C₁₈), 26.3 (C₁₃), 25.6 (C₁₄), 22.1 (C₁₆), 20.2 (C₁₇), 19.5 (C₁₂), 17.4 (C₁₉).

IR *v*_{max} (neat) 2975, 2924, 2865, 1715, 1616, 1575, 1380, 1286, 1128, 1044 cm⁻¹.

HRMS (ESI) *m/z*: [M]⁺ Calcd for C₂₁H₂₇BrO₄ 422.1093; Found 422.1110.

Elemental Analysis Anal. Calcd for C₂₁H₂₇BrO₄: C, 59.58; H, 6.43; Found: C, 59.45; H, 6.57.

11-Bromo-2,2,5,7a,10,10,13a-heptamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one



193b

Bromide **193b** (219 mg, 0.446 mmol, 45 %, 2 : 1 *dr*), prepared from resorcyate **93b** (413 mg, 1.00 mmol), was isolated as a white solid as an inseparable 2 : 1 mixture of diastereoisomers about the highlighted carbon atom favoring the drawn diastereoisomer.

R_f 0.24 (Pentane : Et₂O 9 : 1).

Melting Point 234.0 – 237.4 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.33 (s, 1H, H₆), 4.00 (dd, *J* = 12.6, 4.7 Hz, 1H, H₁₁), 2.57 (s, 3H, H₁₈), 2.51 (dd, *J* = 16.8, 5.1 Hz, 1H, H_{14eq}), 2.37 – 2.13 (m, 3H, H_{12,14ax}), 2.13 – 2.07 (m, 1H, H_{8eq}), 1.91 – 1.84 (m, 1H, H_{9eq}), 1.84 – 1.78 (m, 1H, H_{13eq}), 1.72 (s, 3H, H₁₆), 1.71 – 1.69 (m, 1H, H_{8ax}), 1.69 (s, 3H, H₁₅), 1.59 – 1.46 (m, 2H, H_{9ax,13b}), 1.20 (s, 3H, H₁₉), 1.20 – 1.11 (m, 2H, H_{9a,13ax}), 1.12 (s, 3H, H₂₀), 0.99 (s, 3H, H₂₁), 0.97 (s, 3H, H₂₂).

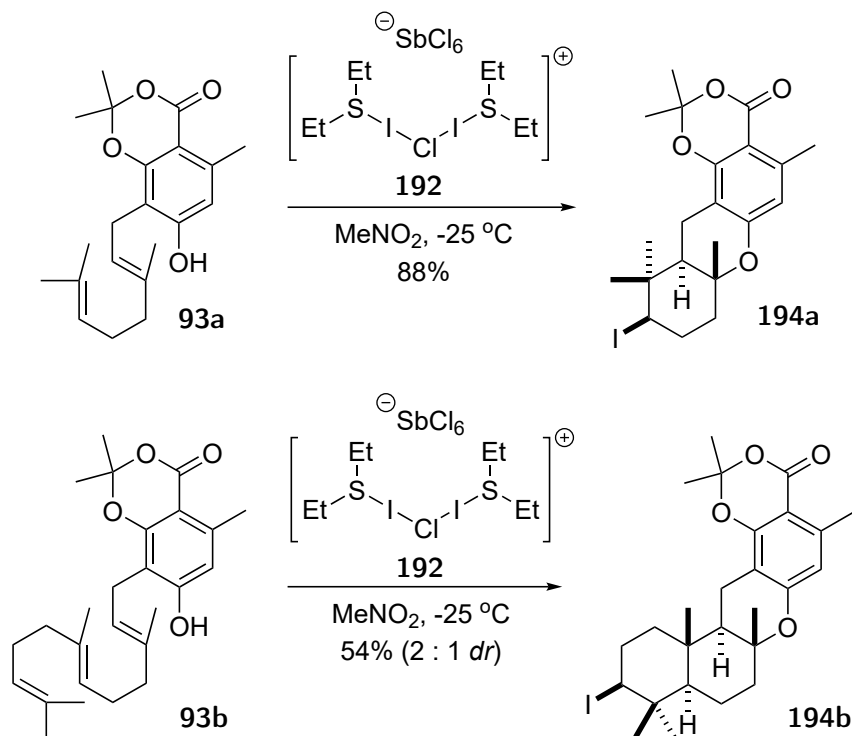
¹³C NMR (100 MHz, CDCl₃) δ 160.8 (C₄), 158.5 (C_{14a}), 156.1 (C_{14b}), 142.2 (C_{4a}), 114.3 (C₆), 107.8 (C_{6a}), 104.8 (C₂), 104.1 (C₅), 77.8 (C_{7a}), 68.4 (C₁₁), 56.3 (C_{9a}), 51.1 (C_{13b}), 40.7 (C₈), 40.5 (C₁₃), 39.6 (C₁₀), 37.0 (C_{13a}), 30.7 (C₁₂), 30.6 (C₂₀), 26.1 (C₁₆), 25.5 (C₁₅), 22.0 (C₁₈), 21.1 (C₉), 20.6 (C₁₉), 18.3 (C₂₁), 16.5 (C₁₄), 14.9 (C₂₂).

IR ν_{max} (neat) 2949, 1718, 1613, 1575, 1376, 1288, 1131, 1042, 902, 844, 693 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₆BrO₄ 491.1797; Found 491.1807.

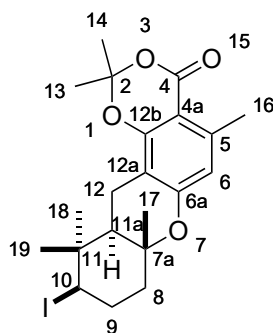
Elemental Analysis Anal. Calcd for C₂₆H₃₅BrO₄: C, 63.54; H, 7.18; Found: C, 63.49; H, 7.07.

General Procedure for IDSI Induced Halocyclisation



IDSI (**192**) (884 mg, 1.10 mmol) was added with stirring to resorcylic acid **93a** or **93b** (1.00 mmol) in MeNO_2 (50 mL) at -25°C . After 10 min, saturated aqueous NaHCO_3 (15 mL) and aqueous Na_2SO_3 (0.5 M; 5 mL) were added and stirring was continued for 15 min. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O 9 : 1) to give the iodo-meroterpenoid **194a** or **194b**.

10-Iodo-2,2,5,7a,11,11-hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-[1,3]dioxino[4,5-*a*]xanthen-4-one



194a

Iodide **194a** (415 mg, 0.882 mmol, 88 %), prepared from resorcyate **93a** (344 mg, 1.00 mmol), was obtained as a white solid.

R_f 0.29 (Pentane : Et₂O 9 : 1).

Melting Point 221.6 – 222.4 °C.

¹H NMR (400 MHz, (CD₃)₂CO) δ .36 (s, 1H, H₆), 4.46 (dd, *J* = 11.9, 4.8 Hz, 1H, H₁₀), 2.82 (dd, *J* = 23.3, 6.7 Hz, 1H, H_{12eq}), 2.52 (s, 3H, H₁₆), 2.50 – 2.44 (m, 1H, H_{12ax}), 2.46 – 2.30 (m, 2H, H₉), 1.91 (dd, *J* = 13.2, 5.0 Hz, 1H, H_{11a}), 1.87 – 1.82 (m, 2H, H₈), 1.70 (s, 3H, H₁₃), 1.67 (s, 3H, H₁₄), 1.28 (s, 3H, H₁₇), 1.16 (s, 3H, H₁₈), 1.09 (s, 3H, H₁₉).

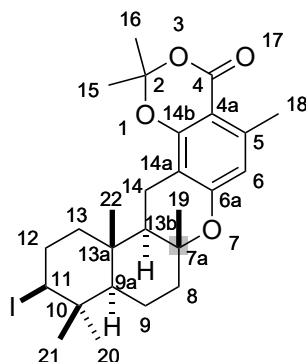
¹³C NMR (100 MHz, (CD₃)₂CO) δ 160.5 (C₄), 158.9 (C_{6a}), 156.7 (C_{12b}), 142.4 (C₅), 114.9 (C₆), 109.3 (C_{12a}), 105.6 (C₂), 105.2 (C_{4a}), 78.2 (C_{7a}), 50.1 (C₁₀), 46.2 (C_{11a}), 42.5 (C₈), 39.6 (C₁₁), 34.9 (C₉), 32.3 (C₁₈), 26.1 (C₁₃), 25.4 (C₁₄), 21.9 (C₁₆), 20.3 (C₁₂), 20.0 (C₁₇), 19.9 (C₁₉).

IR ν_{max} (neat) 2970, 1715, 1616, 1575, 1379, 1285, 1127, 1044, 902 cm⁻¹.

HRMS (EI) *m/z*: [M]⁺ Calcd for C₂₁H₂₇IO₄ 470.0954; Found 470.0947.

Elemental Analysis Anal. Calcd for C₂₁H₂₇IO₄: C, 53.63; H, 5.79; Found: C, 53.55; H, 5.86.

11-Iodo-2,2,5,7a,10,10,13a-heptamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4H,9H-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one



194b

Iodide **194b** (293 mg, 0.544 mmol, 54 %, 2 : 1 *dr*), prepared from resorcyate **93b** (413 mg, 1.00 mmol), was isolated as a white solid as an inseparable 2 : 1 mixture of diastereoisomers about the highlighted carbon atom favoring the drawn diastereoisomer.

R_f 0.24 (Pentane : Et₂O 9 : 1).

Melting Point 189.5 – 192.0 °C.

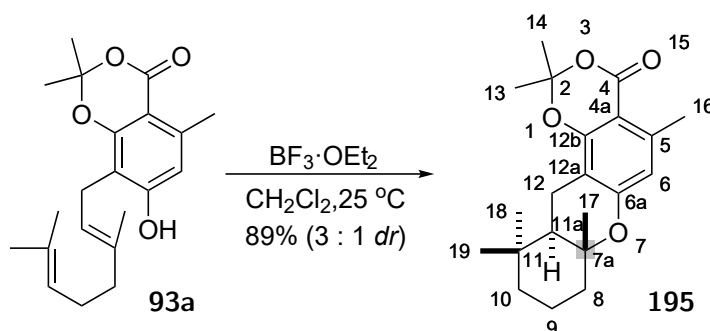
¹H NMR (400 MHz, CDCl₃) δ 6.33 (s, 1H, H₆), 4.24 (dd, *J* = 13.0, 3.2 Hz, 1H, H₁₁), 2.57 (s, 3H, H₁₈), 2.50 (dd, *J* = 16.4, 5.0 Hz, 1H, H_{14eq}), 2.46 – 2.29 (m, 2H, H₁₂), 2.24 (dd, *J* = 16.8, 13.1 Hz, 1H, H_{14ax}), 2.10 – 2.03 (m, 1H, H_{8eq}), 1.95 – 1.87 (m, 1H, H_{9eq}), 1.72 (s, 3H, H₁₆), 1.69 (s, 3H, H₁₅), 1.68 – 1.55 (m, 2H, H_{8ax,13eq}), 1.55 – 1.51 (m, 1H, H_{13b}), 1.51 – 1.45 (m, 1H, H_{9ax}), 1.26 – 1.20 (m, 1H, H_{9a}), 1.20 (s, 3H, H₁₉), 1.20 – 1.10 (m, 1H, H_{13ax}), 1.10 (s, 3H, H₂₀), 1.01 (s, 3H, H₂₁), 0.98 (s, 3H, H₂₂).

¹³C NMR (101 MHz, CDCl₃) δ 160.8 (C₄), 158.5 (C_{14a}), 156.1 (C_{14b}), 142.2 (C_{4a}), 114.3 (C₆), 107.8 (C_{6a}), 104.8 (C₂), 104.1 (C₅), 77.3 (C_{7a}), 54.9 (C_{9a}), 52.9 (C₁₁), 51.2 (C_{13b}), 42.2 (C₁₃), 40.8 (C₈), 39.3 (C₁₀), 37.3 (C_{13a}), 33.6 (C₁₂), 33.2 (C₂₀), 26.1 (C₁₆), 25.5 (C₁₅), 22.2 (C₉), 22.0 (C₁₈), 21.1 (C₂₁), 20.6 (C₁₉), 16.5 (C₁₄), 14.9 (C₂₂)

IR ν_{max} (neat) 2946, 1726, 1615, 1576, 1371, 1285, 1124, 1038, 902 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₆IO₄ 539.1658; Found 539.1664.

**2,2,5,7a,11,11-Hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-
[1,3]dioxino[4,5-*a*]xanthen-4-one**



BF_3OEt_2 (0.31 mL, 2.50 mmol) was added dropwise with stirring to resorcyate **93a** (172 mg, 0.50 mmol) in CH_2Cl_2 (50 mL) at -78°C . The resulting mixture was warmed to 25°C and further stirred for 1.5 h, when saturated aqueous NaHCO_3 (25 mL) and H_2O (25 mL) were added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O : 9 : 1) to provide meroterpenoid **195** (154 mg, 0.447 mmol, 89%, 3 : 1 *dr*) as a white solid as an inseparable 3 : 1 mixture of diastereoisomers about the highlighted carbon atom favoring the drawn diastereoisomer. Recrystallisation from *n*-hexane provided the pure *trans*-fused ring product.

R_f 0.48 (Pentane : EtOAc 19 : 1).

Melting Point $139.5 - 141.3^\circ\text{C}$.

^1H NMR (400 MHz, CDCl_3) δ 6.34 (s, 1H, H_6), 2.62 (dd, $J = 16.8, 4.8$ Hz, 1H, H_{12eq}), 2.57 (s, 3H, H_{16}), 2.22 (dd, $J = 16.8, 13.3$ Hz, 1H, H_{12ax}), 2.01 – 1.94 (m, 1H, H_{8eq}), 1.74 (s, 3H, H_{13}), 1.70 (s, 3H, H_{14}), 1.68 – 1.64 (m, 1H, H_{9eq}), 1.60 (dd, $J = 13.4, 4.8$ Hz, 1H, H_{11a}), 1.60 – 1.55 (m, 2H, $\text{H}_{8ax,9ax}$), 1.54 – 1.47 (m, 1H, H_{10eq}), 1.37 – 1.28 (m, 1H, H_{10ax}), 1.21 (s, 3H, H_{23}), 1.03 (s, 3H, H_{18}), 0.93 (s, 3H, H_{19}).

^{13}C NMR (100 MHz, CDCl_3) δ 160.9 (C_4), 158.8 (C_{6a}), 156.0 (C_{12b}), 142.1 (C_5), 114.4 (C_6), 108.6 (C_{12a}), 104.8 (C_2), 104.0 (C_{4a}), 78.7 (C_{7a}), 47.4 (C_{11a}), 41.4 (C_{10}), 39.7 (C_8), 33.5 (C_{11}), 32.1 (C_{18}),

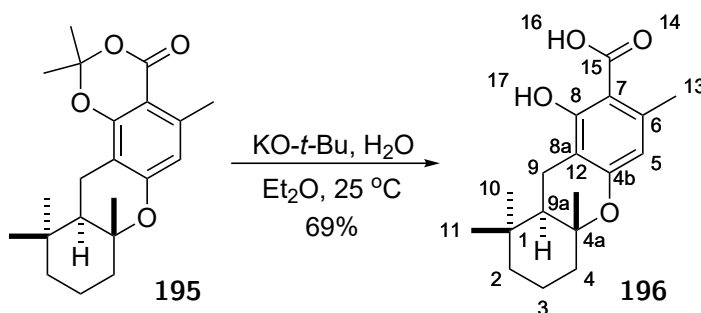
26.2 (C₁₃), 25.5 (C₁₄), 22.0 (C₁₆), 20.6 (C₁₉), 19.8 (C₂₃), 19.7 (C₉), 17.3 (C₁₂).

IR ν_{max} (neat) 2969, 2901, 2921, 1720, 1618, 1576, 1390, 1286, 1043 cm⁻¹.

HRMS (ESI) m/z: [M]⁺ Calcd for C₂₁H₂₈O₄ 344.1988; Found 344.1990.

Elemental Analysis Anal. Calcd for C₂₁H₂₈O₄: C, 73.32; H, 8.19; Found: C, 73.17; H, 8.22.

8-Hydroxy-1,1,4a,6-tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxylic acid



H₂O (8 μ L, 0.400 mmol) was added with stirring to a suspension of KO-*t*-Bu (180 mg, 1.60 mmol) in Et₂O (3 mL) at 0 °C. After 5 min, meroterpenoid **195** (69 mg, 0.200 mmol) was added and the resulting mixture was further stirred at 25 °C for 2 h. The pH was adjusted to ~2 with aqueous HCl (1 M), the two phases were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc : AcOH 9 : 1 : 0.01) to give the carboxylic acid **196** (42 mg, 0.138 mmol, 69 %) as a white solid.

R_f 0.30 (Pentane : EtOAc : AcOH 9 : 1 : 0.01).

Melting Point 176.7 – 178.6 °C.

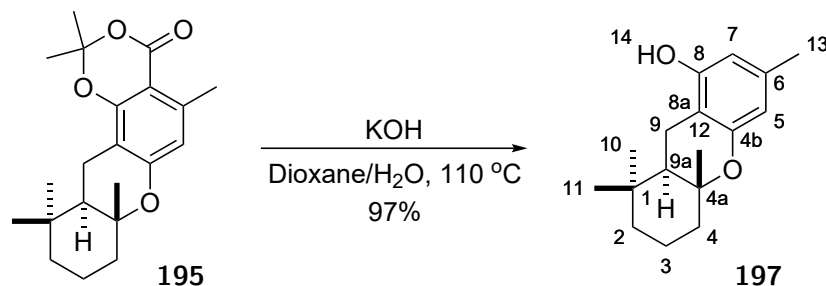
¹H NMR (400 MHz, CDCl₃) δ 11.84 (s, 1H, H₁₇), 11.17 (s, 1H, H₁₆), 6.22 (s, 1H, H₅), 2.77 (dd, *J* = 17.0, 4.8 Hz, 1H, H_{9eq}), 2.52 (s, 3H, H₁₃), 2.28 (dd, *J* = 16.9, 13.4 Hz, 1H, H_{9ax}), 2.01 – 1.94 (m, 1H, H_{4eq}), 1.72 – 1.64 (m, 1H, H_{3eq}), 1.64 – 1.55 (m, 3H, H_{3ax,4ax,9a}), 1.55 – 1.45 (m, 1H, H_{2eq}), 1.40 – 1.27 (m, 1H, H_{2ax}), 1.22 (s, 3H, H₁₂), 1.04 (s, 3H, H₁₀), 0.94 (s, 3H, H₁₁).

¹³C NMR (100 MHz, CDCl₃) δ 175.5 (C₁₅), 163.7 (C_{4b}), 158.9 (C₈), 141.4 (C₆), 112.7 (C₅), 108.4 (C_{8a}), 102.4 (C₇), 78.7 (C_{4a}), 47.6 (C_{9a}), 41.5 (C₂), 39.7 (C₄), 33.6 (C₁), 32.1 (C₁₀), 24.1 (C₁₃), 20.6 (C₁₁), 19.8 (C₁₂), 19.7 (C₃), 17.6 (C₉).

IR ν_{max} (neat) 2694, 2919, 2865, 1619, 1578, 1454, 1268, 1151, 1100 cm⁻¹.

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{24}O_4$ 304.1675; Found 304.1679.

Elemental Analysis Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95; Found: C, 71.17; H, 8.11.

1,1,4a,6-Tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-8-ol

Aqueous KOH (5 M; 1 mL) was added with stirring to meroterpenoid **195** (69 mg, 0.200 mmol) in 1,4-dioxane (2 mL) and the resulting mixture was heated at 110 °C for 23 h. After cooling the reaction mixture to 25 °C, the pH was adjusted to ~2 with aqueous HCl (4 M). The two phases were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 15 : 1) to give the phenol **197** (40 mg, 0.194 mmol, 97 %) as white foam.

R_f 0.33 (Pentane : EtOAc 15 : 1).

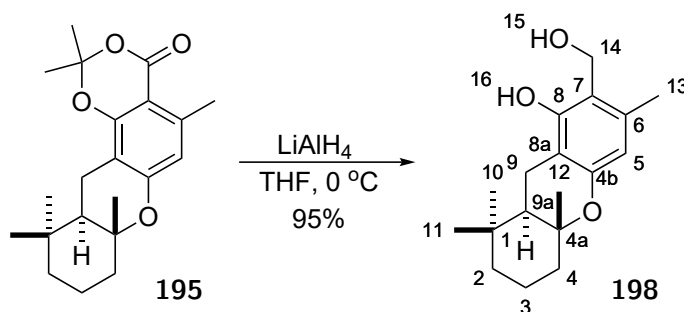
¹H NMR (400 MHz, (CD₃)₂CO) δ 8.00 (s, 1H, H₁₄), 6.21 (s, 1H, H₅), 6.05 (s, 1H, H₇), 2.71 (dd, J = 16.7, 5.0 Hz, 1H, H_{9eq}), 2.26 (dd, J = 16.6, 13.5 Hz, 1H, H_{9ax}), 2.12 (s, 3H, H₁₃), 1.92 – 1.81 (m, 1H, H_{4eq}), 1.68 – 1.53 (m, 4H, H_{3,4ax,9a}), 1.52 – 1.44 (m, 1H, H_{2eq}), 1.40 – 1.27 (m, 1H, H_{2ax}), 1.17 (s, 3H, H₁₂), 1.01 (s, 3H, H₁₀), 0.94 (s, 3H, H₁₁).

¹³C NMR (100 MHz, (CD₃)₂CO) δ 156.2 (C_{4b}), 155.0 (C₈), 137.2 (C₆), 109.7 (C₇), 107.7 (C₅), 107.6 (C_{8a}), 77.0 (C_{4a}), 48.8 (C_{9a}), 42.3 (C₂), 40.8 (C₄), 34.0 (C₁), 32.5 (C₁₀), 21.3 (C₁₃), 20.9 (C₁₁), 20.4 (C₃), 20.0 (C₁₂), 18.6 (C₉).

IR ν_{max} (neat) 3398, 2935, 2866, 1627, 1587, 1516, 1457, 1101, 1063, 1040 cm⁻¹.

HRMS (EI) m/z : [M]⁺ Calcd for C₁₇H₂₄O₂ 260.1776; Found 260.1786.

7-(Hydroxymethyl)-1,1,4a,6-tetramethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-8-ol



LiAlH₄ in THF (1 M; 0.8 mL, 0.800 mmol) was added with stirring to meroterpenoid **195** (69 mg, 0.200 mmol) in THF (4 mL) at 0 °C. After 1 h, H₂O (65 µL) and NaOH (1 M; 150 µL) were added dropwise sequentially and the mixture was further stirred for 30 min. Solid NH₄Cl (100 mg) was added and the solids were filtered and eluted with Et₂O (5 mL). The filtrate was concentrated and chromatographed (pentane : EtOAc 4 : 1) to afford diol **198** (55 mg, 0.189 mmol, 95 %) as white foam.

R_f 0.22 (Pentane : EtOAc 9 : 1).

¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H, OH), 6.19 (s, 1H, H₅), 4.88 (s, 2H, H₁₄), 2.75 (dd, J = 16.6, 5.0 Hz, 1H, H_{9eq}), 2.37 – 2.27 (m, 1H, H_{9ax}), 2.17 (s, 3H, H₁₃), 1.99 – 1.90 (m, 1H, H_{4eq}), 1.69 – 1.54 (m, 4H, H_{3eq,3ax,4ax,9}), 1.52 – 1.40 (m, 1H, H_{2eq}), 1.38 – 1.25 (m, 1H, H_{2ax}), 1.20 (s, 3H, H₁₂), 1.02 (s, 3H, H₁₀), 0.92 (s, 3H, H₁₁).

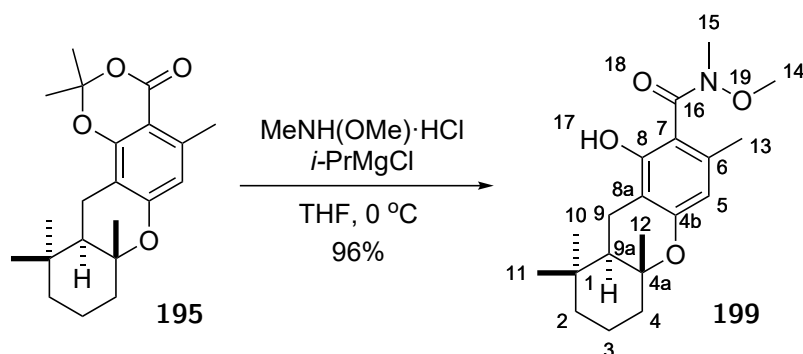
¹³C NMR (100 MHz, CDCl₃) δ 155.0 (C₈), 153.4 (C_{4b}), 133.6 (C₇), 113.6 (C₆), 110.2 (C₅), 109.0 (C_{8a}), 77.1 (C_{4a}), 60.8 (C₁₄), 47.8 (C_{9a}), 41.6 (C₂), 39.9 (C₄), 33.5 (C₁), 32.1 (C₁₀), 20.6 (C₁₁), 19.8 (C₃), 19.6 (C₁₂), 19.2 (C₁₃), 17.7 (C₉).

IR *ν*_{max} (neat) 3344, 2934, 2865, 1627, 1583, 1102 cm⁻¹.

HRMS (ESI) *m/z*: [M - H]⁻ Calcd for C₁₈H₂₅O₃ 289.1804; Found 289.180.

Elemental Analysis Anal. Calcd for C₁₈H₂₆O₃: C, 74.45; H, 9.02; Found: C, 74.59; H, 9.13.

8-Hydroxy-*N*-methoxy-*N*,1,1,4a,6-pentamethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-7-carboxamide



MeNH(OMe)·HCl (59 mg, 0.605 mmol) was added dropwise with stirring to meroterpenoid **195** (69 mg, 0.200 mmol) in THF (4 mL) and cooled to $0\text{ }^{\circ}\text{C}$, followed by dropwise addition of $i\text{-PrMgCl}$ in THF (2 M; 0.6 mL, 1.20 mmol). The resulting mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 3 h, when the reaction was quenched with saturated NH_4Cl (2 mL) and the mixture was acidified to pH ~ 1 with aqueous HCl (1 M). The two phases were separated and the aqueous layer was extracted with EtOAc ($3 \times 5\text{ mL}$). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : EtOAc 7 : 3) to give the amide **199** (67 mg, 0.193 mmol, 96 %) as a white solid.

R_f 0.43 (Pentane : EtOAc 7 : 3).

Melting Point $178.9 - 182.7\text{ }^{\circ}\text{C}$.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.20 (s, 1H, H_5), 3.57 (s, 3H, H_{14}), 3.33 (s, 3H, H_{15}), 2.74 (dd, $J = 16.7, 5.0\text{ Hz}$, 1H, H_{9eq}), 2.28 (dd, $J = 16.7, 13.4\text{ Hz}$, 1H, H_{9ax}), 2.23 (s, 3H, H_{13}), 1.98 – 1.93 (m, 1H, H_{4eq}), 1.71 – 1.64 (m, 1H, H_{3eq}), 1.61 (dd, $J = 13.2, 4.9\text{ Hz}$, 1H, H_{9a}), 1.59 – 1.54 (m, 2H, $\text{H}_{3ax,4ax}$), 1.54 – 1.45 (m, 1H, H_{2eq}), 1.37 – 1.24 (m, 1H, H_{2ax}), 1.20 (s, 3H, H_{12}), 1.02 (s, 3H, H_{10}), 0.92 (s, 3H, H_{11}).

