Synthetic Studies Towards Aromatic Polyketide Derived Natural Products

A thesis submitted in partial fulfilment

of the requirements for the degree of

Doctor of Philosophy

by

Peter Jaein Choi

Department of Chemistry

University of Auckland

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Preface

All the work described in this thesis was carried out by the author in the Department of Chemistry at the University of Auckland, except where due reference to the work of others has been made in the text.

Some parts of this work have been previously published:

"Synthesis of 6,6-bisbenzannulated spiroketals related to the rubromycins using a double intramolecular hetero-Michael addition (DIHMA)" Peter J. Choi, Dominea C. K. Rathwell, Margaret A. Brimble. *Tetrahedron Letters,* **2009**, *50*, 3245-3248, Special Edition to Celebrate 50th Anniversary

"Heteroatom-directed reverse Wacker oxidations. Synthesis of the reported structure of (−)-herbaric acid" Peter J. Choi, Jonathan Sperry, Margaret A. Brimble. *Journal of Organic Chemistry*, **2010**, *75*, 7388-7392.

Abstract

The first part of this thesis describes the successful synthesis of a series of 6,6-bisbenzannulated spiroketal analogues of the rubromycin family. The synthesis of spiroketals **183a-183e** and spiroaminal **237** were successfully executed using a novel microwave-assisted DIHMA approach. Coupling of an aryl acetylene and an aryl aldehyde via acetylide anion addition resulted in the formation of an alkynol which was followed by oxidation to the desired ynone. Spirocyclisation using the DIHMA protocol afforded the desired bisbenzannulated spiroketals **183a-183e** and spiroaminal **237** in good yields. Hydroxy-substituted 6,6-bisbenzannulated spiroketal **182** was successfully furnished by the reduction of keto-substituted 6,6-bisbenzannulated spiroketal **183a** with sodium borohydride.

The second part of this research presents synthetic attempts to access the chiral 3-substituted phthalide containing natural products; aigialospirol (**256**) and herbaric acid (**255**). The synthesis of chiral vinylphthalide **406** proved challenging and was overcome by the use of a microwave-assisted chemoenzymatic resolution to install the C3 stereocenter of phthalide **406**. Despite various attempts to functionalise vinylphthalide **406** towards the synthesis of aigialospirol, results were unsuccessful. With chiral vinylphthalide **406** in hand, the first synthesis and the structural assignment of (−)-herbaric acid (**255**) was accomplished. This was achieved *via* heteroatom-directed Wacker oxidation on vinylphthalide **406** to form aldehyde **460**. Aldehyde **460** underwent smooth oxidation with Oxone® affording acid **488** which underwent facile methyl ester formation to facilitate purification, thus delivering enantioenriched lactone ester **489**. Smooth demethylation with concomitant ester hydrolysis was effected by boron tribromide to give (−)-herbaric acid (**255**). The realisation of this entirely regioselective anti-Markovnikov addition of water during the Wacker oxidation provides a mild alternative to hydroboration/oxidation protocols that are traditionally used for terminal alkenes.

Acknowledgements

First of all, I would like to thank Professor Margaret A. Brimble. She has been an amazing supervisor during my years at the university. Thank you so much for everything!

I will be forever thankful to Dr Jonathan Sperry for finding herbaric acid. Thank God that molecule was made! I will miss his help around the lab and guidance which have got me through the end. Special thanks goes out to the Rathwells (Dom & Kris) who is in Germany, their friendship and company is greatly missed and I miss Dylan! Special thanks to Sung, thank you so much for everything starting from NMR queries to advice about being a father... I owe you a lot. To Tsz, with all her help with throughout the PhD, it was fun working with you! Also to fellow lab/fishing mate Danny who is due to submit with me, YES IT'S OVER!

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To all my past and present members of the MAB group, thank you for your help and support.

To my dear family- BIGGEST SPECIAL thanks to my lovely wife Sophia for supporting me all throughout my PhD, your love and prayers were my strength to carry on. And of course to my little angel, Joanne (4 months old), I love you so much!

Lastly to my parents, for supporting me and always believing in me, thank you. Also to Sophia's mum, for helping our family through the tough times, your love is greatly appreciated. Thank you.

Peter Jaein Choi

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Abbreviations

δ	chemical shift, parts per million downfield from tetramethylsilane
Å	Angstrom
Δ	reflux
°	degrees
µ	micro
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
aq.	aqueous
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
br	broad (spectral)
c	concentration
C	celcious
Ca.	approximately
calc.	calculated

CAN	cerium(IV) ammonium nitrate
cat.	catalytic
CDI	*N*-*N*'-carbonyl diimidazole
CDMT	2-chloro-4,6-dimethoxy-[1,3,5]triazine
CI	chemical ionization
cm^{-1}	wavenumber(s)
conc.	concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transformation
DEAD	diethyl azodicarboxylate
DMAP	4-*N,N*-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid

dr	diastereomeric ratio
EI	electron impact
EOM	ethoxymethyl
Et	ethyl
eq.	equivalent(s)
FAB	fast atom bombardment
g	grams
h	hours
HIV	human immunodeficiency virus
HL	human leukemia
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	2-iodobenzoic acid
IC_{50}	half maximal inhibitory concentration
^{i}Pr	isopropyl
IR	infrared
J	coupling constant

L	liters
LDA	lithium diisopropylamide
m	multiplet (spectral)
m-	*meta*
M	molar
M^+	parent molecular ion
max	maximum
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mg	milligrams
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimoles
mol	moles
MOM	methoxymethyl
mp	melting point
MS	molecular sieves
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
MW	microwave

m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
o-	*ortho*-
p-	*para*-
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PhH	benzene
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	*iso*-propyl
q	quartet (spectral)
R_f	retention factor
RNA	ribonucleic acid

r.t.	room temperature
RT	reverse transcriptase
SAR	structure activity relationship
s	singlet (spectral)
sat.	saturated
s-Bu	*sec*-butyl
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butylhydrogen peroxide
TBDPS	*tert*-butyldiphenylsilyl
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic Acid
TFAA	trifluoroacetic anhydride
Tf	trifluoromethanesulfonate (triflate)
Tf_2O	triflic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine

TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

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Chapter One

Introduction

1.1 Introduction to Spiroketal Chemistry

A spiroketal is a bicyclic compound in which both rings are unified by a common spiro carbon atom. The two ketal oxygens that are connected to the central spiro atom are each part of one of the two rings. Spiroketals are important subunits present in a broad range of bioactive natural products and have been shown to exhibit a variety of interesting biological properties.[1-7] As a result, spiroketals are considered a 'privileged scaffold' for drug discovery programs.[8]

Of interest to our research group are natural products that contain the 5,6- and 6,6-spiroketal moieties fused to an aromatic ring (Figure 1). Natural products that contain such benzannulated spiroketal moieties and synthetic approaches towards the central benzannulated spiroketal core will be discussed in this chapter.

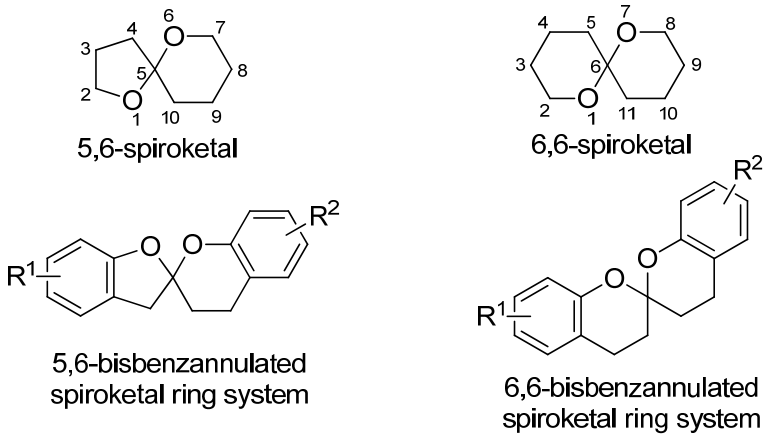


Figure 1. Structures of spiroketals of interest. $R^{1,2}$ = H, O–alkyl.

1.2 The Rubromycins and Related Compounds

The rubromycins are a class of natural antibiotics with a 5,6-spiroketal core which display attractive biological activities.[1-4] The family of the rubromycins include the well-known α-, β- and γ-rubromycins (**1**), (**2**) and (**3**), the structurally related pigments 3′-hydroxy-β-rubromycin (**4**), δ-rubromycin (**5**), purpuromycin (**6**), heliquinomycin (**7**) and the griseorhodins A (**8**), C (**9**) and G (**10**) (Figure 2). These compounds were first isolated from *Streptomyces* cell cultures by Brockmann *et al*.[9] in 1966.

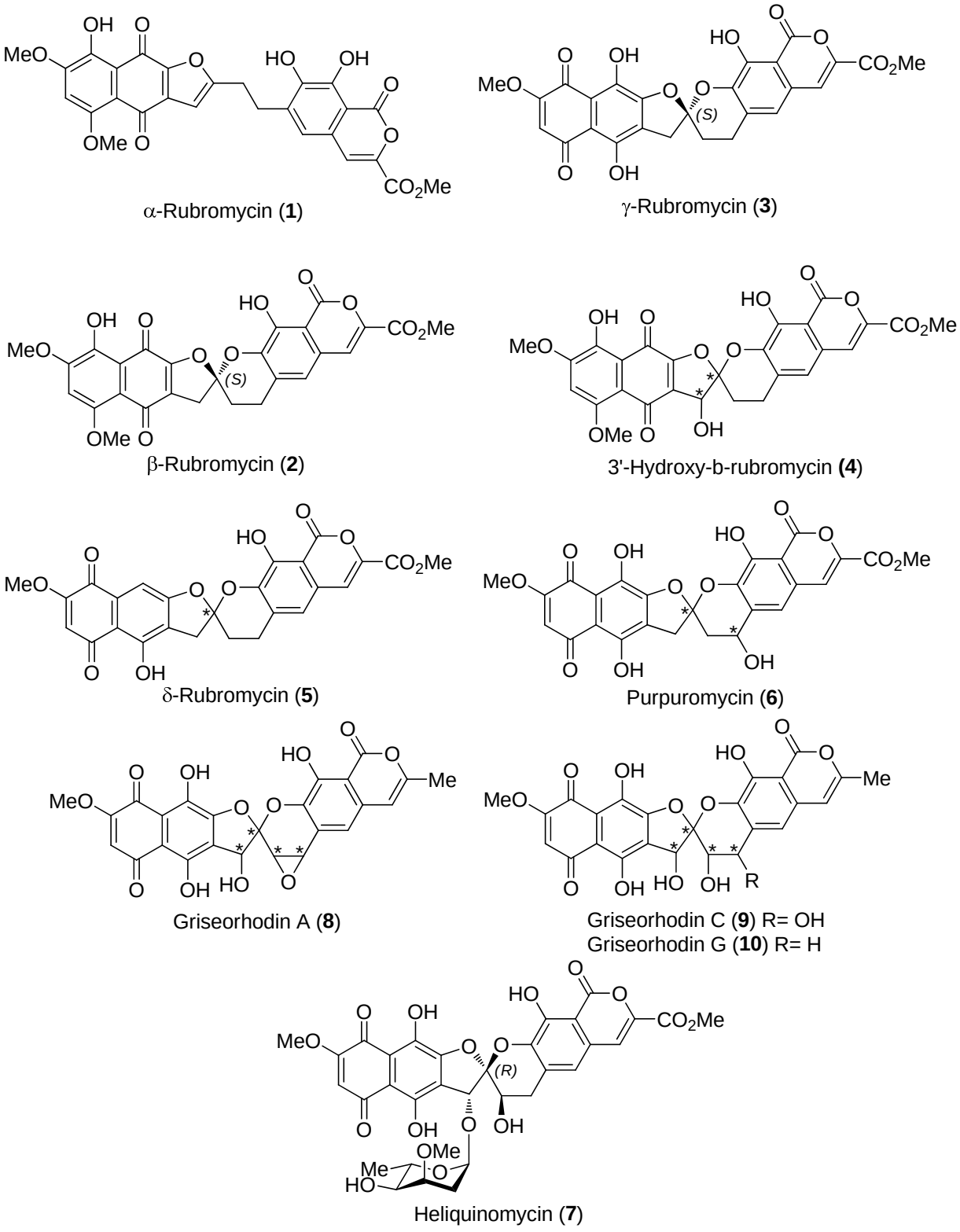


Figure 2. The rubromycin family of antibiotics.

The basic structural motif of these natural products consists of an aliphatic 5,6-spiroketal core fused to aromatic naphthoquinone and isocoumarin moieties (Figure 3). However, α-rubromycin (**1**) is the open-chain form of the spiroketal-containing β-rubromycin (**2**) and does not contain a 5,6-spiroketal core. In addition, heliquinomycin (**7**) contains a glycoside with the rare deoxypyranose L-cymarose. The relative and absolute configurations have so far only been established for β-rubromycin (**2**), γ-rubromycin (**3**) and heliquinomycin (**7**).

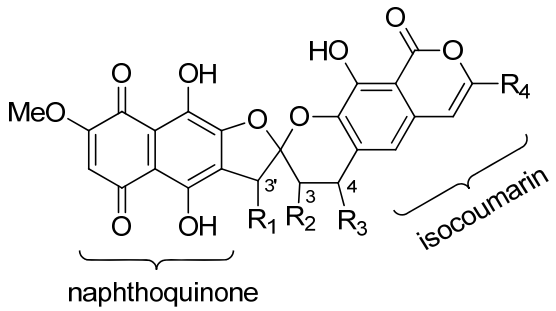


Figure 3. Sub-structures of the rubromycins.

1.3 Biological Activity of the Rubromycins

Even after their discovery more than 40 years ago, the rubromycin family of natural products are still extremely valued due to their intriguing potential for the treatment of cancer and other viruses.[1-4]

The exact biological activities of the rubromycins are summarised in Table 1. The low IC_{50} values (3 to 12 μM) for human telomerase inhibition is evident in β- and γ-rubromycins (**2**) and (**3**) as well as purpuromycin (**6**) and griseorhodins A (**8**) and C (**8**). These compounds possess a unique aromatic spiroketal ring system and the fact that α-rubromycin (**1**) (which lacks this aryl spiroketal moiety) exhibits substantially decreased inhibitory potency towards telomerase (IC_{50} > 200 μM) suggests that the spiroketal unit plays an essential role in the inhibition of telomerase.[10] Telomerase enzymes play a crucial role by reconstructing the chromosome termini (the telomeres) during cell division. If telomerase activity is suppressed, telomeres shorten upon every single cell cycle and ultimately, apoptosis occurs. However, it has been shown that 80-90% of human tumour cells express higher concentration levels of telomerase

than somatic cells which is directly related to the immortalisation of cancer cells.[11] Therefore inhibition of telomerase activity would lead to a decrease in the ability of the malignant cell to continue to replicate endlessly. Since telomerase is not present and inactive in most somatic cells but is essential for immortalisation of tumour cells, it makes this enzyme an ideal target for anticancer therapy.[12]

It is interesting to note that heliquinomycin (**7**) displays selective inhibition of DNA helicases.[13] DNA helicases are responsible for unwinding the double stranded DNA to provide single-stranded DNA, which is crucial for replication, recombination or the repair of DNA.[14] Heliquinomycin (**7**) is the only selective DNA helicase inhibitor known to date and therefore its exploration could lead to a better understanding of the mode of action of these important enzymes.[13]

Compound	**IC_{50} (μM)**	**Other biological activity**
α-rubromycin (1) **(open chain form)**	> 200	Weak telomerase inhibitor (IC_{50} > 200 μM), implying spiroketal structure was important for telomerase inhibition.[10]
β-rubromycin (2)	3.06 ± 0.85	Exhibit inhibitory properties against: • human immunodeficiency virus-1 (HIV-1) reverse transcriptase (RT) (IC_{50} = 0.98 ± 0.16 μM);[15] • avian myeloblastosis virus (AMV) RT (IC_{50} = 0.79 ± 0.14 μM);[15] • moloney murine leukaemia virus (M-MLV) RT (IC_{50} = 3.42 ± 0.28 μM).[10]

γ-rubromycin (3)	2.64 ± 0.09	Exhibit inhibitory properties against: • HIV-1-RT (IC_{50} = 0.62 ± 0.01 μM);[15] • AMV RT (IC_{50} = 0.41 ± 0.04 μM);[15] • M-MLV RT (IC_{50} = 4.37 ± 0.58 μM).[10]
griseorhodin A (8)	12.2 ± 3.1	-
griseorhodin C (9)	5.87 ± 0.44	-
purpuromycin (6)	3.19 ± 0.45	• Exhibits good inhibitory properties against both Gram-positive and Gram-negative bacteria and fungi.[16, 17] • Has been found to inhibit RNA synthesis in *Candida albicans* (fungi) and protein synthesis in *Bacillus subtilis* (bacteria).[18] • Semisynthetic derivatives of purpuromycin **(33)** have shown to be potential topical agents for treatment of vaginal infections.[19]
heliquinomycin (7)	-	• Potent against Gram-positive bacteria, inactive against Gram-negative bacteria or fungi.[20] • Inhibitor of DNA helicase, an enzyme that unwinds double-stranded DNA to allow replication, repair, recombination and transcription.[20]

Table 1. Biological activities of the rubromycin family

1.4 Previous Synthetic Studies Related to the Rubromycins

Only three successful syntheses of the rubromycin family natural products have been reported – the synthesis of heliquinomycinone (**11**) the aglycone of the heliquinomycin (**7**) by Danishefsky *et al*.[21, 22] and two syntheses of (±)-γ-rubromycin (**3**) by Kita *et al*.[23] and Brimble *et al*.[24] These will be summarised in the following section.

1.4.1 Danishefsky *et al.*[21, 22]– Total Synthesis of Heliquinomycinone (11)

Danishefsky *et al*.[21, 22] have reported the total synthesis of heliquinomycinone (**11**), the aglycon of heliquinomycin (**7**) (Figure 4).

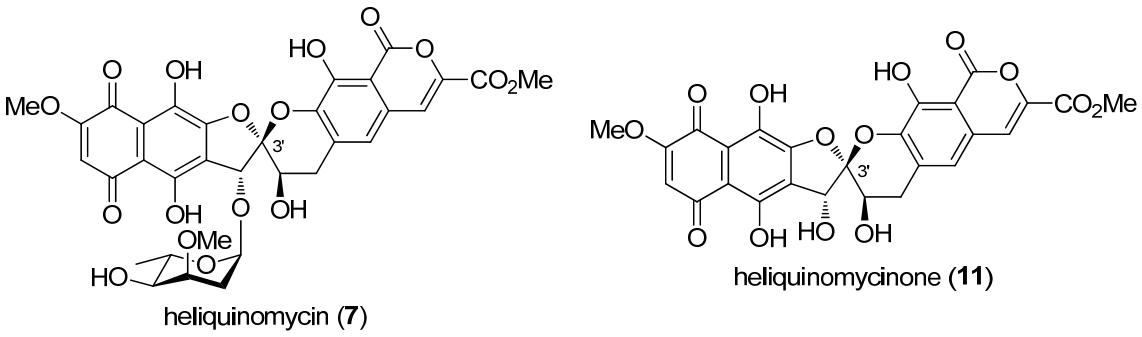
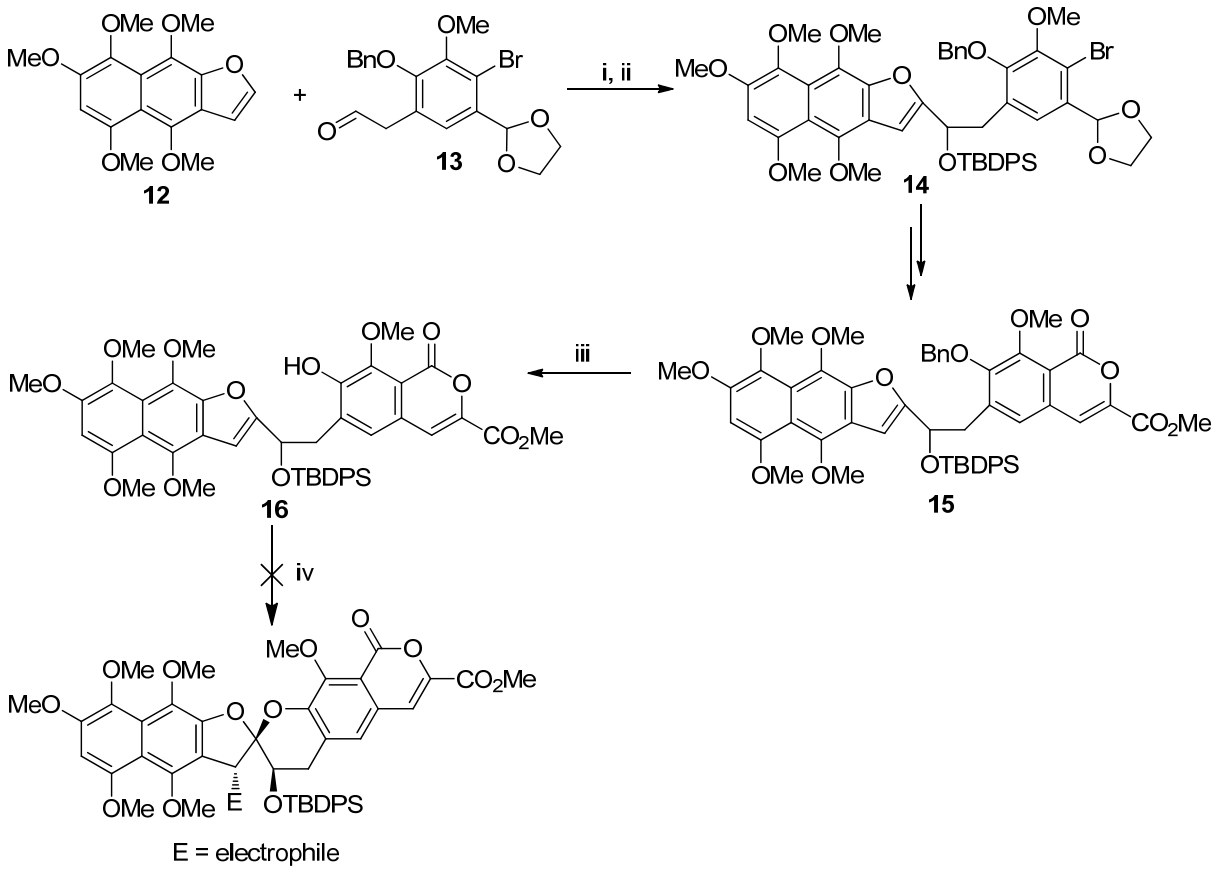


Figure 4. Structures of heliquinomycin (**7**) and heliquinomycinone (**11**).

Danishefsky *et al*.[21] attempted the synthesis of heliquinomycin (**7**) using an electrophile-assisted cyclisation of a benzofuran derivative **16** (Scheme 1). Pentamethoxynaphthofuran **12** was treated with *n*-butyllithium to generate a lithiated naphthofuran intermediate which was coupled to aldehyde **13** affording an alcohol product which was protected as a TBDPS ether to provide **14**. Protected alcohol **14** was further elaborated to naphthofuran **15**. Hydrogenolysis of the benzyl ether in naphthofuran **15** afforded phenol **16**. The electrophilic spirocyclisation step was next attempted with various reagents. However, activating the furan double bond with various halogenating reagents followed by attempted nucleophilic opening of the halonium ion intermediate by the proximal phenol only resulted in oxidative demethylation and quinone formation. Various conditions were attempted including the use of metal salts

such as $Pd(OAc)_2$, $Ti(OAc)_3$, Re_2O_7 and Hg^{2+} as well as various epoxidation conditions were explored but all attempts were unsuccessful.

These results were attributed to the electron rich nature of the pentamethoxynaphthalene moiety present in naphthofuran **15**. Thus, electrophiles reacted with the naphthalene moiety, resulting in oxidative demethylation to the resulting quinone along with deactivation of the furan double bond.

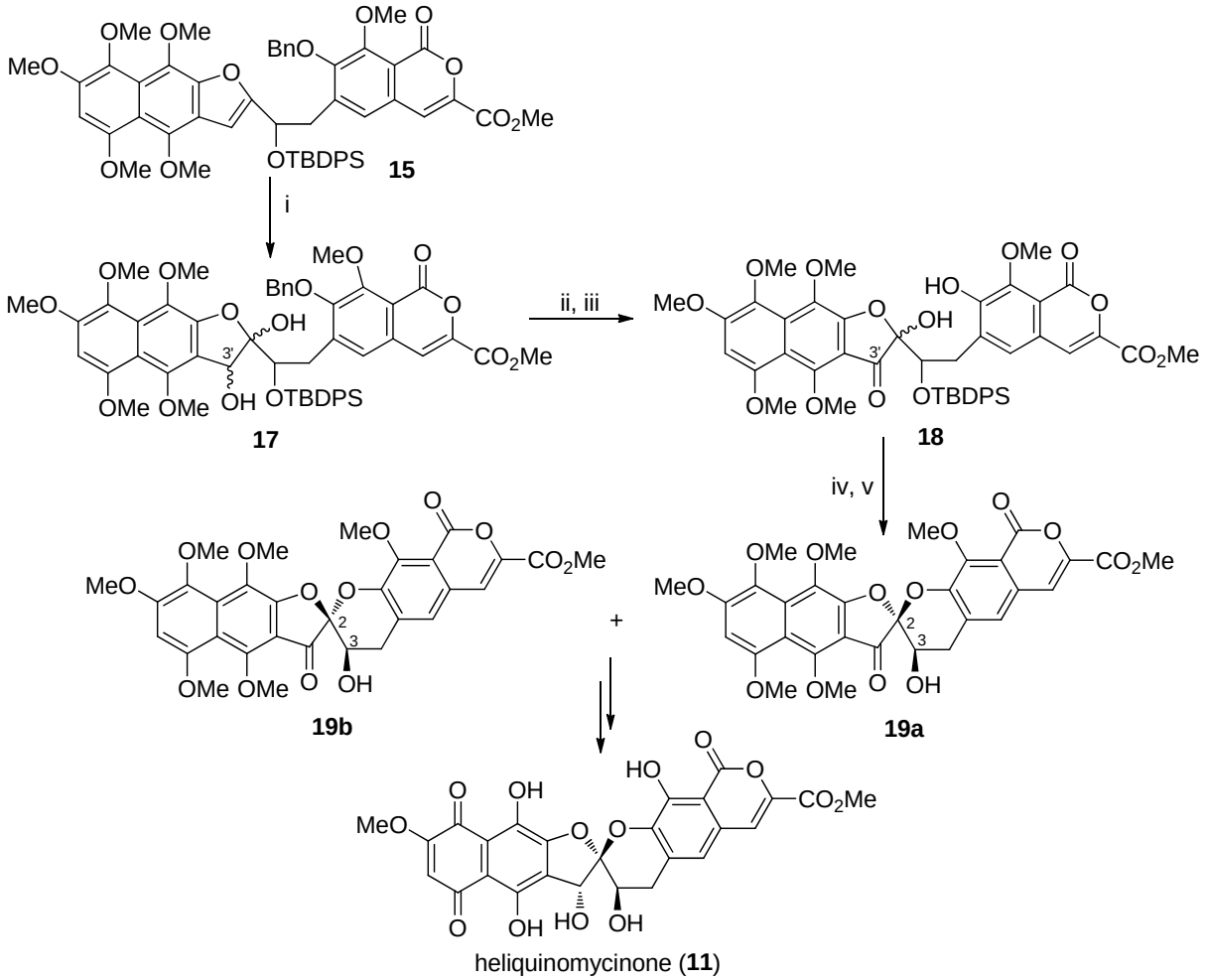


Reagents and conditions: i. *n*-BuLi, THF, -78 °C; ii. TBDPSCl, imidazole, CH_2Cl_2, 64% over two steps; iii. H_2, 5% Pd/C, EtOAc, 92%; iv. various electrophiles.

Scheme 1. Attempted synthesis of spiroketal intermediates during the total synthesis of heliquinomycinone (**11**) by Danishefsky *et al.* [21, 22]

Eventually, the furan double bond in naphthofuran **15** successfully underwent dihydroxylation with osmium tetroxide to afford diol **17** as a mixture of diastereomers (Scheme 2). A chance observation was made by Danishefsky *et al.* [21, 22] that exposure of diol **17** to air with

triethylamine in methanol resulted in the oxidation of the C-3′ hydroxyl group of the naphthofuran moiety to afford an α-hydroxyketone. The benzyl ether of the newly formed α-hydroxyketone was cleaved to produce diol **18** which underwent an intramolecular cyclisation under Mitsunobu conditions followed by subsequent silyl ether cleavage using tetra-*n*-butylammonium fluoride to give spiroketals **19a** and **19b** as a 1:1 mixture of diastereomers. Further reactions on each diastereomeric spiroketal allowed the stereochemistry of each newly formed diastereomeric product to be determined and elaboration to heliquinomycinone (**11**) was successfully executed.[22]

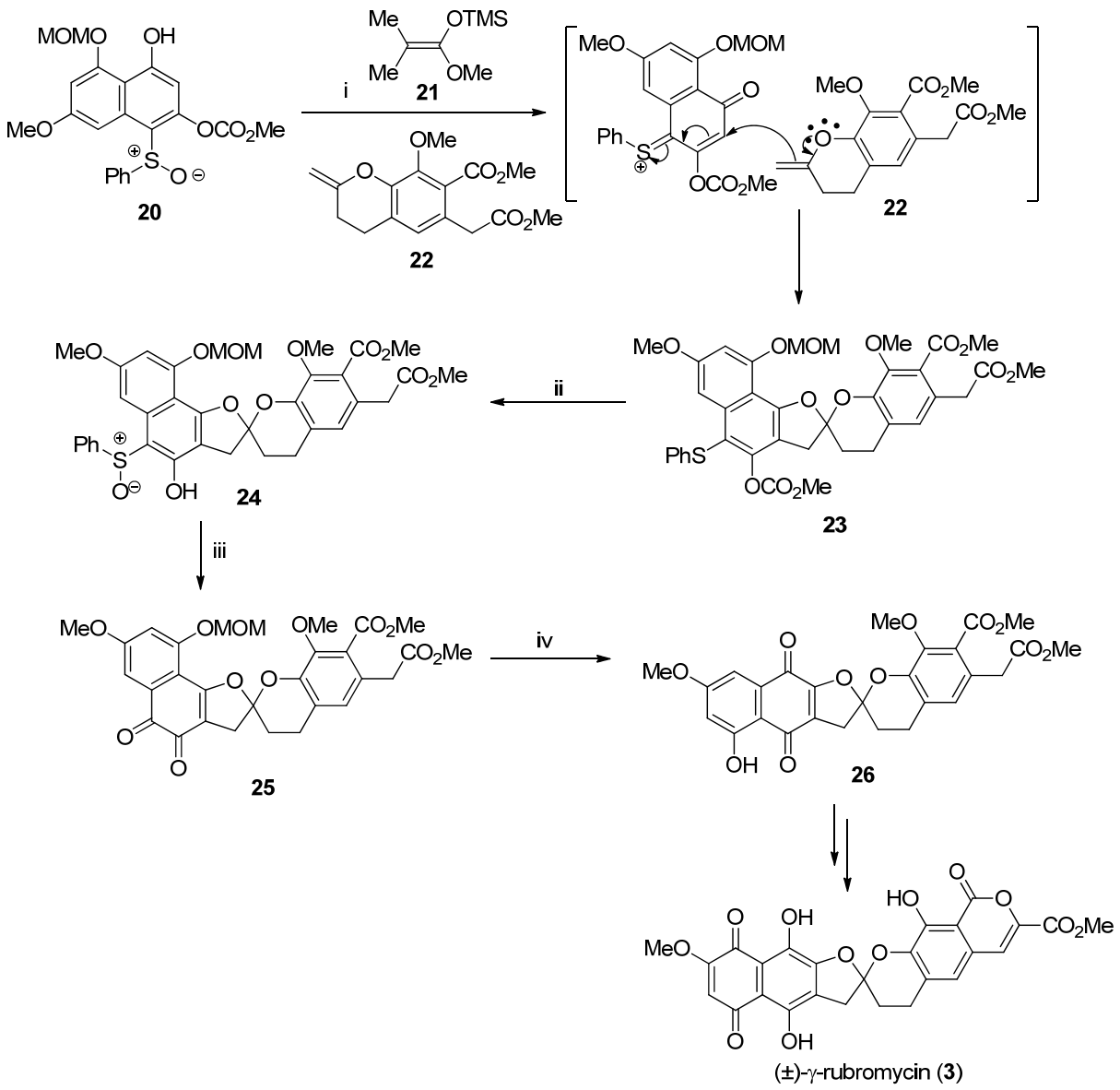


Reagents and conditions: i. a) OsO_4, pyridine, THF–H_2O, b) $NaHSO_3$, 3 days, 50–60%; ii. Et_3N, MeOH, 45%; iii. H_2, 5% Pd/C, EtOAc, 94%; iv. DEAD, PPh_3, CH_2Cl_2, -78 → 25 °C; v. TBAF, THF, 0 °C, 72% (over two steps; *dr* = 1:1).

Scheme 2. Synthesis of spiroketals **19a** and **19b** by Danishefsky *et al*.[22]

1.4.2 Kita *et al.*[23] – Total Synthesis of (±)-γ-Rubromycin (3) using two Aromatic Pummerer-Type Reactions

Kita *et al*.[23] completed the total synthesis of (±)-γ-rubromycin (**3**) using two aromatic Pummerer-type reactions and an acid-catalysed rearrangement of an *o*-quinone to a *p*-quinone as the key steps (Scheme 3). Aryl sulfoxide **30** was converted to its TMS ether using methyl trimethylsilyl dimethylketene acetal **21** prior to its aromatic Pummerer-type reaction with enol ether **22** in the presence of trifluoromethanesulfonic anhydride. With spiroketal **23** in hand, the methoxycarbonyl group was cleaved and the sulfide oxidised to give sulfoxide **24** which underwent a second aromatic Pummerer-type reaction using trifluoroacetic anhydride to afford *o*-quinone **25**. *o*-Quinone **25** underwent an acid-catalysed rearrangment to give *p*-quinone **26** using trifluoroacetic acid *via* a ketal cleavage–recyclisation mechanism. *p*-Quinone **26** was further elaborated to give (±)-γ-rubromycin (**3**).

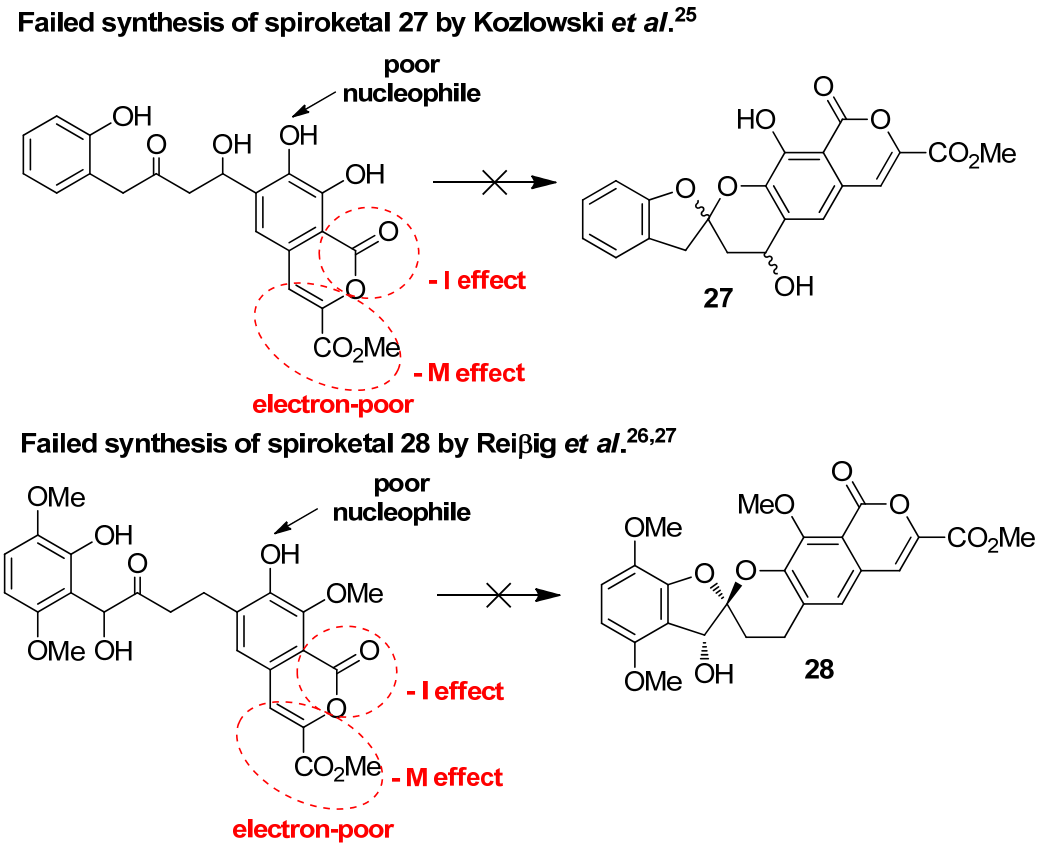


Reagents and conditions: i. a) **21**, MeCN, r.t., b) **22**, Tf_2O, 2,4,6-collidine, MeCN, -78 °C, 39%; ii. a) $^{i}Pr_2NH$, MeCN, r.t., b) *m*-CPBA, CH_2Cl_2, -78 → -20 °C, 88%; iii. TFAA, CH_2Cl_2, 0 °C; iv. TFA, CH_2Cl_2, 0 °C, 58% (over two steps).

Scheme 3. Synthesis of (±)-γ-rubromycin (**3**) by Kita *et al*.[23]

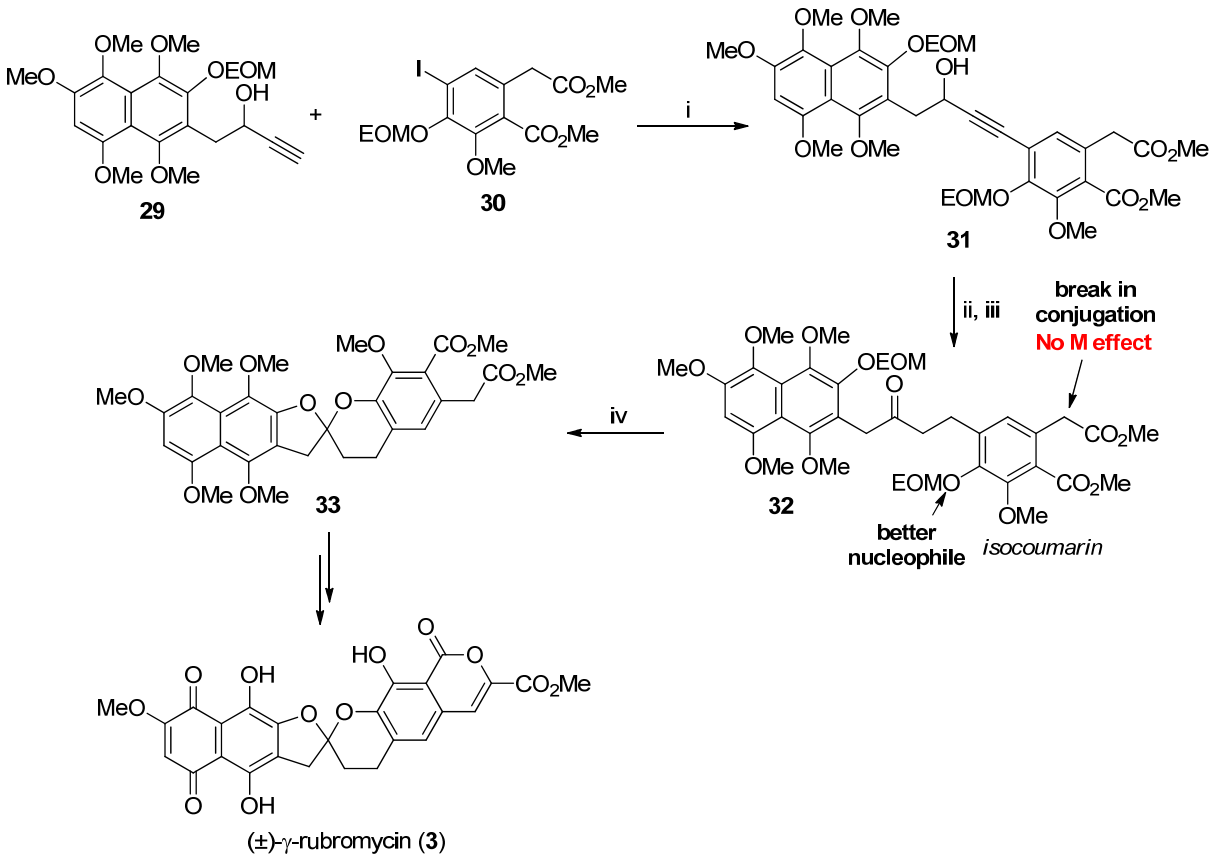
1.4.3 Brimble *et al.*[24] – Formal Synthesis of (±)-γ-Rubromycin (3) by Acid-catalysed Spirocyclisation of a Dihydroxyketone Precursor

Acid-catalysed spirocyclisation of a dihydroxyketone precursor remains the most convenient and popular method for spiroketal synthesis. However, difficulties in executing this classical spirocyclisation protocol have been reported by numerous research groups in the synthetic studies towards the rubromycin natural products.[25 26, 27] The reasons for these difficulties were established through a series of model studies by Kozlowski *et al.*[25] and Reiβig *et al.*,[26, 27] who independently showed that the presence of two electron withdrawing groups (negative mesomeric and inductive groups) on the isocoumarin fragment significantly reduces the nucleophilicity of the phenolic hydroxyl group, a key factor in hindering the key spirocyclisation step which leads to the formation of benzofuran products (Scheme 4).



Scheme 4. Failed synthesis of spiroketals **27** and **28** by Kozlowski *et al.*[25] and Reiβig *et al.*[26, 27]

By correct balancing of the electrons, Brimble *et al.*[24] were able to accomplish the use of acid-catalysed spirocyclisation in their total synthesis of (±)-γ-rubromycin (**3**) (Scheme 5). Spiroketal **33** was synthesised from acetylene **29** and aryl iodide **30**. Sonogashira reaction between acetylene **29** and aryl iodide **30** afforded alkyne **31** which underwent hydrogenation and subsequent oxidation of the alcohol to produce ketone **32**. Cleavage of both ethoxymethyl ethers was accomplished using silica-embedded sodium hydrogen sulfate, unmasking the dihydroxyketone which underwent spirocyclisation to successfully furnish spiroketal **33**. The isocoumarin fragment in ketone **32** lacked the mesomeric effect, which increased the nucleophilicity of the phenolic hydroxyl group thus aiding the pivotal spirocyclisation step. Spiroketal **33** is an advanced intermediate in Kita's total synthesis of (±)-γ-rubromycin (**3**).



Reagents and conditions: i. $Pd(PPh_3)_4$, CuI, Cs_2CO_3, DMF, r.t., 16 h, 91%; ii. H_2, 10% Pd/C, $NaHCO_3$, EtOAc, r.t., 3 h; iii. IBX, DMSO, 60 °C, 20 min, 94% (over two steps); iv. $NaHSO_4{\cdot}SiO_2$, CH_2Cl_2, r.t., 4 h, 80%.

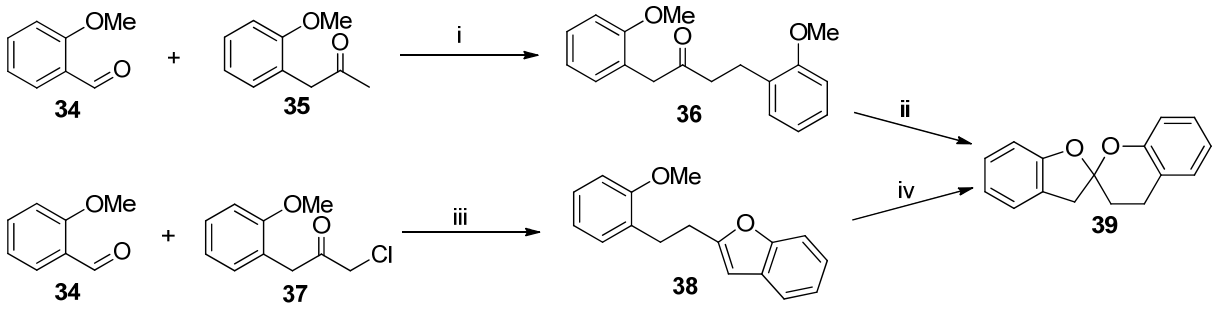
Scheme 5. Synthesis of (±)-γ-rubromycin (**3**) by Brimble *et al.*[24]

1.5 Previous Studies on the Synthesis of Model 5,6-Bisbenzannulated Spiroketals

Over the years many research groups have contributed to the synthesis of the central 5,6-bisbenzannulated spiroketal core of the rubromycin family of antibiotics. Synthetic strategies to prepare such 5,6-bisbenzannulated spiroketals will be discussed herein.

1.5.1 Greul and Brockmann[28] – Cyclisation of Dihydroxyketone and Benzofuran

Greul and Brockmann[28] have synthesised 5,6-bisbenzannulated spiroketal **39** using two alternative pathways (Scheme 6). The first route employed an aldol condensation between 2-methoxybenzaldehyde **34** and methyl ketone **35** followed by hydrogenation to afford ketone **36**. The methyl ethers were removed using boron tribromide and subsequent spirocyclisation produced spiroketal **39**. The second route involved an aldol condensation between 2-methoxybenzaldehyde **34** and chloromethyl ketone **37** followed by Clemmensen reduction of the carbonyl functionality in the resultant adduct. Benzofuran **38** was treated with boron tribromide, which facilitated removal of the methyl ethers and concomitant intramolecular cyclisation of the resultant phenol gave the desired spiroketal **39**.

