Studies Towards The Novel Synthesis Of Benzoisochromane Quinone Polyketides

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Preface

The research in this thesis is, to the best of my knowledge, original except where due reference has been made.

O. J. S. McGaw

September 2014

Abstract

Granaticin is a structurally unique member of the benzoisochromane quinone (BIQ) family of antibiotics. The molecule and its derivative exhibit a sugar moiety fusted to the naphthazarin core, only exhibited by one other natural compound, by a C-C glycosidic bond and an aldol like bond. The mechanism of enzymatic attachment of this substituent is currently unknown.

This project aimed to devise a novel and elegant synthesis towards the granaticin aglycone and other benzoisochromane quinone natural compounds with the long term aim of discerning the mechanism of glycosylation.

This thesis shows a novel route for the synthesis of highly substituted isochromane and isochromane quinone compounds towards the eventual synthesis of the desired natural molecules.

Acknowledgements

First and foremost, I would like to thank Dr G. Richard Stephenson and Dr Rebecca J. M. Goss for their guidance and support throughout the project. I would like to thank them for all the experiences and opportunities they have granted me throughout the course of this Ph.D. I would also like to thank Prof. Philip C. Bulman Page for his immense knowledge and advice on epoxides. I would like Dr Xavier Franck for the time I spent in Rouen, for his endless supply of ideas, his obsessive passion towards synthesis and the inspiration that it brings. I would also like to thank The University of East Anglia and IRCOF Rouen for providing the facilities and training necessary to conduct this research. I would like to extend my gratitude to the INTERREG project for funding the research.

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Contents

Abbreviations

$(DHQD)_2$-PHAL – $(dihydroquinidine)_2$-phalizine

Ac – acetate

AD – asymmetric dihydroxylation

AIBN – azobisisobutylnitrile

Ar – aromatic

BAIB – *bis*acetoxyiodobenzene

BINAP – binaphthalene

BIQ – benzoisochromanequinone

Bn – benzyl

Bz – benzoyl

C – Celsius

Calc. – calculated

CAN – ceric ammonium nitrate ($cerium^{IV}$ ammonium nitrate)

1CBz – carboxybenzyl

cm – centimeters

CoA – coenzyme A

Conc. – concentrated

CSA – camphor sulfonic acid

d – doublet

dba – dibenxylideneacetone

DBU – 1,8-diazabicycloundec-7-ene

DCC – *N*,*N*'-dihcyclohexylcarbodiamide

DDQ – 2,3-dichloro-5,6-dicyanoquinone

DIBAL – diissobutylaluminium

DIPEA – diisopropylethylamine

DMAP – *N*,*N*-dimethylpyridine

DMF – dimethylformamide

DMSO – dimethylsulfoxide

dppf – 1,1'-*bis*(diphenylphosphino)ferrocene

ESI – electron spray ionisation

Et – ethyl

g – gram

HMBC – heteronuclear multiple bond correlation

HRMS – high resolution mass spectrometry

hrs. – hours

HSQC – heteronuclear singular quantum correlation

imid. – imidazole

Ipc – isopinocamphyl

^{i}Pr – isopropyl

IR – infra red

LCMS – liquid chromatography mass spectrometry

LDA – lithium diisopropylamine

LRMS – low resolution mass spectrometry

m – *meta*

M – molar

m – multiplet

m.p. – melting point

MALDI – matrix assisted laser desorption/ionisation

*m*CPBA – *meta*chloroperbenzoic acid

Me – methyl

mg – miligram

mins. – minutes

mL – mililitre

mmol – milimole

MOM – methoxymethylene

Ms – mesyl

Mz – megahertz

NBS – *N*-bromosuccinamide

^{n}Bu – normal butyl

NMO – *N*-methylmorpholine oxide

NMR – nuclear magnetic resonance

NOE – nuclear Overhauser effect

NOSY – nuclear Overhauser effect spectroscopy

^{n}Pr – normal propyl

o – ortho

p – para

PCC – piridiniumchlorochromate

PG – protecting group

Ph – phenyl

pin – pinicol

Piv – pivaloyl

PMA – phosphomolybdic acid

PMB – *para*methoxybenzyl

PPM – parts per million

*p*TSA – *para*toluene sulfonic acid

Py. – pyridine

q – quartet

R – rectus

r.t. – room temperature

s – singlet

S – sinister

^{s}Bu – secondary butyl

t – triplet

TBAB – tetran-*N*-butylammonium bromide

TBAF – tetrabutylammonium fluoride

TBDPS – tertiarybutyldiphenylsilyl

TBS – tertiarybutyldimethylsilyl (TBDMS)

^{t}Bu – tertiary butyl

TEMPO – 2,2,6,6-tetramethylpipridin-1-yl oxide

TES – triethylsilyl

Tf – trifluorosulfonyl

TFA – trifluoroacetic acid

TFAA – trifluoroacetic anhydride

THF – tetrahydrofuran

TLC – thin layer chromatography

TMEDA – tetramethylethylenediamine

TMS – trimethylsilyl

TMTU – tetramethylthiourea

UV – ultra violate

1. Introduction

1.1 Natural Products

The term natural product is used to describe a chemical compound produced by living organisms. Natural products are classified depending on whether their biological activity is intended to affect the organism that produced the compound – primary metabolites; or an extraneous organism – secondary metabolites. Secondary metabolites are a main focus of many biological and chemical sciences due to their use as therapeutic agents. Natural products and natural product derived molecules account for almost 60% of all therapeutic agents (1981 - 2002) particularly as antibiotic (78%) and anticancer (66%) agents.[1,2]

Natural products and their synthesis form a major part of modern organic chemistry. Since the first total synthesis of urea in 1828 by Wohler[3] total synthesis has evolved into a complex and exact science which now employs a vast array of techniques and methodologies as varied as the molecules they are used to construct. Over the past 100 years organic chemistry has witnessed many landmark syntheses of highly complex natural products such as strychnine **1** (R. B. Woodward, 1954),[4] prostaglandin **2** (G. Stork, 1976),[5] erythronolide B **3** (E. J. Corey, 1978),[6] hirsutine **4** (D. P. Curran, 1986),[7] calicheamicin γ^{I} **5** (K. C. Nicolaou, 1992),[8] and taxol **6** (K. C. Nicolaou, 1994)[9] as well as many more. With the increasing occurrence of antibiotic resistant strains of bacteria, natural products total synthesis is an important discipline in organic chemistry and a necessity for the medicinal and biological sciences.

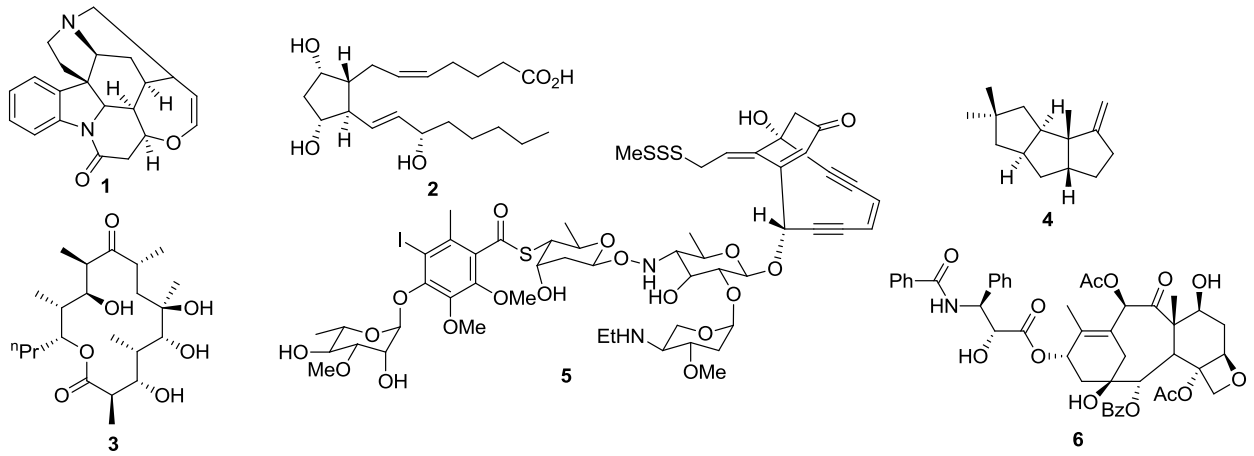


Figure 1.

2.1 Benzoisochromane quinones

Benzoisochromane quinone (BIQ) compounds, also referred to as pyranonaphthoquinones, are a common class of bioactive molecule usually isolated from the *Streptomyces* genus but have been isolated from a wide variety of other bacteria. BIQ compounds usually exhibit one of three skeletal forms. A pyranonaphtho-5,10-dione system is present in all three and frequently contain a γ-lactone ring **(3*S*, 4*R*)-8** and **(3*R*, 4*S*)-8** present at C3, C4 which always exhibit a *cis* fused ring system or as a dihydro analogue exhibiting a carboxylic acid chain **9** at the C3 position[10].

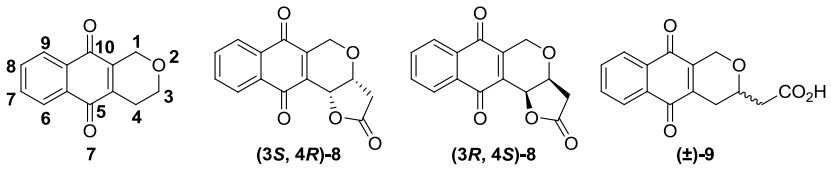
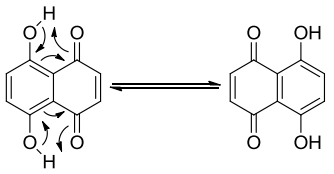


Figure 2: Skeletal structures of common BIQ compounds and ring numbering.

These BIQ natural products are biosynthesised by a type II polyketide synthase. This is an iterative process involving multiple acetyl-CoA and malonyl-CoA units to form a long chain polyketone. This then undergoes a series of eliminations to aromatize the compound and form the naphthoquinone back bone.[11, 12]

Many BIQ molecules contain a 5,8-hydroxylated naphthoquinone component, commonly referred to as naphthazarin **10**. This, in most cases, exhibits tautomerism[13, 14] (scheme 1) but is commonly drawn with the quinone ring on the right.



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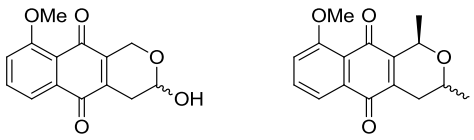
Scheme 1: Tautomerism of naphthazarin.

The simplest known benzoisochromane quinone is pychorubin **11** which exhibits cytotoxic activity against KB cancer cells.[15] Isolated in 1987[16] from *Psycotria rubra*, this compound simply contains a hydroxyl group at the C3 position giving the molecule a hemiacetal motif. Another simple example of this class of molecule is eleutherin **12** (*cis*) and isoeleutherin (*trans*) which were isolated in 1950[17] and 1951[18] respectively from *Eleutherine bulbosa*. Both of these compounds exhibit activity against *Pycococcus aureus* and *Streptococcus haemolyticus*.[17, 18] Another hemiacetal containing BIQ antibiotic is the highly oxygenated compound fusarubin. Unlike most BIQ natural compounds the more favored tautomer of this molecule exhibits the quinone ring of the naphthazarin core to the left of the molecule. This is due to electronic effects of the 7-methoxy substituent. Like other hemiacetal containing BIQ molecules, tautomerism occurs between the closed hydroxpyran ring and opened isomers.[14]



11 **12**

Figure 3.

A class of BIQ antibiotic containing this naphthazarin motif are the martinicins **13**, **14** isolated from *Fusarium martii* in 1963[19]. These again exhibit a C6 methoxy group but contain a dioxobicyclic ring system present at C1 and C3 of the pyran ring.

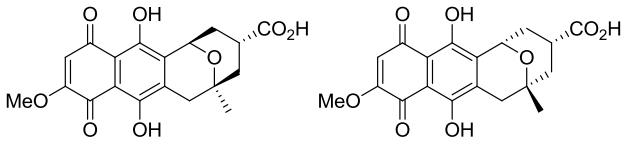


Figure 4.

Many pyranonaphthoquinone natural compounds contain only one hydroxyl group on the naphthoquinone ring system. This is normally present at the C9 position as is the case with the antibiotic kalafungin **15**. This tetracyclic molecule was first isolated in 1968 by Beregy *et al.*[20] and exhibits activity against a wide variety of bacteria, fungi, protozoa and yeast pathogens.[21] Like many compounds of this nature it has a *cis* relationship between the lactone ring present at C3/C4 and the C1 methyl substituent which is the more thermodynamically stable diastereoisomer as it reduces *pseudo* 1,3-diaxial interactions.

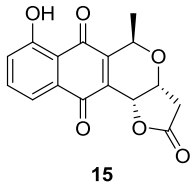


Figure 5.

A series of natural compounds similar to kalafungin are the nanaomycins **16**-**20** isolated from *Streptomyces rosa*.[22-25] Five analogues have been isolated of this class all exhibiting 1*S*, 3*R* (4*R*) stereochemistry. Nanaomycin A **16** and C **17** do not contain the lactone ring observed in kalafungin but a free carboxylic acid chain (A, $R_1 = CO_2H$) and primary amide chain (C, $R_1 = CONH_2$). Nanaomycin B **18** also lacks the presence of a lactone ring but differs as it has a hydroxylated quinone ring with the tertiary alcohol group present at the ring junction. Nanaomycin E **20** also contains a free carboxylic acid chain but, like some other BIQ natural molecules, has an epoxidised quinone ring. All the nanaomycins show broad spectrum antibiotic activity against gram positive bacteria.[26] The frenolicins **21**, **22** isolated from *Streptomyces fradiae*[27-30] also exhibit similar structural analogues. These molecules contain the same 1*R*, 3*S* (4*S*) stereogenicity as kalafungin but differ by the presence of a C1 n-propyl substituent as opposed to a methyl group.

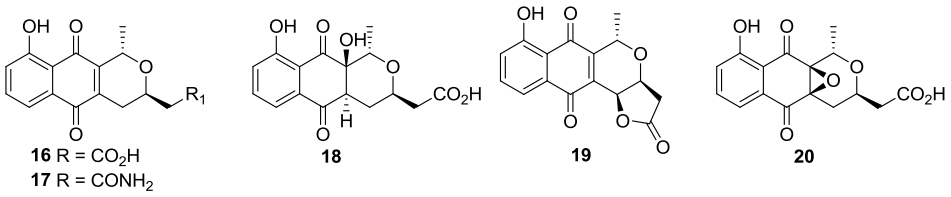


Figure 6: Nanaomycins A-E.

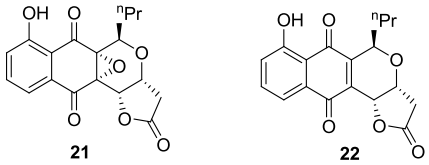


Figure 7: Frenolicin and deoxyfrenolicin.

A unique group of benzoisochromane quinone compounds are the griseusins **23**, **24** isolated in 1976 from *Streptomyces griseus.* These molecules contain a 1,7-dioxaspiro[5,5]undecane around the C1 position. The griseusins have only mild activity against gram positive bacteria.[30, 31]

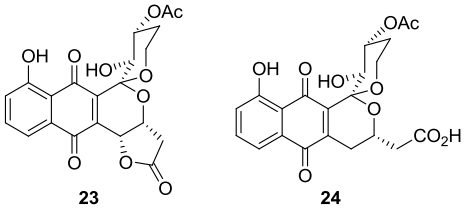


Figure 8: The grisusins.

Other than the granaticins **34**-**37**, there are few carbohydrate derived BIQ natural products. Medermycin **25**, isolated in 1976 from *Streptomyces tanashienis*,[32] contains a tertiary amino pyran ring attached at the C7 position to the juglone core of the molecule *via* a glycosidic bond. This antibiotic exhibits strong activity against gram positive bacteria and leukemia.[33]

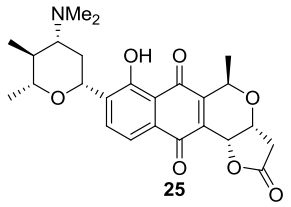


Figure 9: Merdermycin.

Several dimeric and *pseudo*dimeric benzoisochromane quinones have also been reported. The actinorhodins are one class of such dimers isolated from *Streptomyces coelicolor* and *Streptomyces lividens.* These highly coloured pigments are connected at the C7 position of the naphthazarin core. There are six individual actinorhodin analogues however **26** is the most common.[34-36]

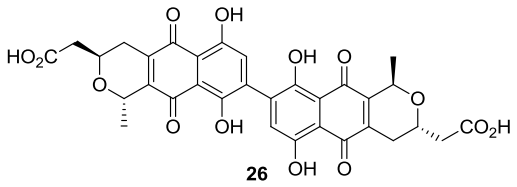


Figure 10: γ-actinorhodin.

One class of structurally simplistic dimers are the cardinalins **27**-**29**. Originally isolated from the toadstool *Dermocybe cardinalis*, these compounds show potent inhibition of leukemia cells. Only cardinalin 3 **29** is a true dimer exhibiting 1*S*, 3*S* methyl substituents, a C6 methoxy group and C8 hydroxyl moiety. Cardinalin 1 **27** contains hydrogenated quinone rings and a single reduced C5 carbonyl whereas cardinalin 2 **28** contains only a single hydrogenated quinone group. The cardinalins do not exhibit rotation around the centre of the molecule and are only isolated as the *R* enantiomer.[37]

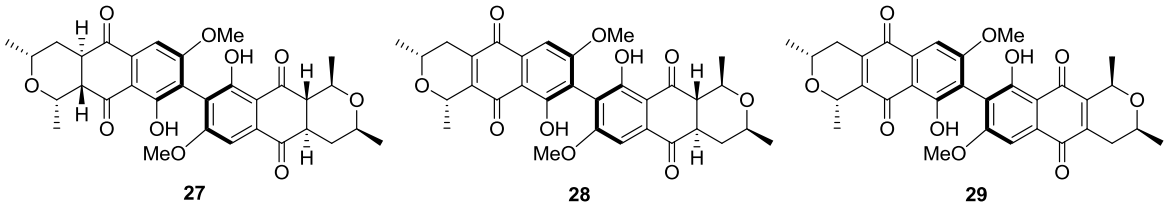


Figure 11: Cardinalin 1 ***27****, 2* ***28*** *and 3* ***29****.*

Another C_2 symmetric group of BIQ dimers are the crisamicins. One of the more recently isolated benzoisochromane quinone compounds (1986)[38] these natural compounds exhibit strong activity against melanoma cells and herpes simplex along with excellent activity against gram positive bacteria.[39] Crisamicin A **30** contains a pyranolactone bicyclic ring system with a methyl substituent present at the C1 position in the more thermodynamically favored *trans* configuration with regards to the γ-lactone. This pyran ring is fused to a juglone moiety which, unusually, has a hydroxyl group present at the C6 position unlike most BIQ compounds where the hydroxyl group is normally present at the C9 position the compound is dimerised by a carbon-carbon bond at the C8 position similar to many BIQ dimers.

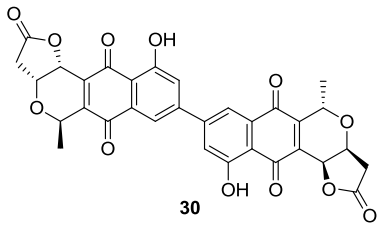


Figure 12: Crisamicin A.

More unusual dimer like benzoisochromane quinones have also been isolated such as the red pigment phenocyclinone **31**, isolated from *Streptomyces coelicolor* which has yet to have its absolute stereochemistry determined,[40] the rhododactynaphins **32** and xanthodactynaphins **33** isolated from the aphid *Dactynotusjacae*.[41]

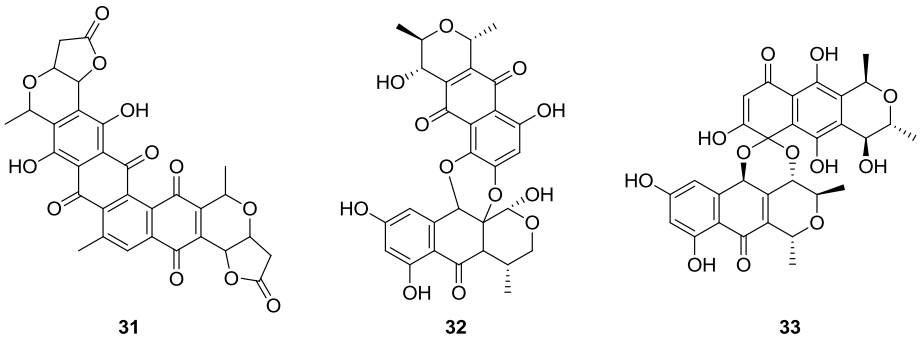


*Figure 13: Pseudodimeric BIQs phenocyclinone **31**, rhododactynaphins **32** and xanthodactynaphins **33**.*

2.1 Granaticin

Granaticin is a structurally unique member of the benzoisochromane quinone family of antibiotics as it has a fused D-glucose derived sugar moiety attached at the C7 and C8 positions of the naphthazarin core. This sugar molecule is attached *via* a C-C glycosidic bond and aldol like bond. Granaticin exists as four analogues. Granaticin **34** and dihydrogranaticin A **36** contain a 2,6-dideoxyglucose substituent whereas granaticin **35** and dihydrogranaticin B **36** exhibit an L-rhodinose molecule attached by an *O*-glycosidic bond to the dideoxyglucose.

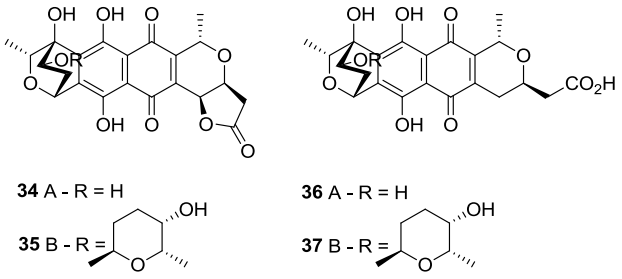


Figure 14: The granaticins and dihydrogranaticins.

This unusual fused sugar motif has only ever been observed in one other natural compound. The quinone containing polyketide sarubicin A **15** (Figure 15).

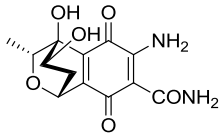


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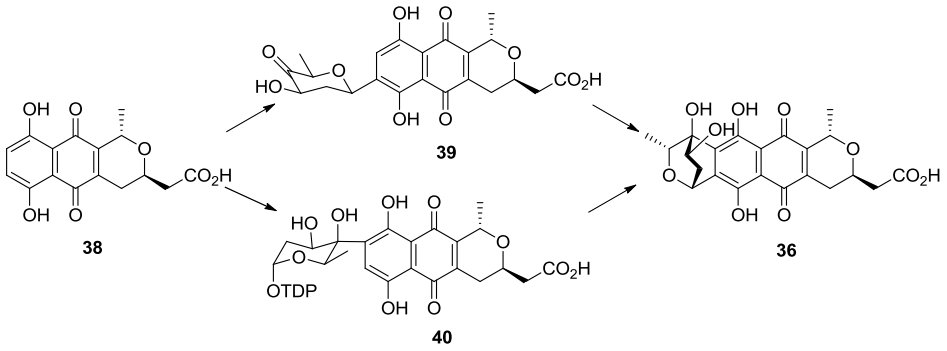
Figure 15: Sarubicin A

The enzymatic mechanism of glycosylation has yet to be elucidated but it is assumed that the gene cluster *gra14* is responsible.[42] Two possible routes have been proposed by Ichinose *et al.*[43] (Scheme 2).



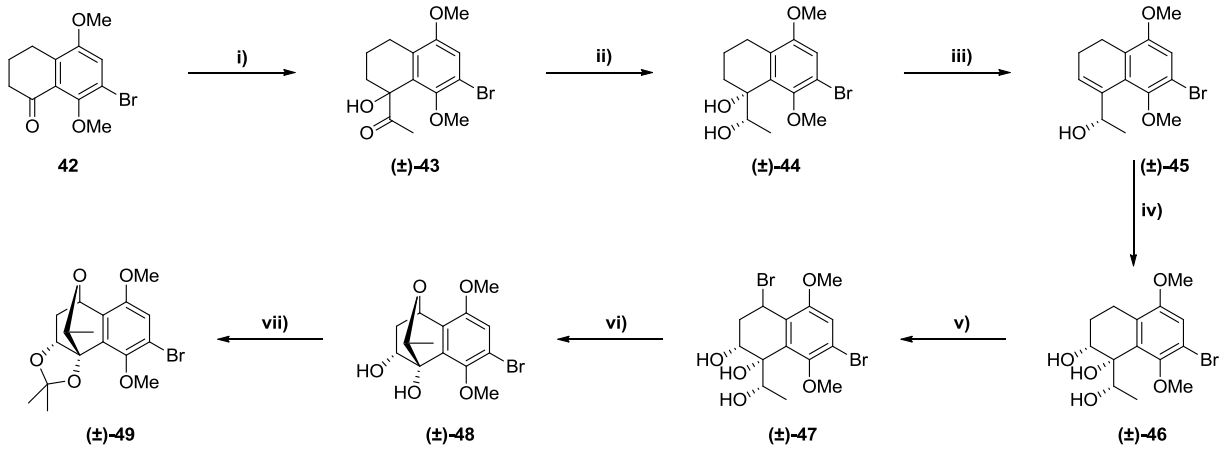
Scheme 2: Proposed enzymatic glycosylation routes.

The granaticins were first isolated in 1957 from *Streptomyces olivaceus,*[44, 45] but has since been isolated from many others such as *Streptomyces litmogenes,*[46] *Streptomyces thermoviolaceus*[47] and *Streptomyces violaceoruber*.[48] Granaticin has been shown to exhibit strong activity against gram positive bacteria with a minimal inhibitory concentration of 0.25 to 1.75 µg/100mL. It has also been shown to have activity against lymphocytic leukemia and cytotoxicity against KB cancer cells.[44-46]

3. Total synthesis of benzoisochromane quinones

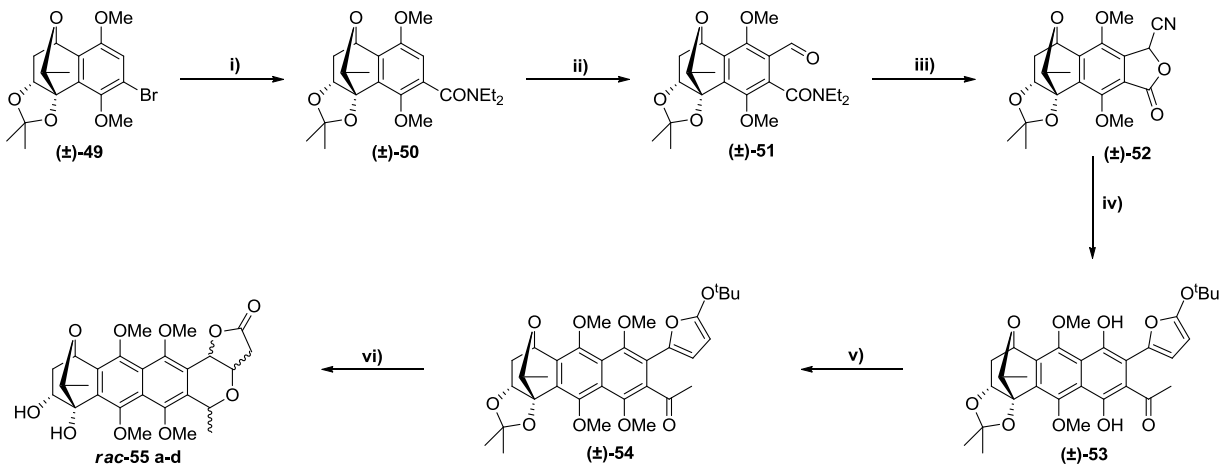
3.1 The first total synthesis of (±)-granaticin

The first total synthesis of racemic granaticin A was completed in 1987 in twenty two steps with an overall yield of 2% by Yoshii *et al.*[49] The group originally attempted to synthesise the BIQ target starting from a naphthalene derivative, however, the group could not install the final oxygen to generate the tetra oxygenated naphthazarin core in the final stages of the synthesis.[50]



Scheme 3: i) Methoxyvinyllithium, THF, −60 °C then HCl, MeOH (90%). ii) $NaBH_4$, $^{i}PrOH$ r.t. (100%). iii) Ac_2O, py., r.t. then $SOCl_2$, py., r.t. then KOH, MeOH, r.t. (65%). iv) $Me_3N(O)$, OsO_4, $^{t}BuOH$, H_2O, 60 °C (65%). v) AIBN, NBS, CCl_4, 40 °C. vi) $AgClO_4$, THF, r.t. (65% 2 steps). vii) 2-methoxypropene, CSA, THF, r.t. (97%).

The modified synthesis (scheme 3) began with addition of the unsaturated organolithium reagent methoxyvinyllithium to ketone containing bicyclic starting material **42**, synthesized in seven steps from 1,4-dimethoxybenzene. Treatment of this methyl enol ether with methanolic hydrochloric acid cleaved the methyl protecting substituent to give ketone **(±)-43** in good yield (90%). Reduction of this compound with sodium borohydride in isopropanol gave the diol as a 9:1 mixture of diastereoisomers of **(±)-44** with the major compound as the desired isomer. Treatment with acetic anhydride acetylated the secondary hydroxyl group only allowing for thionyl chloride induced β-elimination of the tertiary hydroxyl substituent. Potassium hydroxide was then used to remove the acetate protecting substituent in 65% yield over the three transformations. Dihydroxylation of the unsaturated position with osmium tetraoxide, using triethylamine *N*-oxide as a reoxidant, produced a 25:1 diastereomeric mixture of triol **(±)-46** in modest (60%) yield and recrystalisation allowed access to the major pure epimer. AIBN induced radical bromination at the benzyl position provided the cyclisation precursor and treatment with silver perchlorate gave the oxabicyclic ring system of the sugar substituent in excellent yield (65% over two steps). The two remaining hydroxyl groups were then protected as the dimethylacetal using 2-methoxypropene to give **(±)-49**.



Scheme 4: i) ^{n}BuLi, THF, −100 °C then $ClCONEt_2$, −70 °C (70%). ii) ^{t}BuLi, DMF, THF, −75 °C (96%). iii) TMSCN, KCN, 18-crown-6, CH_2Cl_2, r.t. then AcOH, r.t. then 2-methoxypropene, CSA, THF, r.t. (84%). iv) $LiCH_2SO_2Me$, **56**, THF, ^{t}BuOH, −78 °C (87%). v) Me_2SO_4, K_2CO_3, Me_2CO, 56 °C (77%). vi) $LiAlH_4$, Et_2O, −15 °C then *p*TSA, MeCN, 0 °C then DBU, PhMe −10 °C ((**a** = 1*S*, 3*S* 32%) (**b** = 1*R*, 3*S* 26%) (**c**/**d** = 1*S*, 3*R*/1*R*, 3*R* 8%).

The synthesis continued (scheme 4) with metallation of the aromatic **(±)-49** ring with n-butyllithium at low temperature and quenching with *N*,*N*-diethylcarbamoyl chloride provided the tertiary amide **(±)-50** in good yield (70%) and a second lithiation followed by formylation with DMF of the remaining aromatic carbon gave cyclisation precursor **(±)-51** in almost quantative yield (96%). Addition of potassium cyanide to the aldehyde carbonyl in the presence of trimethylsilyl cyanide and 18-crown-6 gave five membered lactone **(±)-52** but also resulted in deprotection of the acetal requiring reprotection with 2-methoxypropene in 84% over the two steps.

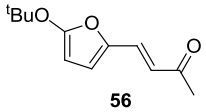
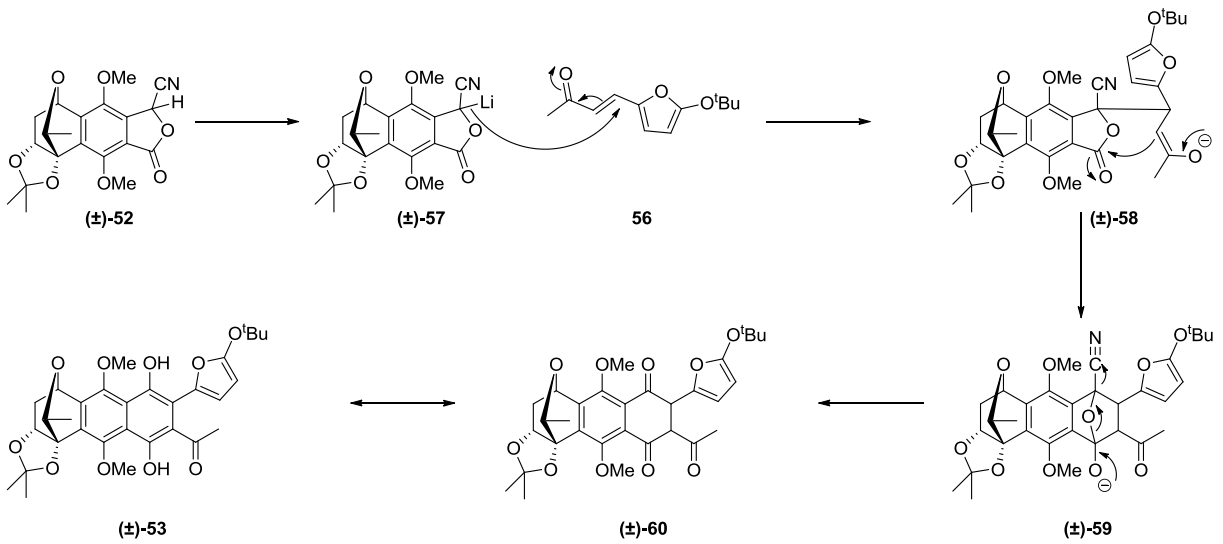


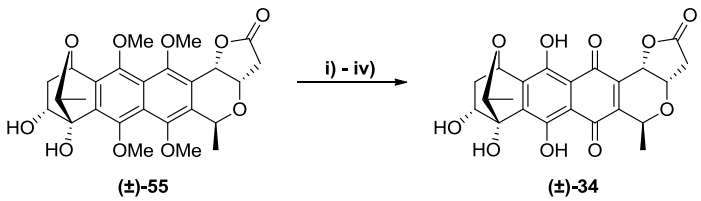
*Figure 16: Michael acceptor **56**.*

Deprotonating with $LiCH_2SO_2Me$ followed by the addition of Michael acceptor **56** resulted in annulation to the tetra oxygenated naphthalene **(±)-56** *via* the mechanism shown below (scheme 5) in excellent yield (87%).



Scheme 5: Mechanism for the generation of the tetraoxygenated core of granaticin.

The generated free hydroxyl groups were then methylated with dimethyl sulfate. The carbonyl was then reduced with lithium aluminium hydride and exposure to *p*TSA deprotected the acetal and tertiary butyl group giving α,β-unsaturated lactone **(±)-54**. DBU induced *oxa*-Michael addition to the lactone gave the pyran ring as all four diastereoisomers ***rac*-55 a-d** with the desired enantiomer (1*S*, 3*R*) isolated in 26%.

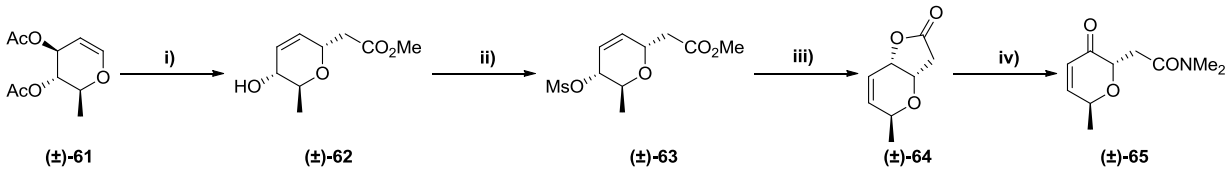


Scheme 6: i) 2-methoxypropene, CSA, THF, r.t. (97%). ii) CAN, MeCN 35 °C. iii) $AlCl_3$, SMe_2, CH_2Cl_2, r.t. iv) 1% HCl, H_2O, r.t. (82% over three steps).

Reaction with 2-methoxypropene reprotected the sugar diol groups as the acetal and ceric ammonium nitrate oxidation gave a 1:1 regiomeric mixture of the naphthaquinone core. Demethylation with aluminium trichloride and dimethylsulfide accessed the deprotected naphthazarin centre of the molecule. A final HCl depotection of the acetal yielded (±)-granaticin A **(±)-34** in 82% over four steps.

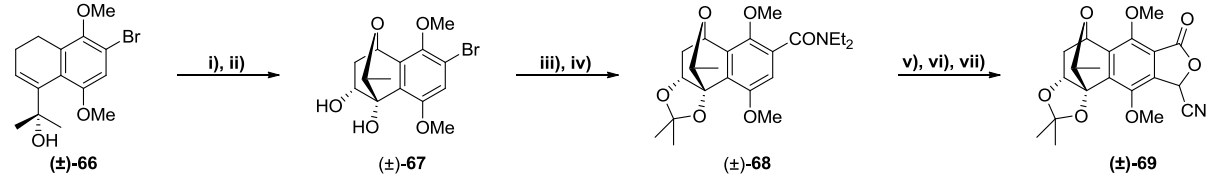
3.2 The first enantioselective total synthesis of (±)-granaticin

The same group then reported a stereocontrolled synthesis of granaticin A in 1989[51] using the same key steps but using an enantiopure dihydropyranone as a Michael acceptor.



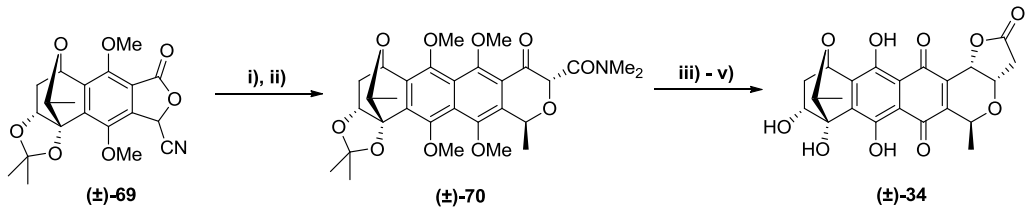
Scheme 7: i) $CH_2C(OMe)OTBS$, $BF_3{\cdot}Et_2O$, PhMe, −78 °C then 1% KOH, MeOH, r.t. (64%). ii) MsCl, Et_3N, CH_2Cl_2, 0 °C (87%). iii) SiO_2, (100%). iv) Me_2AlNMe_2, CH_2Cl_2, 0 °C then PCC, NaOAc, CH_2Cl_2, −10 °C (82%).

The group started from diacetoxydihydropyran **(±)-61**, exposing it to boron triflouride eliminated an acetoxy group and forming an oxonium intermediate of **(±)-61**. Ketene methyl t-butyldimethylsilyl acetal was then used as a nucleophile in the presence of boron trifluoride etherate complex for addition onto the oxonium generating a 3:2 mixture of separable diastereoisomers of **(±)-62**. The free hydroxyl group was then mesylated with $MeSO_2Cl$ resulting in lactonisation of the methyl ester and elimination of the mesyl group upon chromatography generating **(±)-64**. Ring opening of this lactone to generate the amide with dimethylaluminiumdimethylamide followed by pyridinium chlorochromate oxidation gave access to the pyranone Michael acceptor **(±)-65** in a total of 46% yield over three steps. A modified phthalide was synthesised in seven steps in a similar fashion to **(±)-69** in 32 % overall yield.



Scheme 8: i) OsO_4, $Me_3N(O)$, ^tBuOH, H_2O, r.t. ii) NBS, AIBN, CCl_4, 40 °C then $AgClO_4$, THF, r.t. iii) 2-methoxypropane, CSA, THF, r.t. iv) ^nBuLi, THF, −100 °C then Et_2NCOCl, −78 °C - r.t. v) ^tBuLi, −78 °C, DMF, 0 °C, vi) Me_3SiCN, 18-crown-6-KCN complex, CH_2Cl_2, 0 °C then AcOH, r.t. vii) 2-methoxypropane, CSA, THF, r.t.

With the modified cyanophthalide in hand the group could couple **(±)-69** with Michael acceptor **(±)-65**.

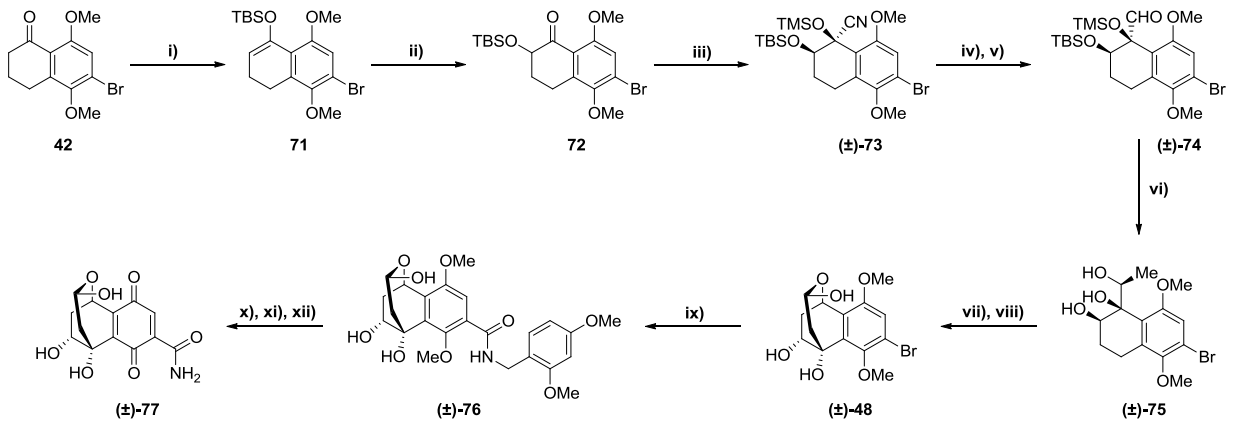


Scheme 9: i) $LiCH_2Ms$, **(±)-65**, ^tBuOH, THF, −78 °C. ii) Me_2SO_4, K_2CO_3, MeCO, 57 °C (50% over 2 steps). iii) Li^sBu_3BH, TMSCl, THF, −78 °C (56%). iv) 2-methoxypropene, CSA, THF, r.t. v) CAN, MeCN then $AlCl_3$, SMe_2, CH_2Cl_2 r.t (62% over 2 steps).

(±)-65 then underwent a benzanulation reaction with the phthalide **(±)-69** in 50% yield. The generated naphthalene hydroxyl groups were then *O*-methylated with dimethyl sulfate. Pyran carbonyl **(±)-70** was then reduced stereoselectivly using lithiumtri-s-butylborohydride and the addition of trimethylsilyl chloride resulted in lactonisation in moderate yield (56%). This transformation, however, resulted in the deprotection of the dihydroxyl substituent of the fused sugar system requiring reprotection with 2-methoxypropene. Similarly to the previous synthesis, CAN oxidation of the central naphthalene system gave the *O,O*-dimethylnaphthazarin core of the BIQ and treatment with aluminium trichloride and dimethylsulfate resulted in deprotection of the remaining methyl groups along with the acetal to give (±)-granaticin A **(±)-34**.

3.3 Towards the total synthesis of (±)-sarubicin A

The methodology used to synthesise the glycosylated half of granaticin A was based on a previous publication by Sammelheck *et al.*[52] reporting the total synthesis of (±)-sarubicin A **(±)-41** (scheme 10). Starting from 1,4-dimethoxybenzene the bicyclic ketone **42** was synthesized in 26% over seven steps.



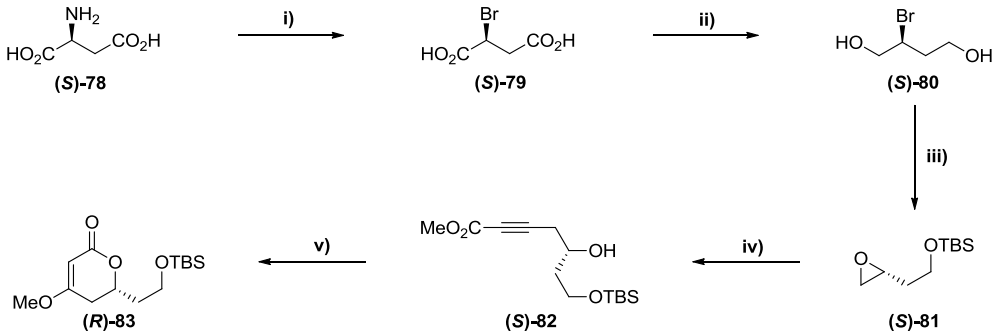
Scheme 10: i) LDA, TBSCl, THF, r.t. ii) *m*CPBA, CH_2Cl_2, 0 °C (57% over 2 steps). iii) 18-crown-6, KCN(cat.), PhMe, −30 °C then TMSCN, r.t. (100%, 86:14 dr). iv) DIBAL-H, NH_4Cl/H_2SO_4, PhMe, r.t. v) AcOH, HCl, H_2O, THF, 65 °C (84% over 2 steps). vi) $TiMe(O^iPr)_3$, THF, r.t. (80%). vii) cyclohexene oxide, AIBN, Br_2, NBS, CCl_4, 10 °C. viii) $AgClO_4$, THF, 0 °C (53% over 2 steps). ix) $Pd(PPh_3)_2Cl_2$, 2,4-dimethoxybenzylamine, $CO_{(g)}$, 90 °C (71%). x) $(imid.)_2CO$, K_2CO_3, EtOAc, 120 °C. xi) CAN, H_2O, MeCN, r.t. xii) NaOH, H_2O, dioxane, r.t. (56%).