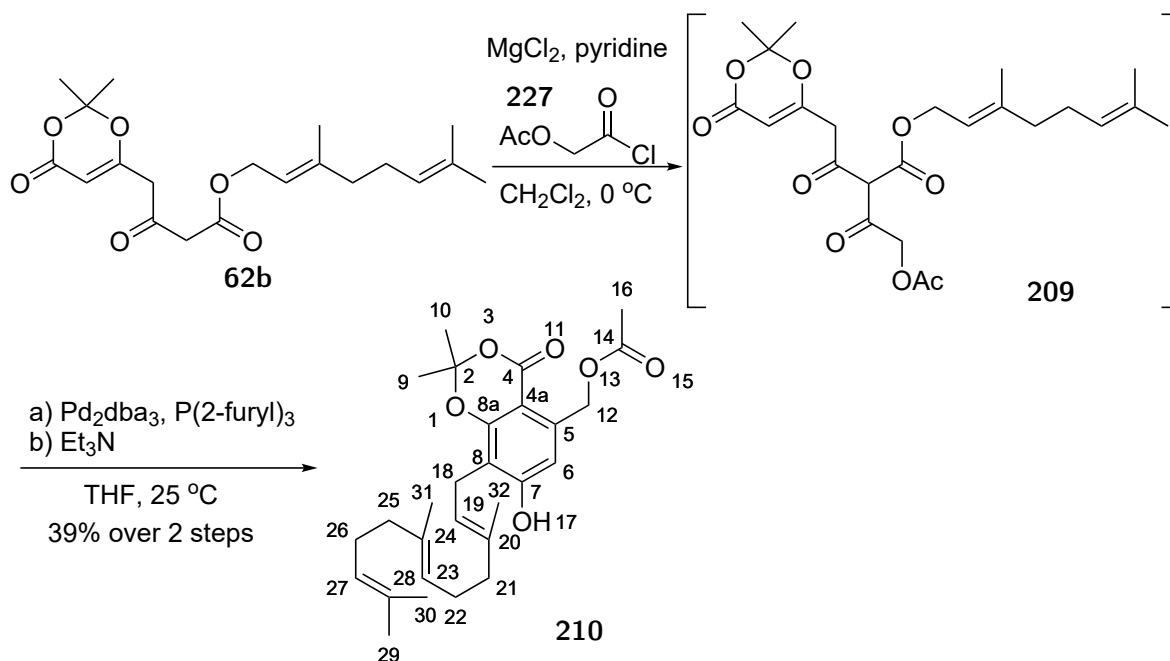
$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.9 (C_{16}), 155.5 (C_{4b}), 154.5 (C_8), 135.3 (C_6), 111.1 (C_7), 110.7 (C_5), 108.5 (C_{8a}), 77.7 (C_{4a}), 61.3 (C_{14}), 47.7 (C_{9a}), 41.6 (C_2), 39.9 (C_4), 34.2 (C_{15}), 33.5 (C_1), 32.1 (C_{10}), 20.6 (C_{11}), 19.9 (C_{12}), 19.8 (C_3), 19.7 (C_{13}), 17.8 (C_9).

IR ν_{max} (neat) 3110, 2933, 1616, 1578, 1456, 1389, 1120, 732 cm^{-1} .

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_4$ 348.2175; Found 348.2188.

Elemental Analysis Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_4$: C, 69.14; H, 8.41; N, 4.03; Found: C, 69.11; H, 8.49; N, 3.97.

(7-Hydroxy-2,2-dimethyl-4-oxo-8-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl acetate



MgCl_2 (7.12 g, 74.8 mmol) and pyridine (23 mL, 288 mmol) were added with stirring to dioxinone β -keto ester **62b** (24.9 g, 57.6 mmol) in CH_2Cl_2 (200 mL) at 0°C . After 15 min, AcCH_2COCl **227** (7.40 mL, 69.1 mmol) was added dropwise and the reaction mixture was further stirred for 2 h at 0°C . Saturated aqueous NH_4Cl (100 mL) was added and the pH was adjusted to ~ 2 with aqueous HCl (1 M). The two phases were separated and the aqueous layer was extracted with EtOAc (3×150 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated under reduced pressure to give the crude dioxinone β,δ -diketo ester **209**. $\text{P}(2\text{-furyl})_3$ (2.67 g, 11.5 mmol) and Pd_2dba_3 (2.64 g, 2.88 mmol) were added sequentially with stirring to this crude dioxinone β,δ -diketo ester **209** in THF (300 mL) at 25°C . After 3 h, Et_3N (24 mL, 173 mmol) was added and the resulting mixture was stirred for additional 18 h. Reaction was quenched with aqueous HCl (1 M; 200 mL) and the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were dried (MgSO_4), filtered,

concentrated under reduced pressure and chromatographed (pentane : EtOAc 19 : 1 to 10 : 1) to give β -resorcyate **210** (10.7 g, 22.7 mmol, 39 % over 2 steps) as a yellow oil.

R_f 0.26 (Pentane : Et₂O 2 : 1).

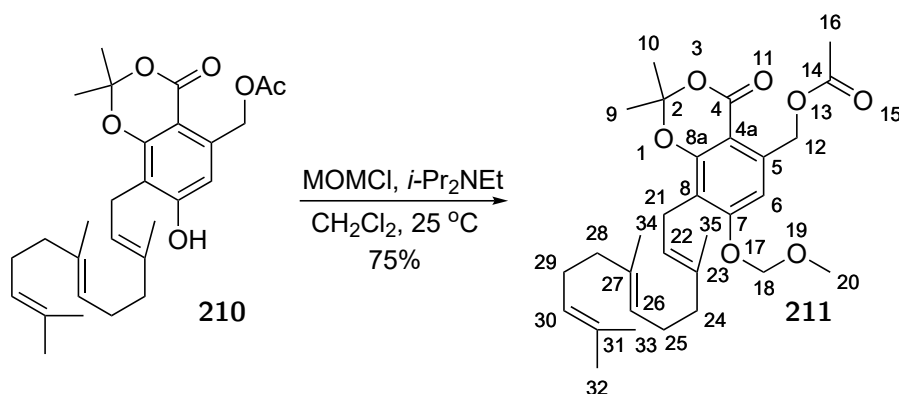
¹H NMR (400 MHz, CDCl₃) δ 6.64 (s, 1H, H₆), 5.53 (s, 2H, H₁₂), 5.23 – 5.12 (m, 1H, H₁₉), 5.11 – 5.00 (m, 2H, H_{23,27}), 3.33 (d, J = 7.2 Hz, 2H, H₁₈), 2.15 (s, 3H, H₁₆), 2.16 – 1.90 (m, 8H, H_{21–22,25–26}), 1.79 (s, 3H, H₃₂), 1.69 (s, 6H, H_{9–10}), 1.66 (s, 3H, H₂₉), 1.58 (s, 6H, H_{30–31}).

¹³C NMR (100 MHz, CDCl₃) δ 170.8 (C₁₄), 160.8 (C₄), 160.5 (C₇), 156.1 (C_{8a}), 139.8 (C₅), 138.7 (C₂₀), 135.5 (C₂₄), 131.3 (C₂₈), 124.3 (C₂₃), 123.5 (C₂₇), 120.3 (C₁₉), 114.5 (C₈), 109.8 (C₆), 105.3 (C₂), 103.6 (C_{4a}), 64.1 (C₁₂), 39.7 (C₂₁), 39.6 (C₂₅), 26.7 (C₂₆), 26.3 (C₂₂), 25.7 (2C, C_{9–10}), 21.9 (C₁₈), 21.0 (C₁₆), 17.7 (C₃₀), 16.2 (C₃₁), 16.0 (C₃₂).

IR v_{max} (neat) 3290, 1724, 1699, 1597, 1422, 1377, 1274, 1207, 1029 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₈H₃₉O₆ 471.2747; Found 471.2731.

(7-(Methoxymethoxy)-2,2-dimethyl-4-oxo-8-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl acetate



MOMCl (1.03 mL, 13.6 mmol) was added with stirring to *i*-Pr₂NEt (5.92 mL, 34.0 mmol) and β-resorcyate **210** (3.19 g, 6.79 mmol) in CH₂Cl₂ (60 mL). After 3 h, saturated aqueous NH₄Cl (30 mL) was added and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated under reduced pressure and chromatographed (pentane : EtOAc 9 : 1) to give MOM ether **211** (2.61 g, 5.07 mmol, 75 %) as a colourless oil.

R_f 0.17 (Pentane : EtOAc 9 : 1).

¹H NMR (400 MHz, CDCl₃) δ 6.90 (s, 1H, H₆), 5.54 (s, 2H, H₁₂), 5.26 (s, 2H, H₁₈), 5.15 – 5.03 (m, 3H, H_{22,26,30}), 3.48 (s, 3H, H₂₀), 3.30 (d, *J* = 7.5 Hz, 2H, H₂₁), 2.16 (s, 3H, H₁₆), 2.08 – 1.89 (m, 8H, H_{24–25,28–29}), 1.76 (s, 3H, H₃₅), 1.69 (s, 6H, H_{9–10}), 1.66 (s, 3H, H₃₂), 1.58 (s, 3H, H₃₃), 1.56 (s, 3H, H₃₄).

¹³C NMR (100 MHz, CDCl₃) δ 170.5 (C₁₄), 160.24 (C₄), 160.17 (C₇), 155.8 (C_{8a}), 139.7 (C₅), 135.7 (C₂₃), 135.1 (C₂₇), 131.3 (C₃₁), 124.3 (C₂₆), 124.0 (C₃₀), 121.0 (C₂₂), 118.2 (C₈), 107.2 (C₆), 105.3 (C₂), 105.0 (C_{4a}), 94.1 (C₁₈), 64.2 (C₁₂), 56.4 (C₂₀), 39.74 (C₂₄), 39.66 (C₂₈), 26.7 (C₂₉), 26.6 (C₂₅),

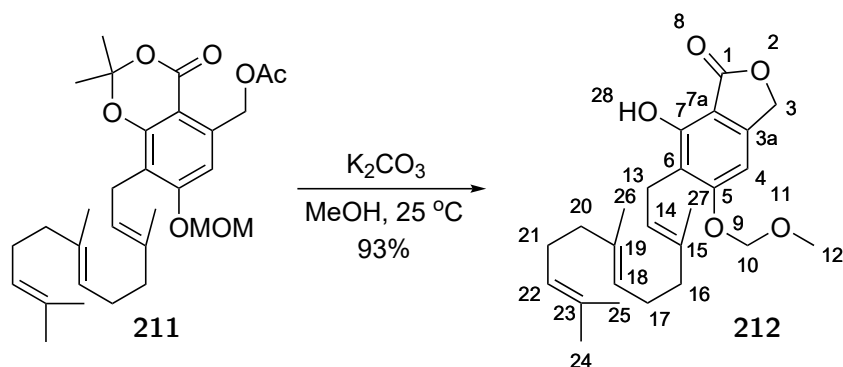
25.70 (2C, C₉₋₁₀), 25.66 (C₃₂), 21.9 (C₂₁), 20.9 (C₁₆), 17.6 (C₃₃), 16.1 (C₃₄), 16.0 (C₃₅).

IR ν_{max} (neat) 2968, 2918, 2856, 1728, 1609, 1582, 1376, 1293, 1222, 1151, 1044, 964 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₃₀H₄₃O₇ 515.3009; Found 515.2994.

Elemental Analysis Anal. Calcd for C₃₀H₄₂O₇: C, 70.01; H, 8.23; Found: C, 69.75; H, 8.37.

7-Hydroxy-5-(methoxymethoxy)-6-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1-(3*H*)-one



K_2CO_3 (3.51 g, 25.4 mmol) was added with stirring to ether **211** (2.61 g, 5.07 mmol) in MeOH (70 mL) at 25 °C. After 18 h, aqueous citric acid (1 M) was added to pH ~3 and the mixture was diluted with CH_2Cl_2 (100 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 50 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O 2 : 1) to provide phthalide **212** (1.96 g, 4.73 mmol, 93 %) a colourless oil which solidified upon standing.

R_f 0.44 (Pentane : Et_2O 2 : 1). **Melting Point** 61 – 62 °C.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.75 (s, 1H, H_{28}), 6.21 (s, 1H, H_4), 4.75 (s, 2H, H_{10}), 4.71 (s, 2H, H_3), 4.71 – 4.66 (m, 1H, H_{14}), 4.58 – 4.53 (m, 2H, $\text{H}_{18,22}$), 2.97 (s, 3H, H_{12}), 2.88 (d, $J = 7.2$ Hz, 2H, H_{13}), 1.61 – 1.37 (m, 8H, $\text{H}_{16-17,20-21}$), 1.28 (s, 3H, H_{27}), 1.16 (s, 3H, H_{24}), 1.07 (s, 3H, H_{25}), 1.05 (s, 3H, H_{26}).

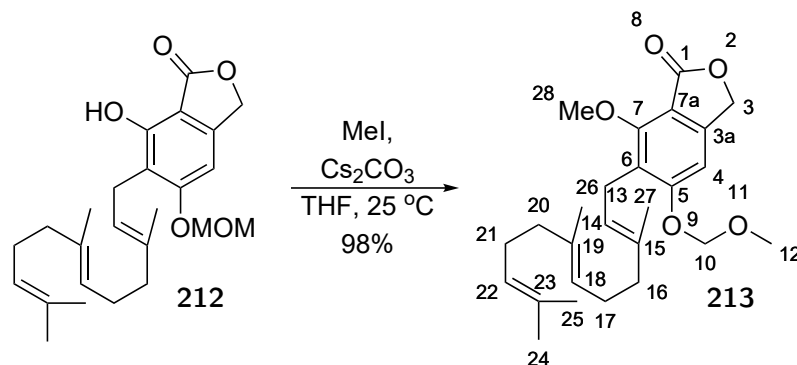
$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 172.7 (C_1), 162.1 (C_5), 154.7 (C_7), 145.5 (C_6), 135.8 (C_{15}), 135.0 (C_{19}), 131.3 (C_{23}), 124.3 (C_{18}), 124.1 (C_{22}), 121.2 (C_{14}), 117.7 (C_{7a}), 104.8 (C_{3a}), 99.1 (C_4), 94.2 (C_{10}), 70.4 (C_3), 56.3 (C_{12}), 39.8 (C_{16}), 39.7 (C_{20}), 26.7 (C_{21}), 26.5 (C_{17}), 25.7 (C_{24}), 21.8 (C_{13}), 17.6 (C_{25}), 16.1 (C_{26}), 16.0 (C_{27}).

IR ν_{max} (neat) 3414, 1730, 1627, 1610, 1151, 1064, 1036, 959 cm^{-1} .

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{35}\text{O}_5$ 415.2484; Found 415.2482.

Elemental Analysis Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_5$: C, 72.44; H, 8.27; Found: C, 72.31; H, 8.35.

7-Methoxy-5-(methoxymethoxy)-6-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1-(3*H*)-one



MeI (0.86 mL, 13.8 mmol) was added dropwise with stirring to a suspension of Cs₂CO₃ (4.50 g, 13.8 mmol) and phthalide **212** (1.91 g, 4.60 mmol) in THF (46 mL) at 25 °C. After 16 h, saturated aqueous NH₄Cl (30 mL) was added and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 2 : 1) to provide methyl ether **213** (1.94 g, 4.53 mmol, 98 %) as a colourless oil.

R_f 0.34 (Pentane : Et₂O 2 : 1).

¹H NMR (400 MHz, CDCl₃) δ 6.88 (s, 1H, H₄), 5.27 (s, 2H, H₁₀), 5.17 (s, 2H, H₃), 5.16 – 5.10 (m, 1H, H₁₄), 5.09 – 5.02 (m, 2H, H_{18,22}), 4.06 (s, 3H, H₂₉), 3.48 (s, 3H, H₁₂), 3.42 (d, *J* = 7.1 Hz, 2H, H₁₃), 2.09 – 1.88 (m, 8H, H_{16–17,20–21}), 1.79 (s, 3H, H₂₇), 1.66 (s, 3H, H₂₄), 1.58 (s, 3H, H₂₅), 1.56 (s, 3H, H₂₆).

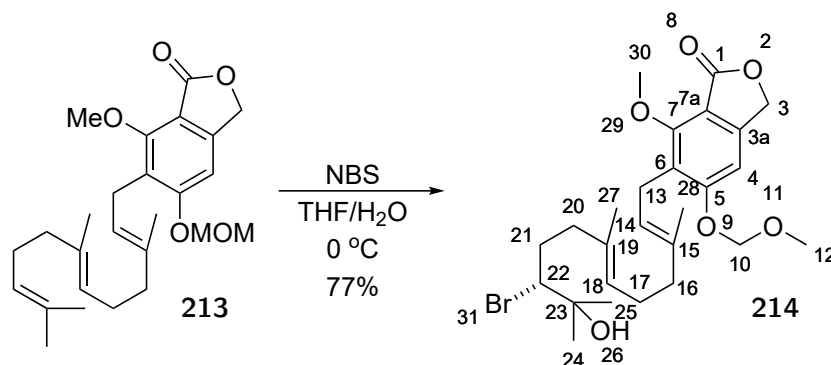
¹³C NMR (100 MHz, CDCl₃) δ 168.8 (C₁), 161.3 (C₅), 158.0 (C₇), 148.2 (C₆), 135.5 (C₁₅), 135.0 (C₁₉), 131.3 (C₂₃), 124.8 (C_{7a}), 124.3 (C₁₈), 124.0 (C₂₂), 122.0 (C₁₄), 110.5 (C_{3a}), 101.9 (C₄), 94.2 (C₁₀), 68.8 (C₃), 62.6 (C₂₉), 56.3 (C₁₂), 39.8 (C₁₆), 39.7 (C₂₀), 26.7 (C₂₁), 26.5 (C₁₇), 25.7 (C₂₄), 22.7 (C₁₃), 17.6 (C₂₅), 16.1 (C₂₆), 16.0 (C₂₇).

IR *ν*_{max} (neat) 1752, 1604, 1232, 1151, 1078, 1041, 926 cm⁻¹.

HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{26}H_{37}O_5$ 429.2641; Found 429.2650.

Elemental Analysis Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.87; H, 8.47; Found: C, 72.79; H, 8.55.

6-((2*E*,6*E*)-10-Bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1-(3*H*)-one



NBS (959 mg, 5.39 mmol) was added with stirring to methyl ether **213** (2.10 g, 4.90 mmol) in THF (46 mL) and H₂O (23 mL) at 0 °C. After 2 h, Na₂S₂O₅ (0.5 M; 30 mL) and EtOAc (30 mL) were added and the two phases were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 2 : 1) to provide bromohydrin **214** (1.99 g, 3.79 mmol, 77 %) as a colourless oil.

R_f 0.14 (Pentane : Et₂O 1 : 1).

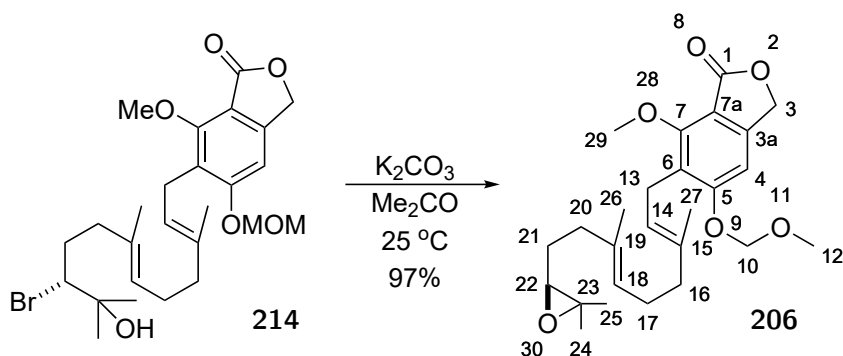
¹H NMR (400 MHz, CDCl₃) δ 6.88 (s, 1H, H₄), 5.28 (s, 2H, H₁₀), 5.17 (s, 2H, H₃), 5.17 – 5.11 (m, 2H, H_{14,18}), 4.07 (s, 3H, H₃₀), 3.95 (dd, *J* = 11.4, 1.9 Hz, 1H, H₂₂), 3.48 (s, 3H, H₁₂), 3.42 (d, *J* = 7.1 Hz, 2H, H₁₃), 2.33 – 2.22 (m, 1H, H₂₀), 2.19 – 1.88 (m, 6H, H_{16–17,20–21}), 1.79 (s, 3H, H₂₇), 1.78 – 1.68 (m, 1H, H₂₁), 1.55 (s, 3H, H₂₈), 1.33 (s, 3H, H₂₄), 1.31 (s, 3H, H₂₅).

¹³C NMR (100 MHz, CDCl₃) δ 168.8 (C₁), 161.4 (C₅), 158.0 (C₇), 148.2 (C₆), 135.3 (C₁₅), 133.1 (C₁₉), 125.8 (C₁₈), 124.8 (C_{7a}), 122.1 (C₁₄), 110.5 (C_{3a}), 102.0 (C₄), 94.3 (C₁₀), 72.4 (C₂₃), 70.8 (C₂₂), 68.8 (C₃), 62.6 (C₃₀), 56.3 (C₁₂), 39.7 (C₁₆), 38.1 (C₂₀), 32.1 (C₂₁), 26.6 (C₂₄), 26.5 (C₁₇), 25.8 (C₂₅), 22.7 (C₁₃), 16.1 (C₂₇), 15.8 (C₂₈).

IR *ν*_{max} (neat) 3484, 1752, 1605, 1233, 1151, 1118, 1077, 1042, 978, 943 cm⁻¹.

HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₇BrO₆ 525.1852; Found 525.1865.

6-((2*E*,6*E*)-9-((*S*)-3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1-(3*H*)-one



K_2CO_3 (1.56 g, 2.96 mmol) was added with stirring to bromohydrin **214** in Me_2CO (60 mL) at $25\text{ }^\circ C$. After 18 h, H_2O (50 mL) and CH_2Cl_2 (100 mL) were added and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 ($3 \times 50\text{ mL}$) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 1 : 1) to provide epoxide **206** (1.28 g, 2.88 mmol, 97 %) as a colourless oil.

R_f 0.14 (Pentane : Et_2O 1 : 1).

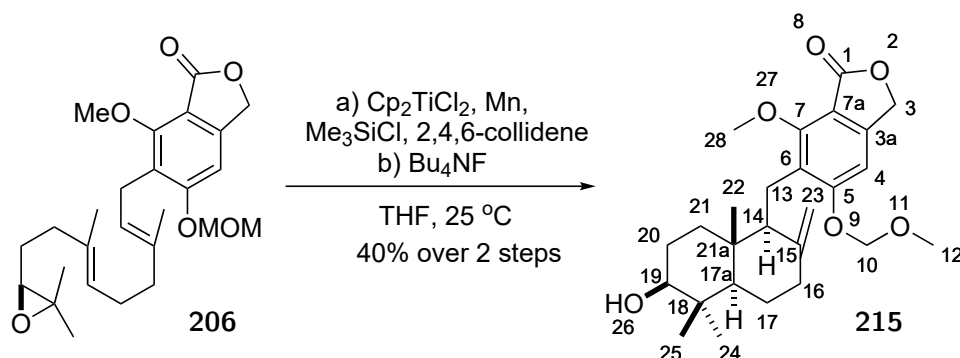
^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H, H_4), 5.27 (s, 2H, H_{10}), 5.17 (s, 2H, H_3), 5.16 – 5.02 (m, 2H, $H_{14,18}$), 4.06 (s, 3H, H_{29}), 3.47 (s, 3H, H_{12}), 3.41 (d, $J = 7.1\text{ Hz}$, 2H, H_{13}), 2.66 (t, $J = 6.3\text{ Hz}$, 1H, H_{22}), 2.29 – 1.89 (m, 6H, $H_{16-17,20}$), 1.78 (s, 3H, H_{27}), 1.63 – 1.58 (m, 1H, H_{21}), 1.57 (s, 3H, H_{26}), 1.56 – 1.50 (m, 1H, H_{21}), 1.28 (s, 3H, H_{24}), 1.23 (s, 3H, H_{25}).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7 (C_1), 161.3 (C_5), 158.0 (C_7), 148.2 (C_6), 135.4 (C_{15}), 134.1 (C_{19}), 124.8 (C_{7a}), 124.7 (C_{18}), 122.1 (C_{14}), 110.5 (C_{3a}), 102.0 (C_4), 94.2 (C_{10}), 68.8 (C_3), 64.1 (C_{22}), 62.6 (C_{29}), 58.2 (C_{23}), 56.3 (C_{12}), 39.7 (C_{16}), 36.2 (C_{20}), 27.4 (C_{21}), 26.5 (C_{17}), 24.9 (C_{24}), 22.7 (C_{13}), 18.7 (C_{25}), 16.1 (C_{27}), 16.0 (C_{26}).

IR ν_{max} (neat) 1752, 1604, 1232, 1117, 1077, 1041, 978 cm^{-1} .

HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{26}H_{37}O_6$ 445.2590; Found 445.2598.

6-(((1*S*,4*aR*,6*S*,8*aR*)-6-Hydroxy-5,5,8*a*-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1-(3*H*)-one



Cp₂TiCl₂ (197 mg, 0.792 mmol) and Mn powder (1.74 g, 31.7 mmol) were added with stirring to THF (50 mL) at 25 °C. After 30 min, when the solution changed from red to green, 2,4,6-collidine (3.67 mL, 27.7 mmol) and Me₃SiCl (2.01 mL, 15.8 mmol) were added sequentially with stirring. After 5 min, epoxide **206** (1.76 g, 3.96 mmol) in THF (50 mL) was added dropwise with stirring. After 16 h, aqueous citric acid (1 M; 100 mL) was added with stirring and, when effervescence has ceased, Et₂O (100 mL) was added and the two phases were separated. The aqueous layer was extracted with Et₂O (3 × 50 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and dissolved in THF (50 mL). Bu₄NF (1 M in THF; 16.0 mL, 16.0 mmol) was added and the resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was concentrated and chromatographed (pentane : Et₂O 1 : 4) to provide alcohol **215** (697 mg, 1.57 mmol, 40 %) as a white foam.

R_f 0.17 (Pentane : Et₂O 1 : 4).

¹H NMR (400 MHz, CDCl₃) δ 6.87 (s, 1H, H₄), 5.31 – 5.23 (m, 2H, H₁₀), 5.15 (s, 2H, H₃), 4.96 (s, 1H, H₂₃), 4.70 (s, 1H, H₂₃), 4.06 (s, 3H, H₂₈), 3.51 (s, 3H, H₁₂), 3.27 (dd, *J* = 11.5, 4.6 Hz, 1H, H₁₉), 2.92 (dd, *J* = 13.8, 9.7 Hz, 1H, H_{13eq}), 2.73 (dd, *J* = 13.8, 3.7 Hz, 1H, H_{13ax}), 2.50 (dd, *J* = 10.0, 3.4 Hz, 1H, H₁₄), 2.39 – 2.22 (m, 1H, H_{16eq}), 1.94 – 1.87 (m, 2H, H_{16ax,21eq}), 1.79 – 1.59 (m,

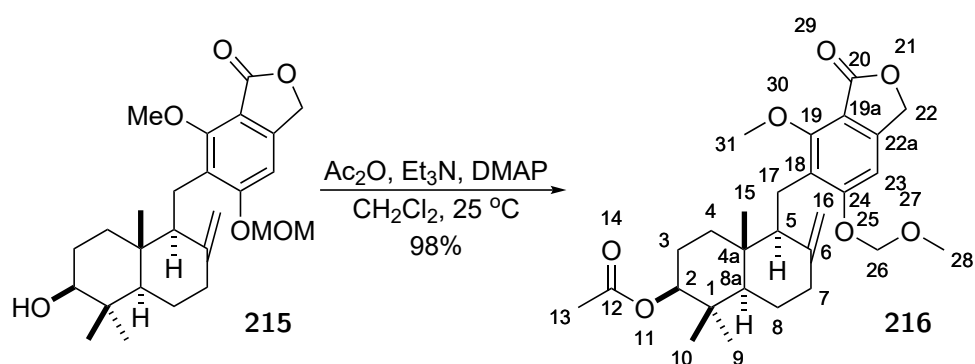
3H, H_{17eq,20}), 1.46 – 1.39 (m, 1H, H_{21ax}), 1.40 – 1.32 (m, 1H, H_{17ax}), 1.15 (dd, $J = 12.5, 2.8$ Hz, 1H, H_{17a}), 1.00 (s, 3H, H₂₂), 0.83 (s, 3H, H₂₄), 0.80 (s, 3H, H₂₅).

¹³C NMR (100 MHz, CDCl₃) δ 168.9 (C₁), 161.6 (C₅), 158.5 (C₇), 148.7 (C₁₅), 148.1 (C_{3a}), 125.2 (C₆), 110.6 (C_{7a}), 106.9 (C₂₃), 102.1 (C₄), 94.6 (C₁₀), 78.9 (C₁₉), 68.7 (C₃), 62.4 (C₂₈), 56.6 (C₁₂), 55.3 (C₁₄), 54.8 (C_{17a}), 40.1 (C_{21a}), 39.2 (C₁₈), 38.4 (C₁₆), 36.5 (C₂₁), 28.3 (C₂₂), 28.0 (C₂₀), 24.1 (C₁₇), 19.6 (C₁₃), 15.4 (C₂₅), 14.2 (C₂₄).

IR ν_{max} (neat) 3489, 1748, 1606, 1463, 1323, 1077, 1042, 732 cm⁻¹.

HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₆H₃₇O₆ 445.2590; Found 445.2592.

(2*S*,4*aR*,5*S*,8*aR*)-5-((4-Methoxy-6-(methoxymethoxy)-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1,1,4*a*-trimethyl-6-methylenedecahydronaphthalen-2-yl acetate



DMAP (9 mg, 0.0704 mmol), Et₃N (108 μ L, 0.774 mmol) and Ac₂O (74 μ L, 0.774 mmol) were added sequentially with stirring to alcohol **215** (313 mg, 0.704 mmol) in CH₂Cl₂ (3 mL) at 25 °C. After 2 h, saturated aqueous NaHCO₃ (2 mL) was added and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 3 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 1 : 1) to provide acetate **216** (337 mg, 0.693 mmol, 98 %) as a white solid.

R_f 0.33 (Pentane : Et₂O 1 : 1).

Melting Point 155 – 158 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.88 (s, 1H, H₂₃), 5.29 – 5.25 (m, 2H, H₂₆), 5.16 (s, 2H, H₂₂), 4.95 (s, 1H, H₁₆), 4.70 (s, 1H, H₁₆), 4.52 (dd, J = 11.6, 4.6 Hz, 1H, H₂), 4.06 (s, 3H, H₃₁), 3.51 (s, 3H, H₂₈), 2.92 (dd, J = 13.8, 9.6 Hz, 1H, H_{17eq}), 2.73 (dd, J = 13.8, 3.9 Hz, 1H, H_{17ax}), 2.57 – 2.48 (m, 1H, H₅), 2.36 – 2.27 (m, 1H, H_{7eq}), 2.06 (s, 3H, H₁₃), 1.93 – 1.83 (m, 2H, H_{4eq,7ax}), 1.81 – 1.59 (m, 3H, H_{3,8eq}), 1.49 – 1.32 (m, 2H, H_{4ax,8ax}), 1.22 (dd, J = 12.5, 2.7 Hz, 1H, H_{8a}), 0.87 (s, 6H, H_{9–10}), 0.85 (s, 3H, H₁₅).

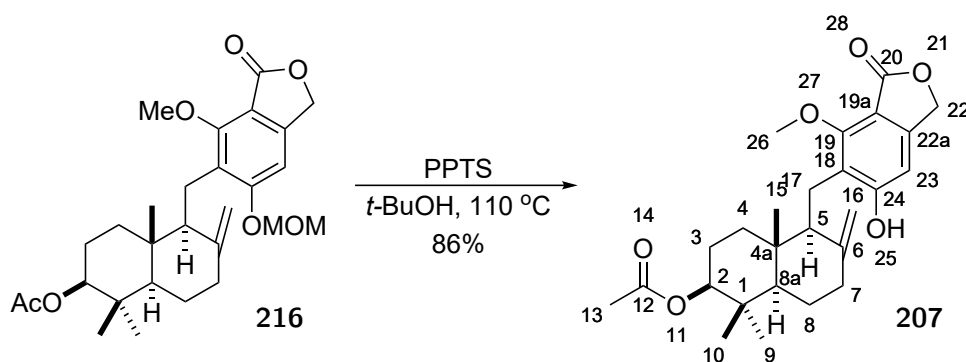
¹³C NMR (100 MHz, CDCl₃) δ 171.1 (C₁₂), 168.9 (C₂₀), 161.6 (C₂₄), 158.4 (C₁₉), 148.5 (C₆), 148.2

(C_{22a}), 125.0 (C₁₈), 110.5 (C_{19a}), 107.1 (C₁₆), 102.1 (C₂₃), 94.5 (C₂₆), 80.8 (C₂), 68.7 (C₂₂), 62.6 (C₃₁), 56.6 (C₂₈), 55.0 (C₅), 54.8 (C_{8a}), 39.9 (C_{4a}), 38.3 (C₇), 38.1 (C₁), 36.2 (C₄), 28.3 (C₁₅), 24.4 (C₃), 24.0 (C₈), 21.3 (C₁₃), 19.8 (C₁₇), 16.6 (C₁₀), 14.2 (C₉).

IR ν_{max} (neat) 1753, 1729, 1606, 1463, 1234, 1078, 1043, 978, 920, 732 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₈H₃₉O₇ 487.2696; Found 487.2674.

(2*S*,4*aR*,5*S*,8*aR*)-5-((6-Hydroxy-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1,1,4*a*-trimethyl-6-methylenedecahydronaphthalen-2-yl acetate



PPTS (842 mg, 3.35 mmol) was added with stirring to acetate **216** (326 mg, 0.670 mmol) in *t*-BuOH (25 mL) and the mixture was heated to 100 °C for 36 h. After cooling, brine (30 mL) and CH₂Cl₂ (40 mL) were added and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : EtOAc 3 : 2) to provide phenol **207** (225 mg, 0.580 mmol, 86 %) as a white solid.

R_f 0.12 (Pentane : Et₂O 1 : 1).

Melting Point 222 – 223 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.55 (s, 1H, H₂₃), 6.15 (s, 1H, H₂₅), 5.13 (s, 2H, H₂₂), 5.03 (s, 1H, H₁₆), 4.81 (s, 1H, H₁₆), 4.51 (dd, *J* = 11.6, 4.6 Hz, 1H, H₂), 4.08 (s, 3H, H₂₆), 2.90 – 2.75 (m, 2H, H₁₇), 2.42 – 2.32 (m, 2H, H_{5,7eq}), 2.06 (s, 3H, H₁₃), 2.02 – 1.87 (m, 2H, H_{4eq,7ax}), 1.78 – 1.62 (m, 3H, H_{3,8eq}), 1.48 – 1.36 (m, 2H, H_{4ax,8ax}), 1.23 (dd, *J* = 12.5, 2.8 Hz, 1H, H_{8a}), 0.87 (s, 6H, H_{9–10}), 0.85 (s, 3H, H₁₅).

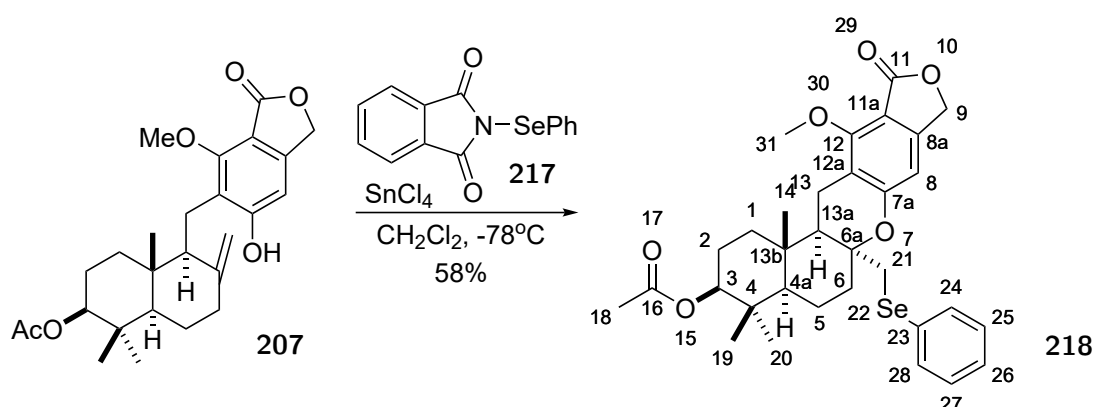
¹³C NMR (100 MHz, CDCl₃) δ 171.1 (C₁₂), 168.9 (C₂₀), 160.9 (C₂₄), 158.8 (C₁₉), 149.4 (C₆), 148.1 (C_{22a}), 122.8 (C₁₈), 109.6 (C_{19a}), 107.3 (C₁₆), 103.8 (C₂₃), 80.8 (C₂), 68.4 (C₂₂), 62.7 (C₂₆), 55.2

(C₅), 54.8 (C_{8a}), 40.2 (C_{4a}), 38.2 (C₇), 38.1 (C₁), 36.2 (C₄), 28.2 (C₁₅), 24.3 (C₃), 24.0 (C₈), 21.3 (C₁₃), 19.2 (C₁₇), 16.5 (C₁₀), 14.2 (C₉).

IR ν_{max} (neat) 3295, 1730, 1605, 1429, 1235, 1077, 1027 cm⁻¹.

HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₆H₃₅O₆ 443.2434; Found 443.2434.

((3*S*,4*aR*,6*aS*,13*aR*,13*bS*)-12-Methoxy-4,4,13*b*-trimethyl-11-oxo-6*a*-(phenylselanyl)methyl)-1,3,4,4*a*,5,6,6*a*,9,11,13,13*a*,13*b*-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate



Phenol **207** (100 mg, 0.226 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring to *N*-(phenylseleno)phthalimide **217** (410 mg, 1.36 mmol) and SnCl_4 (1 M) in CH_2Cl_2 ; 1.13 mL, 1.13 mmol) in CH_2Cl_2 (20 mL) at -78°C . After 7 h, NaOH (2 M; 1 mL) was added and the reaction mixture was filtered through Celite®. NaOH (2 M; 10 mL) was added and the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated and chromatographed (pentane : Et_2O 1 : 1) to provide phenylselenide **218** (79 mg, 0.132 mmol, 58 %) as a colorless oil.

R_f 0.26 (Pentane : Et_2O 1 : 1).

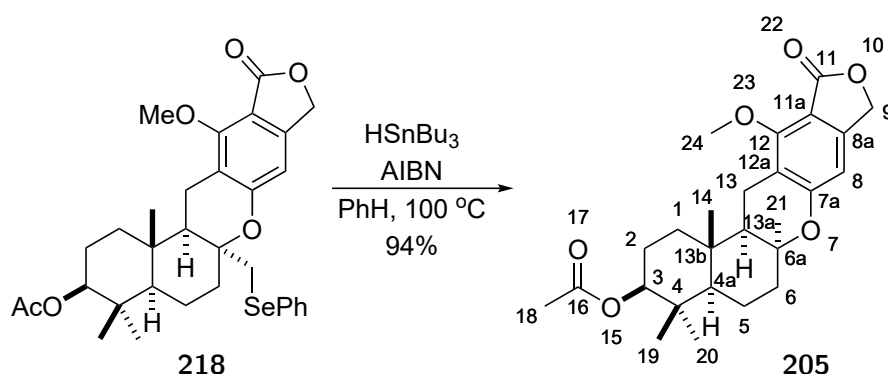
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45 – 7.40 (m, 2H, $\text{H}_{24,28}$), 7.23 – 7.16 (m, 3H, H_{25-27}), 6.39 (s, 1H, H_8), 5.09 (s, 2H, H_9), 4.53 (dd, $J = 11.8, 4.6$ Hz, 1H, H_3), 4.08 (s, 3H, H_{31}), 3.12 (d, $J = 12.6$ Hz, 1H, H_{21}), 2.95 (d, $J = 12.6$ Hz, 1H, H_{21}), 2.77 (d, $J = 18.9$ Hz, 1H, H_{13eq}), 2.44 (dd, $J = 18.9, 8.4$ Hz, 1H, H_{13ax}), 2.30 (dt, $J = 14.0, 3.0$ Hz, 1H, H_{6eq}), 2.05 (s, 3H, H_{18}), 1.94 – 1.57 (m, 7H, $\text{H}_{1eq,2,5,6ax,13a}$), 1.19 (td, $J = 13.2, 3.9$ Hz, 1H, H_{1ax}), 1.03 (dd, $J = 11.3, 2.7$ Hz, 1H, H_{4a}), 0.92 (s, 3H, H_{20}), 0.85 (s, 3H, H_{19}), 0.66 (s, 3H, H_{14}).

^{13}C NMR (100 MHz, CDCl_3) δ 171.0 (C_{16}), 168.8 (C_{11}), 160.7 (C_{7a}), 157.3 (C_{12}), 147.4 (C_{8a}), 133.3 (2C, $\text{C}_{24,28}$), 130.2 (C_{23}), 129.1 (2C, $\text{C}_{25,27}$), 127.3 (C_{26}), 116.0 (C_{12a}), 108.2 (C_{11a}), 105.3 (C_8), 80.4 (C_3), 79.1 (C_{6a}), 68.6 (C_9), 62.1 (C_{31}), 53.9 (C_{4a}), 45.5 (C_{13a}), 38.03 (C_{13b}), 37.97 (C_{21}), 37.8 (C_1), 37.7 (C_4), 37.3 (C_6), 28.4 (C_{20}), 23.4 (C_2), 21.3 (C_{18}), 17.5 (C_5), 17.4 (C_{13}), 16.8 (C_{19}), 14.4 (C_{14}).

IR ν_{max} (neat) 1751, 1734, 1613, 1592, 1429, 1366, 1238, 1131, 1027, 1078, 733 cm^{-1} .

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{32}\text{H}_{38}\text{O}_6\text{Se}$ 599.1912; Found 599.1913.

(3*S*,4*aR*,6*aS*,13*aR*,13*bS*)-12-Methoxy-4,4,6*a*,13*b*-tetramethyl-11-oxo-1,3,4,4*a*,5,6,6*a*,9,11,13,13*a*,13*b*-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate



Phenylselenide **218** (46 mg, 0.0770 mmol), AIBN (13 mg, 0.0770 mmol) and HSnBu₃ (62 µL, 0.231 mmol) in PhH (2 mL) were purged with Ar for 5 min and heated to 100 °C for 5 h. The reaction mixture was directly purified by chromatography (pentane : Et₂O 1 : 1) through a pad of KF to give meroterpenoid **205** (31 mg, 0.0700 mmol, 91 %) as a white solid.

R_f 0.29 (Pentane : Et₂O 1 : 1).

Melting Point 212 – 213 °C.

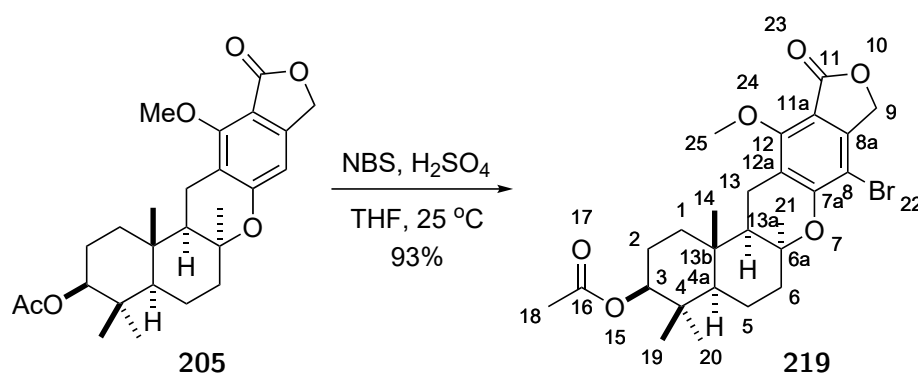
¹H NMR (400 MHz, CDCl₃) δ 6.50 (s, 1H, H₈), 5.13 (s, 2H, H₉), 4.49 (dd, *J* = 11.7, 4.7 Hz, 1H, H₃), 4.13 (s, 3H, H₂₄), 2.88 (d, *J* = 18.7 Hz, 1H, H_{13eq}), 2.71 (dd, *J* = 18.6, 8.0 Hz, 1H, H_{13ax}), 2.23 – 2.14 (m, 1H, H_{6eq}), 2.04 (s, 3H, H₁₈), 1.87 (dt, *J* = 13.3, 3.7 Hz, 1H, H_{1eq}), 1.74 – 1.50 (m, 5H, H_{2,5,6ax}), 1.40 (d, *J* = 8.1 Hz, 1H, H_{13a}), 1.17 (s, 3H, H₂₁), 1.13 (dd, *J* = 13.4, 4.0 Hz, 1H, H_{1ax}), 1.00 (dd, *J* = 11.3, 2.1 Hz, 1H, H_{4a}), 0.89 (s, 3H, H₂₀), 0.84 (s, 3H, H₁₉), 0.66 (s, 3H, H₁₄).

¹³C NMR (100 MHz, CDCl₃) δ 170.9 (C₁₆), 168.9 (C₁₁), 161.6 (C_{7a}), 157.4 (C₁₂), 147.4 (C_{8a}), 116.0 (C_{12a}), 107.9 (C_{11a}), 105.2 (C₈), 80.5 (C₃), 76.6 (C_{6a}), 68.6 (C₉), 62.0 (C₂₄), 54.2 (C_{4a}), 48.1 (C_{13a}), 40.1 (C₆), 37.9 (C₄), 37.8 (C₁), 37.6 (C_{13b}), 28.4 (C₂₀), 27.0 (C₂₁), 23.4 (C₂), 21.2 (C₁₈), 17.7 (C_{5,13}), 16.8 (C₁₉), 14.3 (C₁₄).

IR ν_{max} (neat) 1730, 1752, 1612, 1592, 1366, 1238, 1130, 1081, 1025, 901, 731 cm^{-1} .

HRMS (ES) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_6$ 443.2434; Found 443.2419.

(3*S*,4*aR*,6*aS*,13*aR*,13*bS*)-8-Bromo-12-methoxy-4,4,6*a*,13*b*-tetramethyl-11-oxo-1,3,4,4*a*,5,6,6*a*,9,11,13,13*a*,13*b*-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate



NBS (19 mg, 0.105 mmol) and H₂SO₄ (13 μ L, 0.244 mmol) were added sequentially with stirring to meroterpenoid **205** (31 mg, 0.0700 mmol) in THF (0.4 mL). After 17 h, saturated aqueous NaHCO₃ (0.4 mL) and Na₂S₂O₃ (50 mg, 0.316 mmol) were added and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 0.5 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 7 : 3) to provide bromide **219** (34 mg, 0.0652 mmol, 93 %) as a white foam.

R_f 0.19 (Pentane : Et₂O 7 : 3).

Melting Point 212 – 213 °C.

¹H NMR (400 MHz, CDCl₃) δ 5.07 (s, 2H, H₉), 4.50 (dd, *J* = 11.8, 4.5 Hz, 1H, H₃), 4.15 (s, 3H, H₂₅), 2.90 (d, *J* = 18.8 Hz, 1H, H_{13eq}), 2.75 (dd, *J* = 18.8, 8.1 Hz, 1H, H_{13ax}), 2.38 – 2.29 (m, 1H, H_{6eq}), 2.04 (s, 3H, H₁₈), 1.86 (dd, *J* = 13.5, 3.7 Hz, 1H, H_{1eq}), 1.79 – 1.51 (m, 5H, H_{2,5,6ax}), 1.44 (d, *J* = 8.2 Hz, 1H, H_{13a}), 1.19 (s, 3H, H₂₁), 1.17 – 1.08 (m, 1H, H_{1ax}), 1.01 (d, *J* = 11.0 Hz, 1H, H_{4a}), 0.90 (s, 3H, H₂₀), 0.85 (s, 3H, H₁₉), 0.63 (s, 3H, H₁₄).

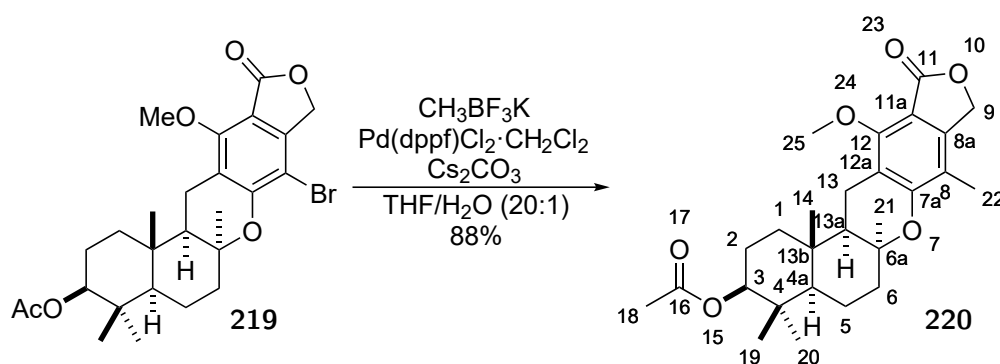
¹³C NMR (100 MHz, CDCl₃) δ 170.9 (C₁₆), 168.4 (C₁₁), 157.4 (C_{7a}), 156.4 (C₁₂), 146.9 (C_{8a}), 117.5 (C_{12a}), 109.2 (C_{11a}), 98.3 (C₈), 80.4 (C₃), 78.1 (C_{6a}), 69.3 (C₉), 62.2 (C₂₅), 54.1 (C_{4a}), 48.0 (C_{13a}),

39.9 (C₆), 37.9 (C₄), 37.8 (C₁), 37.7 (C_{13b}), 28.4 (C₂₀), 27.1 (C₂₁), 23.3 (C₂), 21.3 (C₁₈), 18.3 (C₁₃), 17.8 (C₅), 16.8 (C₁₉), 14.2 (C₁₄).

IR ν_{max} (neat) 1759, 1733, 1603, 1465, 1436, 1366, 1246, 1135, 1029, 904, 732 cm⁻¹.

HRMS (ES) m/z: [M + H]⁺ Calcd for C₂₆H₃₄O₆Br 521.1539; Found 521.1549.

(3*S*,4*aR*,6*aS*,13*aR*,13*bS*)-12-Methoxy-4,4,6*a*,8,13*b*-pentamethyl-11-oxo-1,3,4,4*a*,5,6,6*a*,9,11,13,13*a*,13*b*-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate



A degassed solution of bromide **219** (65 mg, 0.125 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (21 mg, 0.0257 mmol), CH₃BF₃K (23 mg, 0.187 mmol) and Cs₂CO₃ (122 mg, 0.375 mmol) in THF (1.5 mL) and H₂O (75 µL) was heated to 80 °C for 18 h. After cooling to 25 °C, H₂O (1 mL) and Et₂O (1 mL) were added and the two phases were separated. The aqueous layer was extracted with Et₂O (3 × 1 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 7 : 3) to provide arene **220** (50 mg, 0.110 mmol, 88 %) as a white foam.

R_f 0.26 (Pentane : Et₂O 7 : 3).

¹H NMR (400 MHz, CDCl₃) δ 5.11 (s, 2H, H₉), 4.50 (dd, *J* = 11.7, 4.6 Hz, 1H, H₃), 4.09 (s, 3H, H₂₅), 2.90 (d, *J* = 18.6 Hz, 1H, H_{13eq}), 2.74 (dd, *J* = 18.6, 8.1 Hz, 1H, H_{13ax}), 2.33 – 2.16 (m, 1H, H_{6eq}), 2.04 (s, 3H, H₁₈), 2.03 (s, 3H, H₂₂), 1.95 – 1.81 (m, 1H, H_{1eq}), 1.72 – 1.54 (m, 5H, H_{2,5,6ax}), 1.40 (d, *J* = 7.8 Hz, 1H, H_{13a}), 1.21 – 1.16 (m, 1H, H_{1ax}), 1.16 (s, 3H, H₂₁), 1.01 (d, *J* = 9.9 Hz, 1H, H_{4a}), 0.90 (s, 3H, H₂₀), 0.85 (s, 3H, H₁₉), 0.63 (s, 3H, H₁₄).

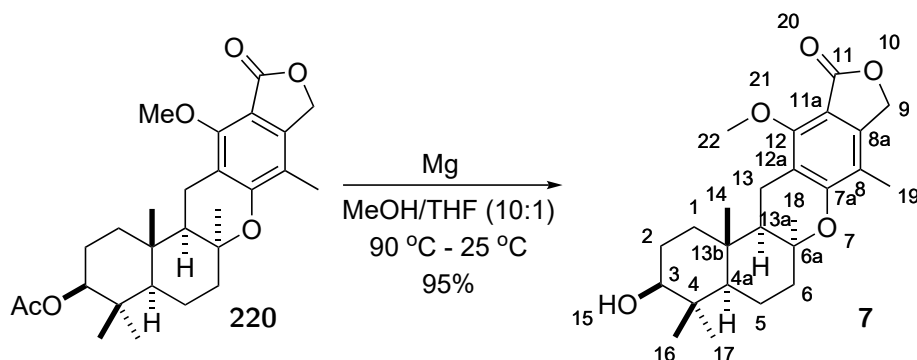
¹³C NMR (100 MHz, CDCl₃) δ 170.9 (C₁₆), 169.5 (C₁₁), 158.8 (C_{7a}), 155.3 (C₁₂), 145.3 (C_{8a}), 115.7 (C_{12a}), 114.3 (C₈), 107.2 (C_{11a}), 80.5 (C₃), 76.4 (C_{6a}), 68.2 (C₉), 61.9 (C₂₅), 54.2 (C_{4a}), 47.9 (C_{13a}), 40.2 (C₆), 37.9 (C₄), 37.8 (C₁), 37.7 (C_{13b}), 28.5 (C₂₀), 27.3 (C₂₁), 23.4 (C₂), 21.3 (C₁₈), 17.9 (C₅),

17.8 (C₁₃), 16.8 (C₁₉), 14.3 (C₁₄), 10.7 (C₂₂).

IR ν_{max} (neat) 1754, 1609, 1368, 1245, 1146, 1135, 1041, 1029, 904, 732 cm⁻¹.

HRMS (ES) m/z: [M + H]⁺ Calcd for C₂₇H₃₇O₆ 457.2590; Found 457.2594.

(3*S*,4*aR*,6*aS*,13*aR*,13*bS*)-3-Hydroxy-12-methoxy-4,4,6*a*,8,13*b*-pentamethyl-1,2,3,4,4*a*,5,6,6*a*,9,13,13*a*,13*b*-dodecahydro-11*H*-benzo[*a*]furo[3,4-*i*]xanthen-11-one



Magnesium turnings (4 mg, 0.164 mmol) was added with stirring to a solution of arene **220** (15 mg, 0.0329 mmol) in MeOH (1 mL) and THF (0.1 mL) and the resulting suspension was heated at 90 °C for 1 h. When the reaction mixture had turned into a milky solution and effervescence has ceased, it was cooled to 25 °C and stirred for additional 20 h. Aqueous HCl (1 M) was added until pH ~1 and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 1 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 1 : 1) to provide (±)-17*S*-dihydroaustalide K (**7**) (13 mg, 0.0314 mmol), 95 %) as a white solid.

R_f 0.12 (Pentane : Et₂O 1 : 1).

Melting Point 198 – 200 °C.

¹H NMR (400 MHz, CDCl₃) δ 5.11 (s, 2H, H₉), 4.09 (s, 3H, H₂₂), 3.24 (dd, *J* = 11.7, 4.5 Hz, 1H, H₃), 2.91 (d, *J* = 18.6 Hz, 1H, H_{13eq}), 2.73 (dd, *J* = 18.7, 8.2 Hz, 1H, H_{13ax}), 2.29 – 2.22 (m, 1H, H_{6eq}), 2.03 (s, 3H, H₁₉), 1.89 (dt, *J* = 13.1, 3.5 Hz, 1H, H_{1eq}), 1.62 – 1.52 (m, 5H, H_{2,5,6ax}), 1.39 (d, *J* = 8.2 Hz, 1H, H_{13a}), 1.18 (d, *J* = 6.2 Hz, 1H, H₁₅), 1.15 (s, 3H, H₁₈), 1.09 (td, *J* = 13.2, 3.8 Hz, 1H, H_{1ax}), 1.03 (s, 3H, H₁₇), 0.93 (d, *J* = 11.5 Hz, 1H, H_{4a}), 0.78 (s, 3H, H₁₆), 0.61 (s, 3H, H₁₄).

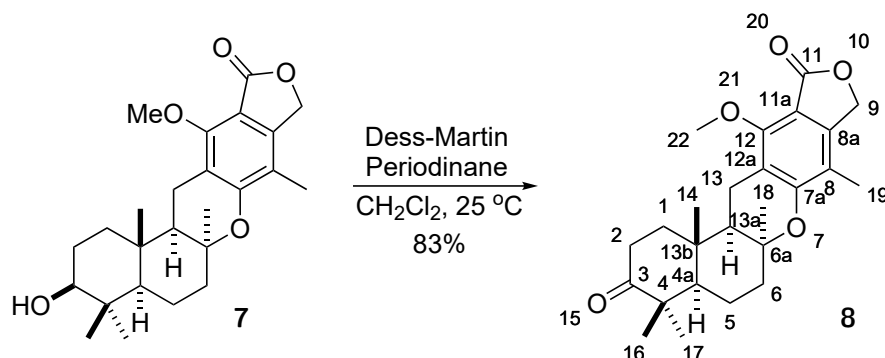
¹³C NMR (100 MHz, CDCl₃) δ 169.5 (C₁₁), 158.9 (C_{7a}), 155.3 (C₁₂), 145.3 (C_{8a}), 115.7 (C_{12a}),

114.3 (C₈), 107.2 (C_{11a}), 78.8 (C₃), 76.4 (C_{6a}), 68.2 (C₉), 61.9 (C₂₂), 54.1 (C_{4a}), 48.0 (C_{13a}), 40.3 (C₆), 38.8 (C₄), 38.1 (C₁), 38.0 (C_{13b}), 28.5 (C₁₇), 27.3 (C₁₈), 27.1 (C₂), 18.0 (C₁₃), 17.9 (C₅), 15.7 (C₁₆), 14.2 (C₁₄), 10.7 (C₁₉).