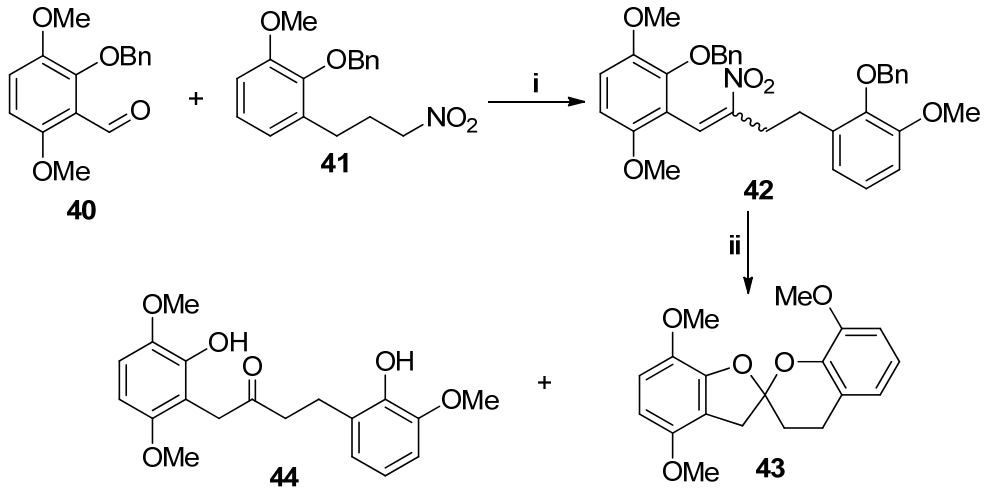


Reagents and conditions: i. a) **35**, aq. NaOH, EtOH, b) H_2, Pd/C, EtOH, 16%; ii. BBr_3, -17 °C to r.t., 15%; iii. a) **37**, Et_3N, pyridine, b) Zn(Hg), aq. HCl, Δ, 14%; iv. BBr_3, CH_2Cl_2, -20 °C, 30%.

Scheme 6. Synthesis of spiroketal **39** by Greul and Brockmann.[28]

1.5.2 de Koning *et al.*[29, 30] – Henry Condensation–Nef-type Reaction Sequence

de Koning *et al*.[29, 30] have used a microwave-assisted Henry condensation between aldehyde **40** and nitroalkane **41** to afford nitroalkene **42** (Scheme 7). Nitroalkene **42** was converted into spiroketal **43** by a Nef-type reaction under reductive conditions using Pearlman's catalyst followed by acid-catalysed cyclisation. Uncyclised dihydroxyketone **44** was also isolated during the Nef-type reaction of nitroalkene **42**.



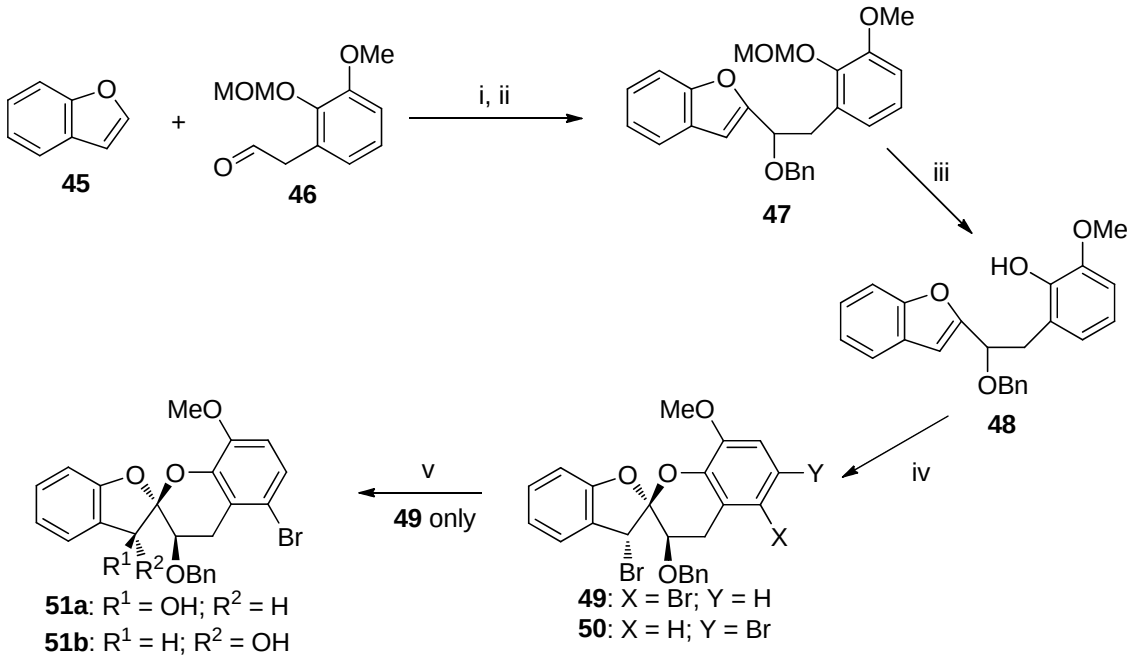
Reagents and conditions: i. NH_4OAc, AcOH, microwave, 57%; ii. H_2, $Pd(OH)_2/C$, cyclohexene, aq. HCl, EtOH; **43**, 64%; **44**, 18%.

Scheme 7. Synthesis of spiroketal **43** by de Koning *et al*.[29, 30]

1.5.3 Danishefsky *et al.*[21] – Electrophilic Cyclisation of a Benzofuran

Danishefsky *et al*.[21] have successfully synthesised the spiroketal core of heliquinomycin (**7**) using an electrophile-assisted cyclisation of a benzofuran derivative, as demonstrated by the synthesis of model spiroketals **51a** and **51b** (Scheme 8). Aldehyde **46** was coupled to the lithio-derivative of benzofuran **45** to form an alcohol adduct which underwent benzylation to afford benzyl ether **47**. The methoxymethyl group was removed from benzofuran **47** to afford phenol **48**. The double bond of the benzofuran moiety in phenol **48** was activated with *N*-

bromosuccinimide and opening of the resultant bromonium ion by the neighbouring phenolic hydroxyl group produced bromospiroketal regioisomers **49** and **50** with high diastereoselectivity. Spiroketal **49** was taken to the next step in which the benzylic bromine atom was replaced by an oxygen-containing nucleophile to produce a 3:1 ratio of diastereomeric spiroketals **51a** and **51b**. This procedure was later attempted in the total synthesis of heliquinomycinone (**11**) (Scheme 1) however it was unsuccessful in forming the desired 5,6-spiroketal moiety.

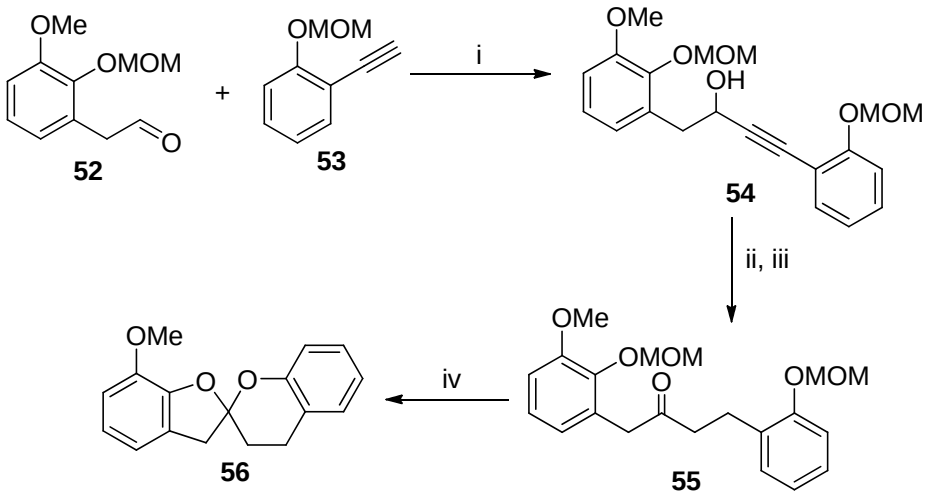


Reagents and conditions: i. *n*-BuLi, -78 °C, THF; ii. KH, BnBr, THF, 70% (over 2 steps); iii. ethereal HCl (1 M), ^{i}PrOH, THF, 93%; iv. NBS, CH_2Cl_2, 85% (**49**:**50** = 56:44; *dr* > 95:5 for each isomer); v. AgOTf, wet THF, 81% (**51a**:**51b** = 3:1).

Scheme 8. Synthesis of spiroketals **51a** and **51b** by Danishefsky *et al*.[21]

1.5.4 Brimble *et al.*[31, 32] – Addition of Lithium Acetylide to Aryl Aldehyde

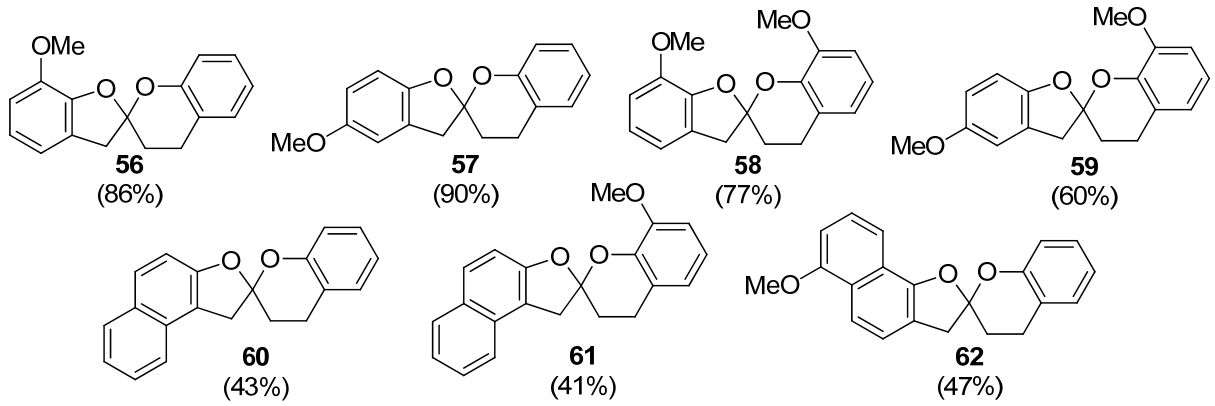
Brimble *et al*.[31, 32] have also prepared a series of 5,6-bisbenzannulated by coupling aryl-substituted acetaldehyde **52** with aryl acetylene **53** (Scheme 9). Treatment of aryl acetylene **53** with *n*-butyllithium resulted in the generation of its acetylide anion which was coupled to aldehyde **52** to afford alkynol **54**. Subsequent hydrogenation followed by oxidation furnished ketone **55**. Removal of both MOM groups and subsequent spirocyclisation of ketone **55** to give spiroketal **56** was achieved using bromotrimethylsilane in dichloromethane.



Reagents and conditions: i. *n*-BuLi, THF, -78 °C → r.t., 61%; ii. H_2, 10% Pd/C, K_2CO_3, EtOAc, r.t., 88%; iii. TPAP, NMO, 4 Å MS, CH_2Cl_2, r.t., 89%; iv. TMSBr, CH_2Cl_2, 4 Å MS, -30 °C → 0 °C → r.t., 86%.

Scheme 9. Synthesis of spiroketal **56** by Brimble *et al*.[31, 32]

This methodology was successfully applied to the synthesis of seven other 5,6-bisbenzannulated spiroketals **56-62** (Figure 5).[31, 32]



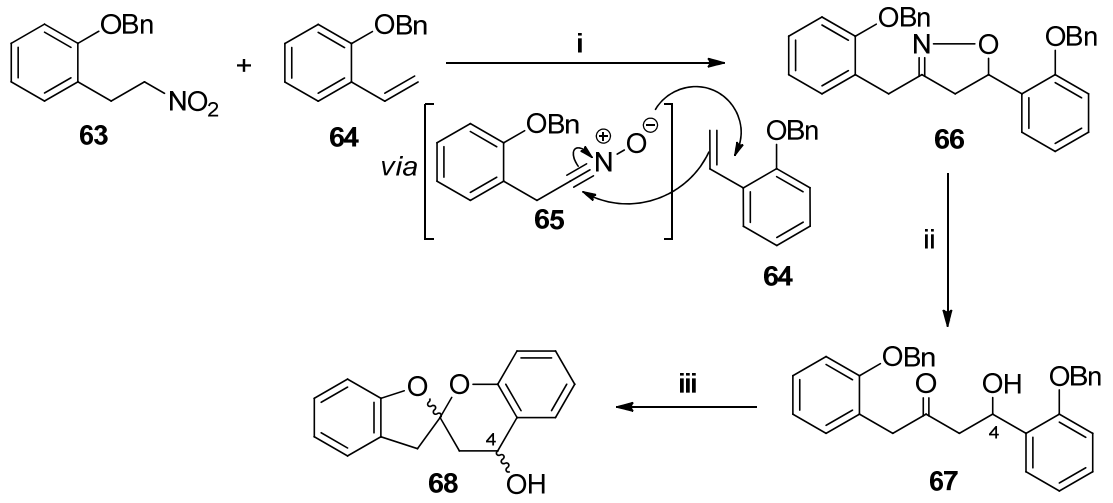
56 (86%) **57** (90%) **58** (77%) **59** (60%)

60 (43%) **61** (41%) **62** (47%)

Figure 5. 5,6-Bisbenzannulated spiroketals **56–62** synthesised by Brimble *et al*.[31, 32]

1.5.5 Kozlowski *et al.*[25, 33] – [3+2] Cycloaddition Using a Nitrile Oxide Intermediate

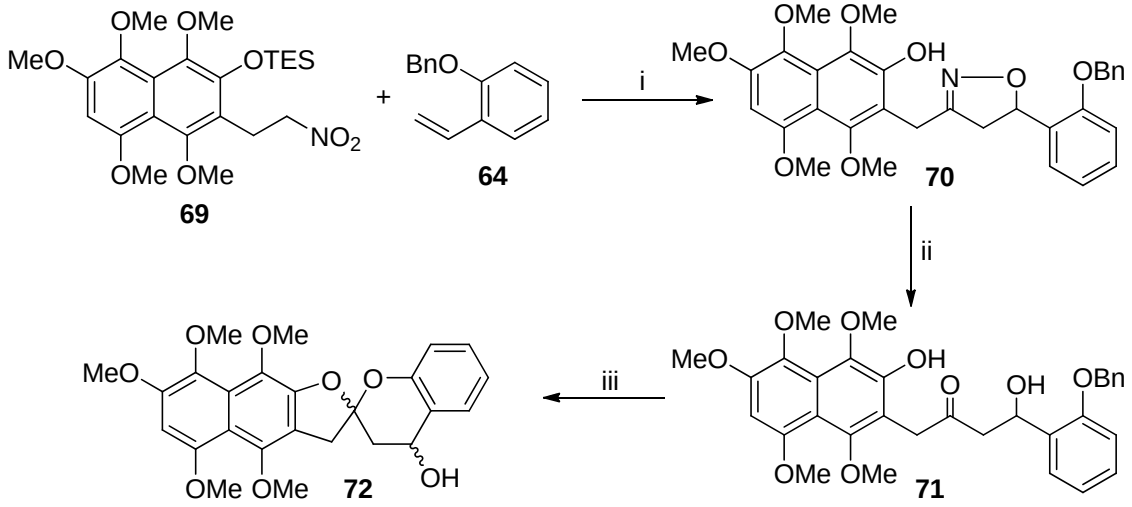
Kozlowski *et al*.[33] have reported their synthetic studies towards the total synthesis of purpuromycin (**6**) using a key isoxazoline intermediate formed from a 1,3-dipolar cycloaddition. The method was first utilised on a model spiroketal **68** which has a hydroxyl group at C-4 which mimics the central 5,6-bisbenzannulated spiroketal moiety of purpuromycin (**6**) (Scheme 10). This spiroketal was prepared by treatment of nitroalkane **63** with phenylisocyanate in the presence of triethylamine, affording nitrile oxide intermediate **65** which underwent regioselective [3+2] cycloaddition with styrene **64** to form isoxazoline **66**. Hydrogenolysis of the isoxazoline **66** furnished β-hydroxyketone **67** which underwent sequential hydrogenolysis and acid-promoted spirocyclisation to produce spiroketal **68** as a 2:1 ratio of diastereomers (Scheme 10).



Reagents and conditions: i. PhNCO, Et_3N, benzene, r.t., 91%; ii. H_2, Raney Ni, $B(OH)_3$, MeOH–H_2O (10:1), r.t., 81%; iii. a) H_2, 10% Pd/C, EtOAc, r.t., b) *p*-TsOH, CH_2Cl_2, r.t., 87% (*dr* = 2:1).

Scheme 10. Synthesis of spiroketal **68** by Kozlowski *et al*.[33]

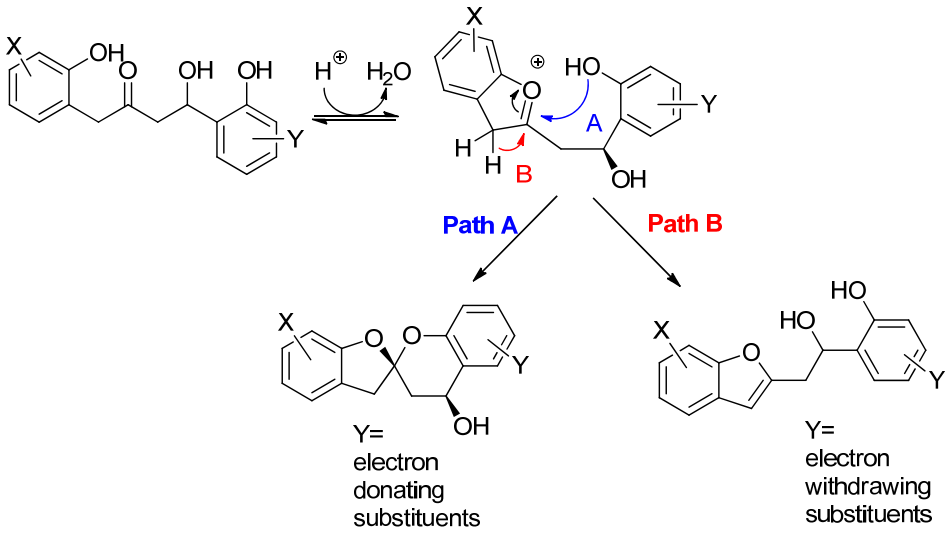
The group successfully applied the same strategy for the synthesis of spiroketal **72** as a 1:1 ratio of diastereomers from nitroalkane **69** and styrene **64** as model studies for an attempted total synthesis of purpuromycin (**6**) (Scheme 11).[25]



Reagents and conditions: i. a) PhNCO, Et_3N, benzene, r.t., b) conc. HCl, MeOH, r.t., 84%; ii. H_2, Raney Ni, $B(OH)_3$, MeOH–H_2O (5:1), r.t., 82%; iii. a) H_2, 10% Pd/C, EtOAc, r.t., b) *p*-TsOH, CH_2Cl_2, r.t., 88% (*dr* = 1:1).

Scheme 11. Synthesis of spiroketal **72** by Kozlowski *et al*.[25]

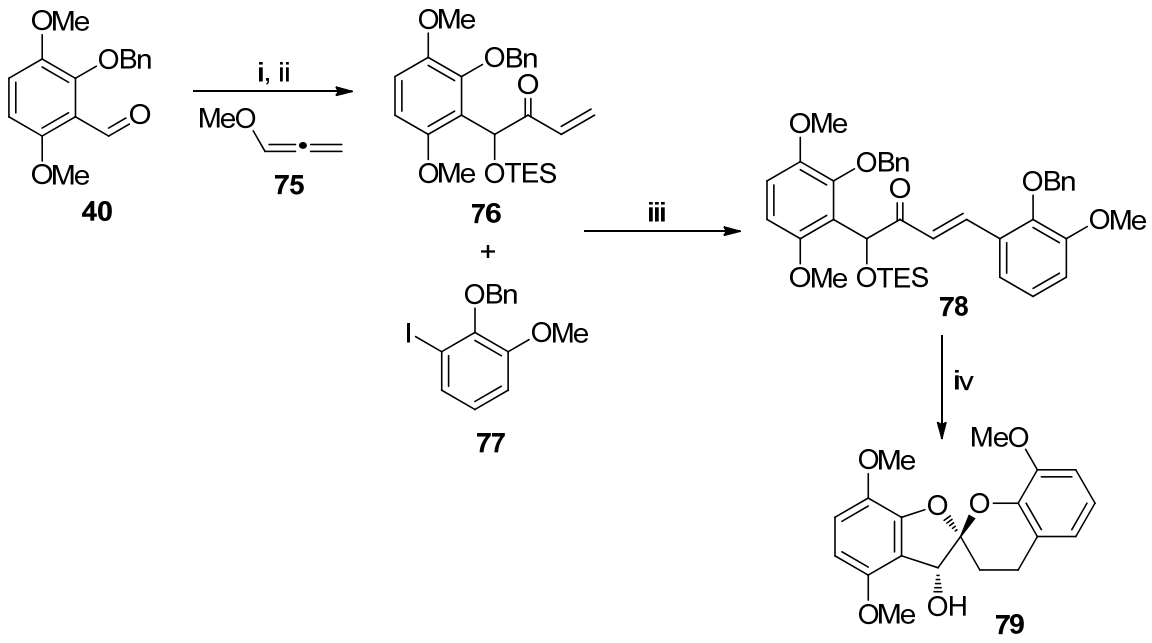
However, this procedure could not be applied in the total synthesis of purpuromycin (**6**) due to the presence of electron-withdrawing substituents on the isocoumarin fragment which significantly reduced the nucleophilicity of the phenolic hydroxyl group. This led to the irreversible formation of aromatic benzofuran **74** (Path B) instead of the desired spiroketal **73** formation (Path A) (Scheme 12).



Scheme 12. Spirocyclisation and elimination pathway[25]

1.5.6 Reiβig *et al.*[27, 34] – Heck Reaction–Cyclisation Sequence

Reiβig *et al.*[34] have reported the synthesis of model 5,6-bisbenzannulated spiroketals with a hydroxyl group at C-3 in which the spiroketal core resembles that of heliquinomycin (**7**). Model spiroketal **79** was synthesised from aldehyde **40** and the lithio-derivative of methoxyallene **75** which acts as a synthetic equivalent of an α,β-unsaturated acyl anion synthon (Scheme 13). Nucleophilic addition of lithio-derivative of methoxyallene **75** to aldehyde **40** followed by subsequent acidic hydrolysis of the methoxyallene functionality and protection of the free hydroxyl group as a triethylsilyl ether furnished enone **76**. Heck reaction of enone **76** with aryl iodide **77** produced enone **78** which underwent simultaneous hydrogenation across the double bond and benzyl ether removal. Silyl group removal and concomitant spirocyclisation were induced with a catalytic amount of acid and thermodynamically favoured spiroketal **79** was exclusively formed.



Reagents and conditions: i. a) **75**, *n*-BuLi, THF, -40 °C, b) -78 °C, **40**, c) aq. H_2SO_4, THF, 0 °C, 98%; ii. TESCl, $^{i}Pr_2NEt$, DMF, r.t., 78%; iii. $Pd(OAc)_2$, $NaHCO_3$, $^{n}Bu_4NCl$, 4 Å MS, DMF, 60 °C, 82%; iv. a) H_2, $Pd(OH)_2/C$, C_6H_{10}, EtOH, r.t., b) aq. HCl, $^{i}PrOH$, 50 °C, 65%.

Scheme 13. Synthesis of spiroketal **79** by Reiβig *et al*.[34]

Using this methodology, four 5,6-bisbenzannulated spiroketals were synthesised (Figure 6).

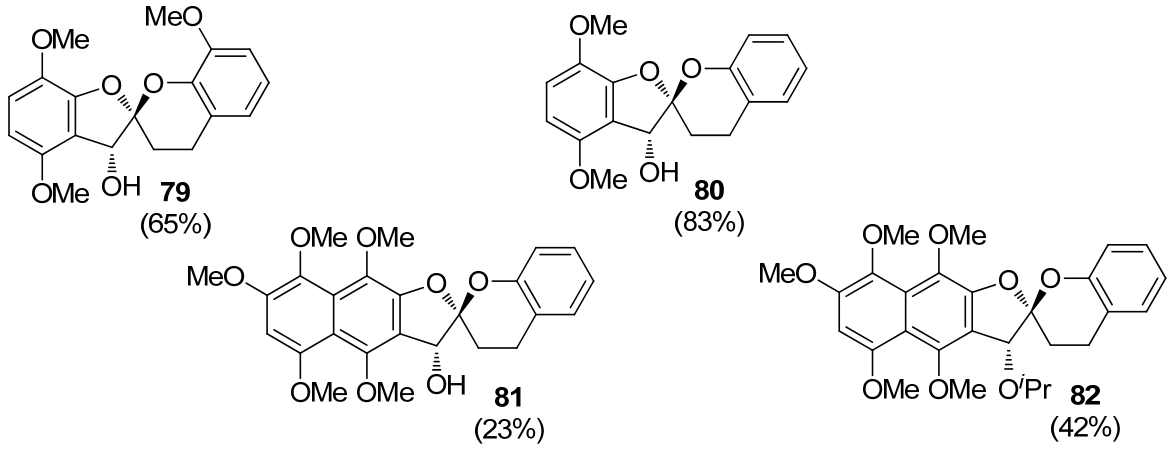
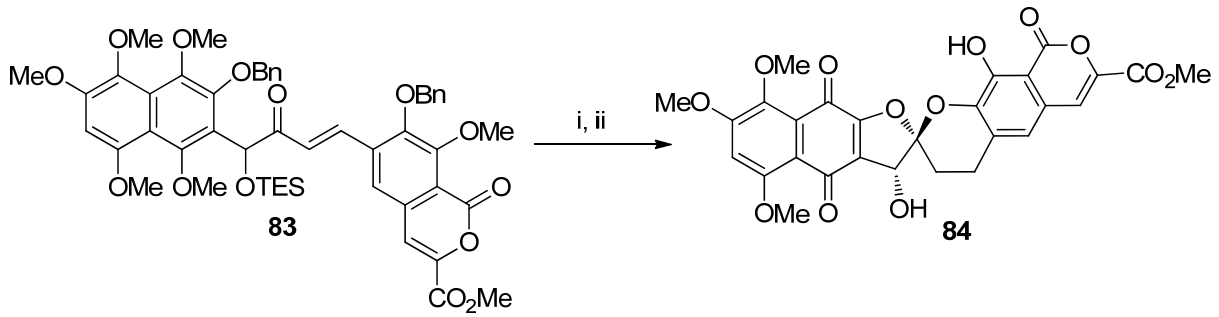


Figure 6. 5,6-Bisbenzannulated spiroketals **79-82** synthesised by Reiβig *et al*.[34]

With this promising model study completed, Reißig *et al.*[26] applied the strategy to the total synthesis of heliquinomycin (**7**) (Scheme 14). However, when advanced intermediate **83** was subjected to the identical conditions described for the model study, a complex product mixture was produced. Dimethoxy-3'-hydroxy-β-rubromcyin **84** was isolated in 7% yield and only characterised by mass spectrometry.



Reagents and Conditions: i. Pd/C, H_2, MeOH; ii. HCl (cat.), *i*-PrOH, 40 °C, 7% over 2 steps

Scheme 14. Attempted spirocyclisation by Reiβig *et al.*[26]

The group attributed the failed ring closure to the reduced nucleophilicity of the hydroxyl group due to the presence of two carbonyl groups on the isocoumarin portion of spiroketal precursor exerting negative mesomeric and inductive effects (Figure 7). This finding is in agreement with the earlier observation by Kozlowski *et al.*[25] in synthetic studies towards purpuromycin (**7**) (Scheme 12).

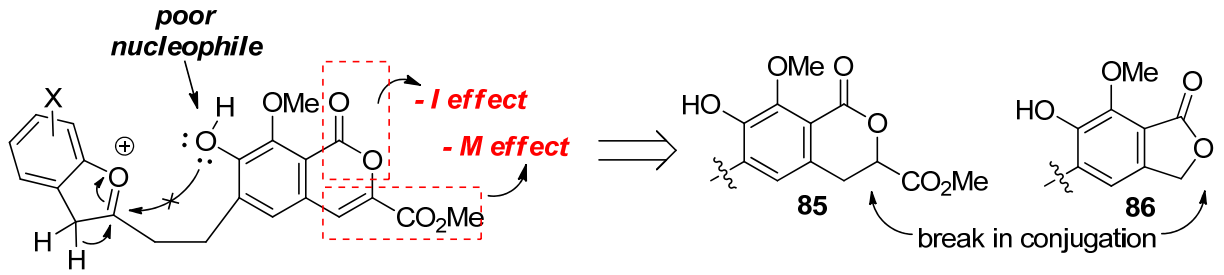
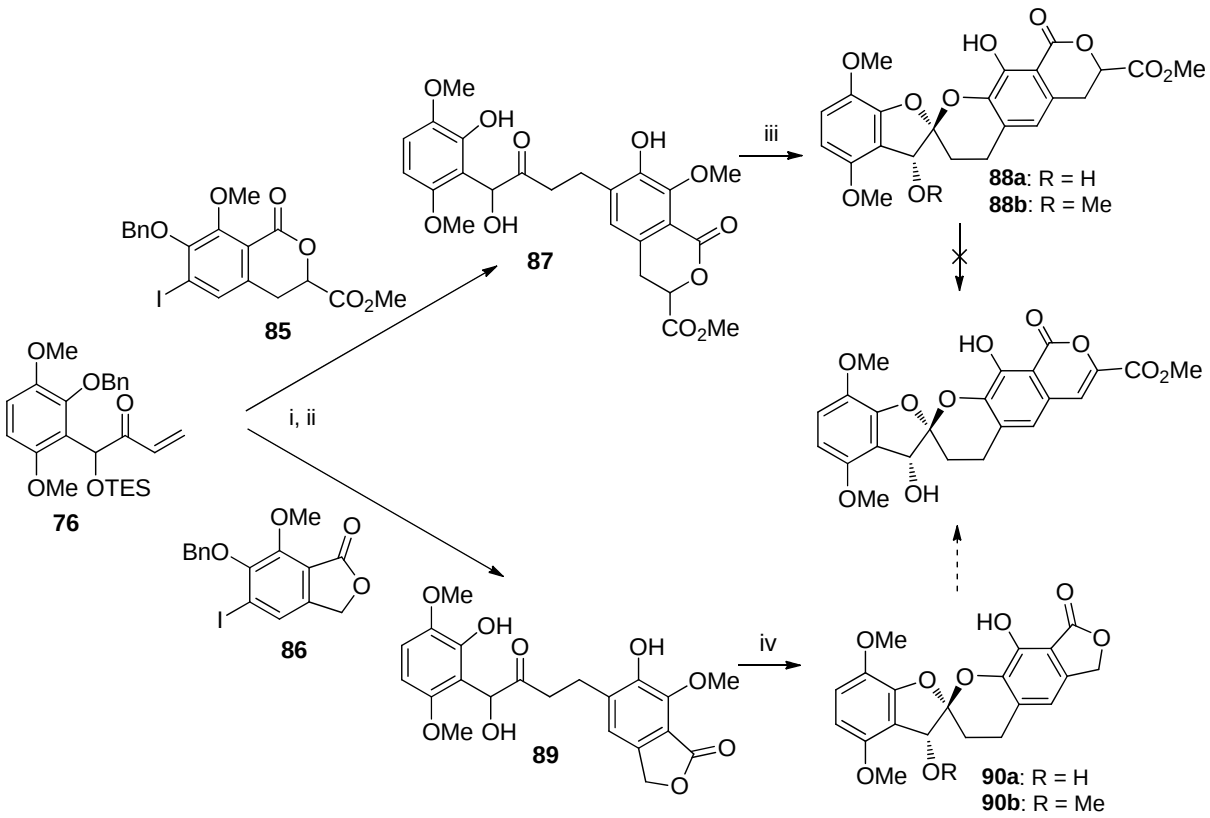


Figure 7. Electronic factors diminishing the nucleophilicity of the phenolic hydroxyl group in the isocoumarin.[27]

Hence, in order to increase the nucleophilicity of the phenolic group, Reißig *et al.*[27] synthesised isocoumarin precursors dihydroisocoumarin **85** and phthalide **86** in which conjugation in the isocoumarin moiety is selectively broken (Scheme 15). It was envisaged

that **85** and **86** could be converted to the full isocoumarin moiety at a later stage, once the vital spiroketal core had been established. Indeed, keto-alcohol **87** (derived from **76** and **85**) bearing the dihydroisocoumarin smoothly converted to spiroketals **88a** and **88b** when subjected to the established conditions as outlined in Scheme 13. The thermodynamically stable *trans*-spiroketal **88a** was formed exclusively however the methyl ether spiroketal **88b** was also observed due to the hydroxyl group being solvolytically displaced by methanol. Unfortunately, all attempts to regenerate the isocoumarin moiety from the dihydroisocoumarin moiety of spiroketals **88a** and **88b** were unsuccessful. Two additional spiroketals **90a** and **90b** containing the phthalide moiety were also synthesised by the group. However, it has yet to be demonstrated that the phthalide moiety could be converted to the isocoumarin after the key spirocyclisation step.

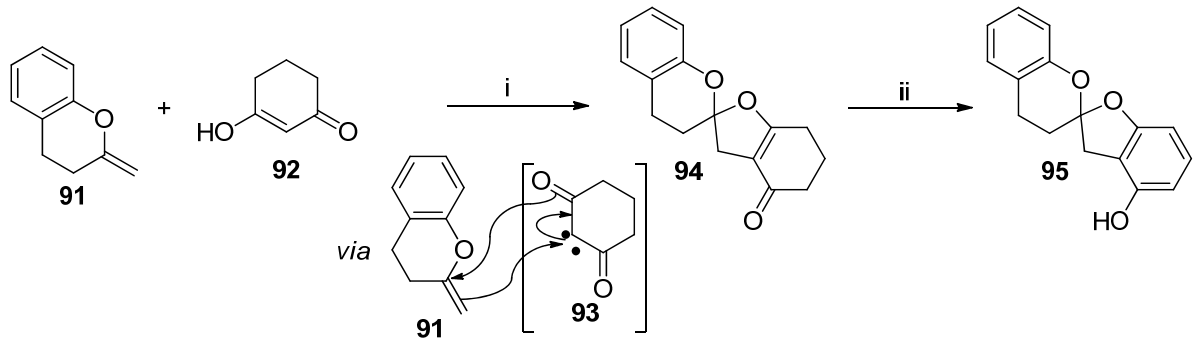


Reagents and Conditions: i. $Pd(OAc)_2$, $NaHCO_3$, $^nBu_4Cl$, DMF; ii. Pd/C, H_2, MeOH, r.t.; iii. AcCl, MeOH, $HC(OMe)_3$, 60 °C, **88a**, 27% (*dr* = 1:1); **88b**, 6% (*dr* = 1:1) (over 3 steps); iv. AcCl, MeOH, $HC(OMe)_3$, 0 °C → r.t., 25 h, **90a**, 25%; **90b**, 11% (over 3 steps).

Scheme 15. Spirocyclisation of advanced model compounds **88a**, **88b** and **90a**, **90b** by Reiβig *et al*.[27]

1.5.7 Pettus *et al.*[35-37] – [3+2] and [4+2] Cycloaddition Strategies

Pettus *et al*.[44] came up with an original approach to bisbenzannulated spiroketals, whereby the spiroketal was prepared in one step from the unification of two fragments *via* a [3+2] or [4+2] cycloaddition. As illustrated in Scheme 16, *exo*-enol ether **91** underwent a [3+2] cycloaddition with carbene intermediate **93** which was formed *in situ* from β-diketone **92** using cerium(IV) ammonium nitrate and sodium bicarbonate at 0 °C.[38] The resultant 5,6-monobenzannulated spiroketal **94** was aromatised with DDQ to afford the desired 5,6-bisbenzannulated spiroketal **95**.



Reagents and conditions: i. **92**, CAN, $NaHCO_3$, THF, 0 °C, 56%; ii. DDQ, dioxane, 100 °C, 64%.

Scheme 16. Synthesis of spiroketal **95** by Pettus *et al*.[35]

Using the same [3+2] cycloaddition approach, 5,6-benzannulated spiroketals **96**, **97** and **98** were also synthesised (Figure 8).[37]

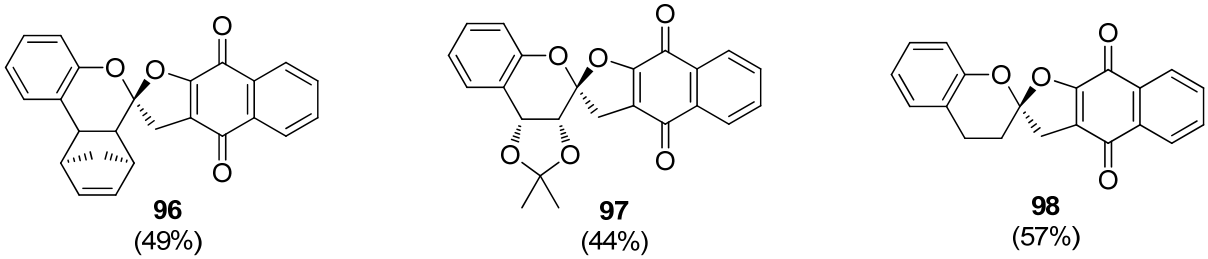
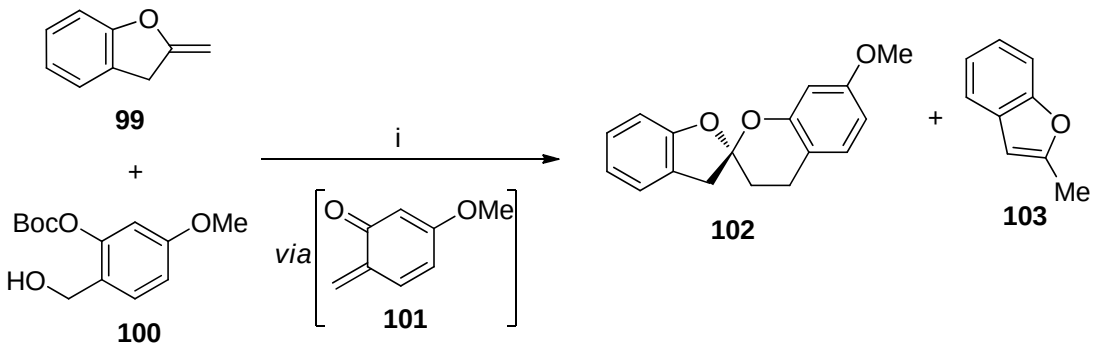


Figure 8. 5,6-Bisbenzannulated spiroketals **96**, **97** and **98** synthesised by Pettus *et al*.[37]

Pettus *et al.*[36] also developed an alternative method for the synthesis of benzannulated spiroketals using [4+2] hetero-Diels–Alder cycloadditions. 5,6-Bisbenzannulated spiroketal **102** was prepared *via* [4+2] hetero-Diels–Alder cycloaddition of *exo*-enol ether **99** to *o*-quinone methide intermediate **100** which itself was formed *in situ* from benzyl alcohol **100** (Scheme 17). Unfortunately, the yield for spiroketal **102** was modest and byproduct benzofuran **103** was also isolated from the isomerisation of enol ether **99** during the reaction.



Reagents and conditions: i. ^{t}BuMgCl, Et_2O, -78 °C → r.t., **102**, 10%.

Scheme 17. Synthesis of spiroketal **102** by Pettus *et al.*[36]

Using this strategy, a total of six 5,6-bisbenzannulated and 5,6-monobenzannulated spiroketals **102**, **104-108** were also synthesised (Figure 9).[36]

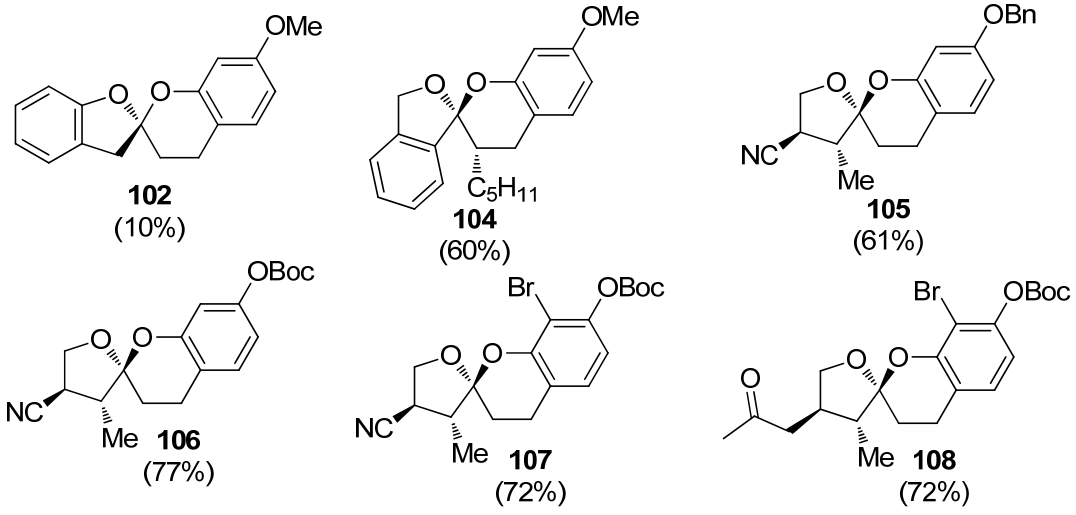
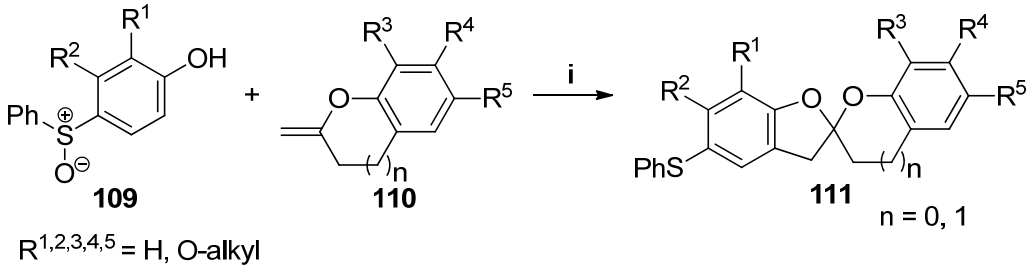


Figure 9. Synthesis of 5,6-Bisbenzannulated and 5,6-monobenzannulated spiroketals **102**, **104-108** by Pettus *et al.*[36]

1.5.8 Kita *et al.*[23, 39] – Aromatic Pummerer-type Reaction

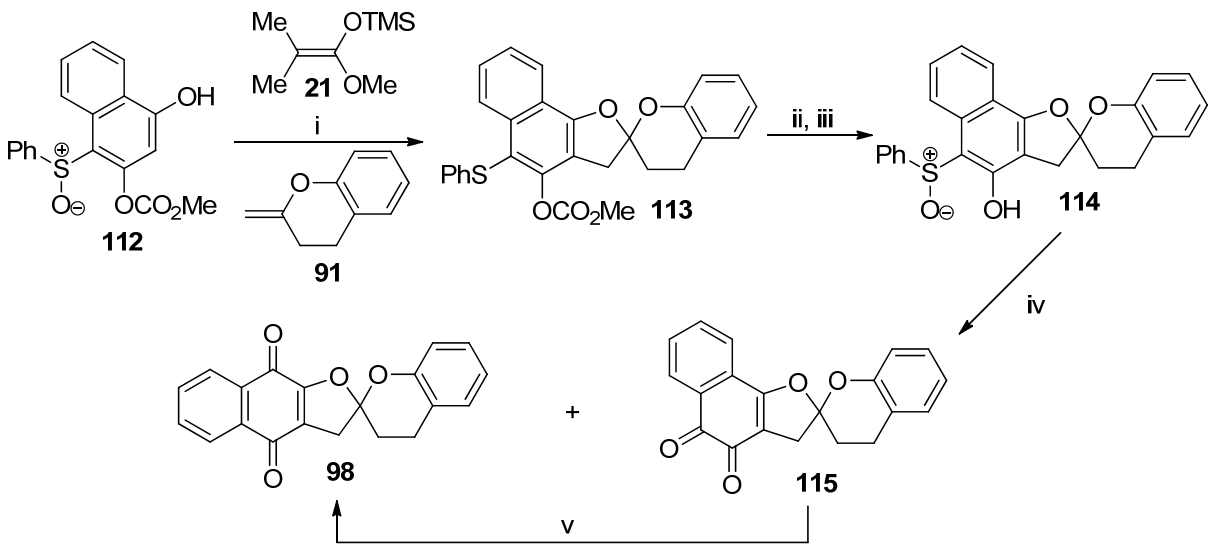
Kita *et al.* [23, 39] synthesised a series of 5,5- and 5,6-bisbenzannulated spiroketals using an aromatic Pummerer-type reaction between substituted aryl sulfoxides **109** and substituted enol ethers **110** in the presence of trifluoroacetic anhydride to form substituted spiroketals **111** (Scheme 18).[39]



Reagents and conditions: i. TFAA, 41–96%.