After generating the silyl enol ether **71** with LDA and TBDMS-Cl the unsaturated bond was oxidized with *m*CPBA to give the α-silyoxyketone **72** in a modest 57% yield over the two steps. Addition of trimethylsilyl cyanide to the ketone in the presence of catalytic 18-crown-6 and potassium cyanide giving 86% conversion to the desired diastereomer of **(±)-73** which was separated by chromatography. This cyano compound **(±)-73** was then hydrolysed to the carboxylic acid under acidic conditions, which also cleaved the silyl protecting group, and then reduced *in situ* to the aldehyde **(±)-74**. Organometallic methyl addition onto aldehyde **(±)-74** occurred using methyltitaniumtriisopropoxide gave the desired diastereoisomer **(±)-75** in 80% yield. Similarly to the total synthesis of (±)-granaticin A by Yoshii[49, 50] the oxobicyclic system was formed by AIBN induced radical bromination at the benzylic position followed by silver perchlorate induced ether formation which occurred in 53% yield over two steps to give **(±)-48**. A palladium catylised carbonylation reaction was then employed using 2,4-dimethoxybenzylamine, as ammonia was not successful, to install the amide moiety and give **(±)-76**. This allowed for concomitant oxidative removal of the 2,4-dimethoxybenzyl substituent and conversion to quinone **(±)-77** with ceric ammonium nitrate. The group,

however, did not report the terminal step for the installation of the remaining amine to give sarubicin A **41** in 13 steps.

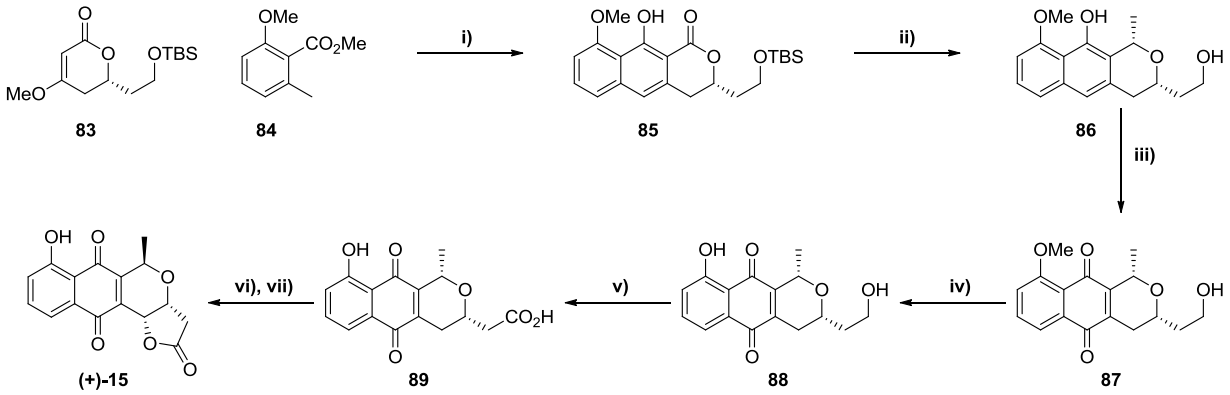
3.4 Synthesis of kalafungin *via* tandem Michael-Diekmann approach

In 2007 Christopher Donner synthesized (+)-kalafungin **15** using a tandem Michael-Diekmann approach as the key step.[53]



Scheme 11: i) KBr, $NaNO_2$, H_2SO_4, H_2O, 0 °C (91%). ii) $BH_3{\cdot}THF$, THF, −30 °C (97%). iii) TBSCl, imid., CH_2Cl_2, r.t. (98%). iv) methyl propiolate, $^{n}BuLi$, $BF_3{\cdot}Et_2O$, THF, −78 °C (72%). v) MeONa, MeOH, r.t. (80%).

The synthesis involved generating epoxide **81** from enantiopure (*S*)-aspartic acid **78**[54] by treating it with sodium nitrite to generate the diazonium salt under acidic conditions resulting in formation of the β-lactone. Potassium bromide was then used to open the lactone, retaining the stereochemistry at the C2 position in high yield. This was then reduced with borane and treatment with sodium hydride and TBDMSCl yielded the desired epoxide **81** in 85% total yield. Lewis acid induced ring opening with methyl propiolate and n-butyllithium gave the corresponding secondary alcohol **82**. Sodium methoxide was then used for conjugate addition onto the alkyne then as a base to induce intramolecular lactonisation forming **83** in good overall yield (62%).



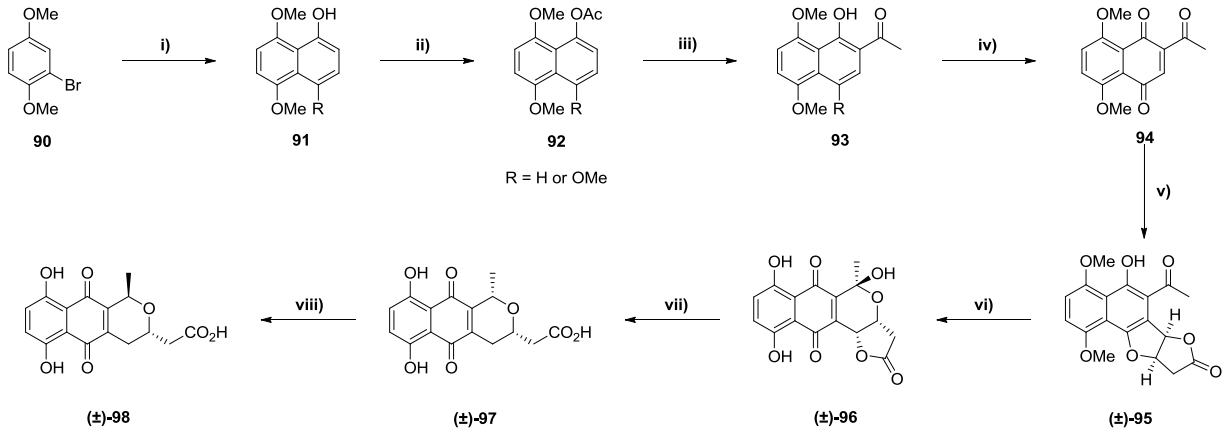
Scheme 12: i) LDA, THF, −60 °C (52%). ii) MeMgBr, THF then TFA, Et_3SiH, CH_2Cl_2, −78 °C then HCl, THF, r.t. (64% over 2 steps). iii) NBS, DMF, r.t. then CAN, H_2O, MeCN, r.t. (82% over 2 steps). iv) $AlCl_3$, CH_2Cl_2, r.t. (92%). v) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, r.t. then $NaClO_2$, NaH_2PO_4, ^tBuOH, H_2O, r.t. (80% over 2 steps). vi) O_2, MeOH, py., 60 °C then $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −45 °C (65% over 2 steps). vii) H_2SO_4, PhH (80%).

Methyl-(2-methoxy-6-methyl)benzoate **84**, in the presence of LDA resulted in a Michael addition onto **83**, by deprotonation of the methyl group, followed by Dieckmann condensation and aromatization to generate the naphthalene backbone **85** in modest yield (52%). This lactone was then treated with methyl magnesium bromide to install the C1 methyl substituent and deoxygeneation with triethylsilane and TFA produced the desired pyran ring **86**. Only the opposite enantiomer of kalafungin was generated as hydride delivery occurs from the opposite side to the substituent present at C3 due to steric hindrance. Subjecting this molecule to hydrochloric acid 2M resulted in silyl deprotection. The quinone core of **87** was installed by aromatic bromination using NBS followed by ceric ammonium nitrate oxidation in high overall yield. The aromatic hydroxyl group was then deprotected using aluminium trichloride to give **88** followed by double oxidation of the primary alcohol with $PhI(OAc)_2$ then a Pinnick oxidation[54] with $NaClO_2$ to give the free carboxylic acid **89**. Exposure to pyridine and atmospheric oxygen resulted in a mixture of the desired lactonised molecule, however, addition of methanol to C1 also occurred to give an unsymmetrical acetal. Fortuitously treatment with triethyl silane and boron trifluoride etherate complex gave only desired compound **89** as a single enantiomer. Epimerisation (+)-kalafungin occurred when the

compound was exposed to concentrated sulfuric acid yielding (+)-kalafungin **(+)-15** in eighteen steps (5.2% overall yield).

3.5 Synthesis of the (±)-γ-actinorhodin monomer *via* ceric ammonium nitrate induced oxidative rearrangement

In 1997, Margret Brimble[55] synthesised the (±)-γ-actinorhodin monomer utilizing three key steps. A benzyne cycloaddition with furan/2-methoxyfuran, a Fries rearrangement[56] and a ceric ammonium nitrate induced oxidative rearrangement to form the pyran ring.

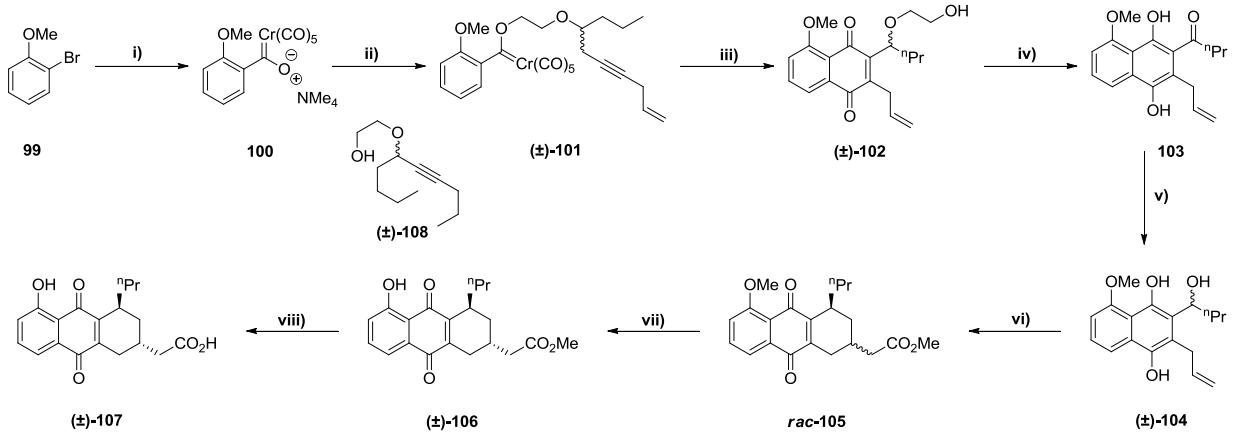


Scheme 13: i) $NaNH_2$, THF, 50 °C then conc. HCl, MeOH, −78 °C (76% over 2 steps, R = H). ii) Et_3N, Ac_2O, DMAP, CH_2Cl_2, r.t. (72% R = H). iii) $BF_3{\cdot}Et_2O$, Et_2O, r.t. (70% R = H). iv) CAN, H_2O, MeCN, r.t. (40% R = H). v) 2-(trimethylsilyloxy)furan, MeCN, H_2O, 0 °C (66%). vi) CAN, H_2O, MeCN, r.t. (75%). vii) TFA, Et_3SiH, CH_2Cl_2, r.t. then CH_2N_2 (68%). viii) BBr_3, CH_2Cl_2, −78 °C (82%).

Treatment of 1-bromo-2,5-dimethoxybenzene **90** with sodium amide and furan followed by reflux in the presence of concentrated hydrochloric acid gave 1-hydroxy-5,8-dimethoxynaphthalene **91** (R = H) in good yield (76%) following previously described methodology.[57] Using 2-methoxyfuran as the diene, 1-hydroxy-4,5,8-trimethoxynaphthalene **91** (R = OMe) could be generated but only in poor yield. Subjecting either of these compounds to triethylamine and acetic anhydride with catalytic DMAP converted the free naphthol group to the corresponding acetate **92**. Exposure to boron trifluoride etherate complex resulted in a Fries rearrangement[57] to install the acetate group at the C2 position generating **93**. CAN was

then used to form the *O*,*O*-dimethylnaphthazarin core **94** on either molecule in low yield. Reaction of this naphthoquinone with 2-(trimethylsiloxy)furan *via* conjugate addition at C5 of the furan to C3 of the quinone followed by Michael addition of the C4 oxygen onto the newly formed α,β-unsaturated lactone gave the desired cyclisation precursor **(±)-95** in a modest 66% yield. Oxidative rearrangement using CAN provided the *cis* fused pyranolactone **(±)-96** in 75%. This was then treated with triethylsilane in the presence of TFA to reduce the hemiacetal to the desired pyran ring **(±)-97**. The group discovered that increasing the reaction time and the addition of diazomethane would also generate the free carboxylic acid chain giving the C1 epimer of the protected γ-actinorhodin monomer. Fortuitously, exposure of this compound to boron tribromide not only cleaved the *O*-methyl protecting substituents but resulted in epimerization at the C1 position to generate the desired (±)-γ-actinorhodin monomer **(±)-98** in a total of nine steps (4.2% overall yield). This strategy was also used for the synthesis of the lactone containing actinorhodin monomer by using only two equivalents of CAN and limiting reaction time in step vi) preventing lactone opening.

3.6 Synthesis of (±)-deoxyfrenolicin *via* Dötz benzannulation

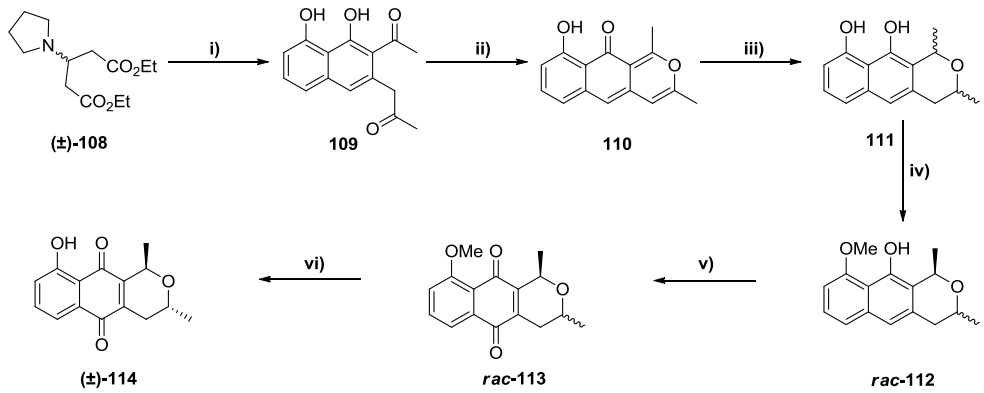


Scheme 14: i) ^{n}BuLi, $Cr(CO)_6$, Et_2O, −78 °C then Me_4NBr, H_2O, r.t. ii) AcCl, −20 °C, CH_2Cl_2 then **(±)-108**, CH_2Cl_2, r.t. (88% over 2 steps). iii) DDQ, Et_2O, MeCN, 35 °C (51%). iv) H_2SO_4, MeOH, r.t (95%). v) $NaBH_4$, THF, r.t. then DDQ, MeOH, 0 °C. vi) $PdCl_2(MeCN)_2$, $CuCl_2$, MeOH, CO, r.t. (70% over 2 steps). vii) BBr_3, CH_2Cl_2, −78 °C (84%). viii) KOH, MeOH, r.t. (97%).

Another common method for the synthesis of benzoisochromane quinones is utilizing a Dötz benzanulation[58, 59] as a key step. In 1982 Sammelheck *et al.*[60] reported the total synthesis of (±)-deoxyfrenolicin **(±)-107** using this approach. Starting from 2-bromomethoxybenzene **99** the group synthesized the necessary chromium carbene complex by metallating with n-butyllithium, quenching with chromium hexacarbonyl and isolating **100** as the tetramethylammonium salt. This hydroxide group was then acetalated with acetal chloride and displaced with 2-(non-5-yl-4-yloxy)ethanol **(±)-108** to give the cyclisation precursor **90** in excellent yield (88% over two steps). Heating this carbene complex resulted in formation of the trioxygenated naphthalene backbone followed by exposure to DDQ gave the naphthoquinone **(±)-102** in modest yield. Treatment of this compound with sulfuric acid resulted in removal of the 2-hydroxyethylene group, oxidizing the secondary alcohol to the corresponding ketone **(±)-103** and reducing the quinone ring to the *para* hydroxylated aromatic analogue in almost quantitative yield (95%). Sodium borohydride was then used to reform the secondary alcohol followed by a second DDQ oxidation to yield the central quinone ring. Palladium catalysed alkoxycarbonylation, in methanol, under an atmosphere of carbon monoxide produced the pyran ring and gave the carboxylic acid chain ***rac*-105** as a 3:1 mixture of *trans*:*cis* diastereoisomers in excellent overall yield (84%). Cleavage of the *O*-methyl substituent fortuitously resulted in epimerization of the C3 position to give only the more thermodynamically stable *trans* isomer **(±)-106** in 84% yield. The final step was then to saponify the methyl ester using potassium hydroxide which occurred in almost quantative yield (97%) to give (±)-deoxyfrenolicin **(±)-107** in 24% total yield over eight steps.

3.7 Biomimetic approaches to benzoisochromane quinone synthesis

Another interesting approach to BIQ synthesis is to a biomimetic synthesis of the hydroxylated naphthalene core *via* double Claisen condensation with a gluterate ester derivative, such as diethyl-3-hydroxygluterate, followed by base induced aromatization. One example of such a biomimetic approach was used by Harris *et al.* in 1977[61] to synthesise (±)-eleutherin **(±)-114** but has since been used for the synthesis of several BIQ compounds and naphthalene based molecules.[62]



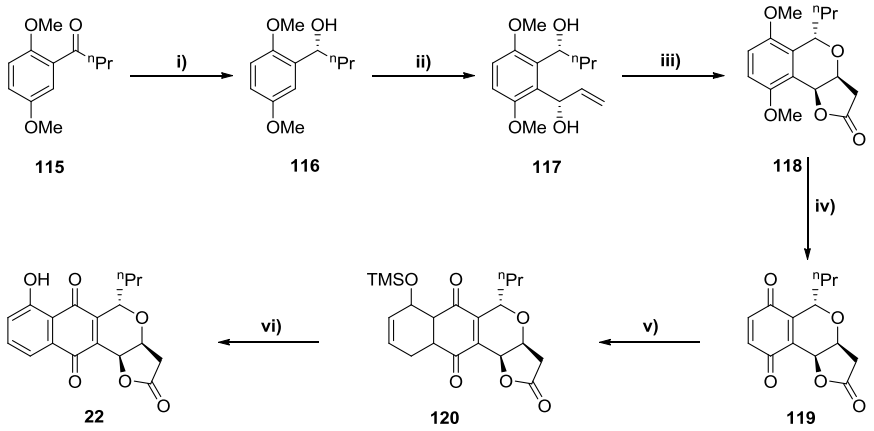
Scheme 15: i) LDA, 2,4-diketopentane, THF, −78 °C (24%). ii) TFA, EtOH, r.t. iii) Pd/C, H_2, EtOH, r.t. iv) CH_2N_2, Et_2O, r.t. v) $(KSO_3)_2NO$, H_2O, r.t. vi) H_3PO_4.

In this synthesis by Harris *et al.*, LDA was employed to generate the dianion of penta-2,4-dione, which was used in excess, followed by the addition of diethyl-3-pyrrolidinylgluterate **(±)-108** to affect dual Claisen condensation and generate a hexaone intermediate. Increasing the temperature from −78 °C to −35 °C, still under basic conditions, resulted in the formation of the highly substituted dihydroxynaphthalene derivative **(±)-109** in 24% yield. Trifluoroacetic acid was then used to induce ring closure and elimination to give isochromanone **(±)-110** followed by palladium catylised hydrogenation to give the racemic naphthopyran core of the molecule **111**. Methylation of the C9 hydroxyl group with diazomethane gave ***rac*-112** followed by oxidation with Fremy's salt provided the *O*-methoxyjuglone ring system **(±)-113**. Exposure to phosphoric acid epimerized the C1 carbon to generate the more stable *trans* isomer giving (±)-eleutherin **(±)-114**. Since this synthesis in the late 70's the biomimetic approach has been optimised[62] using 3-hydroxygluterate and a calcium acetate to induce aromatization producing the naphthalene backbone of many molecules in much higher yield (≈50%).

3.8 Synthesis of (−)-frenolicin B *via* regioselective Diels-Alder cycloaddition

A common method for the synthesis of BIQ targets is by a late stage regioselective Diels-Alder cycloaddition. This methodology was pioneered by Kraus *et al.*[63] for the synthesis of elutherin **14** in 1981 and used again in several synthesis particularly by Kraus in 1993 for the first total synthesis of frenolicin B.[64] The group employed an alkoxycarbonylation similarly to the method of Sammelheck *et al.*[52] in 1985 as a key step to form the pyran ring and γ-

lactone ring and used their previously devised Diels-Alder reaction/Jones oxidation[65] to install the juglone like core of the molecule.



Scheme 16: i) (+)-Ipc_2BCl, CH_2Cl_2, r.t. (100%, 93% *ee*). ii) ^nBuLi, acrolein, THF, −78 °C (56%, 89% *ee*). iii) $Pd(OAc)_2$, CO, THF, r.t. (65%). iv) HNO_3, AgO, r.t. (95%) v) 1-trimethylsiloxy-1,3-butadiene, CH_2Cl_2, −78 °C. vi) Jones reagent, Me_2CO, r.t. (81% over 2 steps).

Starting from 1,4-dimethoxybenzene-2-butyl ketone **115**, the synthesis involved an asymmetric Brown reduction[66] using (+)-Ipc_2BCl followed giving 93% of the (*R*) enantiomer of **116** (determined by analysis of the Mosher ester) by *ortho* lithiation and quenching with acrolein to give a mixture of diols of **117** in high enantiomeric excess (89%, (*S*)) but only in 56% total yield due to *meta* and *para* metallation compounds. Altering the solvent system to a 1:10 ether:pentane improved the yield but lowered the enantiomeric selectivity of the reaction. Palladium catalysed carbonylation of this diol, under an atmosphere of carbon monoxide, afforded the formation of both pyran and lactone ring systems **118** in modest yield (65%). A seldom used Rapoport oxidation[67] with silver oxide and nitric acid then gave the cycloaddition precursor **119** in excellent yield (95%). Diels-Alder reaction with 1-siloxy-1,3-butadiene at low temperature followed by immediate exposure of **120** to Jones reagent yielded the target compound **(–)-24** with excellent conversion from the quinone (81%) observing the presence of only one regioisomer. The rationale for this observed selectivity is the presence of the lactone ring. When the silyl containing diene overlaps with the quinone substituent the trimethylsilyl group forces the lower quinone carbonyl group towards the towards the lactone

oxygen thus making this the disfavored orientation. Therefore, reaction occurs preferentially with the silyl enol ether positioned at the top of the molecule (Figure 17).

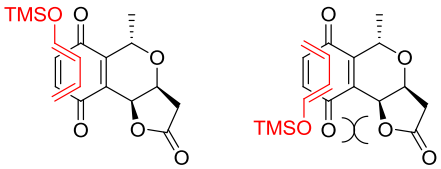
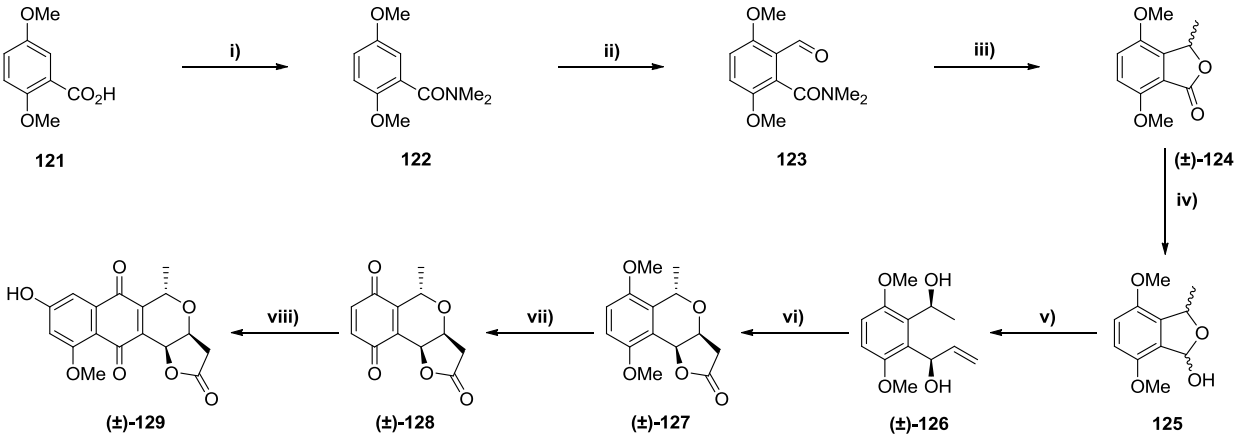


*Figure 17: Diene overlap with **119**.*

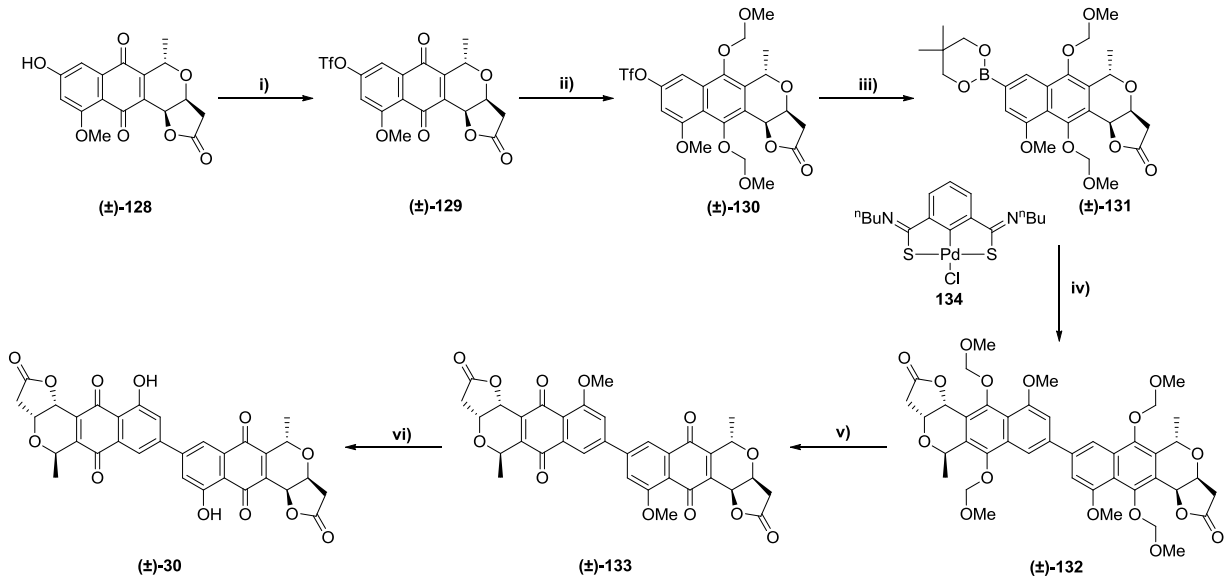
3.9 Synthesis of (±)-crisamicin *via* regioselective Diels-Alder cycloaddition

Zhen Yang *et al.* in 2008 also used a Diels-Alder cycloaddition followed by a Jones oxidation for the synthesis of the dimeric benzoisochromane quinone (±)-crisamicin A[68] **(±)-30**. Again, a palladium catalysed carbonalytive lactonisation was used, similarly to that reported by Kraus *et al.*[65], then the group wanted to employ a homocoupling step to generate the dimer which, to the best of this author's knowledge, was the first example of dimerisation at the C8 position.



Scheme 17: i) $SOCl_2$, 75 °C then Et_2NH, CH_2Cl_2, r.t. (93%). ii) ^tBuLi, TMEDA, DMF, THF, −78 °C (92%). iii) MeMgCl, THF r.t. then *p*TSA, PhMe, r.t. (89%). iv) $LiAlH_4$, THF, 0 °C then TEMPO, BAIB, CH_2Cl_2, r.t. (79%). v) vinylmagnesium chloride, THF, 40 °C (59%). vi) $Pd(OAc)_2$, TMTU, CO, $CuCl_2$, propylene oxide, NH_4OAc, THF, 50 °C (88%). vii) CAN, H_2O, MeCN, v10 °C (89%). viii) 1,1-dimethyl-3-silyoxy-1,3-butadiene then Jones reagent, Me_2CO, r.t. (85%).

The group began the synthesis from 2,5-dimethoxybenzoic acid **121** converting it to the corresponding diethyl amide **122** with thionyl chloride and diethylamine. This allowed for directed *ortho* lithiation using t-butyllithium in the presence of TMEDA and subsequent formylation with dimethylformamide in excellent yield (85% over two steps) to give **123**. Addition of methyl magnesium chloride to the generated aldehyde followed by *p*TSA induced cyclisation gave the five membered lactone **(±)-124** in good yield (89% over two steps). Reduction with lithium aluminium hydride resulted in the ring opened diol and exposure to TEMPO in the presence of BIAB ($PhI(OAc)_2$) reformed the ring as the hemiacetal **125** in high yield. Diastereoselective ring opening with vinyl magnesium chloride generated the alkoxycarbonylation precursor **(±)-126** in a modest 59% yield. Installing the pyran and lactone rings proved to be a challenge with various additives screened to optimize the reaction. The group eventually discovered that the use of a TMTU ligand, addition of $copper^{II}$ chloride along with ammonium acetate and propylene oxide gave the desired carbonylation compound **(±)-127** in 88% yield. This isochromane compound was then subjected to standard ceric ammonium nitrate oxidation conditions to yield the corresponding quinone **(±)-127** (89%). Diels-Alder cycloaddition with the diene ((4,4-dimethoxybuta-1,3-dien-2-yl)oxy)trimethylsilane gave a 20:1 regioisomeric mixture with the desired compound being the major isomer. This is attributed to hydrogen bonding between the lower quinone carbonyl, the lactone oxygen and a methyl proton of the diene favoring this orientation for the pericyclic reaction as opposed to previously observed results were the orientation of the diene favors the more sterically hindered substituents at the top of the isochromane quinone.[69] Exposure to Jones' reagent then provided the crisamicin monomer **(±)-128** in 85% yield with an aromatic hydroxyl group as a functional handle to achieve homocoupling.

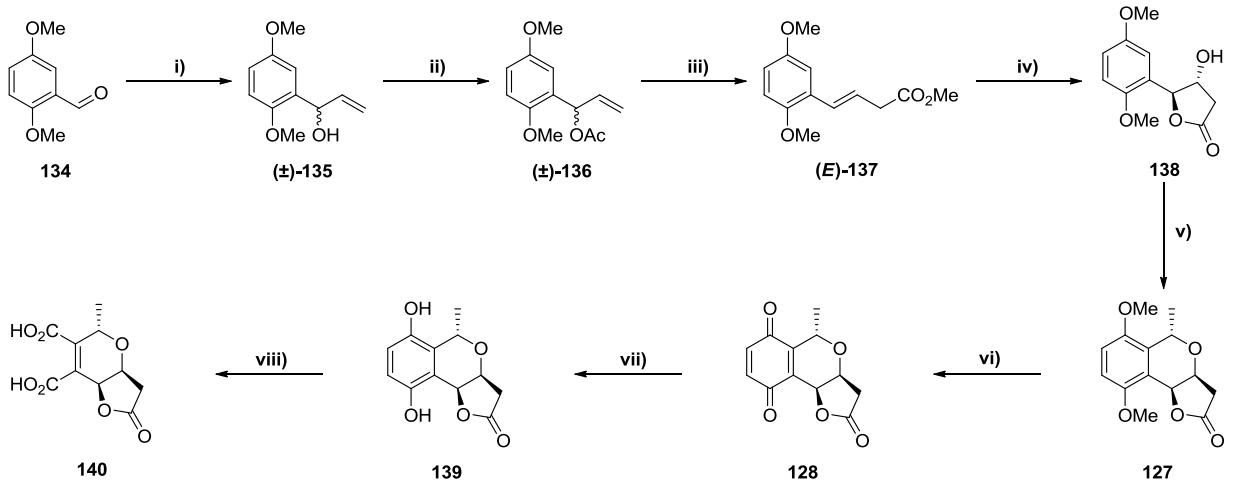


Scheme 18: i) Tf_2O, DMAP, py., r.t. (78%). ii) $Na_2S_2O_4$, Bu_4NBr, THF, H_2O, r.t. then MOMCl, DMAP, DIPEA, CH_2Cl_2, r.t. iii) $PdCl_2(dppf)$, $(Bpin)_2$, dioxane, 85 °C (76% over 2 steps). iv) Catalyst **126**, Ag_2CO_3, DMSO, H_2O (87%). v) TMSBr, CH_2Cl_2, −78 °C then SiO_2 (93%). vi) BCl_3, CH_2Cl_2, −78 °C (91%).

Triflation of the hydroxyl group of **(±)-128** using trifluoromethanesulfonic anhydride in the presence of catalytic DMAP and pyridine gave the Suzuki coupling precursor **(±)-129** in good yield, however several protection steps were required to achieve this transformation. The addition of sodium sulfate and tetrabutylammonium bromide reduced the central quinone ring to the corresponding dihydroxybenzene substituent which was then protected with methoxymethylene chloride to give **(±)-130** using Hünig's base and catalytic DMAP. The aromatic triflate group was then converted to the boronic pinacol ester using $PdCl_2(dppe)_2$ and homocoupling was achieved using palladium complex **134** in the presence of silver carbonate in excellent yield (87%). Treatment with trimethylsilyl bromide under basic conditions allowed for cleavage of the MOM substituents followed by silica gel chromatography induced oxidation to produce the quinone centre of compound **(±)-133**. Then treatment with boron trichloride gave crisamicin A **(±)-30** in a total of 10% yield over twenty steps.

3.10 Synthesis towards the granaticin aglycone *via* Sharpless asymmetric dihydroxylation and benzyne cycloaddition

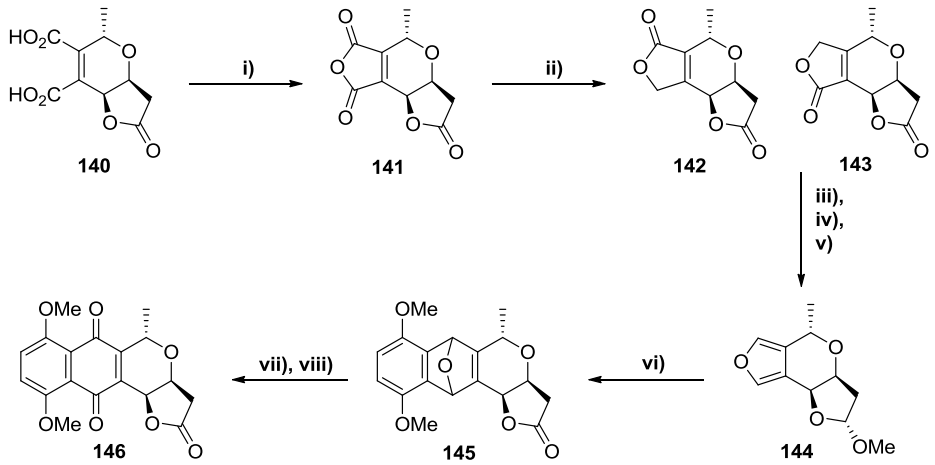
In 2012 and 2013 Ulrich Koert *et al.*[70, 71] published two articles towards the total synthesis of granaticin A with the long term aim of using a benzyne cycloaddition to fuse the two sections of the natural compound together forming the central aromatic ring.



Scheme 19: i) vinylmagnesium bromide, THF, −60 °C (95%). ii) Ac_2O, py., 0 °C (90%). iii) $Pd_2(dba)_3$, CO, PPh_3,DIPEA, NaBr, MeOH, 50 °C (99%). AD-mix-α, $NaHCO_3$, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C (87%). v) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$ TFA, 80 °C (41%, 14:1 *dr*). vi) CAN, MeCN, −20 °C (59%). vii) Pd/C, H_2, EtOAc, 20 °C (99%). viii) O_3, CH_2Cl_2, DMF, −110 °C (42%).

The synthesis of the protected aglycone[70] began with the addition of vinyl magnesium bromide to 2,5-dimethoxybenzaldehyde **134** to give unsaturated alcohol **(±)-135** in almost quantative yield. The secondary hydroxyl group was then acetylated with acetic anhydride in the presence of pyridine in 90% yield forming **(±)-136**. A palladium catalysed carbonylation reaction using Pd_2-$(dba)_3$, triphenylphosphine, Hünigs base and sodium bromide as a methanolic solution under an atmosphere of carbon monoxide yielded β,γ-unsaturated ester **(*E*)-137** in high yield. This compound was not purified due to its high instability towards chromatography. Sharpless asymmetric oxidation[72, 73] with AD-mix α gave the cyclised (4*R*, 5*S*)-hydroxylactone **138** in excellent yield (87%) and enantiomeric excess (95%). The group

then attempted an *oxa*-Pictet-Spengler cyclisation in ethereal solvent using boron trifluoride etherate complex as a Lewis acid. This, however, only generated the undesired *cis* enantiomer, albeit in high yield (88%). The group eventually devised a method to achieve this transformation producing an enantioenriched mixture of diastereoisomers in a 14:1 *trans*:*cis* ratio. This reaction involved the addition of the lactol **138** to an 80 °C TFA solution of $BF_3{\cdot}Et_2O$ and 1,1-dimethoxyethane followed by quenching with base at 0 °C after 60 seconds to yield 41% of the diastereomeric mixture of **127**. This isochromane **127** was then treated with cerium^{IV} ammonium nitrate to remove the phenolic *O*-methyl substituents, generating the corresponding quinone **128**.



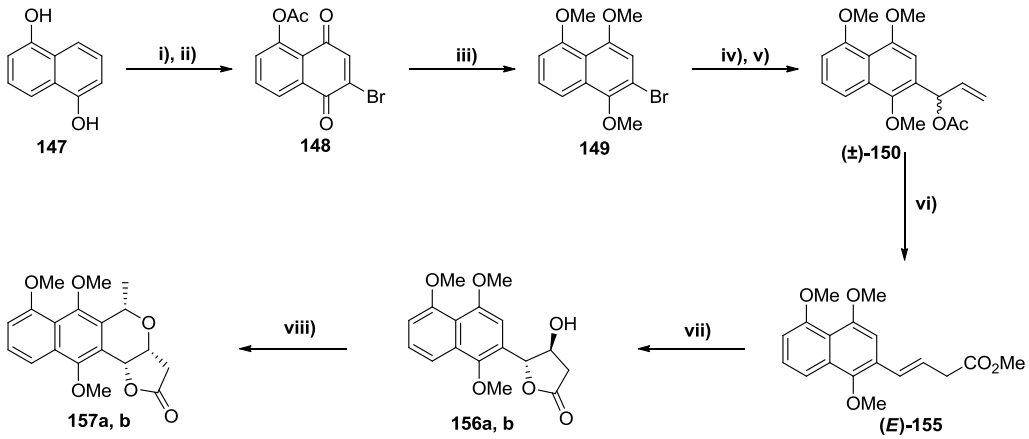
Scheme 20: i) TFAA, $CHCl_3$, 20 °C. ii) $Li(O^tBu)_3AlH$, THF, 0 °C (42% over 2 steps). iii) DIBAL-H, CH_2Cl_2, −78 °C. iv) HCl, H_2O, 0 °C. v) $BF_3{\cdot}Et_2O$, MeOH, 40 °C (55% over 3 steps). vi) 1-bromo-2,5-dimethoxybenzene, LDA, THF, −78 °C (100%). vii) $BF_3{\cdot}Et_2O$,, MeOH, 65 °C then H_2SO_4, Me_2CO, 57 °C. viii) Jones reagent, Me_2CO, 20 °C (26% over two steps).

The group then investigated a series of Diels-Alder reactions based on the method of Kraus[65] to form the naphthoquinone back bone of granaticin **34**, however, only elimination reactions were observed to give the naphthoquinone substituent with no incorporation of oxygen at either the C6 or C8 possition. The group then revised the synthesis to include a benzyne cycloaddition. The quinone **128** was then reduced to the *para* diol using a palladium catalysed hydrogenation in 59% over two steps. Ozonolysis of this aromatic gave the α,β-unsaturated dicarboxylic pyran **139** in high yield (82%). The diacid **140** (scheme 18) was then converted to

the anhydride **141** using TFAA in excellent yield (97%). Nucleophilic addition to the anhydride with *ortho* lithiated 1,4-dimethoxybenzene gave the desired compound as a mixture of regioisomers and generation of the methyl ester with MeI in the presence of cesium carbonate occurred in modest yield (50%). However, formation of the quinone ring by aromatic substitution could not be achieved. The group then attempted a Diels-Alder reaction using 1-acetoxy-1,3-butadiene but only observed a non-hydroxylated naphthoquinone as a result of elimination of the acetoxy group. Finally, the group converted the pyranoanhydride to a furan derivative **144** in an attempt to generate the granaticin aglycone *via* a benzyne cycloaddition. Using lithium tri-t-butoxyaluminium hydride the anhydride was reduced to a regiomeric mixture of unsaturated lactones **142**, **143**. DIBAL-H reduction of both γ-lactones gave the ring opened product. Exposure to aqueous hydrochloric acid followed by reaction with a methanolic solution of boron trifluoride etherate complex not only generated the furan diene but protected the pyran lactone as an unsymmetrical acetal. Two equivalents of this diene **144** were then subjected to a benzyne cycloaddition with 1,4-dimethoxybenzyne to give the desired adduct in almost quantative yield. Exposure of this compound to $BF_3{\cdot}Et_2O$ gave a mixture of ring opened regioisomers which were then oxidized in very low yield (26%) under Jones conditions to give the *O,O*-methyl granaticin aglycone **146** in a total of 1.6% over 17 linear steps. To date the group has not succeeded in performing a regioselective benzyne cycloaddition on fused sugar aromatic bromide.

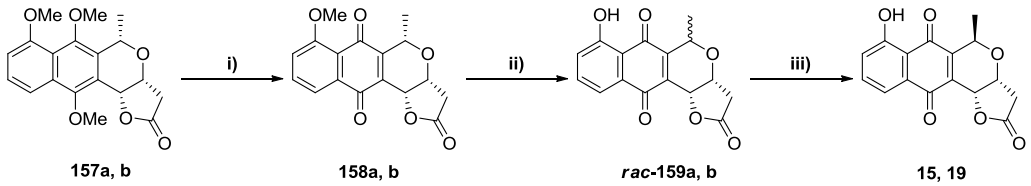
3.11 Synthesis of kalafungin and nanaomycin *via* Sharpless asymmetric dihydroxylation

A similar methodology to Koert *et al.* was used by Rodney Fernandes and Reinhard Brückner for the synthesis of both kalafungin **15** and nanaomycin D **19** in 2005[74]. Again, employing a Sharpless asymmetric dihydroxylation[72, 73] to form the γ-lactone ring of both natural compounds and an *oxa*-Pictet-Spengler cyclisation to give the pyran ring as the key steps of the synthesis using either AD-mix-α or AD-mix-β. The synthesis of kalafungin **15** is shown in schemes 19 and 20 The main difference in the synthetic strategy was to begin with a naphthalene derivative.



Scheme 21: i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t. (87%). ii) NBS, AcOH, H_2O, 55 °C (92%). iii) $Na_2S_2O_4$, TBAB, THF, H_2O, r.t. then KOH, r.t. then Me_2SO_4, r.t. (80%). iv) ^{n}BuLi, acrolein, THF, −85 °C (70%). v) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t. (85%). vi) $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, NBr, $EtN^{i}Pr_2$, CO, MeOH, 50 °C (83%). vii) $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, $K_2Os_2(OH)_4$, ^{t}BuOH, H_2O, 0 °C then r.t. (82%). vii) $BF_3{\cdot}Et_2O$, $MeCH(OMe)_2$, Et_2O, THF, r.t. (92%)

Compound **148** was synthesised from commercially available 1,5-dihydroxynaphthalene **147** by *bis* acetylating with acetic anhydride and achieving an *in situ* bromination/oxidation using *N*-bromosuccinamide in acetic acid to give *O*-acetate protected 6-bromojuglone. In turn this was reduced and methylated to give the trimethoxynaphthalene derivative **149**. Lithiation with n-butyllithium, trapping with acrolin and converting the secondary alcohol to an acetoxy leaving group **(±)-150** with acetic anhydride gave the Tsuji carbonylation precursor **(*E*)-155** in 38% over five steps. The carbonylation generated a 95:5 mixture of inseperable β,γ:α,β-usaturated esters in 83% combined yield which were subjected to Sharpless asymmetric dihydroxylation conditions using AD-mix-α towards the total synthesis of kalafungin **156a** (4*S*, 5*R*) or AD-mix-β towards the total synthesis of nanaomycin **156b** (4*S*, 5*R*) (79% and 82% respectively).