IR ν_{max} (neat) 3494, 1752, 1610, 1477, 1368, 1148, 1135, 1040, 904, 732 cm⁻¹.

HRMS (ES) m/z: [M + H]⁺ Calcd for C₂₅H₃₅O₅ 415.2484; Found 415.2486.

(5a*R*,7a*S*,14a*R*,14b*S*)-13-Methoxy-5,5,7a,9,14b-pentamethyl-1,2,5a,6,7,7a,10,14,14a,14b-decahydro-5*H*-furo[3,4-*i*]oxepino[4,3-*α*]xanthene-3,12-dione



Dess–Martin periodinane (52 mg, 0.123 mmol) was added with stirring to (±)-17*S*-dihydroaustalide K (**7**) (34 mg, 0.0820 mmol) in CH_2Cl_2 (2 mL) at 25 °C. After 1 h, the mixture was concentrated and chromatographed (pentane : Et_2O 1 : 1) to give (±)-austalide K (**8**) (28 mg, 0.0679 mmol, 83 %) as a white solid.

R_f 0.34 (Pentane : Et_2O 1 : 1). **Melting Point** 160 – 164 °C.

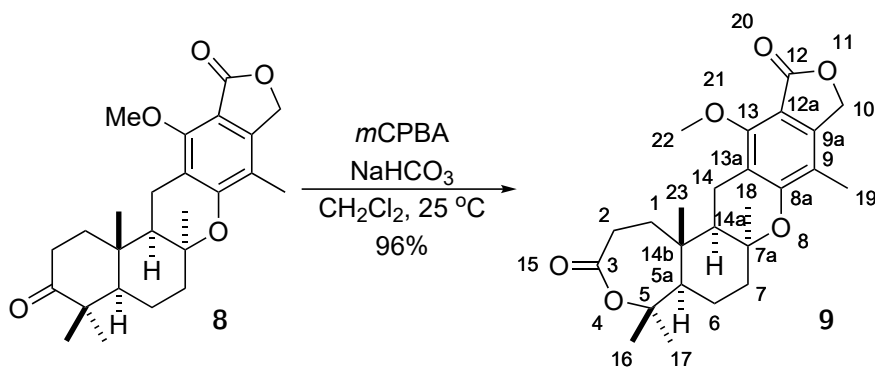
^1H NMR (400 MHz, CDCl_3) δ 5.12 (s, 2H, H_9), 4.11 (s, 3H, H_{22}), 2.93 (d, $J = 18.5$ Hz, 1H, H_{13eq}), 2.81 (dd, $J = 18.6, 8.2$ Hz, 1H, H_{13ax}), 2.54 (ddd, $J = 16.1, 11.7, 7.0$ Hz, 1H, H_{2eq}), 2.47 – 2.36 (m, 1H, H_{2ax}), 2.31 – 2.25 (m, 1H, H_{6eq}), 2.11 (ddd, $J = 13.4, 6.9, 3.8$ Hz, 1H, H_{1eq}), 2.05 (s, 3H, H_{19}), 1.88 – 1.74 (m, 1H, H_{5eq}), 1.72 – 1.60 (m, 1H, H_{6ax}), 1.57 – 1.47 (m, 4H, $\text{H}_{1ax,4a,5ax,13a}$), 1.19 (s, 3H, H_{18}), 1.12 (s, 3H, H_{17}), 1.03 (s, 3H, H_{16}), 0.73 (s, 3H, H_{14}).

^{13}C NMR (100 MHz, CDCl_3) δ 216.6 (C_3), 169.4 (C_{11}), 158.6 (C_{7a}), 155.4 (C_{12}), 145.5 (C_{8a}), 115.3 (C_{12a}), 114.4 (C_8), 107.3 (C_{11a}), 76.2 (C_{6a}), 68.2 (C_9), 62.0 (C_{22}), 54.2 (C_{4a}), 47.3 (C_4), 47.1 (C_{13a}), 39.7 (C_6), 38.4 (C_1), 37.6 (C_{13b}), 34.1 (C_2), 27.1 (C_{18}), 26.7 (C_{17}), 21.7 (C_{16}), 19.1 (C_5), 18.3 (C_{13}), 14.2 (C_{14}), 10.7 (C_{19}).

IR ν_{max} (neat) 1754, 1702, 1610, 1477, 1367, 1141, 904 cm^{-1} .

HRMS (ES) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{33}\text{O}_5$ 413.2328; Found 413.2327.

(5a*R*,7a*S*,14a*R*,14b*S*)-13-Methoxy-5,5,7a,9,14b-pentamethyl-1,2,5a,6,7,7a,10,14,14a,14b-decahydro-5*H*-furo[3,4-*i*]oxepino[4,3-*α*]xanthene-3,12-dione



NaHCO₃ (9 mg, 0.107 mmol) and *m*-CPBA (18.4 mg, 0.107 mmol) were added with stirring to (±)-austalide K (**8**) (22 mg, 0.0533 mmol) in CH₂Cl₂ (1 mL) at 25 °C. After 19 h, saturated aqueous NaHCO₃ (1 mL) was added and phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 1 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (Et₂O) to provide (±)-13-deacetoxyaustalide I (**9**) (22 mg, 0.0513 mmol, 96 %) as a white solid.

R_f 0.37 Et₂O). **Melting Point** 93 – 95 °C.

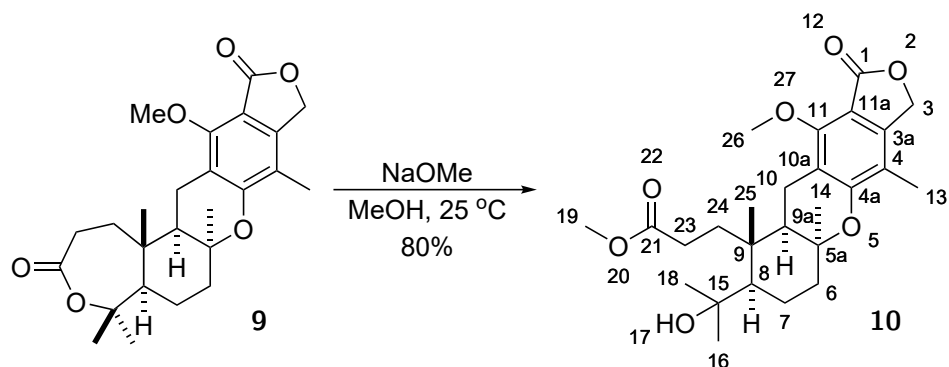
¹H NMR (400 MHz, CDCl₃) δ 5.14 (s, 2H, H₁₀), 4.13 (s, 3H, H₂₂), 2.96 (d, *J* = 18.6 Hz, 1H, H_{14eq}), 2.84 (dd, *J* = 18.7, 8.1 Hz, 1H, H_{14ax}), 2.69 (ddd, *J* = 15.6, 11.2, 3.1 Hz, 1H, H_{2eq}), 2.60 (ddd, *J* = 15.6, 8.3, 2.7 Hz, 1H, H_{2ax}), 2.25 (dt, *J* = 14.2, 3.1 Hz, 1H, H_{7eq}), 2.06 (s, 3H, H₁₉), 2.02 – 1.84 (m, 3H, H_{1eq,5a,6eq}), 1.75 – 1.62 (m, 2H, H_{1ax,7ax}), 1.56 (d, *J* = 7.8 Hz, 1H, H_{14a}), 1.54 – 1.53 (m, 1H, H_{6ax}), 1.52 (s, 3H, H₁₇), 1.42 (s, 3H, H₁₆), 1.21 (s, 3H, H₁₈), 0.83 (s, 3H, H₂₃).

¹³C NMR (100 MHz, CDCl₃) δ 175.1 (C₃), 169.3 (C₁₂), 158.3 (C_{8a}), 155.3 (C₁₃), 145.6 (C_{9a}), 115.1 (C_{13a}), 114.3 (C₉), 107.4 (C_{12a}), 85.8 (C₅), 76.0 (C_{7a}), 68.2 (C₁₀), 62.0 (C₂₂), 53.6 (C_{5a}), 47.3 (C_{14a}), 40.4 (C_{14b}), 39.3 (C₇), 37.3 (C₁), 32.5 (C₁₇), 31.8 (C₂), 27.1 (C₁₈), 25.8 (C₁₆), 22.1 (C₆), 18.7 (C₁₄), 16.7 (C₂₃), 10.6 (C₁₉).

IR ν_{max} (neat) 1749, 1609, 1477, 1372, 1282, 1142, 1112, 905, 731 cm^{-1} .

HRMS (ES) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{33}\text{O}_6$ 429.2277; Found 429.2291.

Methyl 3-((5a*S*,8*R*,9*S*,9a*R*)-8-(2-hydroxypropan-2-yl)-11-methoxy-4,5a,9-trimethyl-1-oxo-3,5a,6,7,8,9,9a,10-octahydro-1*H*-furo[3,4-*b*]xanthen-9-yl)propanoate



NaOMe (0.5 M; 0.50 mL, 0.250 mmol) was added with stirring to (±)-13-deacetoxyaustalide I (**9**) (10.8 mg, 0.0252 mmol) in MeOH (0.50 mL) at 25 °C. After 1 h, saturated aqueous NH₄Cl (1 mL) and Et₂O (2 mL) were added and the phases were separated, and the aqueous layer was extracted with Et₂O (3 × 1 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (pentane : Et₂O 1 : 1) to provide (±)-austalide P (**10**) (9.3 mg, 0.0202 mmol, 80 %) as a white foam.

R_f 0.21 (Pentane : Et₂O 1 : 1).

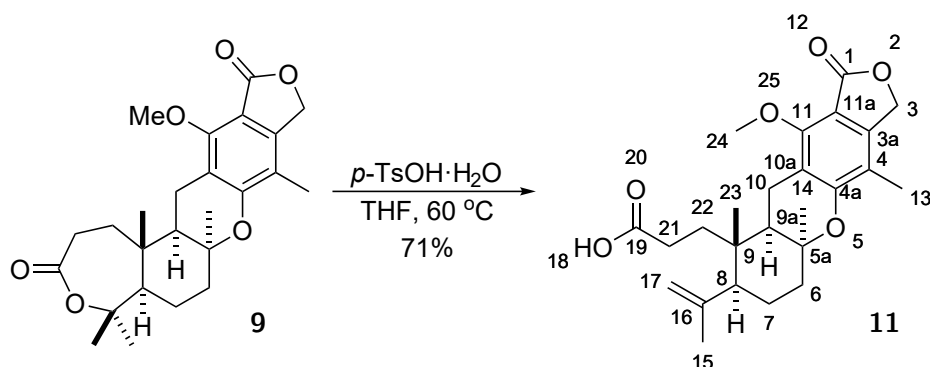
¹H NMR (400 MHz, CD₃OD) δ 5.20 (s, 2H, H₃), 4.04 (s, 3H, H₂₆), 3.67 (s, 3H, H₁₉), 3.01 (d, *J* = 18.6 Hz, 1H, H_{10eq}), 2.76 (dd, *J* = 18.6, 7.9 Hz, 1H, H_{10ax}), 2.65 – 2.55 (m, 1H, H₂₃), 2.42 (tdd, *J* = 11.5, 4.8, 2.5 Hz, 1H, H₂₄), 2.37 – 2.27 (m, 1H, H₂₃), 2.15 – 2.10 (m, 1H, H_{6eq}), 2.05 (s, 3H, H₁₃), 1.88 – 1.75 (m, 2H, H_{7eq,24}), 1.68 (d, *J* = 8.0 Hz, 1H, H_{9a}), 1.66 – 1.57 (m, 1H, H_{6ax}), 1.57 – 1.48 (m, 2H, H_{7ax,8}), 1.27 (s, 3H, H₁₈), 1.20 (s, 3H, H₁₄), 1.19 (s, 3H, H₁₆), 0.70 (s, 3H, H₂₅).

¹³C NMR (100 MHz, CD₃OD) δ 176.9 (C₂₁), 171.8 (C₁), 160.4 (C_{4a}), 156.6 (C₁₁), 147.5 (C_{3a}), 117.3 (C_{10a}), 115.8 (C₄), 108.2 (C_{11a}), 78.3 (C_{5a}), 75.7 (C₁₅), 69.8 (C₃), 62.2 (C₂₆), 52.1 (C₁₉), 52.0 (C₈), 42.8 (C_{9a}), 41.4 (C₉), 40.5 (C₆), 34.9 (C₂₄), 33.2 (C₁₈), 30.1 (C₂₃), 28.1 (C₁₆), 27.7 (C₁₄), 22.6 (C₇), 19.5 (C₂₅), 18.8 (C₁₀), 10.6 (C₁₃).

IR ν_{max} (neat) 3514, 2971, 1740, 1610, 1436, 1368, 1141, 1045, 898, 732 cm^{-1} .

HRMS (ES) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{37}\text{O}_7$ 461.2539; Found 461.2531.

3-((5a*S*,8*S*,9*S*,9a*R*)-11-Methoxy-4,5a,9-trimethyl-1-oxo-8-(prop-1-en-2-yl)-3,5a,6,7,8,9,9a,10-octahydro-1*H*-furo[3,4-*b*]xanthen-9-yl)propanoic acid



(±)-13-Deacetoxyaustalide I (**9**) (14 mg, 0.0327 mmol) was dissolved in THF (1 mL) and *p*-TsOH·H₂O (56 mg, 0.327 mmol) was added. The resulting mixture was heated to 70 °C for 1 h. After cooling back to 25 °C, H₂O (1 mL) and Et₂O (1 mL) were added and the two phases were separated, and the aqueous layer was extracted with Et₂O (3 × 1 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated and chromatographed (Et₂O) to provide (±)-13-deoxyaustalide Q acid (**11**) (10 mg, 0.0233 mmol, 71 %) as a white foam.

R_f 0.42 (Et₂O).

¹H NMR (400 MHz, CDCl₃) δ 5.12 (s, 2H, H₃), 4.90 (s, 1H, H₁₇), 4.69 (s, 1H, H₁₇), 4.11 (s, 3H, H₂₄), 2.89 (d, *J* = 18.5 Hz, 1H, H_{10eq}), 2.77 (dd, *J* = 18.4, 7.8 Hz, 1H, H_{10ax}), 2.52 – 2.26 (m, 2H, H₂₁), 2.23 – 2.06 (m, 3H, H_{6eq,7eq,8}), 2.04 (s, 3H, H₁₃), 1.74 (s, 3H, H₁₅), 1.74 – 1.70 (m, 2H, H₂₂), 1.68 – 1.61 (m, 1H, H_{6ax}), 1.57 (d, *J* = 7.8 Hz, 1H, H_{9a}), 1.49 – 1.44 (m, 1H, H_{7ax}), 1.20 (s, 3H, H₁₄), 0.60 (s, 3H, H₂₃).

¹³C NMR (100 MHz, CDCl₃) δ 179.1 (C₁₉), 169.5 (C₁), 158.6 (C_{4a}), 155.5 (C₁₁), 146.7 (C₁₆), 145.5 (C_{3a}), 115.2 (C_{10a}), 114.4 (C₄), 114.2 (C₁₇), 107.3 (C_{11a}), 76.5 (C_{5a}), 68.3 (C₃), 62.0 (C₂₄), 50.1 (C₈), 40.0 (C₉), 39.6 (C_{9a}), 39.0 (C₆), 32.9 (C₂₂), 28.5 (C₂₁), 27.4 (C₁₄), 23.8 (C₇), 23.6 (C₁₅), 18.1 (2C,

C_{10,23}), 10.7 (C₁₃).

IR ν_{max} (neat) 3261, 2933, 1749, 1705, 1610, 1369, 1148, 1131, 910, 732 cm⁻¹.

HRMS (ES) m/z: [M + H]⁺ Calcd for C₂₅H₃₃O₆ 429.2277; Found 429.2285.

APPENDIX: X-RAY CRYSTAL DATA

2-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid

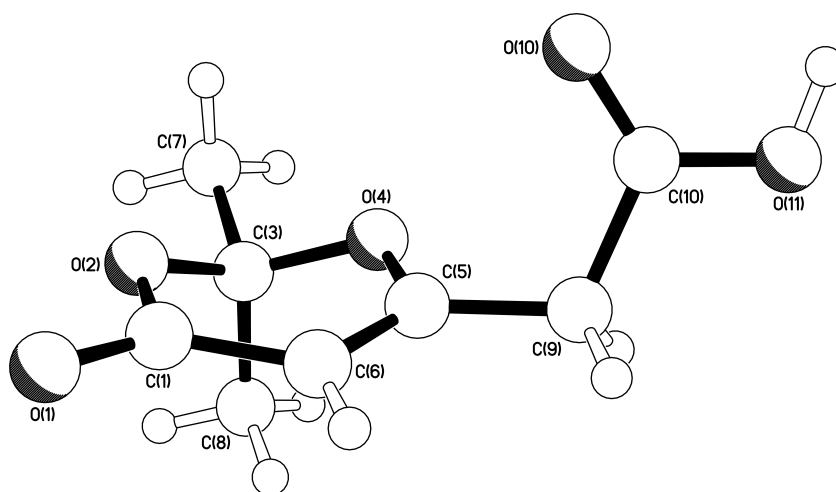


Figure A.1: X-Ray crystal structure of dioxinone acid **64**.

Table A.1: Crystal data and structure refinement for dioxinone acid **64**.

Identification code	AB1614
Formula	C ₈ H ₁₀ O ₅
Formula weight	186.16
Temperature	173(2) K
Diffractionmeter, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, P2 ₁ /c
Unit cell dimensions	a = 10.8907(6) Å α = 90° b = 9.4293(4) Å β = 111.626(7)° c = 9.2878(5) Å γ = 90°
Volume, Z	886.64(9) Å ³ , 4
Density (calculated)	1.395 Mg/m ³
Absorption coefficient	0.118 mm ⁻¹
F(000)	392
Crystal colour / morphology	Colourless blocks
Crystal size	0.48 × 0.37 × 0.29 mm ³
q range for data collection	3.199 to 28.028°
Index ranges	-9 ≤ h ≤ 13, -9 ≤ k ≤ 11, -11 ≤ l ≤ 11
Reflns collected / unique	3013 / 1750 [R(int) = 0.0129]
Reflns observed [F > 4s(F)]	1424
Absorption correction	Analytical
Max. and min. transmission	0.972 and 0.960
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	1750 / 1 / 125
Goodness-of-fit on F²	1.059
Final R indices [F > 4s(F)]	R1 = 0.0345, wR2 = 0.0748
R indices (all data)	R1 = 0.0471, wR2 = 0.0815
Largest diff. peak, hole	0.159, -0.181 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Table A.2: Bond lengths [Å] and angles [°] for dioxinone acid **64**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1)-C(1)	1.2101(16)	O(1)-C(1)-O(2)	118.14(14)
C(1)-O(2)	1.3695(18)	O(1)-C(1)-C(6)	125.94(14)
C(1)-C(6)	1.442(2)	O(2)-C(1)-C(6)	115.74(11)
O(2)-C(3)	1.4428(16)	C(1)-O(2)-C(3)	117.68(11)
C(3)-O(4)	1.4447(16)	O(2)-C(3)-O(4)	109.74(11)
C(3)-C(7)	1.501(2)	O(2)-C(3)-C(7)	106.46(11)
C(3)-C(8)	1.507(2)	O(4)-C(3)-C(7)	106.90(11)
O(4)-C(5)	1.3525(16)	O(2)-C(3)-C(8)	110.40(11)
C(5)-C(6)	1.3351(18)	O(4)-C(3)-C(8)	109.69(11)
C(5)-C(9)	1.4908(19)	C(7)-C(3)-C(8)	113.51(13)
C(9)-C(10)	1.4987(18)	C(5)-O(4)-C(3)	115.04(10)
C(10)-O(10)	1.2165(16)	C(6)-C(5)-O(4)	122.10(13)
C(10)-O(11)	1.3079(16)	C(6)-C(5)-C(9)	124.93(13)
		O(4)-C(5)-C(9)	112.95(11)
		C(5)-C(6)-C(1)	120.04(13)
		C(5)-C(9)-C(10)	112.88(11)
		O(10)-C(10)-O(11)	123.71(12)
		O(10)-C(10)-C(9)	123.55(12)
		O(11)-C(10)-C(9)	112.73(11)

(*E*)-8-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one

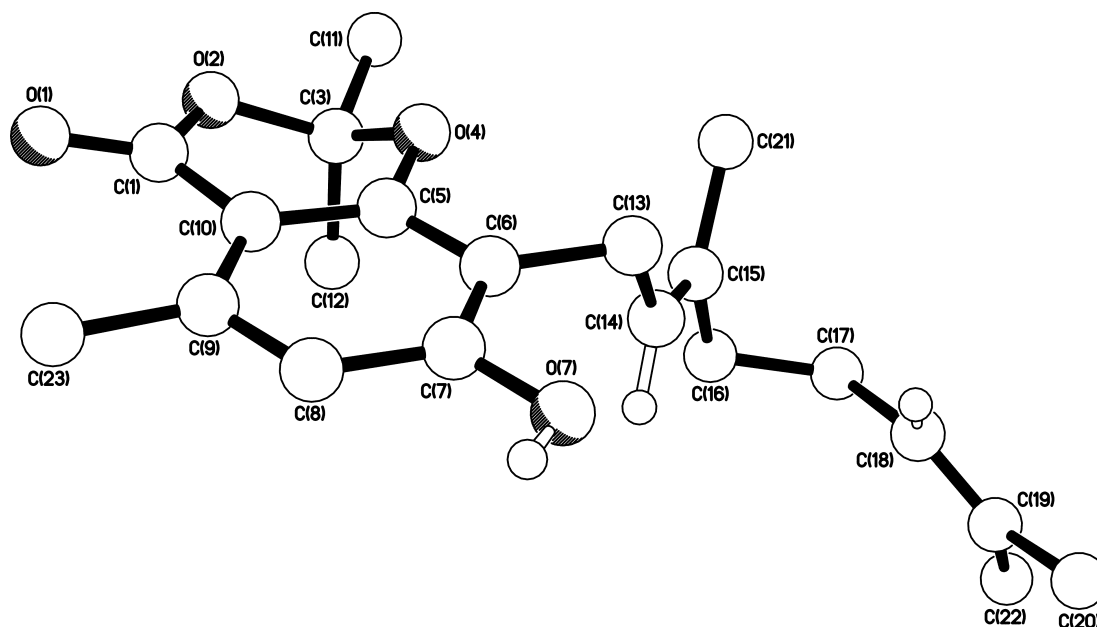


Figure A.2: X-Ray crystal structure of resorcyate **93a**.

Table A.3: Crystal data and structure refinement for resorcyate **93a**.

Identification code	AB1501
Formula	C ₂₁ H ₂₈ O ₄
Formula weight	344.43
Temperature	173 K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, P 2 ₁ /c
Unit cell dimensions	a = 15.5552(10) Å α = 90° b = 15.6415(10) Å β = 94.596(7)° c = 8.1031(7) Å γ = 90°
Volume, Z	1965.2(2) Å ³ , 4
Density (calculated)	1.164 Mg/m ³
Absorption coefficient	0.079 mm ⁻¹
F(000)	744
Crystal colour / morphology	Colourless thin plates
Crystal size	0.64 × 0.26 × 0.02 mm ³
q range for data collection	2.604 to 28.318°
Index ranges	-17 ≤ h ≤ 19, -20 ≤ k ≤ 19, -9 ≤ l ≤ 5
Refns collected / unique	7041 / 3936 [R(int) = 0.0510]
Refns observed [F > 4s(F)]	2179
Absorption correction	Analytical
Max. and min. transmission	0.998 and 0.974
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3936 / 1 / 236
Goodness-of-fit on F²	1.002
Final R indices [F > 4s(F)]	R1 = 0.0751, wR2 = 0.1638
R indices (all data)	R1 = 0.1377, wR2 = 0.2066
Largest diff. peak, hole	0.272, -0.300 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Table A.4: Bond lengths [Å] and angles [°] for resorcyate **93a**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1)-C(1)	1.210(3)	O(1)-C(1)-O(2)	117.3(3)
C(1)-O(2)	1.353(3)	O(1)-C(1)-C(10)	125.6(3)
C(1)-C(10)	1.464(4)	O(2)-C(1)-C(10)	117.0(2)
O(2)-C(3)	1.455(3)	C(1)-O(2)-C(3)	118.7(2)
C(3)-O(4)	1.415(3)	O(4)-C(3)-O(2)	109.3(2)
C(3)-C(11)	1.504(4)	O(4)-C(3)-C(11)	106.8(3)
C(3)-C(12)	1.520(5)	O(2)-C(3)-C(11)	105.8(2)
O(4)-C(5)	1.372(3)	O(4)-C(3)-C(12)	110.9(2)
C(5)-C(6)	1.383(4)	O(2)-C(3)-C(12)	109.7(3)
C(5)-C(10)	1.396(4)	C(11)-C(3)-C(12)	114.1(3)
C(6)-C(7)	1.385(4)	C(5)-O(4)-C(3)	114.2(2)
C(6)-C(13)	1.521(4)	O(4)-C(5)-C(6)	116.8(2)
O(7)-C(7)	1.363(3)	O(4)-C(5)-C(10)	119.3(2)
C(7)-C(8)	1.395(4)	C(6)-C(5)-C(10)	123.9(3)
C(8)-C(9)	1.386(4)	C(5)-C(6)-C(7)	116.1(3)
C(9)-C(10)	1.408(4)	C(5)-C(6)-C(13)	120.5(2)
C(9)-C(23)	1.510(4)	C(7)-C(6)-C(13)	123.4(2)
C(13)-C(14)	1.498(4)	O(7)-C(7)-C(6)	116.7(2)
C(14)-C(15)	1.327(4)	O(7)-C(7)-C(8)	121.4(2)
C(15)-C(16)	1.499(4)	C(6)-C(7)-C(8)	121.9(2)
C(15)-C(21)	1.508(5)	C(9)-C(8)-C(7)	121.2(3)
C(16)-C(17)	1.533(4)	C(8)-C(9)-C(10)	118.1(2)
C(17)-C(18)	1.500(5)	C(8)-C(9)-C(23)	118.6(3)
C(18)-C(19)	1.338(5)	C(10)-C(9)-C(23)	123.3(2)
C(19)-C(22)	1.491(5)	C(5)-C(10)-C(9)	118.7(2)
C(19)-C(20)	1.512(5)	C(5)-C(10)-C(1)	118.2(3)
		C(9)-C(10)-C(1)	123.1(2)
		C(14)-C(13)-C(6)	112.5(2)
		C(15)-C(14)-C(13)	128.2(3)
		C(14)-C(15)-C(16)	120.2(3)
		C(14)-C(15)-C(21)	123.9(3)
		C(16)-C(15)-C(21)	115.8(3)
		C(15)-C(16)-C(17)	114.6(3)
		C(18)-C(17)-C(16)	112.8(3)
		C(19)-C(18)-C(17)	128.3(3)
		C(18)-C(19)-C(22)	124.4(4)
		C(18)-C(19)-C(20)	120.3(4)
		C(22)-C(19)-C(20)	115.3(3)

8-((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2-dimethyl-5-((*E*)-styryl)-4*H*-benzo[*d*][1,3]dioxin-4-one

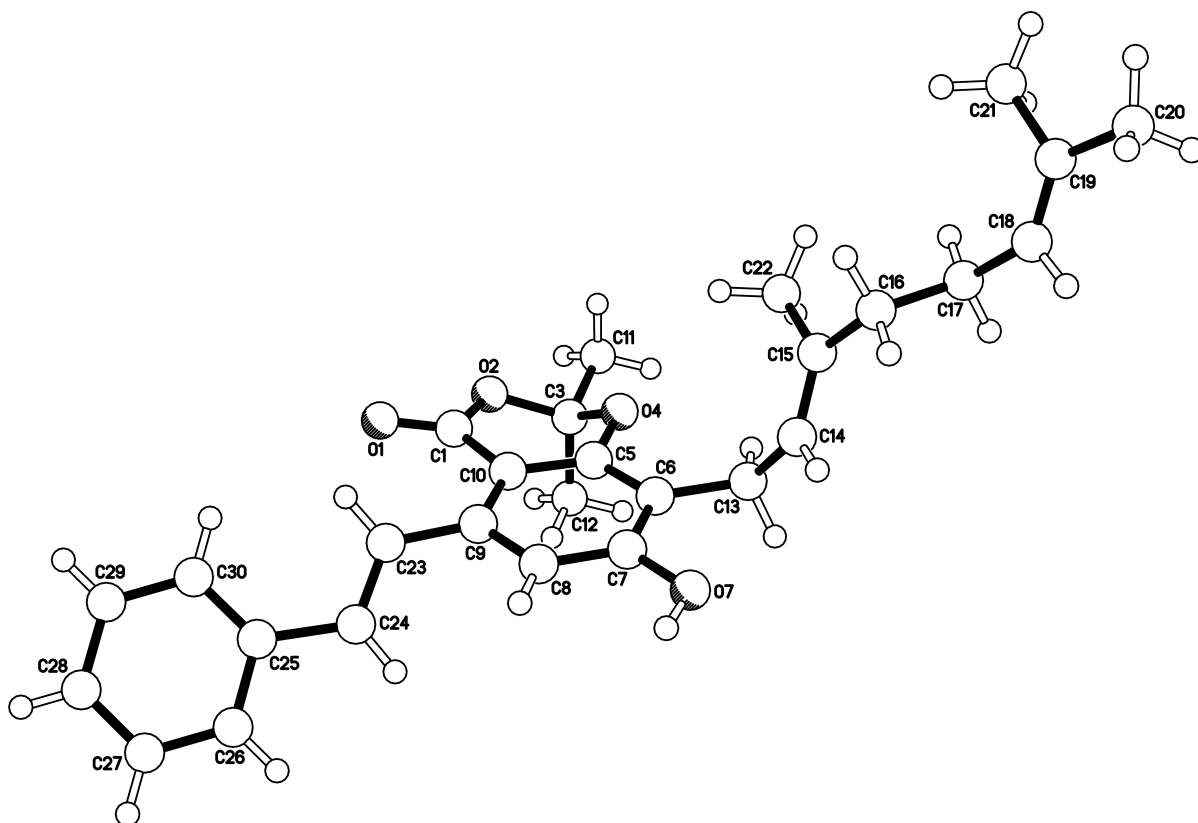


Figure A.3: X-Ray crystal structure of resorcyate **137**.