Scheme 18. Synthesis of spiroketals **111** by Kita *et al*.[39]

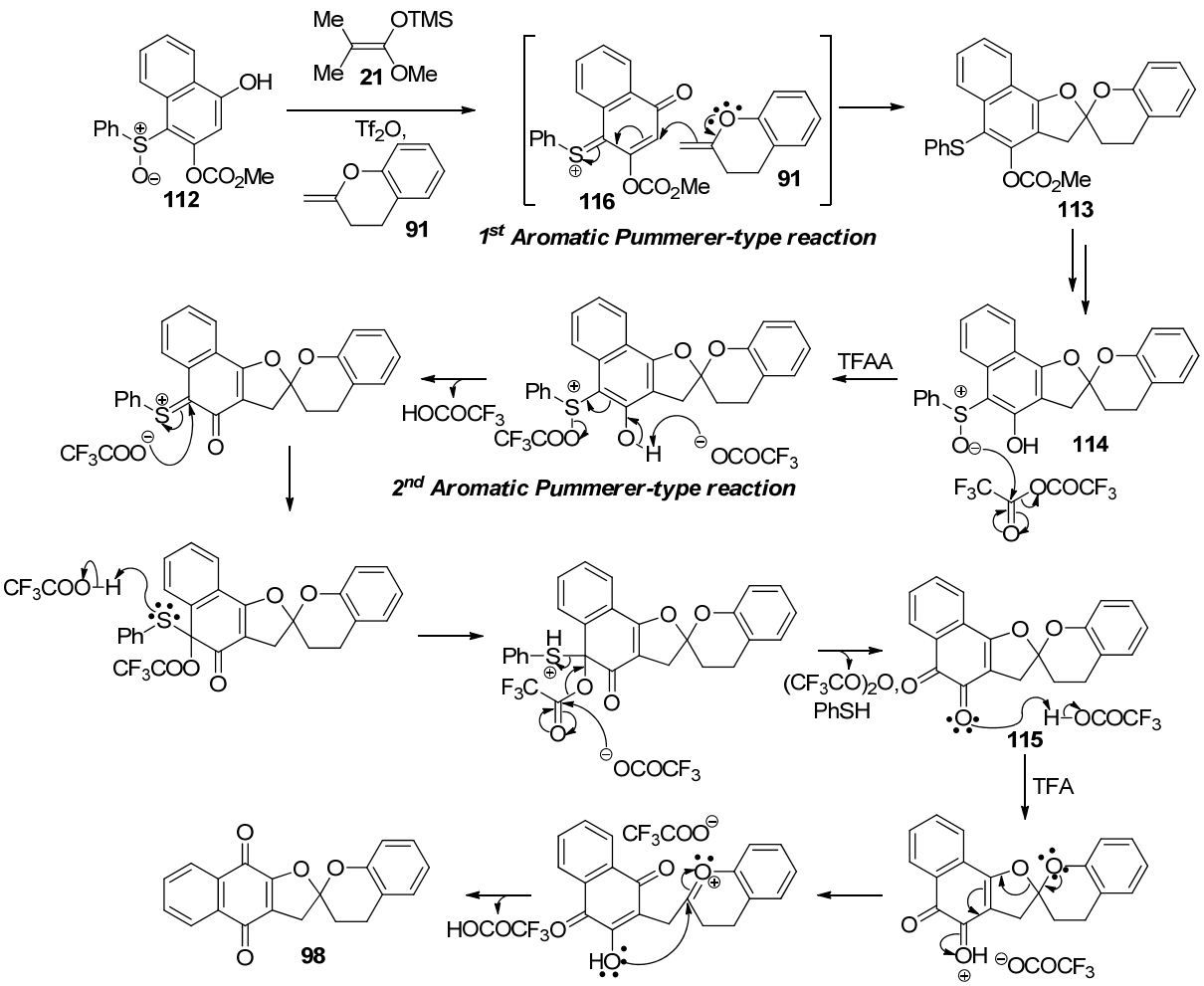
Kita *et al.* [23, 39] have also synthesised model spiroketal **98** which resembles the core of γ-rubromycin (**3**) using two aromatic Pummerer-type reactions and an acid-catalysed rearrangement of an *o*-quinone to a *p*-quinone.[23] Starting from aryl sulfoxide **112** and enol ether **91**, spiroketal **113** was synthesised by an aromatic Pummerer-type reaction (Scheme 19). Due to the low solubility of aryl sulfoxide **112** in acetonitrile, it was initially converted to its TMS ether using methyl trimethylsilyl dimethylketene acetal **21**. With spiroketal **113** in hand, the methoxycarbonyl group was removed with isopropylamine and subsequent oxidation of the sulfide to a sulfoxide using *m*-chloroperoxybenzoic acid afforded spiroketal sulfoxide **114**. Spiroketal sulfoxide **114** underwent a second aromatic Pummerer-type reaction using trifluoromethanesulfonic anhydride to produce a mixture of *p*-quinone **98** and *o*-quinone **115**. However, treatment of spiroketal sulfoxide **114** with trifluoroacetic anhydride instead of trifluoromethanesulfonic anhydride afforded exclusively *o*-quinone **115**. *o*-Quinone **115** was subsequently treated with trifluoroacetic acid which furnished the rearranged *p*-quinone spiroketal **98**.



Reagents and conditions: i. a) **21**, MeCN, r.t., b) **91**, Tf_2O, 2,4,6-collidine, MeCN, -40 °C, 73%; ii. $^{i}PrNH_2$, MeCN, r.t., 89%; iii. *m*-CPBA, CH_2Cl_2, -78 → -35 °C, 85%; iv. Tf_2O, CH_2Cl_2, 0 °C, **98**, 57%; **115**, 27% or TFAA, CH_2Cl_2, 0 °C, **115**, 82%; v. TFA, CH_2Cl_2, 0 °C, 87%.

Scheme 19. Synthesis of spiroketal **98** by Kita *et al*.[23]

The mechanism for the formation of spiroketal **98** *via* two aromatic Pummerer-type reactions and an acid-catalysed rearrangement of an *o*-quinone to a *p*-quinone is shown in Scheme 20. The first aromatic Pummerer-type reaction proceeded *via* nucleophilic addition of enol ether **91** to the *p*-quinone sulfonium intermediate **116** followed by ring closure afforded spiroketal **113**. Once spiroketal **113** was elaborated to spiroketal **114**, a second aromatic Pummerer-type reaction took place using trifluoroacetic anhydride to afford *o*-quinone spiroketal **115**. When spiroketal **115** was treated with trifluoroacetic acid, protonation of the carbonyl oxygen closer to the spiroketal moiety took place followed by cleavage of the spiroketal. The liberated hydroxyl group then underwent cyclisation onto the oxonium ion to furnish *p*-quinone spiroketal **98**.[23,39]

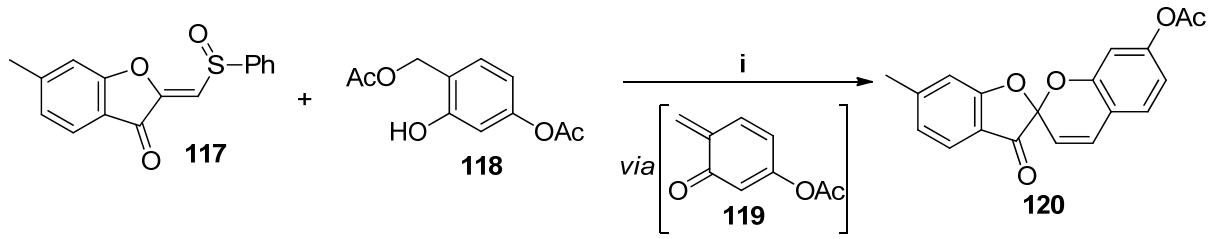


Scheme 20. Mechanism for the formation of spiroketal **98** using two successive aromatic Pummerer-type reactions.[23, 39]

This strategy was also successfully applied to the total synthesis of (±)-γ-rubromycin (**3**) (Scheme 3).[23]

1.5.9 Li *et al.*[40, 41] – [4+2] Hetero-Diels–Alder Cycloaddition Using *o*-Quinone Methides and Gold-catalysed Double Intramolecular Hydroalkoxylation of Alkynes

Li *et al.* [40] synthesised a series of 5,6-bisbenzannulated spiroketals based on the 3*H*-spiro(benzofuran-2,2′-chromen)-3-one skeleton. Model spiroketal **120** (Scheme 21) was formed by a [4+2] hetero-Diels–Alder cycloaddition–pyrolytic sulfoxide elimination reaction. Vinyl sulfoxide **117** was used as the dienophile and *o*-quinone methide intermediate **119** was used as the diene which was formed *in situ* from phenol **118**, affording the desired spiroketal **120** in 55% yield. This strategy was also used for the synthesis of several 6,6-bisbenzannulated spiroketals as described later (Scheme 28).[42]



Reagents and conditions: i. benzene, 110 °C, 39 h, 55%.

Scheme 21. Synthesis of spiroketal **120** by Li *et al.* [40]

Using this methodology, a total of seven 5,6-bisbenzannulated spiroketals **120-126** were also synthesised (Figure 10).[40]

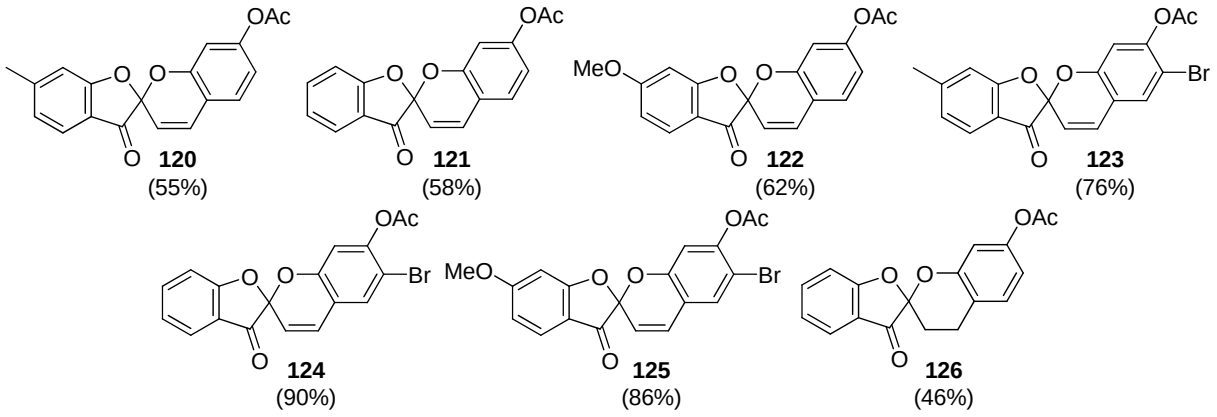
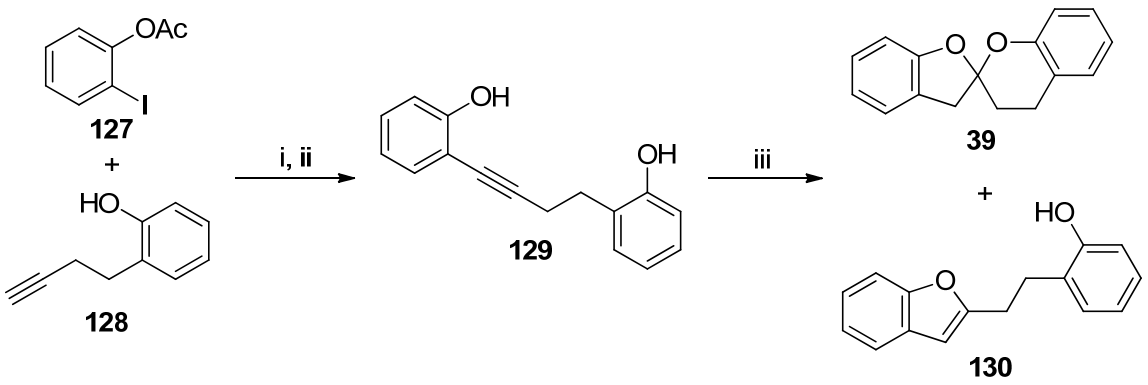


Figure 10. Synthesis of 5,6-bisbenzannulated spiroketals **120-126** by Li *et al.*[40]

Li *et al*.[41] also reported the use of gold-catalysed double intramolecular hydroalkoxylation of alkynes to prepare the spiroketal moiety of a series of 5,6-bisbenzannulated spiroketals. Aryl iodide **127** and acetylene **128** underwent Sonogashira reaction followed by hydrolysis of the acetate which furnished alkyne **129** in good yield. A gold-catalysed double intramolecular hydroalkoxylation of alkyne **129** using catalytic Ph_3PAuCl and silver trifluoromethanesulfonate provided spiroketal **39** along with benzofuran **130** as a side product (Scheme 22).



Reagents and conditions: i. $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N, DMF, 60 °C, 2 h; ii. NaOH, MeOH, r.t., 10 min, 72–81%; iii. Ph_3PAuCl (10 mol %), AgOTf (10 mol %), CH_2Cl_2, r.t., 2 days, **39**, 62%; **130**, 28%.

Scheme 22. Synthesis of spiroketal **39** by Li *et al*.[41]

Using this methodology, 5,6-bisbenzannulated spiroketals **39**, **56**, **131-135** were also synthesised (Figure 10).[41]

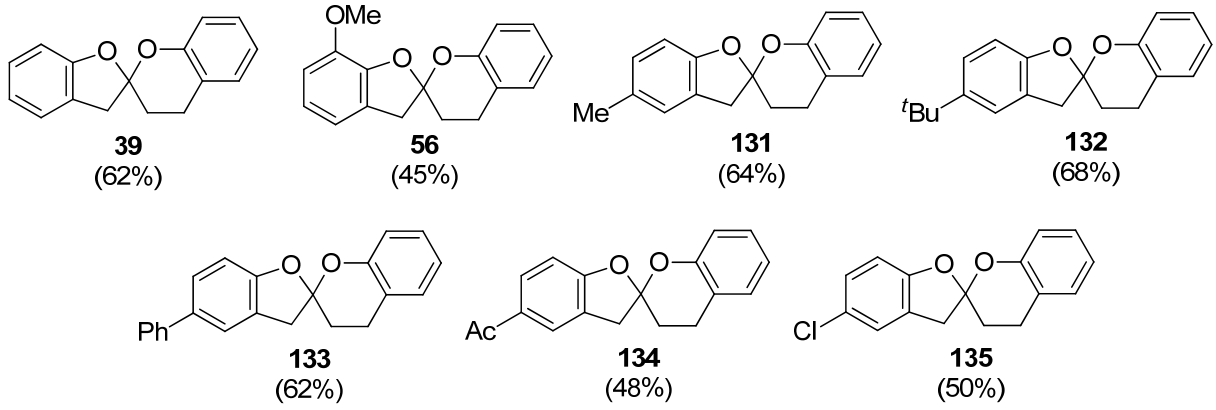
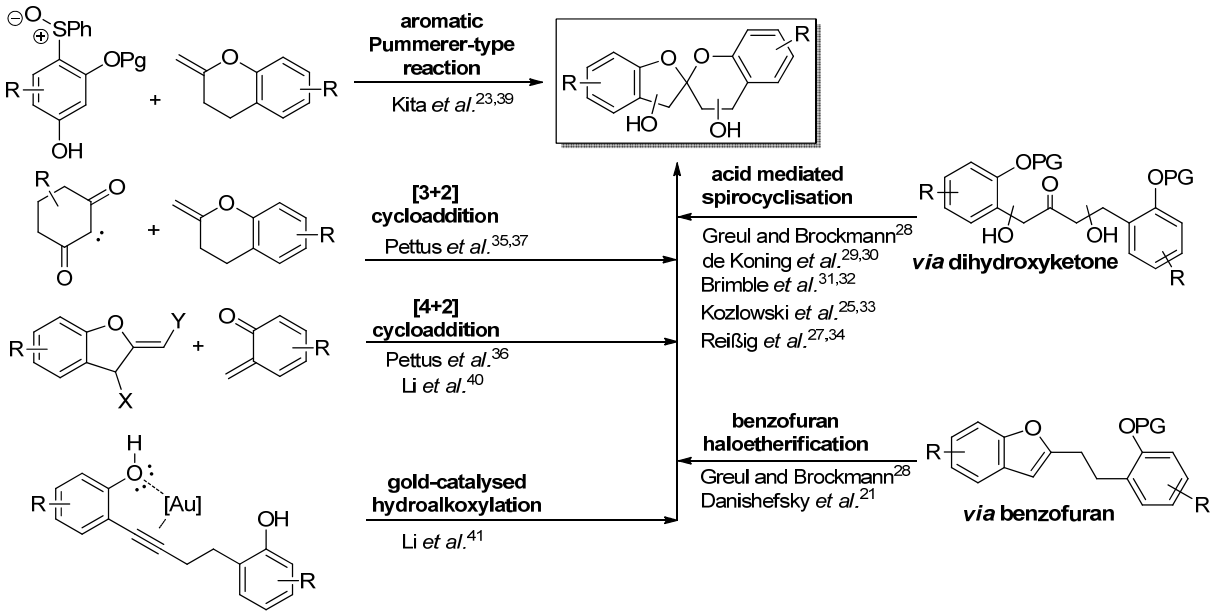


Figure 10. 5,6-Bisbenzannulated spiroketals **39**, **56**, **131–135** synthesised by Li *et al*.[41]

1.5.10 Summary – Synthesis of Model 5,6-Bisbenzannulated Spiroketals

Scheme 23 shows an overview of the various methods used for the synthesis of model 5,6-bisbenzannulated spiroketals.



Scheme 23. Summary of various methods used in the synthesis of model 5,6-bisbenzannulated spiroketals.

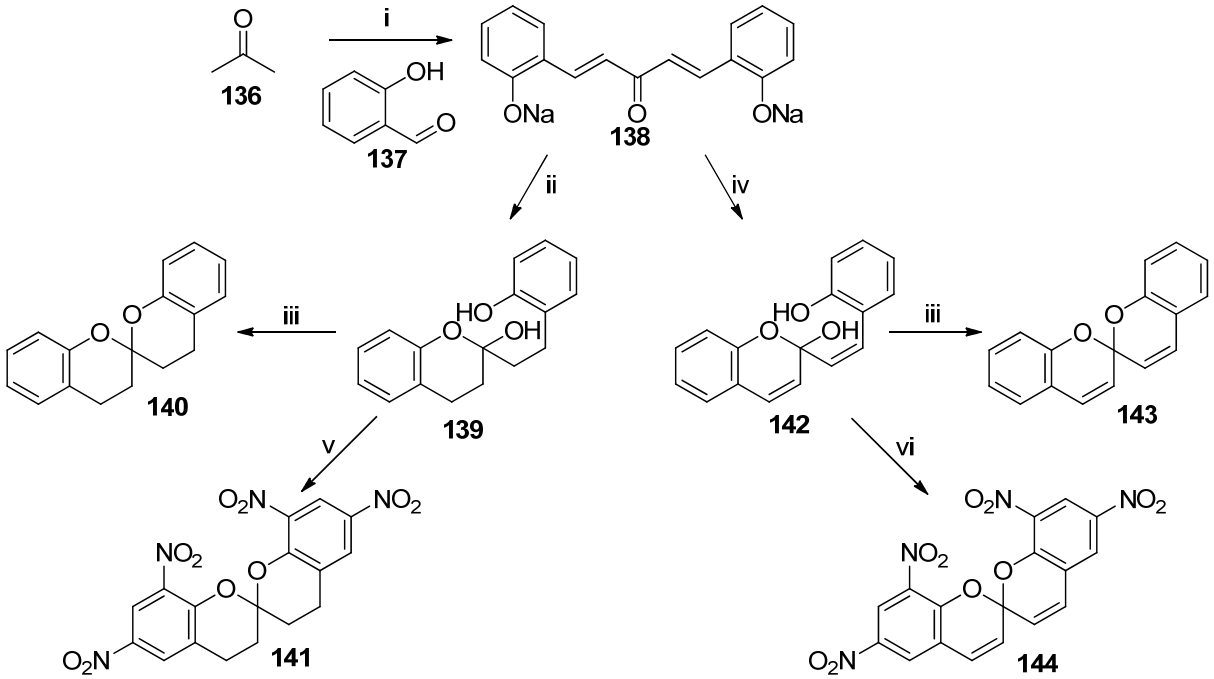
1.6 Previous Studies on the Synthesis of Model 6,6-Bisbenzannulated Spiroketals

Various methods used for the synthesis of model 6,6-bisbenzannulated spiroketals will be discussed herein.

1.6.1 Mora and Széki[43] *via* Condensation of Salicylaldehydes with Acetone 136

Mora and Széki[43] synthesised various 6,6-bisbenzannulated spiroketals by the formation of disalicylideneacetones from the condensation of substituted salicylaldehydes with acetone **136**. As depicted in Scheme 24, by reacting two equivalents of salicylaldehyde **137** and one equivalent of acetone **136**, the disodium salt of disalicylideneacetone **138** was formed which upon hydrogenation followed by treatment with carbon dioxide gave hemiketal **139**. Dehydration of **139** furnished spiroketal **140**. Tetranitro-substituted spiroketal **141** was produced from **139** by acid-mediated cyclisation and aromatic nitration.

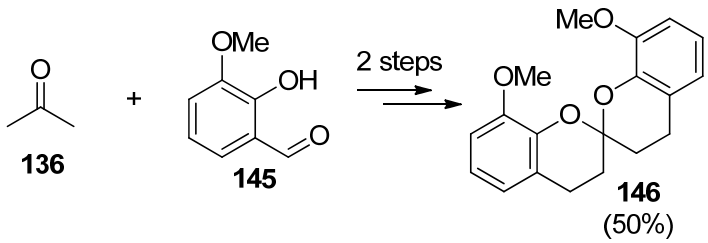
Similarly, spiroketal **143** was also formed from the disodium salt of disalicylideneacetone **138** which was first treated with carbon dioxide to yield diol **142**. Dehydration of diol **142** followed furnishing spiroketal **143**. Tetranitro-substituted spiroketal **144** was produced from **142** by acid-mediated cyclisation and aromatic nitration.



Reagents and conditions: i. **137**, aq. NaOH, EtOH, r.t., 24 h, 98%; ii. a) H_2, Pd/C, H_2O, 50 °C, 2 h, b) CO_2, 72%; iii. either a) Δ (> 160 °C), 10 min, b) H_2O, steam distillation; or a) distillation *in vacuo* (210–215 °C, 16 mmHg), b) crystallisation, **140**, 72%; **143**, 50%; iv. CO_2, H_2O, r.t., 95%; v. HNO_3, AcOH, 40 °C, then stand at r.t., 64%; vi. HNO_3, AcOH, 0 °C, 6 h, then 100 °C, 30 min, 55%.

Scheme 24. Synthesis of spiroketals **140**, **141** and **143-144** by Mora and Széki.[43]

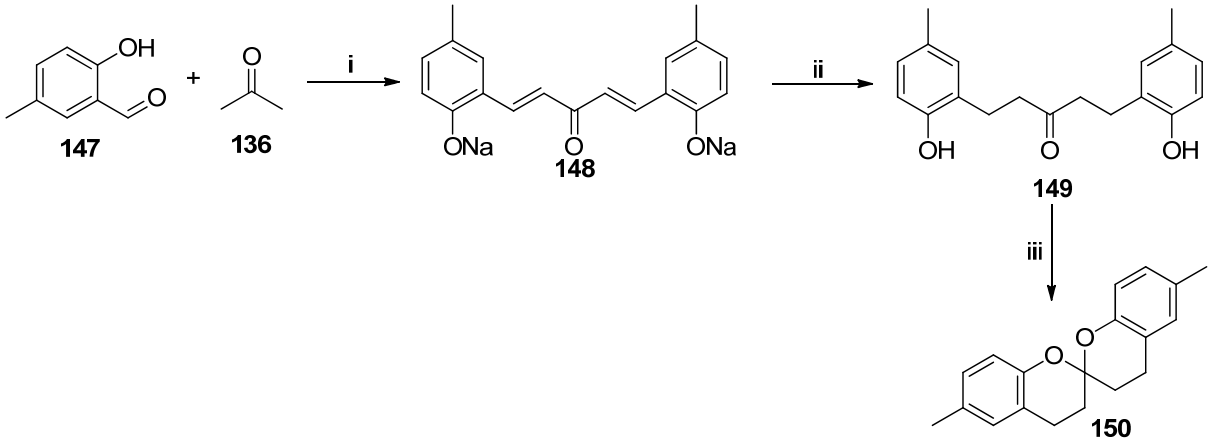
Applying the same procedure, spiroketal **146** was also synthesised using acetone **136** and *o*-vanillin **145** (Scheme 25).



Scheme 25. Synthesis of spiroketal **146** by Mora and Széki.[43]

1.6.2 Tanaka *et al.*[44] *via* Condensation of Salicylaldehydes with Acetone 136

Tanaka *et al*.[44] synthesised 6,6′-dimethyl-2,2′-spirobi(chroman) **150** (Scheme 26) using the procedure reported by Mora and Széki[43] with different conditions for the cyclisation step. Condensation between 5-methylsalicylaldehyde **147** and acetone **136** was carried out yielding the disodium salt of disalicylideneacetone **148**. Hydrogenation of the disodium salt of disalicylideneacetone **148** over palladium on charcoal afforded dihydroxyketone **149** which underwent an acid-mediated cyclisation using sulfuric acid to afford spiroketal **150**.

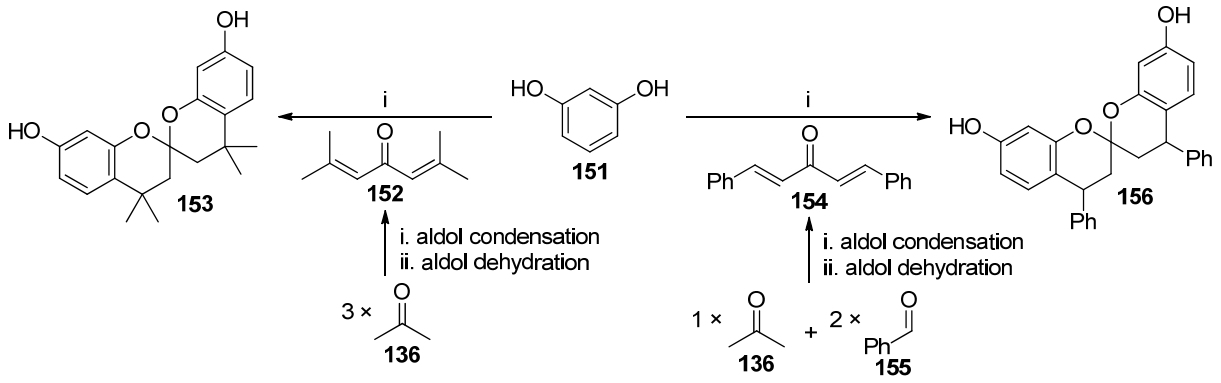


Reagents and conditions: i. aq. NaOH, EtOH, 12 h, 74%; ii. H_2, Pd/C, 55 °C, 18 h, 46%; iii. conc. H_2SO_4, EtOH, 0 °C, 2 h, 63%.

Scheme 26. Synthesis of spiroketal **150** by Tanaka *et al*.[44]

1.6.3 Livant *et al.*[45, 46] *via* Reaction of Resorcinol with Acetone derived Ketones

Livant *et al*.[45, 46] reported the synthesis of two 6,6-bisbenzannulated spiroketals **153** and **156** by reacting resorcinol **151** with either phorone **152** or *trans*,*trans*-dibenzylideneacetone **154** (Scheme 27). Electrophilic alkylation of resorcinol **151** to both ends of phorone **152** followed by acid-catalysed intramolecular cyclisation afforded spiroketal **153** in good yield. Spiroketal **156** was prepared using the same procedure from resorcinol **151** and *trans*,*trans*-dibenzylideneacetone **154**. Phorone **152** was derived from two aldol condensations of three equivalents of acetone **136** followed by two aldol dehydrations while *trans*,*trans*-dibenzylideneacetone **154** was formed from two aldol condensations between one equivalent of acetone **136** and two equivalents of benzaldehyde **155** followed by two aldol dehydrations.

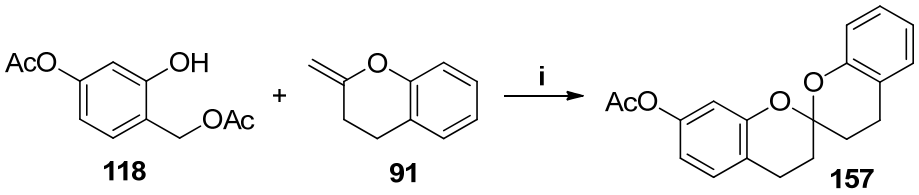


Reagents and conditions: i. **136** or **154**, aq. HCl, Et_2O–CH_2Cl_2 (1:1), Δ, 24 h, **153**, 85%; **156**, 76%.

Scheme 27. Synthesis of spiroketals **153** and **156** by Livant *et al*.[45, 46]

1.6.4 Li *et al.*[42] – [4+2] Hetero-Diels–Alder Reaction Using *o*-Quinone Methide Intermediates

Li *et al*.[40] have reported the synthesis of a series of 5,6-bisbenzannulated spiroketals based on a 3*H*-spiro(benzofuran-2,2′-chromen)-3-one skeleton as mentioned previously in Scheme 21. Similar work had been carried out on the synthesis of 6,6-bisbenzannulated spiroketals (Scheme 28). [42] Spiroketal **157** was formed by [4+2] hetero-Diels–Alder cycloaddition between phenol **118** and *exo*-enol ether **91**. Conducting the reaction in the presence of titanium(IV) chloride as catalyst gave a higher yield.



Reagents and conditions: i. benzene, 110 °C, 28 h, 59% without $TiCl_4$; 71% with $TiCl_4$.

Scheme 28. Synthesis of spiroketal **157** by Li *et al*.[42]

Using this methodology, a total of seven 6,6-bisbenzannulated spiroketals **157-163** were synthesised (Figure 11).[42]

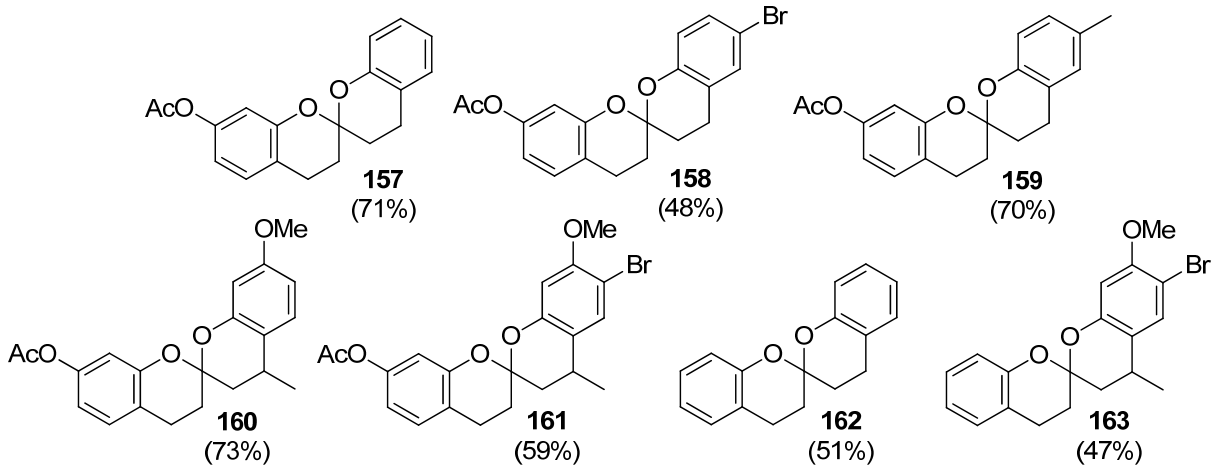
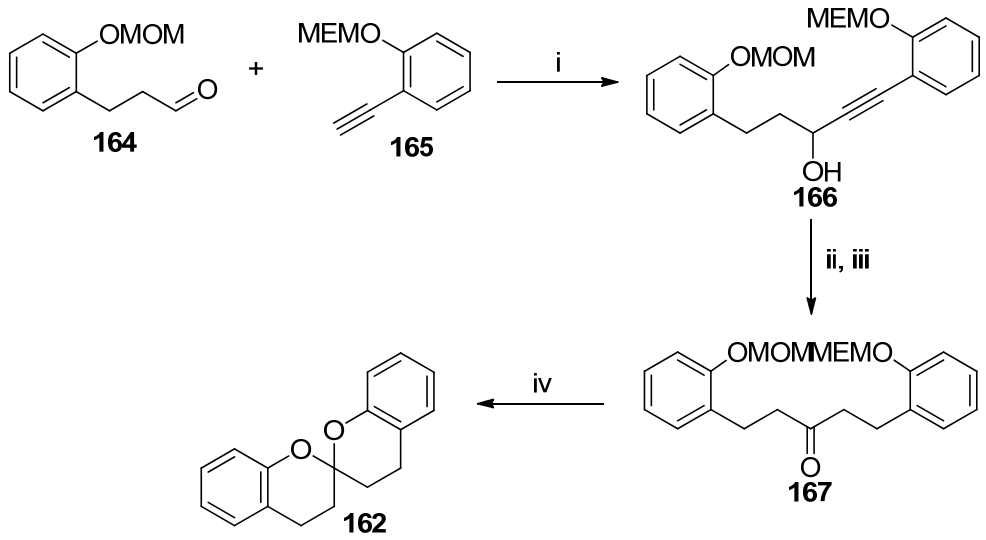


Figure 11. 6,6-Bisbenzannulated spiroketals **157-163** synthesised by Li *et al*.[42]

1.6.5 Brimble *et al.*[47] – Addition of Lithium Acetylide to Aryl Aldehyde

Brimble *et al*.[31, 32] have previously reported the synthesis of 5,6-bisbenzannulated spiroketals from union of aryl acetylides to aryl-substituted acetaldehydes followed by alcohol oxidation and intramolecular spirocyclisation as mentioned in Scheme 9. A series of analogous 6,6-bisbenzannulated spiroketals has also been synthesised by using the same synthetic pathway (Scheme 29).[47] Spiroketal **162** was prepared by coupling aryl acetylene **165** with 3-aryl-substituted propanal **164**. Treatment of acetylene **165** with *n*-butyllithium followed addition of aldehyde **164** provided alkynol **166**. Hydrogenation of the alkyne followed by oxidation of the alcohol moiety afforded ketone **167** which underwent spirocyclisation using bromotrimethylsilane to deliver spiroketal **162**.



Reagents and conditions: i. *n*-BuLi, THF, -78 °C → r.t., 57%; ii. H_2, 10% Pd/C, K_2CO_3, EtOAc, r.t., 71%; iii. TPAP, NMO, 4 Å MS, CH_2Cl_2, r.t., 99%; iv. TMSBr, CH_2Cl_2, 4 Å MS, -30 °C → 0 °C → r.t., 97%.

Scheme 29. Synthesis of spiroketal **162** by Brimble *et al*.[47]

Using this strategy, a total of five 6,6-bisbenzannulated spiroketals **146, 162, 168-170** were synthesised (Figure 12).[47]

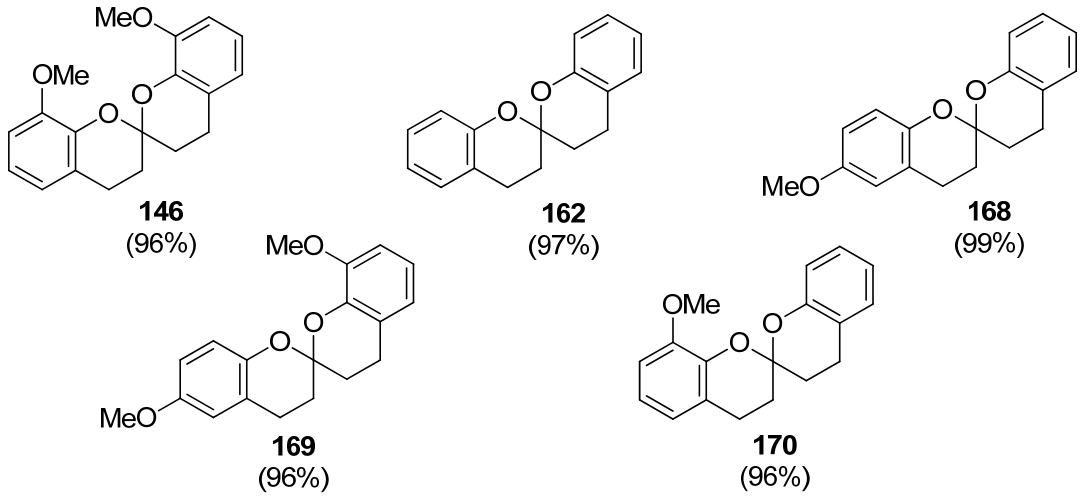
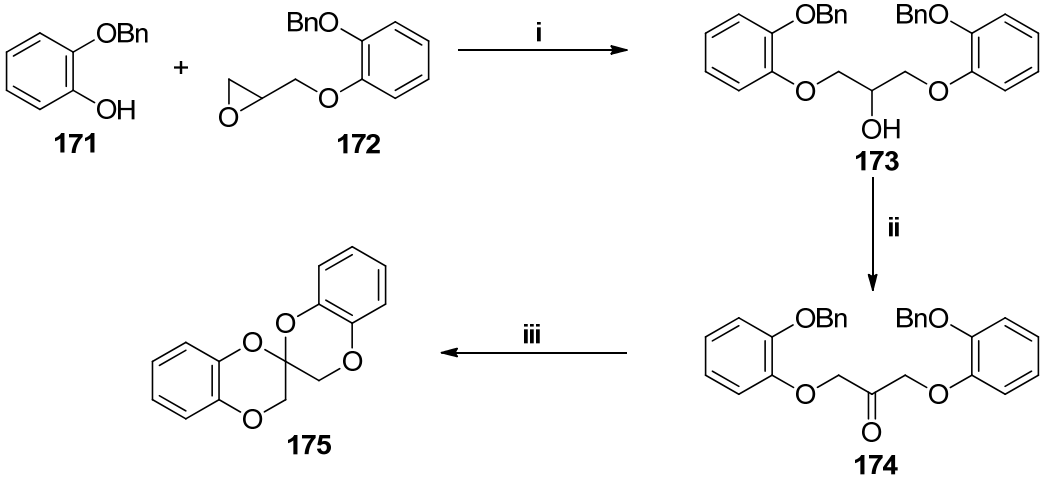


Figure 12. 6,6-Bisbenzannulated spiroketals **146, 162, 168-170** synthesised by Brimble *et al*.[47]

1.6.6 Brimble *et al.*[48] – Epoxide Opening with Naphthol/Phenol Precursor

In an extension of previous work, Brimble *et al*.[31, 32, 47] extended their research to the synthesis of spiroketals based on a 3*H*,3′*H*-2,2′-spirobi(benzo[*b*][1,4]dioxine) ring system. As depicted on Scheme 30, the naphthol/phenol precursor **171** was coupled to its corresponding epoxide **172** using potassium carbonate in acetone under reflux afforded alcohol **173**. Oxidation of alcohol **173** using Dess–Martin periodinane produced ketone **174** which underwent hydrogenolysis and subsequent acid-catalysed spirocyclisation to furnish spiroketal **175**.



Reagents and conditions: i. K_2CO_3, acetone, Δ, 82%; ii. DMP, CH_2Cl_2, r.t., 2-3 h, 60%; iii. a) H_2, 10% Pd/C, EtOH, r.t., 15.5 h, b) *p*-TsOH, CH_2Cl_2, 50 °C, 7.2 h, 56%.

Scheme 30. Synthesis of spiroketal **175** by Brimble *et al*.[48]

Using this methodology, six spiroketals **175-180** containing the 3*H*,3′*H*-2,2′-spirobi(benzo[*b*][1,4]dioxine) ring system were synthesised (Figure 13).

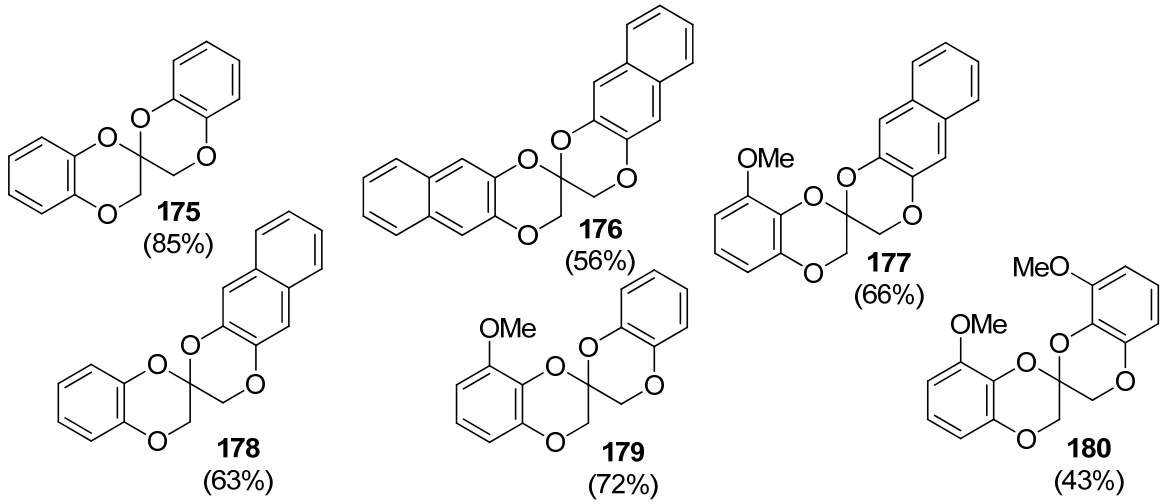


Figure 13. 6,6-spiroketals **175-180** synthesised by Brimble *et al*.[48]

1.7 Concluding Remarks

The recent discovery that the rubromycins exhibit potent inhibition of telomerase and DNA helicase[10], together with the previous successful preparation of 5,6-spiroketals **56-62** and 6,6-spiroketal analogues **146, 162, 168-170** of the rubromycins conducted by this research group, prompted further research aimed at the synthesis of further aryl spiroketal analogues of the rubromycins (Figure 14).

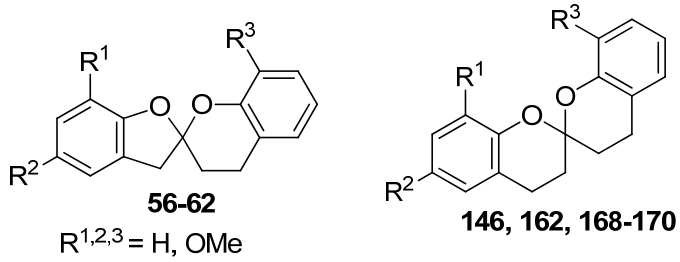
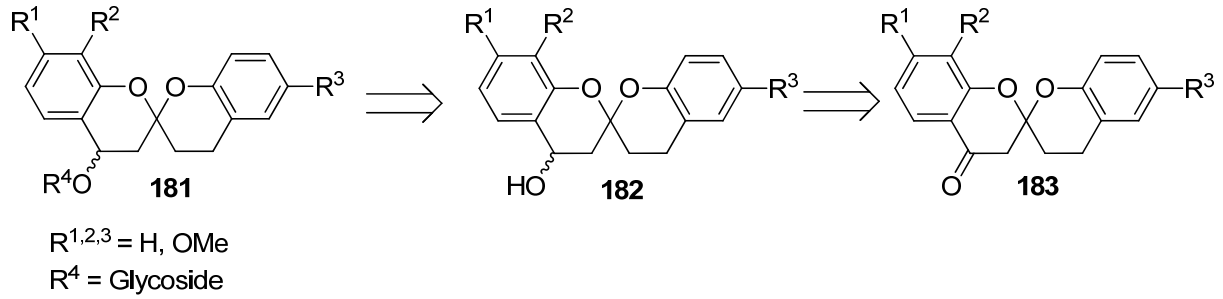


Figure 14. 5,6-spiroketal and 6,6-spiroketal analogues of the rubromycins synthesised by this research group.[31, 32, 47]

It was envisaged that synthesis of 6,6-bisbenzannulated spiroketal analogues **183** would provide access to *O*-glycosylated 6,6-bisbenzannulated spiroketals **181** that are analogous to γ-rubromycin (**3**) and heliquinomycin (**7**) (Scheme 31). Accessing the model hydroxylated bisbenzannulated spiroketals **182**, would enable an investigation into the effect that the level of oxygenation of the spiroketal ring has on the inhibition of telomerase and DNA helicase. The synthesis of the glycosylated spiroketal ring system also provides an opportunity to probe the effect of the sugar moiety on the inhibition of human telomerase and DNA helicase.



Scheme 31. Synthetic target: α-hydroxy-substituted 6,6-bisbenzannulated spiroketals **182**.

The research will focus on the synthesis of the α-hydroxy-substituted 6,6-bisbenzannulated spiroketal analogues **182**. The glycosylation of the α-hydroxy group on the aryl spiroketal core will also be investigated using a variety of glycosylation methods. The execution of the planned synthesis towards α-hydroxy-substituted 6,6-bisbenzannulated spiroketal analogues **182** and the various challenges encountered is discussed in the following chapter.

Chapter Two

Discussion

2.1 Our Approach- Background

Our research group has previously reported the synthesis of a series of simple bisbenzannulated spiroketals based on the 3*H*-spiro(benzofuran-2,2′-chroman) (5,6-system **56-62**)[31, 49] and 2,2′-spirobi(chroman) (6,6-system **146, 162, 168-170**)[47] skeletons that are related to γ-rubromycin (**3**) (Figure 15). Because of our long-standing interest in the synthesis of aryl spiroketal-containing products, we decided to extend our research to the synthesis of novel 6,6-bisbenzannulated spiroketals.

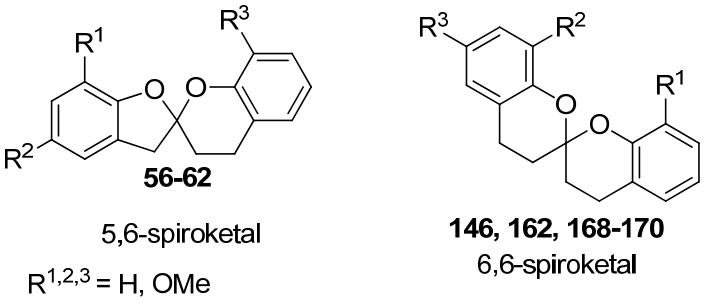
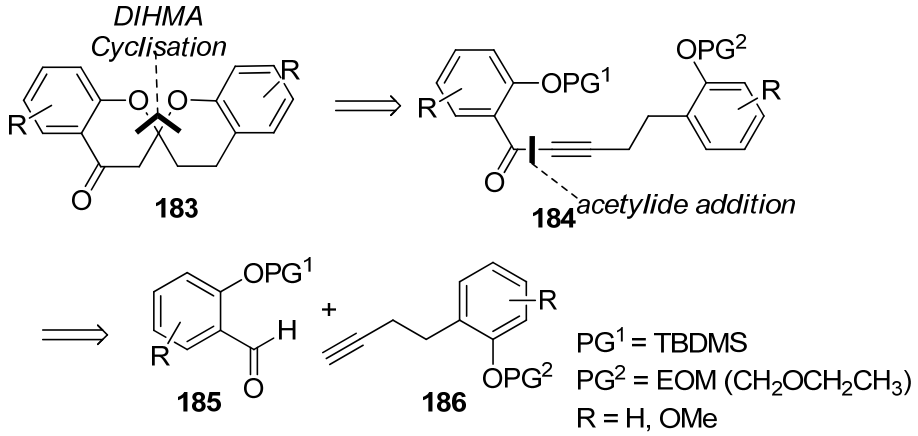


Figure 15. 5,6 and 6,6-bisbenzannulated spiroketals previously synthesised in our group

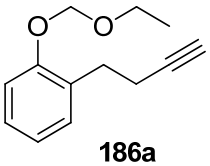
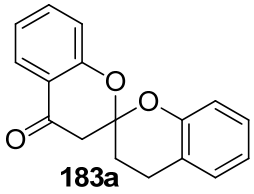
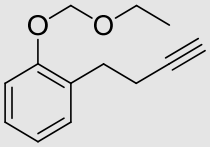
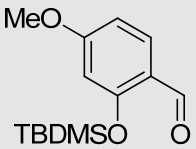
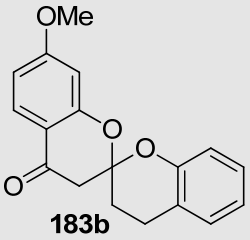
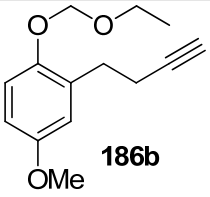
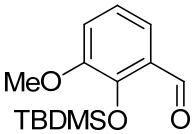
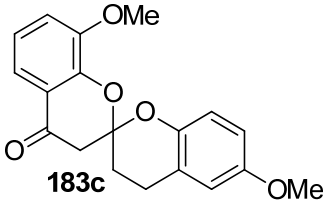
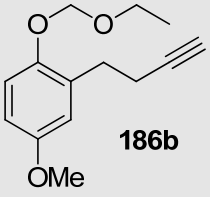
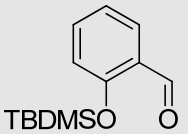
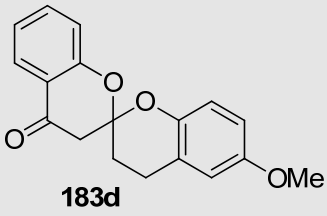
The proposed synthesis of key 6,6-bisbenzannulated spiroketal **183** is shown in Scheme 32. The spiroketal **183** could be assembled *via* double intramolecular hetero-Michael addition (DIHMA) of dihydroxy ynone **184** (Scheme 32). In turn, access to the spiroketal precursor **184** is readily achieved by addition of the acetylide anion generated from acetylene **186** to aldehyde **185**.