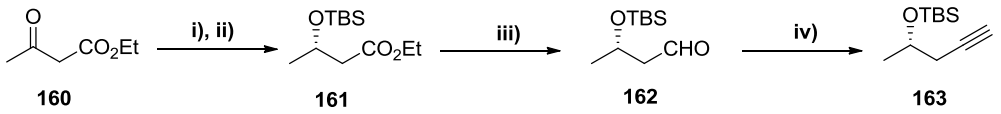


Scheme 22: i) CAN, MeCN, H_2O, r.t. (87%). ii) BBr_3, CH_2Cl_2, −50 °C (82%). iii) conc. H_2SO_4, r.t. (87%).

Oxa-Pictet-Spengler cyclisation of **156a/156b** with boron trifluoride etherate complex and 1,1-dimethoxyethane followed by ceric ammonium nitrate oxidation and boron tribromide deprotection gave either **159a** (72:28 mixture of diastereoisomers at the C1 position) or **159b** (67:33 mixture of diastereoisomers at the C1 position). Enantiopurity could be enriched by exposure to concentrated sulfuric acid followed by recrystalisation to give the pure desired diastereoisomer. Thus the total synthesis of kalafungin **15** and nanaomycin **19** had been achieved in eleven steps in 15% overall yield for both natural compounds.

3.12 Synthesis of demethoxycardinalin *via oxa*-Pictet-Spengler cyclisation

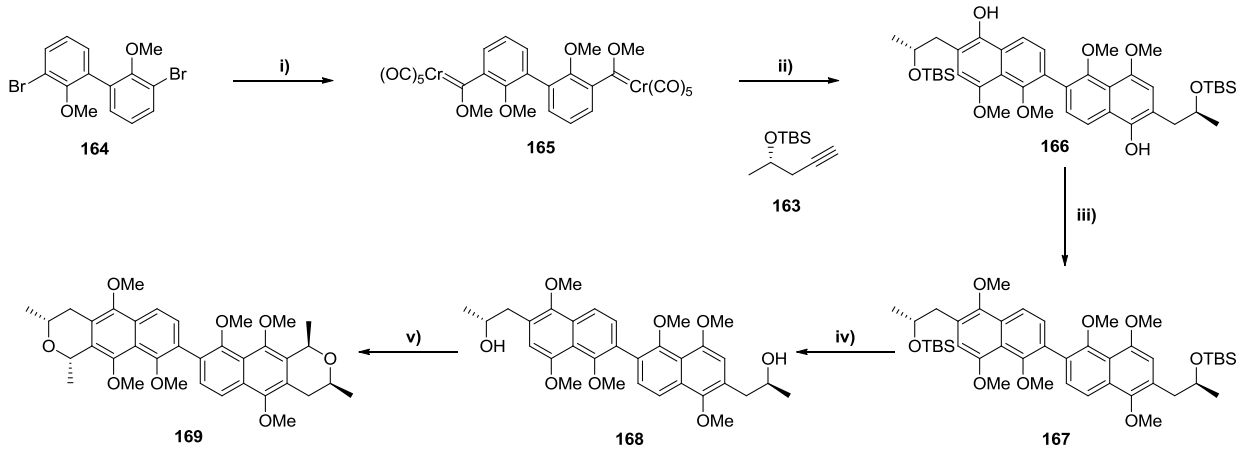
In 2010 Rodney Fernandes *et al.* reported the total synthesis of the dimeric benzoisochromane quinone demethoxycardinalin[76] using three key steps. A Fischer chromium carbene synthesis, Dötz benzanulation[58] and *oxa*-Pictet-Spengler. Similarly to many synthetic strategies of dimeric BIQ molecules[77, 78] two simultaneous reactions are performed building the molecule from the centre outwards.



Scheme 23: i) Baker's yeast, DMSO, EtOH, r.t. (69%) or $[NEt_2H_2]$-[{RuCl(S)-BINAP}$_2$(μ-Cl_3)], MeOH, H_2, 50 °C (100%). ii) TBSCl, imid. CH_2Cl_2, r.t. (98%). iii) DIBAL-H, CH_2Cl_2, −78 °C (97%). iv) CBr_4, PPh_3, CH_2Cl_2, 0 °C then ^{n}BuLi, THF, −78 °C (80%).

The group began with the synthesis of the benzanulation alkyene starting from ethyl acetoacetate and performing an asymmetric reduction to the (*S*) enantiomer either using Baker's yeast (69%) or by a Noyori hydrogenation (100%).[79, 80] Protection of this hydroxyl with TBDMSCl gave **161** in 98% yield. This was followed by reduction of the ethyl ester to

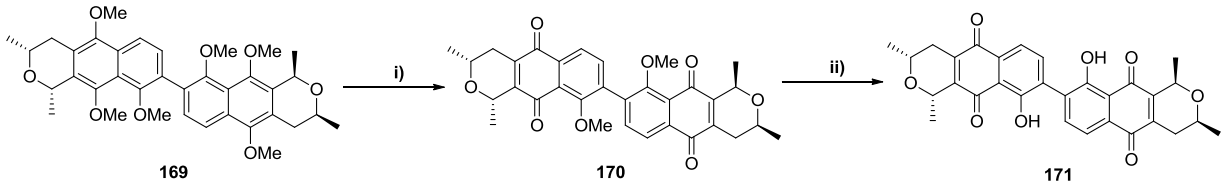
aldehyde **162** with DIBAL-H which occurred in excellent yield (97%). Treatment of this aldehyde carbon tetrabromide and triphenyl phosphine followed by the addition of n-butyllithium to affect a Corey-Fuchs reaction[81] gave the desired alkyne **163** in 80% over two steps.



Scheme 24: i) ^{n}BuLi, Et_2O, −78 °C then $Cr(CO)_6$, 0 °C then Me_3OBF_4, CH_2Cl_2, r.t. (58%). ii) **152**, THF, 45 °C (65%). iii) NaH, MeI, THF, 80 °C (88%). iv) TBAF, THF, r.t. (93%). v) $MeCH(OMe)_2$, $HCl_{(g)}$, Et_2O, r.t. (55%).

Attention was then focused on the Fischer carbene synthesis, taking the diaryl dibromide **164** and metallating with ^{n}BuLi followed by the addition of chromium hexacarbonyl and *in situ* protection of the generated hydroxyl group with trimethyloxonium tetrafluoroborate. After optimising the reaction times of all three additions and solvent systems the reaction gave a modest 59% yield of the dimer. Dötz benzanulation[58] gave the desired substituted (*S, S'*)-naphthalene dimer **166** with two equivalents of the previously synthesised alkyne in modest yield (65%) followed by protection of the newly formed hydroxyl group with methyl iodide generating **167**. Silyl cleavage occurred in almost quantative yield to give the cyclisation precursor **168**. The group then discovered that the use of a Lewis acid and the dimethyl acetal of acetaldehyde the oxa-Pictet-Spengler reaction only yielded the less thermodynamically stable *cis*:*cis* adduct or *cis:trans* adduct. Using a protic acid (HCl gas) in aprotic solvent gave the desired *cis*:*cis* stereochemistry of **169** (55%) at the C1/C1' position which the group

attributes to the formation of the *E*-oxocarbenium with protic acid and predominantly the *Z*-oxocarbenium compound with a Lewis acid.

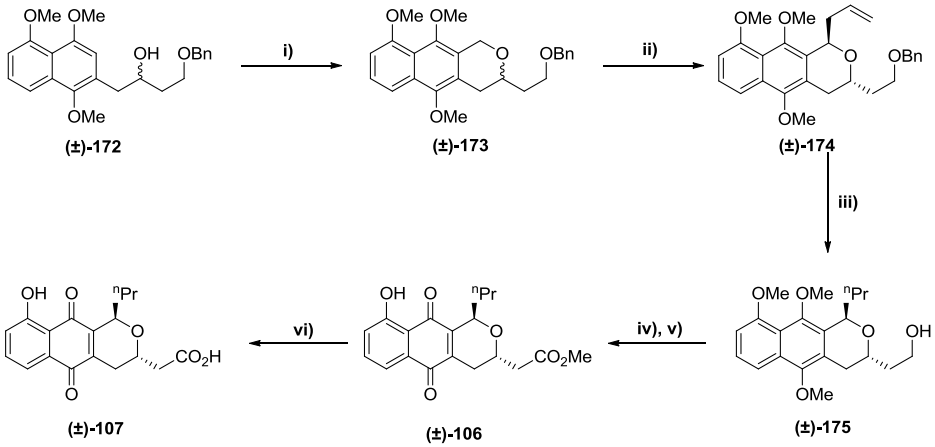


Scheme 25: i) CAN, MeCN, H_2O, r.t. (74%), ii) $AlCl_3$, CH_2Cl_2, 0 °C (77%).

A ceric ammonium nitrate oxidation installed the quinone ring to give **170** and a simple aluminium trichloride deprotection of the two remaining methyl groups gave demethoxycardinalin **171** in a total of 17% over six steps.

3.13 Synthesis of (±)-deoxyfrenolicin *via oxa*-Pictet-Spengler cyclisation

Another synthetic strategy that utilized an *oxa*-Pictet-Spengler was that devised by Xu *et al.*[82] in 1999 for the total synthesis of (±)-deoxyfrenolicin **96**. However, their strategy involved a DDQ induced C-C coupling of the n-propyl C1 substituent to generate only the desired *trans* isomer using allyltriphenyltin.



Scheme 26: i) $CH_2(OMe)_2$, $BF_3{\cdot}Et_2O$, Et_2O, r.t. (85%). ii) $Ph_3SnCH_2CHCH_2$, DDQ, CH_2Cl_2, r.t. (94%). iii) Pd/C, H_2, EtOH, r.t. (77%). iv) $Cr(O)_3$, AcOH, Me_2CO, H_2O, r.t. then MeOH, H_2SO_4, r.t. (43% over 2 steps). v) BBr_3, CH_2Cl_2, −78 °C (85%). vi) KOH, MeOH, r.t. (97%).

Again, a Dötz benzanulation[58] gave the desired substituted naphthalene followed by a series of protecting group transformations produced the *oxa*-Pictet-Spengler precursor **(±)-172** in good overall yield. Starting from allyl alcohol this, precursor was generated in 31% yield over 8 steps. Cyclisation of **(±)-172** with dimethoxymethane in the presence of boron trifluoride etherate complex gave the pyran ring unsubstituted at the C1 position **(±)-173**. The addition of DDQ and allyltriphenyltin installed the allyl substituent in excellent yield (94%) only observing the *trans* diastereoisomer **(±)-174**. This is attributed to the bulky stannane reagent preventing the formation of the more sterically hindered and less thermodynamically favored *cis* isomer. Concomitant hydrogenation of the allyl group to give then n-propyl chain and cleavage of the benzyl protecting moiety, exposing the primary hydroxyl group to give **(±)-176**, occurred in good yield (77%). This was followed by chromium^{VI} oxide global oxidation to give the free carboxylic acid and quinine ring. Esterification using methanol under acidic conditions provided the methyl ester **(±)-106** in 47% over two steps. The remaining methyl ether was then deprotected with boron tribromide and saponification of the ester with potassium hydroxide yielded deoxyfrenolicin **(±)-107** in 82% over two steps with an overall yield of 7% over fifteen steps.

4. Aims

The long term aim of this project is the elucidation of the enzymatic mechanism of glycosylation of the granaticin aglycone, the role of *gra14* in this glycosylation and the potential of the enzyme to glycosylate unnatural substrates.

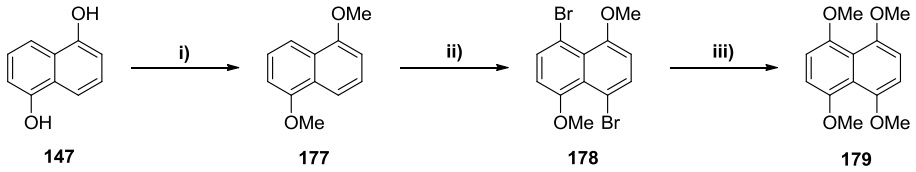
The primary aim off this research is to devise a novel, elegent and divergent synthesis of the dihydrogranaticin aglycone and analogues of the aglycone. As there have been many previously reported total syntheses of benzoisochcromane quinone antibiotics we have placed an importance on step economy, attempting to avoid multiple protection/deprotection steps and oxidations.

We also wish to apply the devised methodology towards the total synthesis of other benzoisochromane quinone antibiotics such as eleutherin **114**, nanaomycin A **16**, frenolicin **22** and kalafungin **15**.

5. Results and discussion

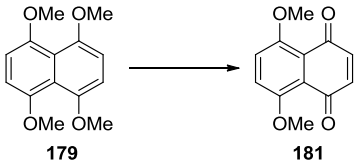
5.1 Previous research

Previous work conducted within this laboratory[83] attempted to synthesise the desired naphthamide **180** from 1,4,5,8-tetrametehoxynaphthalene **179**. This was achieved by *O*-methylation of commercially available 1,5-dihydroxynaphthalene **147** to give **177** and *para* dibromination to generate **178**. This allowed for copper mediated coupling with sodium methoxide generating the tetra oxygenated precursor **179** in modest yield according to the method of Terada *et al*.[84]

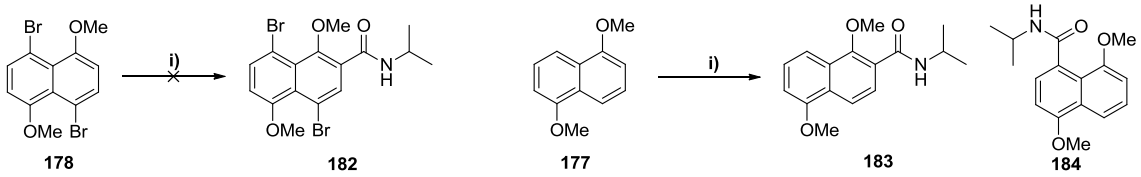


Scheme 27: i) MeI, K_2CO_3, Me_2CO, 56 °C (99%). ii) Br_2, CCl_4, 70 °C (54%). iii) MeONa, CuI, DMF, MeOH, 70 °C (49%).

It was, however, observed that this species underwent rapid oxidation to dimethoxynaphthazarin **168** when exposed to Lewis acids preventing Friedel-Crafts substitution[85] with isopropylisocyanate.



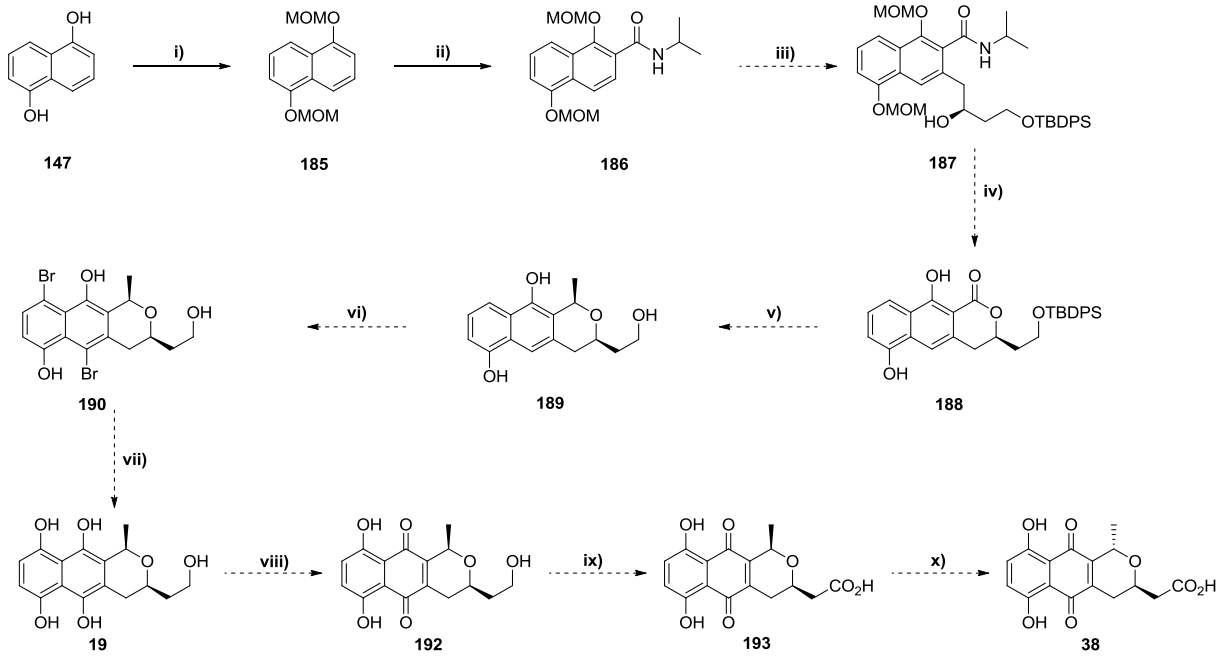
*Scheme 28: Oxidation of **179** to O,O-dimethoxynaphthazarin **181**.*



Scheme 29: i) $AlCl_3$, $^{i}PrNCO$, CH_2Cl_2, 0 °C (**182** = 0%, **183** = 1.3%, **184** = 54%)

Attempts at Friedel-Crafts aromatic substitutions on the dibromodimethoxy species (scheme 29), to allow for later oxidation, resulted in complete degradation of the naphthalene starting material **178**. Regressing back through the synthetic methodology, Friedel-Crafts substitution was next attempted on 1,5-dimethoxynaphthalene **177** (scheme 28) which yielded 1.3% of the desired *ortho* substituted naphthamide **183** and 57% of the *para* substituted regioisomer **184**. This can be attributed to the cross-conjugation of the cationic intermediate. Reaction with isopropylisocyanate was then examined as a method to perform nucleophilic substitution by *ortho* lithiation of 1,5-dimethoxynaphthalene **177**. However, deuterium quenching studies showed only low levels of lithiation even with multiple equivalents of ^{t}BuLi.

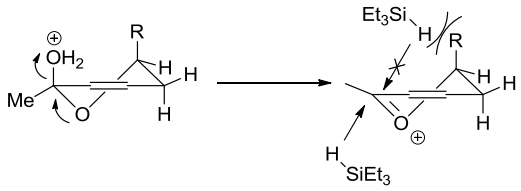
4.1 Synthetic protocol 1



Scheme 30: i) MOM-Cl, NaH (99%) ii) ^{i}PrNCO, ^{t}BuLi, TMEDA (78%) iii) ^{t}BuLi, TMEDA, **184**. iv) CSA. v) MeLi, TFA, Et_3SiH. vi) Br_2. vii) MeONa, CuI, then BBr_3. viii) CAN. ix) $NaClO_2$. x) H_2SO_4.

Methoxymethylene was selected for protection of the hydroxyl groups in order to aid *ortho* lithiation and allow for concomitant cleavage in the desired acid mediated cyclisation later in the synthesis. The treatment of compound **185** with ^{t}BuLi and quenching with isopropylisocyante would hopefully lead to the desired naphthamide 1**86**. It was predicted that

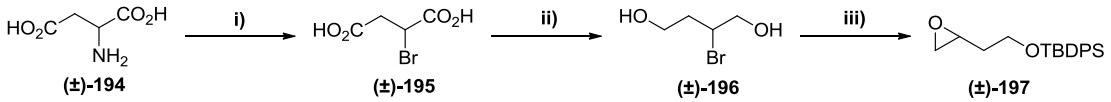
further treatment of this species with ^{t}BuLi (2 eq.) would result in lithiation at the C3 position, as opposed to the C6 position, as the deprotonated amide would be a stronger *ortho* director than the C5 MOM substituent. Quenching this intermediate with (*S*)-t-butyl-(2-(oxiran-2-yl)ethoxy)diphenylsilane **(*S*)-197** would give the cyclisation precursor **187**. Utilising previously described methodology[53, 83] the lactone could then be converted into the methyl substituted tetrahydropyran **188** by treatment with methyllithium followed by TFA and triethylsilylane which has been shown to give the less stable, undesired, *cis* diastereoisomer **189**. This is most likely due to hydride delivery to the generated oxonium intermediate occurring from the least hindered side with regards to the substituent (R) at C3 (Scheme 30). However, this has not yet been mechanistically proven.



Scheme 31: Suspected hydride delivery to generated oxonium species of tetrahydropyranone.

Oxidation of **189** to the tetra oxygenated substituent could then be achieved by bromination to give **190** following an established methodology[53, 83] and substitution *via* copper mediated coupling with sodium methoxide[83, 84]. Treatment with boron tribromide would then generate the desired tetrahydroxynaphthalene moiety **191**, and ceric ammonium nitrate oxidation would give the naphthazarin core, if oxidation was not spontaneous as had been previously observed with simpler systems. Finally, oxidation of the primary alcohol **192** with $NaClO_2$ to form the carboxylic acid would give the C1 epimer of the dihydrogranaticin aglycone and acid mediated inversion, which has precedence in previous synthesis[53, 55] of similar BIQs would yield the desired molecule **38**. This synthetic route was devised due its divergent potential. The addition of different epoxides in the third step would allow access to varying chain lengths and functionality from the C3 carbon and, depending on stereogenicity of the epoxide, allow for generation of all four diastereoisomers. Also, the addition of alternative Grignard/organolithium reagents would allow for the synthesis of other BIQ analogues such as frenolicin **22**.

The silyl protected epoxide **197** could be synthesized in three steps as either enantiomer or in racemic form using literature methods[53, 54] from (*R*), (*S*) or (±)-aspartic acid (scheme 32).

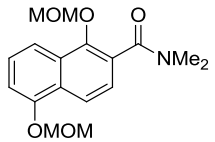


Scheme 32: i) H_2SO_4, KBr, $NaNO_2$. ii) BH_3·THF (71% over 2 steps) iii) NaH, then TBDPS-Cl (61%).

Epoxide **197** was, however, synthesized as a racemate. Treatment of (±)-asapartic acid with sodium nitrite and sulfuric acid resulted in the formation of the diazonium salt at C2 followed by intramolecular nucleophilic substitution of the carboxylic acid to form the β-lactone. A second substitution then occurs at the C2 position from the bromide salt, allowing for retention of stereochemistry. Borane reduction gave diol **(±)-196** in good yield (70% over 2 steps). Finally, treatment with excess sodium hydride resulted in intramolecular epoxide formation which was followed by *in situ* silyl protection to provide epoxide **(±)-197** in modest yield (60%). $^1H/^{13}C$ NMR concurred with literature spectra through all steps[53, 54] showing distinct signals for the alkyl chain at 1.79 (2 H), 2.50 (1 H), 2.78 (1 H), 3.10 (1 H) and 3.89 (2 H) along with the TBDPS moiety at 1.09 (9 H, ^{t}Bu), 7.45 (6 H, Ar) and 7.70 (4 H, Ar).

Protection of both hydroxyl groups of 1,5-dihydroxynaphthalene to yield **185** was achieved in quantitative yield using a large excess of sodium hydride followed by the slow addition of methoxymethylene chloride as a 2.1 M solution in toluene with no need for further purification after extraction. Distinctive MOM peaks at 3.54 (6 H) and 5.39 (4 H) ppm in the ^{1}H NMR spectrum confirmed the presence of these CH_3 and CH_2 groups respectively for the *bis* protected compound **182**. Treatment of naphthalene derivative **185** with TMEDA and ^{t}BuLi at −30 °C followed by the dropwise addition of isopropylisocyanate at −55 °C gave the desired naphthamide **186** in modest yield (60%). Three equivalents of TMEDA and ^{t}BuLi were needed to affect complete lithiation due to aggregation of the organolithium base with the MOM substituents. This, however, resulted in the remaining ^{t}BuLi reacting with the highly elcetrophilic isocyanate to generate *N*-isopropylpivalamide, therefore, an excess of isocyanate was also used. The naphthamide **186** was observed by ^{1}H NMR spectroscopy showing the expected ^{i}Pr peaks at 1.29 (6H, d) and 4.30 (1H, m) ppm along with the presence of a third

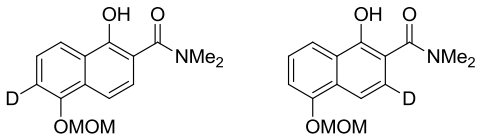
quaternary aromatic carbon and carbonyl signals at 153.4 and 165.4 ppm respectively in the ^{13}C NMR spectrum. Attempted ring opening of commercially available racemic propylene oxide using ^{t}BuLi and TMDEA resulted in degradation of the starting naphthamide. Primarily, the loss of a MOM group was observed in the ^{1}H NMR spectra. This was confirmed as the C1 MOM by HMBC and HSQC ^{1}H NMR. Deuterium quenching experiments (D_2O) using multiple equivalents of base showed no incorporation of deuterium but also exhibited the loss of a MOM substituent indicating that the deprotonation of the secondary amide may be hindering aromatic lithiation. In an attempt to circumvent this issue, the *N,N*-dimethylamide analogue **194** was synthesized following the same procedure and quenching with dimethylcarbamoylchloride.



194

Figure 18: N,N-dimethyl-1,5-bismethoxymethyleneoxy-2-naphthamide.

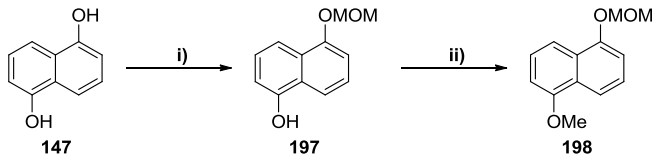
Although the reaction occurred in poor yield, the expected product was verified by the presence of two methyl signals observed in the ^{1}H NMR spectrum at 2.89 and 3.14 ppm, indicative of the desired amide. *Ortho* lithiation with two equivalents of ^{t}BuLi followed by addition of D_2O showed not only observed the loss of the C1 MOM group but showed a 2:1 incorporation of deuterium at C6 and C3 respectively (figure 20).



195 **196**

*Figure 19: Deuterium quenched compounds of lithiated **194**.*

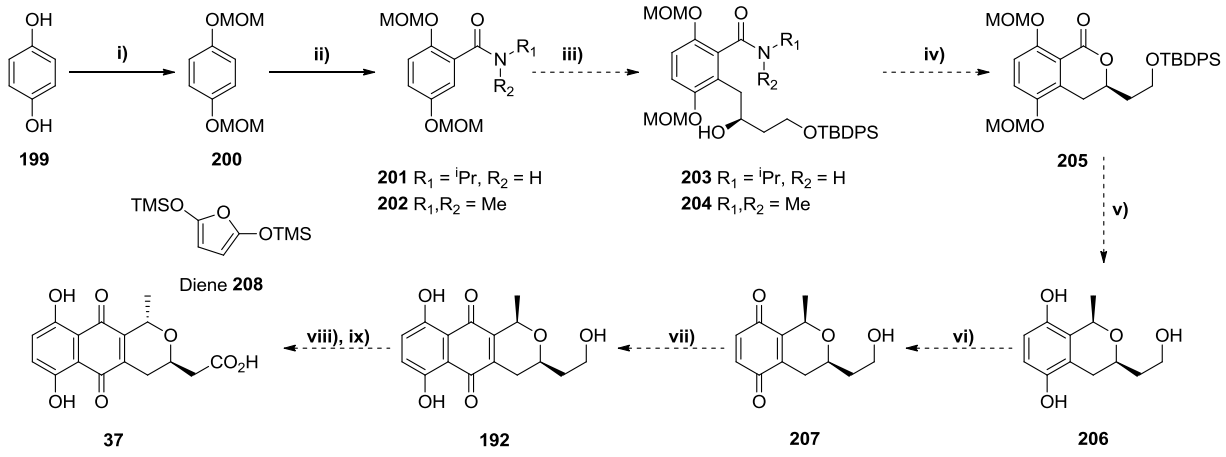
In order to improve lithiation at the C3 position, 1-methoxymethyleneoxy-5-methoxynaphthalene was synthesised (scheme 33) as it was hoped that the *N,N*-dimethylamide would be a stronger *ortho* director than an OMe group.



Scheme 33: i) NaH, MOM-Cl, DMF (99%) ii) NaH, MeI, THF (99%).

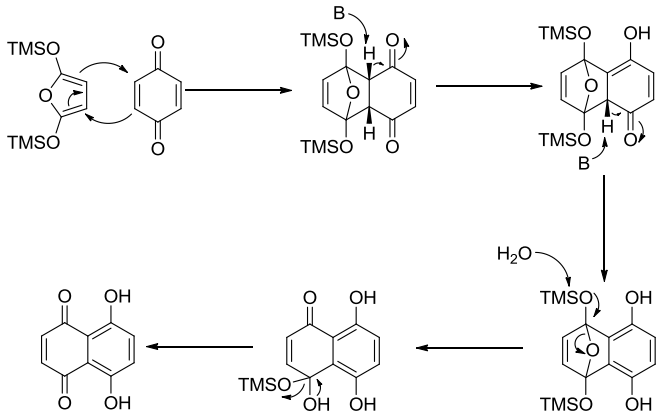
Treatment of dihydroxynaphthalene **147** with 1 equivalent of NaH followed by 1 equivalent of MOM-Cl (2.1 M in PhMe) generated the *mono* protected naphthalene **197** in poor yield (99%) due to partial formation of the *bis* protected compound. The molecule was confirmed through ^{1}H NMR integrations of the methyl (3.48 ppm, 3H) and methylene (5.38 ppm, 2H) protons with the indicative 1,5-disubstituted naphthalene 1H protons. *O*-Methyl protection with sodium hydride and methyl iodide occurred in quantitative yield to give **198** showing a distinct 3H singlet at 4.01 ppm in addition to previously observed signals for the non-substituted naphthalene. However, treatment of this compound with two equivalents of ^{t}BuLi/TMEDA followed by deuterium quenching (D_2O) showed little incorporation of deuterium.

4.3 Synthetic Protocol 1.1

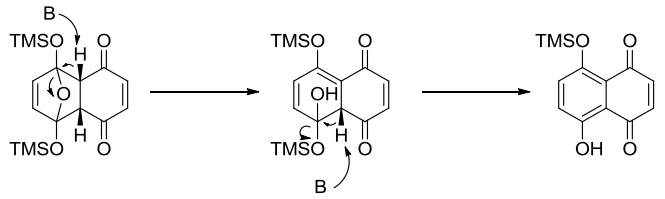


Scheme 34: i) NaH, MOM-Cl (92%) ii) ^{t}BuLi, $ClC(O)NMe_2$ or ^{i}PrNCO (**189** = 71%, **190** = 84%) iii) ^{t}BuLi, **184**. iv) *p*TSA. v) Et_3SiH, MeLi, TFA. vi) CAN. vii) **199**, Et_3N. viii) $NaClO_2$. ix) H_2SO_4.

The key step of our second synthetic strategy was a Diels-Alder cycloaddition (scheme 34, step vii) followed by *in situ* base-mediated rearomatisation, using furan derivative **208**. The reaction was envisioned mechanistically as shown in scheme 35 and scheme 36.



*Scheme 35: Mechanistic rationale for Diels-Alder cycloaddition and base induced aromatization with diene **208**.*

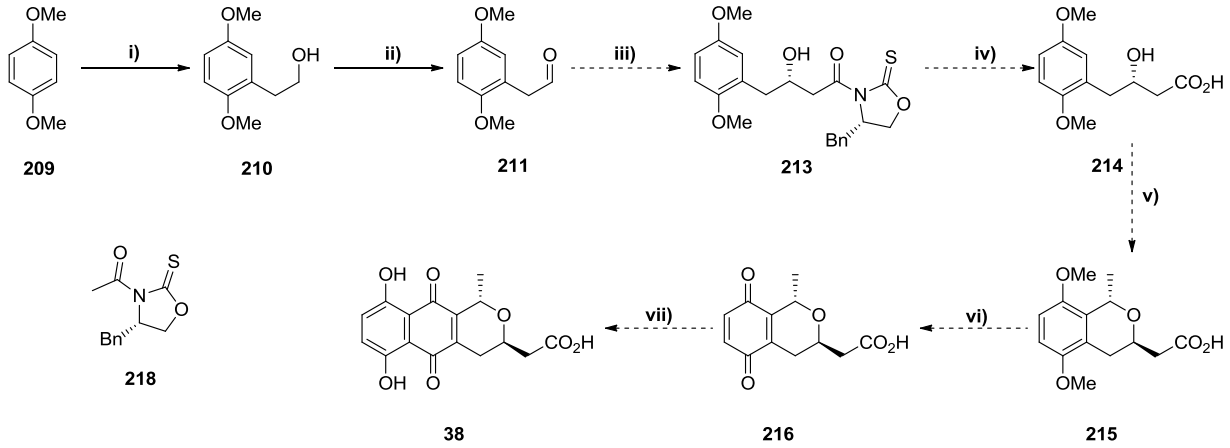


*Scheme 36: Second mechanistic rationale for Diels-Alder cycloaddition and base induced aromatization with diene **208**.*

It was also envisaged that in this synthetic route, global deprotection could be achieved during step v) through the addition of excess TFA to improve the step economy of the strategy. Therefore, although deuterium quenching studies showed that *O*-methyl protection of the aromatic hydroxyls allowed for efficient lithiation with both ^{n}BuLi and ^{t}BuLi, methoxymethyleneoxy protection was chosen as an acid labile protecting fucnctionality. This protocol also maintained the divergent steps of epoxide opening and Grignard addition giving the potential for additional analogues of the aglycone to be synthesised. In addition, alternative dienes, such as 1-(trimethylsiloxy)-1,3-butadiene, could be employed for the Diels-Alder step to synthesise BIQs such as nanaomycin D **19**, dihydrofrenolicin and dihydrokalafungin utilising previous methodology.[63, 64]

Protection of 1,4-dihydroquinone occurred in excellent yield (99%) using an excess of NaH and freshly synthesised MOM-Cl (2.1M in PhMe). Compound **200** was characterized by the distinct methylene and methyl peaks observed in the ^{1}H NMR spectrum at 3.42 and 5.07 ppm respectively. Deuteration studies again showed that three equivalents of either ^{n}BuLi or ^{t}BuLi were required to achieve complete lithiation. Therefore, the synthesis of the *N*-isopropylbenzamide **201** required the addition of three equivalents of the corresponding isocyanate, generating two equivalents of *N*-isopropylpivalamide or *N*-isopropyl-n-butylamide as side products. The n-butylisomer, however, could not be removed *via* silica gel chromatography due to the two compounds similar retention factor of 0.2 (EtOAc/hexanes 1:4). ^{1}H NMR spectroscopy showed distinct isopropyl peaks at 1.28 (6H, d) and 4.21 (1H, m) ppm. Lithiation with four equivalents ^{t}BuLi followed by D_2O quenching resulted in 80% incorporation of deuterium at the C3 position. The need for the excess base was again attributed to aggregation with the MOM substituents and deprotonation of the secondary amide. Nucleophilic epoxide opening of both propylene oxide and silyl protected epoxide **197**, however, did not occur and in the case of epoxide **197** resulted in total degredation of the epoxide. Boron trifluoride etherate was then employed in an attempt to increase the electrophilicity of epoxide **197**. Complete degredation was observed with both substrates. The *N*,*N*-dimethyl analogue **202** was also synthesized in good yield (84%) from the corresponding carbomyl chloride using the same methodology devised. Benzamide **202** was confirmed by signals in the ^{1}H NMR and ^{13}C NMR spectra at 1.21 (6H, s, methyl) ppm and 170.84 (carbonyl) ppm. Attempts at nucleophilic ring opening of propylene oxide again resulted in no reaction indicating that the generated organolithium was too sterically hindered to react with an epoxide.

4.4 Synthetic protocol 2

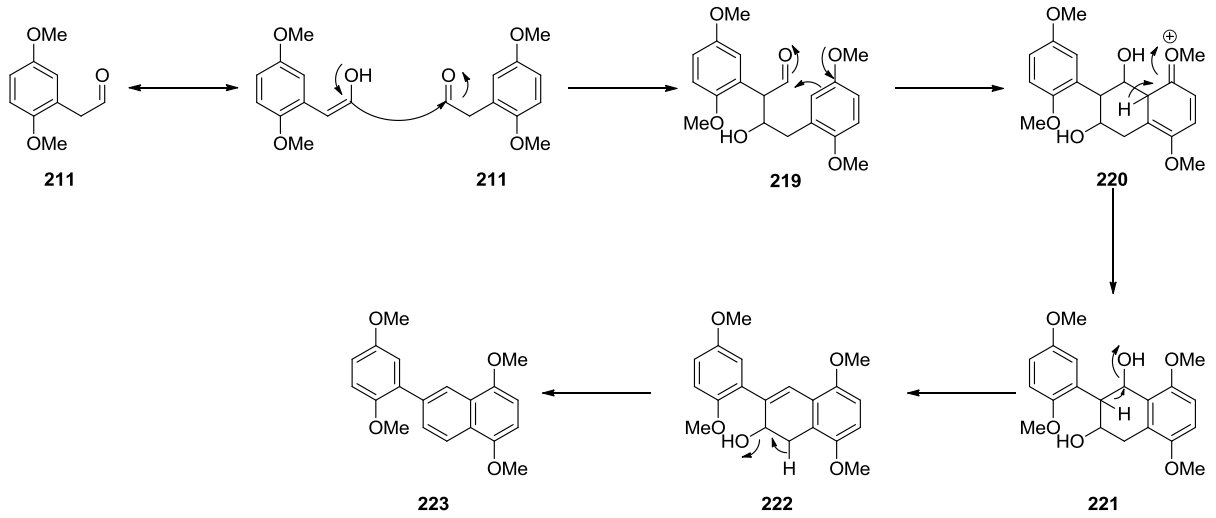


Scheme 37: i) ^{n}BuLi, ethylene oxide (54%) ii) SO_3·Py. EtN(^{i}Pr)$_2$, DMSO (98%) iii) $TiCl_4$, EtN(^{i}Pr)$_2$, **218**, NMO. iv) KOH. v) BF_3·Et_2O, $MeCH(OMe)_2$. vi) CAN. vii) Diene **199**, Et_3N.

The next synthetic strategy (scheme 37) employed two key steps: an Evans aldol[86, 87] like addition to 2-(2,5-dimethoxyphenyl)acetaldehyde **211** and *oxa*-Pictet-Spengler reaction to form the tetrahydropyran ring. Although this route limited the potential number of analogues that could be generated with regards to the substituents at the C3 position, many acetals/aldehydes could be employed for the *oxa*-Pictet-Spengler cyclisation allowing access to various analogues and BIQ natural products.

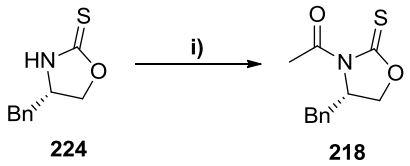
Lithiation of 1,4-dimethoxybenzene **209** with ^{n}BuLi followed by addition of ethylene oxide (liquid cooled to −20 °C) resulted in formation of primary alcohol **210** in modest yield (54%). This was suggested by an LRMS ion signal at $[M+H]^+$ 182.02. ^{1}H NMR showed a distinct geminal triplet at 2H 2.81 ppm observed in along with two distinct 3H OMe signals at 3.69 and 3.72 ppm. Oxidation of this compound could not be achieved under Swern conditions therefore a modified Parikh-Doering was employed. Addition of sulfur trioxide pyridine complex in one portion resulted in formation of 1-(2,5-dimethoxyphenyl)-2-ethyl sulfate which was suggested by LRMS showing an ion signal at $[M]^-$261.20. However, addition over 30 minutes as a solution in DMSO, gave quantitative conversion to aldehyde **211** with no need for purification. Compound **211** was characterised by ^{1}H NMR which showed an indicative aldehyde triplet at 9.96ppm, benzylic 2H doublet at 3.64 ppm and expected OMe signals at

3.79 and 3.80 ppm. The resulting aldehyde, however, proved to be highly air and moisture sensitive and would readily degrade/polymerise upon storage, therefore, all aldol reactions were performed immediately after synthesis of **211**. This instability is believed to be a result of a series of aldol reactions/aromatic substitutions and eliminations between two molecules of the aldehyde. One example of this has been previously reported (scheme 36).[88]



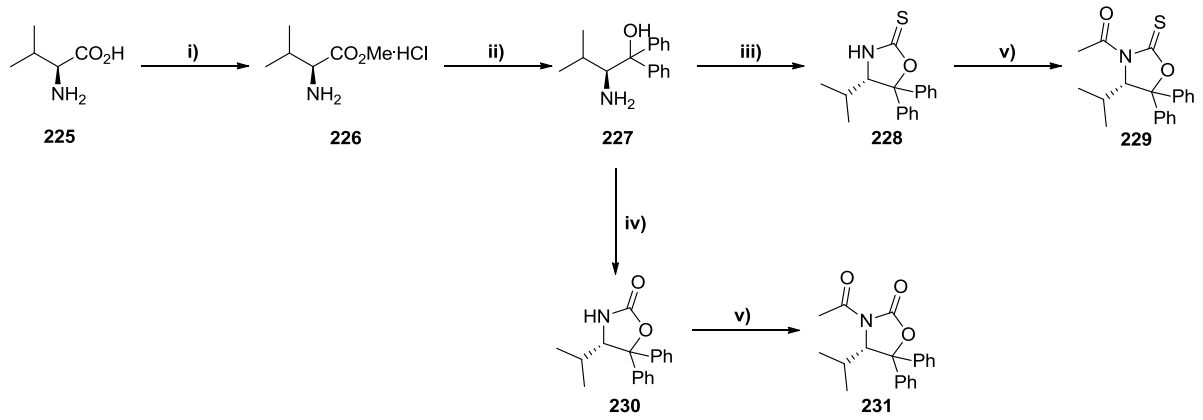
*Scheme 38: Possible side reactions of aldehyde **202**.*

Three Evans like auxiliaries were synthesized (scheme 37 and scheme 38).



Scheme 39: i) ^{n}BuLi, $(Ac)_2O$ (99%).

The first was synthesized from commercially available oxazolidinthione **224** by slow addition of ^{n}BuLi followed by slow addition of freshly distilled acetic anhydride to give auxiliary **218** in quantitative yield. The acetalation product was observed by ^{1}H NMR which showed a distinct α methyl signal at 2.88 ppm (3H, s), along with two 1H doublet of doublets at 2.80 and 3.32 ppm and a 1H multiplet at 4.69 ppm corresponding to the thiooxazolidinone ring protons, in accordance with the literature spectra.[89] A carbonyl carbon was also observed in the ^{13}C NMR spectrum at 171.08 ppm indicating that *N*-acetylation had occurred.



225 226 227 228 229 230 231

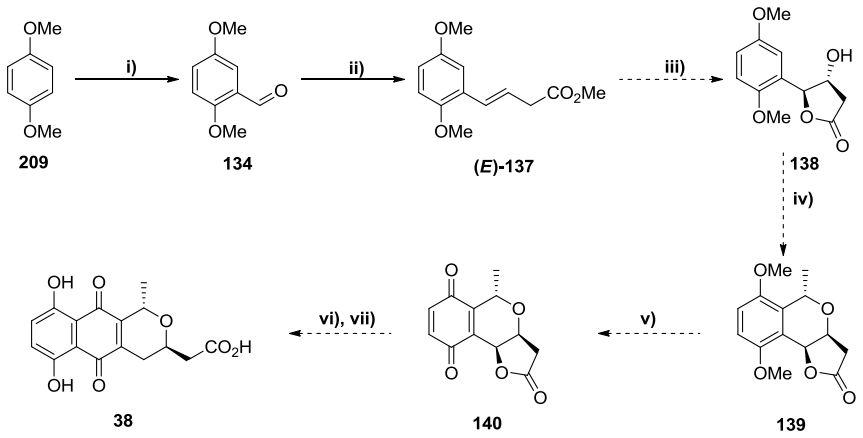
Scheme 40: i) MeOH, $SOCl_2$ (98%) ii) PhMgBr (44%) iii) Et_3N, CS_2 (86%) iv) $CO(CCl_3)_2$, KOH (65%) v) $^{n}BuLi$, $(Ac)_2O$ (**229** = 61%, **231** = 98%).