Table A.5: Crystal data and structure refinement for resorcyate **137**.

Identification code	AB1708
Formula	C ₂₈ H ₃₂ O ₄
Formula weight	432.53
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, P2 ₁ /c
Unit cell dimensions	a = 18.4114(13) Å α = 90° b = 14.9432(9) Å β = 92.830(6)° c = 8.8933(5) Å γ = 90°
Volume, Z	2443.8(3) Å ³ , 4
Density (calculated)	1.176 Mg/m ³
Absorption coefficient	0.077 mm ⁻¹
F(000)	928
Crystal colour / morphology	Colourless plates
Crystal size	0.62 × 0.53 × 0.08 mm ³
q range for data collection	2.601 to 28.185°
Index ranges	-20 ≤ h ≤ 24, -13 ≤ k ≤ 19, -11 ≤ l ≤ 7
Refns collected / unique	8314 / 4876 [R(int) = 0.0151]
Refns observed [F > 4σ(F)]	3324
Absorption correction	Analytical
Max. and min. transmission	0.994 and 0.964
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4876 / 217 / 375
Goodness-of-fit on F²	1.027
Final R indices [F > 4σ(F)]	R1 = 0.0645, wR2 = 0.1534
R indices (all data)	R1 = 0.1019, wR2 = 0.1789
Largest diff. peak, hole	0.284, -0.218 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table A.6: Bond lengths [Å] and angles [°] for resorcyate **137**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
C(1)-O(1)	1.212(3)	O(1)-C(1)-O(2)	116.7(2)
C(1)-O(2)	1.350(3)	O(1)-C(1)-C(10)	125.9(2)
C(1)-C(10)	1.464(3)	O(2)-C(1)-C(10)	117.4(2)
O(2)-C(3)	1.442(3)	C(1)-O(2)-C(3)	118.54(18)
C(3)-O(4)	1.425(3)	O(4)-C(3)-O(2)	107.8(2)
C(3)-C(12)	1.505(4)	O(4)-C(3)-C(12)	111.9(2)
C(3)-C(11)	1.506(4)	O(2)-C(3)-C(12)	110.3(2)
O(4)-C(5)	1.378(3)	O(4)-C(3)-C(11)	107.0(2)
C(5)-C(6)	1.383(3)	O(2)-C(3)-C(11)	106.3(2)
C(5)-C(10)	1.396(3)	C(12)-C(3)-C(11)	113.2(2)
C(6)-C(7)	1.393(3)	C(5)-O(4)-C(3)	113.70(18)
C(6)-C(13)	1.512(3)	O(4)-C(5)-C(6)	117.27(19)
C(7)-O(7)	1.353(2)	O(4)-C(5)-C(10)	119.12(19)
C(7)-C(8)	1.390(3)	C(6)-C(5)-C(10)	123.6(2)
C(8)-C(9)	1.389(3)	C(5)-C(6)-C(7)	116.22(19)
C(9)-C(10)	1.411(3)	C(5)-C(6)-C(13)	121.9(2)
C(9)-C(23)	1.472(3)	C(7)-C(6)-C(13)	121.88(19)
C(13)-C(14)	1.460(8)	O(7)-C(7)-C(8)	121.40(19)
C(13)-C(14'')	1.576(17)	O(7)-C(7)-C(6)	116.49(19)
C(13)-C(14')	1.595(9)	C(8)-C(7)-C(6)	122.10(19)
C(14)-C(15)	1.340(9)	C(9)-C(8)-C(7)	120.9(2)
C(15)-C(22)	1.479(10)	C(8)-C(9)-C(10)	118.3(2)
C(15)-C(16)	1.519(9)	C(8)-C(9)-C(23)	119.2(2)
C(16)-C(17)	1.549(8)	C(10)-C(9)-C(23)	122.46(19)
C(17)-C(18)	1.490(9)	C(5)-C(10)-C(9)	118.85(19)
C(18)-C(19)	1.285(10)	C(5)-C(10)-C(1)	117.4(2)
C(19)-C(20)	1.432(11)	C(9)-C(10)-C(1)	123.7(2)
C(19)-C(21)	1.548(13)	C(14)-C(13)-C(6)	114.9(3)
C(14')-C(15')	1.340(12)	C(6)-C(13)-C(14'')	109.3(7)
C(15')-C(22')	1.489(16)	C(6)-C(13)-C(14')	109.0(3)
C(15')-C(16')	1.533(13)	C(15)-C(14)-C(13)	124.6(7)
C(16')-C(17')	1.584(12)	C(14)-C(15)-C(22)	124.8(7)
C(17')-C(18')	1.467(13)	C(14)-C(15)-C(16)	119.9(8)
C(18')-C(19')	1.288(14)	C(22)-C(15)-C(16)	115.0(6)
C(19')-C(20')	1.421(15)	C(15)-C(16)-C(17)	110.3(6)
C(19')-C(21')	1.577(19)	C(18)-C(17)-C(16)	112.8(7)
C(14'')-C(15'')	1.343(14)	C(19)-C(18)-C(17)	132.5(9)
C(15'')-C(22'')	1.485(15)	C(18)-C(19)-C(20)	127.1(10)
C(15'')-C(16'')	1.514(13)	C(18)-C(19)-C(21)	118.5(9)
C(16'')-C(17'')	1.567(12)	C(20)-C(19)-C(21)	114.2(8)
C(17'')-C(18'')	1.488(12)	C(15')-C(14')-C(13)	123.1(9)
C(18'')-C(19'')	1.325(13)	C(14')-C(15')-C(22')	123.6(11)
C(19'')-C(20'')	1.414(14)	C(14')-C(15')-C(16')	117.2(12)

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C(19'')-C(21'')	1.573(16)	C(22')-C(15')-C(16')	118.0(11)
C(23)-C(24')	1.283(11)	C(15')-C(16')-C(17')	102.0(10)
C(23)-C(24)	1.351(6)	C(18')-C(17')-C(16')	112.6(10)
C(24)-C(25)	1.525(6)	C(19')-C(18')-C(17')	131.7(14)
C(25)-C(26)	1.39	C(18')-C(19')-C(20')	128.0(17)
C(25)-C(30)	1.39	C(18')-C(19')-C(21')	119.2(15)
C(26)-C(27)	1.39	C(20')-C(19')-C(21')	112.3(13)
C(27)-C(28)	1.39	C(15'')-C(14'')-C(13)	122.3(13)
C(28)-C(29)	1.39	C(14'')-C(15'')-C(22'')	123.4(12)
C(29)-C(30)	1.39	C(14'')-C(15'')-C(16'')	118.2(15)
C(24')-C(25')	1.472(11)	C(22'')-C(15'')-C(16'')	118.2(12)
C(25')-C(26')	1.39	C(15'')-C(16'')-C(17'')	115.1(11)
C(25')-C(30')	1.39	C(18'')-C(17'')-C(16'')	115.9(10)
C(26')-C(27')	1.39	C(19'')-C(18'')-C(17'')	136.4(11)
C(27')-C(28')	1.39	C(18'')-C(19'')-C(20'')	127.7(13)
C(28')-C(29')	1.39	C(18'')-C(19'')-C(21'')	116.3(12)
C(29')-C(30')	1.39	C(20'')-C(19'')-C(21'')	116.0(12)
		C(24')-C(23)-C(9)	127.2(8)
		C(24)-C(23)-C(9)	122.0(4)
		C(23)-C(24)-C(25)	118.3(6)
		C(26)-C(25)-C(30)	120
		C(26)-C(25)-C(24)	113.1(3)
		C(30)-C(25)-C(24)	126.6(3)
		C(25)-C(26)-C(27)	120
		C(26)-C(27)-C(28)	120
		C(29)-C(28)-C(27)	120
		C(30)-C(29)-C(28)	120
		C(29)-C(30)-C(25)	120
		C(23)-C(24')-C(25')	148.4(15)
		C(26')-C(25')-C(30')	120
		C(26')-C(25')-C(24')	135.2(9)
		C(30')-C(25')-C(24')	104.5(9)
		C(25')-C(26')-C(27')	120
		C(28')-C(27')-C(26')	120
		C(27')-C(28')-C(29')	120
		C(30')-C(29')-C(28')	120
		C(29')-C(30')-C(25')	120

**(4a*S*,6a*R*,12a*R*,12b*S*)-11-Hydroxy-4,4,6a,9,12b-pentamethyl-
1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-
carboxylic
acid**

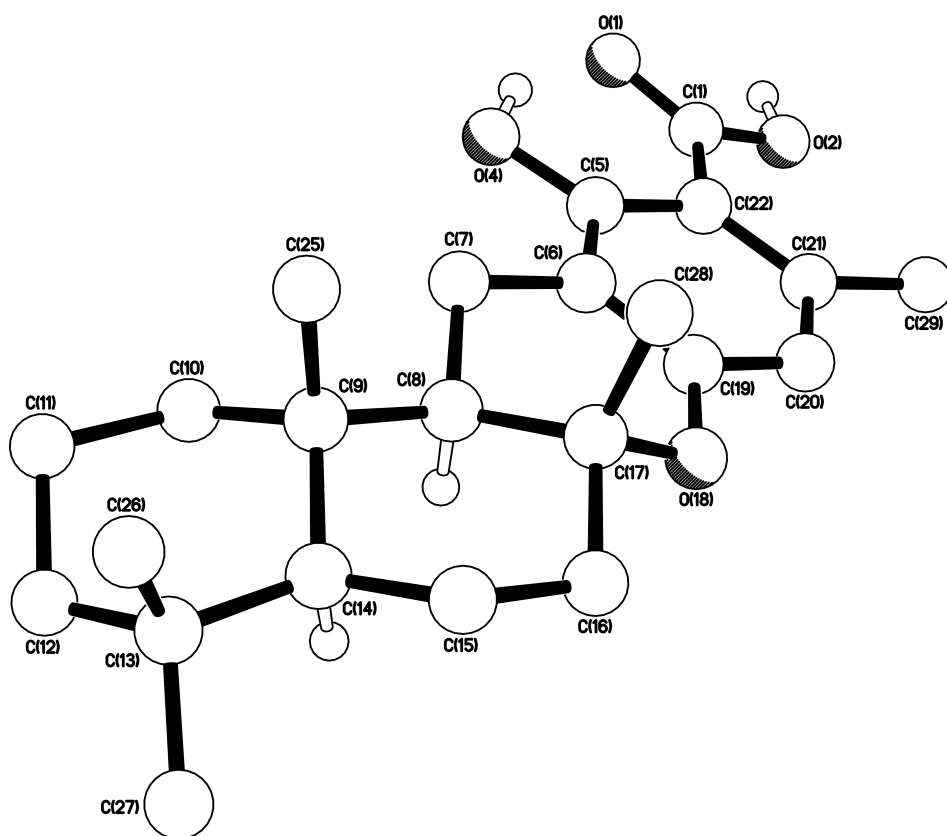


Figure A.4: X-Ray crystal structure of (+)-hongoquercin A (**5**).

Table A.7: Crystal data and structure refinement for (+)-hongoquercin A (**5**).

Identification code	AB1618
Formula	C ₂₃ H ₃₂ O ₄ , H ₂ O
Formula weight	390.5
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.54184 Å
Crystal system, space group	Orthorhombic, P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	a = 10.0281(3) Å α = 90° b = 13.8303(3) Å β = 90° c = 14.9525(3) Å γ = 90°
Volume, Z	2073.79(8) Å ³ , 4
Density (calculated)	1.251 Mg/m ³
Absorption coefficient	0.696 mm ⁻¹
F(000)	848
Crystal colour / morphology	Colourless blocks
Crystal size	0.30 × 0.14 × 0.08 mm ³
q range for data collection	4.355 to 73.827°
Index ranges	-11 ≤ h ≤ 11, -17 ≤ k ≤ 7, -18 ≤ l ≤ 18
Reflns collected / unique	6134 / 3933 [R(int) = 0.0383]
Reflns observed [F > 4s(F)]	3315
Absorption correction	Analytical
Max. and min. transmission	0.954 and 0.907
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3933 / 4 / 274
Goodness-of-fit on F²	1.018
Final R indices [F > 4s(F)]	R1 = 0.0460, wR2 = 0.1059
R indices (all data)	R1 = 0.0586, wR2 = 0.1164
Absolute structure parameter	0.06(17)
Largest diff. peak, hole	0.346, -0.178 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table A.8: Bond lengths [Å] and angles [°] for (+)-hongoquercin A (**5**).

Bond	Bond lengths [Å]	Bond	Bond angles [°]
C(1)-O(1)	1.228(4)	O(1)-C(1)-O(2)	120.6(3)
C(1)-O(2)	1.316(4)	O(1)-C(1)-C(22)	122.9(3)
C(1)-C(22)	1.471(4)	O(2)-C(1)-C(22)	116.5(3)
O(4)-C(5)	1.355(4)	O(4)-C(5)-C(6)	115.5(2)
C(5)-C(6)	1.398(4)	O(4)-C(5)-C(22)	122.2(3)
C(5)-C(22)	1.419(4)	C(6)-C(5)-C(22)	122.3(3)
C(6)-C(19)	1.383(4)	C(19)-C(6)-C(5)	117.3(2)
C(6)-C(7)	1.512(3)	C(19)-C(6)-C(7)	121.8(2)
C(7)-C(8)	1.524(4)	C(5)-C(6)-C(7)	120.9(3)
C(8)-C(17)	1.538(4)	C(6)-C(7)-C(8)	110.5(2)
C(8)-C(9)	1.568(4)	C(7)-C(8)-C(17)	110.0(2)
C(9)-C(10)	1.533(5)	C(7)-C(8)-C(9)	114.7(2)
C(9)-C(25)	1.545(5)	C(17)-C(8)-C(9)	114.9(2)
C(9)-C(14)	1.562(4)	C(10)-C(9)-C(25)	108.3(3)
C(10)-C(11)	1.544(4)	C(10)-C(9)-C(14)	109.1(3)
C(11)-C(12)	1.549(6)	C(25)-C(9)-C(14)	113.7(3)
C(12)-C(13)	1.533(6)	C(10)-C(9)-C(8)	107.6(3)
C(13)-C(27)	1.522(5)	C(25)-C(9)-C(8)	111.7(3)
C(13)-C(26)	1.523(6)	C(14)-C(9)-C(8)	106.2(2)
C(13)-C(14)	1.567(4)	C(9)-C(10)-C(11)	111.9(3)
C(14)-C(15)	1.524(5)	C(10)-C(11)-C(12)	110.3(3)
C(15)-C(16)	1.538(4)	C(13)-C(12)-C(11)	114.5(3)
C(16)-C(17)	1.520(4)	C(27)-C(13)-C(26)	107.6(4)
C(17)-O(18)	1.470(3)	C(27)-C(13)-C(12)	108.4(4)
C(17)-C(28)	1.533(5)	C(26)-C(13)-C(12)	110.5(3)
O(18)-C(19)	1.365(3)	C(27)-C(13)-C(14)	108.4(3)
C(19)-C(20)	1.407(4)	C(26)-C(13)-C(14)	114.3(3)
C(20)-C(21)	1.379(4)	C(12)-C(13)-C(14)	107.5(3)
C(21)-C(22)	1.419(4)	C(15)-C(14)-C(9)	110.5(3)
C(21)-C(29)	1.510(4)	C(15)-C(14)-C(13)	114.1(3)
		C(9)-C(14)-C(13)	116.1(3)
		C(14)-C(15)-C(16)	110.5(3)
		C(17)-C(16)-C(15)	111.9(3)
		O(18)-C(17)-C(16)	103.6(2)
		O(18)-C(17)-C(28)	105.7(2)
		C(16)-C(17)-C(28)	111.7(3)
		O(18)-C(17)-C(8)	108.2(2)
		C(16)-C(17)-C(8)	109.9(3)
		C(28)-C(17)-C(8)	116.8(3)
		C(19)-O(18)-C(17)	116.7(2)
		O(18)-C(19)-C(6)	122.4(2)
		O(18)-C(19)-C(20)	115.7(3)
		C(6)-C(19)-C(20)	121.9(2)

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C(21)-C(20)-C(19)	120.9(3)
C(20)-C(21)-C(22)	118.9(2)
C(20)-C(21)-C(29)	117.0(3)
C(22)-C(21)-C(29)	124.0(3)
C(5)-C(22)-C(21)	118.6(3)
C(5)-C(22)-C(1)	116.8(3)
C(21)-C(22)-C(1)	124.5(2)

(7a*R*,9a*R*,11*S*,13a*S*,13b*R*)-11-Hydroxy-2,2,5,7a,10,10,13a-heptamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one

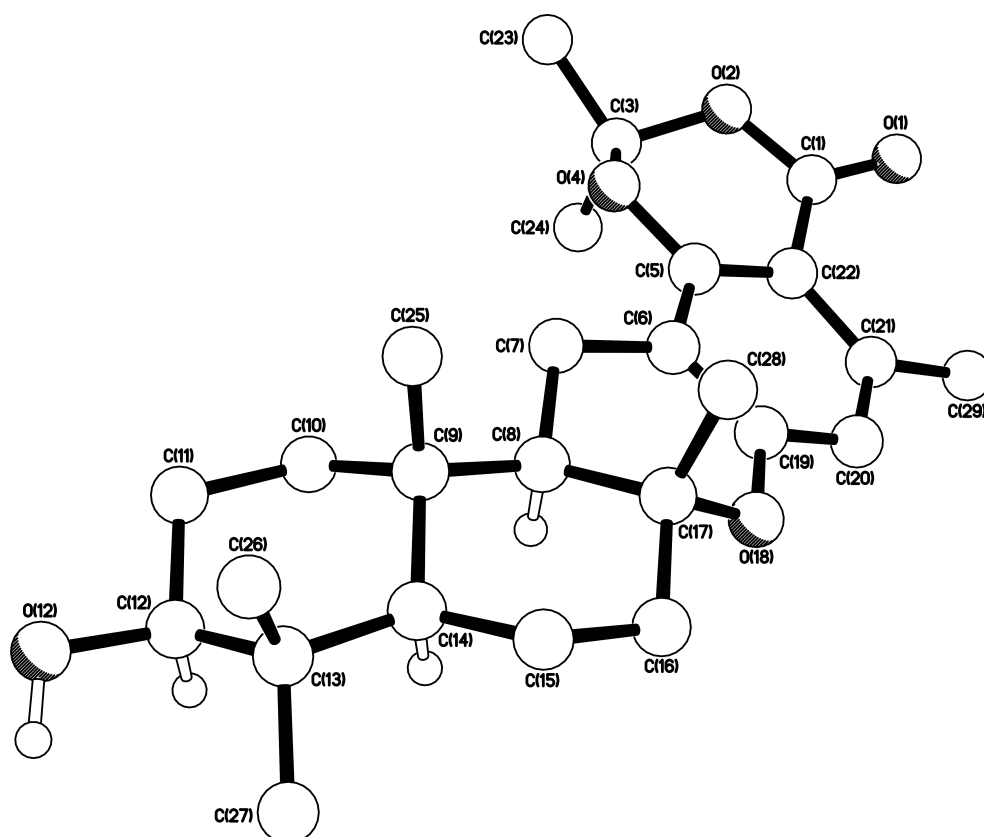


Figure A.5: X-Ray crystal structure of meroterpenoid **159**.

Table A.9: Crystal data and structure refinement for meroterpenoid **159**.

Identification code	AB1619
Formula	C ₂₆ H ₃₆ O ₅
Formula weight	428.55
Temperature	173(2) K
Diffractionmeter, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 32.892(3) Å α = 90° b = 10.8432(6) Å β = 100.510(8)° c = 12.7644(7) Å γ = 90°
Volume, Z	4476.1(5) Å ³ , 8
Density (calculated)	1.272 Mg/m ³
Absorption coefficient	0.086 mm ⁻¹
F(000)	1856
Crystal colour / morphology	Colourless tablets
Crystal size	0.38 × 0.28 × 0.13 mm ³
q range for data collection	2.487 to 28.313°
Index ranges	-37 ≤ h ≤ 43, -13 ≤ k ≤ 13, -10 ≤ l ≤ 16
Reflns collected / unique	7714 / 4462 [R(int) = 0.0150]
Reflns observed [F > 4s(F)]	3655
Absorption correction	Analytical
Max. and min. transmission	0.989 and 0.975
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4462 / 2 / 295
Goodness-of-fit on F²	1.04
Final R indices [F > 4s(F)]	R1 = 0.0419, wR2 = 0.1026
R indices (all data)	R1 = 0.0544, wR2 = 0.1115
Largest diff. peak, hole	0.268, -0.230 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.004

Table A.10: Bond lengths [Å] and angles [°] for meroterpenoid **159**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1)-C(1)	1.2074(18)	O(1)-C(1)-O(2)	117.39(13)
C(1)-O(2)	1.3614(18)	O(1)-C(1)-C(22)	126.18(14)
C(1)-C(22)	1.467(2)	O(2)-C(1)-C(22)	116.28(12)
O(2)-C(3)	1.4433(17)	C(1)-O(2)-C(3)	118.53(11)
C(3)-O(4)	1.4326(17)	O(4)-C(3)-O(2)	109.31(11)
C(3)-C(23)	1.501(2)	O(4)-C(3)-C(23)	106.74(12)
C(3)-C(24)	1.513(2)	O(2)-C(3)-C(23)	106.20(11)
O(4)-C(5)	1.3679(17)	O(4)-C(3)-C(24)	111.02(12)
C(5)-C(6)	1.390(2)	O(2)-C(3)-C(24)	110.23(12)
C(5)-C(22)	1.4013(19)	C(23)-C(3)-C(24)	113.14(13)
C(6)-C(19)	1.391(2)	C(5)-O(4)-C(3)	114.99(11)
C(6)-C(7)	1.5104(19)	O(4)-C(5)-C(6)	116.76(12)
C(7)-C(8)	1.5359(19)	O(4)-C(5)-C(22)	120.13(12)
C(8)-C(17)	1.535(2)	C(6)-C(5)-C(22)	123.09(13)
C(8)-C(9)	1.5625(19)	C(5)-C(6)-C(19)	116.21(13)
C(9)-C(10)	1.539(2)	C(5)-C(6)-C(7)	122.03(12)
C(9)-C(25)	1.544(2)	C(19)-C(6)-C(7)	121.74(13)
C(9)-C(14)	1.5606(19)	C(6)-C(7)-C(8)	110.40(11)
C(10)-C(11)	1.525(2)	C(17)-C(8)-C(7)	109.55(11)
C(11)-C(12)	1.509(2)	C(17)-C(8)-C(9)	114.78(11)
C(12)-O(12)	1.440(2)	C(7)-C(8)-C(9)	115.24(11)
C(12)-C(13)	1.542(2)	C(10)-C(9)-C(25)	109.34(12)
C(13)-C(26)	1.531(2)	C(10)-C(9)-C(14)	106.95(11)
C(13)-C(27)	1.542(2)	C(25)-C(9)-C(14)	114.05(12)
C(13)-C(14)	1.562(2)	C(10)-C(9)-C(8)	107.56(11)
C(14)-C(15)	1.532(2)	C(25)-C(9)-C(8)	111.62(12)
C(15)-C(16)	1.527(2)	C(14)-C(9)-C(8)	107.01(11)
C(16)-C(17)	1.517(2)	C(11)-C(10)-C(9)	112.45(12)
C(17)-O(18)	1.4688(17)	C(12)-C(11)-C(10)	112.19(13)
C(17)-C(28)	1.524(2)	O(12)-C(12)-C(11)	107.19(14)
O(18)-C(19)	1.3590(17)	O(12)-C(12)-C(13)	111.51(13)
C(19)-C(20)	1.399(2)	C(11)-C(12)-C(13)	114.31(13)
C(20)-C(21)	1.374(2)	C(26)-C(13)-C(27)	107.53(13)
C(21)-C(22)	1.411(2)	C(26)-C(13)-C(12)	111.17(14)
C(21)-C(29)	1.510(2)	C(27)-C(13)-C(12)	107.92(13)
		C(26)-C(13)-C(14)	114.26(13)
		C(27)-C(13)-C(14)	108.47(13)
		C(12)-C(13)-C(14)	107.30(12)
		C(15)-C(14)-C(9)	111.10(12)
		C(15)-C(14)-C(13)	113.59(12)
		C(9)-C(14)-C(13)	116.78(12)
		C(16)-C(15)-C(14)	109.97(12)
		C(17)-C(16)-C(15)	112.58(12)

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O(18)-C(17)-C(16)	102.99(11)
O(18)-C(17)-C(28)	106.90(12)
C(16)-C(17)-C(28)	111.99(13)
O(18)-C(17)-C(8)	107.30(11)
C(16)-C(17)-C(8)	110.65(12)
C(28)-C(17)-C(8)	115.99(12)
C(19)-O(18)-C(17)	116.39(11)
O(18)-C(19)-C(6)	122.28(13)
O(18)-C(19)-C(20)	115.88(13)
C(6)-C(19)-C(20)	121.78(13)
C(21)-C(20)-C(19)	121.11(14)
C(20)-C(21)-C(22)	118.49(14)
C(20)-C(21)-C(29)	119.35(14)
C(22)-C(21)-C(29)	122.16(14)
C(5)-C(22)-C(21)	118.89(13)
C(5)-C(22)-C(1)	117.79(13)
C(21)-C(22)-C(1)	122.87(13)

**(7a*S*,10*S*,11a*S*)-10-Hydroxy-2,2,5,7a,11,11-hexamethyl-
7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-[1,3]dioxino[4,5-*a*]xanthen-4-
one**

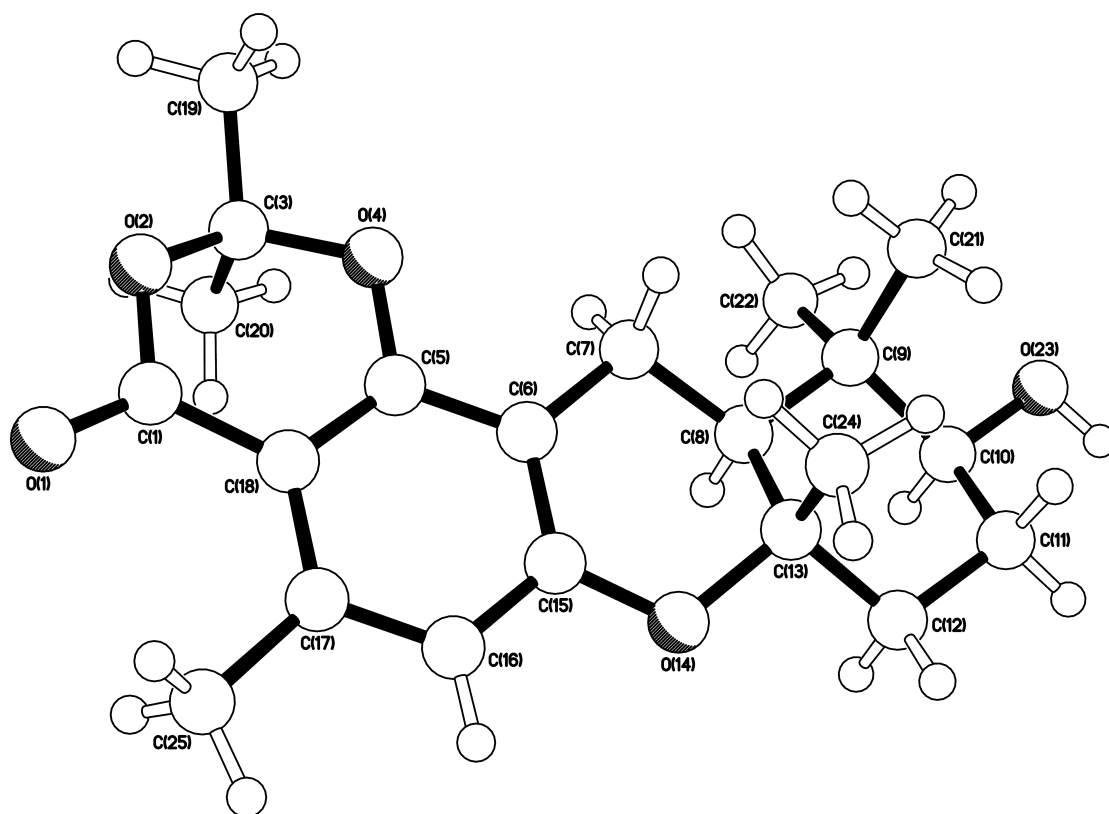


Figure A.6: X-Ray crystal structure of meroterpenoid 190.