Scheme 32. Retrosynthesis of bisbenzannulated spiroketal **183** related to γ-rubromycin (**3**) and heliquinomycin (**7**).

2.2 Synthetic Strategy

Five spiroketal analogues **183a-183e** were chosen as our initial targets hence we set out to synthesise the acetylene and aldehyde starting materials required for their synthesis (Table 2).

Entry	acetylene	aldehyde	6,6-spiroketal analogues
1	 **186a**	 **185a**	 **183a**
2	 **186a**	 **185b**	 **183b**
3	 **186b**	 **185c**	 **183c**
4	 **186b**	 **185a**	 **183d**

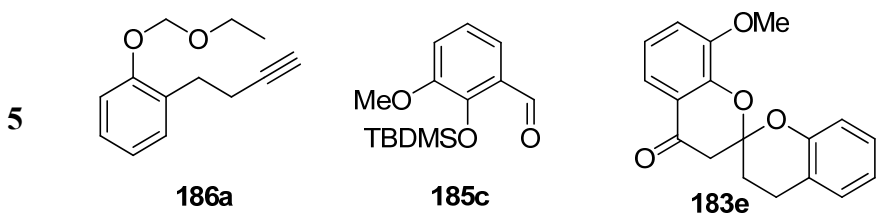


Table 2. Structures of 6,6-bisbenzannulated spiroketal synthetic targets.

For simplicity, the individual synthesis of the acetylenes and the aldehydes will not be described in detail. A generic structure of the aldehyde **185** and the acetylene **186** will be used (Figure 16) to describe the overall synthetic methodology and yields. The spectroscopic data will be described for the series of aldehydes and acetylenes and their respective intermediates.

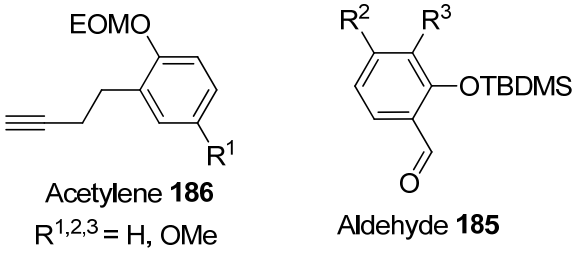
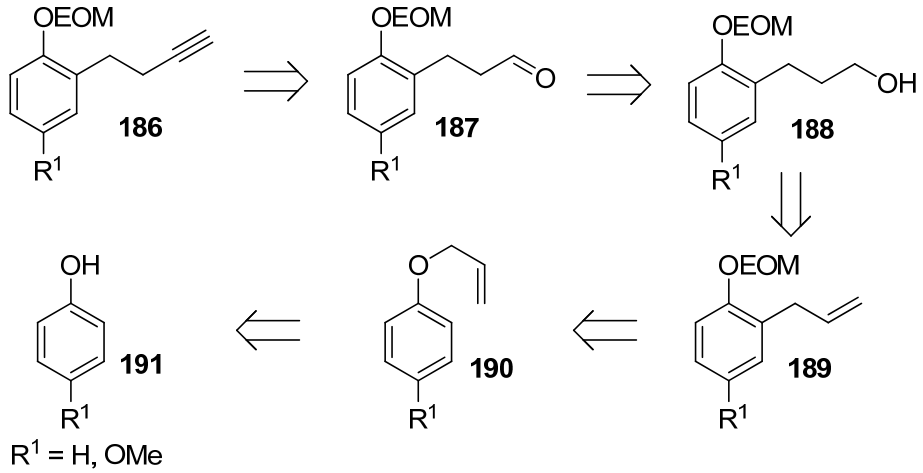


Figure 16. Structures of generic acetylenes and aldehydes.

2.2.1 Retrosynthesis of Acetylenes 186a and 186b

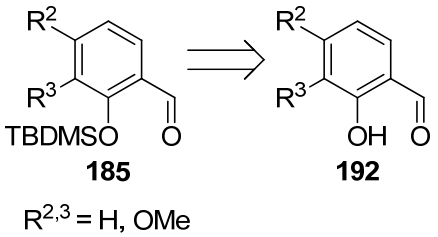
It was envisaged that acetylene **186** can be synthesised via a one carbon homologation of aldehyde **187**. The Ohira-Bestmann modification[50] of the Seyferth-Gilbert[51] homologation will be used to prepare the required terminal alkyne **186**. In turn, aldehyde **187** can be prepared by oxidation of alcohol **188** that is readily accessible *via* hydroboration of alkene **189**. In turn, alkene **189** is accessed via Claisen rearrangement of allyl ether **190** that is prepared via allylation of commercially available phenol **191** (Scheme 33).



Scheme 33. Retrosynthesis of acetylenes **186a** and **186b**.

2.2.2 Retrosynthesis of Aldehydes 185a, 185b and 185c

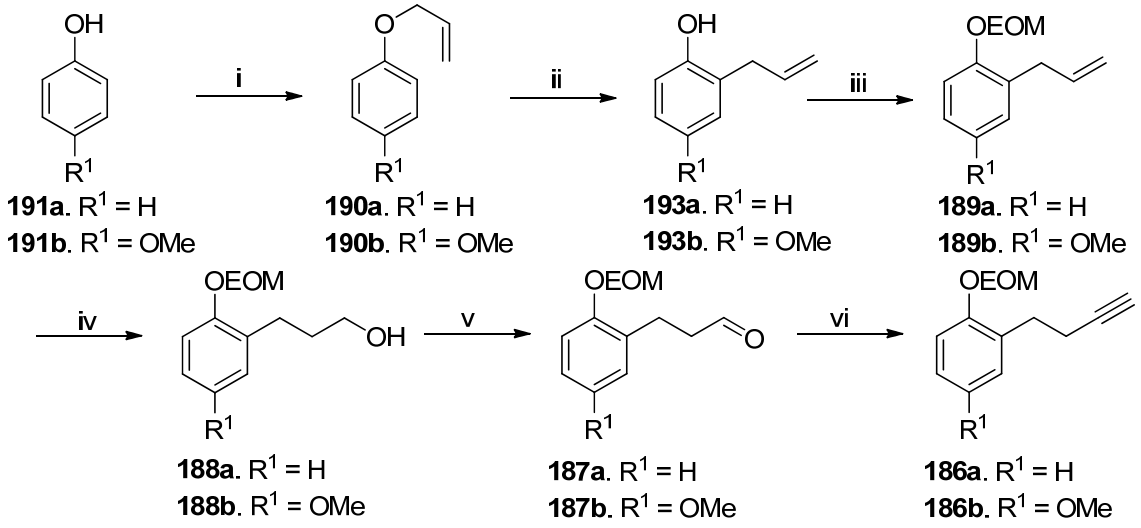
Aldehydes **185a**, **185b** and **185c** could be prepared by *tert*-butyldimethylsilyl chloride protection of the readily available salicylaldehydes **192** (Scheme 34).



Scheme 34. Retrosynthesis of aldehydes **185a, 185b, 185c**.

2.3 Synthesis of Aryl Acetylenes 186a and 186b

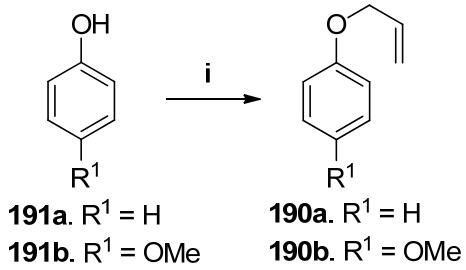
The general synthesis of the aryl acetylene **186** is outlined in Scheme 35.



Reagents and Conditions: i. allyl bromide, K_2CO_3, acetone, reflux, **190a**, 97%; **190b**, 92%; ii. neat, microwave, 210 °C, 300 W, **193a**, 92%; **193b**, 90%; iii. ethoxymethyl chloride, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, **189a**, 85%; **189b**, 86%; iv. $BH_3{\cdot}SMe_2$, NaOH, H_2O_2, **188a**, 81%; **188b**, 80%; v. IBX, DMSO, **187a**, 84%; **187b**, 78%; vi. diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, **186a**, 94%; **186b**, 90%.

Scheme 35. Synthesis of aryl acetylenes **186a** and **186b**.

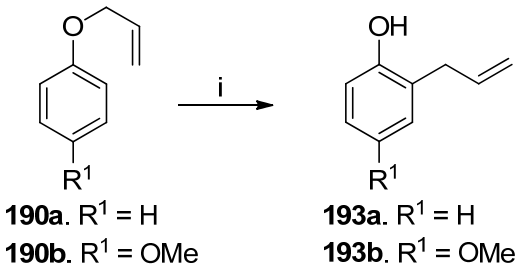
The first step in the reaction sequence involved simple allylation of phenols **191a** and **191b** with allyl bromide to give allyl ethers **190a** and **190b** (Scheme 36). The phenols **191a** and **191b** were heated with allyl bromide and potassium carbonate in acetone under reflux at 65 ^{o}C overnight. After workup the resulting yellow oil was purified by flash chromatography affording the desired product in 97% and 92% yields respectively. The ^{1}H NMR spectra of the isolated products indicated the successful formation of allyl ethers **190a** and **190b** with the OCH_2 protons resonating as a doublet at δ 4.49. The ^{1}H NMR spectra were in agreement with the literature.[52]



Reagents and Conditions: i. allyl bromide, K_2CO_3, acetone, reflux, **190a**, 97%; **190b**, 92%.

Scheme 36. Allylation of phenols **191a** and **191b**.

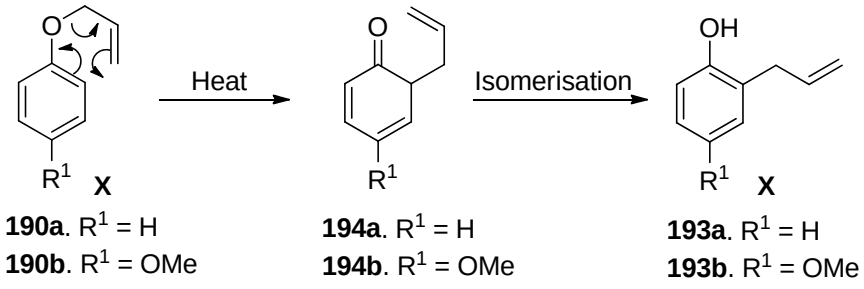
Allyl ethers **190a** and **190b** were then subjected to Claisen rearrangement under microwave conditions at 250 °C and 250 W to afford 2-allylphenols **193a** and **193b** in 92% and 90% yields respectively (Scheme 37).



Reagents and Conditions: i. neat, microwave, 250 °C, 250 W, **193a**, 92%; **193b**, 90%.

Scheme 37. Claisen rearrangement of phenyl allyl ethers **190a** and **190b**.

This is a classical example of the Claisen rearrangement, one of the first recorded examples of a [3,3]-sigmatropic rearrangement (Scheme 38). Allyl ether **190** was in fact the model compound which formed the basis for the discovery of this important reaction that was described by Rainer Ludwig Claisen in 1912.[53]

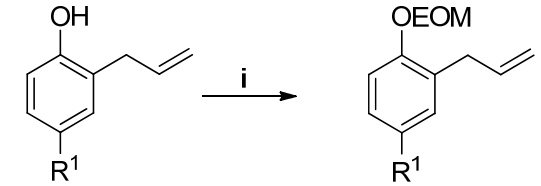


Scheme 38. Mechanism of the Claisen rearrangement of phenyl allyl ethers **190a** and **190b**.

Previous methods for effecting this Claisen rearrangement[53] involved heating neat phenyl allyl ethers **190a** and **190b** under reflux using a sand bath as heat source for 6 hours under argon. This procedure afforded the 2-allylphenols **193a** and **193b** as brown oils that were purified by flash chromatography to afford colourless oils.

The use of a CEM microwave reactor resulted in higher yields for the conversion of **190** to **193** being obtained with shorter reaction times and no side products being observed. Phenyl allyl ethers **190a** and **190b** were dissolved in dimethylformamide and irradiated in a CEM microwave reactor at 250 W and 250 ^{o}C for 30 min. The reaction was monitored by TLC and if the reaction was incomplete the reaction was heated for a further 15 min in the microwave. Subsequent removal of dimethylformamide from the reaction mixture was problematic. The products **193a** and **193b** were purified by distillation under reduced pressure at 2 mm Hg. The dimethylformamide was removed in the first fraction then the reactants **190a** and **190b** were distilled at 40 ^{o}C and finally the desired products **193a** and **193b** at 68 ^{o}C. The optimum rearrangement was carried out using 0.7 mL of phenyl allyl ether in 2 mL of dimethylformamide. The ^{1}H NMR spectra of the products **193a** and **193b** obtained established the presence of the newly introduced OH group as a broad singlet and the spectroscopic data were in agreement with the literature.[54]

The Claisen products **193a** and **193b** were then protected as ethoxymethoxy (EOM) ether derivatives **189a** and **189b** by treatment with diisopropylethylamine and ethoxymethoxy chloride in dichloromethane at 0 ^{o}C (Scheme 18). The protected phenols **189a** and **189b** were obtained as yellow oils after purification by flash chromatography.



193a. R^1 = H
193b. R^1 = OMe

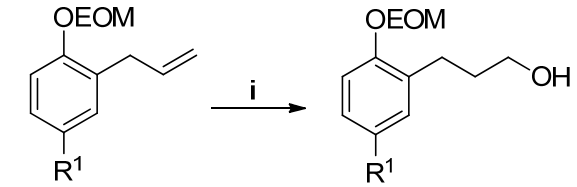
189a. R^1 = H
189b. R^1 = OMe

Reagents and Conditions: i. ethoxymethyl chloride, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, **189a**, 85%; **189b**, 86%.

Scheme 39. Protection of the Claisen products **193a** and **193b**.

The next step in the synthesis required hydroboration of allyl phenols **189a** and **189b** to primary alcohols **188a** and **188b** (Scheme 40).

Borane-dimethylsulfide complex was added to a cooled solution (0 ^{o}C) of the protected allyl phenols **189a** and **189b** in tetrahydrofuran. The reaction mixture was stirred at 0 ^{o}C for 5 hours then the reaction was warmed to room temperature and subjected to an oxidative work-up using sodium hydroxide and hydrogen peroxide. Slow addition of the reagents was required in order to minimise the exothermic process. The desired alcohols **188a** and **188b** were obtained in 81% and 80% yield respectively after purification by flash chromatography.



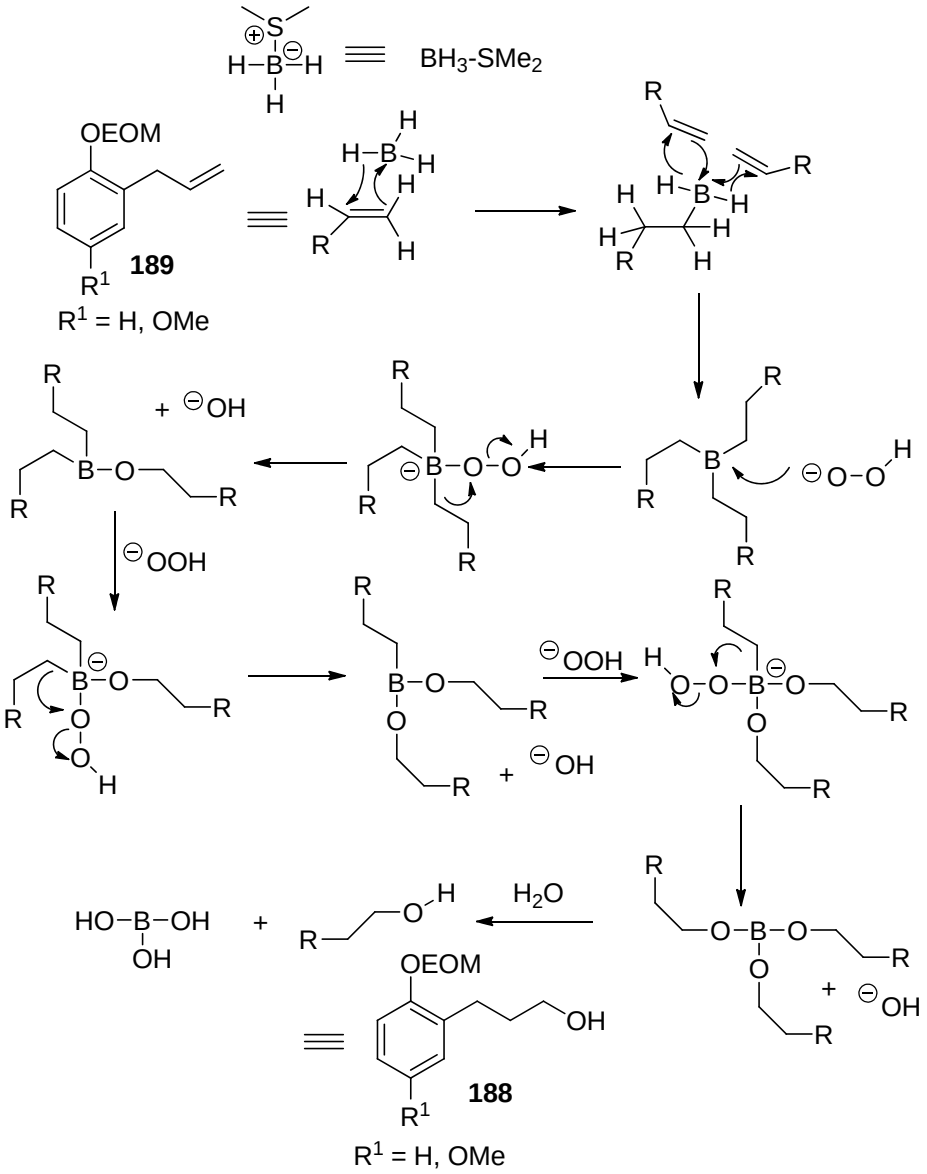
189a. R^1 = H
189b. R^1 = OMe

188a. R^1 = H
188b. R^1 = OMe

Reagents and Conditions: i. BH_3·SMe_2, NaOH, H_2O_2, **188a**, 81%; **188b**, 80%.

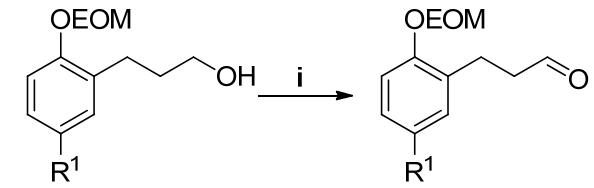
Scheme 40. Hydroboration of the allyl phenols **189a** and **189b**.

Borane-dimethylsulfide complex adds to allyl phenol **189** in a concerted reaction with bond forming and breaking occurring simultaneously (Scheme 41). Borane tends to add to the less substituted carbon as it is less sterically hindered. Once the borane was added to the double bond, the next step is the nucleophilic attack by hydroperoxide anion at the boron atom. Alkyl migration follows then aqueous workup gives the desired alchohol **188**.



Scheme 41. Mechanism for hydroboration of allyl phenols **189a** and **189b**.

The next step was the oxidation of alcohols **188a** and **188b** to aldehydes **187a** and **187b** (Scheme 42). By screening several oxidation methods for the oxidation of alcohol **188a** to aldehyde **187a**, it was established that use of 2-iodoxybenzoic acid[55] in dimethylsulfoxide was the best procedure of choice for effective oxidation of alcohols **188a** and **188b** to aldehydes **187a** and **187b** (Table 3).



188a. R^1 = H
188b. R^1 = OMe

187a. R^1 = H
187b. R^1 = OMe

Reagents and Conditions: i. IBX, DMSO, 50 °C, 30 min, **187a**, 84%; **187b**, 78%.

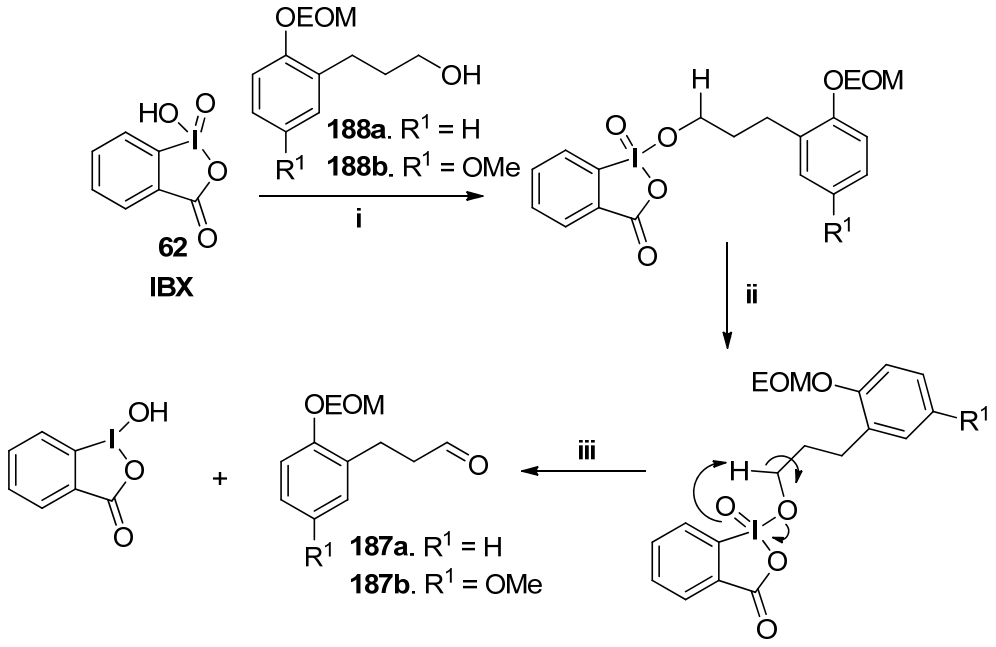
Scheme 42. Oxidation of primary alcohols **188a** and **188b**.

Entry	Reagents and Conditions	Yield of 187a (%)
1	TPAP, NMO, 4Å MS, CH_2Cl_2, r.t., 1 h.	30 - 64%
2	PCC, Celite®, CH_2Cl_2, r.t., 1 h.	78%
3	Dess-Martin periodinane, CH_2Cl_2, r.t., 1 h.	72%
4	**IBX, DMSO, 50 °C, 30 min**	**84%**

Table 3. Various oxidation methods screened on alcohol **188a**.

The reaction mechanism for IBX oxidation of alcohol **188** to aldehyde **187** proceeds via a hypervalent twisting mechanism.[56] This mechanism involves a ligand exchange replacing the hydroxyl group by alcohol **188** followed by the hypervalent twist and an elimination reaction to give the desired aldehyde **187** (Scheme 43). The hypervalent twist is a rearrangement in which the oxygen atom is moved into the correct plane to establish a 5 membered cyclic transition state required for the elimination reaction. Su *et al*.[56] report that the adoption of the twist conformation is a requirement as the iodine-oxygen double bond would otherwise orient

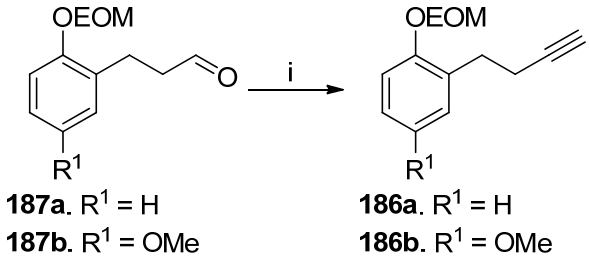
in and out of plane conformation with respect to the alkoxy group and the concerted elimination step would not proceed.



Scheme 43. IBX oxidation mechanism; i. ligand exchange reaction; ii. hypervalent twist; iii. elimination

After stirring the reaction for 30 min, TLC analysis indicated complete conversion of alcohols **188a** and **188b** to aldehydes **187a** and **187b**. The aldehyde was easily identified by the characteristic aldehyde proton that resonated as a triplet at δ_H 9.50 ~ 10.0 (*J* 1.5 Hz) ppm in the ^{1}H-NMR spectrum.

The final step for the synthesis of acetylenes **186a** and **186b** involves use of the Ohira-Bestmann modification[50] of the Seyferth-Gilbert homologation[51] to convert aldehydes **187a** and **187b** to acetylenes **186a** and **186b** (Scheme 44).



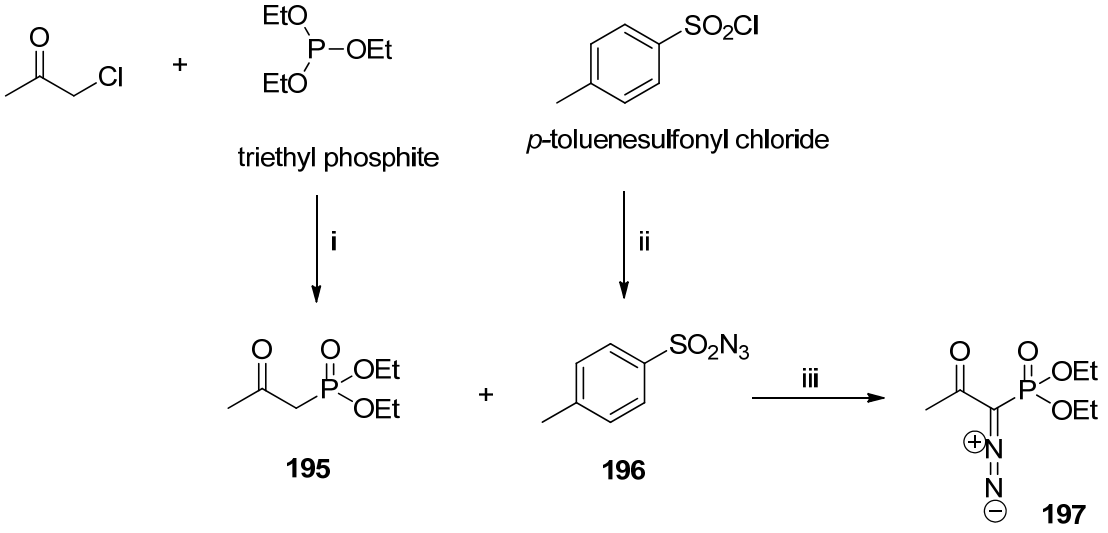
187a. R^1 = H
187b. R^1 = OMe

186a. R^1 = H
186b. R^1 = OMe

Reagents and Conditions: i. diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, **186a**, 94%; **186b**, 90%.

Scheme 44. Conversion of aldehydes **187a** and **187b** to acetylenes **186a** and **186b**.

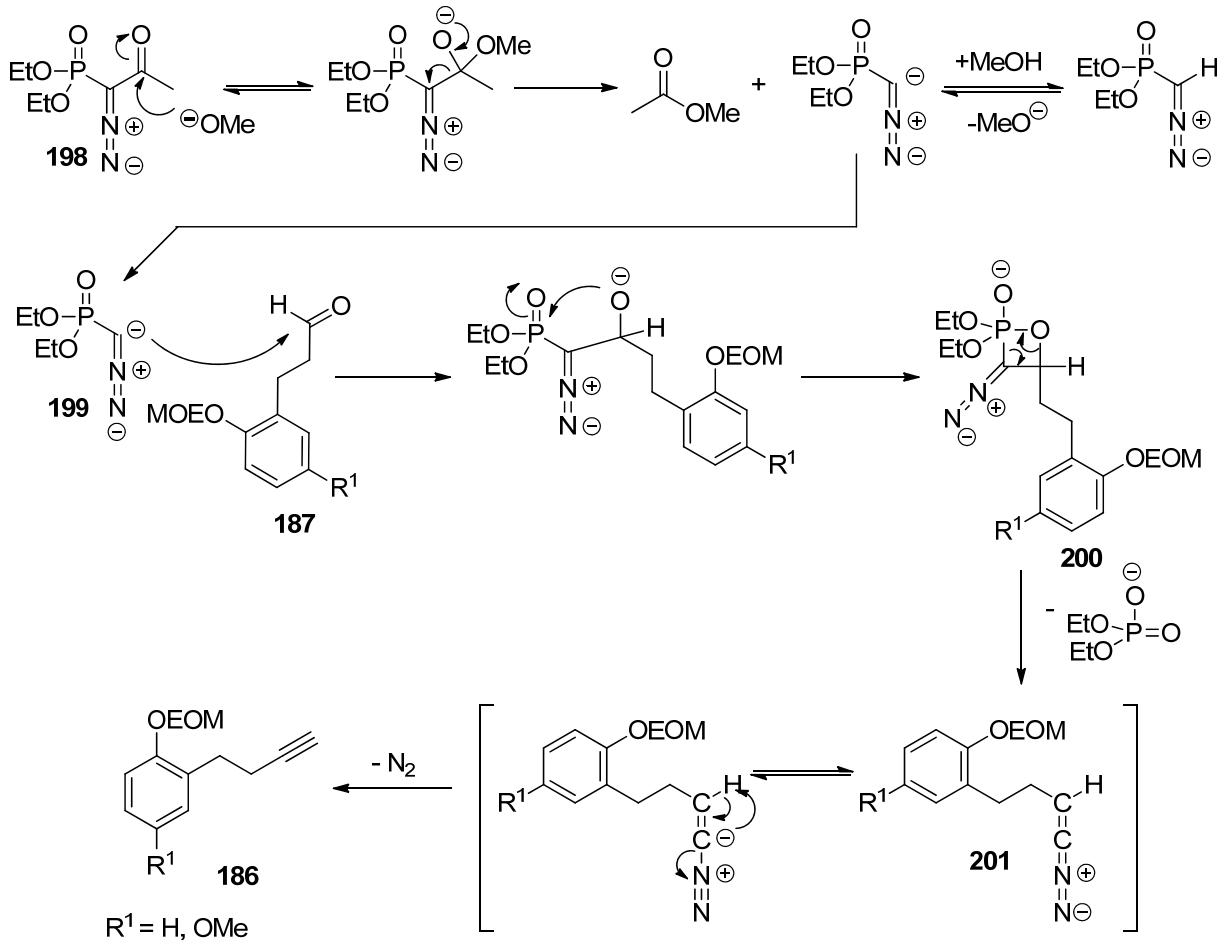
Using the conditions developed by Bestmann *et al.,*[50] aldehydes **187a** and **187b** were reacted with diethyl 1-diazo-2-oxopropylphosphonate **197** and potassium carbonate in methanol. Diethyl 1-diazo-2-oxopropylphosphonate **197** was not commercially available therefore was prepared following a three step literature procedure (Scheme 45).[57-59]



Reagents and Conditions: i. KI, acetone-MeCN, r.t., 6 h then 50 °C, 4 h, 73%; ii. NaN_3, ethanol, r.t., 2.5 h, 91%; iii. NaH, benzene-THF, 0 °C → r.t., 2 h, 97%.

Scheme 45. Preparation of diethyl 1-diazo-2-oxopropylphosphonate **197**.

In the Ohira-Bestmann procedure, the first step is the deacylation of dialkyl 1-diazo-2-oxopropylphosphonate **198** by methoxide ion (Scheme 46). The resulting carbanion; dimethyl (diazomethyl)phosphonate **199**, attacks the carbonyl group of aldehyde **187** and an oxaphosphetane-type intermediate **200** is formed which breaks down to afford a thermally unstable diazoalkene **201**. The diazoalkene **201** loses dinitrogen *via* α-elimination and undergoes a 1,2-shift to give acetylene **186**.



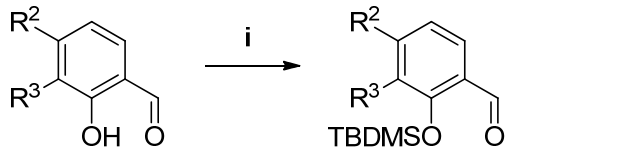
Scheme 46. Formation of acetylene **186** using dialkyl 1-diazo-2-oxopropylphosphonate **198**.

Use of this reagent to effect alkynylation of aldehydes **187a** and **187b** gave the desired acetylenes **186a** and **186b** in 94% and 90% yield respectively after work up and chromatography. Having prepared acetylenes **186a** and **186b**, attention next turned to the

synthesis of aldehydes **185a-185c** that were the coupling partners in the subsequent acetylide anion addition step.

2.4 Synthesis of Aldehyde 185

The synthesis of TBDMS protected aldehydes **185a-185c** is outlined in Scheme 47. Salicylaldehydes **192a-192c** were protected using TBDMS chloride in dichloromethane with imidazole and DMAP. Purification by flash column chromatography gave the desired protected aldehydes **185a-185c** in high yields.



192a. R^2 = H; R^3 = H
192b. R^2 = OMe; R^3 = H
192c. R^2 = H; R^3 = OMe

185a. R^2 = H; R^3 = H
185b. R^2 = OMe; R^3 = H
185c. R^2 = H; R^3 = OMe

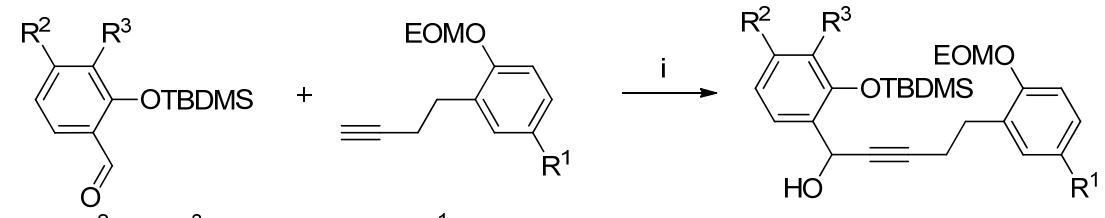
Reagents and Conditions: i. TBDMSCl, imidazole, DMAP, CH_2Cl_2, **185a**, 85%; **185b**, 88%; **185c**, 90%.

Scheme 47. Protection of salicylaldehydes **192a-192c**.

2.5 Synthesis of 6,6-Bisbenzannulated Spiroketal Analogues 183a-183e

With both acetylenes **186a** and **186b** and aldehydes **185a-185c** in hand, the next step involved coupling these two subunits to construct the carbon framework required for spirocyclisation. The coupling step involved treatment of the acetylene fragment with *n*-butyllithium at -78 °C to generate the acetylide anion. After 40 minutes the solution turned light yellow suggesting formation of the acetylide anion and the electrophilic aldehydes **185a-185c** were then added dropwise as a solution in tetrahydrofuran. The solution turned dark yellow after the addition of aldehyde then changed to orange/red solution when the reaction was warmed to room

temperature. Aqueous workup followed by flash chromatography gave the desired alkynols **202a-202e** in pleasing yields ranging from 71%-82% (Table 4). The structure of the coupled product was confirmed by the lack of an acetylene proton at ~δ_H 1.95 ppm in the ^{1}H NMR spectrum and the formation of two quaternary alkyne resonances in the ^{13}C NMR spectrum at ~δ_C 80.1ppm and ~δ_C 85.9 ppm. The structure was further confirmed by the broad OH stretch at 3440-3450 cm^{-1}.



185a. R^2 = H; R^3 = H
185b. R^2 = OMe; R^3 = H
185c. R^2 = H; R^3 = OMe

186a. R^1 = H
186b. R^1 = OMe

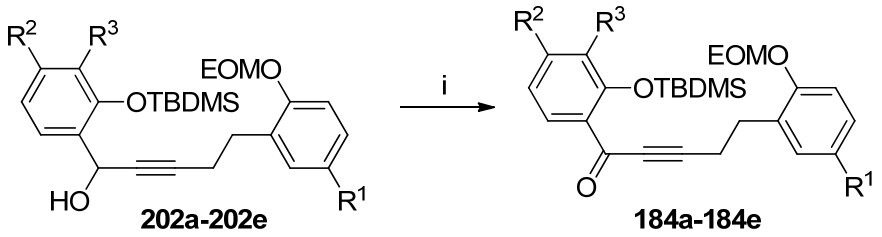
202a-202e

Reagents and Conditions: i. *n*-BuLi, THF, -78 °C to r.t.

Product	R^1	R^2	R^3	Yield (%)
202a	H	H	H	71%
202b	H	OMe	H	75%
202c	OMe	OMe	H	78%
202d	OMe	H	H	82%
202e	H	H	OMe	81%

Table 4. Acetylide anion addition of acetylenes **186a**, **186b** to aldehydes **185a-185c**.

Oxidation of the secondary alcohols **202a-202e** to the desired ynones **184a-184e** was achieved using 2-iodoxybenzoic acid in dimethylsulfoxide. A solution of alcohols **202a-202e** in dimethylsulfoxide was added to a solution of 2-iodoxybenzoic acid in dimethylsulfoxide and the mixture stirred at 50 °C for 30 minutes (Table 5).



202a-202e **184a-184e**

Reagents and Conditions: i. IBX, DMSO, 50 °C, 30 min

Reactant	Product	R^1	R^2	R^3	Yield (%)
202a	**184a**	H	H	H	87%
202b	**184b**	H	OMe	H	88%
202c	**184c**	OMe	OMe	H	78%
202d	**184d**	OMe	H	H	82%
202e	**184e**	H	H	OMe	84%

Table 5. Oxidation of alcohols **202a-202e** to ynones **184a-184e** using IBX.

The IBX oxidation produced the desired ynones **184a-184e** in good yields ranging from 78% to 88%. With the ynones **184a-184e** in hand, attention turned to the key DIHMA step.

2.5.1 The Double Intramolecular Hetero-Michael Addition (DIHMA) Cyclisation

2.5.1.1 Background to DIHMA Cyclisation

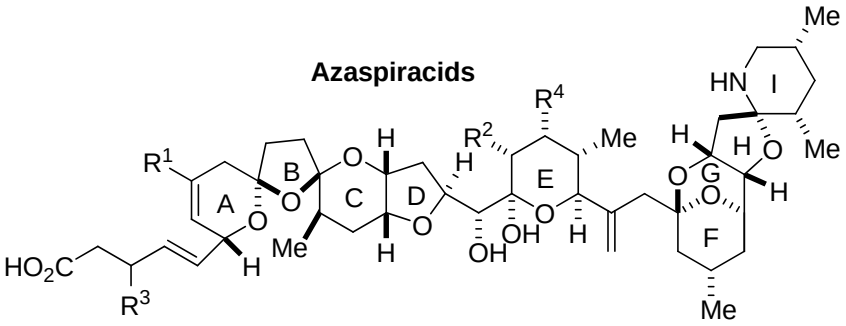
Spiroketals are important subunits present in a broad range of bioactive natural products and are considered a 'privileged scaffold' for drug discovery programs.[8] Synthesis of this unique functionality typically involves dehydrative spirocyclisation. However there have been a few previous syntheses of aliphatic spiroketals using a novel DIHMA strategy. This involves a double conjugate addition of a diol to a ynone system to give a spiroketal ring system with the nature of the ring-closure reactions being dictated by Baldwin's rules.[60] Compared to the typical dehydrative spirocyclisations, spiroketal synthesis via DIHMA strategies has potential advantages in that; 1) the liberation of diols from their masked forms may be integrated into the bis-conjugate addition step by the well-planned choice of the protecting groups and deprotection conditions; and 2) the residual carbonyl functionality on the spiroketal rings can serve as a versatile synthetic handle for further manipulations.

2.5.1.2 Previous Syntheses using DIHMA Strategy

There have been several previous syntheses of spiroketal moieties in natural products using the DIHMA strategy. The crucial DIHMA step will be described in detail.

A. Synthesis of the F-G ring System of the Azaspiracids by Forsyth *et al.*[61]

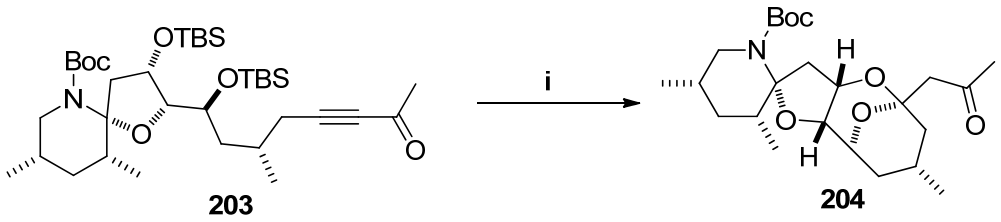
Forsyth *et al*.[61] have elegantly utilised a DIHMA strategy to synthesise various fragments of the azaspiracids (Figure 17).[61-64]



Name	R^1	R^2	R^3	R^4
Aza-1	H	Me	H	H
Aza-2	Me	Me	H	H
Aza-3	H	H	H	H
Aza-4	H	H	OH	H
Aza-5	H	H	H	OH
Aza-6	Me	H	H	H
Aza-7	H	Me	OH	H
Aza-8	H	Me	H	OH
Aza-9	Me	H	OH	H
Aza-10	Me	H	H	OH
Aza-11	Me	Me	OH	H

Figure 17. Structures of the azaspiracids family

The use of DIHMA strategy for the synthesis of the fully functionalised 2,9-dioxabicyclo[3.3.1]nonane system **204** representing the substituted F and G rings of the azaspiracids was established using a TBAF-induced *in situ* desilylation-bis-conjugate addition of **203** (Scheme 48).[61]

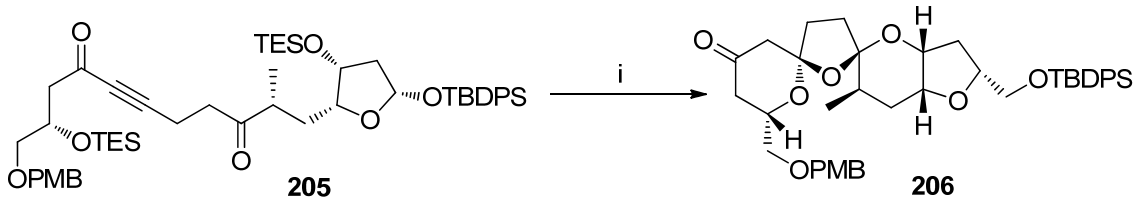


Reagents and Conditions: i. TBAF, THF, r.t., 85%.

Scheme 48. Formation of the F-G ring system of azaspiracid by DIHMA.

B. Synthesis of the Trioxadispiroketal of Azaspiracid-1 by Forsyth *et al.*[63]

Use of DIHMA process was also applied in the synthesis of the trioxadispiroketal system of azaspiracid-1 by Forsyth *et al*.[63] (Scheme 49). *p*-Toluenesulfonic acid-water in toluene was added to ynone **205** at room temperature for 1-2 days giving the desired spiroketal **206** in moderate yield.

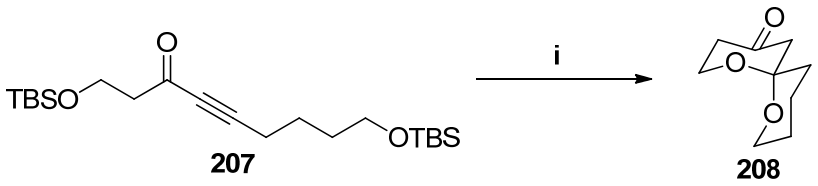


Reagents and Conditions: i. *p*-TsOH-H_2O, toluene, 55%.

Scheme 49. Formation of trioxadispiroketal of azaspiracid-1 by DIHMA.

C. Synthesis of the Spiroketal Core of *Dacus oleae* Olive Fly Pheromone by Forsyth *et al.*[65]

Forsyth *et al*.[65] have also utilised the DIHMA process in the synthesis of the spiroketal motif present in (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]undecane **208**, a *Dacus oleae* olive fly pheromone (Scheme 50). Treatment of ynone **207** with camphorsulfonic acid in methanol and subsequent solvent exchange from methanol to benzene promoted the key DIHMA.

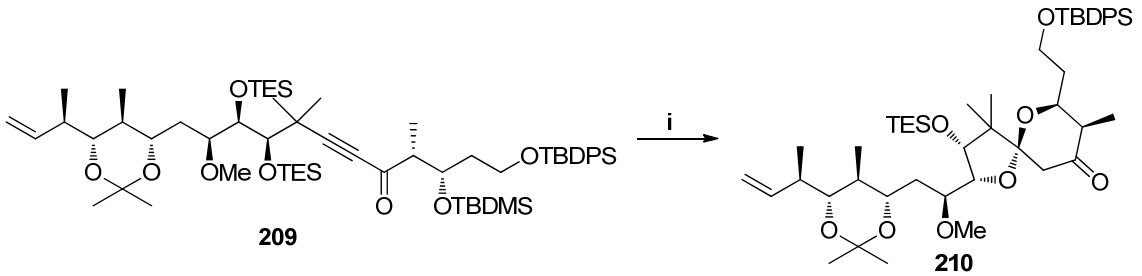


Reagents and Conditions: i. CSA, MeOH then benzene, 70%

Scheme 50. Formation of spiroketal of (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]undecane **208** by DIHMA.

D. Synthesis of the Spiroketal Core of Calyculins by Koskinen *et al.*[66-69]

Koskinen *et al.*[66-69] reported a rapid route to spiroketal core of calyculins based on the use of DIHMA protocol (Scheme 51). Addition of camphorsulfonic acid in methanol to precursor **209** cleaved the *tert*-butyldimethylsilyl protecting groups which resulted in some spirocyclisation taking place. In order to drive the reaction to completion, the solvent was removed and replaced with toluene then *p*-toluenesulfonic acid was added to give the desired spiroketal **210**.

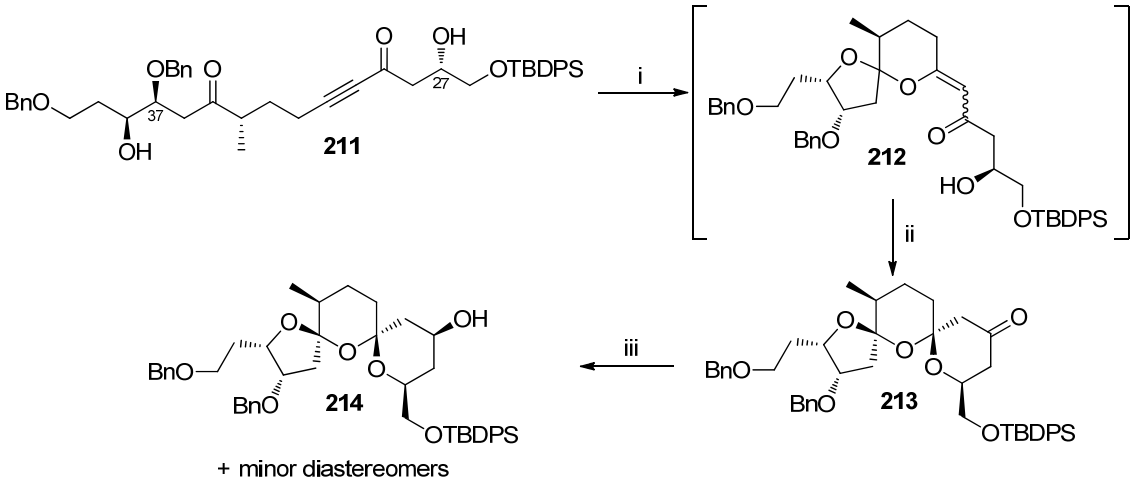


Reagents and Conditions: i. a. (+)-CSA, MeOH, CH_2Cl_2, r.t., 2 h; b. *p*-TsOH, toluene, r.t., 3.5 h, 47% overall.