Oxazolidinthione **229** and oxazolidinone **231** were synthesised in four steps from enantiopure valine **225**. The methyl ester hydrochloride salt **226** was generated by treatment with thionyl chloride in methanol followed by concentration and washing with diethyl ether to give the desired compound in almost quantitative yield with no further need for purification. ^{1}H NMR was consistent with existing literature spectra.[90, 91] The addition of this salt as a solid to an excess of freshly synthesised phenyl magnesium bromide gave 1,1-diphenyl-valinol **227** in low yield (44%) which was confirmed by a ^{1}H NMR signal between 7.19-7.42 ppm (10H, m), ^{i}Pr 3H doublets at 0.69 and 0.81 ppm along with an LRMS ion signal at *m*/*z* $[M + H]^+$: 238.13. The observed spectra were consistent with previously reported literature.[92, 93, 94] (4*S*-isopropyl-(3,3-diphenyl)-thio-oxo-oxazolidin-3-yl)-ethanone **228** was then generated by treatment of the valinol precursor with triethylamine followed by the slow addition of carbon disulfide. Chromatography of the resulting mixture gave oxazolidinthione **228** in good yield (85%) as a yellow solid. ^{13}C NMR displayed a distinct thiocarbonyl signal at 187.9 and LRMS observed an ion at $[M + H]^+$: 298.07. ^{1}H NMR was also consistent with literature precedents showing isopropyl signals at 0.70 ppm (3H, d), 0.90 (3H, d) and 1.90 (1H, m) along with the thiooxazolidinone ring proton at 4.48 ppm (1H, d).[89] *N*-acetylation of this compound with acetic anhydride and sodium hydride gave only modest conversion to **229** after flash chromatography. This is attributed to steric hindrance of the sodium salt intermediate. This compound was characterized by the presence of an α methyl signal observed on ^{1}H NMR spectrum at 2.69 ppm along with a ^{13}C NMR signal at 171.05 ppm indicative of a carbonyl

carbon and consistent with literature spectra.[89] Initial attempts to synthesise (4*S*-isopropyl-(3,3-diphenyl)-oxazolidin-3-yl)-ethanone **231** using diethyl carbonate or ethyl chloroformate in the presence of excess base (NaH or Et_3N) resulted in minimal conversion to **230**. However, treatment with triphosgene and potassium hydroxide followed by recrystalisation from cyclohexane gave the oxazolidinone **230** in a reasonable yield (65%). This product displayed a broad NH singlet at 5.72 ppm on ^{1}H NMR, a ^{13}C NMR signal at 196.8 ppm of the oxazolidinone carbonyl and a LRMS ion at $[M + H]^+$: 282.07 consistent with literature values.[95] *N*-Acetylation with acetic anhydride and sodium hydride again occurred in modest yield, however, the use of ^{n}BuLi as a base gave almost quantitative conversion to the desired auxiliary after recrystalisation to **231**. This auxiliary showed ^{1}H NMR signal for the α methyl group at 2.36 ppm, a ^{13}C NMR carbonyl signal at 153.24 ppm and a LRMS ion at $[M + H]^+$: 282.07 consistent with previously reported literature spectra.[96]

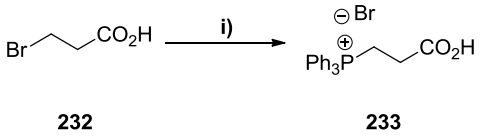
Evans aldol reactions with both oxazolidinethiones **218** and **229** were performed under literature conditions[89] using titanium tetrachloride as a Lewis acid, Hünigs base and *N*-methyl morpholine oxide. Addition of Lewis acid to a solution of the auxiliary in dichloromethane resulted in a distinct bronze mixture, consistent with literature observations, indicating enol formation. However, slow addition to the aldehyde resulted in a highly complex mixture of inseparable compounds observed in the ^{1}H NMR spectrum of the crude mixture and by TLC. No starting aldehyde was present in this mixture. The reaction was performed using alternate amine bases such as TMEDA but gave similar results. Test aldol reactions using simpler aldehydes indicated that complexation of the aromatic aldehyde with the Lewis acid may be generating dimerisation/polymerization compounds, a conclusion was confirmed by exposing the aldehyde to $TiCl_4$ at −78 °C, therefore, the asymmetric aldol reaction was next attempted using a weaker Lewis acid and oxazolidinone **231**. Following literature procedures,[98] di-n-butylboryltriflate was used as the Lewis acid but again caused total degradation of the starting aldehyde and no conversion to the desired aldol product, thus the synthetic strategy was again revised.

4.5 Synthetic protocol 3



Scheme 41: i) ^{n}BuLi, DMF (84%) ii) **233**, ^{t}BuOK, $(MeO)_2SO_2$ (37%) iii) AD-mix-α, $MeSO_2NH_2$. iv) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. v) CAN. vi) **208**, Et_3N. vii) Pd/C, H_2.

The third strategy that was devised, again employed a Diels-Alder cycloadditon and *oxa*-Pictet-Spengler but involved a Sharpless asymmetric dihydroxylation[72] to form a β-hydroxy-γ-lactone ring **138**. This would allow access to granaticin aglycone and hydrogenation of this ring in the final step would give the desired dihydrogranaticin aglycone **38**. It was envisioned that the β ,γ-unsaturated ester precursor **137** could be easily accessed by formylation of 1,4-dimethoxybenzene and *in situ* Wittig/esterification with 3-triphenyl phosphonium bromide propanoic acid **217**. 2,5-dimethoxybenzaldehyde **127** was synthesised in modest yield (50%), *via* lithiation of 1,4-dimethoxybenzene **200** and quenching with DMF. The product concurred with literature spectra showing a distinct aldehyde ^{1}H NMR singlet signal at 10.44 ppm. The ^{13}C NMR spectra also showed an indicative carbonyl signal at 189.6 ppm. This was further confirmed by LRMS showing an ion at $[M + H]^+$ 167.14.

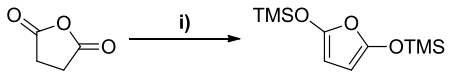


Scheme 42: i) PPh_3 (99%).

3-Triphenylphosphonium bromide propanoic acid **233** was synthesized (scheme 42) as a white solid from the corresponding alkyl bromide **232** and triphenylphosphine in quantitative yield

by treatment with triphenylphosphiene. ^{1}H NMR spectroscopy of the Wittig salt showed two distinct multiplets at 3.11 and 3.77 ppm. The complex splitting observed was expected due to the nuclear spin of the phosphonium substituent. The γ,β-unsaturated ester **137** was synthesised in only a poor yield (37%) despite attempts at optimisation. A solution of ^{t}BuOK in THF was added dropwise over a one hour period to a mixture of the phosphonium salt and the aromatic aldehyde. Two equivalents of Wittig salt **233** and four equivalents of base (^{t}BuOK) were used to increase the yield to 37% after chromatography. After stirring for 30 minutes at 0 °C and 2 hours at r.t., three equivalents of dimethyl sulfate was added to give the esterified product **137**. Analysis of the ^{1}H NMR of the crude material showed significant conversion to the desired unsaturated ester **137**, however, silica gel/alumina gel chromatography led to partial isomerisation giving the α,β-unsaturated compound along with several degradation products. Therefore, essentially pure ester could only be isolated in low yield. This degredation was also observed by Koert *et al.*[70] Analysis of ^{1}H NMR spectra showed a doublet of triplets at 6.29 ppm (J = 16.0, 7.2 Hz) indicative of (*E*)-alkenes along with a third methyl singlet at 3.72 ppm corresponding to the newly installed methyl ester. The same experiment was also performed without the addition of the methylating agent to give the β,γ-unsaturated acid however this could not be isolated as decarboxylation readily occurs during silica/alumina gel chromatography and would subsequently show no conversion under Sharpless AD conditions when used as a crude mixture.

With access to the Sharpless asymmetric dihydroxylation precursor **137** now achieved, investigations into the Deils-Alder cycloaddition reaction using 2,5-(trimethylsiloxy)furan were performed.



234 **208**

*Scheme 43: Synthesis of 2,5-(trimethylsiloxy)furan **199**.*

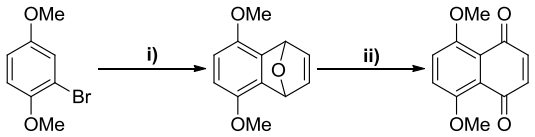
Silylating agent	Base	Lewis Acid
TMS-Cl	Et_3N	-
TMS-Cl	Et_3N	$ZnCl_2$
TMSOTf	Et_3N	-

Table 1: Conditions for i)

Attempts to generate the desired diene under three separate conditions resulted in mixtures of products. The *bis*-silylenolether **199** rapidly decomposed upon exposure to the atmosphere, which has previously been reported.[97, 98] Therefore, test reactions to react the diene with 1,4-naphthoquinone were performed *in situ* with diene formation. These attempts at cyclisations using all three conditions yielded only oxidized naphthoquinone (1,4-dihydroxynaphthalene); therefore, a new strategy was devised for use with the desired diene **199**.

4.5.1 Benzyne cycloadditions

Recent literature[99] was published forming 1,4-quiones fused to aromatic rings *via* a benzyne cycloaddition followed by $PhI(OTf)_2$-induced oxidation.

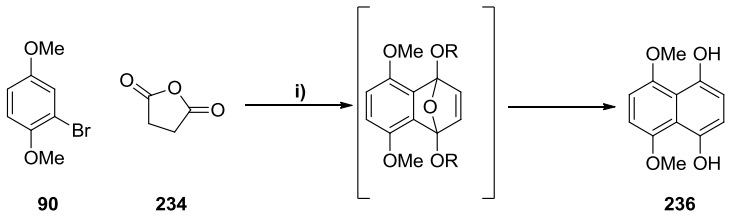


90 **235** **181**

Scheme 44. i) LDA, 2-(trimethylsiloxy)furan (99%) ii) [O]

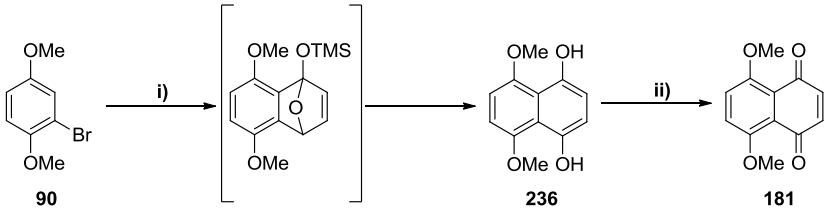
To a solution of freshly prepared LDA was added excess furan in one portion followed by the slow addition of 2-bromo-1,4-dimethoxybenzene **90** over a 1 hour period followed by additional stirring for 1 hour to give the desired cycloaddition adduct **235** in quantitative yield. ^{1}H NMR spectrum observed two triplets of equal *J* value at 5.92 and 7.06 ppm and a LCMS ion signal at $[M + H]^+$ 205.06 consistent with literature spectra.[100] It was discovered that, due to its high reactivity, generation of the benzyne intermediate could not occur prior to the introduction of furan as dimerisation products (namely 2,2',5,5'-tetramethoxy-1,1'-diphenyl) were rapidly generated. Addition of triflic acid to a solution of diacetoxyiodobenzene in DCM

formed a dark solution consistent with literature observations.[100] However, addition of the cycloaddition adduct **235** followed by stirring at 0 °C for 5 minutes before quenching showed total degradation of the starting material. The oxidation was performed again under the same conditions using less reactive difluoroacetoxyiodobenzene but showed similar results. In an attempt to reduce the acidity of the reaction medium a further experiment was carried out using only diacetoxyiodobenzene, under the same conditions, which caused quantitative conversion into the acid mediated ring opened product 1,4-dimethoxy-8-hydroxynaphthalene, distinguished on the ^{1}H NMR spectrum by the distinct 1,4,8-substituted naphthalene signals at 6.91, 7.27 and 7.62 ppm.



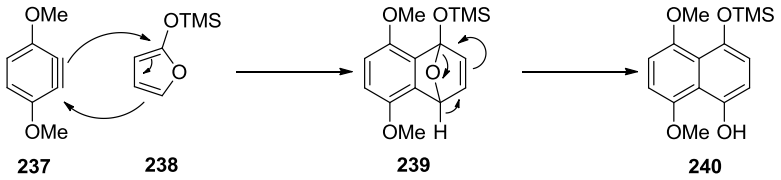
Scheme 45.

In an attempt to circumvent this problem, 2,5-(trimethylsiloxy)furan **218** was again chosen as the diene (scheme 44) for a benzyne cycloaddition. Freshly sublimed succinic anhydride was treated with three equivalents of freshly prepared LDA in order to generate the dienolate followed by the slow addition of aromatic bromide **90**. However, only dimerised compound was observed in the ^{1}H NMR spectrum of the crude material. In an attempt to synthesise the disilylenolether, the anhydride was treated again with three equivalents of LDA but in the presence of two equivalents of TMSOTf followed by the slow addition of aromatic bromide to allow for *in situ* cycloaddition. This resulted in no reaction but showed significant conversion of the starting aromatic compound **90** into 1,4-dimethoxybenzene **209**. This indicated that the generated benzyne intermediate had reacted with the silylating agent and the C-Si bond had been cleaved upon work up. A further experiment was conducted to generate the diene by literature means[98] using trimethylsilyl chloride, triethylamine and $ZnCl_2$ followed by the addition of LDA and 2-bromo-1,4-dimethoxybenzene **90** respectively. No sign of conversion into the benzyne, however was observed in the ^{1}H NMR spectrum of the crude material.



Scheme 46: i) LDA, 2-(trimethylsiloxy)furan (77%) ii) CAN or SiO_2 (99%).

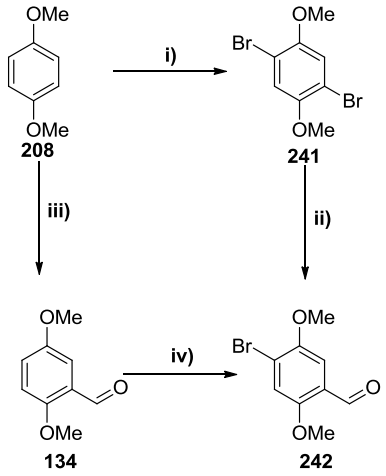
A more stable diene was then selected for the cycloaddition. Commercially available 2-(trimethylsiloxy)furan which was envisaged to undergo acid mediated ring opening to 1,4-dimethoxy-5,8-dihydroxynaphthalene upon work up (scheme 46).



Scheme 47: Predicted mechanism for the cycloaddition between generated benzyne and 2-(trimethylsiloxy)furan.

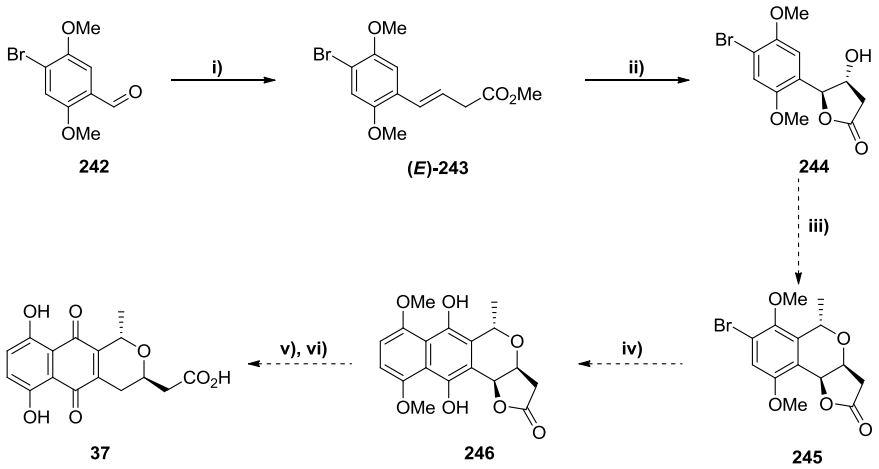
LDA was prepared from freshly distilled DIPA followed by the addition of the substituted furan diene in one portion at −78 °C. The aromatic bromide **90** was then added over 1 hour. After quenching with 1M HCl, extraction and chromatography, the desired tetra oxygenated naphthalene **236** was isolated in modest yield (57%),[101] characterized by, 1H NMR spectroscopy, exhibiting a 2H singlet at 9.08 ppm distinctive to the phenolic OH group as well as two 2H aromatic singlets at 6.61 and 6.82 ppm, along with a small quantity of *O,O*-dimethoxynaphthazarin **281** which oxidized during chromatography. Complete oxidation was observed upon overnight exposure to air or prolonged absorption on silica. Treatment with cerium ^{IV} ammonium nitrate resulted in quantitative conversion into the naphthoquinone **168** within 5 minutes. ^{1}H NMR showed three signals at 3.96 ppm (6H, s), 6.78 ppm (2H, s) and 7.33 ppm (2H, s). ^{13}C NMR spectra as consistent with previously reported results [83, 102, 103] showing a signal for the quinone carbonyl carbons at 184.9 ppm. Utilising two equivalents of diene increased the yield to 77%. Following this success the synthetic route was revised to include an aromatic bromide to allow for the benzyne cycloaddition as a final key step.

4.6 Synthetic protocol 3.1



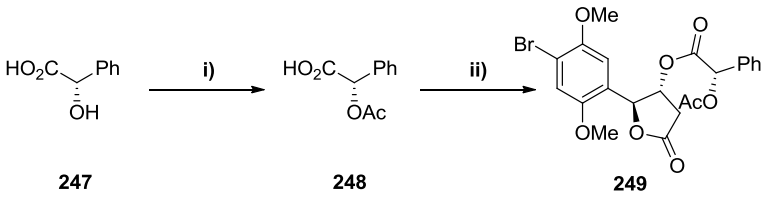
Scheme 48: i) Br_2 (47%) ii) ^{n}BuLi, DMF (90%) iii) ^{n}BuLi, DMF (84%) iv) Br_2, AcOH (53%).

The desired 4-bromo-2,5-dimethoxybenzaldehyde **242** was synthesized *via* two separate methods (scheme 48). Treatment of a solution of dimethoxybenzene **208** in chloroform with bromine gave the *para* dibrominated species **241** in modest yield (47%) after recrystalisation.[104] ^{1}H NMR showed a 6H methyl singlet at 3.85 ppm and aromatic 2H singlet at 7.11 ppm and the ^{13}C NMR observed three aromatic signals at 110.5, 117.1 and 150.5 ppm along with a OMe signal at 57.0 ppm, consistent with literature spectra, however, the compound could not be ionized using ESI. Lithiation followed by addition of DMF and brief reflux in diethyl ether gave benzaldehyde **241** in high yield (89%). ^{1}H NMR showed two distinct aromatic singlets at 7.19 and 7.27 ppm and two methoxy signals at 8.83 and 3.84 ppm along with the characteristic aldehyde peak at 10.33 ppm. The ^{13}C NMR also showed a characteristic carbonyl peak at 188.79 ppm. In order to improve the yield and avoid reflux conditions with n-butyllithium, a second method was devised to synthesise the Wittig precursor involving the previously reported fomylation of 1,4-dimethoxybenzene **208** to give **127** (84%) followed by bromination in acetic acid over 24 hrs allowing alternate access to **242**. Bromination occurred in similar yield to the *para* dibromination (51%) resulting in similar overall yields. Therefore, the first method was preferred due to time economy.



Scheme 49: i) **233**, ^{t}BuOK, $(MeO)_2SO_2$ (51%) ii) AD-mix-α, $MeSO_2NH_2$ (90%) iii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iv) 2-(trimethylsiloxyfuran), LDA. v) BBr_3. vi) Pd/C, H_2.

The Wittig adduct **(*E*)-243** was synthesised and used crude as decomposition to a complex mixture of compounds occurred during silica gel/alumina gel chromatography. Again the ^{1}H NMR spectrum of the crude material showed significant conversion into the (*E*)- β,γ-unsaturated ester, however. The product showed characteristic *trans* alkene peaks by ^{1}H NMR spectroscopy at 6.30 ppm (1H, dt, J = 16.0, 7.1 Hz) and 6.74 ppm (1H, dt, J = 16.0, 1.5 Hz). The carboxylic acid analogue was also synthesized showing distinct *trans* alkene peaks in the ^{1}H NMR spectrum of the crude material but could not be purified due to its high polarity and degredation compounds. The β-hydroxylactone **244** was then synthesised in excellent yield (90%) after chromatography under standard Sharpless asymmetric dihydroxylation conditions[72] using g/mmol of AD-mix-α and 1 equivalent of methane sulfonamide. ^{1}H NMR spectrum observed the loss of the methyl ester singlet and distinct non-equivalent α protons at 2.70 ppm (1H, d, J = 17.7 Hz) and 2.87 ppm (1H, dd, J = 5.3 Hz) along with a benzylic 1H doublet at 5.68 ppm and C**H**OH multiplet at 4.80 ppm. This compound was also confirmed by HRMS showing indicative bromine containing ion signals at $[M + H]^+$ 317.0024 and 319.0032. In order to ascertain enantiomeric excess a diastereoisomer was synthesized (scheme 50).



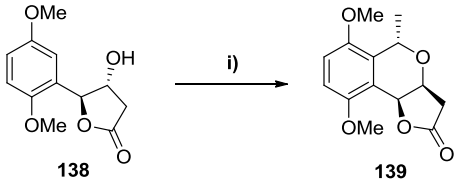
Scheme 50: i) DMAP, Py., $(Ac)_2O$ (99%) ii) DMAP, DCC, lactone **248**(>10%).

O-Acetylmandelic acid **248** was synthesized from the enantiopure starting material **247**. Treatment of mandelic acid **247** with catalytic DMAP and freshly distilled acetic anhydride in a solution of diethyl ether and pyridine yielded the desired *O*-acetylated **248** compound in quantitative yield.[105] $[\alpha]_D$ confirmed no loss of chirality (+149.2° *c* = 1.00 g/100mL MeOH) as the result concurred with previously published results. The presence of a methyl singlet at 2.13 ppm along with benzylic proton singlet at 5.86 ppm also correlated with literature spectra.[105] This pure compound was then treated with catalytic DMAP and DCC in a solution of toluene followed by the addition of the β-hydroxylactone **244** dropwise as a solution in dichloromethane. Esterification of this compound occurred in very low yield preventing isolation of **249**, therefore the *ee* could not be ascertained. No further purification was performed.

With the Sharpless asymmetric dihydroxylation adduct **244** in hand, the next key step was an *oxa*-Pictet-Spengler reaction to form the tetrahydropyran ring. Previously reported literature and preliminary test reactions showed that boron trifluoride etherate complex gave the highest conversion. However, using a twofold excess of the dimethyl acetal of acetaldehyde with this Lewis acid gave no reaction at 0 °C to r.t. Increasing the temperature to reflux in dichloromethane caused decomposition of the hydroxylactone ring. The addition of $BF_3{\cdot}Et_2O$ to a mixture of acetaldehyde and lactone at r.t. also gave zero conversion. When the addition order was reversed a deep red solution formed upon addition of the Lewis acid to the acetal indicating formation of the oxonium ion of the acetal, however, slow addition of a solution of lactone in dichloromethane gave again no conversion. Using a 4:1 mixture of Et_2O:THF (used due to the Sharpless adduct **244** insolubility in diethyl ether) also resulted in no reaction under these conditions. A final attempt at cyclisation was performed using ten equivalents of both acetal and Lewis acid which resulted in partial degradation after 24 hrs. Several possible explanations were postulated for this lack of reactivity. The electron withdrawing capacity of

the lactone ring was deactivating the hydroxyl group, reducing the nucleophilicity and thus preventing reaction with the oxonium intermediate. Coordination of the lactone carbonyl to the boron trifluoride was resulting in enolisation or the combined *meta* deactivating properties of both the bromine and methoxy substituents were preventing aromatic substitution.

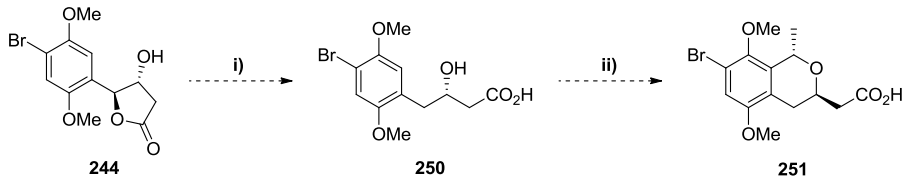
During this period, a publication by Koert *et al.*[71] showed that the *oxa*-Pictet-Spengler reaction could be achieved under harsh conditions on the non-brominated lactone.



Scheme 51: Ulrich Koert's oxa-Pictet-Spengler conditions i) $BF_3{\cdot}Et_2O$, TFA, $MeCH(OMe)_2$, 80 °C, 60 sec. (41%)

The group achieved a 14:1 diastereomeric ratio of *trans:cis* isomers of **138** by the addition of the β-hydroxylactone **139** to a solution of $MeCH(OMe)_2$ (10 equivalents) and boron trifluoride diethyl etherate complex (10 equivalents) in trifluoroacetic acid at 80 °C. The reaction time was kept under 60 seconds before quenching at 0 °C to reduce compound degradation giving the formed pyran ring in 41% yield. It was clear from the publication that the *oxa*-Pictet-Spengler cyclisation on the desired brominated species would be extremely difficult to achieve due to the added *meta* deactivating capability of the bromine. An additional complication observed by the group was the same instability of the β,γ-unsaturated ester confirming our result of degradation during silica gel chromatography.

In an effort to circumvent this issue, the synthesis was revised to open the lactone ring and attempt an *oxa*-Pictet-Spengler reaction on the β-hydroxycarboxylic acid **251**.



Scheme 52: i) Pd/C, H_2 ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$.

Solvent	Temperature	Time
EtOAc	r.t.	17 hrs.
EtOAc	40 °C	30 mins.
MeOH	r.t.	17 hrs.
MeOH	r.t.	2 hrs.
EtOAc + *p*TSA (cat.)	r.t.	2 hrs.

*Table 2: i) Hydrogenation conditions for **244**.*

The β-hydroxylactone **244** was subjected to several hydrogenation conditions (table 2). Overnight reaction using ethyl acetate as the solvent and catalytic palladium on carbon resulted in no reaction. Increasing the temperature gave total degradation of the lactone ring within 30 mins. Using methanol as the solvent resulted in complete isomerisation at the geminal position after 17 hours with no opening of the lactone ring. Reducing the reaction time and monitoring the reaction by ^{1}H NMR showed that partial isomerisation after 2 hours and again no lactone hydrogenation. A final attempt to resolve this problem was to perform the reaction in the presence of catalytic *p*TSA. By monitoring by ^{1}H NMR spectroscopy, degradation products were observed within 2 hrs. The benzylic stereoscrambling is attributed to the high electron density of the aromatic ring resulting in opening of the lactone ring.

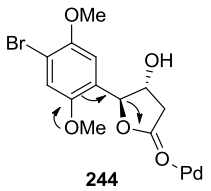
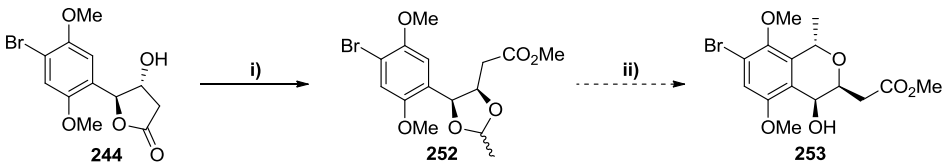
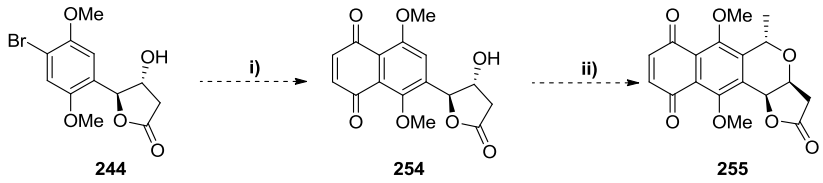


*Figure 20: Possible Pd induced ring opening of **244**.*



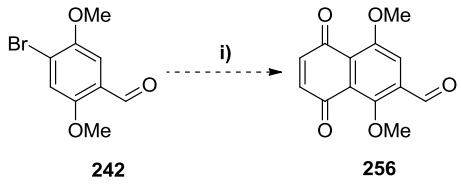
Scheme 53: i) Amberlyst™, $MeCH(OMe)_2$, MeOH (33%) ii) $BF_3{\cdot}Et_2O$

The second attempt to overcome the lack of reactivity towards *oxa*-Pictet-Spengler cyclisation was to perform the reaction intramolecularly by converting the β-hydroxylactone **224** into the corresponding β,γ-ethyl acetal methyl ester **228** and then subjecting the compound to $BF_3{\cdot}Et_2O$ to form the tetrahydropyran ring. Stirring a methanolic solution of lactone with a large excess of 1,1-dimethoxyethane in the presence of amberlyst™ resin gave desired compound **228** in 33.3% yield after three days as a mixture of acetal diastereoisomers. This was characterised by ^{1}H NMR spectroscopy showing two acetal methyl doublets at 1.41 and 1.45 ppm (J = 3.0 Hz) along with two acetal CH quartets at 5.27 and 5.34 ppm (J = 6, 9 Hz). However, exposure to boron trifluoride resulted in the rapid and complete degradation of acetal **228** to a mixture of deoxygenated compounds.



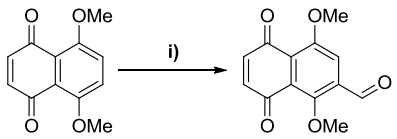
Scheme 54: i) LDA, 2-(trimethylsiloxy)furan. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$.

The strategy was then rearranged to perform the benzyne cycloaddition on β-hydroxylactone **244** using an excess of base to deprotonate the hydroxyl group and form the benzyne intermediate. However, treatment of lactone **244** with LDA, however, did not lead to benzyne formation. This is attributed to the formation of the hydroxyl enolate dianion preventing a third deprotonation.



Scheme 55: i) LDA, 2-(trimethylsiloxy)furan.

The cycloaddition could not be attempted on β,γ-unsaturated ester **(*E*)-243** as it was envisaged that benzyne cycloadditions could occur with the unsaturated bond. Therefore, the reaction was attempted with 4-bromo-2,5-dimethoxybenzaldehyde **242**. This resulted in a complex mixture of inseperable compounds..



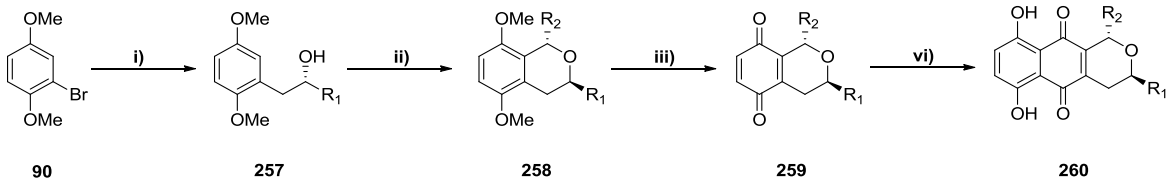
181 257

Scheme 56: i) ^{n}BuLi, DMF.

Ortho-lithiation of *O,O*-dimethoxynaphthazarin **181** at −78 °C did not occur but resulted in degredation of **181** producing an inseperable mixture of compounds. This seemed likely to contain addition products of the organolithium either by conjugate addition or direct addition to the quinone carbonyls.

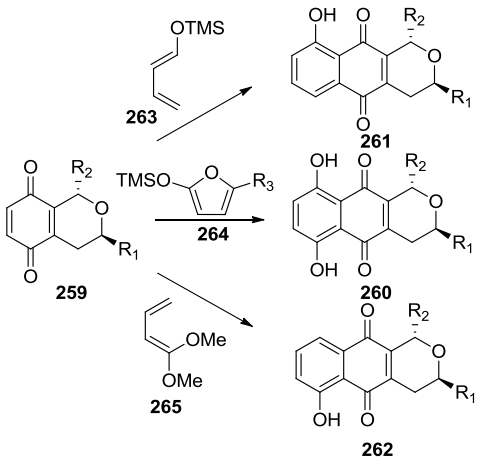
4.7 Synthetic protocol 4

A new divergent strategy was devised to allow for varying chain lengths (R_1) at C3 by opening a variety of epoxides. This would allow for the synthesis of analogues of BIQ natural compounds such as eleutherin **105** by opening propylene oxide as well longer, more functionalised carbon chains such as that present in the granaticin by opening epoxides such as the previously synthesised TBDPS protected epoxyalcohol **197**. Variation at C1 (R_2) could be achieved by utilizing a range of acetals or aldehydes in an *oxa*-Pictet-Spengler cyclisation. This would allow for analogues of BIQ molecules such as deoxyfrenolicin **107** containing an ^{n}Pr chain to be generated. Two alternate starting materials were considered for this synthesis to either incorporate a Diels-Alder reaction or a benzyne cycloaddition.



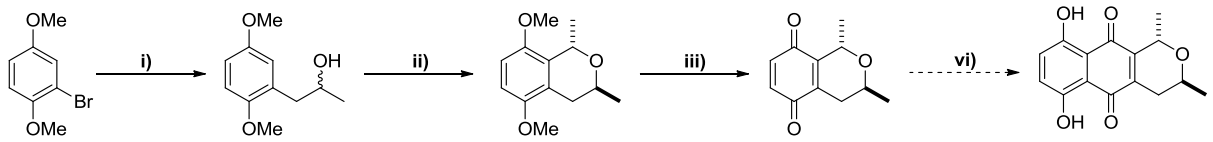
Scheme 57: i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, epoxide. ii) $R_2CH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) CAN. iv) **199**, Et_3N then Jones reagent.

The first cyclisation considered was a Diels-Alder (scheme 57). Starting from 2-bromo-1,4-dimethoxybenzene **79** and including a ceric ammonium nitrate oxidation as the third step would allow for a range of oxidized naphthoquinones to be produced (scheme 58). It is believed that the 5,8-dihydroxynaphthoquinone core is essential for the attachment of the sugar moiety, thus, this methodology would confirm this hypothesis.



Scheme 58: Potential Diels-Alder adducts.

Using previously reported methodology,[74] a Diels-Alder reaction with 1-trimethylsiloxy-1,3-butadiene followed by Jones oxidation would allow for the generation of BIQ molecules such as kalafungin **15** and nanaomycin **16**. Using the methodology reported by Xu *et al.* in the total synthesis of crisamicin,[49] Diels-Alder reaction with 1,1-dimethoxy-1,3-butadiene followed by Jones oxidation could generate unusual BIQ molecules featuring the hydroxyl group at the 6 position. However, the main focus was to synthesise the naphthazarin core by Diels-Alder cycloaddition with 2-(trimethylsiloxy)furan or 2,5-(trimethylsiloxy)furan **207**.



90 **266** **267** **268** **269**

Scheme 59: i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, propylene oxide. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$, (75% over 2 steps) . iii) CAN, (99%). iv) **207**, Et_3N, then Jones reagent.

The first epoxide selected was commercially available propylene oxide which can be bought enantiopure, or the racemic compound can be resolved *via* a Jacobsen kinetic resolution.[106, 107] However, for the purposes of devising the methodology, the epoxide was used as a racemate. Treatment of 2-bromo-1,4-dimethoxybenzene **90** with ^{n}BuLi followed by the addition of neat propylene oxide yielded only starting material. However, the slow addition of boron trifluoride diethyletherate complex before quenching with the epoxide gave the desired secondary alcohol in good yield. However, silica gel chromatography resulted in a complex mixture of compounds which is presumed to be a result of elimination and polymerization.

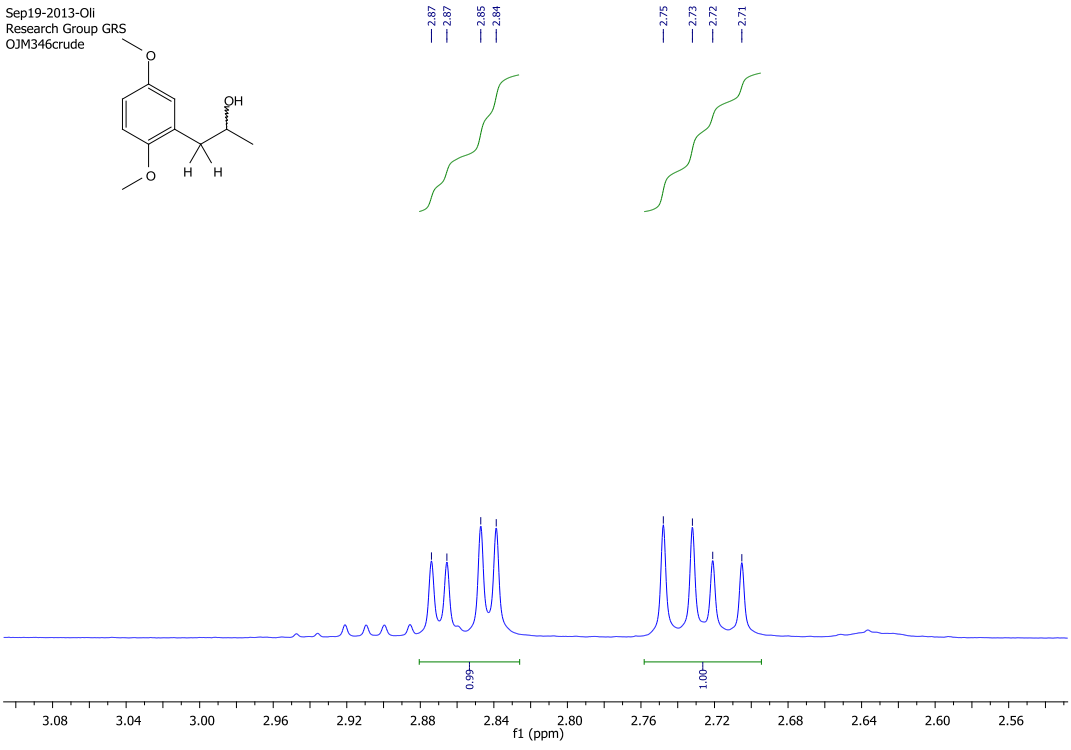


*Figure 21: Geminal protons of 3-(2,5-dimethoxyphenyl)isopropanol **239**.*

Therefore, the compound was identified by ^{1}H NMR spectroscopy of the crude material showing two distinct doublets of doublets at 2.72 and 2.85 ppm (figure 21) and by HRMS [M + H]$^{+}$: 197.1172,[108] and used as a crude mixture for the next step. The impure oil was then dissolved in dichloromethane with two equivalents of the dimethyl acetal of acetaldehyde and slowly treated with $BF_3{\cdot}Et_2O$ giving quantitative conversion to the desired isochromane. ^{1}H NMR NOESY experiments determined the reaction to yield a 2.7:1 mixture of *trans*:*cis* diastereoisomers of **267**. The ^{1}H NMR spectrum shows four distinct methyl doublets at 1.25 and 1.43 ppm (*trans*) and 1.28 and 1.47 ppm (*cis*) corresponding to the methyl groups at C1 and C3. Two distinct tertiary proton signals corresponding to the proton at C1 were also observed as a quartet of triplets at 4.90 ppm (*cis*) and a quartet at 5.01 ppm (*trans*).[109]

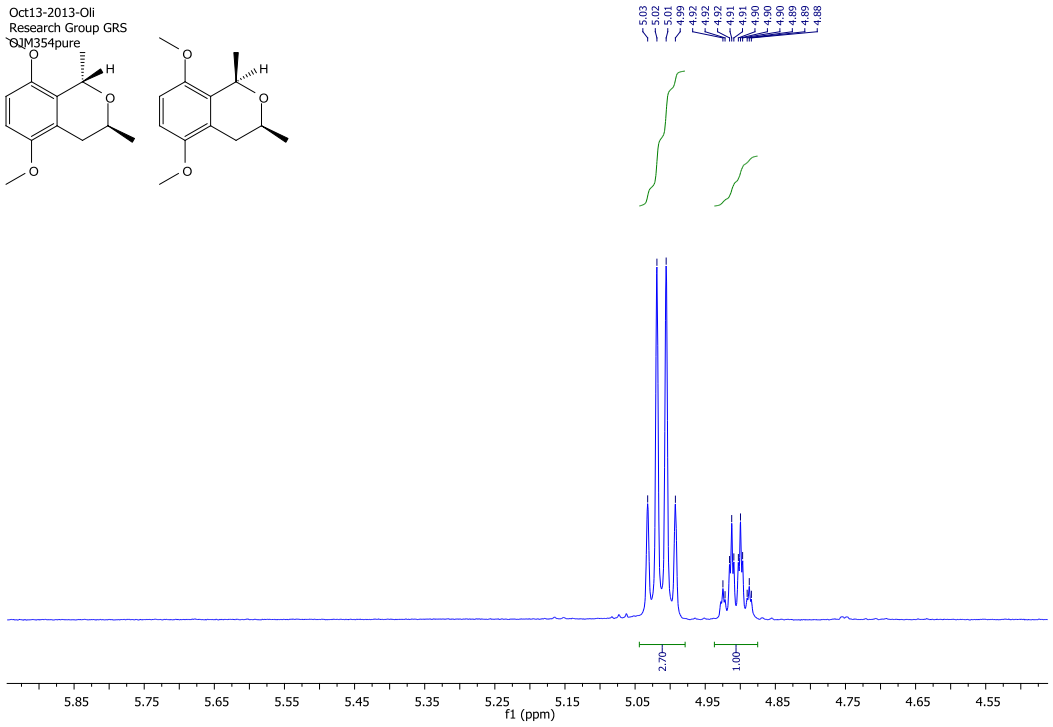
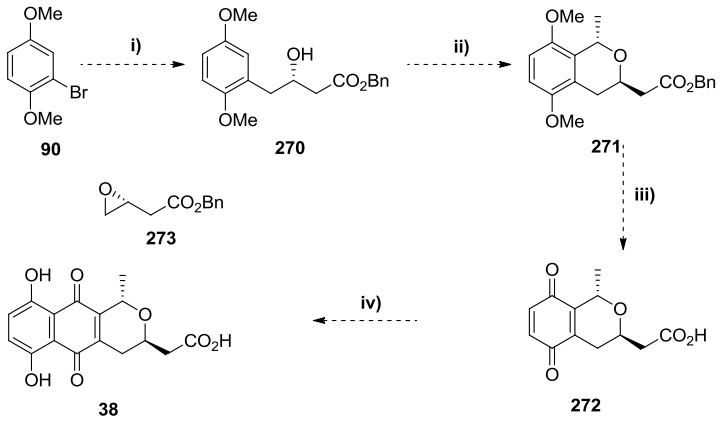


*Figure 22: C1 tertiary protons of 1,3-dimethyl-5,8-dimethoxyisochromane **267**.*

This mixture of diastereoisomers was then treated with ceric ammonium nitrate to give the corresponding isochromane quinone in quantitative yield of **268**, again as a 2.7:1 mixture of diastereoisomers *trans*:*cis*. The desired *trans* isomer was easily isolated by silica gel chromatography. This compound was characterised by ^{1}H NMR showing loss of both methoxy groups, two methyl doublets at 1.31 and 1.45 ppm, two benzylic proton signals at

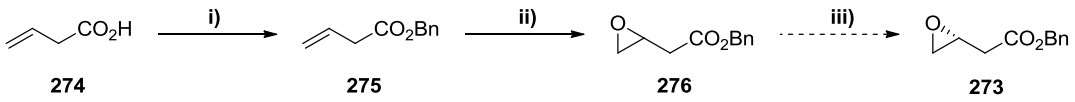
2.12 ppm (ddd) and 2.52 ppm (ddd), a C3 proton multiplet at 3.94 ppm and a doublet of quartets at 4.83 ppm corresponding to the tertiary proton at C1. NOE ^{1}H NMR confirmed the stereogenic configuration by the absence of correlation between the C1 and C3 tertiary protons or methyl protons.[109]

With the simple (±)-1,3-dimethylisochromane quinone **268** in hand attempts were made to replicate the synthesis using a more complex epoxide.



Scheme 60: i) ^{n}BuLi, **273**. ii) MeCH(OMe)$_2$, $BF_3{\cdot}Et_2O$. iii) CAN. iv) Et_3N, diene **199**.

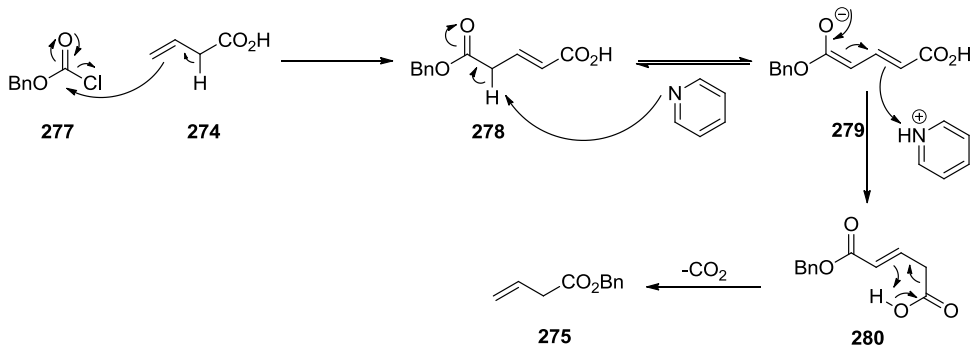
In order to improve step economy, an ester epoxide **273** was chosen rather than a protected primary alcohol to avoid oxidation steps later in the synthesis. Also by using a benzyl protected ester, concomitant ester cleavage and oxidation to the quinone could be achieved allowing for a more elegant synthesis.



Scheme 61. i) CBzCl, Py., (98%). ii) *m*CPBA, $NaHCO_3$, (36%). iii) Co(Salen).

The racemic epoxide was synthesised according to literature procedure[110, 111] starting from vinyl acetic acid **246**. Treatment of this compound with pyridine and benzyl chloroformate, *via* the decarboxylative mechanism described (scheme 62), produced vigorous gas evolution upon cloroformate addition, and gave the desired benzyl ester **247** in high yield (98%). After chromatography, the compound was confirmed by comparison of ^{1}H NMR data with literature spectra showing two distinct signals at 3.16 ppm (2H, dt, J = 7.2, 1.4 Hz) and 5.95 ppm (1H,

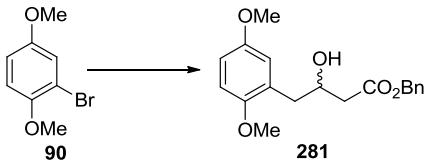
dt, J = 17.4, 9.9 Hz) along with an indicative benzyl 2H singlet at 5.15 ppm. An indicative carbonyl ester signal was observed in the ^{13}C NMR at 170.6 and HRMS ion at $[M + H]^+$: 193.0857, again concurrent with literature spectra[110, 111] also confirmed this compound.