Table A.11: Crystal data and structure refinement for meroterpenoid **190**.

Identification code	AB1601
Formula	C ₂₁ H ₂₈ O ₅
Formula weight	360.43
Temperature	173(2) K
Diffractionmeter, wavelength	Agilent Xcalibur PX Ultra A, 1.54184 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.8319(4) Å α = 94.713(4)° b = 10.1843(5) Å β = 102.968(4)° c = 12.0790(6) Å γ = 114.675(5)°
Volume, Z	942.91(9) Å ³ , 2
Density (calculated)	1.269 Mg/m ³
Absorption coefficient	0.727 mm ⁻¹
F(000)	388
Crystal colour / morphology	Colourless blocky needles
Crystal size	0.37 × 0.17 × 0.10 mm ³
q range for data collection	3.832 to 73.859°
Index ranges	-10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -14 ≤ l ≤ 14
Reflns collected / unique	14928 / 3734 [R(int) = 0.0298]
Reflns observed [F > 4s(F)]	2964
Absorption correction	Analytical
Max. and min. transmission	0.936 and 0.826
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3734 / 1 / 245
Goodness-of-fit on F²	1.025
Final R indices [F > 4s(F)]	R1 = 0.0431, wR2 = 0.1079
R indices (all data)	R1 = 0.0572, wR2 = 0.1192
Largest diff. peak, hole	0.252, -0.206 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.002

Table A.12: Bond lengths [Å] and angles [°] for meroterpenoid **190**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1)-C(1)	1.2091(19)	O(1)-C(1)-O(2)	117.13(13)
C(1)-O(2)	1.3595(18)	O(1)-C(1)-C(18)	126.48(15)
C(1)-C(18)	1.465(2)	O(2)-C(1)-C(18)	116.28(12)
O(2)-C(3)	1.4417(17)	C(1)-O(2)-C(3)	119.06(11)
C(3)-O(4)	1.4287(16)	O(4)-C(3)-O(2)	109.81(12)
C(3)-C(19)	1.503(2)	O(4)-C(3)-C(19)	106.78(12)
C(3)-C(20)	1.508(2)	O(2)-C(3)-C(19)	106.52(12)
O(4)-C(5)	1.3692(16)	O(4)-C(3)-C(20)	110.44(12)
C(5)-C(6)	1.3940(19)	O(2)-C(3)-C(20)	109.76(12)
C(5)-C(18)	1.3968(19)	C(19)-C(3)-C(20)	113.41(14)
C(6)-C(15)	1.392(2)	C(5)-O(4)-C(3)	115.09(11)
C(6)-C(7)	1.5062(19)	O(4)-C(5)-C(6)	115.66(12)
C(7)-C(8)	1.5323(18)	O(4)-C(5)-C(18)	120.60(12)
C(8)-C(13)	1.536(2)	C(6)-C(5)-C(18)	123.68(13)
C(8)-C(9)	1.5597(19)	C(15)-C(6)-C(5)	116.25(13)
C(9)-C(22)	1.533(2)	C(15)-C(6)-C(7)	122.04(12)
C(9)-C(21)	1.538(2)	C(5)-C(6)-C(7)	121.70(12)
C(9)-C(10)	1.5475(19)	C(6)-C(7)-C(8)	110.36(11)
C(10)-O(23)	1.4224(17)	C(7)-C(8)-C(13)	110.47(11)
C(10)-C(11)	1.523(2)	C(7)-C(8)-C(9)	113.86(11)
C(11)-C(12)	1.527(2)	C(13)-C(8)-C(9)	115.62(12)
C(12)-C(13)	1.5249(19)	C(22)-C(9)-C(21)	108.27(14)
C(13)-O(14)	1.4672(17)	C(22)-C(9)-C(10)	108.27(13)
C(13)-C(24)	1.523(2)	C(21)-C(9)-C(10)	110.57(13)
O(14)-C(15)	1.3620(16)	C(22)-C(9)-C(8)	107.88(13)
C(15)-C(16)	1.395(2)	C(21)-C(9)-C(8)	114.82(13)
C(16)-C(17)	1.381(2)	C(10)-C(9)-C(8)	106.84(11)
C(17)-C(18)	1.416(2)	O(23)-C(10)-C(11)	111.57(13)
C(17)-C(25)	1.508(2)	O(23)-C(10)-C(9)	107.81(12)
		C(11)-C(10)-C(9)	112.78(13)
		C(10)-C(11)-C(12)	110.40(12)
		C(13)-C(12)-C(11)	111.47(12)
		O(14)-C(13)-C(24)	106.13(12)
		O(14)-C(13)-C(12)	104.11(11)
		C(24)-C(13)-C(12)	111.63(13)
		O(14)-C(13)-C(8)	108.08(11)
		C(24)-C(13)-C(8)	116.22(13)
		C(12)-C(13)-C(8)	109.83(12)
		C(15)-O(14)-C(13)	116.42(11)
		O(14)-C(15)-C(6)	122.30(13)
		O(14)-C(15)-C(16)	116.21(12)
		C(6)-C(15)-C(16)	121.45(13)
		C(17)-C(16)-C(15)	121.79(14)

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C(16)-C(17)-C(18)	118.22(13)
C(16)-C(17)-C(25)	118.66(14)
C(18)-C(17)-C(25)	123.13(14)
C(5)-C(18)-C(17)	118.60(13)
C(5)-C(18)-C(1)	118.29(13)
C(17)-C(18)-C(1)	122.86(13)

10-Bromo-2,2,5,7a,11,11-hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-[1,3]dioxino[4,5-*a*]xanthen-4-one

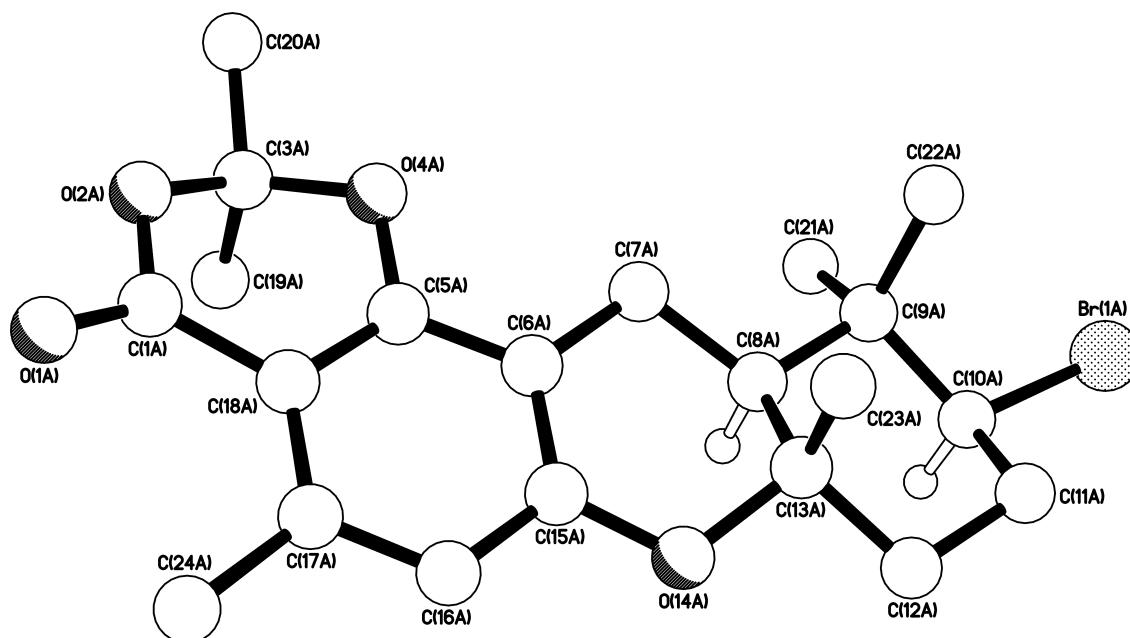


Figure A.7: X-Ray crystal structure of bromide **193a**.

Table A.13: Crystal data and structure refinement for bromide **193a**.

Identification code	AB1613
Formula	C ₂₁ H ₂₇ BrO ₄
Formula weight	423.33
Temperature	173(2) K
Diffractionmeter, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 11.7913(8) Å α = 84.236(3)° b = 12.8318(8) Å β = 83.690(4)° c = 14.3130(4) Å γ = 64.991(6)°
Volume, Z	1947.2(2) Å ³ , 4
Density (calculated)	1.444 Mg/m ³
Absorption coefficient	2.134 mm ⁻¹
F(000)	880
Crystal colour / morphology	Colourless tablets
Crystal size	0.62 × 0.42 × 0.13 mm ³
q range for data collection	2.299 to 28.256°
Index ranges	-15 ≤ h ≤ 15, -16 ≤ k ≤ 16, -18 ≤ l ≤ 18
Reflns collected / unique	12674 / 12674 [R(int) = ?]
Reflns observed [F > 4s(F)]	7571
Absorption correction	Analytical
Max. and min. transmission	0.774 and 0.483
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	12674 / 0 / 482
Goodness-of-fit on F²	0.853
Final R indices [F > 4s(F)]	R1 = 0.0350, wR2 = 0.0713
R indices (all data)	R1 = 0.0736, wR2 = 0.0760
Largest diff. peak, hole	0.595, -0.501 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.002

Table A.14: Bond lengths [Å] and angles [°] for bromide **193a**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1A)-C(1A)	1.204(3)	O(1)-C(1)-O(2)	117.13(13)
C(1A)-O(2A)	1.366(3)	O(1)-C(1)-C(18)	126.48(15)
C(1A)-C(18A)	1.475(4)	O(2)-C(1)-C(18)	116.28(12)
O(2A)-C(3A)	1.448(3)	C(1)-O(2)-C(3)	119.06(11)
C(3A)-O(4A)	1.437(3)	O(4)-C(3)-O(2)	109.81(12)
C(3A)-C(20A)	1.496(4)	O(4)-C(3)-C(19)	106.78(12)
C(3A)-C(19A)	1.511(4)	O(2)-C(3)-C(19)	106.52(12)
O(4A)-C(5A)	1.366(3)	O(4)-C(3)-C(20)	110.44(12)
C(5A)-C(18A)	1.394(4)	O(2)-C(3)-C(20)	109.76(12)
C(5A)-C(6A)	1.399(4)	C(19)-C(3)-C(20)	113.41(14)
C(6A)-C(15A)	1.380(4)	C(5)-O(4)-C(3)	115.09(11)
C(6A)-C(7A)	1.507(4)	O(4)-C(5)-C(6)	115.66(12)
C(7A)-C(8A)	1.535(4)	O(4)-C(5)-C(18)	120.60(12)
C(8A)-C(13A)	1.535(4)	C(6)-C(5)-C(18)	123.68(13)
C(8A)-C(9A)	1.563(4)	C(15)-C(6)-C(5)	116.25(13)
C(9A)-C(22A)	1.531(4)	C(15)-C(6)-C(7)	122.04(12)
C(9A)-C(21A)	1.532(4)	C(5)-C(6)-C(7)	121.70(12)
C(9A)-C(10A)	1.546(4)	C(6)-C(7)-C(8)	110.36(11)
C(10A)-C(11A)	1.505(4)	C(7)-C(8)-C(13)	110.47(11)
C(10A)-Br(1A)	1.975(2)	C(7)-C(8)-C(9)	113.86(11)
C(11A)-C(12A)	1.526(3)	C(13)-C(8)-C(9)	115.62(12)
C(12A)-C(13A)	1.516(4)	C(22)-C(9)-C(21)	108.27(14)
C(13A)-O(14A)	1.467(3)	C(22)-C(9)-C(10)	108.27(13)
C(13A)-C(23A)	1.515(4)	C(21)-C(9)-C(10)	110.57(13)
O(14A)-C(15A)	1.363(3)	C(22)-C(9)-C(8)	107.88(13)
C(15A)-C(16A)	1.395(4)	C(21)-C(9)-C(8)	114.82(13)
C(16A)-C(17A)	1.382(4)	C(10)-C(9)-C(8)	106.84(11)
C(17A)-C(18A)	1.394(4)	O(23)-C(10)-C(11)	111.57(13)
C(17A)-C(24A)	1.511(4)	O(23)-C(10)-C(9)	107.81(12)
O(1B)-C(1B)	1.207(3)	C(11)-C(10)-C(9)	112.78(13)
C(1B)-O(2B)	1.362(3)	C(10)-C(11)-C(12)	110.40(12)
C(1B)-C(18B)	1.471(4)	C(13)-C(12)-C(11)	111.47(12)
O(2B)-C(3B)	1.447(3)	O(1A)-C(1A)-O(2A)	117.3(3)
C(3B)-O(4B)	1.434(3)	O(1A)-C(1A)-C(18A)	126.4(3)
C(3B)-C(20B)	1.501(4)	O(2A)-C(1A)-C(18A)	116.2(3)
C(3B)-C(19B)	1.502(4)	C(1A)-O(2A)-C(3A)	118.7(2)
O(4B)-C(5B)	1.363(3)	O(4A)-C(3A)-O(2A)	108.6(2)
C(5B)-C(6B)	1.393(4)	O(4A)-C(3A)-C(20A)	106.5(2)
C(5B)-C(18B)	1.401(4)	O(2A)-C(3A)-C(20A)	106.5(2)
C(6B)-C(15B)	1.379(4)	O(4A)-C(3A)-C(19A)	111.1(2)
C(6B)-C(7B)	1.513(4)	O(2A)-C(3A)-C(19A)	110.4(2)
C(7B)-C(8B)	1.528(4)	C(20A)-C(3A)-C(19A)	113.5(3)
C(8B)-C(13B)	1.540(4)	C(5A)-O(4A)-C(3A)	113.4(2)

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C(8B)-C(9B)	1.568(4)	O(4A)-C(5A)-C(18A)	120.6(3)
C(9B)-C(21B)	1.531(4)	O(4A)-C(5A)-C(6A)	116.8(2)
C(9B)-C(22B)	1.535(4)	C(18A)-C(5A)-C(6A)	122.5(3)
C(9B)-C(10B)	1.547(4)	C(15A)-C(6A)-C(5A)	116.3(3)
C(10B)-C(11B)	1.510(4)	C(15A)-C(6A)-C(7A)	122.2(3)
C(10B)-Br(1B)	1.974(3)	C(5A)-C(6A)-C(7A)	121.5(3)
C(11B)-C(12B)	1.527(3)	C(6A)-C(7A)-C(8A)	110.5(2)
C(12B)-C(13B)	1.510(4)	C(13A)-C(8A)-C(7A)	110.8(2)
C(13B)-O(14B)	1.469(3)	C(13A)-C(8A)-C(9A)	115.7(2)
C(13B)-C(23B)	1.522(4)	C(7A)-C(8A)-C(9A)	114.4(2)
O(14B)-C(15B)	1.362(3)	C(22A)-C(9A)-C(21A)	107.6(2)
C(15B)-C(16B)	1.406(4)	C(22A)-C(9A)-C(10A)	111.7(2)
C(16B)-C(17B)	1.376(4)	C(21A)-C(9A)-C(10A)	110.1(2)
C(17B)-C(18B)	1.402(4)	C(22A)-C(9A)-C(8A)	114.7(2)
C(17B)-C(24B)	1.522(4)	C(21A)-C(9A)-C(8A)	107.6(2)
		C(10A)-C(9A)-C(8A)	105.0(2)
		C(11A)-C(10A)-C(9A)	114.0(2)
		C(11A)-C(10A)-Br(1A)	108.55(19)
		C(9A)-C(10A)-Br(1A)	112.41(19)
		C(10A)-C(11A)-C(12A)	109.4(2)
		C(13A)-C(12A)-C(11A)	110.8(2)
		O(14A)-C(13A)-C(23A)	106.6(2)
		O(14A)-C(13A)-C(12A)	103.5(2)
		C(23A)-C(13A)-C(12A)	112.0(3)
		O(14A)-C(13A)-C(8A)	107.3(2)
		C(23A)-C(13A)-C(8A)	115.9(2)
		C(12A)-C(13A)-C(8A)	110.5(2)
		C(15A)-O(14A)-C(13A)	117.0(2)
		O(14A)-C(15A)-C(6A)	122.0(2)
		O(14A)-C(15A)-C(16A)	116.0(3)
		C(6A)-C(15A)-C(16A)	122.0(3)
		C(17A)-C(16A)-C(15A)	121.1(3)
		C(16A)-C(17A)-C(18A)	118.2(3)
		C(16A)-C(17A)-C(24A)	118.7(3)
		C(18A)-C(17A)-C(24A)	123.1(3)
		C(5A)-C(18A)-C(17A)	119.8(3)
		C(5A)-C(18A)-C(1A)	117.3(3)
		C(17A)-C(18A)-C(1A)	122.7(3)
		O(1B)-C(1B)-O(2B)	117.4(3)
		O(1B)-C(1B)-C(18B)	126.1(3)
		O(2B)-C(1B)-C(18B)	116.4(2)
		C(1B)-O(2B)-C(3B)	118.9(2)
		O(4B)-C(3B)-O(2B)	108.5(2)
		O(4B)-C(3B)-C(20B)	106.3(2)
		O(2B)-C(3B)-C(20B)	106.4(2)
		O(4B)-C(3B)-C(19B)	111.2(2)
		O(2B)-C(3B)-C(19B)	110.3(2)

C(20B)-C(3B)-C(19B)	114.0(3)
C(5B)-O(4B)-C(3B)	114.0(2)
O(4B)-C(5B)-C(6B)	116.7(2)
O(4B)-C(5B)-C(18B)	120.4(3)
C(6B)-C(5B)-C(18B)	122.8(3)
C(15B)-C(6B)-C(5B)	116.7(2)
C(15B)-C(6B)-C(7B)	121.8(3)
C(5B)-C(6B)-C(7B)	121.6(3)
C(6B)-C(7B)-C(8B)	110.3(2)
C(7B)-C(8B)-C(13B)	110.6(2)
C(7B)-C(8B)-C(9B)	113.9(2)
C(13B)-C(8B)-C(9B)	115.6(2)
C(21B)-C(9B)-C(22B)	108.1(2)
C(21B)-C(9B)-C(10B)	109.9(2)
C(22B)-C(9B)-C(10B)	111.9(3)
C(21B)-C(9B)-C(8B)	107.2(2)
C(22B)-C(9B)-C(8B)	114.9(2)
C(10B)-C(9B)-C(8B)	104.8(2)
C(11B)-C(10B)-C(9B)	114.0(2)
C(11B)-C(10B)-Br(1B)	107.78(19)
C(9B)-C(10B)-Br(1B)	112.85(19)
C(10B)-C(11B)-C(12B)	109.5(2)
C(13B)-C(12B)-C(11B)	111.1(2)
O(14B)-C(13B)-C(12B)	103.3(2)
O(14B)-C(13B)-C(23B)	106.4(2)
C(12B)-C(13B)-C(23B)	112.6(3)
O(14B)-C(13B)-C(8B)	107.4(2)
C(12B)-C(13B)-C(8B)	110.0(2)
C(23B)-C(13B)-C(8B)	116.1(2)
C(15B)-O(14B)-C(13B)	116.9(2)
O(14B)-C(15B)-C(6B)	122.6(2)
O(14B)-C(15B)-C(16B)	115.6(3)
C(6B)-C(15B)-C(16B)	121.7(3)
C(17B)-C(16B)-C(15B)	120.9(3)
C(16B)-C(17B)-C(18B)	118.7(3)
C(16B)-C(17B)-C(24B)	118.8(3)
C(18B)-C(17B)-C(24B)	122.5(3)
C(5B)-C(18B)-C(17B)	119.1(3)
C(5B)-C(18B)-C(1B)	117.1(3)
C(17B)-C(18B)-C(1B)	123.4(3)

**11-Bromo-2,2,5,7a,10,10,13a-heptamethyl-
7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-
benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one**

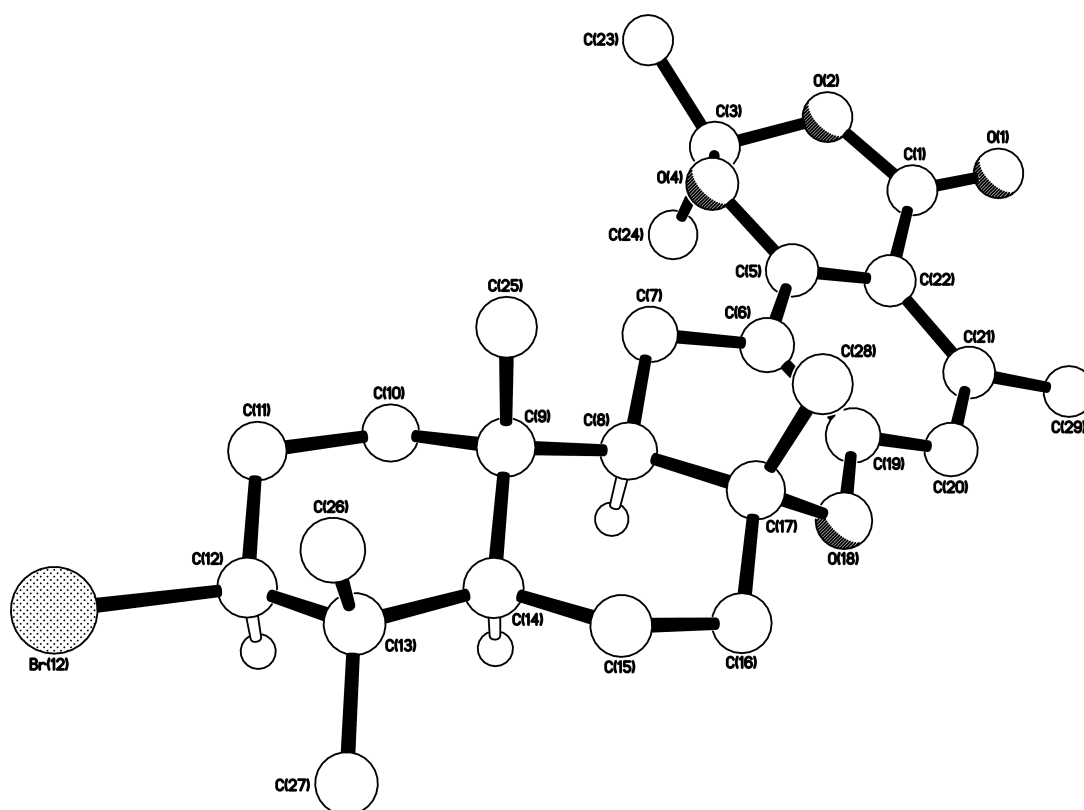


Table A.15: Crystal data and structure refinement for bromide **193b**.