Scheme 51. Formation of the spiroketal core of calyculins by DIHMA.

E. Synthesis of the Trioxadispiroketal Core of Spirastrellolide by Forsyth *et al.*[70, 71]

Forsyth *et al.*[70, 71] have also used a DIHMA process to assemble the trioxadispiroketal core system of spirastrellolide A and B (Scheme 52).



Reagents and Conditions: i. *t*-BuOK, -15 °C, THF: *t*-BuOH (10:1), 20 min; ii. CSA, benzene, 1 h; iii. $NaBH_4$, MeOH, 20 min, 50% overall.

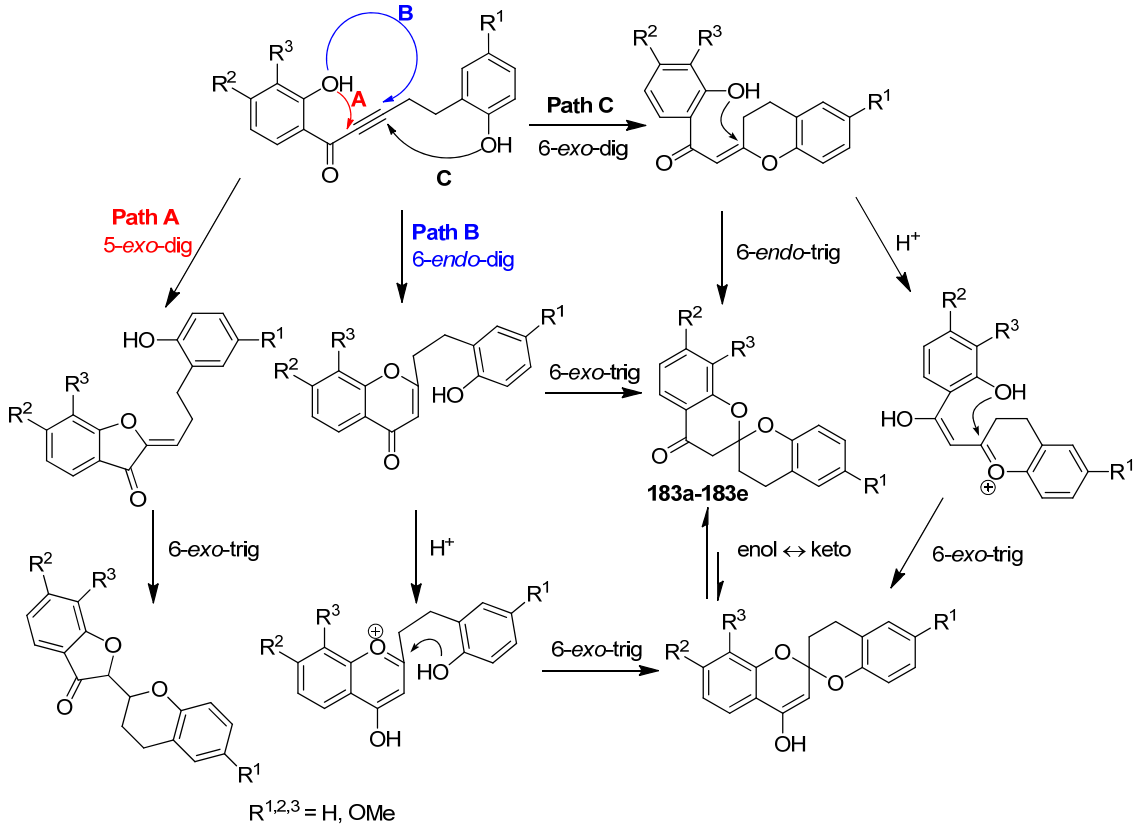
Scheme 52. Formation of trioxadispiroketal core of spirastrellolide A and B by DIHMA.

Basic conditions were utilised to cyclise diol **211**. Upon treatment of **211** with potassium *tert*-butoxide, a single hetero-Michael addition occurred to form spiroketal intermediate **212**. This occurred without elimination of either the C27 or C37 oxygen groups. Efficient execution of the second hetero-Michael addition required use of acidic conditions. Treatment of intermediate **212** with camphorsulfonic acid in benzene, afforded the second spiroketal **213**. However, isolation of **213** was challenging due to its instability on silica gel due to a retro-Michael reaction occurring. This problem was solved by reducing the crude ketone **213** to alcohol **214** which was isolated in moderate overall yield.

All of the literature examples indicate that the DIHMA protocol can be successfully applied to prepare aliphatic systems. Although the feasibility of the DIHMA on aromatic systems was uncertain, it was nevertheless decided to apply the DIHMA protocol to ynones **184a-184e** as a potential method to form the desired 6,6-bisbenzannulated spiroketals **183a-183e**.

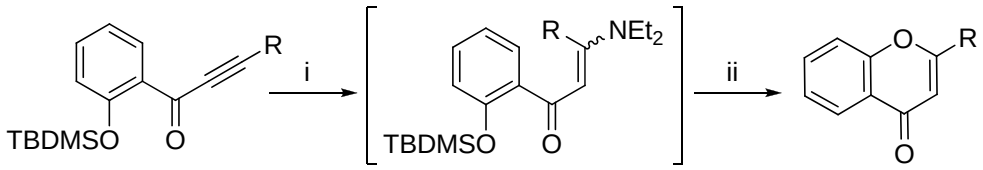
2.5.2 Formation of Benzopyrone 215

With ynones **184a-184e** in hand, the DIHMA cyclisation was next examined. There are several possible mechanisms for the formation of 6,6-spiroketals **183a-183e** from ynones **184a-184e** using a DIHMA cyclisation. This reaction can be rationalised by applying Baldwin's rules[72] and some of the favoured pathways for spiroketal formation are summarised in Scheme 53.



Scheme 53. Possible pathways for DIHMA cyclisation.

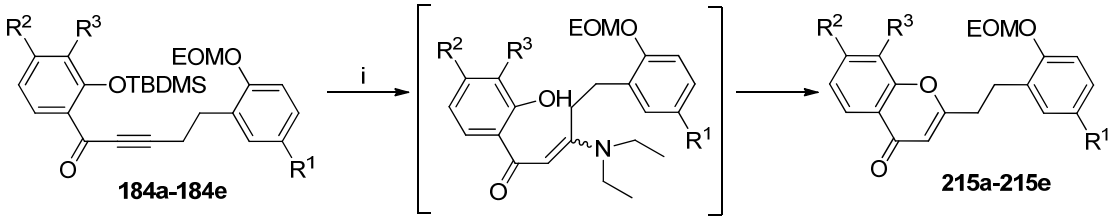
Brueggemeier *et al.*[73] reported an efficient novel synthetic route to a benzopyrone involving conversion of an alkynone to an enaminoketone and subsequent cyclisation in a single step (Scheme 54).



Reagents and Conditions: i. Et_2NH, EtOH, r.t., 30 min; ii. Excess Et_2NH, EtOH, 80 °C (96% over two steps).

Scheme 54. Cyclisation using Et_2NH by Brueggemeier *et al.*[73]

By allowing enaminoketone intermediate to form from addition of diethylamine to ynones **184a-184e**, the competitive 5-*exo*-dig cyclisation pathway (Path A) is effectively eliminated thus promoting the desired 6-*endo*-dig pathway (Path B) leading to the formation of the desired benzopyrone intermediates **215a-215e** via an addition–elimination sequence (Table 6).



Reagents and Conditions: i. excess Et_2NH, CH_2Cl_2, reflux, 16 h.

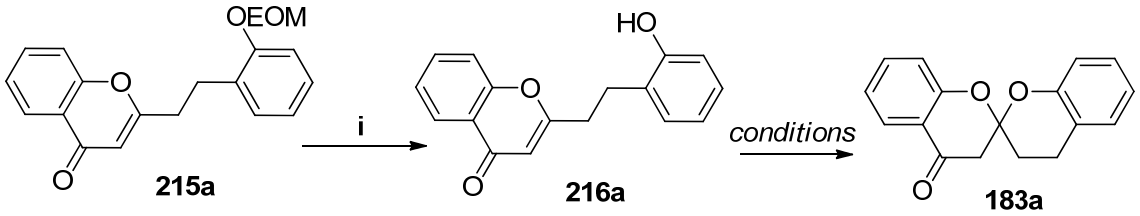
Reactant	Product	R^1	R^2	R^3	Yield (%)
184a	**215a**	H	H	H	97%
184b	**215b**	H	OMe	H	92%
184c	**215c**	OMe	OMe	H	95%
184d	**215d**	OMe	H	H	92%
184e	**215e**	H	H	OMe	92%

Table 6. Cyclisation using Et_2NH.

Addition of diethylamine to a solution of ynones **184a-184e** in dichloromethane led to the deprotection of the TBDMS group with concomitant formation of the isolable enamino-ketone intermediate after 30 min at room temperature. The crude enamino-ketones were then heated under reflux for 16 h, resulting in formation of the desired benzopyrones **215a-215e** in excellent yields. The structure of benzopyrones **215a-215e** were confirmed from the respective ^{1}H NMR spectra by the presence of a vinylic proton that resonated as a singlet at ca. δ_H 6.20 ppm and by the lack of methyl group protons due to the silyl protecting group. With benzopyrone precursors **215a-215e** in hand, the stage was set for the second hetero-Michael addition spirocyclisation step.

2.5.3 Synthesis of 6,6-Bisbenzannulated Spiroketal 183a from Benzopyrone 215a

Spirocyclisation of benzopyrones **215a-215e** to form spiroketals **183a-183e** was next investigated. Initial investigation focused on the formation of spiroketal **183a** from benzopyrone **215a**. The first step required removal of the EOM group with carbon tetrabromide in isopropanol[74] which gave the deprotected benzopyrone **216a** in 97% yield. Next, various conditions were investigated to encourage the second hetero-Michael addition to proceed (Table 7).



Reagents and Conditions: i. CBr_4, ^{i}PrOH, 97%.

Entry	Reagent	Solvent	Conditions	Yield (%)
1	*p*-TsOH	CH_2Cl_2	r.t., 4 h then 45 °C, 10 h	No reaction

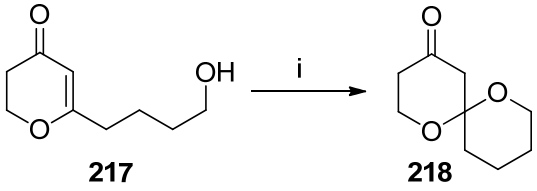
2	CSA	CH_2Cl_2	r.t., 4 h then 45 °C, 10 h	No reaction
3	Neutral Al_2O_3	CCl_4	r.t., 16 h	15
4	Neutral Al_2O_3	CCl_4	65 °C, 16 h	<10
5	Silica gel	CCl_4	r.t., 4 h	<10
6	DOWEX®	CCl_4	r.t., 4 h	<10
7	K_2CO_3	Acetone	120 °C, 0.5 h, conventional heating	No reaction
8	NaH	DMF	0 °C, 3 h then 65 °C, 3 h	No reaction
9	LDA	THF	-78 °C, 3 h	No reaction
10	KHMDS	THF	-78 °C, 3 h	No reaction
11	**K_2CO_3**	**None**	**120 °C, 0.5 h, microwave (300 W)**	**62**

Table 7. Various base conditions attempted to promote cyclisation.

With many research groups reporting positive results involving the use of *p*-toluenesulfonic acid to promote the cyclisation of the stepwise hetero-Micheal additions in related systems,[60, 63, 69, 75] it was decided to employ the condition. The first attempt at spirocyclisation was carried out by treating deprotected benzopyrone **216a** with *p*-toluenesulfonic acid in dichloromethane at room temperature (Entry 1). With no signs of product formation even after 4 h, the reaction was heated at 45 °C for further 10 h. However, no reaction took place and only benzopyrone **216a** was recovered.

The next reagent to be screened was camphorsulfonic acid which was also known to effect successful DIHMA's to give desired spiroketals.[65] Benzopyrone **216a** in dichloromethane was added to camphorsulfonic acid at room temperature and the mixture stirred for 4 h (Entry 2). Disappointingly, no reaction took place and increasing the temperature to 45 °C did not result in formation of any of the desired product.

Danishefsky *et al.*[76] carried out the successful spirocyclisation of a similar pyrone **217** using neutral alumina (Scheme 55). After unrewarding attempts to effect the cyclisation of pyrone **217** using strong acids, successful cyclisation was achieved by exposing pyrone **217** to neutral alumina in chloroform to afford spiroketal **218** in 80% yield.



217 **218**

Reagents and Conditions: i. neutral Al_2O_3, CCl_4, 80%.

Scheme 55. Spirocyclisation of pyrone **217** by Danishefsky *et al*.[76]

Thus, following the conditions used by Danishefsky *et al.*[76] it was decided to examine the use of neutral alumina to effect cyclisation of benzopyrone **216a**. Benzopyrone **216a** was stirred with neutral Al_2O_3 (5 g of Al_2O_3 per 1 mmol of **216a**) at room temperature (Entry 3). After 3 h, the desired spiroketal **183a** was observed by TLC. However the isolated yield was only 15 %. Prolonging the reaction time did not result in any improvement in yield. The reaction temperature was raised to 65 °C (Entry 4) but again no improvement in the yield obtained was observed. Encouraged by the formation of the desired spiroketal **183a**, albeit in low yield, it was decided to investigate the use of alternative solid surface reagents.

Benzopyrone **216a** was stirred with silica gel (5 g of silica per 1 mmol of **216a**) in chloroform at room temperature (Entry 5) affording the desired spiroketal **183a** in low yield. Similar yields were observed when benzopyrone **216a** was stirred with Dowex 50W-X8 in chloroform (Entry 6).

Given the lack of success employing acidic conditions to effect spirocyclisation, a report by Miranda *et al*.[77] came to our attention. The authors postulated that the actual cyclising species is the more nucleophilic phenolate anion rather than the free phenol thus requiring the use of basic conditions for the reaction to proceed. Adopting this idea, benzopyrone **216a** was heated under reflux in acetone at 120 °C with potassium carbonate (Entry 7). Disappointingly, no spiroketal **183a** was observed. Several other strong bases were also evaluated (Entries 8, 9, 10) however no reaction took place.

Microwave-assisted organic synthesis (MAOS) has attracted considerable interest in recent years.[78] The advantages of MAOS include reduced chemical reaction time, milder reaction conditions, increased yields and improved reproducibility. MAOS is even known to make reactions work that fail by conventional heating. These properties render microwave-assisted reactions very attractive hence we decided to apply this methodology to the present DIHMA. Powdered, oven dried, potassium carbonate was added to a solution of benzopyrone **216a** in dichloromethane (Entry 8). The solvent was removed *in vacuo* and the reaction mixture was placed in a CEM microwave reactor at 300 W for 30 min at 120 °C. To our delight, the desired spiroketal **183a** was afforded in a good 62% yield.

The structure of the spiroketal **183a** was confirmed by ^{1}H and ^{13}C NMR, IR and mass spectroscopy. The IR spectrum supported the loss of the phenolic OH group and the ^{13}C NMR spectra lacked the vinylic carbon at δ_C 109.8 ppm present in the starting material. A notable feature in the ^{13}C NMR spectum of the spiroketal **183a** was the presence of a characteristic quaternary spiro-centre at δ_C 100.8 ppm. In the ^{1}H NMR spectrum four sets of doublets of doublets of doublets were assigned to the diastereotopic protons of the 3′-CH_2 and 4′-CH_2 groups in the spiroketal ring system. The methylene protons assigned to 3-CH_2 resonated as a singlet at δ_H 3.06 ppm (Figure 18).

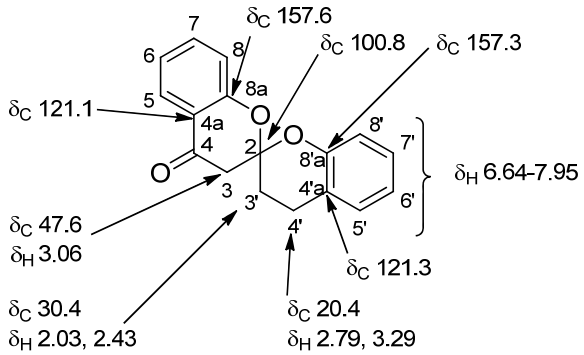
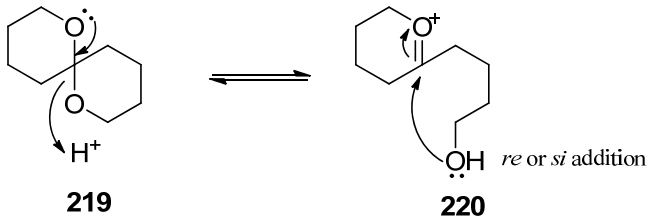


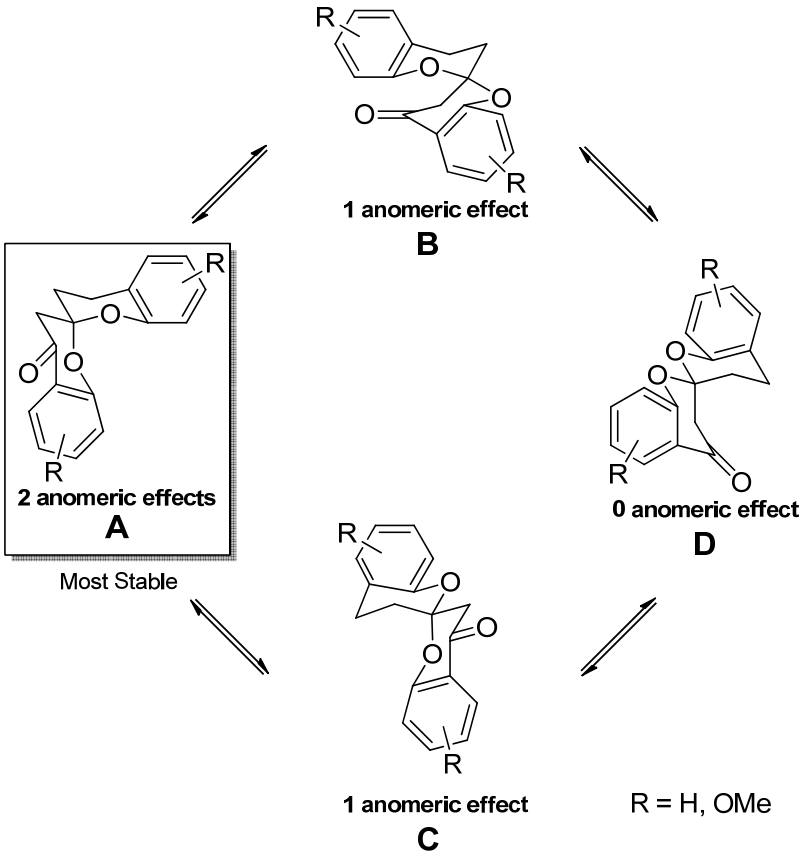
Figure 18. ^{1}H and ^{13}C NMR chemical shifts for 6,6-spiroketal **183a**.

2.6 Stereochemistry of the Unsubstituted Aryl Spiroketal Ring System



Scheme 56. Closed chain-open chain equilibria in 6,6-spiroketal **219**.

Under acidic conditions 6,6-spiroketals are in equilibrium with their open-chain keto-alcohol form. The final conformation of the spiroketal can be altered by ring opening to the open-chain form followed by reclosure of the hydroxyl group onto an oxonium ion from the opposite face (Scheme 56). This process leads to a number of possible conformers which are dependent on the steric and electronic effects and the reaction conditions. Scheme 57 outlines the four possible conformations of 6,6-bisbenzannulated spiroketals labelled **A, B, C, D**.[79,80]



Scheme 57. Equilibriums of 6,6-bisbenzannulated sprioketals.

In the case of simple unsubstituted 6,6-bisbenzannulated spiroketal successfully prepared in this research group, exclusive formation of conformation **A** was established[81] (Scheme 57). This was confirmed by the coupling patterns observed in the ^{1}H NMR spectrum and an X-ray crystal structure.[81]

Such preference for the bis-axial **A** conformation is well documented[79,80] for 6,6-spiroketal rings and is attributed to favourable stereoelectronic effects. Deslongchamps *et al.*[80] have postulated that the conformational stability is based on the number of anomerically stabilised bonds present in each conformer. The anomeric effect involves the stabilising overlap of an oxygen lone-pair and the σ*-orbital of an adjacent C-O bond. Maximum stability is achieved when the orbitals have an anti-periplanar relationship leading to the optimal symmetry for orbital interaction. Thus conformation **A** has two anomeric effects and is therefore the most

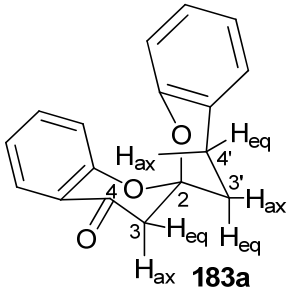
stable conformation whereas conformations **B** and **C** exhibiting only one anomeric effect are less favoured. Conformation **D**, possessing no anomeric effects, is the least favourable.

Based on the observed preference for the bis-axial conformation for 6,6-bisbenzannulated spiroketal[81] it was established that the presence of planar aromatic moieties does not affect the conformation of the central spiroketal ring.

2.7 Keto-substituted 6,6-Bisbenzannulated Spiroketal 183a

Deslongchamps *et al.*[80] also described the steric effects of the R substituents positioned on the spiroketal rings on the equilibria. It was established that substituted spiroketals will almost always exist solely in the bis-axial conformation **A** (Scheme 57) unless there are severe 1,3-diaxial steric interactions between the substituents and the core ring skeleton.[80] In the present work, the keto-substituent in spiroketal **183a** is planar in structure and with no other 1,3-diaxial steric interactions present, keto-substituted 6,6-bisbenzannulated spiroketal **183a** was predicted to adopt the thermodynamically favoured conformation **A** as depicted in Scheme 57.

Upon inspection of the ^{1}H NMR spectrum and the coupling patterns observed for the diastereotopic methylene protons in central spiroketal **183a**, (Table 8) it was concluded that keto-substituted 6,6-bisbenzannulated spiroketal did in fact adopt this flattened chair-chair bis-axial conformation.



183a

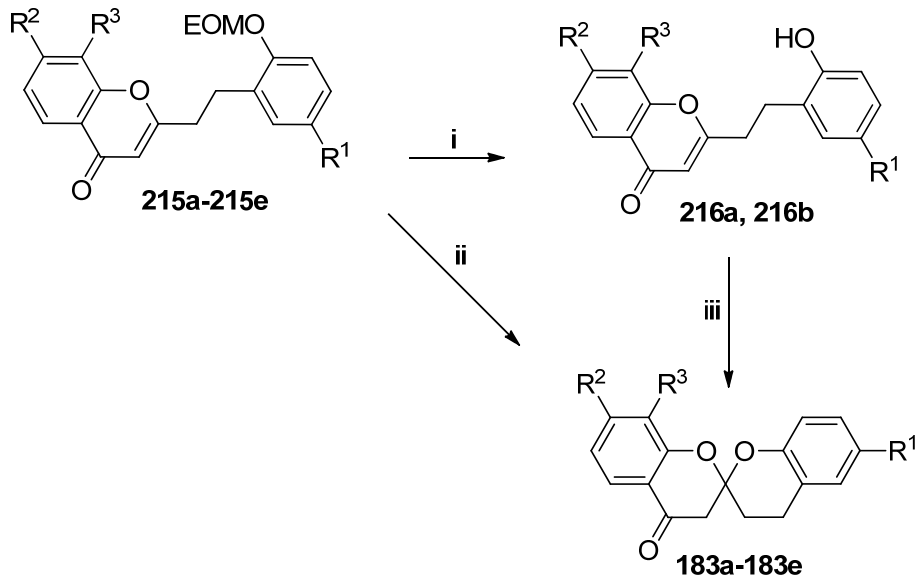
Assignment	Chemical shift (ppm)	Multiplicity	*J* values (Hz)
3′-H_{ax}	2.03	ddd	J_{gem} 13.6, $J_{3'ax,4'ax}$ 13.3, $J_{3'ax,4'eq}$ 6.1
3′-H_{eq}	2.43	ddd	J_{gem} 13.6, $J_{3'eq,4'ax}$ 6.1, $J_{3'eq,4'eq}$ 1.9
4′-H_{eq}	2.79	ddd	J_{gem} 16.4, $J_{4'eq,3'ax}$ 6.0, $J_{4'eq,3'eq}$ 1.9
4′-H_{ax}	3.29	ddd	J_{gem} 16.4, $J_{4'ax,3'ax}$ 13.3, $J_{4'ax,3'eq}$ 6.0
3-CH_2	3.06	s	-

Table 8. Diastereotopic methylene proton stereochemistry.

2.8 Synthesis of 6,6-Bisbenzannulated Spiroketals 183a-183e

After extensive experimentation, cyclisation of benzopyrone **216a** using microwave irradiation in the presence of potassium carbonate proved to be the most reliable method to effect spiroketal formation. This procedure was therefore similarly applied to benzopyrones **215b-215e** for the synthesis of 6,6-bisbenzannulated spiroketals **183b-183e**.

Benzopyrones **215c**, **215d**, and **215e** underwent smooth deprotection of the phenolic EOM ether with carbon tetrabromide in isopropanol[74] and to our surprise, underwent concomitant spirocyclisation affording spiroketals **183c**, **183d** and **183e** respectively, in a single step (Table 9). However, in the case of benzopyrone **215b**, the deprotected benzopyrone **216b** was isolated in 95% yield and was treated with potassium carbonate under microwave irradiation for 30 min at 120 °C, furnishing the desired spiroketal **183b** in 60% yield (57% over 2 steps).

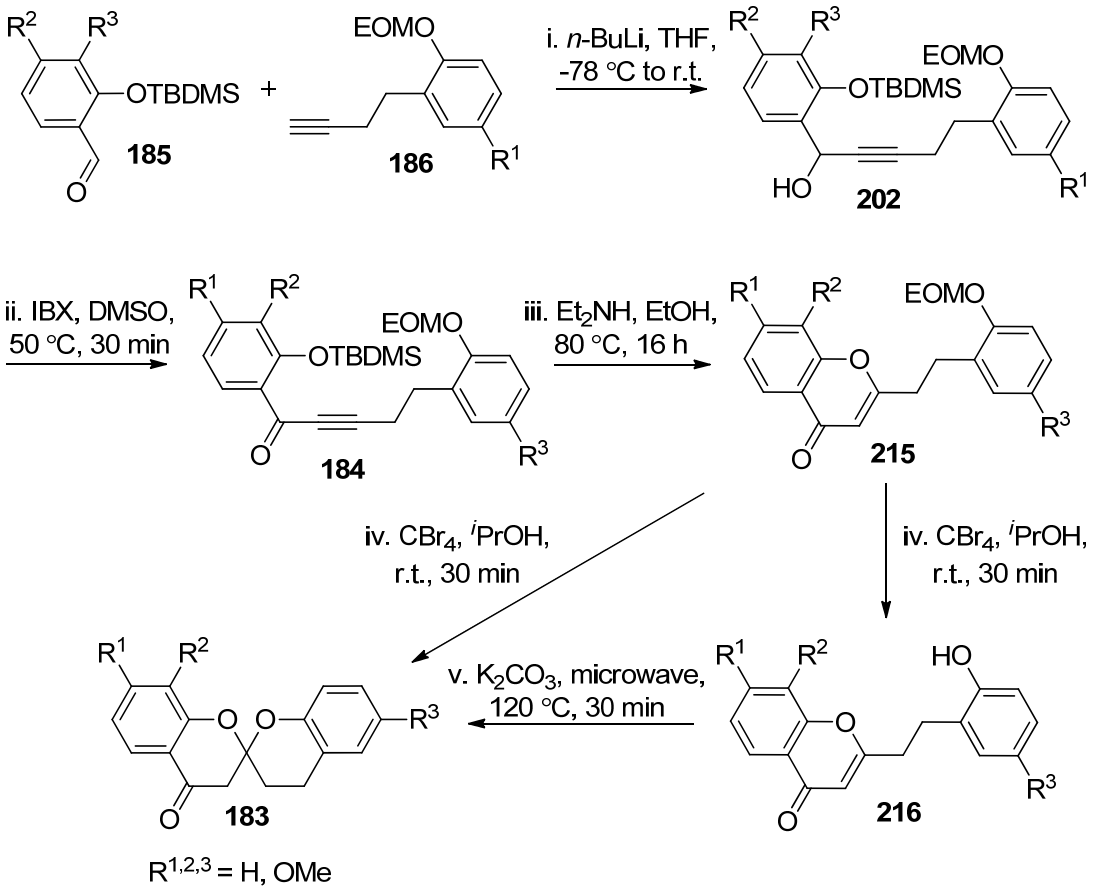


Reagents and Conditions: i. CBr_4, ^{i}PrOH, r.t., 30 min, **216a**, 97%; **216b**, 95%; ii. CBr_4, ^{i}PrOH, r.t., 30 min, **183c**, 54%; **183d**, 36%; **183e**, 64%; iii. K_2CO_3, microwave, 300 W, 120 °C, 30 min, **183a**, 62, **183b**, 60%.

Reactant	R^1	R^2	R^3	Benzopyrone 216, Yield	Spiroketal 183, Yield
215a	H	H	H	**216a**, 97% (i)	**183a**, 62% (iii)
215b	H	OMe	H	**216b**, 95% (i)	**183b**, 60% (iii)
215c	OMe	OMe	H	-	**183c**, 51% (ii)
215d	OMe	H	H	-	**183d**, 36% (ii)
215e	H	H	OMe	-	**183e**, 64% (ii)

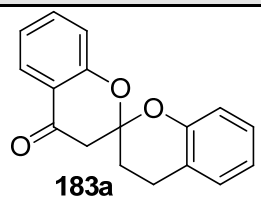
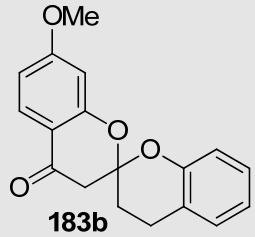
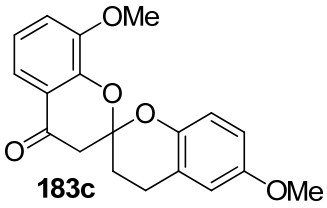
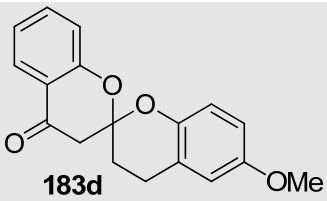
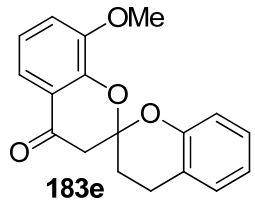
Table 9. Spirocyclisation from benzopyrone **215a-215e**.

2.9 Summary of the Synthesis of 6,6-Bisbenzannulated Spiroketals 183a-183e



Scheme 58. Summary of synthesis of spiroketals **183a-183e**.

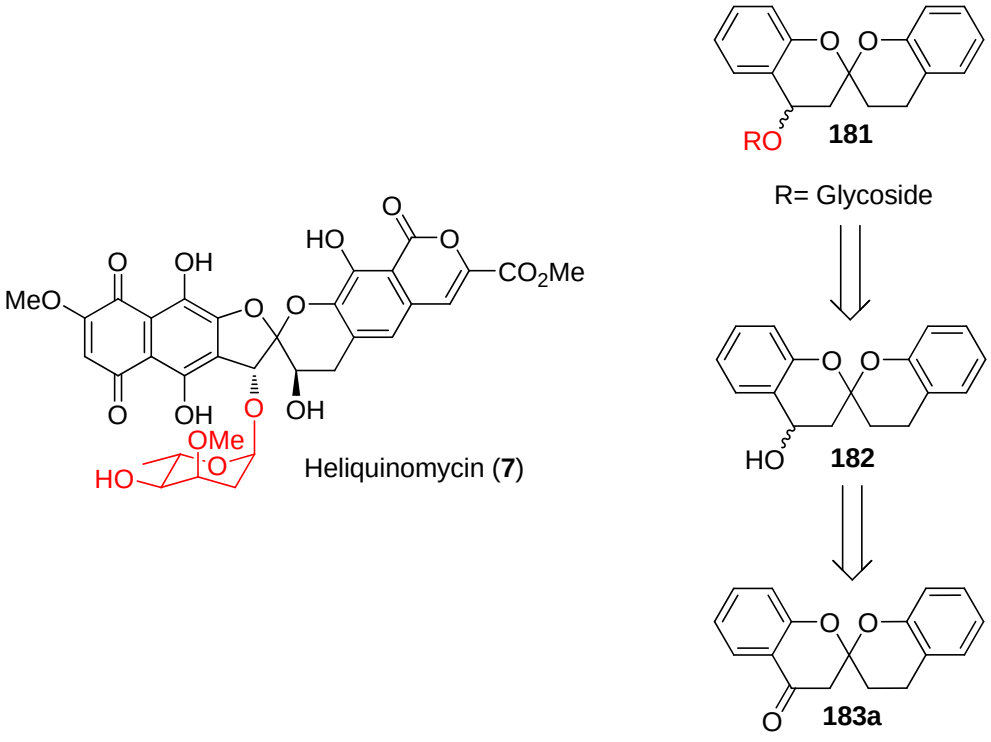
Table 10: Yields for the individual steps in the preparation of spiroketals 183a-183e

Analogue	i. Coupling	ii. Oxidation	iii. Mono-cyclisation	iv. Deprotection	v. Spiro-cyclisation
 **183a**	71%	87%	97%	97%	62%
 **183b**	75%	88%	92%	95%	60%
 **183c**	78%	78%	85%	-	54% (over 2 steps)
 **183d**	82%	82%	92%	-	36% (over 2 steps)
 **183e**	81%	84%	92%	-	64% (over 2 steps)

2.10 Synthesis of α-Hydroxy-Substituted 6,6-Bisbenzannulated Spiroketal 182

Heliquinomycin (**7**) is the only member of the rubromycin family that contains a glycoside unit and has been shown to selectively inhibit DNA helicase (Scheme 59).[82] With analogues of 6,6-bisbenzannulated spiroketals **183a-183e** in hand, it was postulated that by reducing the ketone functionality to an alcohol would provide access to *O*-glycosylated 6,6-bisbenzannulated spiroketals that are analogous to heliquinomycin (**7**). Access to model hydroxylated bisbenzannulated spiroketal **182**, would enable an investigation into the effect that the level of oxygenation of the spiroketal ring has on the inhibition of telomerase and DNA helicase.

It was envisaged that α-hydroxy-substituted 6,6-bisbenzannulated spiroketal analogue **182** could be synthesised from spiroketal **183a** by sodium borohydride reduction of the ketone. With α-hydroxy-substituted bisbenzannulated 6,6-spiroketal **182** in hand, glycosylation of the hydroxyl group could then be investigated further (Scheme 59).



Scheme 59. Structure of heliquinomycin (**7**) and proposed synthesis of α-hydroxy-substituted 6,6-bisbenzannulated spiroketal **182**.

2.10.1 Diastereoselective Reduction of 183a

Initial investigation focused on reduction of keto-substituted spiroketal **183a** to spiroketal **182** using sodium borohydride. There are two possible diastereomeric products due to two possible modes of hydride attack on the carbonyl group (Figure 19).

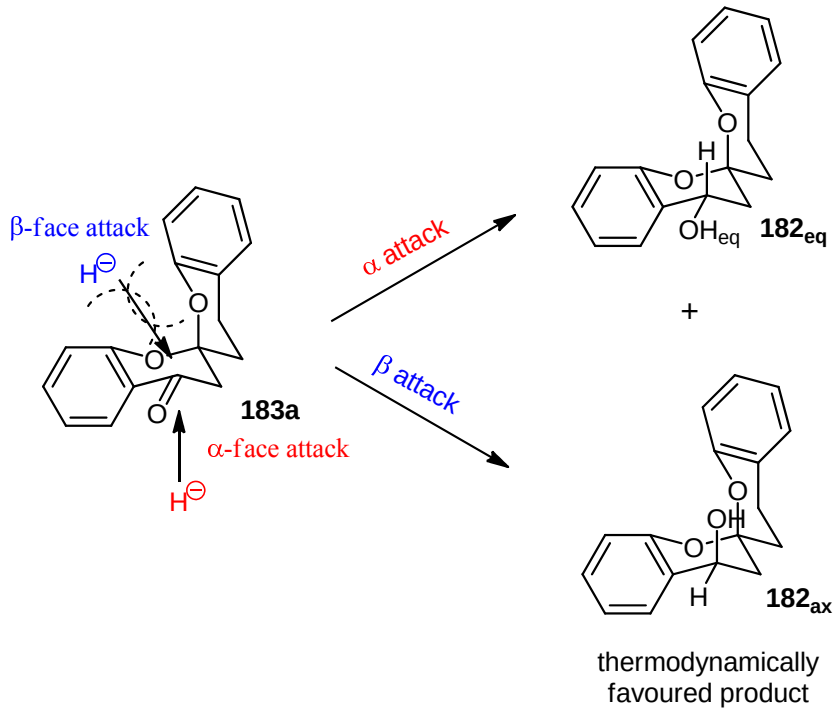
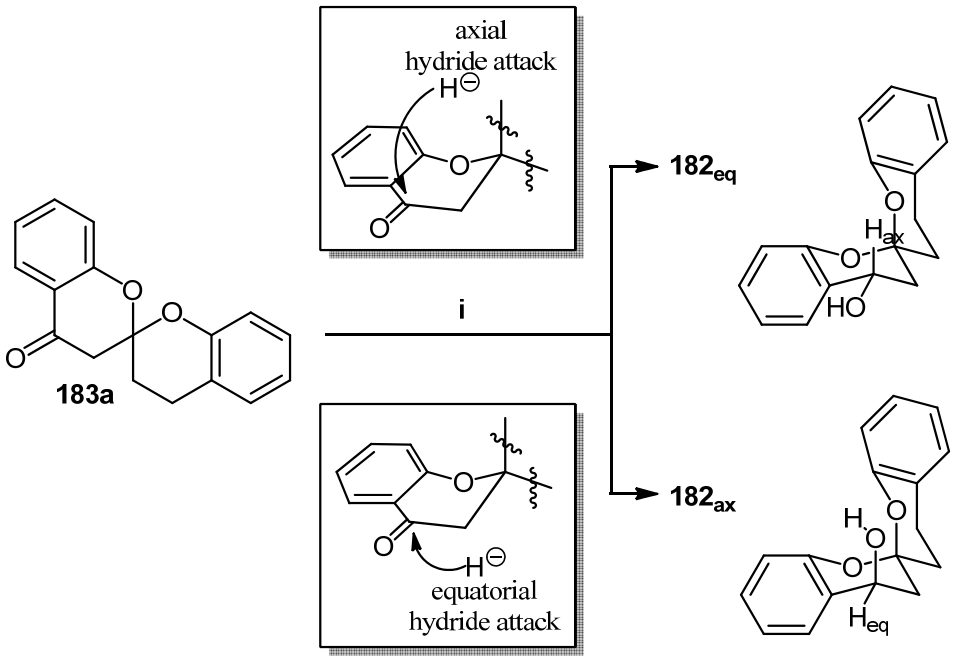


Figure 19. Modes of hydride addition to keto-substituted spiroketal **183a**.

Keto-substituted spiroketal **183a** adopts a pseudo chair-chair bis-axial conformation stabilised by the double anomeric effect. Hydride attack is therefore expected to take place from the less hindered α-face of the ketone resulting in formation of the axial alcohol $\mathbf{182_{ax}}$. The axial hydroxyl group can participate in intramolecular hydrogen bonding to the oxygen of the neighbouring ring. Diastereomer $\mathbf{182_{ax}}$, in which the hydroxyl group adopts an axial position is therefore expected to be the thermodynamically favoured product.

Sodium borohydride was added to an ethanolic solution of spiroketal **183a** at 0 °C. The mixture was allowed to warm to room temperature to afford a 1:4 mixture of the isomeric

hydroxyl substituted spiroketals **182$_{eq}$** and **182$_{ax}$** (Scheme 60). This was in agreement with the predicted diastereoselectivity, in that diastereomer **182$_{ax}$** in which the axial OH group was the major product formed (60% disastereomeric excess (d.e.)). The successful reduction of keto-spiroketal **183a** to hydroxy-spiroketal **182$_{ax}$** was confirmed by the ^{1}H NMR spectrum that exhibited an O*H* proton resonating as a sharp doublet at δ_H 3.68 ppm. Five doublets of doublets of doublets and two doublets of doublets were assigned to the six diastereotopic methylene protons and the methine groups in the spiroketal system. The large vicinal coupling for the O*H* proton ($J_{OH,4eq}$ = 11.5 Hz) supported the fact that the OH group adopted an axial position on the spiroketal ring **182$_{ax}$** that was locked by hydrogen bonding to the two oxygen atoms in the spiroketal ring. Further confirmation for the successful formation of hydroxy-spiroketal **182$_{ax}$** was the absence of a carbonyl carbon in ^{13}C NMR spectrum.

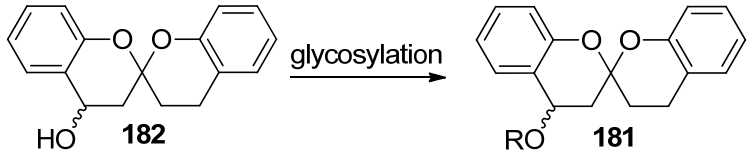


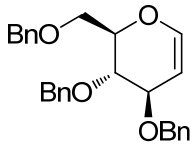
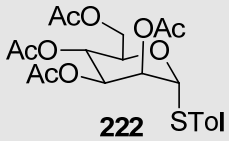
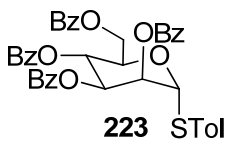
Reagents and Conditions: i. $NaBH_4$, 0 °C →r.t., 15 min, 44%, 1:4 (**182$_{eq}$**:**182$_{ax}$**).

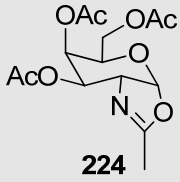
Scheme 60. Diastereoselective reduction of **183a**.

2.11 Attempted Glycosylation of α-Hydroxy-Substituted 6,6-Bisbenzannulated Spiroketal 182

With hydroxy-spiroketal **182** in hand, glycosylation of the hydroxyl group was next investigated (Scheme 61). Our initial glycosylation attempt employed tri-*O*-benzyl-D-(+) glucal **221** with triphenylphosphine hydrobromide in dichloromethane (Entry 1).[83] Even after 5 h at room temperature, no reaction took place. Next, sulfur-activated glycosyl donors **222** and **213** were used (Entry 2, 3).[84, 85] However, no reaction was observed. Oxazoline sugar **224** along with TMSOTf in dichloromethane with spiroketal **182** was stirred at room temperature for 12 h, however no reaction took place (Entry 4).[86]

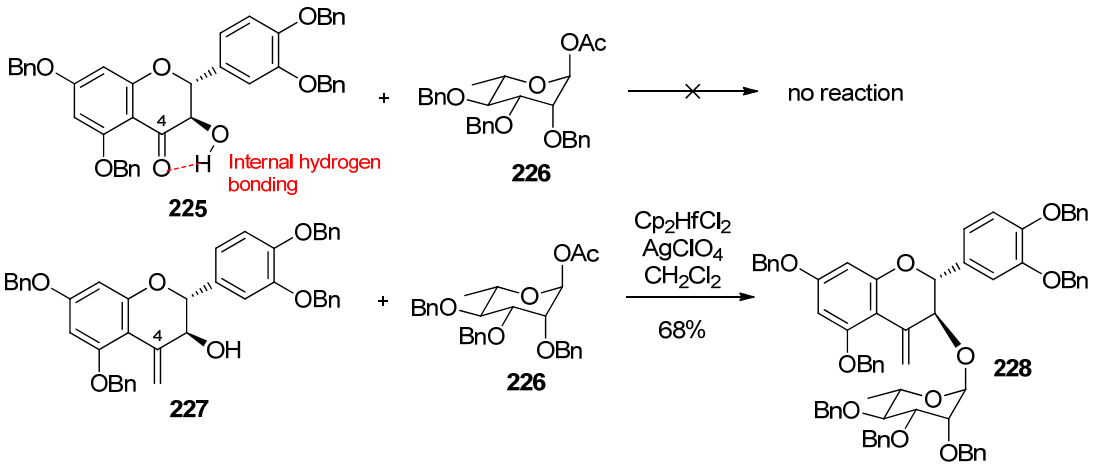


Entry	Glycosides	Reagents	Solvent	Time	Yield (%)
1	 **221**	triphenylphosphine hydrobromide	CH_2Cl_2	5 h	No reaction
2	 **222**	*N*-iodosuccinimide, AgOTf	CH_2Cl_2	3 h	No reaction
3	 **223**	*N*-iodosuccinimide, AgOTf	CH_2Cl_2	3 h	No reaction

4	 **224**	TMSOTf	CH_2Cl_2	12 h	No reaction

Scheme 61. Attempted glycosylation on spiroketal **182**.

With the glycosylation methods proving disappointing, work by Suzuki *et al*.[87] on synthesis of astilbin attracted our attention where these authors reported similar problems (Scheme 62).



Scheme 62. Attempted glycosylation by Suzuki *et al*.[87]

A solution of glycosyl donor **226**, acceptor **225** and the promoters Cp_2HfCl_2 and $AgClO_4$ were stirred in dichloromethane. The authors reported that glycosyl acceptor **225** with a C-4 oxygen group gave none of the glycosylated product **228**. However, for glycosyl acceptor **227** lacking an oxygen function at C-4, glycosylation proceeded in 68% yield using the same conditions. This result was rationalised by the fact that glycosyl acceptor **225** exhibited lower reactivity of the C-3 hydroxyl group due to internal hydrogen bonding to the C-4 carbonyl group.

In the present work, observed lack of reactivity of the hydroxyl group in spiroketals $\mathbf{182_{eq}}$ and $\mathbf{182_{ax}}$ could be attributed to the internal hydrogen bonding between the hydroxyl group and the oxygen functionality in the spiroketal ring (Figure 20) hence preventing glycosylation from taking place.