Scheme 62: Mechanism for the synthesis of but-3-enebenzoate.

The β,γ-unsaturated ester was then subjected to four equivalents of *m*CPBA and stirred for 24hrs. Although conversion was not complete, increasing reaction time resulted in degradation of the epoxide yielding the desired compound in 35%. Compound **275** was characterized by ^1H NMR showing the loss of both vinyl protons and three multiplets at 2.56 ppm (1H), 2.61 ppm (2H) and 2.80 ppm (1H) along with the expected benzyl signals at 5.20 ppm (2H) and 735 ppm (5H). HRMS also confirmed this compound with an ion $[M + H]^+$: 193.0857 signal.[111, 112] This compound could then undergo a Jacobsen kinetic resolution[106] to give the enantiopure epoxide, following literature precedent, however attempts to optimize the methodology of reacting the epoxyester with the aromatic nucleophile were performed on the racemic series before using expensive catalysts.

Several nucleophiles were used in the attempt to ring open the epoxide in the racemic series by metallating 1-bromo-2,5-dimethoxybenzene.

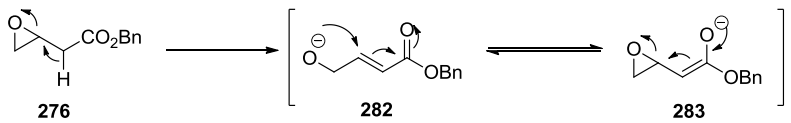


*Scheme 63: Opened ester **276**.*

Metallating agent	Eq. of nucleophile	Temperature of addition (°C)	Lewis acid	Addition order
^{n}BuLi	1	−78	-	Epox. to Nucleophile
^{n}BuLi	3	−78	-	Epox. to Nucleophile
^{n}BuLi	3	−78	-	Nucleophile to epox.
^{n}BuLi	1	−78	$BF_3{\cdot}Et_2O$	Epox. to Nucleophile
^{n}BuLi	3	−78	$BF_3{\cdot}Et_2O$	Epox. to Nucleophile
Mg	3	−78	-	Epox. to Nucleophile
^{n}BuLi/CuI	3/1.5	−78	-	Epox. to Nucleophile
^{n}BuLi/CuCN	3/1.5	−78	-	Epox. to Nucleophile
^{n}BuLi/CuI	3/3	−78	-	Epox. to Nucleophile

*Table 3: Epoxyester **276** addition conditions.*

Generating the aromatic lithium nucleophile with ^{n}BuLi and reacting a solution of electrophile to this resulted in only degradation of the epoxide giving a highly complex mixture of compounds. This occurred regardless of the addition order and number of equivalents of nucleophile used. When boron trifluoride etherate complex was used, again with stoichiometric or excess nucleophile, complete degradation was also observed. One compound that could be observed by ^{1}H NMR spectroscopy, but not isolated, was the opened epoxide *via* α proton abstraction which is assumed to be highly labile to the resonance structures of the anionic intermediates (scheme 64).

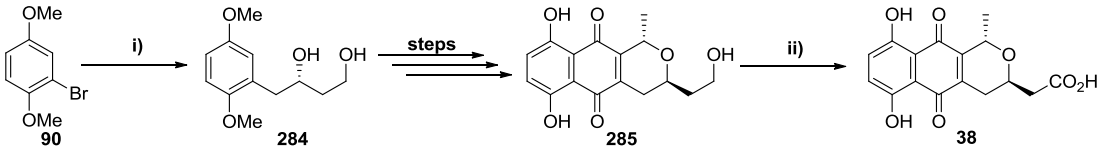


276 282 283

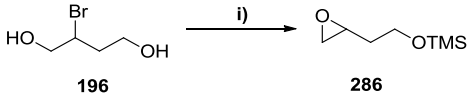
*Scheme 64: degredation of **276**.*

Therefore, a less basic organometallic reagent was required. Using the Grignard reagent of the bromoaromatic also resulted in total degradation of the epoxyester **276** so several attempts were made to generate the organocuprate. Following literature procedure, the starting aromatic was lithiated and added to a solution of copper^{I} iodide or copper^{I} cyanide and allowed to stir at −40 °C overnight giving a distinct green/yellow coloured solution. A solution of epoxide was then added to this at −78 °C and monitored by ^{1}H NMR. In all cases degradation of the epoxyester to the unsaturated ester **276** occurred rapidly.

The synthesis was then revised to use a protected primary alcohol and include the oxidation of this substituent to the required carboxylic acid at the end of the synthesis. It was hoped that a protecting group could be used to still include concomitant cleavage in order to maintain some step economy. TMS protection was selected due to its high lability in the presence of acid and was hoped that this could be cleaved upon quench of the epoxide opening reaction with two molar hydrochloric acid.

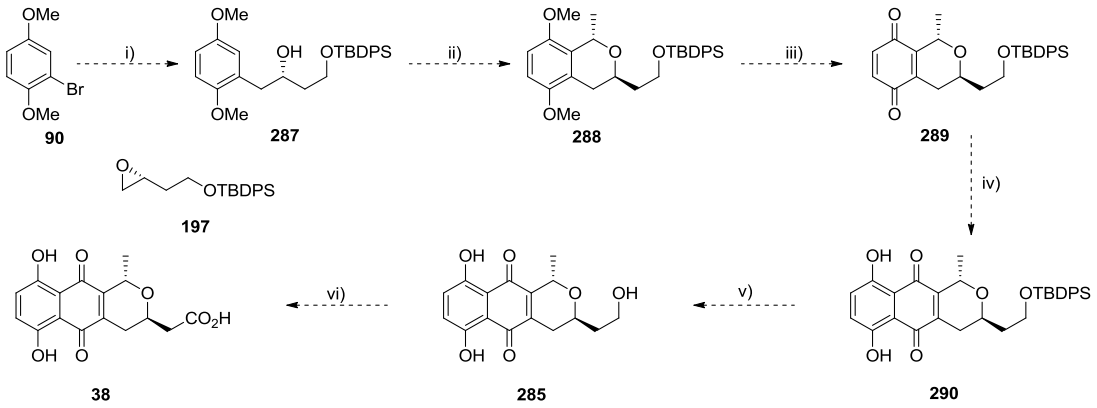


Scheme 65: i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, epoxide, then 2M HCl. ii) $NaClO_2$.



Scheme 66: i) NaH, TMSCl.

Attempts were made to synthesise the trimethylsilyl analogue **286** of the previously synthesised epoxide using the same methodology[54] (scheme 32). However, the final step of the synthesis (scheme 62) did not achieve the incorporation of the silyl protecting group due to its instability towards aqueous extraction TBDPS[54] was then reselected as the protecting moiety with the intention of a deprotection at step five. The possibility to again cleave the oxygen silicon bond upon quenching, but with a stronger acid, was still plausible, however, it was presumed that elimination of the newly formed hydroxyl group could occur. Therefore, for the purposes of developing this reaction procedure, this acidic quench was not conducted. .

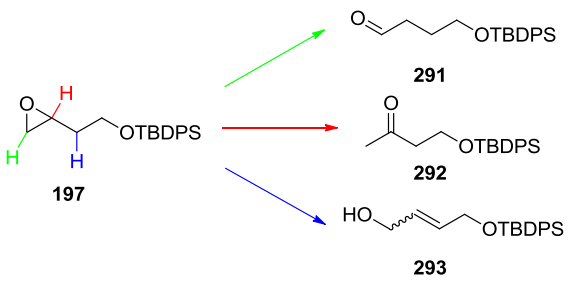


Scheme 67: i) ^{n}BuLi, **197**, $BF_3{\cdot}Et_2O$. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) CAN. iv) Et_3N, 2-(trimethylsiloxy)furan. v) TBAF. vi) $NaOCl_2$.

Metallating agent	**Eq.**	**LA**	**Addition Temperature (°C)**	**Result**
^{n}BuLi	1	-	−78	No reaction
^{n}BuLi	1	$BF_3{\cdot}Et_2O$	−78	No reaction
^{n}BuLi	1	$BF_3{\cdot}Et_2O$	0	Epoxide degradation
^{n}BuLi	1	-	0	Epoxide degradation
^{n}BuLi	1	$BF_3{\cdot}Et_2O$	0 (inverse addition)	Epoxide degradation
^{n}BuLi	1	-	0 (inverse addition)	Epoxide degradation
Mg	1	-	0	Epoxide degredation
Mg	1	-	−78	Epoxide degradation
Mg	1	-	−78 (inverse addition)	Epoxide degradation
^{n}BuLi /CuI	0.5	-	−78	No reaction
^{n}BuLi /$ZnCl_2$	1	-	−78	Epoxide degradation

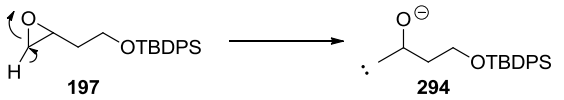
*Table 4: TBDPS protected epoxide **197** opening conditions.*

The dropwise addition of the epoxide to a solution of the organolithium at −78 °C resulted in no reaction with and without the presence of boron trifluoride, therefore, the temperature was increased. In both cases, this led to total degradation of the epoxide even when the addition order was reversed to add a solution of the nuclophile to the protected epoxide. These reactions gave an complex and inseparable mixture of compounds. These observations can be attributed, in part, to abstraction of the three most acidic protons on the epoxide by the highly electron rich aromatic lithium reagent (scheme 68).



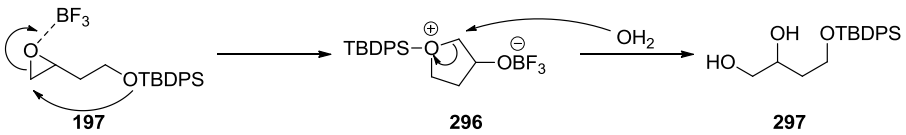
*Scheme 68: β-elimination of epoxide **184**.*

In the first two cases (coloured green and red) a proton is abstracted to generate an enolate which, upon, quenching results in the aldehyde or ketone respectively. In the third case (coloured blue) β-elimination occurs to give the unsaturated alcohol. Another possible explanation for the high number of side compounds is cyclisation under Lewis acid conditions.



*Scheme 69: α-elimination of epoxide **184**.*

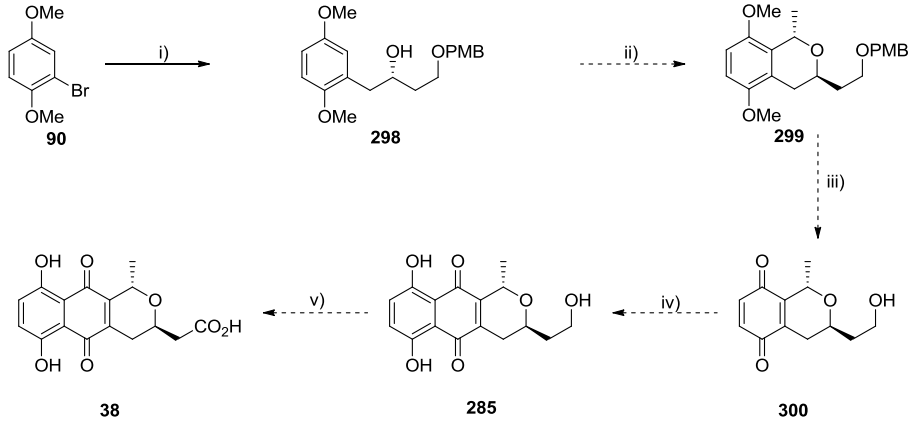
The α-elimination product could also be attributed to the complex mixture observed, generating the primary carbene of epoxide **184**.



*Scheme 70: Lewis acid induced cyclisation of epoxide **184**.*

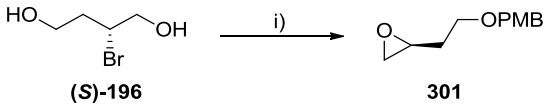
The presence of boron trifluoride could induce the formation of a zwitterionic five membered heterocyclic intermediate **296** which is ring opened upon quenching with water to generate the 1,2-diol **297**. It was clear that a less basic nucleophile would be required therefore the Grignard reagent was synthesised. At 0 °C, a black solution rapidly formed and complete degradation of the starting material was observed by ^{1}H NMR. At −78 °C degradation of the epoxide was also observed. This was attributed to coordination of magnesium salts to the epoxide resulting in similar by products. However, when the addition order was reversed the same result was observed indicating that the aromatic organomagnesium was also deprotonating the epoxide. The organocuprate was then synthesised, however the dropwise addition of the TBDPS protected epoxide at −78 °C warming to 0 °C yielded no reaction. The final organometallic reagent synthesised used zinc^{II} chloride to trans metallate with the generated aromatic lithium species but its use resulted in degradation of the starting epoxide. Therefore, alternative epoxides were considered.

Para-methoxybenzyl was the next choice for protection as it was hoped that it could be removed with ceric ammonium nitrate during step three (scheme 71).



Scheme 71: i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, **301**, (87%). ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) CAN. iv) Et_3N, diene. v) $NaClO_2$.

The PMB protected epoxide **301** was generated in a similar fashion[113] to the previously reported TBDPS protected epoxide from (*2S*)-bromobut-1,4-diol **196** (scheme 67).



(*S*)-196 **301**

Scheme 72: i) NaH, PMBBr, (77%).

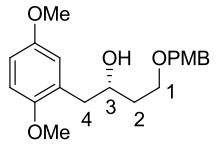
Treatment of 2-bromo-1,4-butanediol **(*S*)-196** with sodium hydride followed by the slow addition of freshly synthesised *p*-methoxybenzyl bromide gave the desired epoxide **301** in 77% yield. The compound was confirmed by comparison of the ^{1}H NMR with literature[113] spectra showing six distinct multiplets for the seven butyl protons at 1.75, 1.85, 2.52, 2.76, 3.06 and 3.59 ppm (each 2 H) along with the indicative PMB doublets at 6.87 ppm (2 H, d, J = 9.0 Hz), 7.26 (2 H, d, J = 9.0 Hz). Optical rotation for the (*S*) enantiomer ($[\alpha]^{25}_{D}$ = +10.5) was consistent with literature values[113]. A series of reactions were attempted to open the epoxide.

Metallating agent	**Lewis acid**	**Solvent**	**Temp. of addition (°C)**	**Result**
^{n}BuLi	-	THF	−78 °C	No reaction
^{n}BuLi	$BF_3{\cdot}Et_2O$	THF	−78 °C	Epoxide degradation
Mg	-	THF	−78 °C	Epoxide degradation
^{n}BuLi/CuI	-	THF	−78 °C	No reaction
^{n}BuLi/$ZnBr_2$	-	THF	−78 °C	No reaction
^{n}BuLi	$BF_3{\cdot}Et_2O$	THF (Diluted epoxide)	−55 °C	43%
^{n}BuLi	$BF_3{\cdot}Et_2O$	Et_2O (Diluted epoxide)	−55 °C	87%

Table 5: Epoxide opening conditions for PMB protected epoxide.

Addition of the neat epoxide dropwise to the lithiated 1,4-dimethoxybenzene resulted only in the recovery of the starting electrophile. Conducting the reaction in the presence of boron trifluoride etherate complex observed degradation compounds after two hours at −78 °C. Similarly generating the Grignard reagent of the aromatic bromide and adding the epoxide showed decomposition. Transmetallating the lithium species with copper^{I} iodide showed no

reaction nor did transmetallation to generate the organozinc nucleophile. A breakthrough was finally achieved by increasing the addition temperature to −55 °C and slowly adding the epoxide as a dilute solution in THF over forty minutes and quenching the mixture with water at 0 °C. This gave the desired ring opened adduct as a clear oil in modest yield (43%) after rapid chromatography. Similarly to the propylene oxide analogue, the compound would decompose if exposed to silica for a prolonged period of time. Many side compounds were observed on TLC but in low quantity. This secondary alcohol was characterised by ^{1}H NMR showing three 2H multiplets at 1.76 ppm (2) 2.77 ppm (4) and 3.59-3.68 ppm (1) and a 1H multiplet at 4.04 ppm (3). Three methoxy peaks were also observed at 3.75, 3.77 and 3.79 ppm corresponding to the aromatic OMe groups and the distinctive *para* substituted doublets at 6.78 and 7.23 ppm confirmed the presence of the PMB substituent. Due to the modest yield, a series of optimistation reactions were conducted, by which it was discovered that simply changing the solvent to diethylether doubled the yield to 87%.



298

Figure 23: Proton labeling for (S)-4-paramethoxybenzyl-1-(2,5-dimethoxyphenyl)butan-2-ol.

These reaction conditions were then applied to the TBDPS protected analogue **197**, however, none of the desired opened epoxide was observed.

Treatment of a dichloromethane solution this compound with the dimethyl acetal of acetaldehyde in the presence of boron trifluoride etherate complex did not however give the *oxa*-Pictet-Spengler adduct. Performing this reaction with two equivalents of both the acetal and the Lewis acid in a dichloromethane solution at 0 °C gave the desired isochromane as a complex mixture of products in very low yield. After extensive chromatography this compound was isolated (>2%, 1 mg).

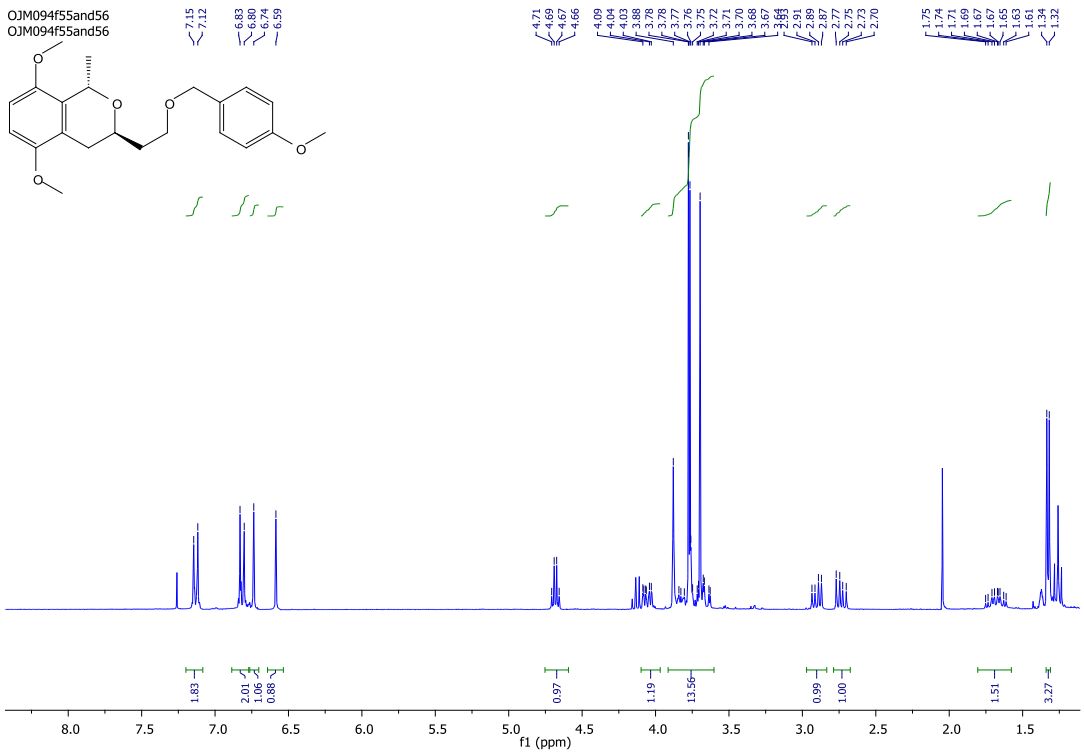
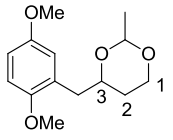


*Figure 24: ^{1}H NMR of PMB protected isochromane **299**.*

Only one diastereoisomer was observed on ^{1}H NMR, however, due to the small quantity of material no further 2D spectra could be obtained to discern the stereogenicity at C1. The compound was charcterised by ^{1}H NMR showing C1 methyl doublet at 1.34 ppm and proton at 4.67 ppm. The PMB substituent remained intact showing indicative signals at 4.09 ppm (2H, s). 6.80 ppm (2H, d) and 7.12 ppm (2H, d) along with three methoxy peaks at 3.70, 3.77 and 3.78 ppm. The two benzylic protons were showed distinct signals at 2.73 and 2.89 ppm. The main compound isolated from the reaction mixture was compound **302**.



302

Figure 25: Acetal isolated from oxa-Pictet-Spengler

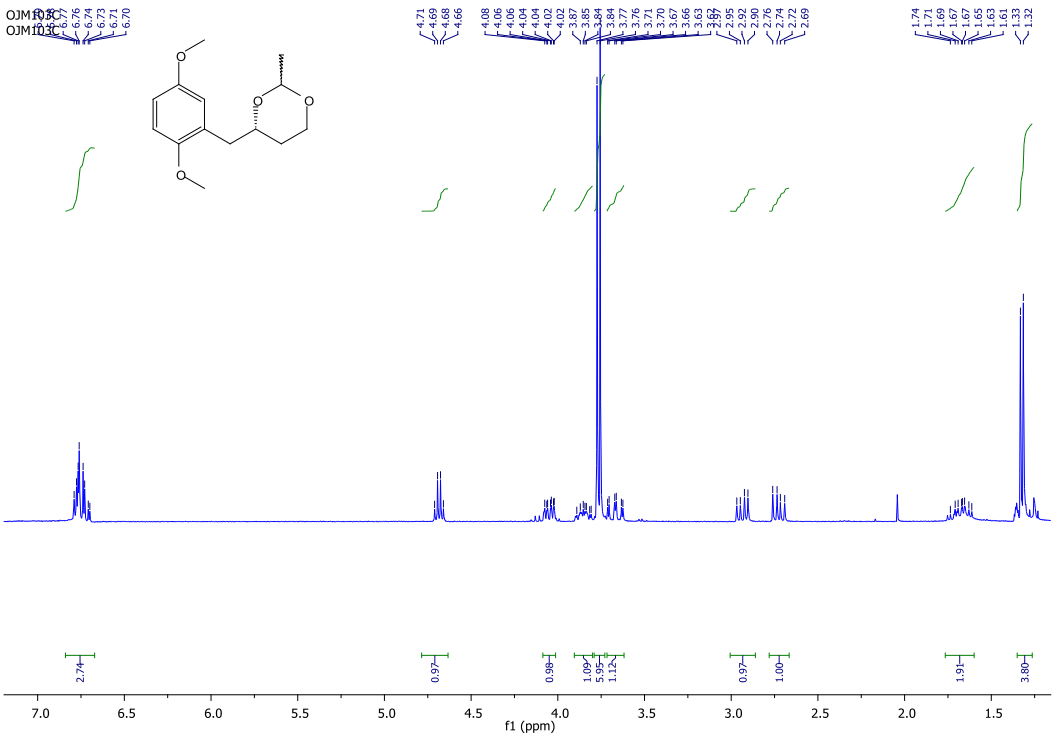
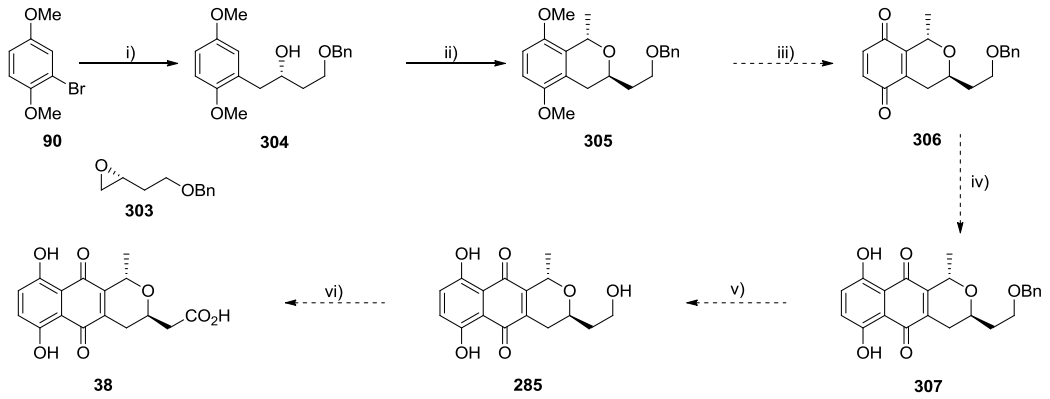


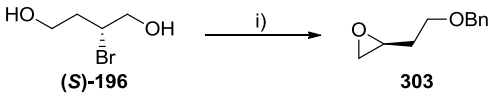
*Figure 26: [1]H NMR of isolated acetal **302**.*

This compound was characterised by [1]H NMR spectroscopy. Similarly, the desired compound observed distinctive geminal proton signals at 2.72 and 2.90 ppm. The acetal also gave signals, similar to that observed at C1 of the desired compound at, 1.32 ppm (3H, d) and 4.68 ppm (1H, q). Labeled aliphatic protons 1 and 3 were almost identical to those of the isochromane observed at 1.67 and 4.69 ppm respectively, however, protons labeled 2 showed more well defined splitting as a doublet of triplets and a doublet of quartets at 3.70 and 4.04 ppm respectively. The aromatic protons integrated as three as a multiplet and [13]C NMR showed only three quaternary aromatic signals indicating that this was the predicted acetal and not the deprotected isochromane. Therefore, it was clear that another protecting group was required.



Scheme 77. i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, **303** (88%). ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$, (99%). iii) CAN. iv) Et_3N, diene. v) H_2, Pd/C. vi) $NaClO_2$.

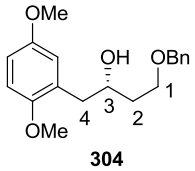
The next protecting substituent chosen was benzyl. This group was previously not used due to foreseen complications with exposure to hydrogenation conditions as the carbon oxygen bond at C1 may also be cleaved. However, due to the group's somewhat inert characteristics towards the preceding reactions it was selected as the next logical choice.



Scheme 77: i) NaH, BnBr, (89%).

The benzyl protected epoxide was synthesised according to previously published literature[114], similarly to previous epoxides, from optically pure aspartic acid. The final step involved the slow addition of a solution of benzyl bromide in DMF to a THF solution of 2-bromo-1,4-butanediol **(*S*)-196** to achieve the desired epoxide in modest yield (89%). The compound was characterized by ^{1}H NMR showing the indicative 5H benzyl multiplet and CH_2 singlet at 7.34 and 4.53 ppm respectively. The aliphatic chain was observed showing six multiplet signals at 1.81, 1.91, 2.51, 2.78, 3.08 and 3.63 ppm (each 2H) similar to the previously synthesised epoxides. Both ^{1}H and ^{13}C NMR correlated with literature spectra[114] as did the HRMS spectrum showing an ion $[M + H]^+$: 179.1060. Comparison of the observed optical rotation ($[\alpha]_D^{25}$ = + 15.8) confirmed retention of stereochemistry of **303**. Treatment of 1-bromo-2,5-dimethoxybenzene **90** with ^{n}BuLi followed by the slow addition of boron trifluoride then the addition of a dilute solution of the benzyl protected epoxide **303** over forty minutes yielded the

opened epoxide (88%) **304**. As with the PMB analogue, many side compounds were observed on TLC but in small quantity. Also, exposure to silica gel more than thirty minutes resulted in decomposition of the compound. This can be attributed to β-elimination of the hydroxyl substituent to generate a conjugated styrene like analogue.



304

*Figure 27: Proton assignments for **304**.*

The ^{1}H NMR spectrum showed two aromatic multiplets at 6.76 ppm (3H), 7.30 ppm (5H) corresponding to the dimethoxy aromatic and benzyl substituents, and a benzyl CH_2 signal at 4.51 ppm. Three 2H multiplet signals were present at 1.78, 2.79 and 3.70 ppm for protons 1, 2 and 4 and a 1H multiplet was observed at 4.11 ppm for tertiary proton 3. An *oxa*-Pictet-Spengler cyclisation using two equivalents of 1,1-dimethoxyethane and $BF_3{\cdot}Et_2O$ in a dichloromethane solution gave isochromane **205**.

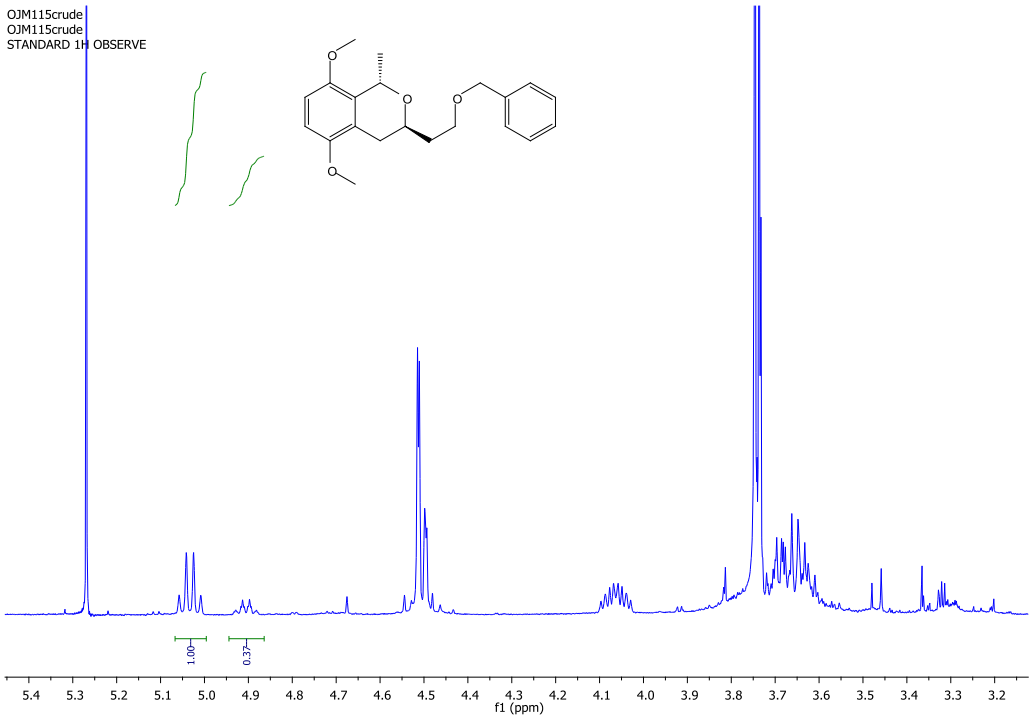


Figure 28: Mixture of trans(1.00):cis(0.37) isomers observed in the crude ^{1}H NMR spectrum.

Again ^{1}H NMR NOE experiments showed a 2.7:1 mixture of *trans:cis* isomers. The major *cis* isomer could be partially isolated by silica gel chromatography and showed 1H NMR signals at 1.50 ppm (3H) and 4.91 ppm (1H) corresponding to the C1 methyl group and tertiary proton. A 5H multiplet at 7.25 ppm and 2H singlet at 4.50 ppm confirmed that the benzyl protecting group was still present. Indicative geminal signals were observed at 2.34 and 2.72 ppm. The stereogenic assignment of this diastereoisomer was confirmed by NOESY (figure 29) experiments showing no correlation between the tertiary protons at C1 (5.00 ppm) and at C3 (4.07 ppm).

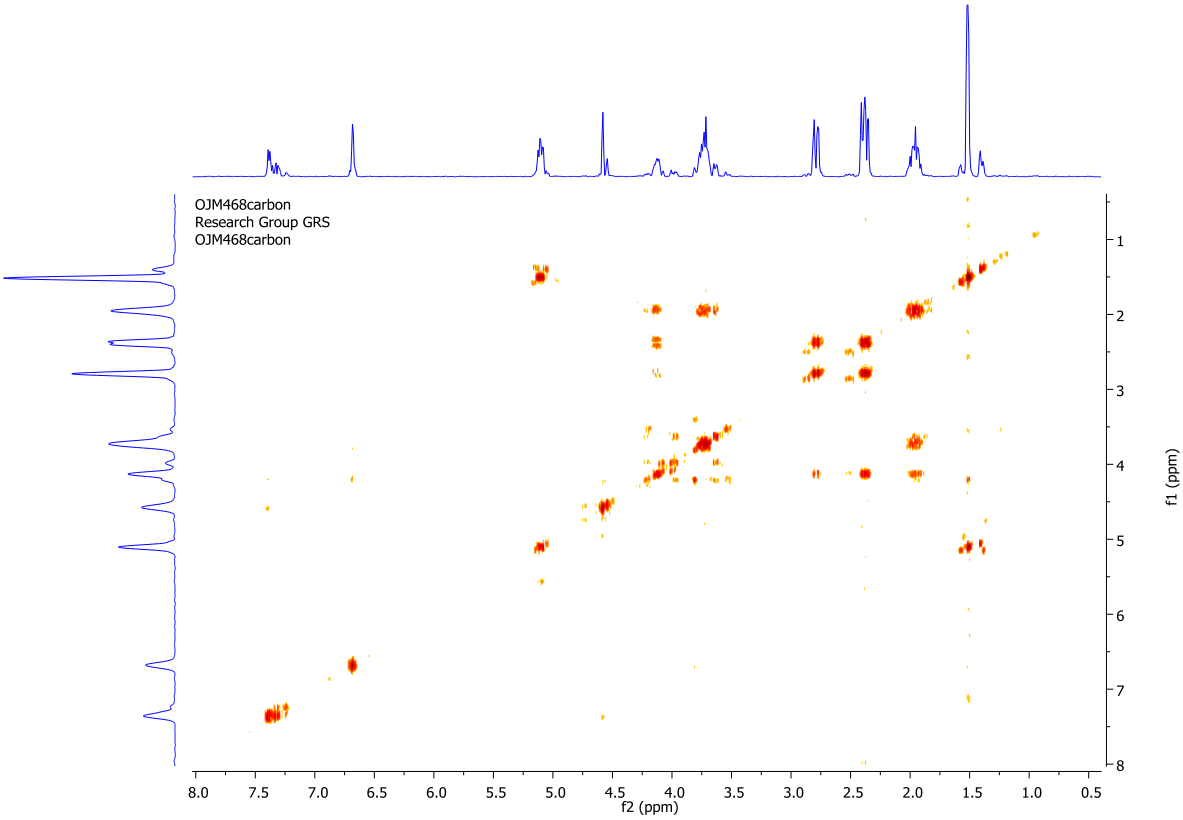
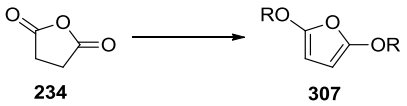


*Figure 29: ^{1}H NMR NOESY showing no correlation between C1 and C3 tertiary protons for the cis diastereoisomer of **305**.*

In an effort to isomerise the diastereoisomers mixture, the isochromane mixture was exposed to H_2SO_4 as a solution in benzene according to literature procedures.[53] However, within two minutes at 0 °C the solution had become black and ^{1}H NMR of the mixture after work up showed no starting material remained. This was also reported by Koert *et al.*[71] on similar

compounds. Whilst the epimerization of BIQ molecules is well known *via* this method and others,[53, 115] simple isochromane quinones are not stable towards these conditions.

With access to this isochromane **305** and the previously synthesised 1,3-dimethylisochromane quin0ne **268**, attempts were made to perform the Diels-Alder cycloaddition and base induced aromatization. The diene selected for the reaction was the previously synthesised 2,5-(trimethylsiloxy)furan **208** along with the dimethoxy and diacetoxy analogues generated by literature procedures from succinic anhydride. Due to the sensitivity of this molecule, generation of the diene and Diels-Alder reactions were carried out *in situ*.

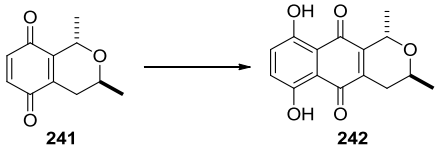


234 **307**

Scheme 78: Dihydroxylated diene synthesis.

R	Electrophile	Base	Lewis acid
TMS	TMSCl	Et_3N	-
TMS	TMSCl	Et_3N	$ZnCl_2$
Me	MeI	Et_3N	-
Ac	$(Ac)_2O$	Et_3N	-

Table 6: Diene formation conditions.



241 **242**

Scheme 79: Diels-Alder cycloaddition.

The diene was generated in an etherial solution at 0 °C then cooled to −78 °C before the dropwise addition of the isochromane quinone as a solution in diethylether and the reaction was monitored by ^{1}H NMR. The methyl and acetate analogues showed no reaction with the quinone but ^{1}H NMR did not show the presence of any succinic anhydride indicating that the

dienol had formed. The TMS analogues, both with and without the presence of a Lewis acid, gave a highly complex mixture of inseparable compounds, which exhibited a variety of yellow, orange and red colours after attempted chromatography. No characteristic signals above 12 ppm were seen in the ^{1}H NMR spectrum which would be indicative of a naphthazarin like core. However, analysis by MALDI-TOF showed one ion signal at 266.13 which is believed to be one of the isochromanes (figure 30).

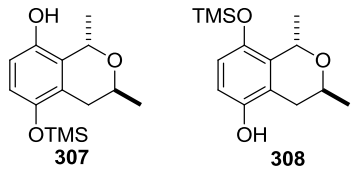
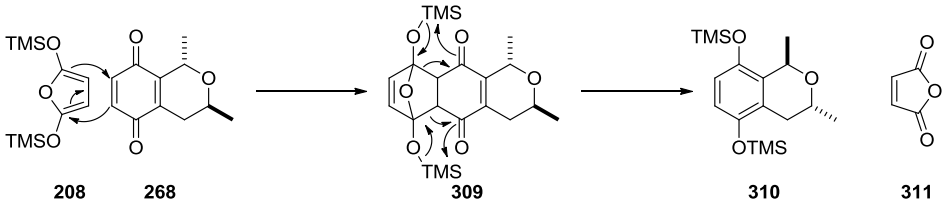


Figure 30: Suspected isochromanes from Diels-Alder reactions.

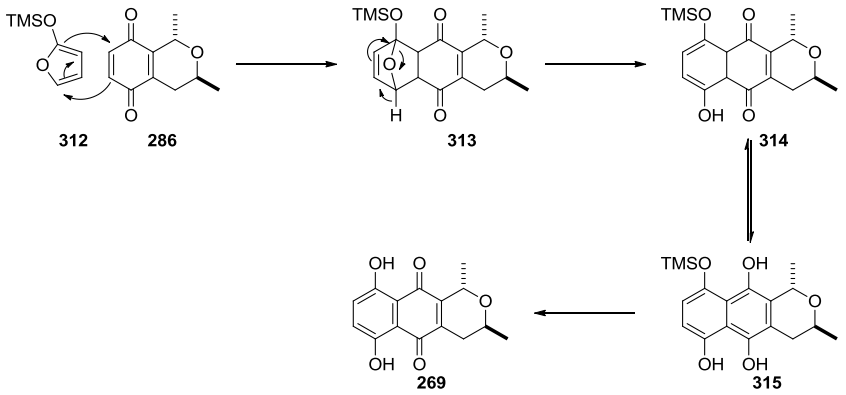
A mechanistic rationalisation for this observation is due the symmetrical nature of the diene (scheme 80).



Scheme 80: Proposed rearomatisation mechanism.

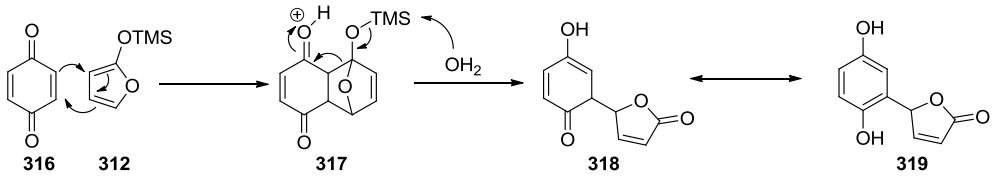
After undergoing the initial Diels-Alder reaction the intermediate can undergo two symmetrical pericyclic reactions to aromatize the dione and transfer the silyl protecting groups to the now phenolic oxygens whilst forming maleic anhydride in the process. As the driving force for this reaction will be the aromatization of the quinone, loss of the ring junction protons to aromatize to give the less stable naphthazarin core is less likely. However, as no compound could be isolated pure and fully characterized, this cannot be certain.

As the rationale for this was due to the symmetry of the diene, the same reaction was attempted with 2-(trimethylsiloxy)furan which was expected to occur *via* the mechanism in scheme 81.



Scheme 81: Expected mechanism for cycloaddition of 2-(trimethylsiloxy)furan.

It was hoped that quenching the reaction with acid would result in ring opening of the Diels-Alder adduct followed by tautomerisation of the dione to give a tetra substituted naphthalene along with removing the TMS protecting group. Then, as previously observed, exposure to oxygen or silica gel chromatography would result in the desired naphthazarin core. Quenching the reaction with either water or aqueous NH_4OH resulted in the isochromane, however, quenching with 1M HCl or saturated NH_4Cl gave a highly complex mixture of non-isolable compounds. A possible explanation of the observed mixture is through the rearomatisation of the quinone ring shown in scheme 31. As presumed with 2,5-(trimethylsiloxy)furan **312**, after the [4+2] cyclisation, aromatisation of the quinone ring is preferential to formation of the naphthazarin bicyclic structure. However, is can be envisaged mechanistically that two regioisomers can be generated when the Diels-Alder is performed with 1,3-dimethylisochromane **267** (figure 31).



Scheme 31: Possible rearomatisation mechanism.

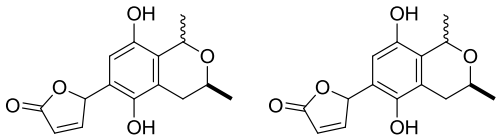
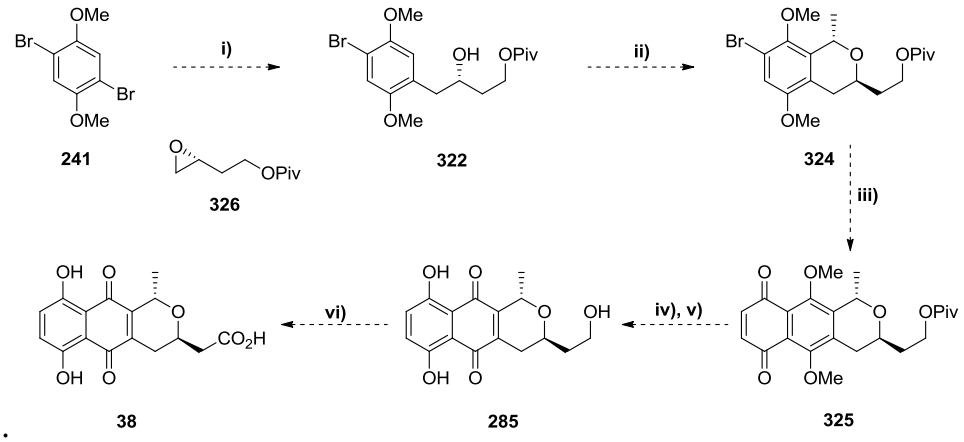


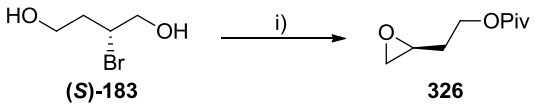
Figure 32: Possible side products of the Diels-Alder cycloaddition of isochromane 268 and 2-(trimethylsiloxy)furan.

Therefore, focus was shifted to the benzyne cycloaddition methodology previously devised. Starting from 1,4-dibromo-2,5-dimethoxybenzene, the same methodology could be applied to generate the benzyne cycloaddition precursor in two steps by litiation followed by the addition of an epoxide then an *oxa*-Pictet-Spengler reaction to produce the brominates isochromane. It was envisaged that upon deprotection of the methoxy groups that oxidation to the naphthazarin core of the aglycone would be spontaneous as previously observed with similar systems.



Scheme 82: i) ^{n}BuLi, **326**, $BF_3{\cdot}Et_2O$. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) LDA, 2-(trimethylsiloxy)furan. iv) KOH, H_2O. v) BBr_3. vi) $NaClO_2$.

It was envisaged that the synthesis of the granaticin aglycone could be realized in six steps. Three key steps to form the tricyclic core ending with the deprotection of both methoxy groups using boron tribromide, cleavage of the pivaloyl group with potassium hydroxide and finally oxidation of the primary alcohol to give the carboxylic acid chain. Pivaloyl was chosen as the protecting group for this synthesis as it can be easily removed with sodium hydroxide and does not require hydrogenation.



(*S*)-183 **326**

Scheme 83: i) NaH, PivCl, (83%).

The epoxide **326** was synthesized enantiopure from (*S*)-aspartic acid **194**, similarly to the previous epoxides. Treatment of 2-bromo-1,4-butanediol with sodium hydride followed by the dropwise addition of pivaloyl chloride gave the desired compound in 83% yield **326**. The compound was characterized by ^{1}H NMR showing the large 9H tertiary butyl peak at 1.24 consistent with the pivaloyl group. Also observed was the butyl chain showing five expected aliphatic signals at 1.86 ppm (2H, m), 2.55 ppm (1H, dd), 2.82 ppm (1H, m), 3.05 ppm (1H, ddd), 4.25 ppm (2H, t). ^{13}C NMR also showed the pivaloyl carbonyl signal at 178.4 ppm. The optical rotation ($[\alpha]_D^{25}$ = +4.4) of **326** was comparable to the previously synthesized epoxides indicating that stereochemistry was retained. Previously devised methodology showed a dramatic increased yield when the epoxide opening were conducted in diethylether, however, the dibrominated aromatic **241** was insoluble below 0 °C therefore THF was the chosen solvent. Lithiating with ^{n}BuLi followed by the dropwise addition of a THF solution of the pivaloyl protected epoxide did not however generate the desired secondary alcohol.