Identification code	AB1611
Formula	C ₂₆ H ₃₅ BrO ₄
Formula weight	491.45
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, P2 ₁ /c
Unit cell dimensions	a = 16.6717(11) Å $\alpha = 90^\circ$ b = 10.9343(5) Å $\beta = 102.860(7)^\circ$ c = 13.0037(8) Å $\gamma = 90^\circ$
Volume, Z	2311.0(2) Å ³ , 4
Density (calculated)	1.412 Mg/m ³
Absorption coefficient	1.809 mm ⁻¹
F(000)	1032
Crystal colour / morphology	Colourless blocks
Crystal size	0.44 × 0.25 × 0.12 mm ³
q range for data collection	2.460 to 28.265°
Index ranges	-20 ≤ h ≤ 10, -14 ≤ k ≤ 8, -16 ≤ l ≤ 16
Reflns collected / unique	7946 / 4629 [R(int) = 0.0270]
Reflns observed [F > 4s(F)]	3424
Absorption correction	Analytical
Max. and min. transmission	0.806 and 0.609
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4629 / 0 / 287
Goodness-of-fit on F²	1.029
Final R indices [F > 4s(F)]	R1 = 0.0582, wR2 = 0.1459
R indices (all data)	R1 = 0.0846, wR2 = 0.1635
Largest diff. peak, hole	1.428, -0.555 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table A.16: Bond lengths [Å] and angles [°] for bromide **193b**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1)-C(1)	1.196(5)	O(1)-C(1)-O(2)	117.8(4)
C(1)-O(2)	1.363(5)	O(1)-C(1)-C(22)	126.3(4)
C(1)-C(22)	1.472(6)	O(2)-C(1)-C(22)	115.7(3)
O(2)-C(3)	1.442(5)	C(1)-O(2)-C(3)	118.8(3)
C(3)-O(4)	1.429(5)	O(4)-C(3)-O(2)	109.0(3)
C(3)-C(23)	1.500(6)	O(4)-C(3)-C(23)	106.3(3)
C(3)-C(24)	1.504(6)	O(2)-C(3)-C(23)	106.3(3)
O(4)-C(5)	1.374(5)	O(4)-C(3)-C(24)	111.4(3)
C(5)-C(6)	1.387(5)	O(2)-C(3)-C(24)	110.2(4)
C(5)-C(22)	1.388(5)	C(23)-C(3)-C(24)	113.3(4)
C(6)-C(19)	1.388(6)	C(5)-O(4)-C(3)	114.7(3)
C(6)-C(7)	1.501(5)	O(4)-C(5)-C(6)	116.1(3)
C(7)-C(8)	1.529(5)	O(4)-C(5)-C(22)	120.3(3)
C(8)-C(17)	1.538(6)	C(6)-C(5)-C(22)	123.5(4)
C(8)-C(9)	1.559(5)	C(5)-C(6)-C(19)	115.9(4)
C(9)-C(10)	1.542(6)	C(5)-C(6)-C(7)	122.4(4)
C(9)-C(25)	1.544(6)	C(19)-C(6)-C(7)	121.7(4)
C(9)-C(14)	1.558(5)	C(6)-C(7)-C(8)	110.9(3)
C(10)-C(11)	1.530(6)	C(7)-C(8)-C(17)	109.8(3)
C(11)-C(12)	1.514(6)	C(7)-C(8)-C(9)	115.4(3)
C(12)-C(13)	1.534(6)	C(17)-C(8)-C(9)	114.4(3)
C(12)-Br(12)	1.990(4)	C(10)-C(9)-C(25)	108.7(3)
C(13)-C(26)	1.510(6)	C(10)-C(9)-C(14)	107.0(3)
C(13)-C(27)	1.533(6)	C(25)-C(9)-C(14)	114.0(3)
C(13)-C(14)	1.573(5)	C(10)-C(9)-C(8)	107.8(3)
C(14)-C(15)	1.522(6)	C(25)-C(9)-C(8)	112.3(3)
C(15)-C(16)	1.527(6)	C(14)-C(9)-C(8)	106.8(3)
C(16)-C(17)	1.515(6)	C(11)-C(10)-C(9)	112.4(3)
C(17)-O(18)	1.468(5)	C(12)-C(11)-C(10)	110.0(4)
C(17)-C(28)	1.519(6)	C(11)-C(12)-C(13)	116.3(4)
O(18)-C(19)	1.356(5)	C(11)-C(12)-Br(12)	107.0(3)
C(19)-C(20)	1.395(6)	C(13)-C(12)-Br(12)	111.1(3)
C(20)-C(21)	1.371(6)	C(26)-C(13)-C(27)	109.1(4)
C(21)-C(22)	1.415(6)	C(26)-C(13)-C(12)	113.2(4)
C(21)-C(29)	1.507(6)	C(27)-C(13)-C(12)	106.9(4)
		C(26)-C(13)-C(14)	113.3(4)
		C(27)-C(13)-C(14)	108.5(3)
		C(12)-C(13)-C(14)	105.6(3)
		C(15)-C(14)-C(9)	111.4(3)
		C(15)-C(14)-C(13)	113.0(3)
		C(9)-C(14)-C(13)	117.1(3)
		C(14)-C(15)-C(16)	110.6(4)
		C(17)-C(16)-C(15)	111.9(4)

O(18)-C(17)-C(16)	102.8(3)
O(18)-C(17)-C(28)	107.1(3)
C(16)-C(17)-C(28)	112.4(4)
O(18)-C(17)-C(8)	107.4(3)
C(16)-C(17)-C(8)	110.5(3)
C(28)-C(17)-C(8)	115.7(4)
C(19)-O(18)-C(17)	116.9(3)
O(18)-C(19)-C(6)	122.3(4)
O(18)-C(19)-C(20)	115.8(3)
C(6)-C(19)-C(20)	121.9(4)
C(21)-C(20)-C(19)	121.5(4)
C(20)-C(21)-C(22)	117.8(4)
C(20)-C(21)-C(29)	119.4(4)
C(22)-C(21)-C(29)	122.8(4)
C(5)-C(22)-C(21)	119.2(4)
C(5)-C(22)-C(1)	118.1(4)
C(21)-C(22)-C(1)	122.4(4)

10-Iodo-2,2,5,7a,11,11-hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-[1,3]dioxino[4,5-*a*]xanthen-4-one

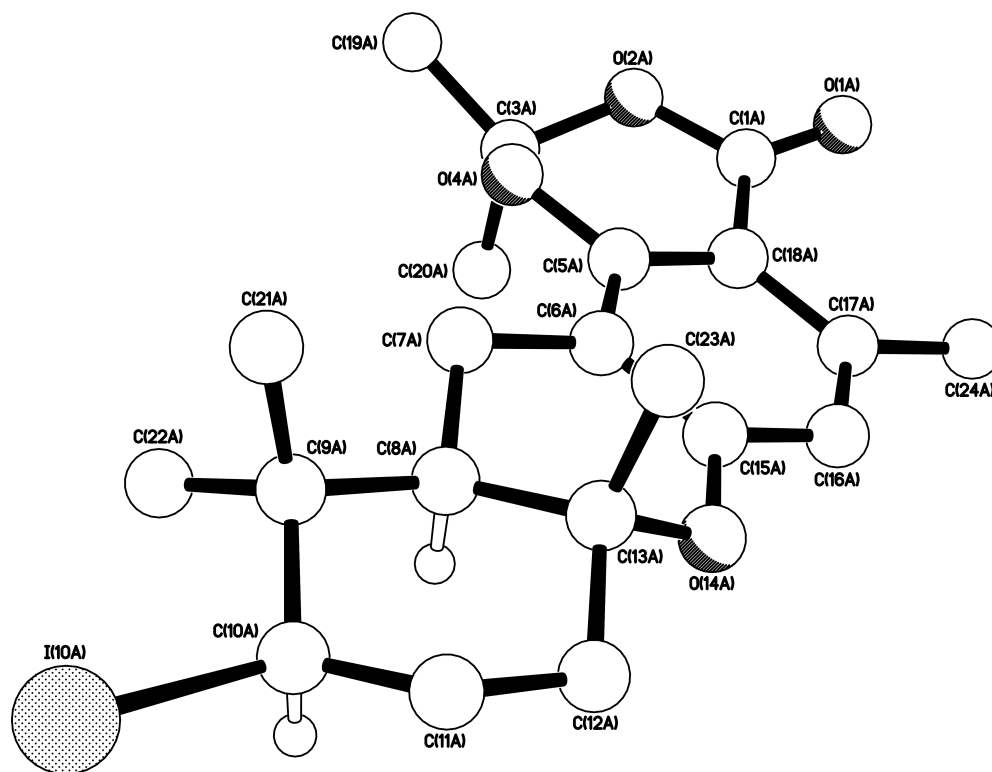


Figure A.9: X-Ray crystal structure of iodide **194a**.

Table A.17: Crystal data and structure refinement for bromide **194a**.

Identification code	AB1616
Formula	C ₂₁ H ₂₇ IO ₄
Formula weight	470.32
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 11.9049(8) Å α = 82.833(4)° b = 13.0663(7) Å β = 82.432(4)° c = 14.3669(6) Å γ = 65.736(6)°
Volume, Z	2013.5(2) Å ³ , 4
Density (calculated)	1.552 Mg/m ³
Absorption coefficient	1.613 mm ⁻¹
F(000)	952
Crystal colour / morphology	Colourless tablets
Crystal size	0.49 × 0.32 × 0.07 mm ³
q range for data collection	2.467 to 28.183°
Index ranges	-13<=h<=14, -15<=k<=11, -15<=l<=17
Reflns collected / unique	11767 / 7953 [R(int) = 0.0227]
Reflns observed [F>4s(F)]	6250
Absorption correction	Analytical
Max. and min. transmission	0.904 and 0.565
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7953 / 0 / 481
Goodness-of-fit on F²	1.065
Final R indices [F>4s(F)]	R1 = 0.0432, wR2 = 0.0921
R indices (all data)	R1 = 0.0607, wR2 = 0.1035
Largest diff. peak, hole	1.392, -0.951 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.002

Table A.18: Bond lengths [Å] and angles [°] for bromide **194a**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1A)-C(1A)	1.206(5)	O(1A)-C(1A)-O(2A)	117.3(4)
C(1A)-O(2A)	1.365(5)	O(1A)-C(1A)-C(18A)	126.5(4)
C(1A)-C(18A)	1.473(6)	O(2A)-C(1A)-C(18A)	116.1(4)
O(2A)-C(3A)	1.445(5)	C(1A)-O(2A)-C(3A)	118.9(3)
C(3A)-O(4A)	1.437(5)	O(4A)-C(3A)-O(2A)	109.0(3)
C(3A)-C(19A)	1.502(6)	O(4A)-C(3A)-C(19A)	106.2(4)
C(3A)-C(20A)	1.515(6)	O(2A)-C(3A)-C(19A)	106.5(3)
O(4A)-C(5A)	1.372(5)	O(4A)-C(3A)-C(20A)	111.1(3)
C(5A)-C(18A)	1.393(6)	O(2A)-C(3A)-C(20A)	110.0(4)
C(5A)-C(6A)	1.395(5)	C(19A)-C(3A)-C(20A)	113.8(4)
C(6A)-C(15A)	1.385(6)	C(5A)-O(4A)-C(3A)	113.3(3)
C(6A)-C(7A)	1.506(6)	O(4A)-C(5A)-C(18A)	120.7(3)
C(7A)-C(8A)	1.534(5)	O(4A)-C(5A)-C(6A)	116.3(4)
C(8A)-C(13A)	1.551(5)	C(18A)-C(5A)-C(6A)	123.0(4)
C(8A)-C(9A)	1.578(6)	C(15A)-C(6A)-C(5A)	116.4(4)
C(9A)-C(22A)	1.538(6)	C(15A)-C(6A)-C(7A)	122.2(4)
C(9A)-C(21A)	1.540(7)	C(5A)-C(6A)-C(7A)	121.3(4)
C(9A)-C(10A)	1.542(6)	C(6A)-C(7A)-C(8A)	110.4(3)
C(10A)-C(11A)	1.518(6)	C(7A)-C(8A)-C(13A)	110.6(3)
C(10A)-I(10A)	2.184(4)	C(7A)-C(8A)-C(9A)	114.7(3)
C(11A)-C(12A)	1.530(6)	C(13A)-C(8A)-C(9A)	115.5(3)
C(12A)-C(13A)	1.504(6)	C(22A)-C(9A)-C(21A)	107.8(4)
C(13A)-O(14A)	1.461(5)	C(22A)-C(9A)-C(10A)	109.9(4)
C(13A)-C(23A)	1.533(6)	C(21A)-C(9A)-C(10A)	112.7(4)
O(14A)-C(15A)	1.364(5)	C(22A)-C(9A)-C(8A)	107.0(3)
C(15A)-C(16A)	1.403(6)	C(21A)-C(9A)-C(8A)	114.2(4)
C(16A)-C(17A)	1.383(6)	C(10A)-C(9A)-C(8A)	105.0(3)
C(17A)-C(18A)	1.419(6)	C(11A)-C(10A)-C(9A)	114.0(4)
C(17A)-C(24A)	1.506(6)	C(11A)-C(10A)-I(10A)	106.8(3)
O(1B)-C(1B)	1.209(5)	C(9A)-C(10A)-I(10A)	113.9(3)
C(1B)-O(2B)	1.363(6)	C(10A)-C(11A)-C(12A)	109.3(3)
C(1B)-C(18B)	1.472(6)	C(13A)-C(12A)-C(11A)	112.1(3)
O(2B)-C(3B)	1.446(5)	O(14A)-C(13A)-C(12A)	104.3(3)
C(3B)-O(4B)	1.447(5)	O(14A)-C(13A)-C(23A)	106.4(3)
C(3B)-C(19B)	1.500(6)	C(12A)-C(13A)-C(23A)	112.2(4)
C(3B)-C(20B)	1.507(6)	O(14A)-C(13A)-C(8A)	107.8(3)
O(4B)-C(5B)	1.370(5)	C(12A)-C(13A)-C(8A)	110.0(3)
C(5B)-C(6B)	1.391(6)	C(23A)-C(13A)-C(8A)	115.4(4)
C(5B)-C(18B)	1.400(6)	C(15A)-O(14A)-C(13A)	117.3(3)
C(6B)-C(15B)	1.387(6)	O(14A)-C(15A)-C(6A)	122.2(4)
C(6B)-C(7B)	1.505(5)	O(14A)-C(15A)-C(16A)	115.8(4)
C(7B)-C(8B)	1.535(6)	C(6A)-C(15A)-C(16A)	121.9(4)
C(8B)-C(13B)	1.539(6)	C(17A)-C(16A)-C(15A)	121.4(4)

C(8B)-C(9B)	1.569(5)	C(16A)-C(17A)-C(18A)	117.6(4)
C(9B)-C(21B)	1.535(6)	C(16A)-C(17A)-C(24A)	119.6(4)
C(9B)-C(10B)	1.538(6)	C(18A)-C(17A)-C(24A)	122.9(4)
C(9B)-C(22B)	1.539(6)	C(5A)-C(18A)-C(17A)	119.6(4)
C(10B)-C(11B)	1.515(6)	C(5A)-C(18A)-C(1A)	117.5(4)
C(10B)-I(10B)	2.187(4)	C(17A)-C(18A)-C(1A)	122.6(4)
C(11B)-C(12B)	1.534(6)	O(1B)-C(1B)-O(2B)	117.6(4)
C(12B)-C(13B)	1.508(6)	O(1B)-C(1B)-C(18B)	126.2(5)
C(13B)-O(14B)	1.471(5)	O(2B)-C(1B)-C(18B)	116.1(4)
C(13B)-C(23B)	1.533(6)	C(1B)-O(2B)-C(3B)	119.3(3)
O(14B)-C(15B)	1.369(5)	O(2B)-C(3B)-O(4B)	108.1(3)
C(15B)-C(16B)	1.396(6)	O(2B)-C(3B)-C(19B)	106.4(3)
C(16B)-C(17B)	1.379(6)	O(4B)-C(3B)-C(19B)	106.4(4)
C(17B)-C(18B)	1.419(6)	O(2B)-C(3B)-C(20B)	110.9(3)
C(17B)-C(24B)	1.507(6)	O(4B)-C(3B)-C(20B)	110.9(4)
		C(19B)-C(3B)-C(20B)	113.9(4)
		C(5B)-O(4B)-C(3B)	113.7(3)
		O(4B)-C(5B)-C(6B)	117.1(4)
		O(4B)-C(5B)-C(18B)	119.6(4)
		C(6B)-C(5B)-C(18B)	123.2(4)
		C(15B)-C(6B)-C(5B)	116.2(4)
		C(15B)-C(6B)-C(7B)	122.1(4)
		C(5B)-C(6B)-C(7B)	121.7(4)
		C(6B)-C(7B)-C(8B)	110.6(3)
		C(7B)-C(8B)-C(13B)	110.8(3)
		C(7B)-C(8B)-C(9B)	114.8(3)
		C(13B)-C(8B)-C(9B)	115.5(3)
		C(21B)-C(9B)-C(10B)	112.6(4)
		C(21B)-C(9B)-C(22B)	107.8(4)
		C(10B)-C(9B)-C(22B)	109.8(4)
		C(21B)-C(9B)-C(8B)	114.2(3)
		C(10B)-C(9B)-C(8B)	104.9(3)
		C(22B)-C(9B)-C(8B)	107.3(3)
		C(11B)-C(10B)-C(9B)	114.4(4)
		C(11B)-C(10B)-I(10B)	107.7(3)
		C(9B)-C(10B)-I(10B)	113.2(3)
		C(10B)-C(11B)-C(12B)	108.9(4)
		C(13B)-C(12B)-C(11B)	111.6(4)
		O(14B)-C(13B)-C(12B)	103.8(3)
		O(14B)-C(13B)-C(23B)	106.0(3)
		C(12B)-C(13B)-C(23B)	111.6(4)
		O(14B)-C(13B)-C(8B)	107.7(3)
		C(12B)-C(13B)-C(8B)	111.3(3)
		C(23B)-C(13B)-C(8B)	115.5(4)
		C(15B)-O(14B)-C(13B)	116.5(3)
		O(14B)-C(15B)-C(6B)	122.3(4)
		O(14B)-C(15B)-C(16B)	115.6(4)

C(6B)-C(15B)-C(16B)	122.1(4)
C(17B)-C(16B)-C(15B)	121.4(4)
C(16B)-C(17B)-C(18B)	118.0(4)
C(16B)-C(17B)-C(24B)	119.4(4)
C(18B)-C(17B)-C(24B)	122.6(4)
C(5B)-C(18B)-C(17B)	119.0(4)
C(5B)-C(18B)-C(1B)	117.8(4)
C(17B)-C(18B)-C(1B)	123.1(4)

**11-Iodo-2,2,5,7a,10,10,13a-heptamethyl-
7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-
benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one**

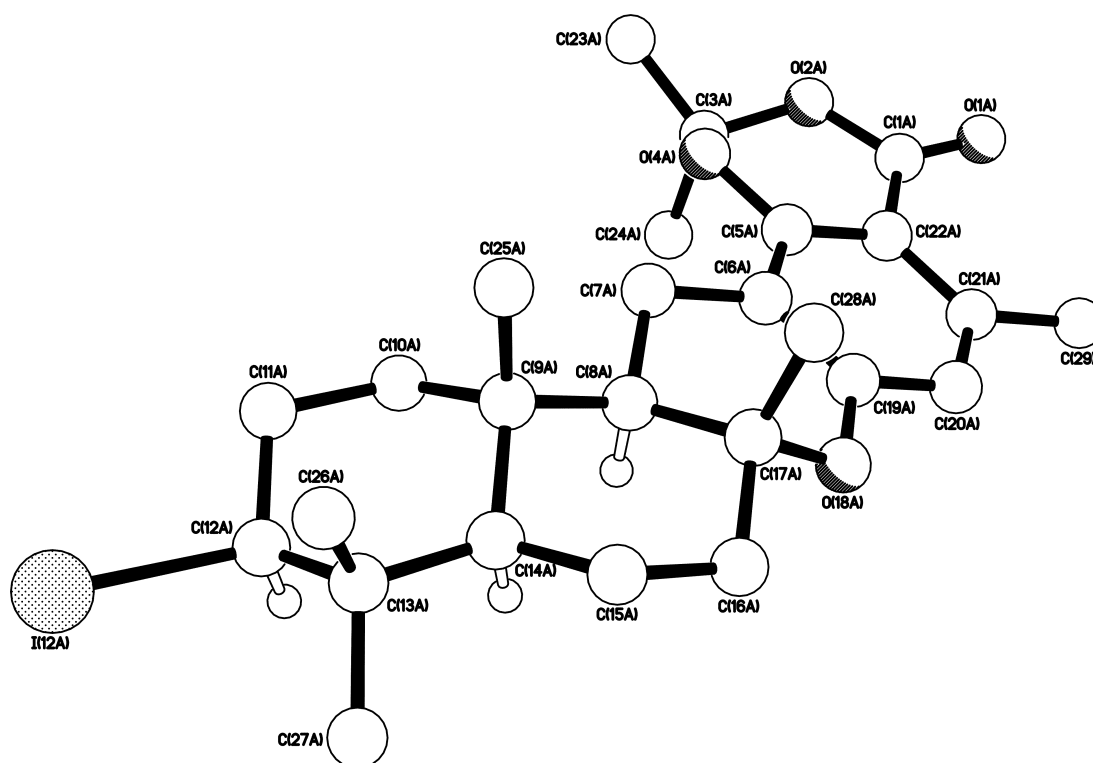


Figure A.10: X-Ray crystal structure of iodide **194b**.

Table A.19: Crystal data and structure refinement for iodide **194b**.

Identification code	AB1615
Formula	C ₂₆ H ₃₅ IO ₄
Formula weight	538.44
Temperature	173(2) K
Diffractionmeter, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$\alpha = 12.0848(5)^\circ$ $a = 100.616(3)^\circ$ $b = 12.2104(5)^\circ$ $\beta = 91.338(3)^\circ$ $c = 18.6095(8)^\circ$ $\gamma = 117.941(4)^\circ$
Volume, Z	2365.32(18) Å ³ , 4
Density (calculated)	1.512 Mg/m ³
Absorption coefficient	1.383 mm ⁻¹
F(000)	1104
Crystal colour / morphology	Colourless tablets
Crystal size	0.44 × 0.22 × 0.10 mm ³
q range for data collection	2.245 to 28.305°
Index ranges	-15 ≤ h ≤ 10, -16 ≤ k ≤ 15, -24 ≤ l ≤ 24
Refins collected / unique	13698 / 9309 [R(int) = 0.0193]
Refins observed [F > 4s(F)]	7257
Absorption correction	Analytical
Max. and min. transmission	0.887 and 0.695
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9309 / 0 / 573
Goodness-of-fit on F²	1.038
Final R indices [F > 4s(F)]	R1 = 0.0417, wR2 = 0.0837
R indices (all data)	R1 = 0.0591, wR2 = 0.0921
Largest diff. peak, hole	1.249, -0.739 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table A.20: Bond lengths [Å] and angles [°] for iodide **194b**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1A)-C(1A)	1.201(5)	O(1A)-C(1A)-O(2A)	117.7(4)
C(1A)-O(2A)	1.364(5)	O(1A)-C(1A)-C(22A)	126.6(4)
C(1A)-C(22A)	1.467(5)	O(2A)-C(1A)-C(22A)	115.6(3)
O(2A)-C(3A)	1.435(5)	C(1A)-O(2A)-C(3A)	119.4(3)
C(3A)-O(4A)	1.426(4)	O(4A)-C(3A)-O(2A)	110.1(3)
C(3A)-C(23A)	1.507(5)	O(4A)-C(3A)-C(23A)	106.2(3)
C(3A)-C(24A)	1.518(5)	O(2A)-C(3A)-C(23A)	106.2(3)
O(4A)-C(5A)	1.370(4)	O(4A)-C(3A)-C(24A)	110.4(3)
C(5A)-C(6A)	1.383(5)	O(2A)-C(3A)-C(24A)	110.5(3)
C(5A)-C(22A)	1.406(5)	C(23A)-C(3A)-C(24A)	113.3(3)
C(6A)-C(19A)	1.389(5)	C(5A)-O(4A)-C(3A)	113.8(3)
C(6A)-C(7A)	1.513(5)	O(4A)-C(5A)-C(6A)	116.9(3)
C(7A)-C(8A)	1.528(5)	O(4A)-C(5A)-C(22A)	119.5(3)
C(8A)-C(17A)	1.545(4)	C(6A)-C(5A)-C(22A)	123.6(3)
C(8A)-C(9A)	1.563(4)	C(5A)-C(6A)-C(19A)	116.5(3)
C(9A)-C(25A)	1.540(5)	C(5A)-C(6A)-C(7A)	122.1(3)
C(9A)-C(10A)	1.543(5)	C(19A)-C(6A)-C(7A)	121.4(3)
C(9A)-C(14A)	1.558(5)	C(6A)-C(7A)-C(8A)	110.8(3)
C(10A)-C(11A)	1.525(5)	C(7A)-C(8A)-C(17A)	110.6(3)
C(11A)-C(12A)	1.515(5)	C(7A)-C(8A)-C(9A)	115.2(3)
C(12A)-C(13A)	1.537(5)	C(17A)-C(8A)-C(9A)	114.5(3)
C(12A)-I(12A)	2.198(3)	C(25A)-C(9A)-C(10A)	108.1(3)
C(13A)-C(26A)	1.530(5)	C(25A)-C(9A)-C(14A)	115.0(3)
C(13A)-C(27A)	1.539(5)	C(10A)-C(9A)-C(14A)	108.0(3)
C(13A)-C(14A)	1.567(5)	C(25A)-C(9A)-C(8A)	112.6(3)
C(14A)-C(15A)	1.540(5)	C(10A)-C(9A)-C(8A)	107.4(3)
C(15A)-C(16A)	1.527(5)	C(14A)-C(9A)-C(8A)	105.5(3)
C(16A)-C(17A)	1.515(5)	C(11A)-C(10A)-C(9A)	112.7(3)
C(17A)-O(18A)	1.474(4)	C(12A)-C(11A)-C(10A)	110.3(3)
C(17A)-C(28A)	1.520(5)	C(11A)-C(12A)-C(13A)	115.2(3)
O(18A)-C(19A)	1.352(4)	C(11A)-C(12A)-I(12A)	107.4(2)
C(19A)-C(20A)	1.404(5)	C(13A)-C(12A)-I(12A)	113.3(2)
C(20A)-C(21A)	1.370(5)	C(26A)-C(13A)-C(12A)	113.1(3)
C(21A)-C(22A)	1.410(5)	C(26A)-C(13A)-C(27A)	108.0(3)
C(21A)-C(29)	1.501(5)	C(12A)-C(13A)-C(27A)	108.3(3)
O(1B)-C(1B)	1.209(5)	C(26A)-C(13A)-C(14A)	113.4(3)
C(1B)-O(2B)	1.356(6)	C(12A)-C(13A)-C(14A)	105.4(3)
C(1B)-C(22B)	1.481(6)	C(27A)-C(13A)-C(14A)	108.5(3)
O(2B)-C(3B)	1.433(5)	C(15A)-C(14A)-C(9A)	110.2(3)
C(3B)-O(4B)	1.428(4)	C(15A)-C(14A)-C(13A)	113.8(3)
C(3B)-C(23B)	1.507(6)	C(9A)-C(14A)-C(13A)	117.5(3)
C(3B)-C(24B)	1.515(5)	C(16A)-C(15A)-C(14A)	110.5(3)
O(4B)-C(5B)	1.371(5)	C(17A)-C(16A)-C(15A)	112.6(3)

APPENDIX A. APPENDIX: X-RAY CRYSTAL DATA

C(5B)-C(22B)	1.397(5)	O(18A)-C(17A)-C(16A)	103.0(3)
C(5B)-C(6B)	1.406(5)	O(18A)-C(17A)-C(28A)	106.6(3)
C(6B)-C(19B)	1.382(5)	C(16A)-C(17A)-C(28A)	112.6(3)
C(6B)-C(7B)	1.505(5)	O(18A)-C(17A)-C(8A)	107.4(3)
C(7B)-C(8B)	1.537(5)	C(16A)-C(17A)-C(8A)	110.0(3)
C(8B)-C(17B)	1.541(5)	C(28A)-C(17A)-C(8A)	116.2(3)
C(8B)-C(9B)	1.567(5)	C(19A)-O(18A)-C(17A)	116.4(2)
C(9B)-C(10B)	1.537(5)	O(18A)-C(19A)-C(6A)	123.0(3)
C(9B)-C(25B)	1.551(5)	O(18A)-C(19A)-C(20A)	115.7(3)
C(9B)-C(14B)	1.557(5)	C(6A)-C(19A)-C(20A)	121.3(3)
C(10B)-C(11B)	1.528(5)	C(21A)-C(20A)-C(19A)	121.6(3)
C(11B)-C(12B)	1.511(5)	C(20A)-C(21A)-C(22A)	118.6(3)
C(12B)-C(13B)	1.536(5)	C(20A)-C(21A)-C(29)	118.4(3)
C(12B)-I(12B)	2.199(3)	C(22A)-C(21A)-C(29)	123.0(4)
C(13B)-C(26B)	1.529(5)	C(5A)-C(22A)-C(21A)	118.4(3)
C(13B)-C(27B)	1.537(5)	C(5A)-C(22A)-C(1A)	118.6(3)
C(13B)-C(14B)	1.568(5)	C(21A)-C(22A)-C(1A)	122.9(3)
C(14B)-C(15B)	1.544(5)	O(1B)-C(1B)-O(2B)	118.2(4)
C(15B)-C(16B)	1.527(5)	O(1B)-C(1B)-C(22B)	125.2(5)
C(16B)-C(17B)	1.519(5)	O(2B)-C(1B)-C(22B)	116.6(4)
C(17B)-O(18B)	1.468(4)	C(1B)-O(2B)-C(3B)	119.0(3)
C(17B)-C(28B)	1.514(5)	O(4B)-C(3B)-O(2B)	110.0(3)
O(18B)-C(19B)	1.365(4)	O(4B)-C(3B)-C(23B)	106.6(3)
C(19B)-C(20B)	1.391(5)	O(2B)-C(3B)-C(23B)	105.4(3)
C(20B)-C(21B)	1.381(6)	O(4B)-C(3B)-C(24B)	110.6(3)
C(21B)-C(22B)	1.403(6)	O(2B)-C(3B)-C(24B)	109.8(3)
C(21B)-C(29B)	1.509(5)	C(23B)-C(3B)-C(24B)	114.2(4)
		C(5B)-O(4B)-C(3B)	114.2(3)
		O(4B)-C(5B)-C(22B)	120.3(3)
		O(4B)-C(5B)-C(6B)	116.8(3)
		C(22B)-C(5B)-C(6B)	122.9(4)
		C(19B)-C(6B)-C(5B)	115.8(3)
		C(19B)-C(6B)-C(7B)	122.5(3)
		C(5B)-C(6B)-C(7B)	121.7(3)
		C(6B)-C(7B)-C(8B)	111.0(3)
		C(7B)-C(8B)-C(17B)	111.0(3)
		C(7B)-C(8B)-C(9B)	115.1(3)
		C(17B)-C(8B)-C(9B)	114.6(3)
		C(10B)-C(9B)-C(25B)	108.2(3)
		C(10B)-C(9B)-C(14B)	108.1(3)
		C(25B)-C(9B)-C(14B)	114.2(3)
		C(10B)-C(9B)-C(8B)	108.3(3)
		C(25B)-C(9B)-C(8B)	112.4(3)
		C(14B)-C(9B)-C(8B)	105.4(3)
		C(11B)-C(10B)-C(9B)	112.7(3)
		C(12B)-C(11B)-C(10B)	110.4(3)
		C(11B)-C(12B)-C(13B)	114.6(3)