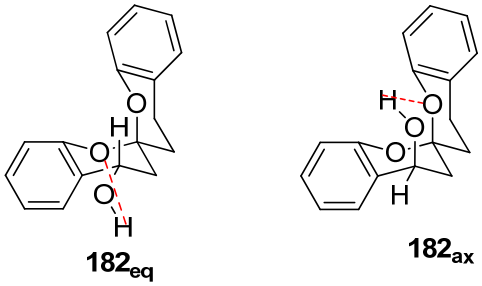


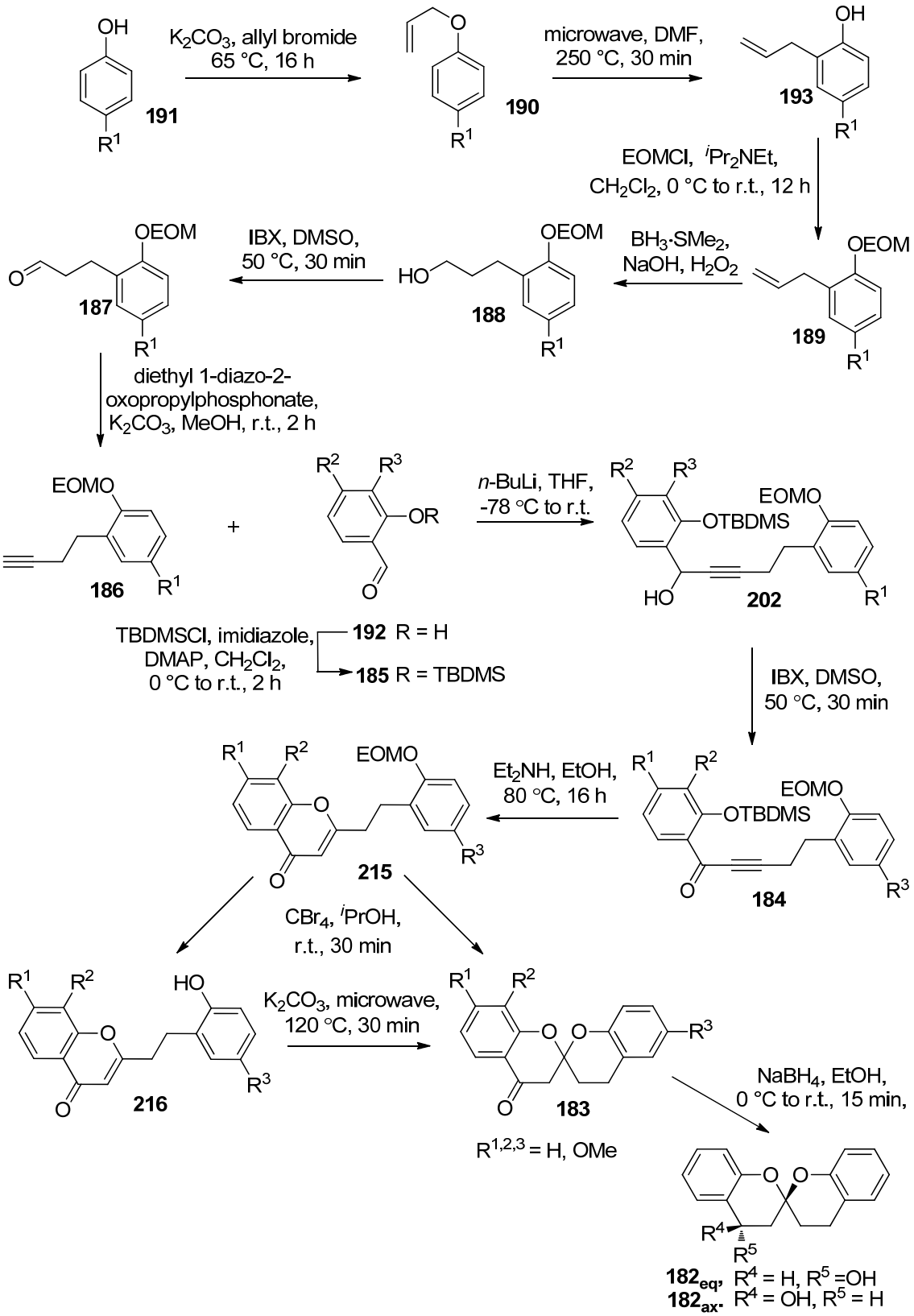
Figure 20. Possible internal hydrogen bonding in spiroketals **182**$_{eq}$ and **182**$_{ax}$.

2.14 Summary and Conclusions

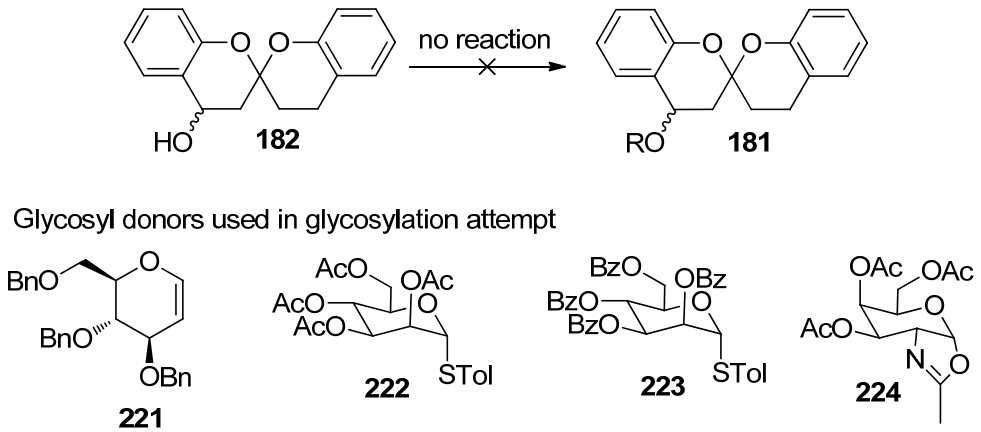
Hydroxy-substituted 6,6-bisbenzannulated spiroketals **182**$_{eq}$ and **182**$_{ax}$ that are analogues of the spiroketal ring system of the rubromycin family of antibiotics have been successfully synthesised (Scheme 63). The hydroxyl functionality was required to access the *O*-glycosylated 6,6-bisbenzannulated spiroketals in order to evaluate the importance of the sugar moiety on the biological activity of the rubromycin family of antibiotics.

The synthesis of bisbenzannulated spiroketals **183a-183e** was successfully executed by using the DIHMA protocol as a method of spirocyclisation. The Ohira-Bestmann modification[50] of the Seyferth-Gilbert homologation[51] was used to prepare acetylene precursors **186a** and **186b** from aldehydes **187a** and **187b**. Acetylenes **186a** and **186b** were then coupled to TBDMS protected aldehydes **185a-185c** via generation of the corresponding acetylide anions.

Cyclisation of the benzopyrone **216a** to the desired 6,6-spiroketal moiety proved to be challenging. After attempting various conditions, the cyclisation of **216a** to **183a** was affected using potassium carbonate under microwave irradiation. The keto-substituted 6,6-bisbenzannulated spiroketal **183a**, underwent diastereoselective reduction to 2,2'-spirobi[chroman]-4-ol **182** using sodium borohydride. However, the hydroxyl group on spiroketal **182** showed a lack of reactivity possibly due to the presence of internal hydrogen bonding to the oxygen atom in the neighbouring spiroketal ring. The synthesis of an *O*-glycosylated 6,6-bisbenzannulated spiroketal was therefore unsuccessful (Scheme 64).



Scheme 63. Summary of the synthesis of hydroxy-substituted 6,6-bisbenzannulated spiroketals $\mathbf{182_{eq}}$ and $\mathbf{182_{ax}}$.



Scheme 64. Summary of the attempted glycosylation of hydroxy-substituted 6,6-bisbenzannulated spiroketal **182**.

2.13 Synthesis of Spiroaminal 237

2.13.1 Introduction to Spiroaminals

Spiroaminals are oxa-aza spirobicyclic frameworks that are found in a number of biologically active compounds such as the herbicide hydantocidin **229**,[88] the marine phycotoxins, the azaspiracids **230**,[89] the immunosuppressant sanglifehrin **231**[90] and the aza-spiropyrans **232**,[91-93] a well known class of photochromic compounds with practical applications in optical switching and nonlinear optics (Figure 21).

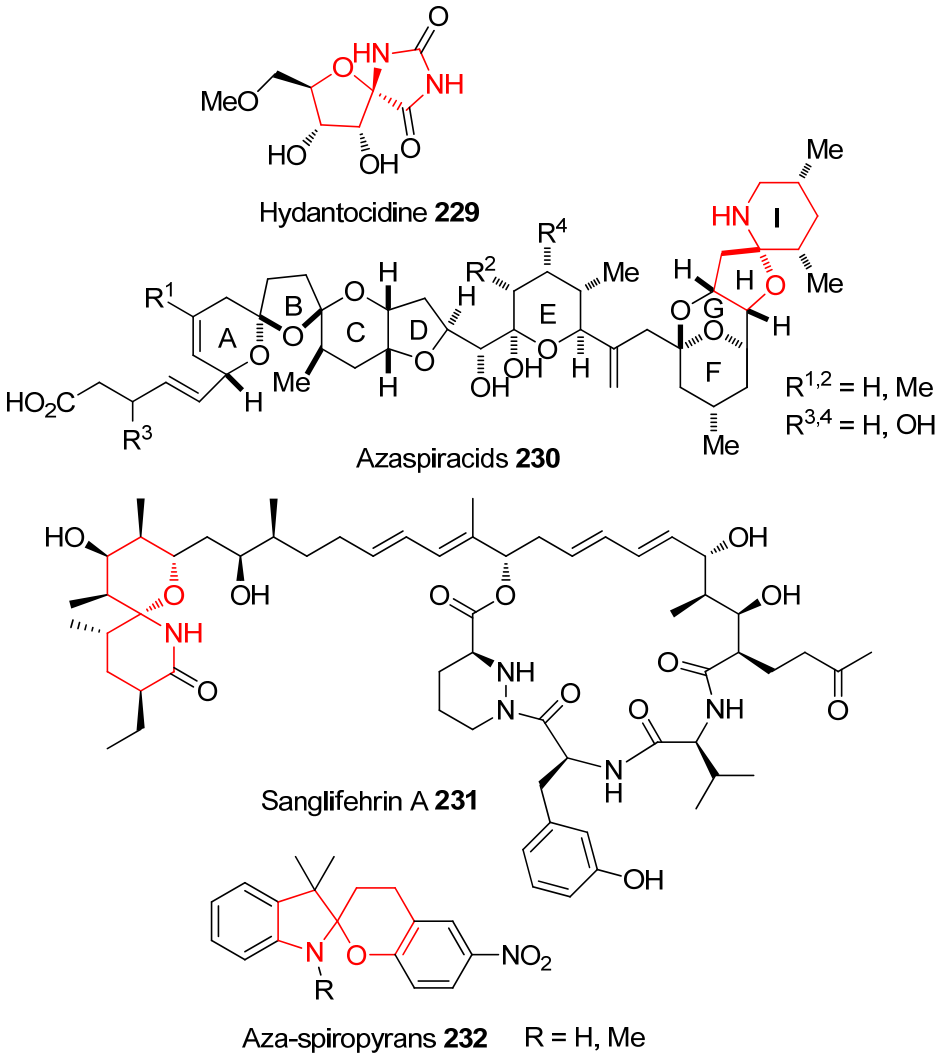
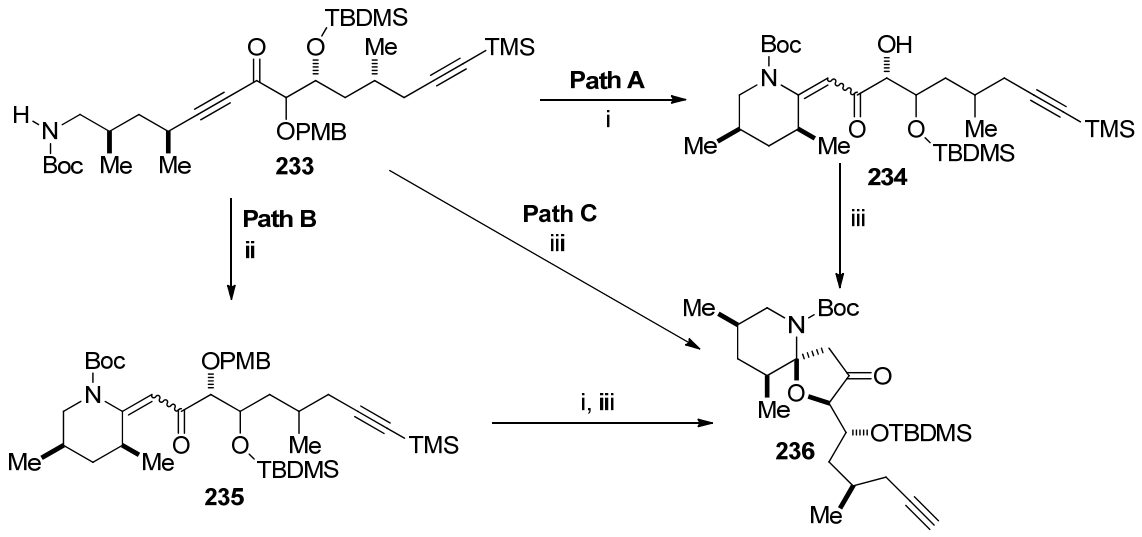


Figure 21. Biologically active compounds containing spiroaminals.

In spite of their structural similarities to closely related spiroketals, spiroaminals have received less attention from synthetic chemists and fewer methods to synthesise these novel and attractive motifs are available.

2.13.2 Synthesis of Azaspiracid Intermediate Using DIHMA by Forsyth *et al.*[94]

There has been only one reported synthesis of a spiroaminal using a DIHMA, namely the synthesis of azaspiracid intermediate **236** by Forsyth *et al.*[94] Key intermediate **233** was converted into the spiroaminal **236** using three different pathways. In Path A, addition of DDQ to ketone **233** led to PMB ether cleavage with concomitant conjugate addition of the carbamate nitrogen atom to the ynone, leading to hydroxyl enaminone **234**. This was subjected to silver trifluoroacetate and subsequent addition of ethanolic potassium iodide gave **236** in two steps. Path B was based on the prior addition of the carbamate nitrogen atom to the ynone system by treatment with $MgBr_2{\cdot}OEt_2$ to give intermediate **235**. Upon PMB deprotection, a second conjugate addition took place using the same conditions as in Path A, affording spiroaminal **236** in good yield. Treatment of ketone **233** with silver trifluoroacetate/ethanolic potassium iodide system allowed direct conversion to spiroaminal **236** (Path C) in 56% yield (Scheme 65).

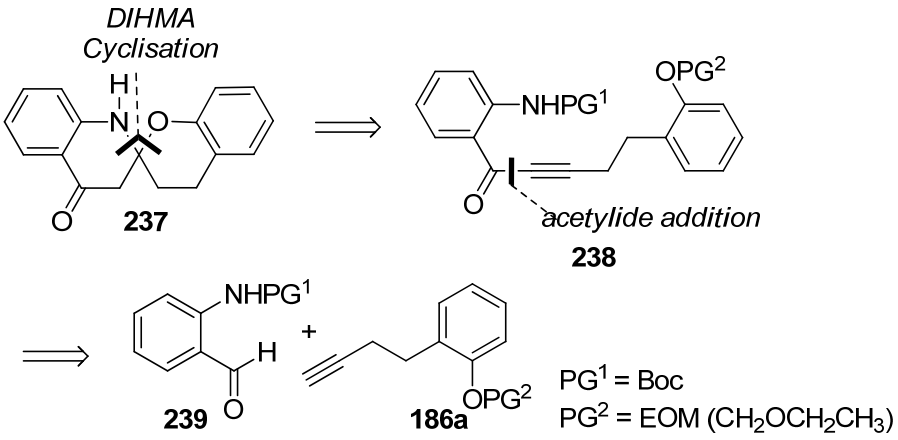


Reagents and Conditions: i. DDQ, CH_2Cl_2, *t*-BuOH, pH 7 buffer; ii. $MgBr_2{\cdot}OEt_2$, CH_2Cl_2; iii. a. $Ag(OCOCF_3)$, CH_2Cl_2, b. EtOH, H_2O, KI (**233** to **236**, 56%).

Scheme 65. Spiroaminal formation via DIHMA by Forsyth *et al.*[94]

2.13.3 Synthetic Strategy

Having established a reliable route to 6,6-spiroketals, the use of the DIHMA protocol to synthesise spiroaminal **237** was next examined.

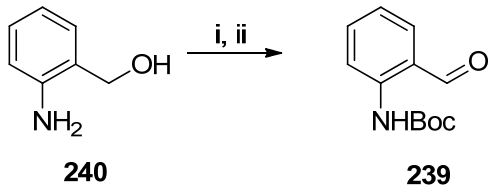


Scheme 66. Retrosynthesis of spiroaminal **237**.

The proposed spiroaminal **237** could be assembled via DIHMA of ynone **238** (Scheme 66). In turn, the spiroaminal precursor **238** is synthesised by addition of the acetylide anion generated from acetylene **186a** to aldehyde **239**.

2.13.4 Synthesis of Spiroaminal 237

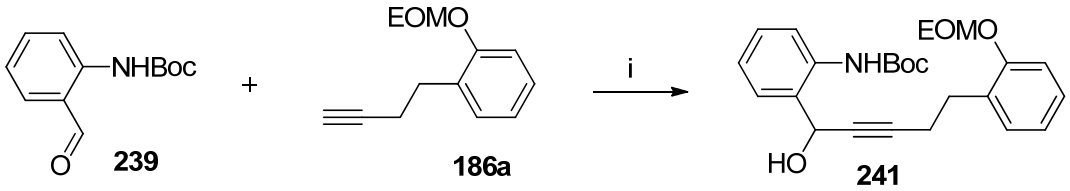
The synthesis of Boc protected aldehyde **239** is outlined in Scheme 67. Commercially available 2-aminobenzyl alcohol **240** was protected using di-*tert*-butyl dicarbonate (Boc) and converted to aldehyde **239** by Dess-Martin oxidation. Purification by flash column chromatography gave the desired protected aldehyde **239** in 81% yield. The ^{1}H NMR spectra were in agreement with the literature (Scheme 67).[95]



Reagents and Conditions: i. Boc_2O, THF, 25 °C for 12 h; ii. DMP, CH_2Cl_2, pyridine, 0 °C, 2 h, 81% over two steps.

Scheme 67. Synthesis of aldehyde **239**.

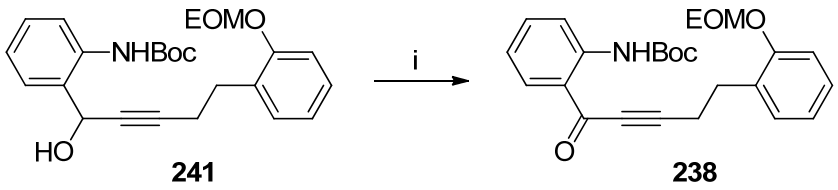
The next step involved coupling of aldehyde **239** and acetylene **186a** which has been synthesised previously (Scheme 44). The coupling step involved treatment of the acetylene **186a** with *n*-butyllithium at -78 °C. After 40 minutes, the solution turned bright yellow, suggesting successful formation of the acetylide anion. A solution of aldehyde **239** in tetrahydrofuran was then added dropwise. The solution was stirred for 30 min and the reaction was warmed to room temperature. Aqueous workup followed by flash chromatography gave the desired alkynol **241** in 65% yield (Scheme 68).



Reagents and Conditions: i. *n*-BuLi, THF, -78 °C to r.t., 30 min, 65%.

Scheme 68. Acetylide anion addition of acetylene **186a** to aldehyde **239**.

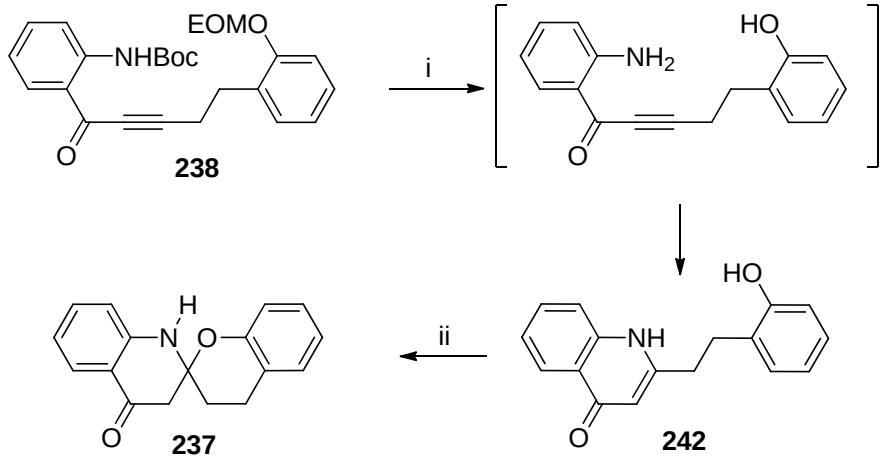
Oxidation of the secondary alcohol **241** was next achieved using 2-iodoxybenzoic acid in dimethylsulfoxide at 50 °C for 30 min, affording the desired ynone **238** in 84% yield (Scheme 69).



Reagents and Conditions: i. IBX, DMSO, 50 °C, 30 min, 84%.

Scheme 69. Oxidation of alcohol **241** to ynone **238** using IBX.

The next step was the deprotection of the Boc protecting group to facilitate 6-*endo*-dig cyclisation to give the monocyclised spiroaminal precursor. Trifluoroacetic acid was added to a solution of ynone **238** in dichloromethane dropwise and the reaction mixture stirred at room temperature for 10 min. The deprotection proceeded smoothly, forming the monocyclised quinolone **242** in 82% yield (Scheme 70). There was no need for a second deprotection step (of the EOM group) as the trifluoroacetic acid also effected concomitant deprotection of the EOM ether.



Reagents and Conditions: i. TFA, CH_2Cl_2, 82%; ii. K_2CO_3, CH_2Cl_2, microwave, 300 W, 32%.

Scheme 70. Deprotection followed by formation of spiroaminal **237**.

The synthesis of quinolone **242** intermediate proved to be valuable as it contains the same pharmacophore as 2-aryl-4-quinolones **243** which are well known for their wide range of pharmacological properties, such as antibacterial,[96-98] antiplatelet,[99] antitumoral,[100] antimitotic and anticancer activity.[97, 98] They are also known to act as inhibitors of *in vitro* tubulin polymerisation[97, 98, 101] and act as cytotoxic agents[100] and cardiovascular protectors.[101, 102] Cavaleiro *et al*.[103] synthesised various analogues of 2-styryl-4-quinolones which showed structural similarities to quinolone **244** (Figure 22).

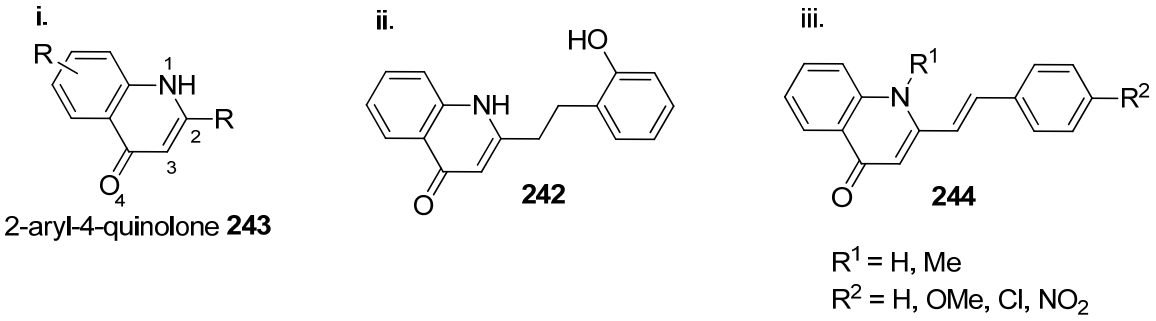
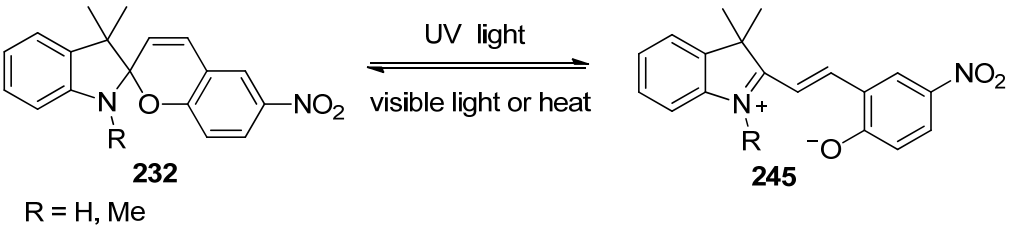


Figure 22. Structures of i. 2-aryl-4-quinolone **243**; ii. quinolone **242**; iii. 2-styryl-4-quinolones **244** by Cavaleiro *et al*.[103]

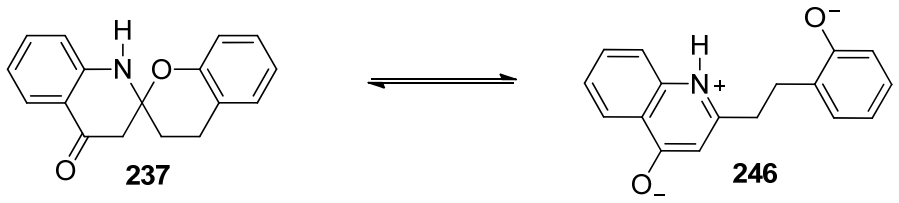
Having established a reliable protocol for the formation of spiroketals using DIHMA, the same conditions were applied to quinolone **242**. Powdered, oven-dried potassium carbonate was added to a solution of quinolone **242** in dichloromethane (Scheme 70). The solvent was removed *in vacuo* and the reaction mixture was placed in a CEM microwave reactor at 300 W for 30 min at 120 °C. TLC analysis showed the formation of two new products. When viewed at 365 nm, the less polar of the two spots was blue while the more polar spot was green. The isolation of these two spots proved challenging due to their sensitivity to light that caused extensive degradation. The use of neutralised deuterated chloroform for NMR analysis was essential and the compounds were covered in tin foil to avoid decomposing **242** in light.

The related spirobenzopyrans **232**[93] are known for their photochromic properties in that they undergo photoisomerisation from the electrically neutral closed spiropyran form to the zwitterionic merocyanine form **245** upon irradiation with UV light (Scheme 71).



Scheme 71. Photoionization of photochromic spirobenzopyran **232**.

As **237** possesses similar structural properties to the spirobenzopyrans **232**, it was proposed that spiroaminal **237** adopted an equilibrium between the closed and the open-chain form **246** (Scheme 72). This postulate may account for the colour differences in the spots and the unstable nature of spiroaminal **237**.

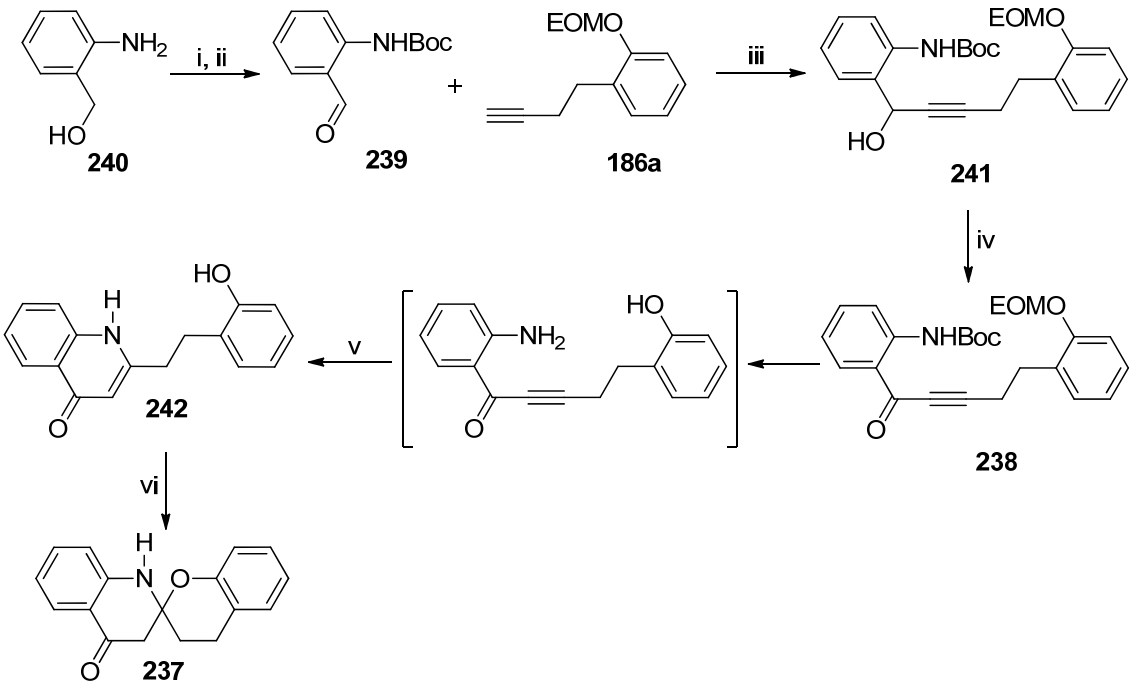


Scheme 72. Possible photoionisation of photochromic spiroaminal **237**.

The less polar blue spot could be isolated and subjected to ^{1}H and ^{13}C NMR analysis which subsequently established that it was in fact the desired spiroaminal **237**. The structure of the spiroaminal **237** was confirmed by ^{1}H and ^{13}C NMR, IR and mass spectrometry. The IR spectrum supported the loss of the phenolic OH group and the ^{13}C NMR spectrum lacked the vinylic carbon at δ_C 99.1 ppm present in quinolone **242**. The characteristic quaternary spiro-centre in the ^{13}C NMR spectrum of the spiroaminal **237** was also supported by the characteristic resonance at δ_C 98.9 ppm.

2.13.5 Summary and Conclusions

Spiroaminal **237** was successfully synthesised by extension of the novel DIHMA protocol used for the synthesis of 6,6-bisbenzannulated spiroketals. Quinolone **242** which is the precursor to spiroaminal **237** was also successfully synthesised that may possess interesting biological activity as it possesses the same pharmacophore as bioactive 2-aryl-4-quinolones **243** (Scheme 73). The unstable nature of spiroaminal **237** rendered isolation and characterisation difficult, however spiroaminal **237** may exhibit photochromic properties that could be harnessed for the use as potential molecular switches. Investigation into the photochromic properties of spiroaminal **237** and quinolone **242** warrant further work.



Reagents and Conditions: i. Boc_2O, THF, 25 °C for 12 h; ii. DMP, CH_2Cl_2, pyridine, 0 °C, 2 h, 81% over two steps; iii. *n*-BuLi, THF, -78 °C to r.t., 30 min, 65%; iv. IBX, DMSO, 50 °C, 30 min, 84%; v. TFA, CH_2Cl_2, 82%; vi. K_2CO_3, CH_2Cl_2, microwave, 300 W, 32%.

Scheme 73. Summary of the synthesis of quinolone **242** and spiroaminal **237**.

Chapter Three

Experimental

3.1 General Details

All reactions were carried out in flame or oven dried glassware under a dry nitrogen or argon atmosphere. Diethyl ether (Et_2O), dioxane and tetrahydrofuran (THF) were freshly distilled over sodium/benzophenone. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2), ethanol (EtOH) and toluene were freshly distilled from calcium hydride. Acetone ($(CH_3)_2CO$) was freshly distilled from calcium chloride. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were freshly distilled from molecular sieves (Linde type 4 Å). Reactions performed at low temperature were either cooled with an acetone–dry ice bath to reach –78 °C or using a water–ice bath to reach 0 °C. Flash chromatography was carried out using 0.063 – 0.1 mm Riedel-de-Häen silica gel with the denoted solvent.

Thin-layer chromatography (TLC) was carried out using E. Merck silica gel plates using UV light as the visualising agent and/or developed using an ethanolic solution of vanillin or ammonium molybdate and cerium sulfate in aqueous sulfuric acid. Optical rotations were measured with a Perkin Elmer 341 polarimeter, using the sodium-D line (589 nm), with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum 1000 FT-IR spectrometer with the absorption peaks expressed in wavenumbers (cm^{-1}) and recorded using a range of 450 to 4000 cm^{-1}. NMR spectra were recorded in $CDCl_3$ on either a Bruker BRX300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei or a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported as parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the solvent in which the sample was analysed ($CDCl_3$: δ 7.26 for ^1H NMR, δ 77.0 for ^{13}C NMR) and coupling constants (J) are reported in hertz (Hz) to the nearest 0.1 ppm. ^1H NMR data is reported as chemical shift in ppm, followed by multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad), relative integral, coupling

constants where applicable, and assignment. Infrared (IR) spectra were recorded as a thin film between NaCl plates or a composite of zinc selenide and diamond crystal on a FT-IR System transform spectrometer. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained using a VG70SE spectrometer operating at a nominal accelerating voltage of 70 eV.

3.2 Experimental Procedures

3.2.1 Standard Procedures for the Preparation of Aryl Acetylene Precursors.

A. Allylation of Phenols

To a stirred solution of the appropriate phenol (6.0 g, 64 mmol) in acetone (50 mL) was added potassium carbonate (16.6 g, 120 mmol) and allyl bromide (5.50 mL, 65 mmol). The mixture was heated under reflux at 65 ^{o}C for 16 h, cooled to r.t., filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and washed sequentially with 1M aq. NaOH (15 mL), H_2O (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash chromatography using the specified solvent system.

B. Claisen Rearrangement of Allyl Ethers

Phenyl allyl ether (0.5 g, 3.7 mmol) in dimethylformamide (2 ml) was irradiated in a CEM microwave reactor at 250 W and 250 ^{o}C for 30 min. The reaction mixture was allowed to cool to r.t. and the thick oil purified by distillation using the specified temperature and pressure.

C. Protection of Allylated Phenols as Ethoxymethly Ethers

A stirred solution of the appropriate 2-allylphenol (2.8 g, 20.9 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 ^{o}C under nitrogen. Diisopropylethylamine (5.45 mL, 31.3 mmol) was added followed by ethoxymethoxy chloride (2.86 mL, 25.0 mmol) dropwise. CH_2Cl_2 was removed *in*

vacuo and the residue was taken up in EtOAc (20 mL) and washed sequentially with H_2O (20 mL), 1 M aq. NaOH (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by column chromatography using the specified solvent system.

D. Hydroboration of Protected Allylphenols

Allylphenol **50** (3.3 g, 17.2 mmol) was dissolved in THF (100 mL) and the solution cooled to 0 ^oC. Borane-dimethyl sulphide complex (2.13 mL, 22.4 mmol) was added dropwise and the mixture stirred at 0 ^oC for 5 h then warmed to r.t. and stirred overnight. The reaction was quenched by the addition of MeOH (20 mL). 1 M aq. NaOH (20 mL) was carefully added followed by the dropwise addition of 30% aq. hydrogen peroxide (20 mL) and the resultant mixture stirred overnight. The mixture was extracted with EtOAc (2 × 25 mL) and the combined organic extracts were dried over $MgSO_4$. The solvents were concentrated *in vacuo* and the resultant residue purified by flash chromatography using the specified solvent system.

E. IBX Oxidation of Alcohols

o-Iodoxybenzoic acid (376 mg, 1.34 mmol) in DMSO (5 mL) was added to a stirred solution of secondary alcohol (200 mg, 0.44 mmol) in DMSO (5 mL) at r.t. The mixture was stirred at 50 °C for 30 min. The reaction mixture was poured into EtOAc (20 mL) and washed with sat. sodium thiosulphate (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and the resultant residue purified by flash chromatography using the specified solvent system.

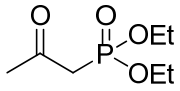
F. Ohira-Bestmann Modified Procedure for Synthesis of Acetylenes

To a stirred solution of aldehyde (1.14 g, 5.0 mmol) and potassium bicarbonate (1.4 g, 10.0 mmol) in MeOH (80 mL), was added a solution of diethyl diazo 2-oxopropylphosphonate **197** (1.32 g, 6.0 mmol) in MeOH (10 mL) and the mixture left to stir at r.t. for 2 h. MeOH was

removed *in vacuo* and the residue was taken up in Et_2O (50 mL) and washed with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash chromatography using the specified solvent system.

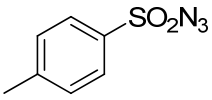
3.2.2 Synthesis of Diethyl 1-diazo-2-oxopropylphosphonate 197

A. Diethyl 2-oxopropylphosphonate 195



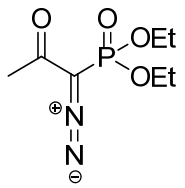
To a stirred mixture of 1-chloropropan-2-one (18.9 mL, 234 mmol) and potassium iodide (39 g, 234 mmol) in acetone-acetonitrile (55:45, 120 mL), was added triethyl phosphite (31 mL, 181 mmol). The mixture was left to stir at r.t. for 6 h then heated at 50 ^oC for 4 h, filtered and the filtrate concentrated *in vacuo*. The resultant residue was purified by column chromatography using hexanes/EtOAc (4:6) as eluent to give the *title compound* **195** (17 g, 73%) as a pale yellow oil. The ^1H NMR data were in agreement with the literature.[58]

B. 4-Methylbenzenesulfonyl azide 196



To a stirred solution of sodium azide (1.9 g, 28.8 mmol) in H_2O (5 mL) diluted with 90% aq. ethanol (10 mL), was added a solution of 4-methylbenzenesulfonyl chloride (5.0 g, 26.2 mmol) in 99% aq. ethanol (27 mL). The reaction mixture was stirred at r.t. for 2.5 h, filtered and the solvent was removed *in vacuo*. The residue was added H_2O (30 mL) and extracted with EtOAc (3 × 30 mL) and organic layer was dried over Na_2SO_4. The resultant residue was concentrated *in vacuo* to give the *title compound* **196** (4.7 g, 91%) as a colourless oil which crystallised upon standing at 5 °C. (**M.p.** = 22 ^oC, literature **M.p.** = 22 ^oC). The melting point was in agreement with the literature.[104]

C. Diethyl 1-diazo-2-oxopropylphosphonate 197



To a suspension of sodium hydride in toluene-THF (5:1, 18 mL) cooled to 0 °C, was added a solution of phosphonate **195** (1.0 g, 5.15 mmol) in toluene (2.5 mL). After stirring for 1 h, a solution of tosyl azide **196** (1.01 g, 5.15 mmol) in toluene (2.5 mL) was added and the mixture allowed to warm to r.t. and stirred for 2 h. The resultant orange mixture was filtered through a plug of Celite® and concentrated *in vacuo.* The resultant residue was purified by flash column chromatography using hexanes/EtOAc (60:40) as eluent to give the *title compound* **197** (1.1 g, 97%) as a yellow oil. The ^{1}H NMR data were in agreement with the literature.[58]

3.2.3 Standard Procedure for the Preparation of the Aldehyde Precursors.

To a stirred mixture of imidazole (3.22 g, 47.3 mmol), 4-dimethylaminopyridine (0.24 g, 1.97 mmol) and *tert*-butyldimethylsilyl chloride (3.76 g, 55.2 mmol) in CH_2Cl_2 (70 mL) cooled to 0 ^{o}C, was added a solution of the appropriate salicylaldehyde (3.0 g, 19.7 mmol) in CH_2Cl_2 (10 mL) dropwise. The mixture was allowed to warm to r.t. and stirred for 2 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using the specified solvent system.

3.2.4 Standard Procedure for the Synthesis of 6,6-Bisbenzannulated Spiroketals

A. Coupling of Acetylenes with Aldehydes

n-Butyllithium (1.73 mL, 1.6 M in hexanes 2.69 mmol) was added dropwise to a stirred solution of acetylene (500 mg, 2.45 mmol) in THF (10 mL) at -78 ^{o}C under nitrogen. After stirring for 40 min at the same temperature, a solution of aldehyde (579 mg, 2.45 mmol) in THF (5 mL) was added dropwise and the mixture stirred for 30 min. The reaction mixture was

allowed to warm to the r.t., H_2O (30 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography using the specified solvent system.

B. Oxidation of Secondary Alcohols to Ketones

o-Iodoxybenzoic acid (94 mg, 0.33 mmol) in DMSO (1.1 mL) was added to a stirred solution of secondary alcohol (50 mg, 0.11 mmol) in DMSO (1.1 mL) at r.t. The mixture was stirred at 50 °C for 30 min. The reaction mixture was poured into EtOAc (10 mL) and washed with sat. sodium thiosulphate (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and the resultant residue purified by flash chromatography using the specified solvent system.

C. Synthesis of Benzopyrones

To a solution of ynone (135 mg, 0.31 mmol) in ethanol (2 mL) was added diethylamine (0.63 mL, 6.16 mmol) at r.t. and the mixture heated under reflux for 16 h. The reaction mixture was concentrated *in vacuo*. The resultant residue was taken up in Et_2O (5 mL) then washed with H_2O (1 mL) and brine (1 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* and the resultant residue purified by flash chromatography using the specified solvent system.

D. Deprotection of Ethoxymethyl Ethers

To a solution of ynone (8.5 mg, 26 μmol) in isopropanol (2 mL) was added carbon tetrabromide (34 μL, 262 μmol) and the reaction mixture stirred under nitrogen for 30 min at

r.t. The solution was quenched with H_2O (1 mL) and extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash chromatography using the specified solvent system.

E. Cyclisation of Benzopyrones to 6,6-Spiroketals

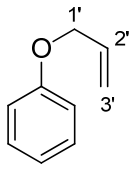
A solution of benzopyrone (18 mg, 0.07 mmol) in CH_2Cl_2 (10 mL) was added to oven-dried ground potassium carbonate (2.0 g, 14.5 mmol). The solvent was evaporated *in vacuo* and the reaction mixture was placed in a CEM microwave reactor at 300 W for 30 min at 120 °C. The reaction mixture was allowed to cool to r.t., then H_2O (10 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (8 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography using the specified solvent system.

3.3 Experimental Data

3.3.1 Analogue A- 2,2'-Spirobi[chroman]-4-one 183a

3.3.1.1 Synthesis of Aryl Acetylene 186a

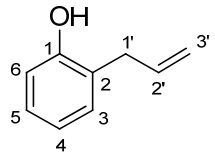
Allyloxybenzene 190a



The allylation reaction was carried out according to the standard procedure **3.2.1.A** using phenol **191a** (6 g, 64 mmol), allyl bromide (5.50 mL, 65 mmol) and potassium carbonate (16.6 g, 120 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **190a** (8.31 g, 97%) as a colourless oil. **^{1}H NMR** (400

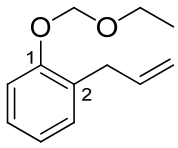
MHz, $CDCl_3$): δ 4.49 (2 H, dt, *J* 5.3, 1.5 Hz, 1′-H), 5.26 (1 H, dt, *J* 10.5, 1.5 Hz, 3′-H_α), 5.39 (1 H, dt, *J* 17.3, 1.5 Hz, 3′-H_β), 6.03 (1 H, ddt, *J* 17.3, 10.5, 5.3 Hz, 2′-H), 6.89-7.28 (5 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 68.6 (CH_2, O*C*H_2), 117.5 (CH_2, C-3′), 133.2 (CH, C-2′), 114.6, 120.7, 129.3 (CH, Ar-*C*H), 158.5 (C, Ar-C). The ^{1}H NMR data were in agreement with the literature.[52]

2-Allylphenol 193a



The Claisen rearrangement reaction was carried out according to the standard procedure **3.2.1.B** using allyl phenyl ether **190a** (0.5 g, 3.7 mmol). The product was purified by distillation at 68 °C/ 2mm Hg to give the *title compound* **193a** (0.47 g, 94%) as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.39 (2 H, m, 1′-H), 5.08-5.16 (2 H, m, 3′-H), 5.33 (1 H, br s, O*H*), 6.00 (1 H, m, 2′-H), 6.73-7.11 (4 H, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 34.8 (CH_2, C-1′), 116.2 (CH_2, C-3′), 125.5 (C, C-2), 115.7, 120.8, 127.7, 130.3 (Ar-*C*H), 136.4 (CH, C-2′), 153.9 (C, C-1). The ^{1}H NMR data were in agreement with that reported above and with the literature.[54]

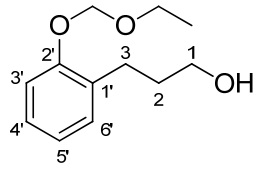
1-Allyl-2-(ethoxymethoxy)benzene 189a



The protection step was carried out according to the standard procedure **3.2.1.C** using 2-allylphenol **193a** (2.8 g, 20.9 mmol), diisopropylamine (5.45 mL, 31.3 mmol) and ethoxymethoxy chloride (2.86 mL, 25.0 mmol). The product was purified by flash chromatography using hexanes/EtOAc (9:1) as eluent to give the *title compound* **189a** (3.6 g,

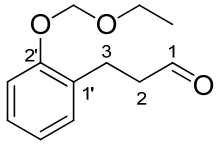
89%) as a pale yellow oil. **IR:** ν_{max}(film): 2977, 2358, 1638, 1600, 1588, 1228 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (3 H, t, *J* 7.1 Hz, OCH_2CH_3), 3.50 (2 H, d, *J* 6.6 Hz, $CH_2CH{=}CH_2$), 3.82 (2 H, q, *J* 7.1 Hz, CH_3CH_2O), 5.12-5.17 (2 H, m, $CH_2CH{=}CH_\alpha H_\beta$), 5.33 (2 H, s, OCH_2O), 6.09 (1 H, ddt, *J* 16.8, 10.2, 6.6 Hz, $CH{=}CH_2$), 7.01-7.28 (4 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (CH_3, OCH_2CH_3), 34.4 (CH_2, $CH_2CH{=}CH_2$), 64.1 (CH_2, OCH_2CH_3), 93.0 (CH_2, OCH_2O), 115.3 (CH_2, $CH_2CH{=}CH_2$), 113.9, 121.5, 127.3, 129.8 (CH, Ar-*C*H), 129.1 (C, C-2), 136.9 (CH, vinylic), 155.0 (C, C-1); ***m/z*** (EI, %) 192 (M^+, 11), 149 (27), 147 (31), 119 (12), 91 (22), 59 (100); **HRMS** Found (EI): (M^+), 192.1150, $C_{12}H_{16}O_2$ requires 192.1147.