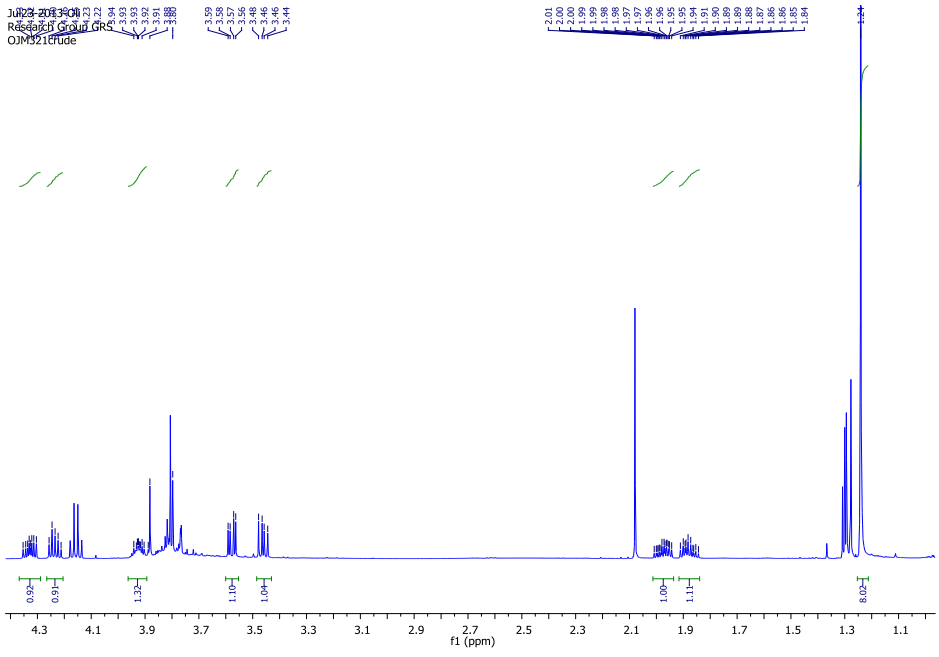
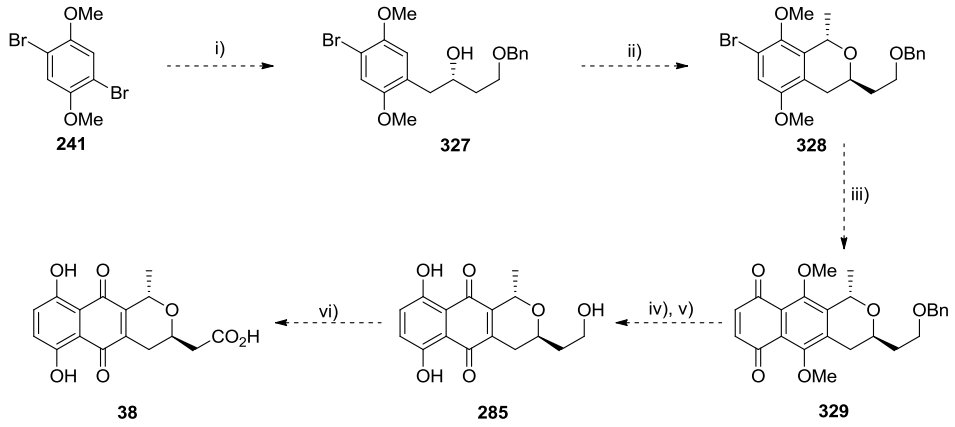


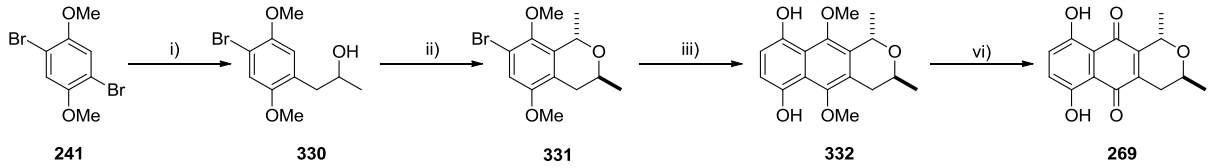
Figure 33: ^{1}H NMR of crude opened pivaloyl epoxide.

Analysis of the crude ^{1}H NMR spectrum (figure 33) showed five multiplets and two doublets of doublets similar to what is expected from the ring opened compound. It is suspected that the presence of boron trifluoride resulted in ring opening of the compound upon quenching the reaction with water generated the 1,2-diol. However, this compound could not be isolated.



Scheme 84: i) ^{n}BuLi, **326**, $BF_3{\cdot}Et_2O$. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) LDA, 2-(trimethylsiloxy)furan. iv) H_2, Pd/C. v) BBr_3. vi) $NaClO_2$.

The benzyl protected analogue was then reselected for study, as it had been previously successful for these reactions, with the ambition to remove the protecting functionality by hydrogenation as the penultimate step of the synthesis. Again THF was used as the solvent due to the insolubility of the dibromobenzene compound **241**. This resulted in the same complex mixture of compounds showing the suspected diol as the main product.



Scheme 84: i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, propylene oxide. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) LDA, 2-(trimethylsiloxy)furan. iv) BBr_3.

The synthesis was then attempted with racemic propylene oxide. Again THF was the chosen solvent. Lithiating with normal butyllithium followed by the dropwise addition of neat propylene oxide gave the desired secondary alcohol in good yield. This compound was observed in the ^{1}H NMR spectrum of the crude material (figure 34) showing the two

distinctive benzylic protons at 3.29 and 3.43 ppm and a methyl doublet at 1.23 ppm. The tertiary proton was also visible as an expected multiplet at 3.92 ppm along with two OMe singlets at 3.69 and 3.70 ppm. HRMS observed a ion at $[M - OH + H]^+$: 259.0151.[116] This compound was not stable towards silica or alumina gel chromatography therefore no further purification or spectral analysis was conducted. The instability of the secondary alcohol is attributed to elimination of the hydroxyl group to produce an unsaturated molecule with a styrene motif which can then polymerise due to the increased electron density within the aromatic ring.

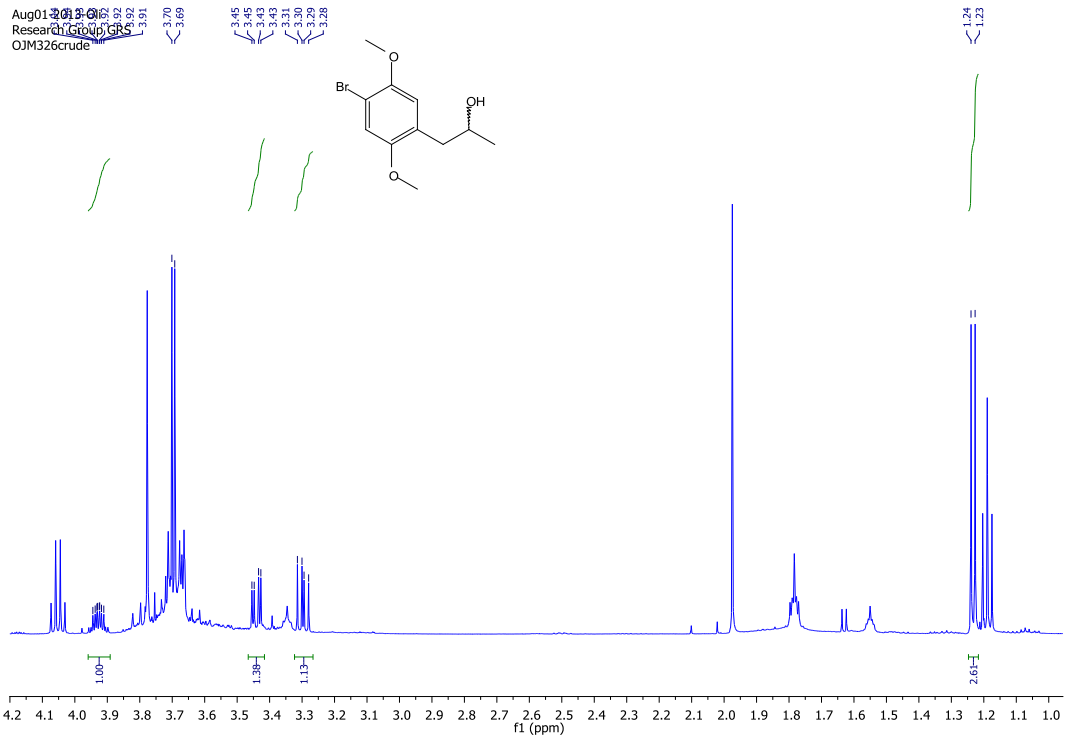
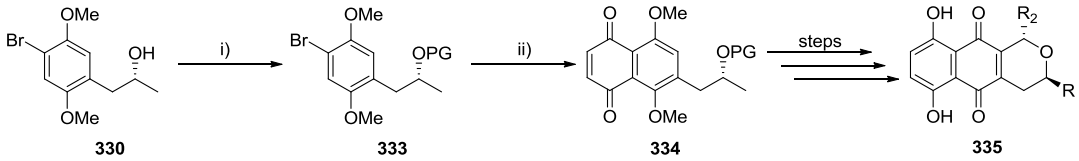


*Figure 34: ^{1}H NMR of crude **330**.*

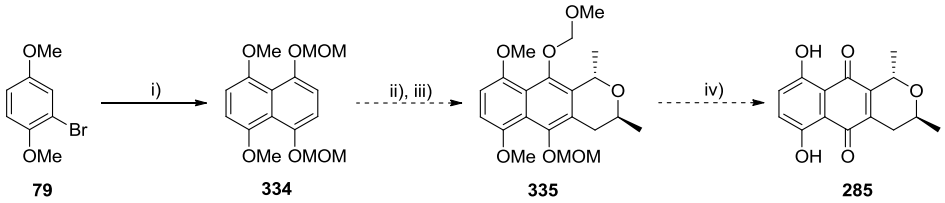
The brominated secondary alcohol **330** was then treated with boron trifluoride etherate complex and 1,1-dimethoxyethane to affect the *oxa*-Pictet-Spengler cyclisation. However, no reaction of the crude material was observed by ^{1}H NMR spectroscopy when attempted at 0 °C or ambient temperature. Increasing the temperature to reflux resulted in decomposition giving a highly complex mixture of compounds. This lack of reactivity is attributed to the presence of the *meta* bromine substituent preventing aromatic substitution. Attempts were then made to

protect the secondary hydroxyl group and perform the benzyne cycloaddition before deprotecting and forming the tetrahydropyran ring by an *oxa*-Pictet-Spengler reaction.



Scheme 85: i) NaH, PG-X. ii) LDA, diene.

Triethylsilyl was chosen as a protecting substituent as it was hoped that it could be cleaved upon the addition of 2M hydrochloric acid during the quench of the benzyne cycloaddition. However, treatment of the free hydroxyl group with sodium hydride followed by the dropwise addition of a THF solution of TESCl at −78 °C which was then allowed to warm to 0 °C before the addition of H_2O resulted in a highly complex mixture of compounds with no incorporation of the silyl group observed in the ^1H NMR spectrum. This can be attributed to elimination of the formed siloxy substituent to again generate a compound with a styrene motif which can then undergo polymerization reactions. An attempt to *O*-methylate the hydroxyl group by treatment with sodium hydride followed by the slow addition of methyl iodide again resulted in a complex mixture of compounds.

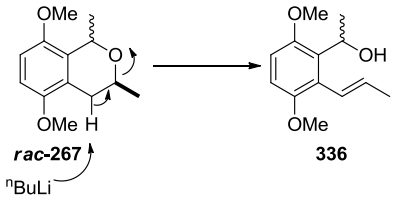


Scheme 86: i) LDA, 2-(trimethylsiloxy)furan, then ^{n}BuLi, MOMCl, (28% over 2 steps). ii) ^{n}BuLi, $BF_3{\cdot}Et_2O$, propylene oxide. iii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iv) BBr_3.

The synthesis was then reorganised to begin with the benzyne cycloaddition and, as previous studies had illustrated 1,4,5,8-tetramethoxynaphthalene **179** to be unstable, protect the two generated hydroxyl protons with methoxymethylene substituents as compound **334**. This naphthalene derivative could then be used to form the secondary alcohol, undergo an *oxa*-Pictet-Spengler reaction and then it was hoped that exposure to boron tribromide would result in global deprotection of all hydroxyl groups. Using the previously devised benzyne

cycloaddition conditions 1,4-dihydroxy-5,8-dimethoxynaphthalene **236** was synthesized. The reaction was quenched, extracted and solvent removed before being dissolved in THF. Treatment of the resulting diol with sodium hydride did not result in deprotonation of the hydroxyl protons, therefore, a stronger base was required. This is likely due to hydrogen bonding between the methoxy oxygens and the hydroxyl protons. Treatment with ^{n}BuLi and the addition of freshly synthesized 2.1M MOMCl in toluene generated the desired compound **334** in 28% yield over the two steps. This product was characterized by ^{1}H NMR showing five distinct singlets at 3.53 ppm (6H, CH_3), 3.82 ppm (6H, CH_3), 5.08 ppm (4H, CH_2), 6.75 ppm (2H, Ar), 6.97 ppm (2H, Ar). However, similarly to the tetramethoxy analogue, the product underwent rapid oxidation to *O,O*-dimethylnaphthazarin **181** therefore the subsequent reaction was conducted immediately after isolation. The addition of this compound with n-butyllithium resulted in total degradation of the naphthalene derivative.

As the synthesis of 1,3-dibromo-2,5-dimethoxybenzene would prove to be a three step and costly synthesis, the synthesis was again rearranged to incorporate the bromine later. This would allow for the *oxa*-Pictet-Spengler cyclisation but increase the synthesis by one step. Attempts were made to install the bromine substituent at either C6 or C7 (as this would not affect the generation of the benzyne intermediate in the subsequent reaction) by subjecting the previously synthesised isochromane (as a mixture of diastereoisomers) to ^{n}BuLi and quenching the generated organolithium with 1,2-dibromoethane.



Scheme 87: ^{n}BuLi induced ring opening.

Instead of deprotonating *ortho* to either methoxy group, the benzylic proton was abstracted resulting in ring opening of the pyran ring (scheme 87). This compound was characterised as a mixture of diastereoisomers by ^{1}H NMR (figure 35) showing a distinctive doublet of doublets at 6.21ppm and by HRMS showing two ion signals at *m/z* $[M + H]^+$: 222.1485 and $[M - OH]^+$: 205.1221.

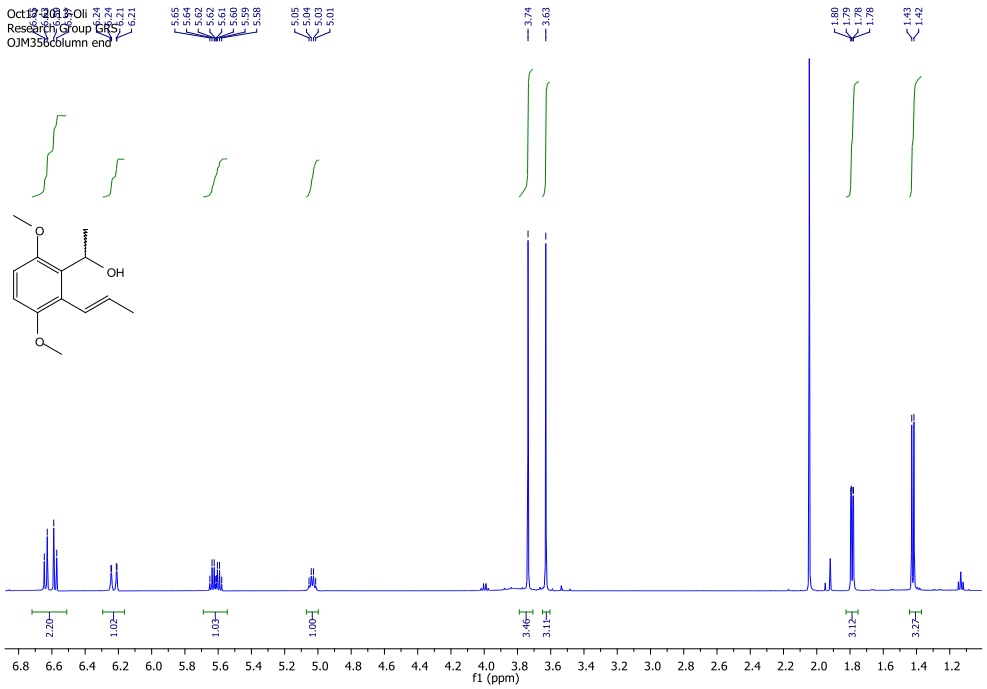
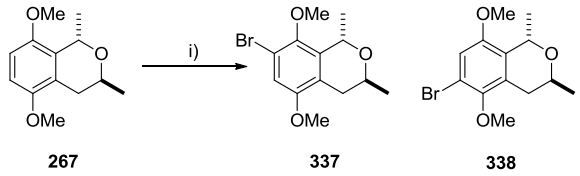


*Figure 35: ^{1}H NMR of opened pyran ring **336**.*



267 **337** **338**

Scheme 88: i) Br_2, AcOH (75%).

The brominated compounds **337** and **338** was synthesized by an aromatic substitution *via* the dropwise addition of molecular bromine to a solution of the isochromane **267** in acetic acid. This produced a 1:1 mixture of regioisomers.

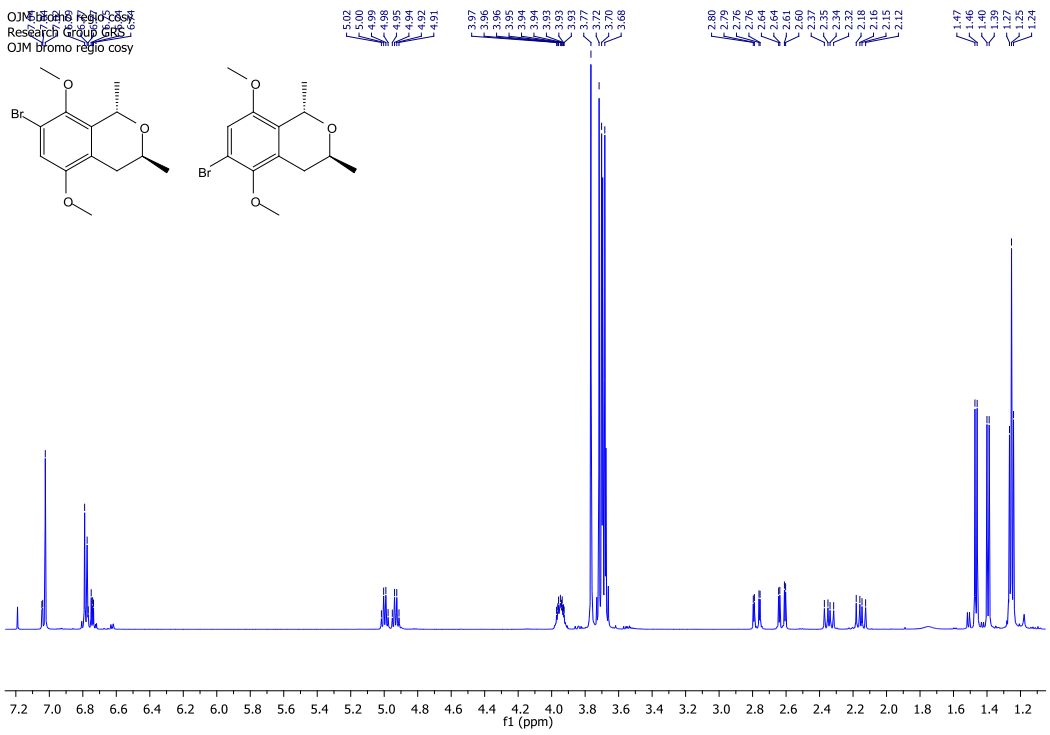


Figure 36: ^{1}H NMR of brominated isochromane regioisomers.

These compounds were characterised by HRMS which showed isotopic pattern *m/z* $[M + H]^{+}$: 301.0434, 303.0305 and by ^{1}H NMR. Signals were observed for the major isomers as two quartets for the C1 quaternary protons at 4.95 and 5.01 ppm along with two sets of geminal proton doublets of doublets at 2.16, 2.35, 2.62 and 2.80 ppm. These isomeric compounds were then subjected to benzyne cycloaddition conditions by the slow addition of a solution of the brominated material to freshly synthesised LDA and 2-(trimethylsiloxy)furan. However, no cycloaddition product was observed by ^{1}H NMR spectrum. A complex mixture of compounds was produced which can be attributed to deprotonation of a geminal proton and ring opening the pyran ring. The use of lithium hexamethyldisilamide also produced a complex mixture indicating that the benzyne intermediate could not be generated for this substituent.

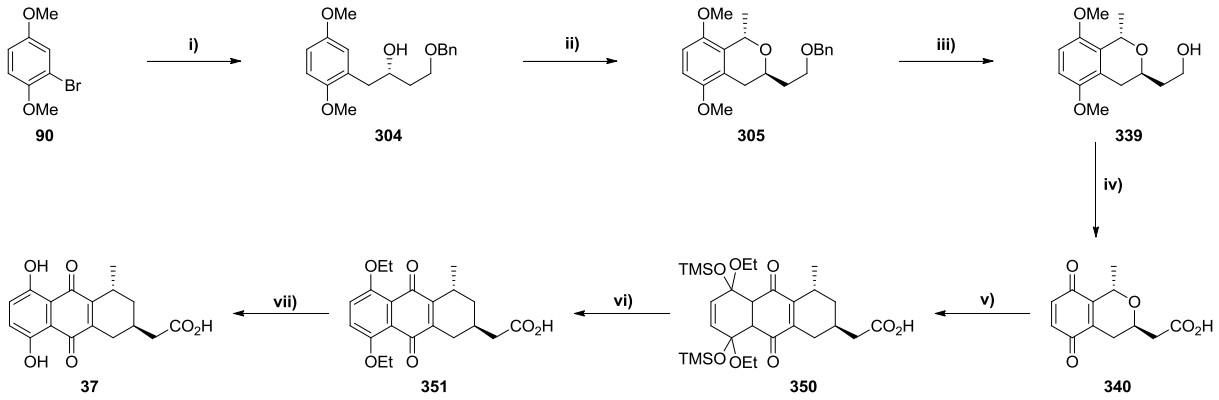
5. Conclusions

In conclusion, we have developed a novel synthetic strategy for the synthesis of functionalised isochromanes and isochromane quinones. This divergent strategy can be used to generate a range of compounds by altering the epoxide used in the first step and by using varying acetals for an *oxa*-Pictet-Spengler cyclisation.

Although the final Diels-Alder step has yet to be realized, this strategy has the potential to provide a quick and inexpensive route to a variety of benzoisochromane quinone compounds.

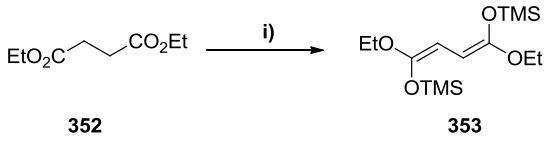
In addition, we have also developed, to the best of this authors knowledge, a novel method for the synthesis of naphthazarin analogues in a single step from inexpensive reagents *via* a benzyne cycloaddition and acidic reaction quench.

6. Future work



Scheme 89: i) ^{n}BuLi, $BF_3{\cdot}Et_2O$, **303**. ii) $MeCH(OMe)_2$, $BF_3{\cdot}Et_2O$. iii) Pd/C, H_2. iv) $Cr(O)_3$, AcOH. v) Et_3N, **353**. vi) Jones reagent. vii) BBr_3.

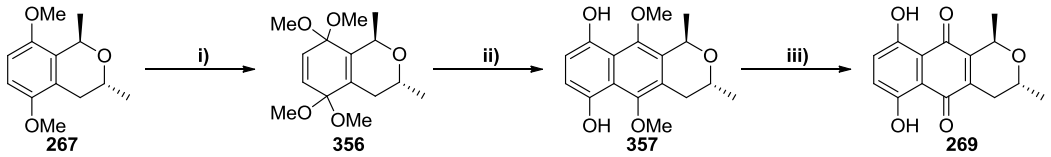
Building on the previously described isochromane synthesis, it is hoped that the benzyl protecting substituent can be cleaved by hydrogenation in the presence of catalytic Pd/C to generate primary hydroxyl **339**. Utilising methodology developed by Xu *et al.*,[76] global oxidation to give the quinone ring and carboxylic acid **340** can be achieved using chromium trioxide under acidic conditions. In order to avoid ring opening degredation side products during the Diels-Alder reaction with the previously used furan derivatives (**208** and 2-(trimethylsiloxy)furan), an acyclic tetraoxygenated diene may be required. 1,4-trimethylsiloxy-1,4-ethoxybuta-1,3-diene can be synthesized in a single step (scheme 90) from diethylsuccinate[117, 118]. This intermediate **350** can then be treated with Jones reagent following similar literature methodology[63, 64] to the synthesis of eleutherin **107** and frenolicin **22** by Kraus *et al.* to give the naphthazarin core. The remaining ethyl protecting substituents can then be cleaved to give the aglycone **37**.



Scheme 90: i) TMSCl, Et_3N.

An alternative strategy is to protect the quinone ring as the tetramethyl diacetal (scheme 91) according to literature methods[119, 120] by anodic methoxylation of dimethoxy isochromane

267 using Pt or Ti plate electrodes. This would prevent rearomatisation during the subsequent Diels-Alder cycloaddition with 2-(trimethylsiloxy)furan allowing for generation of protected aglycone **357**.



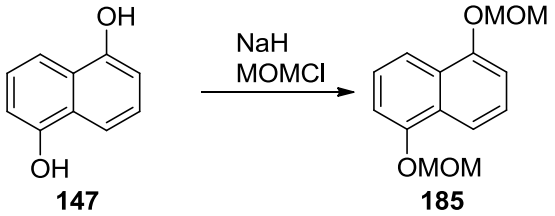
267 **356** **357** **269**

Scheme 91: i) MeOH, KOH, Pt or Ti electrode. ii) Et_3N, 2-(trimethylsiloxy)furan. iii) BBr_3.

7. Experimental

Chemicals of reagent grade were used as purchased unless stated otherwise. When mentioned as distilled, THF, Et_2O were freshly distilled from sodium benzophenone ketyl. CH_2Cl_2, and acetonitrile were distilled from calcium hydride. Toluene was distilled from sodium. All non-aqueous reactions were carried out under oxygen-free nitrogen or argon using flame-dried glassware. Flash column chromatography was carried out using Davisil LC60A 40-63 micron silica (amorphous silicon dioxide). Thin layer chromatography was carried out using commercially available Macherey-Nagel pre-coated TLC-sheets (ALUGRAM® SIL G/UV_{254}silica plates) and visualised under UV or stained with PMA or $KMnO_4$. Proton and carbon NMR spectra were recorded on a Varian Gemini 300 MHz with a 5 mm Inverse detect broad band z-gradient probe. A Varian UNITYplus 400 MHz spectrometer with a 5 mm Inverse detect broad band z-gradient probe A Bruker Avance III nanobay 400 MHz spectrometer with a 5 mm broad band observe $BBFO^{plus}$ probe fitted with an actively shielded z-gradient coil. A Bruker Avance III 500 MHz spectrometer with a 5mm broad band observe $BBFO^{plus}$ smart probe™ fitted with an actively shielded z-gradient coil. NMR signals were measured using the residual non-deuteriated NMR solvent signal as a reference. For ^1H NMR, $CHCl_3$ at 7.27ppm, MeOH at 3.31ppm H_2O at 4.79ppm and DMSO at 2.50ppm ppm. For ^{13}C NMR, $CDCl_3$ at 77.0 ppm was used. Infra-red spectra were recorded on a PerkinElmer Spectrum 100FT-IR spectrometer. The specific rotations were measured on aADP 440 polarimeter from Bellingham + Stanley. Chemical ionisation and high resolution mass spectra were measured at the EPSRC Mass Spectrometry Centre at the University of Wales, Swansea.

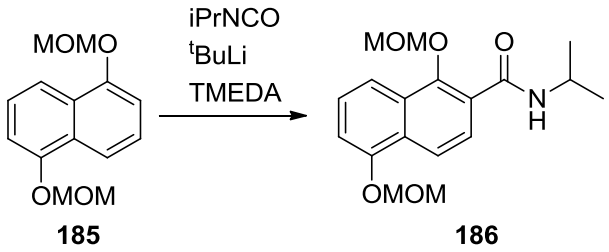
1,5-*Bis*methoxymethyleneoxynaphthalene 185[121]



Scheme 92.

1,5-Dihydroxynaphthalene **147** (5.00 g, 31 mmol) was slowly added to a suspension of sodium hydride 95% (3.75 g, 156 mmol) in anhydrous DMF (100 mL) under an atmosphere of argon at 0 °C, resulting in a dark purple slurry. MOMCl (44 mL, 94 mmol, 2.1 M in toluene) was introduced dropwise resulting in the mixture gradually becoming yellow. The reaction mixture was slowly allowed to rise to r.t. After stirring for 3 hrs the reaction mixture was quenched with H_2O (150 mL) and extracted into Et_2O (5 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ (2 x 80 mL) and dried using $MgSO_4$. Evaporation of solvent resulted in a yellow solid of 1,5-*bis*methoxymethyleneoxynaphthalene **185** (99%, 1.41 g). R_f = 0.25 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 3.54 (6 H, s, OCH_3), 5.39 (4 H, s, CH_2), 7.11 (2 H, d, *J* = 8.4, 4,8-H_{Ar}), 7.38 (2 H, t, *J* = 8.4, 3,7-H_{Ar}), 7.90 (2 H, d, *J* = 8.4, 2,6-H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 56.7, 95.3, 109.1, 115.9, 125.9, 127.6, 153.3. IR (ATR): υ (cm^{-1}) 1389, 1418, 1594, 2993. HRMS calcd. for $C_{14}H_{16}O_4$ $[M + H]^+$: 249.1121 found: 249.1123. mp: 77-80 °C.

***N*-isopropyl-1,5-*bis*methoxymethyleneoxynaphthamide 186**

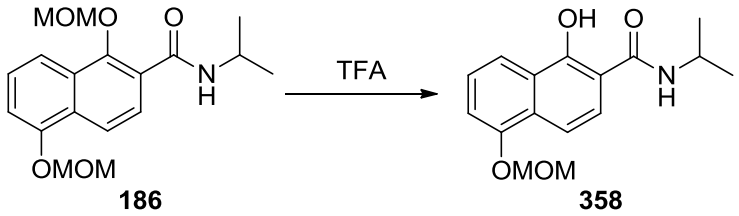


185 **186**

Scheme 93.

TMEDA (1.8 mL, 12.1 mmol) was added under argon at −30 °C to a solution of **185** (1.00 g, 4.03 mmol) in anhydrous THF (100 mL). ^{t}BuLi (7.11 mL, 12.1 mmol, 1.7 M in pentane) was slowly added resulting in a dark red solution, consistent with the presence of *ortho*-lithiated aromatics. After stirring at −55 °C for 20 mins., isopropylisocyanate (1.2 mL, 12.1 mmol) was introduced dropwise causing the solution to return to a pale yellow colour. The reaction mixture was slowly brought to r.t. over 30 mins followed by addition of H_2O (50 mL) and extraction into ethyl acetate (3 x 50 mL). The combined organic fractions were washed with $NaHCO_3$ (50 mL) and the solution was dried ($MgSO_4$) then filtered and concentrated under reduced pressure. Chromatography on alumina (EtOAc/hexanes, 1:4) produced *N*-isopropyl-1,5-bis(methoxymethyleneoxy)-2-naphthamide **186** as a yellow solid (82%, 879 mg). R_f = 0.20 (EtOAc/hexanes, 1:4). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.29 (6 H, d, J = 6.6, CH_3), 3.53 (3 H, s, OCH_3), 3.60 (3 H, s, OCH_3), 4.30 (1H, m, CH) 5.19 (2 H, s, CH_2), 5.38 (2 H, s, CH_2), 7.17 (1 H, d, J = 7.4, 8-H_{Ar}), 7.44 (1 H, t, J = 8.4, 7-H_{Ar}), 7.55 (1 H, br d, J = 6.8, NH), 7.78 (1 H, d, J = 8.4, 6-H_{Ar}), 8.00 (1 H, d, J = 8.8, 4-H_{Ar}), 8.10 (1 H, d, 8.8, 3-H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 23.03, 42.08, 56.64, 58.89, 95.06, 101.78, 109.91, 116.53, 119.15, 124.46, 126.45, 127.08, 128.95, 129.65, 151.58, 153.39, 165.41. IR (ATR): υ (cm^{-1}) 1249, 1369, 1459, 1540, 1632 (C=O stretch), 3275 (N-H stretch), 3330. HRMS calcd. for $C_{18}H_{24}NO_5$ $[M + H]^+$: 334.1649 found 334.1650. mp: 54-56 °C.

***N*-Isopropyl-1-hydroxy-5-methoxymethyleneoxy-2-naphthamide 358**

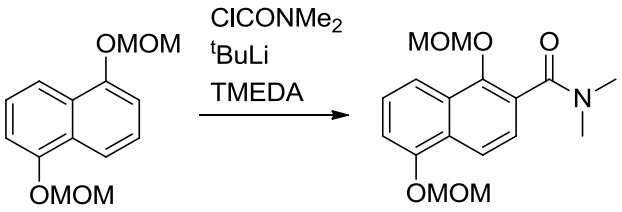


186 **358**

Scheme 94.

Under an atmosphere of nitrogen, TFA (0.023 mL, 0.3 mmol) was added to an anhydrous solution of **186** (89 mg, 0.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C and stirred for 3 hrs. H_2O (20 mL) was then added and mixture was extracted into CH_2Cl_2 (2 x 20 mL) which was washed with $NaHCO_3$ (2 x 10 mL). After drying ($MgSO_4$) solvent was removed to give *N*-isopropyl-1-hydroxy-5-methoxymethyleneoxy-2-naphthamide **358** as a yellow solid. (99%, 86 mg). R_f = ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.27 (6 H, d, *J* = 6.5, CH_3), 3.50 (3 H, s, OCH_3), 4.30 (1 H, m, CH), 5.34 (2 H, s, CH_2), 6.16 (1H, br d, *J* = 7.3, NH), 7.17 (1 H, d, *J* = 7.7, 6-H_{Ar}), 7.26 (1 H, d, *J* = 9.0, 4-H_{Ar}), 7.38 (1 H, t, *J* = 7.7, 7-H_{Ar}), 7.61 (1 H, d, *J* = 9.0, 4-H_{Ar}), 8.01 (1 H, d, *J* = 9.0, 3-H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 23.3, 42.0, 56.3, 95.5, 107.7, 111.3, 113.4, 117.5, 120.3, 126.1, 127.0, 128.9, 152.0, 162.9, 170.0. IR (ATR): υ (cm^{-1}) 1245, 1371, 1444, 1540, 1630 (C=O stretch), 3275 (O-H stetch), 3403 (N-H stetch). HRMS calcd. for $C_{16}H_{19}NO_4$ $[M + H]^+$: 290.1387 found: 290.1384. mp: 112-114 °C.

***N*,*N*-dimethyl-1,5-*bis*methoxymethyleneoxy-2-naphthamide 194**

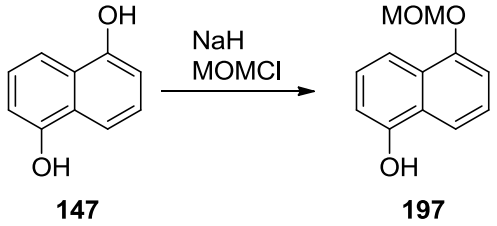


185 **194**

Scheme 95.

TMEDA (1.8 mL, 12.1 mmol) was added under nitrogen at −55 °C to a solution of 1,5-*bis*methoxymethyleneoxynaphthalene **185** (1.00 g, 4.00 mmol) in THF (100 mL) followed by dropwise addition of ^{t}BuLi (7.1 mL, 12.1 mmol, 1.7 M in pentane) resulting in a dark red solution. After stirring for 20 mins *N*,*N*-dimethylcarbamyl chloride (0.29 mL, 4.00 mmol) was slowly added and reaction mixture stirred for 1 hr resulting in a pale yellow solution. Reaction was quenched using H_2O (50 mL), extracted into ethyl acetate (3 x 40 mL) and washed with $NaHCO_3$ (2 x 40 mL). After drying ($MgSO_4$), solvent was removed and purification by alumina gel chromatography (EtOAc/hexanes, 1:2) gave desired naphthamide **194** as a pink solid (38%, 485 mg). R_f = 0.20 (EtOAc/hexanes, 1:2) ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 2.89 (3 H, s, NCH_3), 3.14 (3 H, s, NCH_3), 3.51 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3), 5.14 (2 H, s, CH_2), 5.36 (2 H, s, CH_2), 7.11 (1 H, d, *J* = 8.0, 8-H_{Ar}), 7.31 (1 H, d, *J* = 8.6, 4-H_{Ar}), 7.41 (1 H, t, *J* = 8.0, 7-H_{Ar}), 7.80 (1 H, d, *J* = 8.0, 3-H_{Ar}), 8.05 (1 H, d, *J* = 8.6, 6-H_{Ar}). ^{13}C NMR (400 Mz, $CDCl_3$): δ (ppm) 34.9, 38.5, 56.3, 57.7, 94.9, 100.5, 108.5, 116.0, 118.9, 124.2, 125.4, 126.7, 126.7, 129.5, 149.2, 153.0, 169.7. IR (ATR): υ (cm^{-1}) 1260, 1371, 1545, 1574, 1665 (C=O stretch), 3133. HRMS calcd. for $C_{17}H_{21}NO_5$ $[M + H]^+$: 320.1498 found: 320.1492. mp: 81-83 °C.

1-Methoxymethyleneoxy-5-hydroxynaphthalene 197

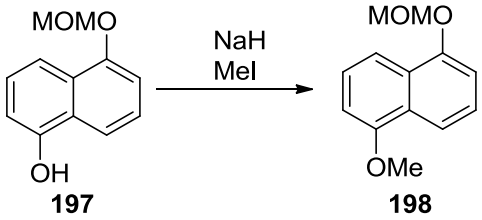


147 **197**

Scheme 96.

Under an atmosphere of nitrogen, sodium hydride 60% (250 mg, 6.25 mmol) was added to a solution of 1,5-dihydroxynaphthalene **147** (1.00 g, 6.25 mmol) in anhydrous DMF (50 mL) at r.t. resulting in a purple slurry. After 15 mins MOMCl (3 mL, 6.25 mmol, 2.1M in toluene) was added and solution stirred for 17 hrs. The resulting yellow mixture was quenched with water and extracted into ethyl acetate (5 x 50 mL) and washed with H_2O (5 x 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and solvent evaporated to give the mono-substituted compound **197** as a light brown solid (95%, 350 mg). R_f = 0.43 (EtOAc/hexanes, 1:4). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 3.48 (3 H, s, OCH_3), 5.32 (2 H, s, CH_2), 5.61 (1 H, br s, OH), 6.76 (1 H, d, *J* = 7.4, 4-H_{Ar}), 7.03 (1 H, d, *J* = 7.4, 8-H_{Ar}), 7.23 (1 H, t, *J* = 8.4, 3-H_{Ar}), 7.30 (1 H, t, *J* = 8.4, 7-H_{Ar}), 7.73 (1 H, d, *J* = 8.4, 6-H_{Ar}), 7.76 (1 H, d, *J* = 8.4, 2-H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 56.4, 94.9, 108.7, 109.4, 114.7, 115.2, 125.4, 125.5, 125.6, 127.9, 151.6, 154.3. IR (ATR): υ (cm^{-1}) 1309, 3100, 3617 (O-H stretch). HRMS calcd. for $C_{12}H_{12}O_3$ $[M + H]^+$: 205.0859 found: 205.0860. mp: 101-104 °C.

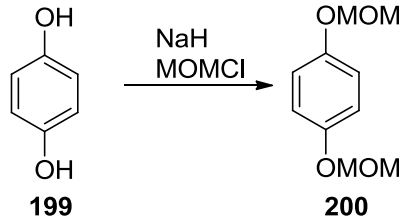
1-Methoxymethyleneoxy-5-methoxynaphthalene 198[122]



Scheme 97.

Under nitrogen, at r.t., NaH 60% (71 mg, 1.72 mmol) was slowly added to a solution of 1-methoxymethyleneoxy-5-hydroxynaphthalene **197** (350 mg, 1.72 mmol) in DMF (20 mL), at 0 °C and stirred for 10 mins producing a red solution. Methyl iodide (0.11 mL, 1.72 mmol) was then added dropwise and mixture stirred for 3 hrs. H_2O (30 mL) was added and mixture extracted into ethyl acetate (2 x 30 mL). After washing with H_2O (3 x 30 mL), $NaHCO_3$ (2 x 20 mL), drying ($MgSO_4$) and filtration solvent was removed to give desired product **198** as a light brown solid (99% 371 mg). R_f = 0.30 (EtOAc/hexanes, 1:8). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 3.50 (3 H, s, OCH_3), 4.01 (3 H, s, OCH_3), 5.39 (2 H, s, CH_2), 6.81 (1 H, d, *J* = 7.6, 8-H_{Ar}), 7.09 (1 H, d, *J* = 7.6, 8-H_{Ar}), 7.34 (2 H, m, 3,7-H_{Ar}), 7.82 (1 H, d, *J* = 8.4, 2-H_{Ar}), 7.90 (1 H, d, *J* = 8.4, 4-H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 55.7, 56.4, 94.9, 104.5, 108.8, 114.3, 115.6, 125.4, 125.5, 126.9, 127.1, 152.8, 155.4. IR (ATR): υ (cm^{-1}) 1234, 1343, 1539, 3100. HRMS calcd. for $C_{13}H_{15}O_3$ $[M + H]^+$: 219.1016 found: 219.1016. mp: 75-76 °C, lit. 75-76 °C.

1,4-Methoxymethyleneoxybenzene 200[123]

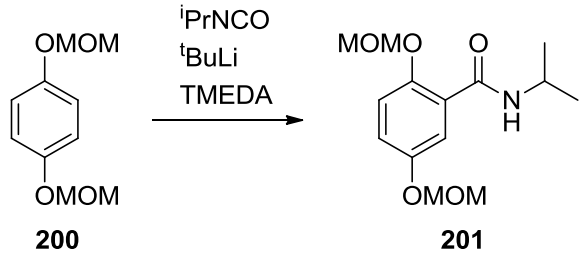


199 **200**

Scheme 98.

Sodium hydride (5.7 g, 136 mmol, 60% in mineral oil) was added to a solution of hydroquinone **199** (5.00 g, 45.5 mmol) in DMF (80 mL) at 0 °C, resulting in a dark yellow slurry. MOMCl (65 mL, 136 mmol, 2.1M in toluene) was then added dropwise and the solution was stirred at 0 °C for two hrs. The gray reaction mixture was quenched with water (100 mL) and extracted into EtOAc (3 x 100ml). The combined organic fractions where washed with $NaHCO_3$ (2 x 50 mL), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by silica gel chromatography (EtOAc/hexanes, 1:9) gave *bis*-protected product **200** as colourless oil (92% 8.25 g). R_f = 0.35 (EtOAc/hexanes, 1:9) ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 3.42 (6 H, s, OCH_3), 5.07 (4 H, s, CH_2), 6.94 (4 H, s, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 55.9, 95.2, 117.5, 152.4. IR (ATR): υ (cm^{-1}) 1289, 1531, 3200. HRMS calcd. for $C_{10}H_9O_4$ $[M + NH_4]^+$: 216.2130 found: 216.2131.

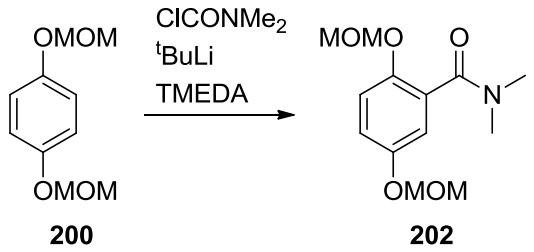
***N*-isopropyl-1,4-*bis*methoxymethyleneoxy-2-benzamide 201**



Scheme 99.