C(11B)-C(12B)-I(12B)	108.3(2)
C(13B)-C(12B)-I(12B)	113.1(2)
C(26B)-C(13B)-C(12B)	113.0(3)
C(26B)-C(13B)-C(27B)	108.4(3)
C(12B)-C(13B)-C(27B)	108.5(3)
C(26B)-C(13B)-C(14B)	113.1(3)
C(12B)-C(13B)-C(14B)	105.2(3)
C(27B)-C(13B)-C(14B)	108.4(3)
C(15B)-C(14B)-C(9B)	110.5(3)
C(15B)-C(14B)-C(13B)	113.8(3)
C(9B)-C(14B)-C(13B)	118.0(3)
C(16B)-C(15B)-C(14B)	110.2(3)
C(17B)-C(16B)-C(15B)	111.7(3)
O(18B)-C(17B)-C(28B)	106.3(3)
O(18B)-C(17B)-C(16B)	103.0(3)
C(28B)-C(17B)-C(16B)	112.4(3)
O(18B)-C(17B)-C(8B)	107.8(3)
C(28B)-C(17B)-C(8B)	116.7(3)
C(16B)-C(17B)-C(8B)	109.6(3)
C(19B)-O(18B)-C(17B)	116.5(3)
O(18B)-C(19B)-C(6B)	121.8(3)
O(18B)-C(19B)-C(20B)	116.0(4)
C(6B)-C(19B)-C(20B)	122.2(4)
C(21B)-C(20B)-C(19B)	121.5(4)
C(20B)-C(21B)-C(22B)	118.1(4)
C(20B)-C(21B)-C(29B)	118.0(4)
C(22B)-C(21B)-C(29B)	123.9(4)
C(5B)-C(22B)-C(21B)	119.3(4)
C(5B)-C(22B)-C(1B)	117.6(4)
C(21B)-C(22B)-C(1B)	123.1(4)

**2,2,5,7a,11,11-Hexamethyl-7a,8,10,11,11a,12-hexahydro-4*H*,9*H*-
[1,3]dioxino[4,5-*a*]xanthen-4-one**

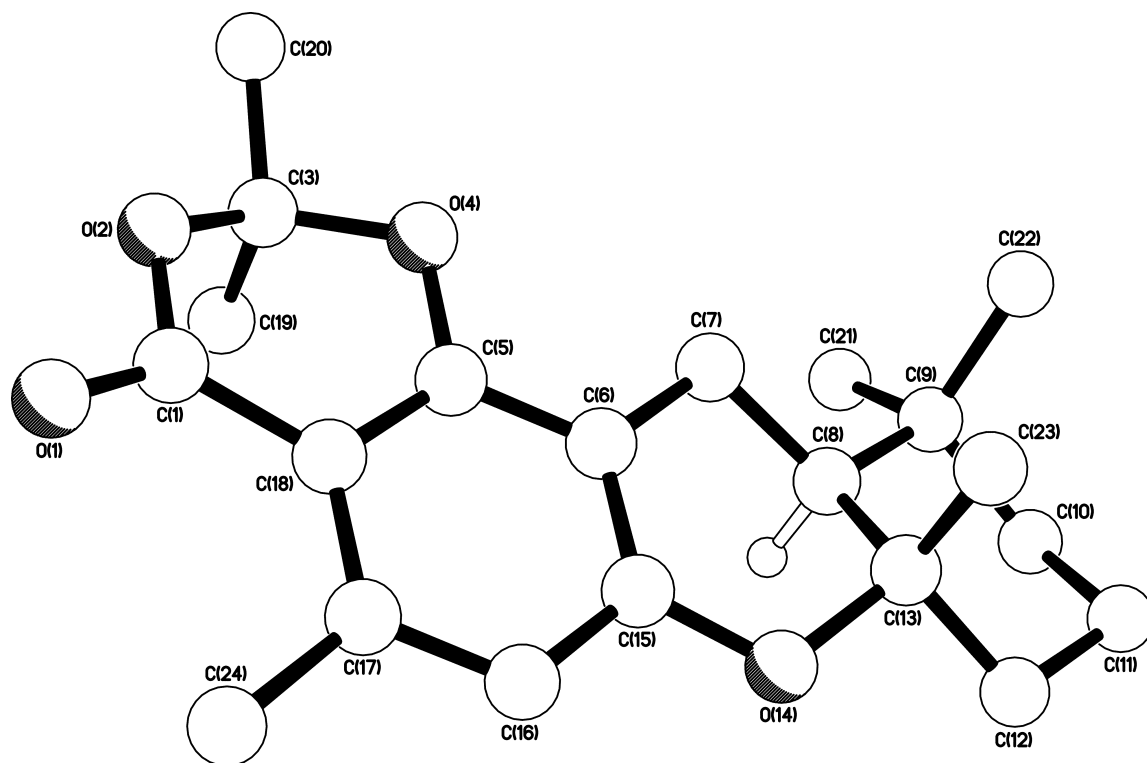


Figure A.11: X-Ray crystal structure of meroterpenoid **195**.

Table A.21: Crystal data and structure refinement for meroterpenoid **195**.

Identification code	AB1612
Formula	C ₂₁ H ₂₈ O ₄
Formula weight	344.43
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, P2 ₁ /n
Unit cell dimensions	a = 11.1181(7) Å α = 90° b = 12.8001(6) Å β = 110.718(7)° c = 13.9682(7) Å γ = 90°
Volume, Z	1859.30(19) Å ³ , 4
Density (calculated)	1.230 Mg/m ³
Absorption coefficient	0.084 mm ⁻¹
F(000)	744
Crystal colour / morphology	Colourless tablets
Crystal size	0.42 × 0.22 × 0.04 mm ³
q range for data collection	2.523 to 28.074°
Index ranges	-14 ≤ h ≤ 10, -16 ≤ k ≤ 9, -17 ≤ l ≤ 17
Reflns collected / unique	6444 / 3715 [R(int) = 0.0226]
Reflns observed [F > 4s(F)]	2712
Absorption correction	Analytical
Max. and min. transmission	0.997 and 0.974
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3715 / 0 / 232
Goodness-of-fit on F²	1.043
Final R indices [F > 4s(F)]	R1 = 0.0460, wR2 = 0.0929
R indices (all data)	R1 = 0.0721, wR2 = 0.1055
Largest diff. peak, hole	0.182, -0.191 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table A.22: Bond lengths [Å] and angles [°] for meroterpenoid **195**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1)-C(1)	1.2082(18)	O(1)-C(1)-O(2)	117.20(14)
C(1)-O(2)	1.3620(19)	O(1)-C(1)-C(18)	126.36(15)
C(1)-C(18)	1.465(2)	O(2)-C(1)-C(18)	116.36(13)
O(2)-C(3)	1.4442(17)	C(1)-O(2)-C(3)	119.17(12)
C(3)-O(4)	1.4294(17)	O(4)-C(3)-O(2)	109.38(12)
C(3)-C(20)	1.503(2)	O(4)-C(3)-C(20)	106.66(12)
C(3)-C(19)	1.505(2)	O(2)-C(3)-C(20)	105.87(12)
O(4)-C(5)	1.3703(18)	O(4)-C(3)-C(19)	110.81(12)
C(5)-C(6)	1.388(2)	O(2)-C(3)-C(19)	110.52(12)
C(5)-C(18)	1.395(2)	C(20)-C(3)-C(19)	113.39(13)
C(6)-C(15)	1.385(2)	C(5)-O(4)-C(3)	114.12(12)
C(6)-C(7)	1.505(2)	O(4)-C(5)-C(6)	116.37(13)
C(7)-C(8)	1.527(2)	O(4)-C(5)-C(18)	120.28(13)
C(8)-C(13)	1.538(2)	C(6)-C(5)-C(18)	123.32(15)
C(8)-C(9)	1.551(2)	C(15)-C(6)-C(5)	116.40(14)
C(9)-C(21)	1.528(2)	C(15)-C(6)-C(7)	121.55(14)
C(9)-C(22)	1.536(2)	C(5)-C(6)-C(7)	121.98(14)
C(9)-C(10)	1.540(2)	C(6)-C(7)-C(8)	109.70(13)
C(10)-C(11)	1.522(2)	C(7)-C(8)-C(13)	109.93(12)
C(11)-C(12)	1.524(2)	C(7)-C(8)-C(9)	114.85(13)
C(12)-C(13)	1.519(2)	C(13)-C(8)-C(9)	115.96(12)
C(13)-O(14)	1.4727(18)	C(21)-C(9)-C(22)	107.79(13)
C(13)-C(23)	1.518(2)	C(21)-C(9)-C(10)	108.04(13)
O(14)-C(15)	1.3602(17)	C(22)-C(9)-C(10)	110.42(13)
C(15)-C(16)	1.398(2)	C(21)-C(9)-C(8)	108.53(12)
C(16)-C(17)	1.378(2)	C(22)-C(9)-C(8)	114.34(13)
C(17)-C(18)	1.412(2)	C(10)-C(9)-C(8)	107.55(13)
C(17)-C(24)	1.508(2)	C(11)-C(10)-C(9)	113.41(12)
		C(10)-C(11)-C(12)	110.28(13)
		C(13)-C(12)-C(11)	111.37(14)
		O(14)-C(13)-C(23)	106.39(12)
		O(14)-C(13)-C(12)	103.62(13)
		C(23)-C(13)-C(12)	111.66(13)
		O(14)-C(13)-C(8)	107.39(11)
		C(23)-C(13)-C(8)	116.20(14)
		C(12)-C(13)-C(8)	110.60(12)
		C(15)-O(14)-C(13)	117.63(12)
		O(14)-C(15)-C(6)	122.80(14)
		O(14)-C(15)-C(16)	115.36(14)
		C(6)-C(15)-C(16)	121.80(14)
		C(17)-C(16)-C(15)	121.18(16)
		C(16)-C(17)-C(18)	118.28(14)
		C(16)-C(17)-C(24)	118.92(16)

C(18)-C(17)-C(24)	122.79(14)
C(5)-C(18)-C(17)	118.95(14)
C(5)-C(18)-C(1)	117.98(15)
C(17)-C(18)-C(1)	122.87(14)

(2*S*,4*aR*,5*S*,8*aR*)-5-((6-Hydroxy-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1,1,4*a*-trimethyl-6-methylenedecahydronaphthalen-2-yl acetate

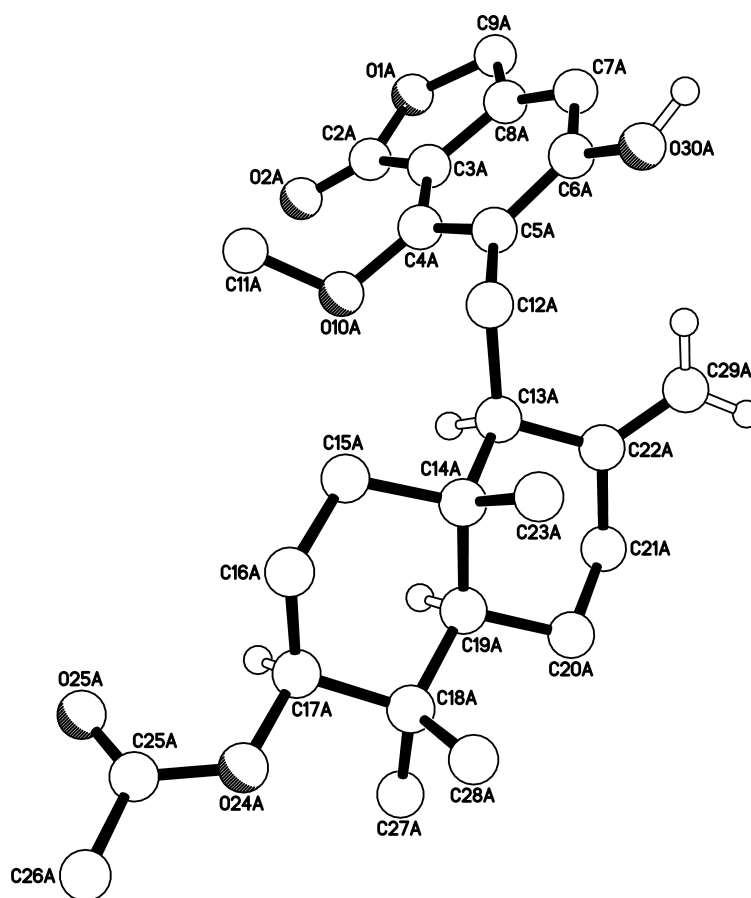


Figure A.12: X-Ray crystal structure of phenol **207**.

Table A.23: Crystal data and structure refinement for phenol **207**.

Identification code	AB1816
Formula	C ₂₆ H ₃₄ O ₆
Formula weight	442.53
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.54184 Å
Crystal system, space group	Monoclinic, P2 ₁ /n
Unit cell dimensions	a = 12.0357(2) Å $\alpha = 90^\circ$ b = 18.1671(4) Å $\beta = 91.8761(16)^\circ$ c = 21.3736(4) Å $\gamma = 90^\circ$
Volume, Z	4670.92(16) Å ³ , 8
Density (calculated)	1.259 Mg/m ³
Absorption coefficient	0.717 mm ⁻¹
F(000)	1904
Crystal colour / morphology	Colourless plates
Crystal size	0.210 × 0.098 × 0.021 mm ³
q range for data collection	4.139 to 73.440°
Index ranges	-14 ≤ h ≤ 14, -20 ≤ k ≤ 21, -16 ≤ l ≤ 26
Reflns collected / unique	15803 / 8939 [R(int) = 0.0360]
Reflns observed [F > 4s(F)]	5893
Absorption correction	Analytical
Max. and min. transmission	0.985 and 0.913
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8939 / 278 / 701
Goodness-of-fit on F²	1.01
Final R indices [F > 4s(F)]	R1 = 0.0538, wR2 = 0.1226
R indices (all data)	R1 = 0.0905, wR2 = 0.1446
Largest diff. peak, hole	0.413, -0.220 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.004

Table A.24: Bond lengths [Å] and angles [°] for phenol **207**.

Bond	Bond lengths [Å]	Bond	Bond angles [°]
O(1A)-C(2A)	1.385(6)	C(2A)-O(1A)-C(9A)	111.2(3)
O(1A)-C(9A)	1.440(6)	O(2A)-C(2A)-O(1A)	120.9(4)
C(2A)-O(2A)	1.200(6)	O(2A)-C(2A)-C(3A)	132.8(5)
C(2A)-C(3A)	1.463(5)	O(1A)-C(2A)-C(3A)	106.3(4)
C(3A)-C(8A)	1.384(6)	C(8A)-C(3A)-C(4A)	119.5(3)
C(3A)-C(4A)	1.398(6)	C(8A)-C(3A)-C(2A)	110.2(4)
C(4A)-O(10A)	1.393(5)	C(4A)-C(3A)-C(2A)	130.3(5)
C(4A)-C(5A)	1.395(5)	O(10A)-C(4A)-C(5A)	116.9(4)
C(5A)-C(6A)	1.412(5)	O(10A)-C(4A)-C(3A)	121.5(4)
C(5A)-C(12A)	1.507(4)	C(5A)-C(4A)-C(3A)	121.5(4)
C(6A)-O(30A)	1.352(5)	C(4A)-C(5A)-C(6A)	116.0(4)
C(6A)-C(7A)	1.393(5)	C(4A)-C(5A)-C(12A)	122.2(4)
C(7A)-C(8A)	1.373(6)	C(6A)-C(5A)-C(12A)	121.6(4)
C(8A)-C(9A)	1.494(4)	O(30A)-C(6A)-C(7A)	120.2(4)
O(10A)-C(11A)	1.430(5)	O(30A)-C(6A)-C(5A)	116.7(4)
O(1')-C(2')	1.373(17)	C(7A)-C(6A)-C(5A)	123.1(4)
O(1')-C(9')	1.409(17)	C(8A)-C(7A)-C(6A)	118.2(4)
C(2')-O(2')	1.181(17)	C(7A)-C(8A)-C(3A)	121.2(3)
C(2')-C(3')	1.464(16)	C(7A)-C(8A)-C(9A)	131.6(4)
C(3')-C(8')	1.355(15)	C(3A)-C(8A)-C(9A)	107.2(4)
C(3')-C(4')	1.390(15)	O(1A)-C(9A)-C(8A)	105.1(4)
C(4')-O(10')	1.389(14)	C(4A)-O(10A)-C(11A)	115.7(3)
C(4')-C(5')	1.404(15)	C(2')-O(1')-C(9')	112.4(14)
C(5')-C(6')	1.404(16)	O(2')-C(2')-O(1')	124.3(18)
C(5')-C(12A)	1.497(15)	O(2')-C(2')-C(3')	129.3(19)
C(6')-O(30')	1.367(17)	O(1')-C(2')-C(3')	106.3(13)
C(6')-C(7')	1.399(16)	C(8')-C(3')-C(4')	121.6(14)
C(7')-C(8')	1.370(16)	C(8')-C(3')-C(2')	109.4(13)
C(8')-C(9')	1.513(16)	C(4')-C(3')-C(2')	128.5(15)
O(10')-C(11')	1.439(17)	O(10')-C(4')-C(3')	128.0(14)
C(12A)-C(13A)	1.542(3)	O(10')-C(4')-C(5')	116.1(13)
C(13A)-C(22A)	1.515(3)	C(3')-C(4')-C(5')	115.1(13)
C(13A)-C(14A)	1.569(3)	C(4')-C(5')-C(6')	122.0(14)
C(14A)-C(23A)	1.540(3)	C(4')-C(5')-C(12A)	114.1(13)
C(14A)-C(15A)	1.541(3)	C(6')-C(5')-C(12A)	122.7(15)
C(14A)-C(19A)	1.557(3)	O(30')-C(6')-C(7')	121(2)
C(15A)-C(16A)	1.532(3)	O(30')-C(6')-C(5')	115.3(19)
C(16A)-C(17A)	1.506(3)	C(7')-C(6')-C(5')	120.2(18)
C(17A)-O(24A)	1.470(3)	C(8')-C(7')-C(6')	116.0(17)
C(17A)-C(18A)	1.530(3)	C(3')-C(8')-C(7')	123.7(15)
C(18A)-C(28A)	1.532(3)	C(3')-C(8')-C(9')	108.1(13)
C(18A)-C(27A)	1.534(3)	C(7')-C(8')-C(9')	128.1(17)
C(18A)-C(19A)	1.564(3)	O(1')-C(9')-C(8')	103.8(13)

C(19A)-C(20A)	1.539(3)	C(4')-O(10')-C(11')	114.8(18)
C(20A)-C(21A)	1.542(4)	C(5')-C(12A)-C(13A)	119.7(14)
C(21A)-C(22A)	1.484(4)	C(5A)-C(12A)-C(13A)	114.2(3)
C(22A)-C(29A)	1.333(4)	C(22A)-C(13A)-C(12A)	114.56(19)
O(24A)-C(25A)	1.324(3)	C(22A)-C(13A)-C(14A)	110.41(19)
C(25A)-O(25A)	1.214(3)	C(12A)-C(13A)-C(14A)	112.99(18)
C(25A)-C(26A)	1.494(3)	C(23A)-C(14A)-C(15A)	109.71(19)
O(1B)-C(2B)	1.381(8)	C(23A)-C(14A)-C(19A)	114.3(2)
O(1B)-C(9B)	1.441(8)	C(15A)-C(14A)-C(19A)	107.62(17)
C(2B)-O(2B)	1.208(8)	C(23A)-C(14A)-C(13A)	109.01(17)
C(2B)-C(3B)	1.448(6)	C(15A)-C(14A)-C(13A)	108.84(18)
C(3B)-C(8B)	1.388(7)	C(19A)-C(14A)-C(13A)	107.20(17)
C(3B)-C(4B)	1.402(7)	C(16A)-C(15A)-C(14A)	112.95(19)
C(4B)-C(5B)	1.388(8)	C(17A)-C(16A)-C(15A)	110.02(19)
C(4B)-O(10B)	1.403(7)	O(24A)-C(17A)-C(16A)	108.98(18)
C(5B)-C(6B)	1.415(7)	O(24A)-C(17A)-C(18A)	106.56(18)
C(5B)-C(12B)	1.504(6)	C(16A)-C(17A)-C(18A)	114.48(19)
C(6B)-O(30B)	1.356(7)	C(17A)-C(18A)-C(28A)	111.6(2)
C(6B)-C(7B)	1.388(6)	C(17A)-C(18A)-C(27A)	107.57(19)
C(7B)-C(8B)	1.380(7)	C(28A)-C(18A)-C(27A)	107.7(2)
C(8B)-C(9B)	1.505(6)	C(17A)-C(18A)-C(19A)	106.02(18)
O(10B)-C(11B)	1.438(7)	C(28A)-C(18A)-C(19A)	115.16(19)
O(1'')-C(2'')	1.362(12)	C(27A)-C(18A)-C(19A)	108.47(19)
O(1'')-C(9'')	1.435(13)	C(20A)-C(19A)-C(14A)	111.50(18)
C(2'')-O(2'')	1.186(12)	C(20A)-C(19A)-C(18A)	112.8(2)
C(2'')-C(3'')	1.460(11)	C(14A)-C(19A)-C(18A)	116.96(18)
C(3'')-C(8'')	1.364(11)	C(19A)-C(20A)-C(21A)	110.3(2)
C(3'')-C(4'')	1.397(11)	C(22A)-C(21A)-C(20A)	110.9(2)
C(4'')-O(10'')	1.372(10)	C(29A)-C(22A)-C(21A)	121.0(3)
C(4'')-C(5'')	1.398(12)	C(29A)-C(22A)-C(13A)	125.1(3)
C(5'')-C(6'')	1.424(12)	C(21A)-C(22A)-C(13A)	113.8(2)
C(5'')-C(12B)	1.519(11)	C(25A)-O(24A)-C(17A)	117.88(18)
C(6'')-O(30'')	1.362(11)	O(25A)-C(25A)-O(24A)	123.2(2)
C(6'')-C(7'')	1.394(12)	O(25A)-C(25A)-C(26A)	125.2(2)
C(7'')-C(8'')	1.376(11)	O(24A)-C(25A)-C(26A)	111.5(2)
C(8'')-C(9'')	1.509(12)	C(2B)-O(1B)-C(9B)	111.0(4)
O(10'')-C(11'')	1.410(11)	O(2B)-C(2B)-O(1B)	119.4(5)
C(12B)-C(13B)	1.543(3)	O(2B)-C(2B)-C(3B)	133.4(7)
C(13B)-C(22B)	1.516(3)	O(1B)-C(2B)-C(3B)	107.2(6)
C(13B)-C(14B)	1.570(3)	C(8B)-C(3B)-C(4B)	118.7(5)
C(14B)-C(15B)	1.536(3)	C(8B)-C(3B)-C(2B)	110.0(5)
C(14B)-C(23B)	1.540(3)	C(4B)-C(3B)-C(2B)	131.2(6)
C(14B)-C(19B)	1.558(3)	C(5B)-C(4B)-C(3B)	121.8(6)
C(15B)-C(16B)	1.525(3)	C(5B)-C(4B)-O(10B)	117.9(5)
C(16B)-C(17B)	1.508(4)	C(3B)-C(4B)-O(10B)	120.2(5)
C(17B)-O(24B)	1.470(3)	C(4B)-C(5B)-C(6B)	116.5(5)
C(17B)-C(18B)	1.529(3)	C(4B)-C(5B)-C(12B)	122.4(6)

APPENDIX A. APPENDIX: X-RAY CRYSTAL DATA

C(18B)-C(27B)	1.536(4)	C(6B)-C(5B)-C(12B)	121.0(6)
C(18B)-C(28B)	1.537(3)	O(30B)-C(6B)-C(7B)	120.1(5)
C(18B)-C(19B)	1.560(3)	O(30B)-C(6B)-C(5B)	116.8(5)
C(19B)-C(20B)	1.537(3)	C(7B)-C(6B)-C(5B)	123.1(6)
C(20B)-C(21B)	1.538(3)	C(8B)-C(7B)-C(6B)	117.6(5)
C(21B)-C(22B)	1.498(4)	C(7B)-C(8B)-C(3B)	122.1(4)
C(22B)-C(29B)	1.331(3)	C(7B)-C(8B)-C(9B)	130.8(5)
O(24B)-C(25B)	1.320(3)	C(3B)-C(8B)-C(9B)	107.1(5)
C(25B)-O(25B)	1.209(3)	O(1B)-C(9B)-C(8B)	104.6(5)
C(25B)-C(26B)	1.490(4)	C(4B)-O(10B)-C(11B)	117.0(5)
		C(2'')-O(1'')-C(9'')	112.5(8)
		O(2'')-C(2'')-O(1'')	122.3(9)
		O(2'')-C(2'')-C(3'')	130.9(9)
		O(1'')-C(2'')-C(3'')	106.8(9)
		C(8'')-C(3'')-C(4'')	119.3(8)
		C(8'')-C(3'')-C(2'')	109.3(8)
		C(4'')-C(3'')-C(2'')	131.4(9)
		O(10'')-C(4'')-C(3'')	123.7(8)
		O(10'')-C(4'')-C(5'')	116.7(9)
		C(3'')-C(4'')-C(5'')	119.7(9)
		C(4'')-C(5'')-C(6'')	118.0(10)
		C(4'')-C(5'')-C(12B)	120.4(9)
		C(6'')-C(5'')-C(12B)	121.5(9)
		O(30'')-C(6'')-C(7'')	122.8(11)
		O(30'')-C(6'')-C(5'')	114.6(10)
		C(7'')-C(6'')-C(5'')	122.6(10)
		C(8'')-C(7'')-C(6'')	115.6(9)
		C(3'')-C(8'')-C(7'')	124.7(8)
		C(3'')-C(8'')-C(9'')	108.5(9)
		C(7'')-C(8'')-C(9'')	126.7(10)
		O(1'')-C(9'')-C(8'')	103.0(9)
		C(4'')-O(10'')-C(11'')	114.2(10)
		C(5B)-C(12B)-C(13B)	116.5(7)
		C(5'')-C(12B)-C(13B)	114.2(14)
		C(22B)-C(13B)-C(12B)	114.82(18)
		C(22B)-C(13B)-C(14B)	109.43(18)
		C(12B)-C(13B)-C(14B)	113.57(18)
		C(15B)-C(14B)-C(23B)	109.63(19)
		C(15B)-C(14B)-C(19B)	107.79(17)
		C(23B)-C(14B)-C(19B)	114.27(19)
		C(15B)-C(14B)-C(13B)	109.25(18)
		C(23B)-C(14B)-C(13B)	108.97(17)
		C(19B)-C(14B)-C(13B)	106.80(17)
		C(16B)-C(15B)-C(14B)	113.5(2)
		C(17B)-C(16B)-C(15B)	110.3(2)
		O(24B)-C(17B)-C(16B)	108.73(19)
		O(24B)-C(17B)-C(18B)	106.75(19)

C(16B)-C(17B)-C(18B)	114.30(19)
C(17B)-C(18B)-C(27B)	108.2(2)
C(17B)-C(18B)-C(28B)	111.1(2)
C(27B)-C(18B)-C(28B)	107.7(2)
C(17B)-C(18B)-C(19B)	106.15(18)
C(27B)-C(18B)-C(19B)	109.0(2)
C(28B)-C(18B)-C(19B)	114.57(19)
C(20B)-C(19B)-C(14B)	111.87(18)
C(20B)-C(19B)-C(18B)	112.90(19)
C(14B)-C(19B)-C(18B)	116.73(18)
C(19B)-C(20B)-C(21B)	111.4(2)
C(22B)-C(21B)-C(20B)	110.4(2)
C(29B)-C(22B)-C(21B)	121.3(2)
C(29B)-C(22B)-C(13B)	125.5(2)
C(21B)-C(22B)-C(13B)	112.94(19)
C(25B)-O(24B)-C(17B)	118.7(2)
O(25B)-C(25B)-O(24B)	122.8(2)
O(25B)-C(25B)-C(26B)	125.0(2)
O(24B)-C(25B)-C(26B)	112.1(2)

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