3-(2′-(Ethoxymethoxy)phenyl)propan-1-ol 188a



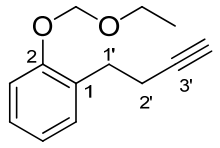
The hydroboration reaction was carried out according to the standard procedure **3.2.1.D** using 1-Allyl-2-(ethoxymethoxy)benzene **189a** (3.3 g, 17.2 mmol) and borane-dimethyl sulfide complex (2.13 mL, 22.4 mmol). The product was purified by flash chromatography using hexanes/EtOAc (95:5) as eluent to give the *title compound* **188a** (3.3 g, 91%) as a pale yellow oil. **IR** ν_{max}(film): 3365, 2934, 2358, 1601, 1587, 1455, 1492, 1228 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (3 H, t, *J* 7.1 Hz, CH_3CH_2O), 1.86 (2 H, quintet, *J* 7.4 Hz, 2-H), 1.96 (1 H, br s, O*H*), 2.73 (2 H, t, *J* 7.4 Hz, 3-H), 3.62 (2 H, t, *J* 7.4 Hz, 1-H), 3.73 (2 H, q, *J* 7.1 Hz, CH_3CH_2O), 5.25 (2 H, s, OCH_2O), 6.90-7.19 (4 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (CH_3, CH_3CH_2O), 26.1 (CH_2, C-3), 33.0 (CH_2, C-2), 61.9 (CH_2, C-1), 64.3 (CH_2, CH_3CH_2O), 93.3 (CH_2, OCH_2O), 114.0, 121.7, 127.1, 130.1 (CH, Ar-*C*H), 130.5 (C, C-1'), 155.2 (C, C-2'); ***m/z*** (EI, %) 210 (M^+, 2), 164 (24), 135 (21), 134 (100), 107 (25), 119 (14), 59 (61); **HRMS** Found (EI): (M^+), 210.1256, $C_{12}H_{18}O_3$ requires 210.1256.

3-(2′-(Ethoxymethoxy)phenyl)propanal 187a



The IBX oxidation was carried out according to the standard procedure **3.2.1.E** using secondary alcohol (200 mg, 0.44 mmol) **188a** and *o*-Iodoxybenzoic acid (376 mg, 1.34 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **187a** (1.67 g, 84%) as a pale yellow oil. **IR** ν_{max}(film): 2934, 2826, 2724, 1722, 1492, 1235 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (3 H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 2.68 (2 H, t, *J* 7.4 Hz, 2-H), 2.93 (2 H, t, *J* 7.5 Hz, 3-H), 3.69 (2 H, q, *J* 7.0 Hz, CH$_3$C*H*$_2$O), 5.20 (2 H, s, OC*H*$_2$O), 6.86-7.16 (4 H, m, Ar-*H*), 9.74 (1 H, t, *J* 1.5 Hz, C*H*O); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8 (CH$_3$, *C*H$_3$CH$_2$O), 23.2 (CH$_2$, C-3), 43.6 (CH$_2$, C-2), 64.0 (CH$_2$, CH$_3$*C*H$_2$O), 92.7 (CH$_2$, O*C*H$_2$O), 113.6, 121.2, 127.4, 129.7 (CH, Ar-*C*H), 128.9, (C, C-1'), 155.0 (C, C-2'), 201.9 (CH, *C*HO); ***m/z*** (EI, %) 208 (M^+, 3), 162 (4), 132 (16), 121 (6), 91 (6), 77 (5), 59 (100); **HRMS** Found (EI): (M^+), 208.1096, $C_{11}H_{14}O_3$ requires 208.1099.

1-(But-3′-ynyl)-2-(ethoxymethoxy)benzene 186a

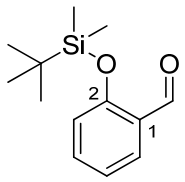


The Ohira-Bestmann modification was carried out according to the standard procedure **3.2.1.F** using aldehyde **187a** (1.14 g, 5.0 mmol), potassium carbonate (1.4 g, 10.0 mmol) and diethyl diazo-2-oxopropylphosphonate **197** (1.32 g, 6.0 mmol). The product was purified by flash chromatography using hexanes/EtOAc (6:4) as eluent to give the *title compound* **186a** (1.1 g, 94%) as a pale yellow oil. **IR** ν_{max}(film): 3296, 2977, 1602, 1588, 1493, 1229 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (3 H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 1.95 (1 H, t, *J* 2.6 Hz, C≡C*H*), 2.47 (2 H, dt, *J* 7.6, 2.6 Hz, 2′-H), 2.87 (2 H, t, *J* 7.6 Hz, 1′-H), 3.72 (2 H, q, *J* 7.1 Hz, CH$_3$C*H*$_2$O), 5.24 (2 H, s, OC*H*$_2$O), 6.90-7.19 (4 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (CH$_3$, *C*H$_3$CH$_2$O), 18.9 (CH$_2$, C-2′), 29.7 (CH$_2$, C-1′), 64.2 (CH$_2$, CH$_3$*C*H$_2$O), 68.5 (C, C-3′), 84.3

(CH, C≡*C*H), 93.0 (CH_2, O*C*H_2O), 113.8, 121.4, 127.6, 130.1 (CH, Ar-*C*H), 129.2, (C, C-1), 155.3 (C, C-2); ***m/z*** (FAB, %) 204 (M^+, 7), 175 (4), 159 (19); **HRMS** Found (FAB): (M^+), 204.1155, $C_{13}H_{16}O_2$ requires 204.1150.

3.3.1.2 Synthesis of Aldehyde 185a

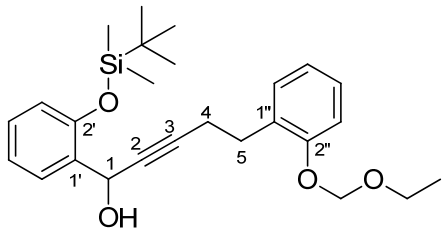
2-(*tert*-Butyldimethylsilyloxy)benzaldehyde 185a



The protection step was carried out according to the standard procedure **3.2.3** using 2-hydroxybenzaldehyde **192a** (1.0 g, 8.2 mmol), imidazole (2.68 mL, 19.7 mmol), 4-dimethylaminopyridine (100 mg, 0.82 mmol) and *tert*-butyldimethylsilyl chloride (4.0 mL, 22.9 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **185a** (3.3 g, 85%) as a colourless oil. **IR** ν_{max}(film): 2879, 2752, 1690, 1599, 1479, 1223, 1099, 840 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.28 (6 H, s, 2 × SiCH_3), 1.03 (9 H, s, C(CH_3)$_3$), 6.87-7.83 (4 H, m, Ar-*H*), 10.48 (1 H, s, C*H*O); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.4 (CH_3, Si(*C*H_3)$_2$), 18.3 (C, *C*(CH$_3$)$_3$), 25.6 (CH_3, C(*C*H_3)$_3$), 120.2, 121.4, 128.3, 135.6 (CH, Ar-*C*H), 127.2, (C, C-1), 158.8 (C, C-2), 190.0 (C, *C*HO); ***m/z*** (CI, %) 237 (MH^+, 60), 179 (76), 105 (72), 94 (100), 78 (94); **HRMS** Found (CI): (MH^+), 237.1307, $C_{13}H_{20}O_2Si$ requires 237.1311

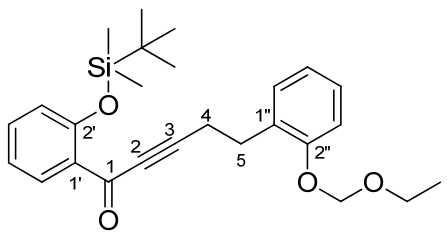
3.3.1.3 Synthesis of Spiroketal 183a

1-(2′-(*tert*-Butyldimethylsilyloxy)phenyl)-5-(2″-(ethoxymethoxy)phenyl)pent-2-yn-1-ol 202a



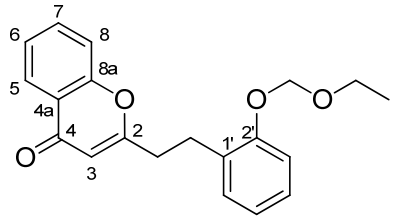
The coupling reaction was carried out according to the standard procedure **3.2.4.A** using acetylene **186a** (500 mg, 2.45 mmol), aldehyde **185a** (579 mg, 2.45 mmol), and *n*-butyllithium (1.73 mL, 1.6 M in hexanes, 2.69 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **202a** (770 mg, 71%) as a yellow oil. **IR** ν_{max}(film): 3448, 2930, 2245, 1599, 1479, 1255, 1100, 839 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.24 (3 H, s, SiCH_3), 0.26 (3 H, s, SiCH_3), 1.02 (9 H, s, C(CH_3)$_3$), 1.17 (3 H, t, *J* 7.1 Hz, CH_3CH$_2$O), 2.51 (2 H, dt, *J* 7.7, 1.8 Hz, 4-H), 2.85 (2 H, t, *J* 7.7 Hz, 5-H), 3.04 (1 H, br s, O*H*), 3.65 (2 H, q, *J* 7.1 Hz, CH$_3$CH_2O), 5.20 (2 H, s, OCH_2O), 5.70 (1 H, s, 1-H), 6.78-7.53 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.1 (CH$_3$, Si(*C*H$_3$)$_2$), 14.8 (CH$_3$, *C*H$_3$CH$_2$O), 17.9 (C, *C*(CH$_3$)$_3$), 19.2 (CH$_2$, C-4), 25.5 (CH$_3$, C(*C*H$_3$)$_3$), 29.7 (CH$_2$, C-5), 60.1 (CH, C-1), 63.8 (CH$_2$, CH$_3$*C*H$_2$O), 80.1 (C, C-2), 85.9 (C, C-3), 92.6 (CH$_2$, O*C*H$_2$O), 113.5, 118.0, 121.1, 121.1, 127.3, 127.7, 128.7, 129.9 (CH, Ar-*C*H), 129.1 (C, C-1″), 131.6 (C, C-1′), 152.4 (C, C-2′), 154.9 (C, C-2″); ***m/z*** (CI, %) 441 (MH^+, 4), 423 (3), 377 (100), 249 (45), 179 (60); **HRMS** Found (CI): (MH^+), 441.2455, $C_{26}H_{37}O_4Si$ requires 441.2383.

1-(2′-(*tert*-Butyldimethylsilyloxy)phenyl)-5-(2″-(ethoxymethoxy)phenyl)pent-2-yn-1-one 184a



The IBX oxidation was carried out according to the standard procedure **3.2.4.B** using secondary alcohol **202a** (50 mg, 0.11 mmol) and *o*-Iodoxybenzoic acid (94 mg, 0.33 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **184a** (42 mg, 87%) as a yellow oil. **IR** ν_{max}(film): 2930, 2209, 1719, 1651, 1479, 1295, 1231, 1101, 840 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.22 (6 H, s, 2 × SiCH_3), 1.01 (9 H, s, C(CH_3)$_3$), 1.22 (3 H, t, *J* 7.1 Hz, CH_3CH_2O), 2.73 (2 H, t, *J* 7.6 Hz, 4-H), 2.96 (2 H, t, *J* 7.6 Hz, 5-H), 3.71 (2 H, q, *J* 7.1 Hz, CH_3CH_2O), 5.25 (2 H, s, OCH_2O), 6.78-7.53 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.1 (CH_3, Si(CH_3)$_2$), 14.8 (CH_3, CH_3CH_2O), 17.9 (C, $C(CH_3)_3$), 19.2 (CH_2, C-4), 25.5 (CH_3, C(CH_3)$_3$), 29.7 (CH_2, C-5), 64.2 (CH_2, CH_3CH_2O), 81.7 (C, C-2), 92.9 (CH_2, OCH_2O), 94.4 (C, C-3), 113.7, 120.8, 121.4, 127.9, 130.2, 132.9, 133.9, 134.5 (CH, Ar-*C*H), 128.5 (C, C-1″), 129.2 (C, C-1′), 155.2 (C, C-2′), 155.5 (C, C-2″) 177.6 (C, *C*=O); ***m/z*** (FAB, %) 439 (MH^+, 39), 377 (9), 363 (4), 307 (17), 235 (100); **HRMS** Found (FAB): (MH^+), 439.2306, $C_{26}H_{35}O_4Si$ requires 439.2305.

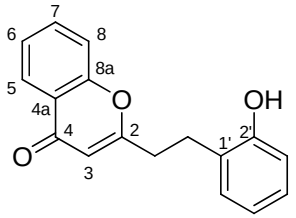
2-(2′-(Ethoxymethoxy)phenethyl)-4*H*-chromen-4-one 215a



The reaction was carried out according to the standard procedure **3.2.4.C** using ynone **184a** (135 mg, 0.31 mmol) and diethylamine (0.63 mL, 6.16 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **215a** (97 mg, 97 %) as a yellow oil. ; **IR** ν_{max}(film): 2929, 1654, 1595, 1495, 1228 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.30 (3 H, t, *J* 7.1 Hz, CH_3CH_2O), 3.00 (2 H, t, *J* 7.6 Hz, C-2–CH_2CH_2–C-1′), 3.15 (2 H, t, *J* 7.6 Hz, C-2–CH_2CH_2–C-1′), 3.77 (2 H, q, *J* 7.1 Hz, CH_3CH_2O), 5.30 (2 H, s, OCH_2O), 6.23 (1 H, s, 3-H), 6.97-8.23 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (CH_3, CH_3CH_2O), 28.1 (CH_2, C-2–CH_2CH_2–C-1′), 34.7 (CH_2, C-2–CH_2CH_2–C-1′), 64.3 (CH_2, CH_3OCH_2), 93.0 (CH_2, OCH_2O), 110.0 (CH, C-3), 113.9, 117.8, 121.6, 124.9, 125.6,

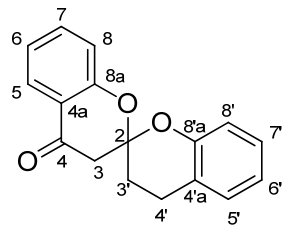
127.9, 129.9, 133.4 (CH, Ar-*C*H), 127.7, (C, C-4a), 128.6 (C, C-1′), 155.3 (C, C-8a), 156.5 (C, C-2′), 169.1 (C, C-2), 178.3 (C, C-4); ***m/z*** (EI, %) 324 (M^+, 78), 265 (18), 188 (68), 173 (10), 92 (12), 59 (100); **HRMS** Found (EI): (M^+), 324.1362, $C_{20}H_{20}O_4$ requires 324.1362.

2-(2′-Hydroxyphenethyl)-4*H*-chromen-4-one 216a



The deprotection step was carried out according to the standard procedure **3.2.4.D** using chromenone **215a** (8.5 mg, 26 μmol) and carbon tetrabromide (34 μL, 26 μmol). The product was purified by flash chromatography using hexanes/EtOAc (6:4) as eluent to give the *title compound* **216a** (6.77 mg, 97%) as a pale yellow solid. **M.p.** = 145-147 ^oC; **IR** ν_{max}(film): 3406, 1650, 1634, 1231 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.98 (2 H, t, *J* 7.6 Hz, C-2–CH_2CH$_2$–C-1′), 3.09 (2 H, t, *J* 7.6 Hz, C-2–CH$_2$CH_2–C-1′), 6.23 (1 H, s, 3-H), 6.51 (1 H, br s, O*H*), 6.79-8.21 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3 (CH_2, C-2–CH$_2$*C*H$_2$–C-1′), 34.5 (CH_2, C-2–*C*H$_2$CH$_2$–C-1′), 109.8 (CH, C-3), 115.4, 117.9, 120.4, 125.0, 125.6, 127.9, 130.2, 133.7 (CH, Ar-*C*H), 123.4, (C, C-4a), 126.1 (C, C-1′), 154.2 (C, C-8a), 156.6 (C, C-2′), 169.9 (C, C-2), 179.0 (C, C-4); ***m/z*** (EI, %) 266 (M^+, 49), 173 (4), 160 (100), 121 (21), 107 (26); **HRMS** Found (EI): (M^+), 266.0952, $C_{17}H_{14}O_3$ requires 266.0943.

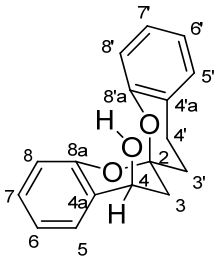
2,2'-Spirobi[chroman]-4-one 183a



The spirocyclisation was carried out according to the standard procedure **3.2.4.E** using chromemone **216a** (18 mg, 0.07 mmol) and potassium carbonate (2.0 g, 14.5 mmol). The resultant residue was purified by flash column chromatography using hexanes/EtOAc (9:1) as eluent to give the *title compound* **183a** as a pale yellow oil (11 mg, 0.041 mmol, 62%); **IR** ν_{max}(film): 2923, 1684, 1459 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.03 (1 H, ddd, *J* 13.6, 13.3, 6.1 Hz, 3′-H_α), 2.43 (1 H, ddd, *J* 13.6, 6.1, 1.9 Hz, 3′-H_β), 2.79 (1 H, ddd, *J* 16.4, 6.1, 1.9 Hz, 4′-H_β), 3.06 (2 H, s, 3-H), 3.29 (1 H, ddd, *J* 16.4, 13.3, 6.1 Hz, 4′-H_α), 6.64-7.95 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.4 (CH_2, C-4′), 30.4 (CH_2, C-3′), 47.6 (CH_2, C-3), 100.8 (C, C-2), 117.1, 118.2, 121.5, 121.9, 126.3, 127.4, 129.0, 136.0 (CH, Ar-*C*H), 121.1 (C, C-4a), 121.3 (C, C-4a′), 151.3 (C, C-8a′), 157.6 (C, C-8a), 190.5 (C, C-4); **HRMS** Found (EI): (M^+), 266.0949, $C_{17}H_{14}O_3$ requires 266.0946.

3.3.1.4 Diastereoselective Reduction of 183a

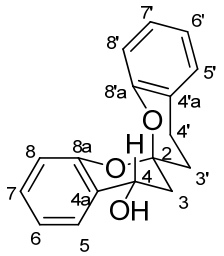
(2*R*,4*R*)-2,2'-Spirobi[chroman]-4-ol 182_{ax}



To a stirred solution of ketone **183a** (9 mg, 0.03mmol) in ethanol (1 mL) cooled to 0 ^oC under N_2, was added sodium borohydride (2 mg, 0.05 mmol). The cooling bath was removed after 5 min and the solution was warmed to r.t. and stirred for 10 min. Ethanol was removed *in vacuo* and the resultant residue was taken up in EtOAc (1 mL) then washed with H_2O (0.5 mL) and brine (0.5 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash chromatography using hexanes/EtOAc (7:3) as eluent to give *title compounds* **182_{ax}** and **182_{eq}** (ratio of 4:1, 4 mg, 44%) as colourless oils. **IR** ν_{max}(film): 3568, 2928, 1584, 1487, 1458, 1210, 1096, 1063, 874, 751 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.10 (1 H, ddd, *J* 13.3, 13.3, 5.9 Hz, 3′-H_α), 2.27 (2 H, m, 3-H), 2.61 (1 H, dd,

J 14.6, 1.7 Hz, 3′-H_β), 2.76 (1 H, ddd, *J* 16.3, 5.8, 2.0 Hz, 4′-H_β), 3.31 (1 H, ddd, *J* 16.3, 13.3, 6.1 Hz, 4′-H_α), 3.68 (1 H, d, *J* 11.6 Hz, O*H*), 4.76 (1 H, ddd, *J* 11.6, 5.0, 1.7 Hz, 4-H_β), 6.62-7.48 (8 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 20.4 (CH_2, C-4′), 31.2 (CH_2, C-3′), 39.3 (CH_2, C-3), 63.5 (CH, C-4), 97.9 (C, C-2), 116.9, 117.4, 121.5, 121.9, 127.3, 129.3, 129.5, 130.5 (Ar-*C*H), 124.4 (C, C-4a), 125.9 (C, C-4a′), 151.0 (C, C-8a′), 151.1 (C, C-8a); ***m/z*** (EI, %) 268 (M^+, 18), 250 (73), 146, (63), 144 (100), 131 (22), 107 (29), 77 (19); **HRMS** Found (EI): (M^+), 268.1100, $C_{17}H_{16}O_3$ requires 268.1099.

(2*R*,4*S*)-2,2'-Spirobi[chroman]-4-ol 182$_{eq}$

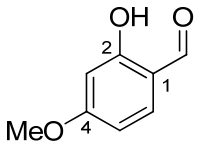


IR ν_{max}(film): 3413, 2930, 1713, 1583, 1487, 1455, 1217, 1145, 1055, 920, 879, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.99 (2 H, m, 3-H), 2.26 (1 H, ddd, *J* 13.4, 5.9, 2.5 Hz, 3′-H_α), 2.59 (1 H, dd, *J* 13.0, 6.2 Hz, 3′-H_β), 2.76 (1 H, ddd, *J* 16.3, 5.8, 2.5 Hz, 4′-H_β), 3.26 (1 H, ddd, *J* 16.3, 13.0, 6.0 Hz, 4′-H_α), 5.32 (1 H, ddd, *J* 10.9, 6.3 Hz, 4-H), 6.68-7.55 (8 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 20.6 (CH_2, C-4′), 31.2 (CH_2, C-3′), 41.1 (CH_2, C-3), 62.8 (CH, C-4), 97.9 (C, C-2), 116.9, 117.0, 121.1, 121.4, 126.2, 127.3, 128.9, 129.1 (Ar-*C*H), 125.9 (C, C-4a), 126.1 (C, C-4a′), 151.1 (C, C-8a′), 151.3 (C, C-8a); ***m/z*** (EI, %) 268 (M^+, 18), 250 (79), 146, (63), 144 (100), 131 (22), 107 (26), 77 (15); **HRMS** Found (EI): (M^+), 268.1099, $C_{17}H_{16}O_3$ requires 268.1099.

3.3.2 Analogue B- 7-Methoxy-2,2'-spirobi[chroman]-4-one 183b

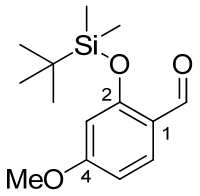
3.3.2.1 Synthesis of Aldehyde 185b

2-Hydroxy-4-methoxybenzaldehyde 192b



To a solution of 2,4-dimethoxybenzaldehyde (2 g, 12.0 mmol) in CH_2Cl_2 (50 mL) was added a solution of BCl_3 (2.4 mL, 1 M in CH_2Cl_2, 24.0 mmol) dropwise at 0 °C. After stirring at r.t. for 16 h the mixture was cooled to 0 °C and the reaction was washed with 1 M HCl (30 mL) followed by H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (2 × 50 mL). It was then dried over $MgSO_4$, and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography using hexanes/EtOAc (3:1) as eluent to give the *title compound* **192b** as a pale yellow oil (2.4 g, 74 %). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.87 (3 H, s, OC*H*$_3$), 6.43 (1 H, d, *J* 1.5 Hz, 3-H), 6.54 (1 H, dd, *J* 8.6, 1.5 Hz, 5-H), 7.42 (1 H, d, *J* 8.6 Hz, 6-H), 9.72 (1 H, s, O*H*), 11.50 (1 H, s, C*H*O). The ^{1}H NMR data were in agreement with the literature.[105]

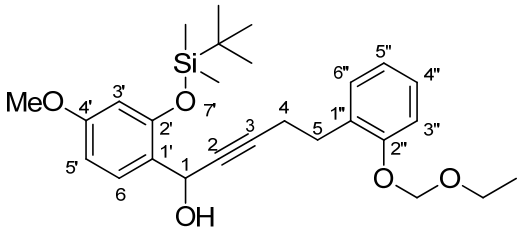
2-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzaldehyde 185b



The protection step was carried out according to the standard procedure **3.2.3** using benzaldehyde **192b** (1.0 g, 7.24 mmol), imidazole (1.18 mL, 17.4 mmol), 4-dimethylaminopyridine (100 mg, 0.82 mmol) and *tert*-butyldimethylsilyl chloride (3.06 g, 20.3 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **185b** (1.69 g, 88%) as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.22 (6 H, s, Si(C*H*$_3$)$_2$), 0.95 (9 H, s, C(C*H*$_3$)$_3$), 3.76 (3 H, s, OC*H*$_3$), 6.27-7.72 (3 H, m, Ar-*H*), 10.2 (1 H, s, C*H*O). The ^{1}H NMR data were in agreement with the literature.[106]

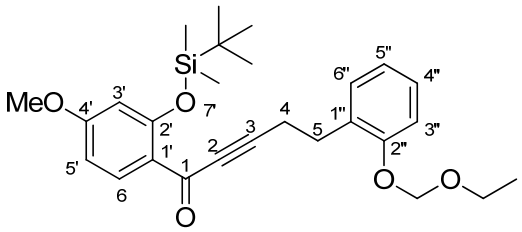
3.3.2.2 Synthesis of Spiroketal 183b (Analogue B)

1-(2′-(*tert*-Butyldimethylsilyloxy)-4′-methoxyphenyl)-5-(2″-(ethoxymethoxy)phenyl)pent-2-yn-1-ol 202b



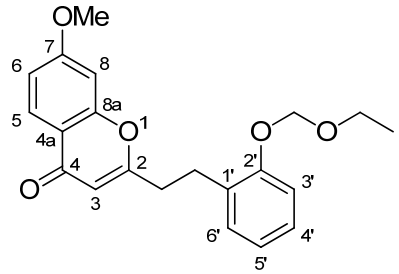
The coupling reaction was carried out according to the standard procedure **3.2.4.A** using acetylene **186a** (500 mg, 2.45 mmol), aldehyde **185b** (652 mg, 2.45 mmol), and *n*-butyllithium (1.73 mL, 1.6 M in hexanes, 2.69 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **202b** (864 mg, 75%) as a yellow oil. **IR** ν_{max}(film): 3156, 2929, 2165, 1607, 1583, 1503, 1254, 1099, 838 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.32 (6 H, s, 2 × SiCH_3), 1.06 (9 H, s, C(CH_3)$_3$), 1.24 (3 H, t, *J* 6.8 Hz, CH_3CH$_2$O), 1.77 (1 H, br s, O*H*), 2.60 (2 H, t, *J* 6.8 Hz, 4-H), 2.91 (2 H, t, *J* 6.8 Hz, 5-H), 3.73 (2 H, q, *J* 6.8 Hz, CH$_3$CH_2O), 3.79 (3 H, s, OCH_3), 5.26 (2 H, s, OCH_2O), 5.68 (1 H, s, 1-H), 6.41-7.47 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.3 (CH$_3$, Si(*C*H$_3$)$_2$), 15.0 (CH$_3$, *C*H$_3$CH$_2$O), 18.1 (C, *C*(CH$_3$)$_3$), 19.4 (CH$_2$, C-4), 25.7 (CH$_3$, C(*C*H$_3$)$_3$), 30.0 (CH$_2$, C-5), 55.2 (CH$_3$, O*C*H$_3$), 60.3 (CH$_2$, CH$_3$*C*H$_2$O), 64.2 (CH, C-1), 80.2 (C, C-2), 86.3 (C, C-3), 92.9 (CH$_2$, O*C*H$_2$O), 105.2, 105.8, 113.7, 121.3, 127.5, 128.8, 130.2 (CH, Ar-*C*H), 127.7 (C, C-1″), 129.4 (C, C-1′), 153.8 (C, C-2′), 155.2 (C, C-4′), 160.3 (C, C-2″); ***m/z*** (CI, %) 470 (M^+, 9), 338 (38), 209 (46), 73 (100), 59 (74); **HRMS** Found (CI): (M^+), 470.2479, $C_{27}H_{38}O_5Si$ requires 470.2489.

1-(2′-(*tert*-Butyldimethylsilyloxy)-4′-methoxyphenyl)-5-(2″-(ethoxymethoxy)phenyl)pent-2-yn-1-one 184b



The IBX oxidation was carried out according to the standard procedure **3.2.4.B** using secondary alcohol **202b** (52 mg, 0.11 mmol) and *o*-Iodoxybenzoic acid (94 mg, 0.33 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **184b** (46 mg, 88%) as a yellow oil. **IR** ν_{max}(film): 2929, 2213, 1639, 1601, 1230, 1099, 838 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.23 (3 H, s, Si-CH_3), 0.24 (3 H, s, Si-CH_3), 1.02 (9 H, s, C(CH_3)$_3$), 1.22 (3 H, t, *J* 7.4 Hz, CH_3CH$_2$O), 2.72 (2 H, t, *J* 7.6 Hz, 4-H), 2.96 (2 H, t, *J* 7.6 Hz, 5-H), 3.72 (2 H, q, *J* 7.4 Hz, CH$_3$CH_2O), 3.82 (3 H, s, OCH_3), 5.26 (2 H, s, OCH_2O), 6.35-7.72 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.3 (CH_3, Si(*C*H$_3$)$_2$), 15.1 (CH_3, *C*H$_3$CH$_2$O), 18.5 (C, *C*(CH$_3$)$_3$), 19.8 (CH_2, C-4), 25.8 (CH_3, C(*C*H$_3$)$_3$), 29.3 (CH_2, C-5), 55.4 (CH_3, O*C*H$_3$), 64.3 (CH_2, CH$_3$*C*H$_2$O), 81.5 (C, C-2), 93.0 (CH_2, O*C*H$_2$O), 93.4 (C, C-3), 106.8, 106.9, 113.8, 121.5, 127.9, 130.3, 135.5 (CH, Ar-*C*H), 122.6 (C, C-1″), 128.7 (C, C-1′), 155.3 (C, C-2″), 157.9 (C, C-2′), 164.4 (C, C-4′), 175.9 (C, C-1); ***m/z*** (FAB, %) 468 (M^+, 1), 411 (36), 365 (58), 246 (20), 51 (100); **HRMS** Found (FAB): (M^+), 468.2330, $C_{27}H_{36}O_5Si$ requires 468.2332.

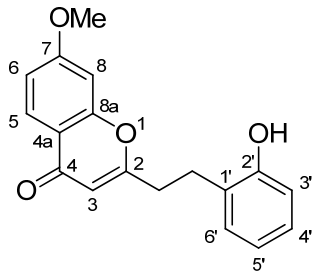
2-(2′-(Ethoxymethoxy)phenethyl)-7-methoxy-4H-chromen-4-one 215b



The reaction was carried out according to the standard procedure **3.2.4.C** using ynone **184b** (145 mg, 0.31 mmol) and diethylamine (0.63 mL, 6.16 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **215b**

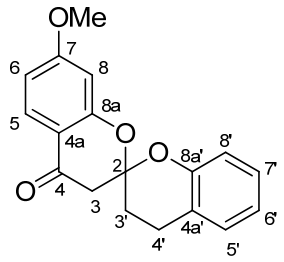
(101 mg, 92 %) as a yellow oil. ; **IR** ν_{max}(film): 2977, 1644, 1229 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.23 (3 H, t, *J* 6.9 Hz, C*H*$_3$CH$_2$O), 2.89 (2 H, t, *J* 6.3 Hz, C-2–C*H*$_2$CH$_2$–C-1′), 3.06 (2 H, t, *J* 6.3 Hz, C-2–CH$_2$C*H*$_2$–C-1′), 3.70 (2 H, q, *J* 6.9 Hz, CH$_3$C*H*$_2$O), 3.90 (3 H, s, OC*H*$_3$), 5.23 (2 H, s, OC*H*$_2$O), 6.08 (1 H, s, 3-H), 6.81-8.09 (7 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.1 (CH$_3$, *C*H$_3$CH$_2$O), 28.1 (CH$_2$, C-2–CH$_2$*C*H$_2$–C-1′), 34.5 (CH$_2$, C-2–*C*H$_2$CH$_2$–C-1′), 55.7 (CH$_3$, O*C*H$_3$), 64.3 (CH$_2$, CH$_3$*C*H$_2$O), 93.1 (CH$_2$, O*C*H$_2$O), 100.2 (CH, C-3), 109.8, 113.9, 113.9, 121.6, 127.0, 127.9, 129.9 (CH, Ar-*C*H), 117.6, (C, C-4a), 128.7 (C, C-1′), 155.3 (C, C-8a), 158.2 (C, C-2′), 163.9 (C, C-7), 168.5 (C, C-2), 177.5 (C, C-4); ***m/z*** (EI, %) 354 (M^+, 99), 218 (97), 190 (92), 151 (53), 51(89); **HRMS** Found (EI): (M^+), 354.1470, $C_{21}H_{22}O_5$ requires 354.1467.

2-(2′-Hydroxyphenethyl)-7-methoxy-4H-chromen-4-one 216b



The deprotection step was carried out according to the standard procedure **3.2.4.D** using chromenone **215b** (9.2 mg, 26 μmol) and carbon tetrabromide (34 μL, 26 μmol). The product was purified by flash chromatography using hexanes/EtOAc (6:4) as eluent to give the *title compound* **216b** (7.3 mg, 95%) as a pale yellow solid. **IR** ν_{max}(film): 3091, 1628 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.92-2.98 (2 H, m, C-2–C*H*$_2$CH$_2$–C-1′), 3.04-3.09 (2 H, m, C-2–CH$_2$C*H*$_2$–C-1′), 3.91 (3 H, s, OC*H*$_3$), 6.18 (1 H, s, 3-H), 6.77-8.08 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.4 (CH$_2$, C-2–CH$_2$*C*H$_2$–C-1′), 34.4 (CH$_2$, C-2–*C*H$_2$CH$_2$–C-1′), 55.8 (CH$_3$, O*C*H$_3$), 100.2 (CH, C-3), 109.5, 114.3, 115.5, 120.2, 127.0, 127.9, 130.1 (CH, Ar-*C*H), 125.0, (C, C-4a), 126.2 (C, C-1′), 145.5 (C, C-2′), 154.5 (C, C-8a), 158.4 (C, C-7), 164.1 (C, C-2), 169.4 (C, C-4); ***m/z*** (EI, %) 266 (M^+, 46), 190 (100), 129 (30), 57 (56); **HRMS** Found (EI): (M^+), 296.1046, $C_{18}H_{16}O_4$ requires 296.1049.

7-Methoxy-2,2'-spirobi[chroman]-4-one 183b

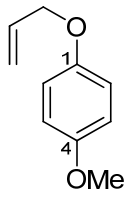


The spirocyclisation was carried out according to the standard procedure **3.2.4.E** using chromemone **216b** (20 mg, 0.07 mmol) and potassium carbonate (2.0 g, 14.5 mmol). The resultant residue was purified by flash column chromatography using hexanes/EtOAc (9:1) as eluent to give the *title compound* **183b** as a pale yellow oil (12 mg, 60%); **IR** ν_{max}(film): 2925, 1684, 1440 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.02 (1 H, ddd, *J* 13.6, 13.3, 6.0 Hz, 3′-H$_\alpha$), 2.41 (1 H, ddd, *J* 13.6, 6.0, 2.0 Hz, 3′-H$_\beta$), 2.76 (1 H, ddd, *J* 16.3, 6.0, 2.0 Hz, 4′-H$_\beta$), 2.99 (2 H, s, 3-H), 3.25 (1 H, ddd, *J* 16.3, 13.3, 6.0 Hz, 4′-H$_\alpha$), 3.75 (3 H, s, OC*H*$_3$), 6.28-7.58 (7 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 20.4 (CH_2, C-4′), 30.4 (CH_2, C-3′), 47.3 (CH_2, C-3), 55.6 (CH_3, O*C*H$_3$), 101.0 (C, C-2), 101.5, 110.0, 117.1, 121.5, 127.5, 128.1, 129.0 (CH, Ar-*C*H), 121.0 (C, C-4a), 122.0 (C, C-4a′), 145.2 (C, C-7), 151.6 (C, C-8a′), 152.0 (C, C-8a), 172.3 (C, C-4); ***m/z*** (CI, %) 296 (M^+, 50), 190 (100), 151 (25), 107 (16); **HRMS** Found (CI): (M^+), 296.1050, $C_{18}H_{16}O_4$ requires 296.1049.

3.3.3 Analogue C- 6',8-Dimethoxy-2,2'-spirobi[chroman]-4-one 183c

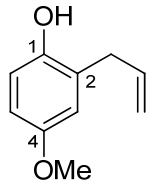
3.3.1.1 Synthesis of Aryl Acetylene 186b

1-(Allyloxy)-4-methoxybenzene 190b



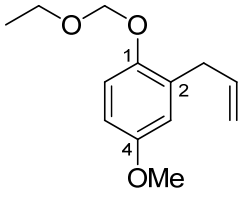
The allylation reaction was carried out according to the standard procedure **3.2.1.A** using 4-methoxyphenol **191c** (5.0 g, 40 mmol), allyl bromide (3.5 mL, 40 mmol) and potassium carbonate (11.0 g, 80 mmol). The product was purified by column chromatography using hexanes/EtOAc (9:1) as the eluent to give the *title compound* **190b** (6.04 g, 92%) as colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.74 (3 H, s, OC*H*$_3$), 4.56 (2 H, m, OC*H*$_2$CH=CH$_2$), 5.41 (1 H, m, OCH$_2$CH=C*H*$_\alpha$H$_\beta$), 5.42 (1 H, m, OCH$_2$CH=CH$_\alpha$*H*$_\beta$), 6.10 (1 H, m, OCH$_2$C*H*=CH$_2$), 6.80-6.95 (4 H, m, Ar-*H*). The ^{1}H NMR data were in agreement with the literature.[107]

2-Allyl-4-methoxyphenol 193b



The Clasien was carried out according to the standard procedure **3.2.1.B** using 1-(allyloxy)-4-methoxybenzene **190b** (6.37 g, 39 mmol). The product was purified by column chromatography using hexanes/EtOAc (1:1) as the eluent to give the *title compound* **193b** (5.76 g, 90%) as colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.36 (2 H, m, C*H*$_2$CH=CH$_2$), 3.74 (3 H, s, OC*H*$_3$), 5.10 (1 H, m, CH$_2$CH=C*H*$_\alpha$H$_\beta$), 5.16 (1 H, m, CH$_2$CH=CH$_\alpha$*H*$_\beta$), 5.20 (1 H, br s, O*H*), 6.00 (1 H, m, CH$_2$C*H*=CH$_2$), 6.60-6.80 (3 H, m, Ar-*H*). The ^{1}H NMR data were in agreement with the literature.[108]

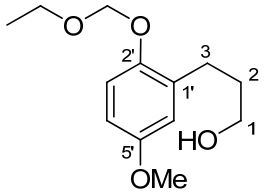
2-Allyl-1-(ethoxymethoxy)-4-methoxybenzene 189b



The protection step was carried out according to the standard procedure **3.2.1.C** using 2-allyl-4-methoxyphenol **193b** (6.37 g, 39 mmol), diisopropylamine (12.2 mL, 70 mmol) and

ethoxymethyl chloride (4.87 mL, 43 mmol). The product was purified by column chromatography using hexanes/EtOAc (8:2) as the eluent to give the *title compound* **189b** (7.45 g, 86%) as colourless oil. **IR** ν_{max}(film): 3077, 2934, 1285, 1150 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.23 (3 H, t, *J* 7.0 Hz, OCH_2CH_3), 3.37 (2 H, m, $CH_2CH=CH_2$), 3.71 (2 H, q, *J* 7.0 Hz, OCH_2CH_3), 3.74 (3 H, s, OCH_3), 5.03 (1 H, m, $CH_2CH=CH_\alpha H_\beta$), 5.07 (1 H, m, $CH_2CH=CH_\alpha H_\beta$), 5.15 (2 H, s, OCH_2O), 5.98 (1 H, m, $CH_2CH=CH_2$), 6.60-7.10 (3 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.1 (CH_3, OCH_2CH_3), 34.4 (CH_2, $CH_2CH=CH_2$), 55.5 (CH_3, OCH_3), 64.1 (CH_2, OCH_2CH_3), 94.1 (CH_2, OCH_2O), 115.8 (CH_2, $CH_2CH=CH_2$), 111.6, 115.4, 115.7 (CH, Ar-*C*H), 132.7 (CH, $CH_2CH=CH_2$), 136.7 (C, C-2), 149.2 (C, C-1), 154.4 (C, C-4); ***m/z*** (EI, %) 222 (M^+, 65), 192 (22), 163 (36), 149 (31), 103 (11), 77 (10), 59 (100), 41 (10); **HRMS** Found (EI): (M^+), 222.1255 , $C_{13}H_{18}O_3$ requires 222.1256.

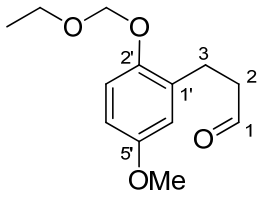
3-[2′-(Ethoxymethoxy)-5′-methoxyphenyl]propan-1-ol 188b



The hydroboration reaction was carried out according to the standard procedure **3.2.1.D** using 2-allyl-1-(ethoxymethoxy)-4-methoxybenzene **189b** (3.0 g, 13.5 mmol) and borane-dimethyl sulfide complex (2.7 mL, 27 mmol). The product was purified by column chromatography using hexanes/EtOAc (8:2) as the eluent to give the *title compound* **188b** (2.59 g, 80%) as colourless oil. **IR** ν_{max}(film): 3411, 2936, 2834, 1278, 1151 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (3 H, t, *J* 7.0 Hz, OCH_2CH_3), 1.84 (2 H, quintet, *J* 7.7, 6.2 Hz, 2-H), 2.60 (1 H, br s, O*H*), 2.70 (2 H, t, *J* 7.7 Hz, 3-H), 3.70 (2 H, t, *J* 6.2 Hz CH_2OH), 3.71 (2 H, q, *J* 7.0 Hz, OCH_2CH_3), 3.80 (3 H, s, OCH_3), 5.13 (2 H, s, OCH_2O), 6.60-7.10 (3 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.0 (CH_3, OCH_2CH_3), 26.1 (CH_2, C-2), 32.9 (CH_2, C-3), 55.4 (CH_3, OCH_3), 61.6 (CH_2, C-1), 64.2 (CH_2, OCH_2CH_3), 94.0 (CH_2, OCH_2O), 111.3, 115.5, 115.9 (CH, Ar-*C*H), 132.6 (C, C-1′), 149.3 (C, C-2′), 154.3 (C, C-5′); ***m/z*** (EI, %) 240 (M^+, 10), 194

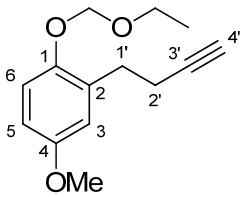
(10), 164 (100), 149 (25), 137 (16), 77 (9), 59 (35), 41 (10); **HRMS** Found (EI): (M^+), 240.1362 , $C_{13}H_{20}O_4$ requires 240.1362.

3-[2′-(Ethoxymethoxy)-5′-methoxyphenyl]propanal 187b



The IBX oxidation was carried out according to the standard procedure **3.2.1.E** using secondary alcohol (107 mg, 0.45 mmol) **188b** and *o*-iodoxybenzoic acid (376 mg, 1.34 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **187b** (83 mg, 78%) as colourless oil. **IR** ν_{max}(film): 2975, 2834, 2724, 1725, 1504, 1280 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.23 (3 H, t, *J* 7.0 Hz, OCH_2CH_3), 2.72 (2 H, dt, *J* 7.6, 1.5 Hz, 2-H), 2.92 (2 H, t, *J* 7.6 Hz, 3-H), 3.67 (2 H, q, *J* 7.0 Hz, OCH_2CH_3), 3.73 (3 H, s, OCH_3), 5.17 (2 H, s, OCH_2O), 6.70-7.00 (3 H, m, Ar-*H*), 9.80 (1 H, t, *J* 1.5 Hz, 1-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.0 (CH_3, OCH_2CH_3), 23.5 (CH_2, C-3), 43.9 (CH_2, C-2), 55.4 (CH_3, OCH_3), 64.1 (CH_2, OCH_2CH_3), 93.7 (CH_2, OCH_2O), 111.7, 115.2, 115.8 (CH, Ar-*C*H), 130.5 (C, C-1′), 149.3 (C, C-2′), 154.2 (C, C-5′), 202.0 (C, C-1); ***m/z*** (EI, %) 238 (M^+, 43), 208 (30), 180 (14), 151 (17), 136 (24), 77 (7), 59 (100), 41 (6); **HRMS** Found (EI): (M^+), 238.1206, $C_{13}H_{18}O_4$ requires 238.1205.

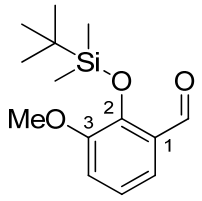
2-(But-3′-ynyl)-1-(ethoxymethoxy)-4-methoxybenzene 186b



The Ohira-Bestmann modification was carried out according to the standard procedure **3.2.1.F** using aldehyde **187b** (2.50 g, 10.5 mmol), potassium carbonate (2.90 g, 21.0 mmol) and diethyl diazo-2-oxopropylphosphonate **197** (2.77 g, 12.6 mmol). The product was purified by flash chromatography using hexanes/EtOAc (6:4) as eluent to give the *title compound* **186b** (2.21 g, 90%) as a pale yellow oil. **IR** ν_{max}(film): 3292, 2935, 1590, 1499, 1229 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.24 (3 H, t, *J* 7.0 Hz, OCH_2CH_3), 1.97 (1 H, t, *J* 2.7 Hz, 4′-H), 2.47 (2 H, dt, *J* 7.8, 2.6 Hz, 2′-H), 2.84 (2 H, t, *J* 7.5 Hz, 1′-H), 3.71 (2 H, q, *J* 7.0 Hz, CH_3CH_2O), 3.74 (3 H, s, OCH_3), 5.17 (2 H, s, OCH_2O), 6.70-7.04 (3 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.0 (CH_3, OCH_2CH_3), 18.9 (CH_2, C-2′), 29.9 (CH_2, C-1′), 55.4 (CH_3, OCH_3), 64.0 (CH_2, OCH_2CH_3), 68.5 (CH, C-4′), 84.3 (C, C-3′), 93.8 (CH_2, OCH_2O), 111.7, 115.2, 116.0, (CH, Ar-*C*H), 130.6, (C, C-2), 149.3 (C, C-1), 154.0 (C, C-4); ***m/z*** (FAB, %) 234 (M^+, 37), 189 (49), 137 (58), 59 (95); **HRMS** Found (EI): (M^+), 234.1251, $C_{13}H_{16}O_2$ requires 234.1256.