At −55 °C and under an atmosphere of nitrogen, TMEDA (1.5 mL, 10.1 mmol) was added to a solution of 1,4-methoxymethyleneoxybenzene **200** (1.00 g, 5.0 mmol) in THF (60 mL) followed by slow addition of ^{t}BuLi (5.9 mL, 10.1 mmol, 1.6 M in pentane) resulting in a yellow solution. Isopropylisocyanate (0.25 mL, 5.30 mmol) was then added to the yellow solution dropwise, and the mixture was stirred for 1 hr. The reaction mixture was quenched at 0 °C with H_2O (50 mL) and extracted into EtOAc (2 x 40 mL). The combined organic fractions were then washed with NaCl (30 mL) and $NaHCO_3$(40 mL). After drying ($MgSO_4$), the solution was filtered and concentrated under reduced pressure. Purification by alumina gel chromatography (EtOAc/hexanes, 1:4) gave benzamide **201** as a green oil. (71%, 1.008 g). R_f = 0.22 (EtOAc/hexanes, 1:4). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.21 (6 H, d, *J* = 7.2, CH_3), 3.43 (3 H, s, OCH_3), 3.48 (3 H, s, OCH_3), 4.24 (1 H, m, CH), 5.12 (2 H, s, CH_2), 5.21 (2 H, s, CH_2), 7.02 (2 H, br s, H_{Ar}), 7.64 (1 H, br s, H_{Ar}), 7.80 (1 H, s, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 22.3, 45.4, 55.0, 55.8, 94.9, 96.8, 111.0, 115.4, 119.1, 121.7, 151.1, 153.7, 164.6. IR (ATR): υ (cm^{-1}) 1240, 1444, 1532, 1632 (C=O stretch), 2978, 3180 (N-H stretch), 3275. HRMS calcd. for $C_{14}H_{21}NO_5$ $[M + H]^+$: 284.1492 found 284.1491.

***N*,*N*-dimethyl-1,4-methoxymethyleneoxy-2-benzamide 202**

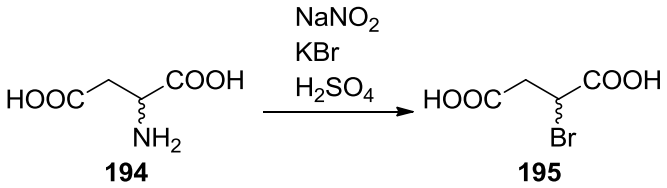


200 **202**

Scheme 100.

At −55 °C and under an atmosphere of nitrogen, TMEDA (1.5 mL, 10.1 mmol) was added to a solution of 1,4-methoxymethyleneoxybenzene **200** (1.00 g, 5.0 mmol) in THF (60 mL) followed by slow addition of ^{t}BuLi (5.9 mL, 10.1 mmol, 1.6M in pentane) resulting in a yellow solution. *N*,*N*-dimethylcarbamyl chloride (0.48 mL, 5.3 mmol) was then added to the solution dropwise and the reaction mixture was stirred for 3 hrs. The reaction mixture was quenched with H_2O (50 mL) and extracted into EtOAc (2 x 40 mL). The combined organic fractions were then washed with NaCl (30 mL) and $NaHCO_3$ (40 mL) followed by drying ($MgSO_4$), filtration and removal of solvent under reduced pressure. Purification by alumina gel chromatography (EtOAc/hexanes, 1:2) gave desired benzamide **202** as a pale green oil. (84 %, 1.11 g). R_f = 0.25 (EtOAc/hexanes, 1:2). ^{1}H NMR (400 Mz, $CDCl_3$): 1.21 (6 H, br s NCH_3), 3.23 (3 H, s, OCH_3), 3.41 (3 H, s, OCH_3), 4.86 (2 H, s, CH_2), 5.07 (2 H, s, CH_2), 7.01 (1 H, s, H_{Ar}), 7.04 (1 H, d, J = 2.9, H_{Ar}), 7.14 (1 H, d, J = 2.9, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 38.8, 39.9, 51.7, 95.5, 95.9, 112.2, 114.4, 119.7, 123.3, 151.0, 152.8, 170.8. IR (ATR): υ (cm^{-1}) 1262, 1501, 1555, 1700 (C=O), 3212. HRMS calcd. for $C_{12}H_{19}NO_5$ $[M + H]^+$: 270.1336 found 170.1337.

(±)-2-Bromosuccinic acid 195[54]



194 **195**

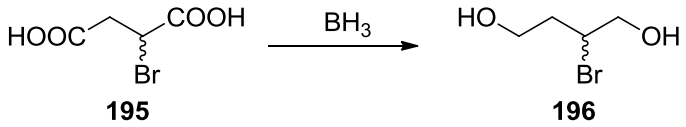
Scheme 101.

To a solution on (±)-aspartic acid **194** (2.5 g, 18.8 mmol) in H_2O/H_2SO_4 (50 mL/6.65 mL, 125 mmol) was added KBr (10 g, 85 mmol) followed by the dropwise addition of $NaNO_2$(2.30 g, 34 mmol) in H_2O (4.5 mL) at −5 °C over 20 mins. During the addition of $NaNO_2$ a brown gas was evolved. The yellow mixture was then stirred at 0 °C for 3 hrs. After extraction into EtOAc (3 x 50 mL) solvent was removed to produce a white solid to give 2-bromosuccinic acid **195** in quantitaitive yield (3.70 g). R_f = 0.50 (AcOH/EtOAc/hexanes, 1:20:20). ^{1}H NMR (400 Mz, D_2O): δ (ppm) 2.92 (1 H, dd, *J* = 6.2, CH_2), 3.13 (1 H, dd, *J* = 8.7, CH_2), 4.54 (1 H, dd, *J* = 6.2, CH). ^{13}C NMR (100 Mz, D_2O): δ (ppm) 40.9, 42.2, 173.3, 174.3. IR (ATR): υ (cm^{-1}) 1404, 1700 (C=O stretch), 1742 (C=O stretch), 3001 (O-H stretch br). mp: 163-166 °C, lit. 163-164 °C.

(*S*)-2-bromosuccinic acid (*S*)-195[124]

$[\alpha]_D^{25}$: −43.5° (*c* 1g/100mL, H_2O). lit.: −42.7° (*c* 1g/100mL, H_2O).

(±)-2-Bromo-1,4-butandiol 196[125]



195 **196**

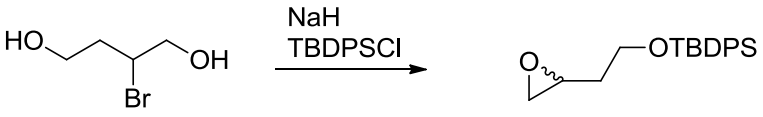
Scheme 102.

Under an atmosphere of nitrogen at −5 °C (ice/NaCl water bath), BH_3 (45.7 mL, 45.7 mmol, 1M THF complex) was added over a period of 1 hr, *via* dropping funnel, to a solution of (±)-bromosuccinic acid **195** (3.0 g, 15.2 mmol) in THF (50 mL) and the reaction mixture was stirred for 1 hr at this temperature resulting in a cloudy suspension. The cooling bath was removed and stirring continued for 1.5 hrs at r.t. H_2O (3 mL) was added followed by K_2CO_3 (5.5 g) and the mixture stirred at 0 °C for a further 20 mins. After filtration, solvent was removed and purification by silica gel chromatography (MeOH/EtOAc, 1:50) gave the desired diol **196** as a colourless oil (88%, 2.26 g over 2 steps from aspartic acid). R_f = 0.45 (MeOH/EtOAc, 1:50). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 2.00 - 2.10 (2 H, br m, CH_2), 2.42 (2 H, br s, OH), 3.78 (4 H, m, CH_2), 4.23 (1 H, m, CH). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 37.6, 55.0, 60.0, 67.0. IR (ATR): υ (cm^{-1}) 1420, 2859, 2930, 3107 (O-H stretch), 3399 (O-H stretch).

(*S*)-2-Bromo-1,4-butandiol (*S*)-196[124]

$[\alpha]_D^{25}$: −23.0° (*c* 1.05g/100mL, $CHCl_3$). lit.: −26.2° (*c* 1.05g/100mL, $CHCl_3$).

(±)-^{t}Butyl-(2-(oxiran-2-yl)ethoxy)diphenylsilane 197[54]

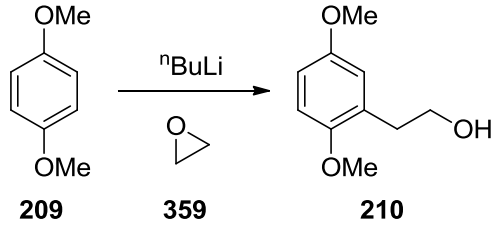


196 **197**

Scheme 103.

To a suspension of NaH 60% (1.53 g, 39.7 mmol) in THF (30 mL) was added (±)-2-bromo-1,4-butanediol (2.24 g, 13.2 mmol) in THF (10 mL) over 20 mins. at −16 °C and under an atmosphere of nitrogen. TBDPS-Cl (3.61 mL, 13.92 mmol) in THF (10 mL) was then slowly added at −10 °C and the mixture was stirred for 30 mins. after which stirring was continued for 45 mins. At r.t. H_2O (20 mL) and NH_4Cl (20 mL) were then added and mixture extracted into ethyl acetate (3 x 50 mL). The combined organic fractions were then dried ($MgSO_4$), filtered, solvent evaporated and compound was purified by silica gel chromatography (EtOAc/hexanes, 1:20) to give the desired epoxide **197** as a colourless oil (61%, 2.76 g). R_f = 0.40 (EtOAc/hexanes, 1:20). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.09 (9 H, s, ^{t}Bu), 1.79 (2 H, m, CH_2), 2.50 (1 H, m, CH_2), 2.78 (1 H, m, CH_2), 3.10 (1 H, m, CH), 3.89 (2 H, m, CH_2), 7.45 (6 H, m, H_{Ar}), 7.70 (4 H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 20.1, 27.0, 36.1, 47.4, 50.6, 61.3, 128.8, 131.0, 133.8, 133.9, 136.0, 136.7. IR (ATR): υ (cm^{-1}): 1197, 1305, 1466, 1483, 3050.

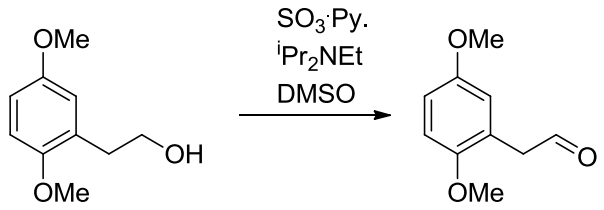
2-(2,5-Dimethoxyphenyl)ethanol 210[126, 127]



Scheme 104.

To a solution, cooled to 0 °C, of dimethoxybenzene **209** (6.9 g, 50 mmol) in THF (100 mL) was added ^{n}BuLi (20 mL, 50 mmol, 2.5 M in hexane) resulting in a pale yellow solution and the reaction mixture stirred at this temperature for 30 mins. Neat ethylene oxide **359**, cooled to below −20 °C, was then added in one portion and mixture stirred at r.t. for 2 hrs. Reaction was then quenched at 0 °C with 50% saturated solution NH_4Cl (50 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/hexanes, 1:5) gave pure alcohol **210** as a yellow oil (54%, 4.8 g). R_f = 1.5 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 2.81 (2H, t, J = 6.4, CH_2), 3.69 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.76 (2H, m, CH_2), 6.64-6.74 (3H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 34.2, 55.7, 55.9, 62.9, 111.42, 111.72, 111.74, 128.3, 151.9, 153.6. IR (ATR): υ (cm^{-1}) 1046, 1501, 1590, 1741, 2938, 3386 (O-H stretch br). LRMS $C_{10}H_{14}O_3$ $[M + H]^+$: 182.02. HRMS calcd. for $C_{10}H_{14}O_3$ $[M + Na]^+$: 205.0835 found 205.0833.

2-(2,5-Dimethoxyphenyl)acetaldehyde 211[128]

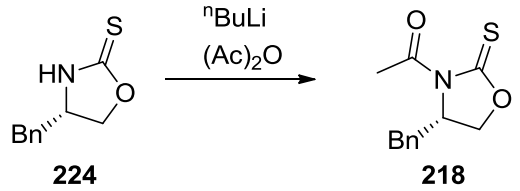


210 **211**

Scheme 105.

To a solution of the alcohol **210** (500 mg, 3.30 mmol) in CH_2Cl_2 (10 mL) and DMSO (5 mL) was added $^{i}Pr_2NEt$ (2.86 mL, 16.20 mmol) at 0 °C and the reaction mixture was stirred for 20 mins. A solution of sulfur trioxide pyridine complex (1.59 g, 9.98 mmol) in DMSO (2 mL) was then slowly added, maintaining low temperature. Reaction was stirred at this temperature for 30 mins and at r.t. for a further 30 mins before being diluted with CH_2Cl_2 (30 mL), washed with $CuSO_4$ (2 x 30 mL), $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated to give pure aldehyde **211** as an orange oil (99%, 574 mg). R_f = 0.33 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.64 (2H, d, *J* = 2.1, CH_2), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.74-6.85 (3H, m, H_{Ar}), 9.96 (1H, t, *J* = 2.1, CHO). ^{13}C NMR (100 Mz): δ (ppm) 45.5, 55.8, 55.9, 111.4, 113.1, 117.4, 122.2, 151.9, 153.7, 200.0. IR (ATR): υ (cm^{-1}) 1523, 1588, 1720 (C=O stretch), 1751, 2835 (C-H aldehyde stretch), 2948. HRMS calcd. for $C_{10}H_{12}O_3$ $[M - H]^+$: 179.0703 found 179.0698.

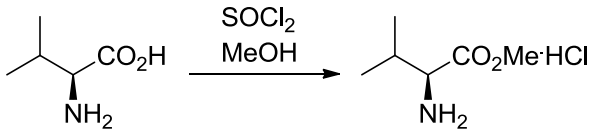
(4*S*-benzyl-thio-oxo-oxazolidin-3-yl)-ethanone 218[90]



Scheme 106.

To a solution, cooled to −78 °C, of the oxazolidinthione **224** (200 mg, 1.04 mmol) in THF (10 mL) was added ^{n}butyllithium (0.416 mL, 1.04 mmol, 2.5 M in hexanes) dropwise and mixture stirred at this temperature for 20 mins. Acetic anhydride (0.1 mL, 1.14 mmol) was then slowly added and the mixture was stirred for 30 mins. at r.t. A 50% saturated solution of $NaHCO_3$ (20 mL) was used to quench the reaction at 0 °C and the THF evaporated. The remaining suspension was then extracted into CH_2Cl_2 (2 x 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the acylated compound **218** as a pure white solid (99%, 231 mg). R_f = 0.50 (EtOAc/hexanes, 1:4) ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 2.80 (1H, dd, *J* = 9.0, 13.3, CH_2), 2.88 (3H, s, CH_3), 3.32 (1H, dd, *J* = 9.0 13.3, CH_2), 4.34 (2H, m, CH_2), 4.96 (1H, m, CH), 7.23-7.39 (5H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 26.2, 37.5, 59.8, 70.3, 127.4, 129.4, 135.2, 171.1, 185.8. IR (ATR): υ (cm^{-1}) 1170, 1290, 1460 (C=S stretch), 1690 (C=O stretch). mp: 163-166 °C, lit. 163-164 °C. $[\alpha]_D^{25}$: +25.0° (*c* 0.40/100mL, $CDCl_3$). lit.: +26.3° (*c* 0.40g/100mL, $CDCl_3$).

L-Valine methyl ester hydrochloride 226[91]

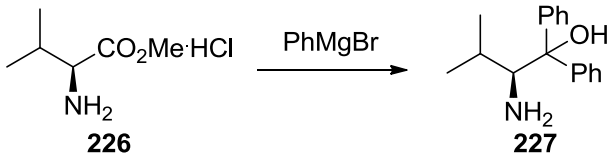


225 **226**

Scheme 107.

L-valine **225** (5.00g, 42 mmol) as a suspension in MeOH (50 mL) was treated with thionyl chloride (9.23 mL, 127 mmol) dropwise over 5 minutes at 0 °C and stirred at r.t. for 17 hrs. The reaction mixture was then concentrated and washed with Et_2O to give methyl ester **226** as a solid yellow hydrochloride salt (98%, 6.90 g). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 1.16 (6H, d, *J* = 6.8, CH_3), 2.47 (1H, m, CH), 3.84 (3H, s, CO_2CH), 3.93 (1H, d, *J* = 4.4, CH). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 17.7, 18.3, 29.0, 38.9, 57.2, 170.1. IR (ATR): υ (cm^{-1}) 1235, 1766 (C=O stretch), 2899, 3345 (N-H stretch). mp: 171-173 °C, lit. 171-173 °C. $[\alpha]_D^{25}$: +25.0° (*c* 1.00/100mL, MeOH). lit.: +24.2° (*c* 1.00g/100mL, MeOH).

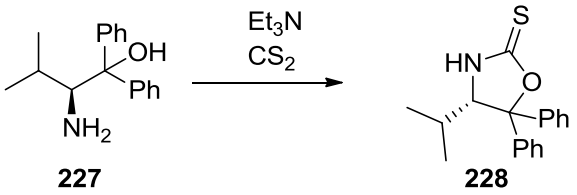
(*S*)-1,1-Diphenylvalinol 227[92, 93, 130]



Scheme 108.

Bromobenzene (21.6 mL, 206 mmol) was added dropwise to a three necked round bottom flask charged with Mg turnings (5.00 g) and Et_2O (50 mL) at a rate to maintain gentle reflux. After addition was complete the dark brown coloured mixture was diluted more with Et_2O (30 mL) and stirred for 30 mins. before the slow addition of methyl ester hydrochloride **226** (6.7 g, 40 mmol) which also resulted in gentle reflux over 30 min. After stirring at r.t. for 17 hrs. The yellow reaction mixture was poured onto 2 M NaOH (200 mL), filtered through a pad of Celite and the aqueous phase was extracted into CH_2Cl_2 (4 x 40 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/hexanes, 1:4) gave pure compound **227** as a pale yellow solid (44%, 4.56 g). R_f = 0.15 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 0.69 (3H, d, *J* = 6.9, CH_3), 0.81 (3H, d, *J* = 6.9, CH_3), 1.91 (1H, m, CH), 5.19 (1H, d, *J* = 3.4, CH), 7.19-7.42 (10H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 16.1, 23.0, 27.8, 60.2, 79.7, 125.5, 125.9, 126.3, 127.6, 128.0, 128.4, 144.9, 148.0. IR (ATR): υ (cm^{-1}) 1601, 3017, 3261 (N-H stretch), 3607 (O-H stretch). LRMS $C_{17}H_{21}NO$ $[M + H]^+$: 238.13. mp: 99-101 °C, lit. 98-99 °C. $[\alpha]_D^{25}$: −124.0° (*c* 1.10/100mL, $CHCl_3$). lit.: −130.2° (*c* 1.10g/100mL, $CHCl_3$).

(4*S*)-isopropyl-(3,3-diphenyl)-thio-oxo-oxazolidinone 228[89]

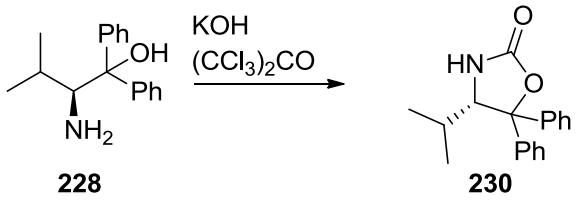


227 **228**

Scheme 109.

To a solution of amino alcohol **227** (1.00 g, 4.10 mmol) in THF (30 mL) was added Et_3N (1.70 mL, 12.3 mmol) and CS_2 (0.74 mL, 12.3 mmol) respectively before being refluxed for 14 hrs. The reaction was then cooled to r.t., quenched with saturated NH_4Cl (20 mL) and extracted into EtOAc (2 x 20 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by silica gel chromatography (4:1 hexanes:EtOAc) gave the oxazolidinthione **228** as a pale yellow solid (85%, 1.05 g). R_f = 0.20 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 0.70 (3H, d, *J* = 6.7, CH_3), 0.90 (3H, d, *J* = 6.7, CH_3), 1.90 (1H, m, CH), 4.48 (1H, d, *J* = 4.4, CH), 7.30-7.38 (8H, m, H_{Ar}), 7.50 (2H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 16.3, 20.9, 29.7, 69.6, 95.7, 125.8, 126.6, 128.2, 128.7, 138.1, 142.4, 187.9. IR (ATR): υ (cm^{-1}) 1170, 1177, 1509 (C=S stretch), 2910 (N-H stretch). LRMS $C_{18}H_{19}NOS$ $[M + H]^+$: 298.07. mp: 220-223 °C, lit. 223 °C. $[\alpha]_D^{25}$: −310.0° (*c* 0.50g/100mL, MeOH). lit.: −295.0° (*c* 0.50g/100mL, MeOH).

(4*S*)-isopropyl-(3,3-diphenyl)-oxazolidinone 230[89, 95]

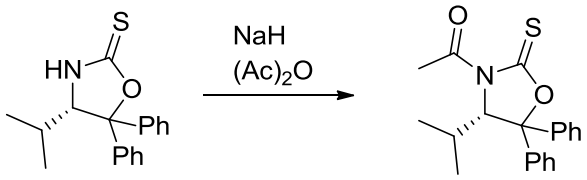


228 **230**

Scheme 110.

To a suspension of the amino alcohol **228** (1.00 g, 4.10 mmol) in toluene (20 mL) and 10% aqueous KOH (20 mL) was added triphosgene (4.19 g, 14.1 mmol) at r.t. and the slurry stirred for 2 hrs. The newly formed white solid was then filtered, washed with toluene and cold water before being recrystalised from cyclohexane to give desired oxazolidinone **230** as white crystals (65%, 760 mg). R_f = 0.35 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 0.66 (3H, d, *J* = 6.6, CH_3), 0.87 (3H, d, *J* = 6.9, CH_3), 1.85 (1H, m, CH), 4.33 (1H, d, *J* = 3.6, CH), 5.72 (1H, br s, NH), 7.24-7.39 (8H, m, H_{Ar}), 7.52 (2H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 15.6, 20.8, 29.5, 65.7, 89.3, 125.7, 126.3, 128.1, 128.8, 158.2, 196.8. IR (ATR): υ (cm^{-1}) 1185, 1217, 1759 (C=O stretch), 3079, 3315 (N-H stretch) LRMS $C_{18}H_{19}NO_2$ $[M + H]^+$: 282.07. mp: 252-255 °C, lit. 252-253 °C. $[\alpha]_D^{25}$: −255.1° (*c* 0.50g/100mL, $CDCl_3$). lit.: −263.4° (*c* 0.50g/100mL, $CDCl_3$).

(4*S*-isopropyl-(3,3-diphenyl)-thio-oxo-oxazolidin-3-yl)-ethanone 229[89, 93]

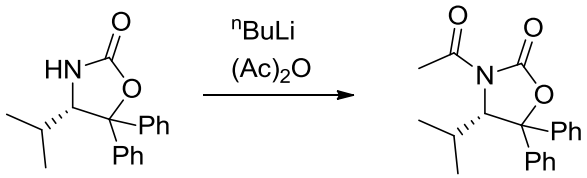


228 **229**

Scheme 111.

To a solution of the oxazolidinthione **228** (1.00 g, 3.36 mmol) in THF, at 0 °C was added oil free NaH and stirred for 20 mins. Acetic anhydride (0.34 mL, 3.69 mmol) was then added dropwise and reaction mixture was stirred at r.t. for 17 hrs. NH_4Cl (20 mL) was then added and the mixture extracted into EtOAc (2 x 20 mL). The combined organic fractions were then washed with $NaHCO_3$ (40 mL), dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography (EtOAc/hexanes, 1:8) gave acylated compound **229** as a white powder (61%, 674 mg). R_f = 0.45 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 0.79 (3H, d, *J* = 6.0, CH_3), 0.84 (3H, d, *J* = 6.0, CH_3), 2.03 (1H, m, CH), 2.69 (3H, s, CH_3), 5.59 (1H, d, *J* = 3.0, CH), 7.29-7.49 (10h, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 17.0, 21.5, 25.7, 30.0, 68.0, 93.3, 125.4, 126.1, 128.4, 137.4, 141.6, 171.0, 185.4. IR (ATR): υ (cm^{-1}) 1220, 1334 (C=S stretch), 1374, 1703, 1756 (C=O stretch), 3016. LRMS $C_{20}H_{21}NO_2S$ $[M + H]^+$: 340.00. mp: 90-92 °C, lit. 89-90 °C. $[\alpha]_D^{25}$: −201.1° (*c* 0.50g/100mL, $CDCl_3$). lit. −192.0° (*c* 0.50g/100mL, $CDCl_3$).

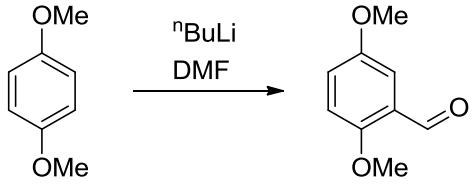
(4*S*-isopropyl-(3,3-diphenyl)-oxazolidin-3-yl)-ethanone 231[96]



Scheme 112.

At −78 °C, ^{n}BuLi (0.71 mL, 1.79 mmol, 2.5 M in hexanes) was added to a solution of oxazolidinone **230** (505 mg, 1.79 mmol) in THF (20 mL) and stirred at this temperature for 20 mins. Freshly distilled acetic anhydride (0.18 mL, 2.00 mmol) was then added and the reaction mixture temperature warmed to 0 °C. After stirring for 2 hrs, 50% aqueous NH_4Cl (20 mL) was added and the mixture was extracted into EtOAc (3 x 20 mL). The combined organic fractions were then washed with saturated $NaHCO_3$ (30 mL). After drying ($MgSO_4$), filtration and concentration under reduced pressure the acetylated oxazolidinone was recrystalised from cyclohexane to give a white solid of **231** (98%, 576 mg). R_f = 0.40 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 0.69 (3H, d, *J* = 6.8, CH_3), 0.77 (3H, d, *J* = 6.0, CH_3), 1.91 (1H, m, CH), 2.36 (3H, s, CH_3), 5.29 (1H, d, *J* = 3.4, CH), 7.14-7.31 (8H, m, H_{Ar}), 7.41 (2H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 16.4, 21.7, 23.4, 29.9, 64.4, 89.3, 125.6, 125.9, 128.4, 128.9, 138.2, 142.3, 153.2, 170.1. IR (ATR): υ (cm^{-1}) 1450, 1706 (C=O stretch), 1787 (C=O stretch), 2994. LRMS $C_{20}H_{21}NO_3$ $[M + H]^+$: 324.07. mp: 121-123 °C, lit. 121-122 °C. $[\alpha]_D^{25}$: −261.5° (*c* 1.33g/100mL, $CDCl_3$). lit. −252.5° (*c* 1.33g/100mL, $CDCl_3$).

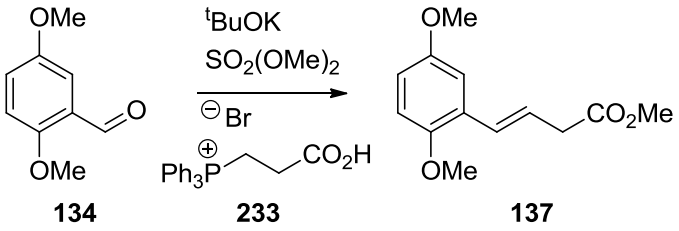
2,5-Dimethoxybenzaldehyde 134[131]



Scheme 113.

To a solution, cooled to 0 °C, of 1,4-dimethoxybenzene **209** (4.00 g, 28.98 mmol) in THF (60 mL) was added ^{n}BuLi (15.0 mL, 37.7 mmol, 2.5 M in hexanes) dropwise and the solution was stirred for 20 mins. Freshly distilled DMF (2.90 mL, 37.7 mmol) was then added in one portion and mixture was stirred for 1 hr at 0 °C. 50% aqueous NH_4Cl (50 mL) was then added and mixture extracted into EtOAc (3 x 30 mL), washed with saturated $NaHCO_3$ (30 mL) before being dried ($MgSO_4$). After filtration, solvent was evaporated under reduced pressure and the crude mixture was purified by silica gel chromatography (EtOAc/hexanes, 1:4) to give 2,5-dimethoxybenzaldehyde **134** as a yellow crystalline solid (84%, 3.94 g). R_f = 0.30 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.93 (1H, d, *J* = 9.1, H_{Ar}), 7.14 (1H, dd, *J* = 9.1, H_{Ar}), 7.33 (1H, d, *J* = 3.3, H_{Ar}), 10.44 (1H, s, CHO). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 55.8, 56.1, 110.4, 113.4, 123.5, 124.9, 153.6, 156.7, 189.6. IR (ATR): υ (cm^{-1}) 1224, 1300, 1592, 1599, 1710 (C=O stretch), 2891 (C-H stretch aldehyde), 3076. LRMS $C_9H_{10}O_3$ $[M + H]^+$: 167.14. mp: 46-48 °C, lit. 46-48 °C.

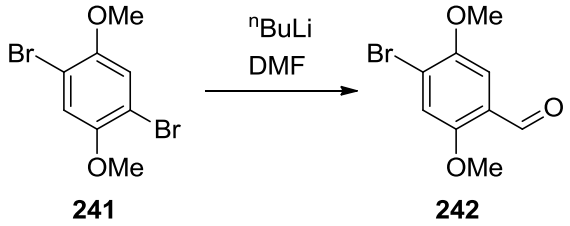
(*E*)-Methyl-4-(2,5-dimethoxyphenyl)but-3-enoate 137[70]



Scheme 114.

To a stirred solution of 3-triphenylphosphonium bromide propanoic acid **233** (3.74 g, 9.0 mmol) in THF (40 mL) at 0 °C was added 2,5-dimethoxybenzaldehyde **134** (730 mg, 4.5 mmol) followed by the dropwise addition of a solution of ^{t}BuOK (2.0g, 18.0 mmol) in THF (40 mL) over 1 hr. This mixture was stirred for 30 mins at 0 °C and a further 2 hrs at r.t. before the addition of dimethylsulfate (1.14ml, 12.0 mmol). After stirring for 1 hr H_2O (40 mL) was added and the reaction mixture extracted into EtOAc (2 x 30 mL). After washing with saturated $NaHCO_3$ (30 mL) and saturated NaCl (30 mL) the solution was dried ($MgSO_4$), filtered and solvent removed. Purification by silica gel chromatography (EtOAc:pentane, 1:5) gave β,γ-unsaturated ester **137** as a colourless oil (37%, 387 mmol). R_f = 0. 25 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.27 (2H, d, *J* = 6.1, CH_2), 3.72 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.80 (3H, s, CO_2CH_3), 6.29 (1H, dt, *J* = 7.2 16.0, CH), 6.78 (1H, dd, *J* = 7.2 16.0, CH). 6.87-7.00 (3H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 39.0, 52.1, 55.9, 56.3, 112.0, 112.0, 113.9, 122.7, 126.8, 128.2, 150.7, 154.1, 172.3. IR (ATR): υ (cm^{-1}) 1040, 1179, 1212, 1433, 1751 (C=O stretch), 2845 (C-H stretch alkene), 2995 (C-H stretch alkene), 3000. LRMS $C_{13}H_{16}O_4$ $[M + H]^+$: 238.86.

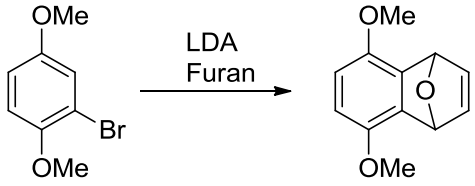
2,5-Dimethoxy-4-bromobenzaldehyde 242[100, 132]



Scheme 115.

To a stirred solution of 1,4-dibromo-2,5-dimethoxybenzene **241** (2 g, 6.7 mmol) in THF (20 mL) at 0 °C under an atmosphere of argon was added dropwise ^{n}BuLi (2.8 mL 7.1 mmol, 2.5 M in hexanes) and the mixture was stirred for 5 mins. DMF (0.67 mL, 8.8 mmol) was then added and mixture allowed to warm to r.t. over 10 mins and then refluxed for 10 mins. H_2O (20 mL) was then added and mixture extracted into EtOAc (2 x 20 mL). The combined organic fractions were then washed with $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/hexanes, 1:6) gave the desired substituted benzaldehyde **242** as a yellow solid (90%, 1.46 g). R_f = 0.35 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 7.19 (1H, s, H_{Ar}), 7.27 (1H, s, H_{Ar}), 10.33 (1H, s, CHO). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 56.4, 56.7, 109.6, 117.7, 120.3, 124.1, 150.4, 156.2, 188.8. IR (ATR): υ (cm^{-1}) 1393, 1448, 1485, 1600, 1677 (C=O), 2890, (C-H stretch aldehyde), 3076. mp: 129-130 °C, lit. 132-134 °C.

5,8-Dimethoxy-1,4-dihydro-1,4-epoxynaphthalene 235[119]

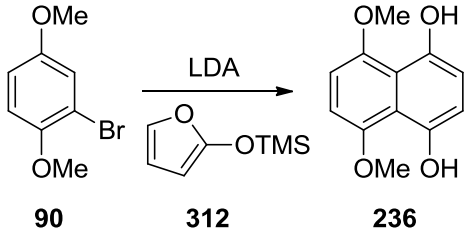


90 **235**

Scheme 116.

At −20 °C under an atmosphere of argon was added ^{n}BuLi (0.92 mL, 2.3 mmol, 2.5 M in hexanes) to a stirred solution of diisopropylamine (0.32 mL, 2.3 mmol) in THF (10 mL) and briefly warmed to r.t. The resulting solution of LDA was then cooled to −78 °C and furan slowly added over 30 minutes. A solution of 2,5-dimethoxybromobenzene **90** (0.34 mL, 2.3 mmol) in THF (10 mL) was then added over 15 minutes and the reaction mixture was stirred for a further 30 mins at −78 °C. At this temperature H_2O (20 mL) was added and the solution allowed to warm to r.t. before being extracted into EtOAc (3 x 20 mL). The combined extracts were then washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Silica gel chromatography (EtOAc/hexanes, 1:4) gave cycloaddition adduct **235** (99%, 455 mg). R_f = 0.20 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.79 (6H, s, OCH_3), 5.92 (2H, t, *J* = 1.0, CH), 6.54 (2H, s, H_{Ar}), 7.06 (2H, t, *J* = 1.0, CH). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 56.4, 80.4, 111.6, 137.4, 143.0, 147.9. IR (ATR): υ (cm^{-1}) 1177, 1254, 1495, 1614, 2835, 2941. LRMS $C_{12}H_{12}O_3$ $[M + H]^+$: 205.06. mp: 85-87 °C, lit. 86-87 °C.

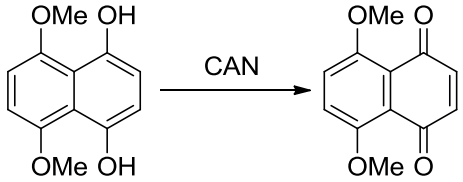
1,4-Dihydroxy-5,8-dimethoxynaphthlene 236[101]



Scheme 117.

To a solution of diisopropylamine (0.42 mL, 3 mmol) in THF (3 mL) was added ^{n}BuLi (1.2 mL, 3 mmol, 2.5 M in hexanes) dropwise at 0 °C and the reaction mixture was stirred for 10 mins. The resulting LDA solution was then cooled to −78 °C and 2-siloxyfuran **213** (0.67 mL, 4 mmol) was then added in one portion followed by the slow addition of 2-bromo-1,4-dimethoxybenzene **90** (3.02 mL, 2 mmol) in THF (10 mL) over 20 minutes. After addition was complete the reaction mixture was stirred for 30 minutes at −78 °C and quenched with water (10 mL) at this temperature. The biphasic solution was allowed to warm to r.t. and 1 M HCl (20 mL) was added producing a yellow solution. The mixture was extracted into EtOAc (4 x 10 mL), washed with $NaHCO_3$ (20 mL), dried ($MgSO_4$) and filtered before being concentrated under reduced pressure. Silica gel chromatography (EtOAc/hexanes, 1:2) gave the aromatised adduct as an orange solid **236** (77%, 333 mg). The compound readily oxidised in air/silica gel to naphthoquinone **181**. R_f = 0.40 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.99 (6H, s, OCH_3), 6.61 (2H, s, H_{Ar}), 6.82 (2H, s, H_{Ar}), 9.08 (2H, s, OH). ^{13}C NMR (100 Mz, $CDCl_3$) δ (ppm) 56.4, 56.9, 112.6, 114.6, 146.9, 154.0. HRMS calcd. for $C_{12}H_{12}O_4$ $[M + H]^+$: 221.0812 found 221.0810.

***O,O*-dimethoxynaphthazarin 181**[102, 103]

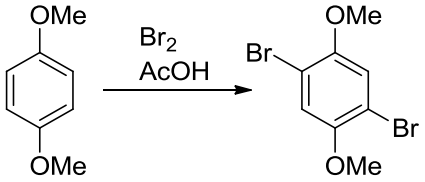


236 **181**

Scheme 118.

Acetonitrile (4 mL) and H_2O (1 mL) were added to 1,4-dihydroxy-5,8-dimethoxynaphthalene **236** (90 mg, 0.41 mmol) followed by the addition of ceric ammonium nitrate (914 mg, 1.66 mmol) at 0 °C, and the reaction mixture was stirred for 10 minutes. The solution was then diluted with H_2O (10 mL), extracted into EtOAc (4 x 5 mL) and the combined organic fractions washed with H_2O (3 x 10 mL). The bright orange solution was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give naphthazarin analogue **181** in quantitative yield as red crystals (89 mg). R_f = 0.22 (EtOAc/hexanes, 1:4). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.96 (2H, s, OCH_3), 6.78 (2H, s, H_{Ar}), 7.33 (2H, s, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 56.9, 120.3, 138.4, 153.7, 184.9. IR (ATR): υ (cm^{-1}) 964, 1652 (C=O stretch), 2848, 2933. HRMS calcd. for $C_{10}H_{10}O_4$ $[M + Na]^+$: 219.0555 found 219.0553. mp: 157-160 °C, lit. 157-159 °C.

2,5-Dibromo-1,4-dimethoxybenzene 241[104, 133]

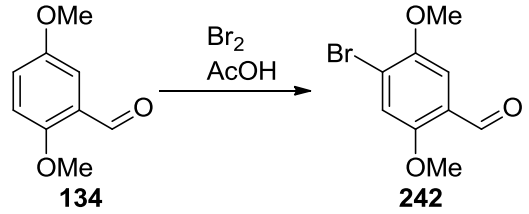


209 **241**

Scheme 119.

1,4-Dimethoxybenzene **209** (5 g, 69 mmol) was dissolved in chloroform (50 mL) at 0 °C and bromine (8.9 mL, 172.5 mmol) was slowly added to the solution over 1 hr. The reaction mixture was stirred at this temperature for 3 hrs and quenched with saturated Na_2SO_4 solution (50 mL). After extraction with CH_2Cl_2 (3 x 30 mL), drying ($MgSO_4$), filtration and concentration under reduced pressure the brominated compound **241** was recrystallised from EtOH to give yellow plates (47%, 9.5 g). R_f = 0.45 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.85 (6H, s, OCH_3), 7.11 (2H, s, H_{Ar}). ^{13}C NMR (300 Mz, $CDCl_3$): δ (ppm) 57.0, 110.4, 117.1, 150.5. IR (ATR): υ (cm^{-1}) 1237, 1599, 3047. mp: 139-141 °C, lit. 144-145 °C.

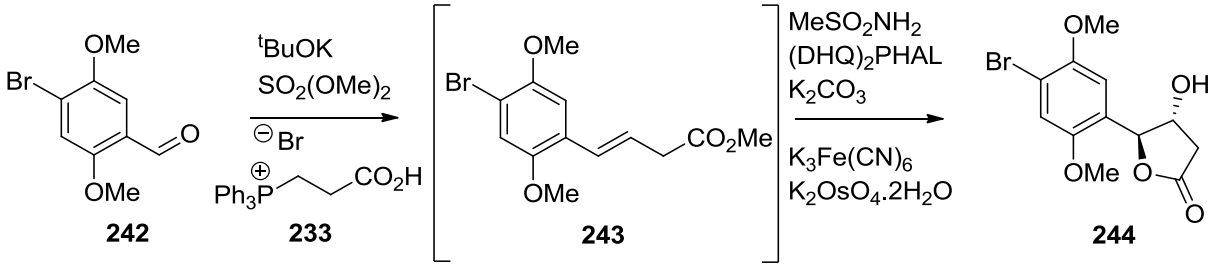
2,5-Dimethoxy-4-bromobenzaldehyde 242[104, 132]



Scheme 120.

To a stirred solution of 2,5-dimethoxybenzaldehyde **134** (5 g, 30 mmol) in AcOH (50 mL) was added bromine (4.6 mL, 90 mmol) dropwise at r.t. and solution stirred for 48 hrs. The reaction mixture was then concentrated under reduced pressure and the brominated compound **242** was crystallised at −20 °C form EtOAc as bright yellow plates (53%, 3.83 g). R_f = 0.35 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 7.19 (1H, s, H_{Ar}), 7.27 (1H, s, H_{Ar}), 10.33 (1H, s, CHO). ^{13}C NMR (300 Mz, $CDCl_3$): δ (ppm) 56.4, 56.7, 109.6, 117.6, 120.3, 124.1, 140.4, 156.2, 188.8. IR (ATR): υ (cm^{-1}) 1393, 1448, 1485, 1600, 1677 (C=O), 2890, (C-H stretch aldehyde), 3076. HRMS calcd. for $C_9H_9O_3Br$ $[M + H]^+$: 244.9808, 246.9787 found 244.9804, 246.9782. mp: 129-130 °C, lit. 132-134 °C.

(4*R*,5*S*)-5-(4-bromo-2,5-dimethoxyphenyl)-4-hydroxydihydrofuran-2(3H)-one 244

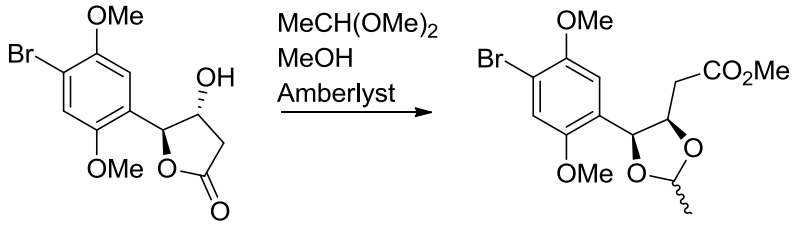


Scheme 121.

To a solution of 4-bromo-2,5-dimethoxybenzaldehyde **242** (612 mg, 2.50 mmol) and 3-triphenylphosphonium bromide propanoic acid **233** (1.55 g, 3.75 mmol) in THF (20 mL) was added a solution of ^{t}BuOK (0.841 g, 7.49 mmol) in THF (20 mL) at 0 °C over a period of 1 hr. And the reaction mixture was then stirred at this temperature for an additional 2 hrs. Me_2SO_4 (0.356 mL, 3.75 mmol) was then added and reaction brought to r.t. After stirring for 2 hrs the reaction was quenched with HCl (1 M, 40 mL) and extracted into EtOAc (3 x 20 mL) before being washed with $NaHCO_3$ (30 mL). The solution was dried ($MgSO_4$), filtered, concentrated and **243** was used as a crude mixture. R_f = 0.25 (EtOAc/hexanes, 1:6).

Methane sulfonamide (49 mg, 0.51 mmol) and AD-mix-α (510 mg) were dissolved in ^{t}BuOH (3 mL) and H_2O (3 mL) and cooled to 0 °C. The crude Wittig adduct **243** (161 mg, 0.15 mmol) was then added in solution ^{t}BuOH/H_2O (2 mL/2 mL) and the reaction mixture stirred for 14 hours. The temperature was then increased to r.t. and mixture stirred for an additional 10 hrs. A saturated solution of Na_2SO_4 (5 mL) was then added and the solution stirred for 1 hr at ambient temperature before being extracted into EtOAc (6 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (EtOAc/hexane, 1:1 to 1:2) on silica gave the desired lactone product **244** as a yellow solid (90%, 140 mg). R_f = 0.25 (EtOAc/hexane, 1:1). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 2.70 (1H, d, *J* = 17.5, CH_2), 2.87 (1H, dd, *J* = 5.3, 17.5, CH_2), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.80 (1H, m, CH), 5.68 (1H, d, *J* = 3.2, CH), 7.08 (1H, s, H_{Ar}), 7.13 (1H, s, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 38.2, 56.2, 57.0, 68.7, 81.6, 111.4, 111.7, 115.9, 121.6, 149.6, 150.6, 175.3. IR (ATR): υ (cm^{-1}) 1031, 1279, 1390, 1464, 1497, 1778 (C=O stretch), 2940, 3454 (O-H stretch br). HRMS calcd. for $C_{12}H_{13}O_5Br$ $[M + H]^+$: 317.0019, 318.9999 found 317.0024, 319.0003. mp: 65-67 °C. $[\alpha]_D^{25}$: +49.0° (*c* 1.00g/100mL, $CHCl_3$).

Methyl 2-((4*R*,5*S*)-5-(4-bromo-2,5-dimethoxyphenyl)-2-methyl-1,3-dioxolan-4-yl)acetate 252

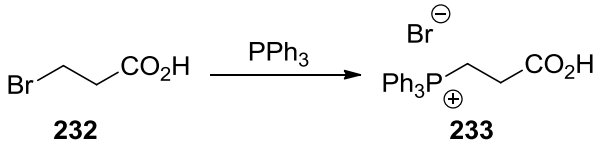


243 **252**

Scheme 122.

To a solution of lactone **243** (100 mg, 0.32 mmol) in MeOH (0.19 mL, 5.12 mmol) and 1,1-dimethoxyethane (0.34 mL, 3.2 mmol) was added Amberlyst resin at r.t. The mixture was stirred for 3 days. The Amberlyst resin was then filtered and all volatile materials evaporated to give desired acetal methyl ester. Purification by silica gel chromatography (EtOAc/hexanes, 1:9) gave an inseperable mixture of isomers of **252** at the acetal position (33%, 40 mg). R_f = 0.20 (EtOAc/hexanes, 1:6). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.14 (3H, d, *J* = 3, CH_3 (minor)), 1.45 (3H, d, *J* = 3, CH_3 (major)), 2.63-2.69 (1H, m, CH_2), 2.81-2.85 (1H, m, CH_2), 3.62 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.80 (3H, s, CO_2Me (minor)), 3.81 (3H, s, CO_2Me (major)), 4.14-4.21 (1H, m, CH), 4.89 (1H, d, *J* = 3, CH, (minor)), 4.94 (1H, d, *J* = 3, CH (major)), 5.26 (1H, q, *J* = 3, 6, CH (major)), 5.33(1H, q, *J* = 3, 6, CH (minor)), 6.98 (2H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 20.0 (major), 20.5 (minor), 37.8 (major), 37.9 (minor), 51.8, 56.0 (minor), 56.1 (major), 56.9 (major), 57.0 (minor), 77.5, 79.5 (major), 80.3 (minor), 101.0 (major), 102.2 (minor), 110.5, 110.6, 110.8, 115.8, 116.0, 127.4, 127.5, 150.4, 150.6, 150.8, 171.1 (major), 171.2 (minor). IR (ATR): υ (cm^{-1}) 1211 (C-O stretch), 1492, 1739 (C=O stretch), 2999. HRMS calcd. for $C_{15}H_{19}O_6Br$ $[M + NH_4]^+$: 392.0703, 394.0683 found 392.0706, 394.0685. mp: 161-165 °C.

3-triphenyl phosphonium bromide propanoic acid 233

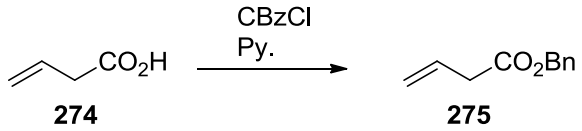


232 **233**

Scheme 123.

Under an atmosphere of argon, triphenylphosphine (8 g, 30.5 mmol) was added to a solution of 3-bromopropanoic acid **232** (5.60 g, 36.6 mmol) in toluene (90 mL) and the mixture was refluxed for 24 hrs. The cloudy solution was then allowed to cool to r.t. resulting in the formation of a white solid. The toluene was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL) before being filtered. The filtrate was concentrated to give phosphonium salt **233** in quatative yield as a white solid (15.2 g). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 3.11 (2H, m, CH_2), 3.77 (2H, m, CH_2), 7.75 (15H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 18.8 (d), 28.2, 117.1 (d), 130.6, 133.6, 135.4, 171.2. IR (ATR): υ (cm^{-1}) 1212, 1455, 1765 (C=O stretch), 3345 (O-H stretch). HRMS calcd. for $C_{21}H_{20}O_2BrP$ $[M - H]^+$: 413.0312, 415.0291 found 413.0310, 415.0289. mp: <300 °C.

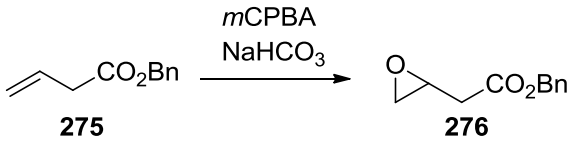
benzyl but-3-enoate 275[110]



Scheme 124.

To a solution of vinyl acetic acid **274** (500 mg, 5.81 mmol) in CH_2Cl_2 (30 mL) was added pyridine (0.934 mL, 11.60 mmol) followed by a solution of benzyl chloroformate (0.912 mL, 6.40 mmol) in CH_2Cl_2 (10 mL) and reaction mixture stirred at r.t. for 17 hrs. Saturated NH_4Cl (50 mL) was then added and organic phase was separated. The solution was then washed with $CuSO_4$ (2 x 40 mL), $NaHCO_3$ (2 x 40 mL), brine (2 x 40 mL) before drying ($MgSO_4$), filtration and concentration under reduced pressure. Silica gel chromatography (EtOAc/hexanes, 1:9) gave benzyl ester **275** as a clear oil (98%, 1.02 g). Rf = 0.4 (EtOAc/hexanes, 1:9). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 3.16 (2H, dt, *J* = 1.4, 7.2, CH_2), 5.15 (2H, s, $PhCH_2$), 5.20 (2H, m, CH_2), 5.95 (1H, dt, *J* = 7.2, 17.4, CH), 7.35 (5H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 39.1, 66.5, 118.7, 128.2, 128.3, 128.6, 130.2, 135.9, 171.3. IR (ATR): υ (cm^{-1}) 1160, 1685 C=C stretch,1730 (C=O stretch), 3158.

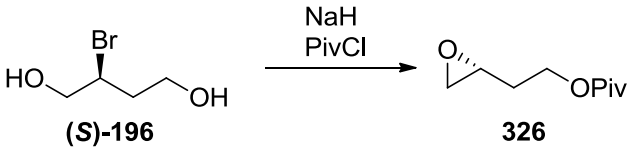
Benzyl-(2-oxiran-2-yl)acetate 276[111]



Scheme 125.

Benzyl ester **275** (1.84 g, 10.4 mmol) was dissolved in CH_2Cl_2 (100 mL) and $NaHCO_3$ (3.51 g, 41.8 mmol) added at 0 °C followed by *m*CPBA (6.54 g, 41.8 mmol) and the reaction mixture was stirred at r.t. for 24 hrs. Organic phase was then washed with H_2O (3 x 50 mL), dried ($MgSO_4$) and filtered before being concentrated under reduced pressure. Silica gel chromatography (EtOAc/hexanes, 1:9) gave epoxide **276** as a colourless oil (35%, 725 mg). R_f = 0.20 (EtOAc/hexanes, 1:6). ^{1}H NMR (300 Mz, $CDCl_3$): δ (ppm) 2.56 (1H, m CH), 2.61 (2H, m, CH_2), 2.80 (2H, m, CH_2), 5.20 (2H, s, $PhCH_2$), 7.35 (5H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 38.4, 47.1, 48.4, 67.7, 128.9, 128.9, 129.1, 136.1, 170.6. IR (ATR): υ (cm^{-1}) 1208, 1765 (C=O stretch), 3039. HRMS calcd. for $C_{11}H_{12}O_3$ $[M + H]^+$: 193.0859 found 193.0857.

(*S*)-2-((2-pivaloyloxy)ethyl)oxirane 326

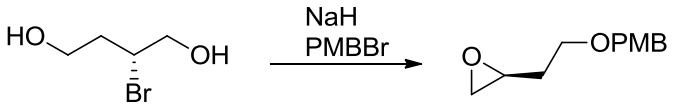


(*S*)-196 **326**

Scheme 126.

Under an atmosphere of argon, at 0 °C, was slowly added NaH (3.20g, 80 mmol, 60% in mineral oil) to a solution of bromo-diol **(*S*)-196** (4.50g, 26.6 mmol) in THF (100 mL). The cloudy solution was then allowed to stir at this temperature for 2 hrs. Pivaloyl chloride (4.9 mL, 40 mmol) was then added dropwise over 15 mins maintaining 0 °C. After stirring for a further 5 hrs the reaction mixture was then quenched at 0 °C with H_2O (50 mL) and extracted into EtOAc (2 x 50 mL). The combined organic fractions were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (EtOAc/hexanes, 1:10) gave desired epoxide **326** as a colourless oil (83.1%, 3.811 g). R_f = 0.28 (EtOAc/hexanes, 1:6). ^{1}H NMR (500 Mz, $CDCl_3$): δ (ppm) 1.24 (9H, s, CH_3), 1.86 (2H, m, CH_2), 2.55 (1H, dd, *J* = 5.0, 2.7, CH_2), 2.82 (1H, m, CH), 3.05 (1H, ddd, *J* = 11.4, 5.3, 3.7, CH_2), 4.25 (2H, t, *J* = 6.3, CH_2). ^{13}C NMR (500 Mz, $CDCl_3$): δ (ppm) 27.1, 32.0, 38.7, 46.9, 49.6, 60.9, 66.9, 68.9, 178.4. IR (ATR): υ (cm^{-1}) 1158, 1285, 1366, 1398, 1461, 1481, 1731 (C=O stretch), 2931. HRMS calcd. for $C_9H_{16}O_3$ $[M + H]^+$: 173.1168 found 173.1168. **[**$\alpha]_D^{25}$ = + 4.4° (*c* 1.00 g/100mL $CHCl_3$).

(*S*)-2-((2-*p*-methoxybenzyloxy)ethyl)oxirane 301[113]

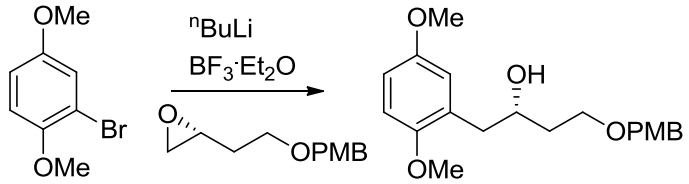


(*S*)-196 **301**

Scheme 127.

To a suspension of NaH (60%, 370 mg, 8.9 mmol) in THF (30 mL) was added a solution of diol **(*S*)-196** (454 mg, 2.9 mmol) at 0 °C and stirred for 5 hrs at r.t. *P*-methoxybenzyl bromide (500 mg, 2.9 mmol) in DMF (10 mL) was then added at r.t. and the reaction stirred for a further 3 hrs. The mixture was then quenched with saturated NH_4Cl (50 mL), extracted into EtOAc (2 x 30 mL) and washed with saturated $NaHCO_3$ (2 x 20 mL). The solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (EtOAc/hexanes, 1:6) gave desired epoxide as clear oil **301** (77%, 469 mg). R_f = 0.25 (EtOAc/hexanes, 1:4). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.75 (1 H, m, CH_2), 1.85 (1 H, m, CH_2), 2.52 (1 H, m, CH), 2.76 (1 H, m, CH_2), 3.06 (1 H, m, CH_2), 3.59 (2 H, mCH_2), 3.81 (3 H, s, OCH_3), 4.45 (2 H, s, ArCH_2), 6.87 (2 H, d, J = 9.0, H_{Ar}), 7.26 (2 H, d, J = 9.0, H_{Ar}). ^{13}C NMR (400 Mz,. $CDCl_3$): δ (ppm) 32.8, 47.0, 55.2, 66.7, 72.7, 113.8, 129.3, 130.4, 159.3. IR (ATR): υ (cm^{-1}) 1178, 1201, 1366, 1308, 1454, 1467, 2999. $[\alpha]_D^{25}$ = + 10.5°. (*c* = 1.05 g/100mL, $CHCl_3$) lit. +12.1° (*c* = 1.05 g/100mL, $CHCl_3$).

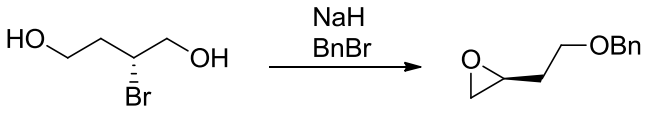
(*S*)-4-*para*-methoxybenzyl-1-(2,5-dimethoxyphenyl)butan-2-ol 298



Scheme 128.

To a solution of 2-bromo-1,4-dimethoxybenzene **90** (473 mg, 2.18 mmol) in Et_2O (20 mL) was added ^{n}BuLi (0.300 mL, 2.40 mmol, 1.6 M in hexanes) dropwise and the mixture was stirred for 20 minutes at −78 °C resulting in a pale yellow solution of the transmetallated compound. Freshly distilled $BF_3{\cdot}Et_2O$ (0.300 mL, 2.40 mmol) was then added slowly. PMB protected epoxyalcohol **301**(500 mg, 2.40 mmol) was then added as a dilute solution in Et_2O (10 mL) over 40 minutes at −55 °C and reaction mixture stirred at this temperature for 2 hrs. Mixture was then quenched at 0 °C with 50% aqueous NH_4Cl (40 mL), extracted into EtOAc (3 x 20 mL) and the combined organic fractions were washed with $NaHCO_3$ (30 mL). After drying ($MgSO_4$), filtration and concentrating under reduced pressure. Purification by silica gel chromatography (EtOAc/hexanes, 1:4 to 1:2) to give a clear oil of **298** (87%, 656 mg). R_f = 0.25 (EtOAc/ hexanes, 1:2). ^{1}H NMR. (400 Mz, $CDCl_3$): δ (ppm) 1.76 (2H, m, CH_2), 2.77 (2H, m, CH_2), 3.59-3.68 (2H, br m, CH_2), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.04 (1H, m, CH), 4.44 (2H, s, $ArCH_2$), 6.73 (3H, m, H_{Ar}), 6.78 (2H, d, J = 9.0, H_{Ar}), 7.23 (2H, d, J = 9.0, H_{Ar}). ^{13}C NMR (400 Mz, $CDCl_3$): δ (ppm) 36.0, 38.5, 55.2, 55.5, 55.8, 68.5, 70.8, 72.8, 111.4, 111.7, 113.8, 117.6, 128.3, 129.4, 130.3, 151.9, 153.5, 159.3. IR (ATR): υ (cm^{-1}) 1019, 1201, 1457, 3117, 3609 (O-H stretch). HRMS calcd. for $C_{20}H_{26}O_5$ $[M + H]^+$: 347.1850 found 347.1851. $[\alpha]_D$ = + 39.7° (*c* 1.00 g/100mL, $CHCl_3$).

(*S*)-2-((2-benzyloxy)ethyl)oxirane 303[114, 124]

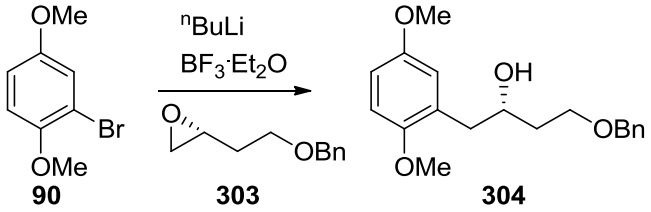


(*S*)-196 **303**

Scheme 129.

Oil free NaH (3.92 g, 98 mmol) was added slowly to a solution of diol **(*S*)-196** (5.52 g, 32.7 mmol) in THF (90 mL) and stirred for 2 hrs at 0 °C. BnBr (11.8 mL, 98 mmol) in THF (10 mL) was then added at this temperature and reaction warmed to r.t. After stirring for 5 hrs, saturated NH_4Cl (100 mL) was added and the reaction mixture was extracted into EtOAc (3 x 40 mL). The combined organic fractions were washed with $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Silica gel chromatography (EtOAc/hexanes, 1:19) gave pure epoxide **303** as a yellow oil (73%, 4.24 g). R_f = 0.30 (EtOAc/hexanes, 1:19). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.81 (1 H, m, CH_2), 1.91 (1 H, m, CH_2), 2.51 (1 H, mCH_2), 2.78 (1 H, mCH_2), 3.08 (1 H, m, CH), 3.63 (2 H, m, CH_2), 4.53 (2 H, s, PhCH_2), 7.34 (5 H, m, H_{Ar}). ^{13}C NMR (400 Mz, $CDCl_3$): δ (ppm) 32.9, 47.0, 50.1, 67.0, 76.7, 127.6, 128.4, 138.2. IR (ATR): υ (cm^{-1}) 1229., 1470, 1607, 2984, 3049. HRMS calcd. for $C_{11}H_{13}O_2$ [M + NH_4]$^+$: 226.1438 found 226.1436. $[\alpha]_D^{25}$ = +15.8° (*c* = 1.05 g/100mL, $CHCl_3$), lit. +14.6° (*c* = 1.05 g/100mL, $CHCl_3$).

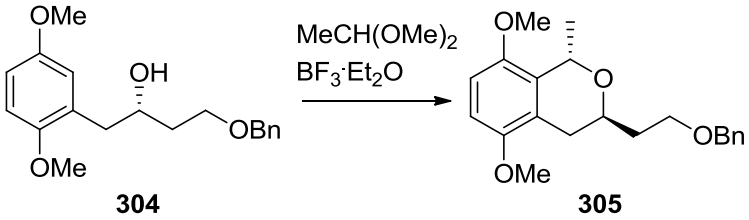
(*S*)-4-benzyloxy-1-(2,5-dimethoxyphenyl)butan-2-ol 304



Scheme 130.

To a solution of 2-bromo-1,4-dimethoxybenzene **90** (546 mg, 2.55 mmol), at −78 °C in Et_2O (30 mL) was added ^{n}BuLi (1.75 mL, 2.81 mmol, 1.6 M in hexanes) and stirred for 20 mins. $BF_3{\cdot}Et_2O$ (0.34 mL, 2.81 mmol) was then added and a solution of epoxide **303** in Et_2O (5 mL) was added dropwise over 20 minutes. Mixture was then stirred at −55 °C for 2 hrs before quenching with a 50% aqueous solution of NH_4Cl (50 mL) at 0 °C, extracting into Et_2O (2 x 20 mL) and washing the combined organic fractions with $NaHCO_3$ (50 mL). After drying ($MgSO_4$), filtration and concentrating under reduced pressure, the compound was purified by silica gel chromatography (EtOAc/hexanes, 1:4 to 1:2) to give essentially pure alcohol **304** as a pale yellow oil (88%, 705 mg). R_f = 0.30 (EtOAc/hexanes, 1:2). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.78 (2H, m, CH_2), 2.79 (2H, m, CH_2), 3.70 (2H, br m, CH_2), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.11 (1H, m, CH), 4.51 (2H, s, $PhCH_2$), 6.76 (3H, m, H_{Ar}), 7.30 (5H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 22.5, 25.1, 31.7, 36.3, 37.3, 55.5, 56.5, 60.2, 71.4, 101.8, 104.2, 111.5, 127.7, 128.5, 138.0. IR (ATR): υ (cm^{-1}) 1116, 1499, 2899, 3077, 3643 (O-H stretch). HRMS calcd. for $C_{19}H_{24}O_4$ $[M + H]^+$: 317.1747 found 317.1749. $[\alpha]_D^{25}$ = +45.5° (*c* = 1.00 g/100mL, $CHCl_3$).

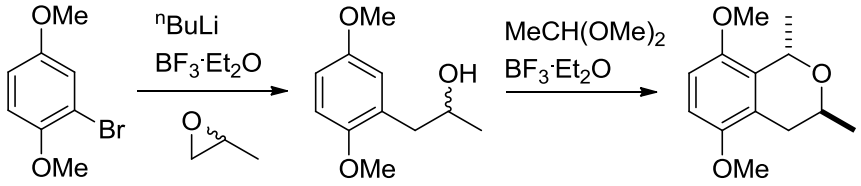
(1*S*,3*R*)-3-(2-(benzyloxy)ethyl)-5,8-dimethoxy-1-methylisochromane 305



Scheme 131.

$BF_3{\cdot}Et_2O$ (0.14 mL, 1.12 mmol) was added at 0 °C, to a solution of alcohol **304** (306 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) followed by dimethyl acetaldehyde (0.12 mL, 1.12 mmol) and stirred at r.t. for 17 hrs. The reaction was then quenched with saturated $NaHCO_3$ (20 mL) and extracted into CH_2Cl_2 (2 x 20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give isochromane **305** as a mixture of diastereoisomers (98%, 333 mg, 1:2.7 *cis*:*trans*). Purification by silica gel chromatography (EtOAc/hexanes, 1:9) gave the desired *trans* isomer as a yellow solid (61%, 205 mg). R_f = 0.60 (EtOAc/hexanes, 1:4). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.40, (3H, d, *J* = 3, CH_3), 1.84 (2H, m, CH_2), 2.62 (1H, dd, *J* = 3, 6, CH_2), 2.67 (1H, dd, *J* = 3, 6, CH_2), 3.61 (2H, m, CH_2), 3.69 (H, s, OCH_3), 3.70 (3H, s, OCH_3), 4.66 (2H, s, $ArCH_2$), 5.00 (1H, qd, *J* = 6, 4, CH), 6.54 (2H, m, H_{Ar}), 7.25 (5H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 19.5, 28.9, 36.4, 55.5, 55.6, 63.3, 66.9, 68.3, 73.1, 107.2, 107.5, 123.5, 127.5, 127.7, 128.4, 129.4, 138.6, 149.5, 151.0. IR (ATR): υ (cm^{-1}) 1075, 1094, 1256, 1437, 1453, 1482, 2935. HRMS calcd. for $C_{21}H_{26}O_4$ $[M + H]^+$: 343.1904 found 343.1904. mp: 145-147 °C. $[\alpha]_D^{25}$ = +77.7° (*c* = 1.00 g/100mL, $CHCl_3$).

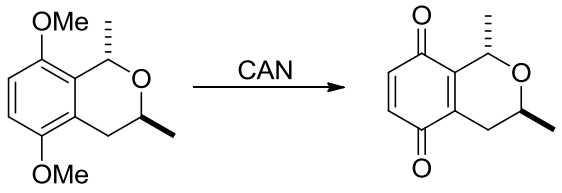
(±)-(1*S*, 3*R*)-5,8-dimethoxy-1,3-dimethylchroman 267[108, 109]



Scheme 132.

2-bromo-1,4-dimethoxybenzene **90** (500 mg, 2.30 mmol) was added to a flame dried round bottom flask followed by THF (20 mL). ^{n}BuLi (1.51 mL, 2.42 mmol, 1.6 M in hexanes) was then added at −78 °C and warmed to −40 °C before the addition of propylene oxide (0.169 mL, 2.42 mmol) and $BF_3{\cdot}Et_2O$ (0.299 mL, 2.42 mmol). Mixture was then stirred for 3 hrs. The reaction was quenched at 0 °C with 50% aqueous NH_4Cl, (30 mL) extracted into EtOAc (2 x 20 mL) and washed with $NaHCO_3$ (2 x 30ml). Solution was dried ($MgSO_4$) and concentrated under reduced pressure. Compound (±)-**266** was taken forward without further purification. Under an atmosphere of argon, at 0 °C, was added $MeCH(OMe)_2$ (2.01 mL, 18.41 mmol) followed by $BF_3{\cdot}Et_2O$ (2.27 mL, 18.41 mmol) to a solution of alcohol **266** (1.777 g, 9.21 mmol) in CH_2Cl_2 (50 mL). The mixture was then warmed to r.t. and stirred for 4 hrs. Saturated $NaHCO_3$ (40 mL) was then added and the mixture was extracted into CH_2Cl_2 (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give isochromane **267** as a mixture of diastereoisomers (98 %, 2.00 g, 2.7:1 *trans:cis* determined by ^{1}H NMR NOESY). Silica gel chromatography (EtOAc/hexanes, 1:19) afforded the *trans* isochromane as a yellow solid (65% over 2 steps, 1.26 g). R_f = 0.25 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.66 (3H, d, *J* = 6.0, CH_3), 1.50 (3H, d, *J* = 6.0, CH_3), 2.30 (1H, dd, *J* = 15.0, 9.0, CH_2), 2.76 (1H, dd, *J* = 15.0, 3.0, CH_2), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.05 (1H, m, CH), 5.09 (1H, m, CH), 6.67 (2H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 19.4, 21.9, 30.2, 55.3, 62.2, 68.2, 107.2, 107.5, 114.7, 123.5, 129.2, 149.5, 150.9. IR (ATR): υ (cm^{-1}) 1060, 1127, 1456, 1481, 1459, 2965. HRMS calcd. for $C_{13}H_{18}O_3$ $[M + H]^+$: 222.1328 found 222.1328. mp: 65- 66 °C. $[\alpha]_D^{25}$ = +40.8 (*c* = 1.00 g/100mL, $CHCl_3$) lit. +32.8° (*c* = 1.00 g/100mL, $CHCl_3$).

(1*S*, 3*R*)-5,8-dimethoxy-1,3-dimethylchroman quinone 268[110]

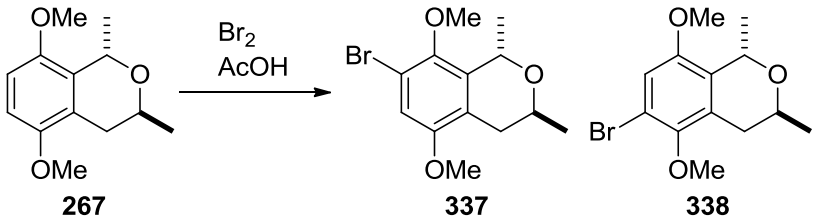


267 **268**

Scheme 133.

To a solution of isochromane **268** (752 mg, 3.39 mmol) in MeCN:H_2O (20 mL:5 mL) was added ceric ammonium nitrate (5.57 g, 10.1 mmol) in one portion and solution stirred at r.t. for 17 hrs. Reaction mixture was then extracted into EtOAc (5 x 20 mL) and the combined organic fractions were washed with $NaHCO_3$ (2 x 20 mL). Solution was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the quinine **268** as a bright yellow solid (99%, 647 mg). R_f = 0.45 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 1.31 (3H, d, *J* = 6.2, CH_3), 1.45 (3H, d, *J* = 6.8, CH_3), 2.12 (1H, ddd, *J* = 19.2, 10.1, 2.2, CH_2), 2.52 (1H, ddd, J = 19.2, 3.4, 0.8, CH_2), 3.94 (1H, m, CH), 4.83 (1H, m, CH), 6.71 (2H, dq, *J* = 10.1, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 19.7, 21.6, 29.4, 62.6, 67.0, 136.2, 136.7, 139.5, 144.3, 185.9, 186.5. IR (ATR): υ (cm^{-1}) 1130, 1303, 1332, 1490, 1667 (C=O stretch), 1689, (C=O stretch). HRMS calcd. for $C_{11}H_{12}O_3$ $[M + H]^+$: 193.0857 found 193.0859. mp: 122-123 °C. lit. 122-123. $[\alpha]_D^{25}$ = +177.0 (*c* = 1.00 g/100mL, $CHCl_3$), lit. +178.1° (*c* = 1.00 g/100mL, $CHCl_3$).

(±)-1,3-Dimethyl-5,8-dimethoxy-6-bromoisochromane 337/(±)-1,3-dimethyl-5,8-dimethoxy-6-bromoisochromane 338

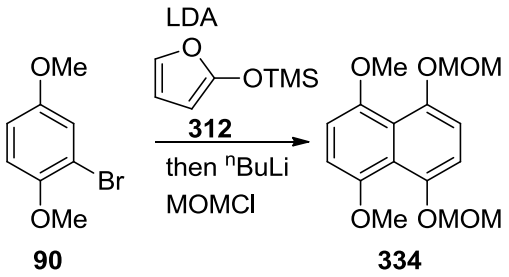


267 **337** **338**

Scheme 134.

(±)-isochromane **267** (444 mg, 2.0 mmol) was dissolved in AcOH (10 mL) at 0 °C. Bromine (0.11 mL, 2.2 mmol) was then slowly added and the reaction mixture stirred at this temperature for 5 hrs. The mixture was then diluted with H_2O (30 mL) and extracted into EtOAc (4 x 10 mL). The combined organic fractions were then sequentially washed with $NaHCO_3$ (2 x 10 mL), $Na_2S_2O_3$ (2 x 10 mL) and brine (2 x 10 mL) before being dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (EtOAc/hexanes, 1:19) gave brominated isochromanes **337**/**338** as an approximate 1:1 mixture of inseperable regioisomers (76%, 457 mg). R_f = 0.35 (EtOAc/hexanes, 1:9). ^{1}H NMR (500 Mz, $CDCl_3$): δ (ppm) 1.24 (3H, d, *J* = 5, CH_3), 1.27 (3H, d, *J* = 5, CH_3), 1.39 (3H, d, *J* = 5, CH_3), 1.46 (3H, d, *J* = 5, CH_3), 2.12 (1H, dd, *J* = 15, 20, CH_2), 2.35, (1H, dd, *J* = 15, 20, CH_2), 2.75, (1H, d, *J* = 15, CH_2), 2.79 (1H, d, *J* = 15, CH_2), 3.68 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.94 (1H, m, CH), 4.91 (1H, q, *J* = 5, 15, CH), 4.99 (1H, q, *J* = 5, 15, CH), 6.74-6.79 (2H, m, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 19.3, 20.4, 21.9, 22.0, 30.0, 31.0, 55.6, 55.7, 62.0, 62.3, 68.1, 68.7, 112.4, 112.9, 113.5, 113.6, 119.4, 121.9, 128.5, 129.4, 146.7, 148.2, 152.0, 153.5. IR (ATR): υ (cm^{-1}) 1230, 1361, 1459, 1471, 1485, 1578, 2934 HRMS calcd. for $C_{13}H_{17}O_3Br$ $[M + H]^+$: 301.0434, 303.0413 found 301.0434, 303.0413.

1,4-Methoxymethyleneoxy-5,8-methoxynaphthalene 334



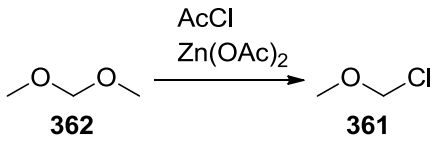
Scheme 135.

To a flame dried round bottom flask, under an atmosphere of argon, was added bromo-1,4-dimethoxybenzene **90** (0.22 mL, 1.5 mmol) and this was then dissolved in freshly distilled THF (4 mL). The solution was then cooled to −78 °C and 2-trimethylsiloxyfuran **312** (0.5 mL, 3 mmol) was slowly added. A solution of freshly prepared LDA (3 mmol) in THF (6 mL) was then added dropwise over 1 hr. and the mixture stirred at this temperature for a further 1 hr. The reaction was allowed to warm then quenched at 0 °C with H_2O (5 mL) before being rapidly extracted into EtOAc (10 mL), dried ($MgSO_4$), filtered and evaporated to dryness. This crude mixture was then placed under an atmosphere of argon, cooled to −78 °C and dissolved in freshly distilled THF (10 mL). ^{n}BuLi (1.2 mL, 3 mmol, 2.5 M in hexane) was then added dropwise over 5 mins. and mixture stirred for 15 mins. A solution of MOM-Cl (3.14 mL, 6.6 mmol, 2.1 M in toluene) was then added dropwise over 5 mins and the reaction mixture was stirred for 2 hrs. at 0 °C. H_2O (10 mL) was then added and the reaction mixture was extracted with EtOAc (3 x 10 mL) before being washed with $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Purification by alumina gel chromatography (EtOAc/hexanes, 1:6) gave naphthalene compound **334** as a red powder (67% over 2 steps, 305 mg). R_f = 0.45 (EtOAc/hexanes, 1:6). ^{1}H NMR (500 Mz, $CDCl_3$): δ (ppm) 3.53 (6H, s, OCH_3), 3.82 (6H, s, OCH_3), 5.08 (4H, s, CH_2), 6.75 (2H, s, H_{Ar}), 6.97 (2H, s, H_{Ar}). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 56.4, 57.4, 98.0, 108.0, 116.3, 122.0, 149.3, 150.9. IR (ATR): υ (cm^{-1}) 1152, 1265, 1371, 1456, 1595, 2975. HRMS calcd for $C_{16}H_{20}O_6$ $[M + Na]^+$: 331.1155 found 331.1155. mp: 59-61.

6. Appendix

6.1 Synthesised protecting reagents and reagents to ascertain optical purity

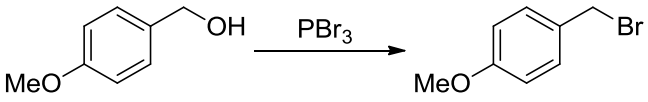
Methoxymethylenechloride 361[111]



Scheme 136.

A 250 mL three neck round bottom flask flushed with argon was charged with dimethoxymethane **362** (17.6 mL, 200 mmol) in anhydrous toluene (53 mL). $Zn(OAc)_2$ (4 mg, 0.002 mmol, 0.01 mol%) was then added followed by dropwise addition of acetyl chloride over 5 mins. The exothermic reaction resulted in the reaction mixture to rise to 50 °C. After stirring for 3 hrs the solution was cooled to r.t. and analysis by ^{1}H NMR showed 99% conversion to methoxymethylene chloride **361** 2.1M in toluene. ^{1}H NMR (400 Mz, $CDCl_3$): δ (ppm) 5.43 (2 H, s, CH_2), 3.49 (3 H, s, OCH_3). ^{13}C NMR (100 Mz, $CDCl_3$): δ (ppm) 51.1, 59.1.

4-Methoxybenzyl bromide 363[113]

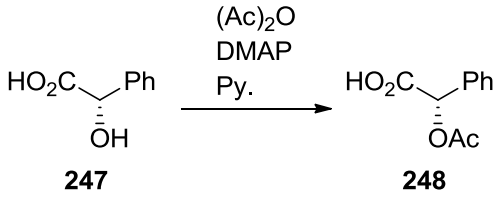


364 **363**

Scheme 137.

To a solution of *p*-methoxybenzyl alcohol **364** (0.498 mL, 4.00 mmol) in CH_2Cl_2 (20 mL) at r.t. was added PBr_3 (0.494 mL, 5.20 mmol) under inert atmosphere. The mixture was then stirred for 3 hrs before being cooled to 0 °C and quenched with H_2O (20 mL). Extraction into CH_2Cl_2 (2 x 20 mL), drying ($MgSO_4$), filtration and concentrating gave pure PMBBr **363** as a yellow oil (99%, 0.80 g). ^{1}H NMR (400 Mz, $CDCl_3$): 3.81 (3 H, s, OCH_3), 4.51 (2 H, s, $ArCH_2$), 6.85 (2 H, d, J = 9.0, H_{Ar}), 7.34 (2 H, d, J = 9.0, H_{Ar}).

_O_-Acetylmandelic acid 248[105]



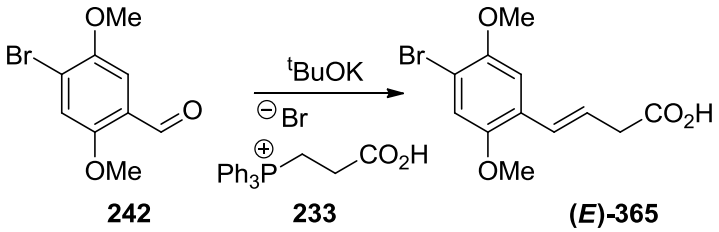
247 **248**

Scheme 138.

To a solution of mandelic acid **247** (1.52 g, 10 mmol) in Et_2O (30 mL) and pyridine (4.02 mL, 50 mmol) was added acetic anhydride (1.04 mL, 11 mmol) followed by a catalytic amount of DMAP at 0 °C under an atmosphere of argon. The mixture was then allowed to warm to r.t. and stirred for 8 hrs. H_2O (20 mL) was then added and the mixture extracted with EtOAc (2 x 20 mL). The organic phase was then washed with saturated $CuSO_4$ (2 x 20 mL) then $NaHCO_3$ (2 x 20 mL) before being dried ($MgSO_4$), filtered and evaporated to dryness to give pure acylmandelic acid **248** in quantative yield as a yellow solid (1.860 g). ^{1}H NMR (500 Mz, $CDCl_3$): 2.13 (3H, s, CH_3), 5.86 (1H, s, CH), 7.30-7.48 (5H, m, H_{Ar}). ^{13}C NMR (500 Mz, $CDCl_3$): 20.8, 74.2, 126.0, 127.0, 129.2, 129.5, 133.3, 170.0, 175.0. IR (ATR): υ (cm^{-1}) 1210, 1701, 1688, 1741, 3035. $[\alpha]_D^{25}$ = + 149.2. (*c* = 1.00, MeOH), lit. +152.0 (*c* = 1.00, MeOH).

6.2 Non-isolable compounds

(*E*)-methyl-4-(4-bromo-2,5-dimethoxyphenyl)but-3-enoic acid 365



Scheme 139.

To a solution of 4-bromo-2,5-dimethoxybenzaldehyde **242** (612 mg, 2.50 mmol) and 3-triphenylphosphonium bromide propanoic acid **233** (1.55 g, 3.75 mmol) in THF (20 mL) was added a solution of ^{t}BuOK (0.841 g, 7.49 mmol) in THF (20 mL) at 0 °C over a period of 1 hr. And the reaction mixture was then stirred at this temperature for an additional 3 hrs. The reaction was then quenched with saturated NH_4Cl (30 mL) extracted into EtOAc (4 x 40 mL) and the combined organic layers were washed with 1 M HCl (30 mL) and saturated $NaHCO_3$ (30 mL) solutions consecutively. After drying ($MgSO_4$), filtration through a pad of silica eluting with EtOAc, the eluent was concentrated under reduced pressure and **(*E*)-365** was used without further purification.

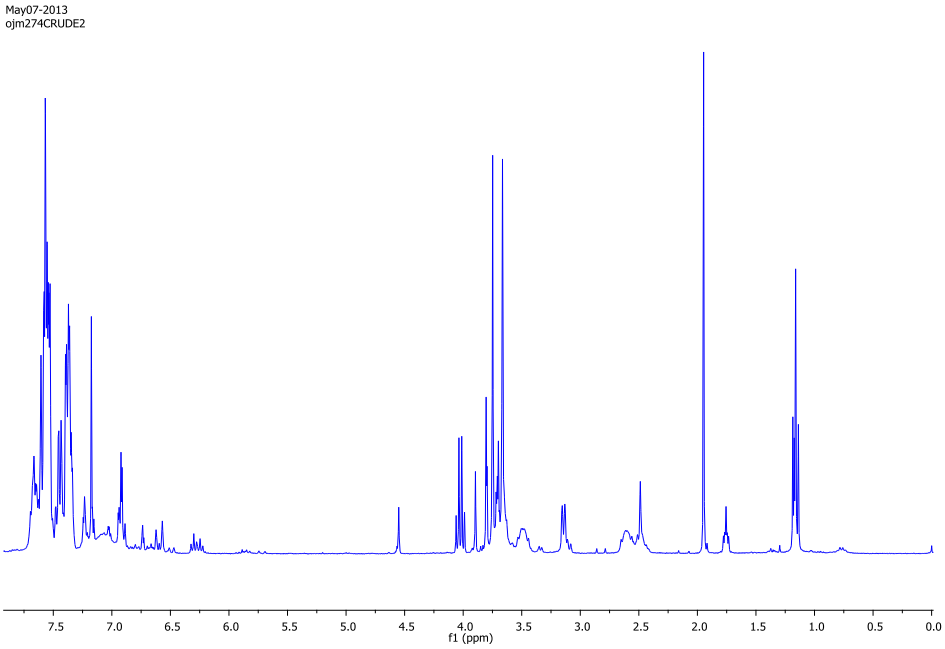
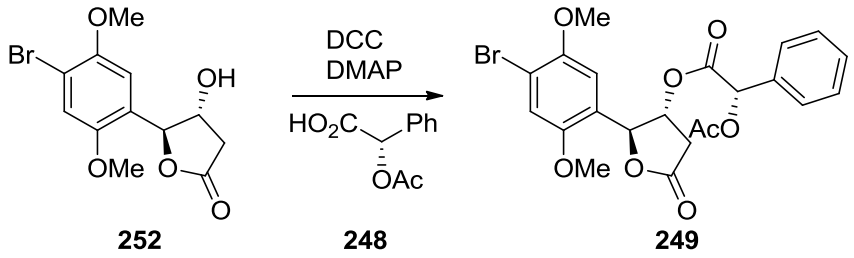


Figure 37: ^{1}H NMR of crude 365.

1-Bromo-(2's,3's)-2-(2'',5''dimethoxyphenyl)-5'-oxotetrahydrofuran-3'-yl-(2s)-2-(acetyl)phenylacetate 249



Scheme 140.

To a solution of acylmandelic acid **248** (136 mg, 0.70 mmol) in toluene (10 mL) was added a catalytic amount of DMAP and DCC (150 mg, 0.70 mmol) at 0 °C. A solution of β-hydroxylactone **252** (150 mg, 0.46 mmol) in CH_2Cl_2 (2 mL) was then added dropwise to the suspension at 0 °C and the reaction mixture was stirred for 2 hrs at this temperature. The mixture was then diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL) and the organic phase was dried ($MgSO_4$) and filtered before being concentrated under reduced pressure. Analysis by ^1H NMR of the crude mixture showed little of ester **249** which could not be isolated.

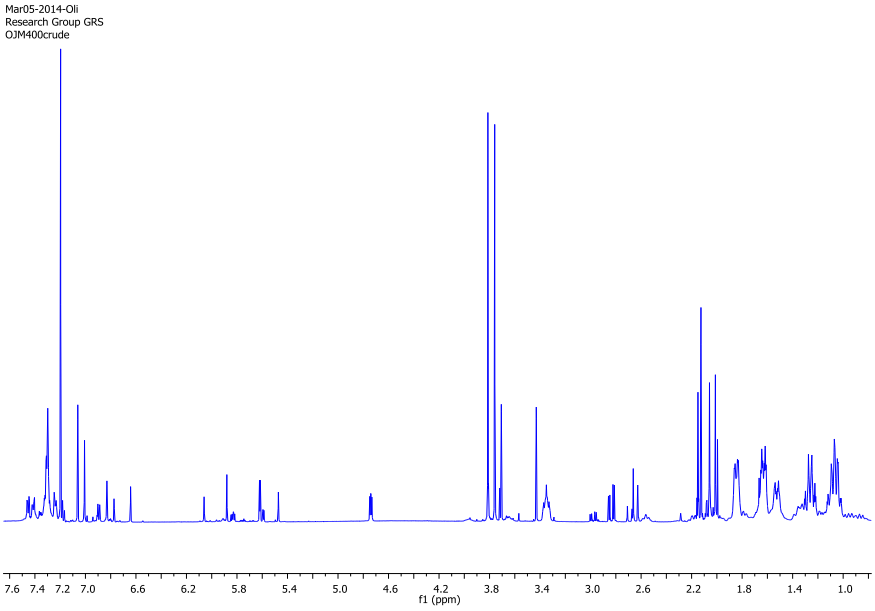
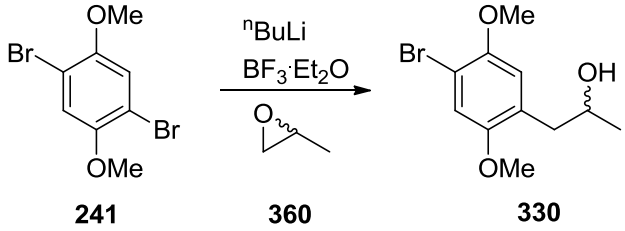


Figure 38: ^1H NMR of crude 249.

3-(4-bromo-2,5-dimethoxyphenyl)isopropanol 330[110]



Scheme 141.

To a solution of 2,5-dibromo-1,4-dimethoxybenzene **241** (1 g, 3.16 mmol) in THF (30 mL) at −78 °C under an atmosphere of argon was added dropwise ^{n}BuLi (1.33 mL, 3.32 mmol, 2.5 M in hexane) and the reaction mixture was then stirred for 30 mins. At this temperature was added $BF_3.Et_2O$ (0.4 mL, 3.32 mmol) dropwise followed by the slow addition of a solution of propylene oxide **360** (183 mg, 3.16 mmol) in THF (10 mL) over 30 minutes. The reaction mixture was then allowed to slowly warm to 0 °C and then stirred for a further 3 hrs. The mixture was then quenched at 0 °C with H_2O (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic fractions were then washed with brine (2 x 30 mL), dried ($MgSO_4$), filtered and evaporated to dryness to give crude opened epoxide **330**. The crude material was used without further purification. HRMS $[M - OH + H]^+$: 259.0151. calc. for $C_{11}H_{15}O_3Br$: 274.02

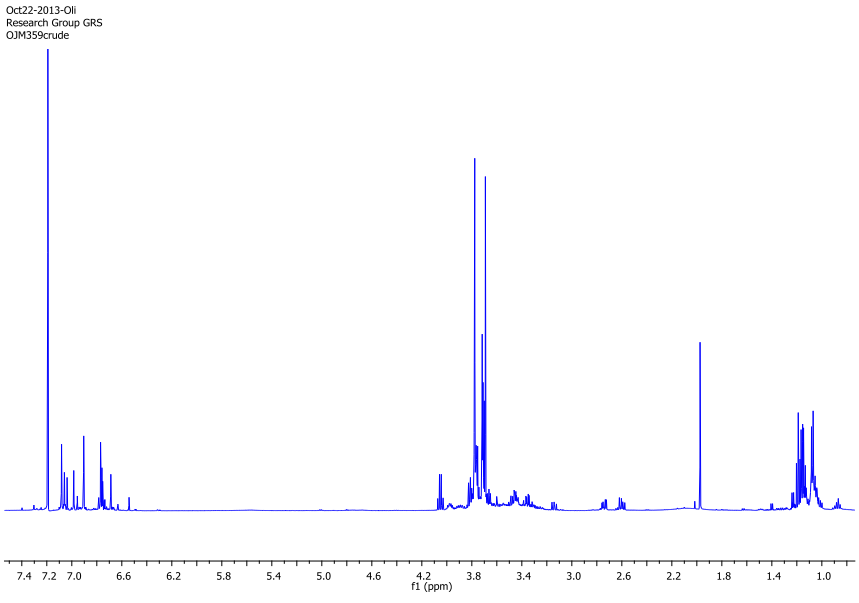


Figure 39: ^{1}H NMR of crude 330.

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