3.3.3.2 Synthesis of Aldehyde 185c

2-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzaldehyde 185c

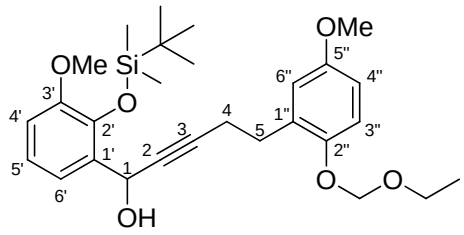


The protection step was carried out according to the standard procedure **3.2.3** using 2-hydroxy-3-methoxybenzaldehyde **192c** (3.0 g, 19.7 mmol), imidazole (3.22 g, 47.3 mmol), 4-dimethylaminopyridine (0.24 g, 1.97 mmol) and *tert*-butyldimethylsilyl chloride (3.76 g, 55.2 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **185c** (4.72 g, 90%) as a colourless oil. **IR** ν_{max}(film): 2930, 2734, 1696, 1593, 1505, 1285, 1151, 896 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.16 (6 H, s, 2 × $SiCH_3$), 0.96 (9 H, s, $C(CH_3)_3$), 3.82 (3 H, s, OCH_3), 6.87-7.38 (3 H, m, Ar-*H*), 9.80 (1 H, s, C*H*O); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.7 (CH_3, $Si(CH_3)_2$), 18.3 (C, $C(CH_3)_3$), 25.4 (CH_3,

C(*C*H_3)$_3$), 55.2 (CH_3, O*C*H_3), 110.1, 120.5, 126.0 (CH, Ar-*C*H), 130.9, (C, C-1), 151.0 (C, C-2), 151.4 (C, C-3), 190.2 (C, *C*HO); ***m/z*** (CI, %) 267 (M^+, (3), 225 (99), 210 (95), 195 (18); **HRMS** Found (CI): (M^+), 267.1423, $C_{14}H_{22}O_3Si$ requires 267.1417.

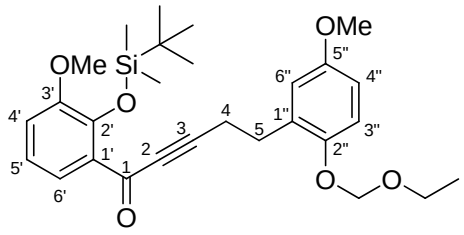
3.3.3.3 Synthesis of Spiroketal 183c (Analogue C)

1-(2′-(*tert*-Butyldimethylsilyloxy)-3′-methoxyphenyl)-5-(2″-(ethoxymethoxy)-5″-methoxyphenyl)pent-2-yn-1-ol 202c



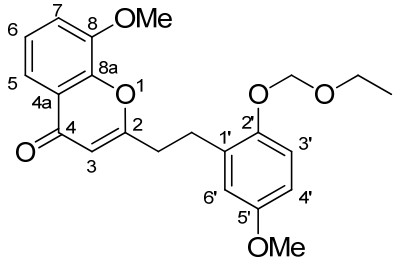
The coupling reaction was carried out according to the standard procedure **3.2.4.A** using acetylene **186b** (574 mg, 2.45 mmol), aldehyde **185c** (653 mg, 2.45 mmol), and *n*-butyllithium (1.73 mL, 1.6 M in hexanes, 2.69 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **202c** (880 mg, 76%) as a yellow oil. **IR** ν_{max}(film): 3417, 2930, 2248, 1500, 1464, 1416, 1281, 1101, 837 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.15 (6 H, s, SiCH_3), 1.00 (9 H, s, C(CH_3)$_3$), 1.21 (3 H, t, *J* 7.1 Hz, CH_3CH$_2$O), 2.56 (2 H, dt, *J* 7.6, 1.9 Hz, 4-H), 2.85 (2 H, t, *J* 7.6 Hz, 5-H), 3.71 (2 H, q, *J* 7.1 Hz, CH$_3$CH_2O), 3.71 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 5.15 (2 H, s, OCH_2O), 5.34 (1 H, s, 1-H), 6.66-7.02 (6 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ -4.7 (CH_3, Si(*C*H_3)$_2$), 15.0 (CH_3, *C*H$_3$CH$_2$O), 18.4 (C, *C*(CH$_3$)$_3$), 19.5 (CH_2, C-4), 25.7 (CH_3, C(*C*H_3)$_3$), 29.9 (CH_2, C-5), 55.4 (CH_3, O*C*H_3), 55.5 (CH_3, O*C*H_3), 64.1 (CH_2, CH$_3$*C*H$_2$O), 64.5 (CH, C-1), 80.7 (C, C-2), 86.7 (C, C-3), 93.8 (CH_2, O*C*H$_2$O), 110.7, 111.8, 115.4, 116.1, 119.1, 120.5 (CH, Ar-*C*H), 130.8 (C, C-1″), 134.7 (C, C-1′), 144.9 (C, C-2′), 149.4 (C, C-5″), 150.8 (C, C-2″), 154.1 (C, C-3′); ***m/z*** (CI, %) 500 (M^+, 7), 297 (100), 195 (80), 73 (65), 59 (61); **HRMS** Found (CI): (M^+), 500.2587, $C_{26}H_{37}O_4Si$ requires 500.2594.

1-(2′-(*tert*-Butyldimethylsilyloxy)-3′-methoxyphenyl)-5-(2″-(ethoxymethoxy)-5″-methoxyphenyl)pent-2-yn-1-one 184c



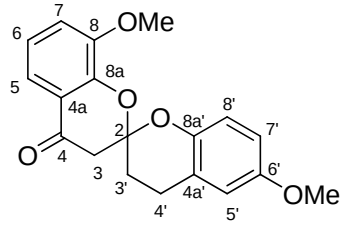
The IBX oxidation was carried out according to the standard procedure **3.2.4.B** using secondary alcohol **202c** (50 mg, 0.10 mmol) and *o*-iodoxybenzoic acid (84 mg, 0.30 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **184c** (39 mg, 78%) as a yellow oil. **IR** ν_{max}(film): 2931, 2224, 1633, 1589, 1282, 1212 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.17 (3 H, s, SiCH_3), 0.19 (3 H, s, SiCH_3), 0.99 (9 H, s, C(CH_3)$_3$), 1.21 (3 H, t, *J* 6.9 Hz, CH_3CH$_2$O), 2.76 (2 H, t, *J* 7.5 Hz, 4-H) 2.95 (2 H, t, *J* 7.5 Hz, 5-H), 3.69 (2 H, q, *J* 6.9 Hz, CH$_3$CH_2O), 3.72 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 5.19 (2 H, s, OCH_2O), 6.70-7.60 (6 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ -4.6 (CH_3, Si(*C*H$_3$)$_2$), 15.2 (CH_3, *C*H$_3$CH$_2$O), 18.5 (C, *C*(CH$_3$)$_3$), 19.8 (CH_2, C-4), 25.6 (CH_3, C(*C*H$_3$)$_3$), 29.4 (CH_2, C-5), 55.4 (CH_3, O*C*H$_3$), 55.5 (CH_3, O*C*H$_3$), 64.2 (CH_2, CH$_3$*C*H$_2$O), 80.1 (C, C-2), 93.8 (CH_2, O*C*H$_2$O), 95.1 (C, C-3), 110.9, 112.3, 115.3, 116.1, 120.3, 125.7 (CH, Ar-*C*H), 129.9 (C, C-1″), 131.2 (C, C-1′), 149.5 (C, C-2′), 151.0 (C, C-3′), 151.0 (C, C-5″), 154.2 (C, C-2″), 177.0 (C, C-1); ***m/z*** (FAB, %) 498 (M^+, 4), 367 (45), 265 (81), 193 (93), 59 (100); **HRMS** Found (FAB): (M^+), 498.2440, $C_{28}H_{38}O_6Si$ requires 498.2438.

2-(2′-(Ethoxymethoxy)-5′-methoxyphenethyl)-8-methoxy-4H-chromen-4-one 215c



The reaction was carried out according to the standard procedure **3.2.4.C** using ynone **184c** (154 mg, 0.31 mmol) and diethylamine (0.63 mL, 6.16 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **215c** (93 mg, 85 %) as a yellow oil. **IR** ν_{max}(film): 2979, 1647, 1235 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.22 (3 H, t, *J* 6.8 Hz, CH_3CH$_2$O), 2.90 (2 H, t, *J* 6.4 Hz, C-2–CH_2CH$_2$–C-1′), 3.16 (2 H, t, *J* 6.4 Hz, C-2–CH$_2$CH_2–C-1′), 3.70 (2 H, q, *J* 6.8 Hz, CH$_3$CH_2O), 3.77 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 5.19 (2 H, s, OCH_2O), 5.98 (1 H, s, 3-H), 6.66-7.67 (7 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.1 (CH$_3$, *C*H$_3$CH$_2$O), 29.5 (CH$_2$, C-2–CH$_2$*C*H$_2$–C-1′), 34.9 (CH$_2$, C-2–*C*H$_2$CH$_2$–C-1′), 55.7 (CH$_3$, O*C*H$_3$), 55.9 (CH$_3$, O*C*H$_3$), 64.1 (CH$_2$, CH$_3$*C*H$_2$O), 93.9 (CH$_2$, O*C*H$_2$O), 101.2 (CH, C-3), 112.2, 113.2, 115.0, 116.1, 118.6, 120.7 (CH, Ar-*C*H), 118.6, (C, C-4a), 131.7 (C, C-1′), 147.7 (C, C-8), 152.2 (C, C-8a), 154.5 (C, C-5′), 164.0 (C, C-2′), 165.0 (C, C-2), 184.5 (C, C-4); ***m/z*** (EI, %) 384 (M^+, 99), 218 (86), 190 (76), 151 (43), 51(23); **HRMS** Found (EI): (M^+), 384.1620, $C_{22}H_{23}O_6$ requires 384.1622.

6',8-Dimethoxy-2,2'-spirobi[chroman]-4-one 183c



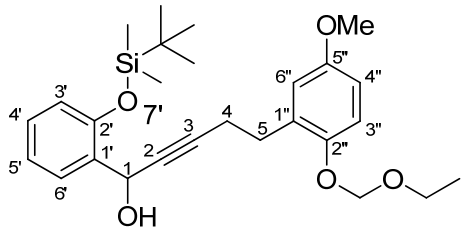
The deprotection/spirocyclisation step was carried out according to the standard procedure **3.2.4.D** using chromenone **215c** (11 mg, 0.03 mmol) and carbon tetrabromide (100 mg, 0.30 mmol). The product was purified by flash chromatography using hexanes/EtOAc (9:1) as eluent to give the *title compound* **183c** (5 mg, 54%) as a pale yellow oil. **IR** ν_{max}(film): 2923, 1684, 1497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.87 (1 H, ddd, *J* 13.0, 12.8, 6.1 Hz, 3′-H$_\alpha$), 2.15 (1 H, ddd, *J* 13.0, 6.1, 2.5 Hz, 3′-H$_\beta$), 2.56 (1 H, ddd, *J* 16.5, 6.1, 2.5 Hz, 4′-H$_\beta$), 3.01 (2 H, s, 3-H), 3.16 (1 H, ddd, *J* 16.5, 12.8, 6.1 Hz, 4′-H$_\alpha$), 3.95 (3H, s, OCH_3), 3.97 (3 H, s, OCH_3), 6.64-7.59 (6 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4 (CH$_2$, C-4′), 31.8 (CH$_2$, C-3′), 45.1 (CH$_2$, C-3), 56.1 (CH$_3$, O*C*H$_3$), 56.1 (CH$_3$, O*C*H$_3$), 95.5 (C, C-2), 109.8,

112.8, 113.3, 113.7, 113.9, 117.7 (CH, Ar-*C*H), 124.3 (C, C-4a′), 128.7 (C, C-4a), 130.6 (C, C-8), 145.2 (C, C-6′), 146.2 (C, C-8a′), 151.0 (C, C-8a), 172.3 (C, C-4); ***m/z*** (CI, %) 327 (MH^+, 50), 307 (100), 289 (9), 154 (18), 136 (12); **HRMS** Found (CI): (MH^+), 327.1237, $C_{19}H_{19}O_5$ requires 327.1233.

3.3.4 Analogue D- 6'-Methoxy-2,2'-spirobi[chroman]-4-one 183d

3.3.4.1 Synthesis of Spiroketal 183d (Analogue D)

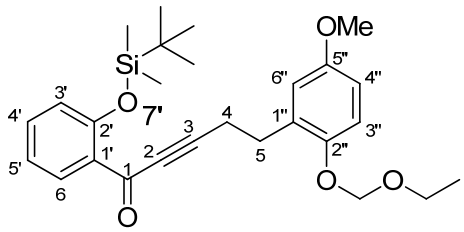
1-(2′-(*tert*-Butyldimethylsilyloxy)phenyl)-5-(2″-(ethoxymethoxy)-5″-methoxyphenyl)pent-2-yn-1-ol 202d



The coupling reaction was carried out according to the standard procedure **3.2.4.A** using acetylene **186b** (574 mg, 2.45 mmol), aldehyde **185a** (653 mg, 2.45 mmol), and *n*-butyllithium (1.73 mL, 1.6 M in hexanes, 2.69 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **202d** (945 mg, 82%) as a yellow oil. **IR** ν_{max}(film): 3414, 3366, 2225, 1586, 1473, 1461, 1253, 1074, 837 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.23 (6 H, s, SiCH_3), 0.99 (9 H, s, C(CH_3)$_3$), 1.17 (3 H, t, *J* 6.8 Hz, CH_3CH$_2$O), 1.98 (1 H, br s, O*H*), 2.50 (2 H, dt, *J* 7.2, 1.9 Hz, 4-H), 2.81 (2 H, t, *J* 7.2 Hz, 5-H), 3.65 (2 H, q, *J* 6.8 Hz, CH$_3$CH_2O), 3.66 (3 H, s, OCH_3), 5.11 (2 H, s, OCH_2O), 5.68 (1 H, s, 1-H), 6.64-7.50 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.3 (CH$_3$, Si(*C*H$_3$)$_2$), 15.0 (CH$_3$, *C*H$_3$CH$_2$O), 18.0 (C, *C*(CH$_3$)$_3$), 19.4 (CH$_2$, C-4), 25.6 (CH$_3$, C(*C*H$_3$)$_3$), 29.9 (CH$_2$, C-5), 55.3 (CH$_3$, O*C*H$_3$), 60.5 (CH$_2$, CH$_3$*C*H$_2$O), 64.0 (CH, C-1), 80.0 (C, C-2), 86.2 (C, C-3), 93.7 (CH$_2$, O*C*H$_2$O), 111.8, 115.2, 115.8, 118.2, 121.2, 127.9, 128.9 (CH, Ar-*C*H), 130.7 (C, C-1″), 131.5 (C, C-1′), 149.3 (C, C-2′), 152.7 (C, C-5″), 154.0 (C, C-2″); ***m/z*** (CI, %) 469

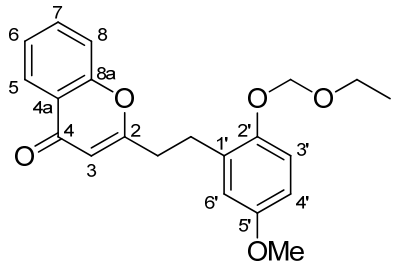
(M^+, 2), 293 (35), 279 (52), 137 (31), 73(100); **HRMS** Found (CI): (M^+), 470.2488, $C_{26}H_{37}O_4Si$ requires 470.2489.

1-(2′-(*tert*-Butyldimethylsilyloxy)phenyl)-5-(2″-(ethoxymethoxy)-5″-methoxyphenyl)pent-2-yn-1-one 184d



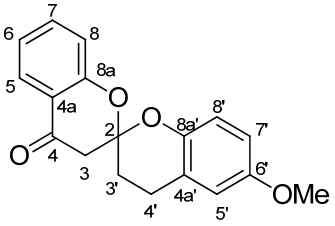
The IBX oxidation was carried out according to the standard procedure **3.2.4.B** using secondary alcohol **202d** (50 mg, 0.11 mmol) and *o*-iodoxybenzoic acid (94 mg, 0.33 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **184d** (41 mg, 82%) as a yellow oil. **IR** ν_{max}(film): 2931, 2209, 1647, 1597, 1258, 1233, 1073, 839 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.15 (3 H, s, SiCH_3), 0.18 (3 H, s, SiCH_3), 0.91 (9 H, s, C(CH_3)$_3$), 1.22 (3 H, t, *J* 7.1 Hz, CH_3CH$_2$O), 2.52 (2 H, dt, *J* 7.7, 1.9 Hz, 4-H) 2.88 (2 H, t, *J* 7.7 Hz, 5-H), 3.80 (2 H, q, *J* 7.1 Hz, CH$_3$CH_2O), 3.81 (3 H, s, OCH_3), 5.11 (2 H, s, OCH_2O), 6.75-7.85 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.3 (CH_3, Si(*C*H$_3$)$_2$), 15.2 (CH_3, *C*H$_3$CH$_2$O), 18.4 (C, *C*(CH$_3$)$_3$), 20.3 (CH_2, C-4), 25.8 (CH_3, C(*C*H$_3$)$_3$), 29.1 (CH_2, C-5), 55.7 (CH_3, O*C*H$_3$), 65.5 (CH_2, CH$_3$*C*H$_2$O), 81.7 (C, C-2), 94.3 (CH_2, O*C*H$_2$O), 97.5 (C, C-3), 110.9, 120.8, 121.4, 122.0, 124.2, 133.0, 133.9 (CH, Ar-*C*H), 129.4 (C, C-1″), 134.1 (C, C-1′), 144.5 (C, C-5″), 152.1 (C, C-2″), 155.5 (C, C-2′), 177.6 (C, C-1); ***m/z*** (FAB, %) 468 (M^+, 3), 365 (99), 235 (67), 73 (36), 59 (68); **HRMS** Found (FAB): (M^+), 468.2329, $C_{27}H_{36}O_5Si$ requires 468.2332.

2-(2′-(Ethoxymethoxy)-5′-methoxyphenethyl)-4H-chromen-4-one 215d



The reaction was carried out according to the standard procedure **3.2.4.C** using ynone **184d** (136 mg, 0.29 mmol) and diethylamine (0.60 mL, 5.76 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **215d** (94 mg, 92 %) as a yellow oil. ; **IR** ν_{max}(film): 3004, 1710, 1220 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (3 H, t, *J* 6.7 Hz, C*H*$_3$CH$_2$O), 2.90 (2 H, t, *J* 8.1 Hz, C-2–C*H*$_2$CH$_2$–C-1′), 3.02 (2 H, t, *J* 8.1 Hz, C-2–CH$_2$C*H*$_2$–C-1′), 3.66 (2 H, q, *J* 6.7 Hz, CH$_3$C*H*$_2$O), 3.69 (3 H, s, OC*H*$_3$), 5.13 (2 H, s, OC*H*$_2$O), 6.14 (1 H, s, 3-H), 6.67-8.17 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (CH_3, *C*H$_3$CH$_2$O), 28.2 (CH_2, C-2–CH$_2$*C*H$_2$–C-1′), 34.6 (CH_2, C-2–*C*H$_2$CH$_2$–C-1′), 55.5 (CH_3, O*C*H$_3$), 64.1 (CH_2, CH$_3$*C*H$_2$O), 93.8 (CH_2, O*C*H$_2$O), 110.0 (CH, C-3), 112.0, 115.3, 115.8, 117.7, 124.8, 125.6, 133.4 (CH, Ar-*C*H), 123.7, (C, C-4a), 129.9 (C, C-1′), 149.5 (C, C-5′), 154.2 (C, C-2′), 156.4 (C, C-8a), 168.9 (C, C-2), 178.3 (C, C-4); ***m/z*** (EI, %) 354 (M^+, 65), 309 (20), 188 (76), 160 (100), 59 (87); **HRMS** Found (EI): (M^+), 354.1472, $C_{21}H_{22}O_5$ requires 354.1467.

6'-Methoxy-2,2'-spirobi[chroman]-4-one 183d



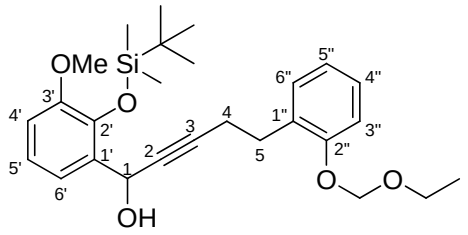
The deprotection/spirocyclisation step was carried out according to the standard procedure **3.2.4.D** using chromenone **215d** (9.2 mg, 0.03 mmol) and carbon tetrabromide (100 mg, 0.30 mmol). The product was purified by flash chromatography using hexanes/EtOAc (9:1) as eluent to give the *title compound* **183d** (2.9 mg, 36%) as a pale yellow oil. **IR** ν_{max}(film):

2930, 1693, 1461 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.03 (1 H, ddd, *J* 13.4, 13.3, 6.0 Hz, 3′-H_α), 2.38 (1 H, ddd, *J* 13.4, 6.0, 1.9 Hz, 3′-H_β), 2.76 (1 H, ddd, *J* 16.4, 6.0, 1.9 Hz, 4′-H_β), 3.04 (2 H, s, 3-H), 3.27 (1 H, ddd, *J* 16.4, 13.3, 6.0 Hz, 4′-H_α), 3.74 (3 H, s, OCH_3), 6.55-7.93 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.4 (CH_2, C-4′), 30.4 (CH_2, C-3′), 47.6 (CH_2, C-3), 55.6 (CH_3, O*C*H_3), 100.7 (C, C-2), 113.2, 113.6, 117.7, 118.2, 121.8, 126.3, 136.0 (CH, Ar-*C*H), 121.1 (C, C-4a), 122.3 (C, C-4a′), 145.3 (C, C-6′), 154.1 (C, C-8a′), 157.7 (C, C-8a), 190.8 (C, C-4); ***m/z*** (CI, %) 296 (M^+, 45), 281 (8), 160 (100), 137 (7), 121 (12); **HRMS** Found (CI): (M^+), 296.1046, $C_{18}H_{16}O_4$ requires 296.1049.

3.3.5 Analogue E- 8-Methoxy-2,2'-spirobi[chroman]-4-one 183e

3.3.5.1 Synthesis of Spiroketal 183e (Analogue E)

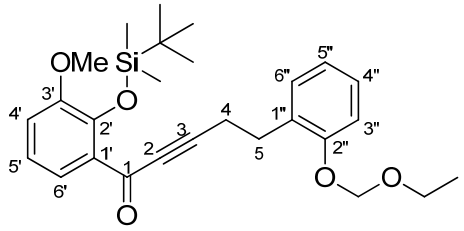
1-(2′-(*tert*-Butyldimethylsilyloxy)-3′-methoxyphenyl)-5-(2′′-(ethoxymethoxy)phenyl)pent-2-yn-1-ol 202e



The coupling reaction was carried out according to the standard procedure **3.2.4.A** using acetylene **186a** (500 mg, 2.45 mmol), aldehyde **185c** (653 mg, 2.45 mmol), and *n*-butyllithium (1.73 mL, 1.6 M in hexanes, 2.69 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **202e** (1.02 g, 81%) as a yellow oil. **IR** ν_{max}(film): 3414, 2929, 2232, 1510, 1492, 1286, 1100, 839 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.19 (6 H, s, SiCH_3), 1.04 (9 H, s, C(CH_3)$_3$), 1.24 (3 H, t, *J* 7.1 Hz, CH_3CH$_2$O), 2.56 (1 H, br s, O*H*), 2.58 (2 H, dt, *J* 7.7, 1.8 Hz, 4-H), 2.92 (2 H, t, *J* 7.7 Hz, 5-H), 3.75 (2 H, q, *J* 7.1, CH$_3$CH_2O), 3.81 (3 H, s, OCH_3), 5.25 (2 H, s, OCH_2O), 5.38 (1 H, s, 1-H), 6.81-7.23 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.7 (CH_3, Si(*C*H_3)$_2$), 15.0 (CH_3, *C*H$_3$CH$_2$O), 18.3 (C, *C*(CH$_3$)$_3$), 19.3 (CH_2, C-4), 25.6 (CH_3, C(*C*H_3)$_3$), 29.8 (CH_2, C-5),

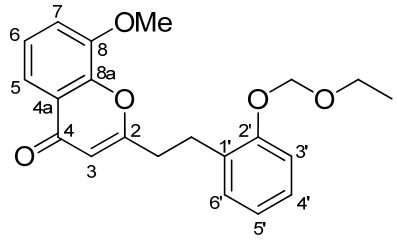
55.3 (CH_3, O*C*H_3), 64.2 (CH_2, CH_3*C*H_2O), 64.5 (CH, C-1), 80.7 (C, C-2), 86.8 (C, C-3), 92.9 (CH_2, O*C*H_2O), 110.7, 113.8, 119.1, 120.5, 121.3, 127.5, 130.1 (CH, Ar-*C*H), 129.1 (C, C-1″), 134.8 (C, C-1′), 145.0 (C, C-2′), 150.8 (C, C-3′), 155.1 (C, C-2″); ***m/z*** (CI, %) 470 (M^+, 13), 413 (27), 229 (61), 205 (63), 59 (100); **HRMS** Found (CI): (M^+), 470.2486, $C_{26}H_{37}O_4Si$ requires 470.2489.

1-(2′-(*tert*-Butyldimethylsilyloxy)-3′-methoxyphenyl)-5-(2″-(ethoxymethoxy)phenyl)pent-2-yn-1-one 184e



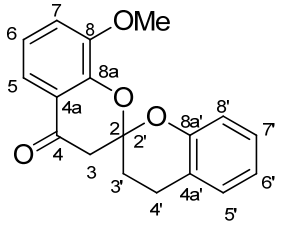
The IBX oxidation was carried out according to the standard procedure **3.2.4.B** using secondary alcohol **202e** (50 mg, 0.11 mmol) and *o*-iodoxybenzoic acid (94 mg, 0.33 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **184e** (42 mg, 84%) as a yellow oil. **IR** ν_{max}(film): 2930, 2223, 1637, 1589, 1282, 1219, 1101, 840 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.20 (6 H, s, SiC*H*$_3$), 1.02 (9 H, s, C(C*H*$_3$)$_3$), 1.22 (3 H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 2.82 (2 H, t, *J* 7.6 Hz, 4-H), 3.02 (2 H, t, *J* 7.6 Hz, 5-H), 3.73 (2 H, q, *J* 7.1 Hz, CH$_3$C*H*$_2$O), 3.83 (3 H, s, OC*H*$_3$), 5.27 (2 H, s, OC*H*$_2$O), 6.84-7.62 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.7 (CH_3, Si(*C*H$_3$)$_2$), 15.0 (CH_3, *C*H$_3$CH$_2$O), 18.1 (C, *C*(CH$_3$)$_3$), 19.6 (CH_2, C-4), 25.5 (CH_3, C(*C*H$_3$)$_3$), 29.1 (CH_2, C-5), 55.3 (CH_3, O*C*H$_3$), 64.2 (CH_2, CH$_3$*C*H$_2$O), 79.9 (C, C-2), 93.0 (CH_2, O*C*H$_2$O), 95.2 (C, C-3), 111.0, 113.8, 120.1, 121.4, 125.4, 127.9, 130.2 (CH, Ar-*C*H), 128.5 (C, C-1″), 131.2 (C, C-1′), 146.5 (C, C-2′), 151.0 (C, C-3′), 155.2 (C, C-2″), 177.9 (C, C-1); ***m/z*** (FAB, %) 468 (M^+, 6), 337 (35), 322 (29), 193 (100), 59 (41); **HRMS** Found (FAB): (M^+), 468.2340, $C_{27}H_{36}O_5Si$ requires 468.2332.

2-(2′-(Ethoxymethoxy)phenethyl)-8-methoxy-4H-chromen-4-one 215e



The reaction was carried out according to the standard procedure **3.2.4.C** using ynone **184e** (135 mg, 0.29 mmol) and diethylamine (0.60 mL, 5.76 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **215e** (95 mg, 92 %) as a yellow oil. ; **IR** ν_{max}(film): 2932, 1587, 1464, 1279 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24 (3 H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 2.70 (2 H, t, *J* 7.7 Hz, C-2–C*H*$_2$CH$_2$–C-1′), 3.04 (2 H, t, *J* 7.7 Hz, C-2–CH$_2$C*H*$_2$–C-1′), 3.75 (2 H, q, *J* 7.1 Hz, CH$_3$C*H*$_2$O), 3.96 (3 H, s, OC*H*$_3$), 5.27 (2 H, s, OC*H*$_2$O), 6.07 (1 H, s, 3-H), 6.91-7.48 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (CH$_3$, *C*H$_3$CH$_2$O), 26.9 (CH$_2$, C-2–CH$_2$*C*H$_2$–C-1′), 38.7 (CH$_2$, C-2–*C*H$_2$CH$_2$–C-1′), 56.0 (CH$_3$, O*C*H$_3$), 64.3 (CH$_2$, CH$_3$*C*H$_2$O), 93.2 (CH$_2$, O*C*H$_2$O), 95.3 (CH, C-3), 109.3, 114.0, 114.2, 121.6, 121.7, 127.6, 130.0 (CH, Ar-*C*H), 127.7, (C, C-4a), 129.6 (C, C-1′), 146.6 (C, C-8), 149.8 (C, C-8a), 155.3 (C, C-2′), 184.8 (C, C-2), 193.1 (C, C-4); ***m/z*** (EI, %) 354 (M^+, 65), 309 (20), 188 (76), 160 (100), 59 (87); **HRMS** Found (EI): (M^+), 354.1472, $C_{21}H_{22}O_5$ requires 354.1467.

8-Methoxy-2,2'-spirobi[chroman]-4-one 183e



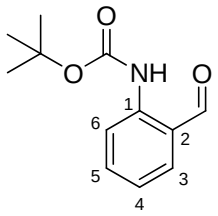
The deprotection/ spirocyclisation step was carried out according to the standard procedure **3.2.4.D** using chromenone **215e** (20 mg, 0.06 mmol) and carbon tetrabromide (100 mg, 0.30 mmol). The product was purified by flash chromatography using hexanes/EtOAc (9:1) as

eluent to give the *title compound* **183e** (10.6 mg, 64%) as a pale yellow oil. **IR** ν_{max}(film): 2923, 1684, 1459 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.88 (1 H, ddd, *J* 13.6, 13.3, 6.1 Hz, 3′-H_α), 2.17 (1 H, ddd, *J* 13.6, 6.1, 2.9 Hz, 3′-H_β), 2.69 (1 H, ddd, *J* 16.6, 6.1, 2.9 Hz, 4′-H_β), 3.01 (2 H, s, 3-H), 3.16 (1 H, ddd, *J* 16.6, 13.3, 6.1 Hz, 4′-H_α), 3.96 (3H, s, OC*H*$_3$), 6.68-7.39 (7 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (CH_2, C-4′), 31.8 (CH_2, C-3′), 45.1 (CH_2, C-3), 56.1 (CH_3, O*C*H$_3$), 95.5 (C, C-2), 109.1, 116.9, 117.1, 120.6, 121.6, 127.2, 129.1 (CH, Ar-*C*H), 124.3 (C, C-4a′), 127.6 (C, C-4a), 130.9 (C, C-8), 146.6 (C, C-8a′), 149.9 (C, C-8a), 180.1 (C, C-4); ***m/z*** (EI, %) 296 (M^+, 9), 166 (37), 151 (100), 148 (18), 120 (22), 91 (19); **HRMS** Found (EI): (M^+), 296.1048, $C_{18}H_{16}O_4$ requires 296.1049.

3.3.6 Spiroaminal- 1'H-Spiro[chroman-2,2'-quinolin]-4'(3'H)-one 237

3.3.6.1 Synthesis of Aldehyde 239

***tert*-Butyl 2-formylphenylcarbamate 239**

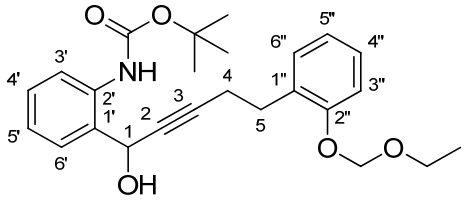


2-aminobenzyl alcohol **240** (2.01 g, 16.3 mmol) in THF (45 mL) was added di-*tert*-butyl carbonate (3.7 g, 16.9 mmol) and the reaction mixture was stirred at 25 °C for 12 h. The solvent was removed *in vacuo* and the residue was filtered over silica gel using hexanes/EtOAc (80:20). Removal of solvent *in vacuo* furnished crude 2-(*tert*-butoxycarbonylamino)benzyl alcohol which was subjected to oxidation without further purification. The crude benzyl alcohol (1.17 g, 5.2 mmol) in CH_2Cl_2 (35 mL) and pyridine (2.1 mL, 26 mmol) at 0 °C was treated with the Dess–Martin periodinane (3.41 g, 8.0 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was washed with sat. aq. $Na_2S_2O_3$, $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to

give the *title compound* **239** (2.92 g, 81%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.53 (9 H, s, C(CH_3)$_3$), 7.10-8.46 (4 H, m, Ar-*H*), 9.88 (1 H, s, C*H*O), 10.39 (1 H, s, N*H*). The ^{1}H NMR data were in agreement with the literature.[95]

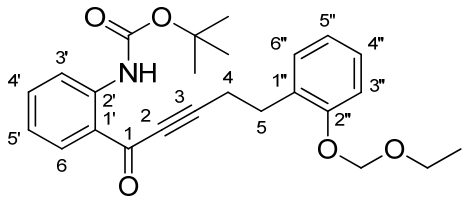
3.3.6.2 Synthesis of Spiroaminal 237

***tert*-Butyl 2′-(5-(2″-(ethoxymethoxy)phenyl)-1-hydroxypent-2-ynyl)phenylcarbamate 241**



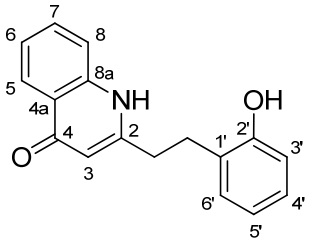
The coupling reaction was carried out according to the standard procedure **3.2.4.A** using acetylene **186a** (500 mg, 2.45 mmol), aldehyde **239** (542 mg, 2.45 mmol), and *n*-butyllithium (1.73 mL, 1.6 M in hexanes, 2.69 mmol). The product was purified by flash column chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **241** (677 mg, 65%) as a yellow oil. **IR** ν_{max}(film): 3381, 2977, 2245, 1591, 1524 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.22 (3 H, t, *J* 7.0 Hz, CH_3CH$_2$O), 1.50 (9 H, s, C(CH_3)$_3$), 2.51 (1 H, br s, O*H*), 2.60 (2 H, dt, *J* 7.6, 7.4 Hz, 4-H), 2.91 (2 H, t, *J* 7.6 Hz, 5-H), 3.72 (2 H, q, *J* 7.0 Hz, CH$_3$CH_2O), 5.25 (2 H, s, OCH_2O), 5.49 (1 H, s, 1-H), 6.91-7.92 (8 H, m, Ar-*H*), 7.51 (1 H, s, N*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.0 (CH_3, *C*H$_3$CH$_2$O), 19.4 (CH_2, C-4), 28.3 (CH_3, C(*C*H$_3$)$_3$), 29.8 (CH_2, C-5), 63.3 (CH, C-1), 64.3 (CH_2, CH$_3$*C*H$_2$O), 78.5 (C, C-2), 80.3 (C, *C*(CH$_3$)$_3$), 88.6 (C, C-3), 93.0 (CH_2, O*C*H$_2$O), 113.8, 121.4, 123.1, 127.7, 127.7, 129.1, 129.1, 130.2 (CH, Ar-*C*H), 121.6 (C, C-1″), 129.2 (C, C-1′), 136.9 (C, C-2′), 153.3 (C, NH*C*=O), 155.2 (C, C-2″); ***m/z*** (FAB, %) 425 (M$^+$, 1), 352 (23), 306 (43), 262 (88), 248 (100), 107 (63); **HRMS** Found (FAB): (M$^+$), 425.2199, $C_{26}H_{37}O_4Si$ requires 425.2202.

***tert*-Butyl 2′-(5-(2″-(ethoxymethoxy)phenyl)pent-2-ynoyl)phenylcarbamate 238**



The IBX oxidation was carried out according to the standard procedure **3.2.4.B** using secondary alcohol **241** (100 mg, 0.24 mmol) and *o*-iodoxybenzoic acid (198 mg, 0.71 mmol). The product was purified by flash chromatography using hexanes/EtOAc (8:2) as eluent to give the *title compound* **238** (84 mg, 84%) as a yellow oil. **IR** ν_{max}(film): 3272, 2928, 2215, 1730, 1618, 1581, 1244 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.21 (3 H, t, *J* 7.1 Hz, CH_3CH_2O), 1.52 (9 H, s, $C(CH_3)_3$), 2.84 (2 H, t, *J* 7.5 Hz, 4-H), 3.00 (2 H, t, *J* 7.5 Hz, 5-H), 3.72 (2 H, q, *J* 7.1 Hz, CH_3CH_2O), 5.27 (2 H, s, OCH_2O), 6.94-8.44 (8 H, m, Ar-*H*), 10.73 (1 H, s, N*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.1 (CH_3, CH_3CH_2O), 19.7 (CH_2, C-4), 28.2 (CH_3, $C(CH_3)_3$), 29.1 (CH_2, C-5), 64.4 (CH_2, CH_3CH_2O), 80.2 (C, $C(CH_3)_3$), 80.7 (C, C-2), 93.1 (CH_2, OCH_2O), 97.3 (C, C-3), 113.9, 118.5, 120.9, 121.5, 128.1, 130.4, 134.9, 135.5 (CH, Ar-CH), 121.5 (C, C-1″), 128.3 (C, C-1′), 142.6 (C, C-2′), 152.9 (C, NH*C*=O), 155.4 (C, C-2″), 180.8 (C, *C*=O); ***m/z*** (FAB, %) 424 (MH^+, 1), 322 (61), 278 (80), 276 (55), 264 (100); **HRMS** Found (FAB): (MH^+), 424.2117, $C_{26}H_{35}O_4Si$ requires 424.2124.

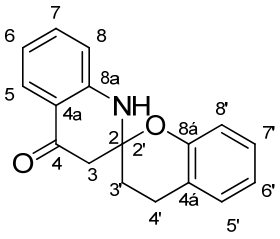
2-(2′-Hydroxyphenethyl)quinolin-4(1H)-one 242



To a mixture of ketone **238** (199 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) was added trifluroacetic acid (5 mL) and the reaction was stirred at r.t. for 10 min. The black reaction mixture was quenched with H_2O (30 mL), followed by extraction with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography purification using

hexanes/EtOAc (7:3) as eluent to give the *title compound* **242** (102 mg, 82%) as a bright yellow oil. **IR** ν_{max}(film): 3471, 3406, 1644 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.44 (2 H, s, C-2–CH_2CH$_2$–C-1′), 3.78 (2 H, s, C-2–CH$_2$CH_2–C-1′), 4.87 (1 H, t, *J* 3.0 Hz, H-3), 6.30 (1 H, br s, N*H*), 6.64-7.82 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.2 (CH_2, C-2–CH_2*C*H$_2$–C-1′), 44.2 (CH_2, C-2–CH_2*C*H$_2$–C-1′), 99.1 (CH, C-3), 115.8, 116.4, 117.3, 123.1, 127.3, 129.0, 131.7, 134.6 (CH, Ar-*C*H), 117.5, (C, C-4a), 119.5 (C, C-1′), 146.2 (C, C-8a), 150.8 (C, C-2′), 160.5 (C, C-2), 197.9 (C, C-4); ***m/z*** (EI, %) 265 (M^+, 21), 120 (100), 92 (23), 65 (17); **HRMS** Found (EI): (M^+), 265.1103, $C_{17}H_{14}O_3$ requires 265.1103.

1'H-Spiro[chroman-2,2'-quinolin]-4'(3'H)-one 237



The spirocyclisation was carried out according to the standard procedure **3.2.4.E** using quinolone **242** (18 mg, 0.068 mmol) and potassium carbonate (2.0 g, 14.47 mmol). The resultant residue was purified by flash column chromatography using hexanes/ EtOAc (9:1) as eluent to give the *title compound* **237** as a pale yellow oil (5.8 mg, 32%); **IR** ν_{max}(film): 3445, 3349, 2917, 1616, 1583, 1488, 1227, 1105, 751 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93 (1 H, ddd, *J* 13.5, 12.8, 5.9, 3′-H_α), 2.36 (1 H, ddd, *J* 13.5, 5.9, 2.5, 3′-H_β), 2.62 (1 H, ddd, *J* 16.3, 5.9, 2.5, 4′-H_β), 2.81 (1 H, m, 3-H_α), 3.06 (2 H, ddd, *J* 16.3, 12.8, 5.9, 4′-H_α), 3.36 (1 H, m, 3-H_β), 6.31 (1 H, s, N*H*), 6.62-7.91 (8 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2 (CH_2, C-4′), 22.8 (CH_2, C-3′), 29.9 (CH_2, C-3), 98.9 (C, C-2), 115.6, 116.7, 117.3, 120.7, 127.0, 129.1, 132.2, 134.4 (CH, Ar-*C*H), 118.8 (C, C-4a), 122.7 (C, C-4a′), 150.7 (C, C-8a), 152.2 (C, C-8a′), 198.6 (C, C-4); ***m/z*** (EI, %) 265 (M^+, 38), 190 (6), 159 (34), 120 (100), 92 (24), 65 (17); **HRMS** Found (EI): (M^+), 265.1105, $C_{17}H_{15}NO_2$ requires 265.1103.

PART 2:

Synthetic Studies Towards Chiral 3-Substituted Phthalide-Containing Natural Products

Chapter Four

Introduction

4.1 Background to Chiral 3-Substituted Phthalides

The phthalide [1(3*H*)-isobenzofuranone] moiety (Figure 23) is present in a rich and diverse group of natural products.[109] A smaller subset of this class of compounds are phthalides that contain a chiral C3-substituent, many of which possess a vast array of biological activities.

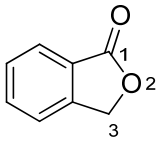


Figure 23. 1(3*H*)-isobenzofuranone.

Representative examples include (−)-hydrastine (**248**),[110] which is active at the opioid receptor[111] and also possesses anti-paclitaxel-resistant human ovarian cancer activity through c-Jun kinase-mediated apoptosis.[112] Vermastatin (**249**)[113] and (−)-alcyopterosin E (**250**)[114] both show cytotoxic activity whilst cytosporone E (**251**),[115] is an antibacterial reagent. 3-Butylphthalide (**253**),[116] a component in Chinese folk medicine extracted from celery seed oil, was shown to reduce brain damage in mice[117] and increase the duration of anesthesia[118] and exhibits cerebral antiischemic action.[119] 3-Butylphthalide (**253**) also exhibited muscle relaxant effects on animal tracheal smooth muscle and it has been demonstrated that the phthalide moiety is required for the anti-asthmatic activity.[120]

Spirolaxine methyl ether (**247**)[121] has shown inhibitory activity against the micro-aerophilic Gram-negative bacterium *Helicobacter pylori*[122] which is linked to the development of gastric and duodenal ulcers. Spirolaxine methyl ether (**247**) also exhibits cholesterol lowering properties[123] and exhibit cytotoxic activity toward endothelial cells (BMEC and Huvec) as well as a variety of tumor cell lines (LoVo and HL60).[123]

The exact biological activities of (+)-aigialospirol (**256**) is unknown, however it is biosynthetically related to the known resorcylic macrolactone hypothemycin (**257**), which possesses potent antimalarial[124] and anticancer[125] properties.

Furthermore, most of these classes of natural products are only found as one enantiomer hence further highlighting the importance of asymmetric synthesis of chiral phthalides. The exact bioactivities of typhaphthalide (**252**),[126] 4-hydroxy-3-butylphthalide (**254**)[127] and herbaric acid (**255**)[128] are unknown (Figure 24).

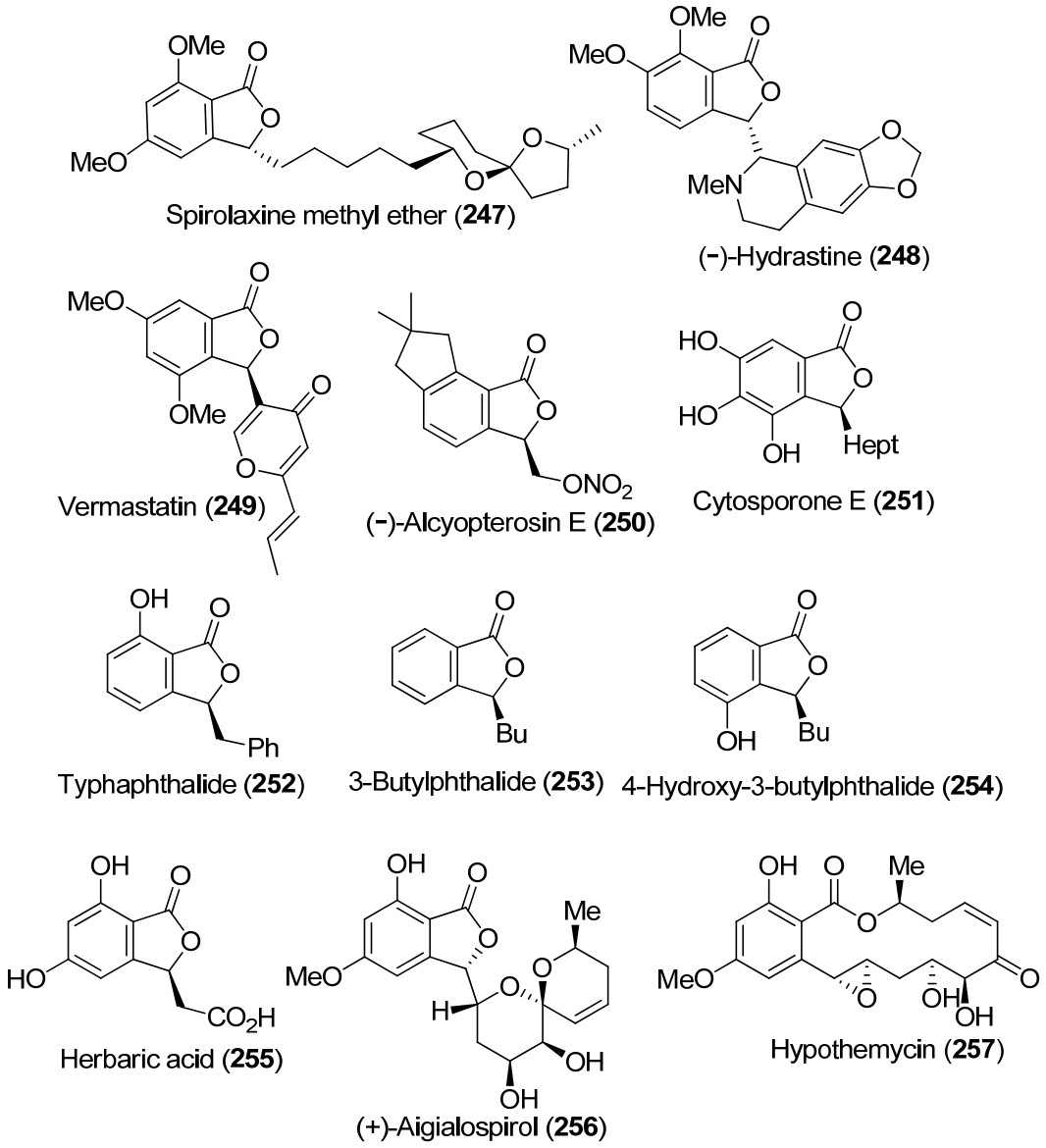


Figure 24. Phthalide natural products and hypothemycin (**257**).

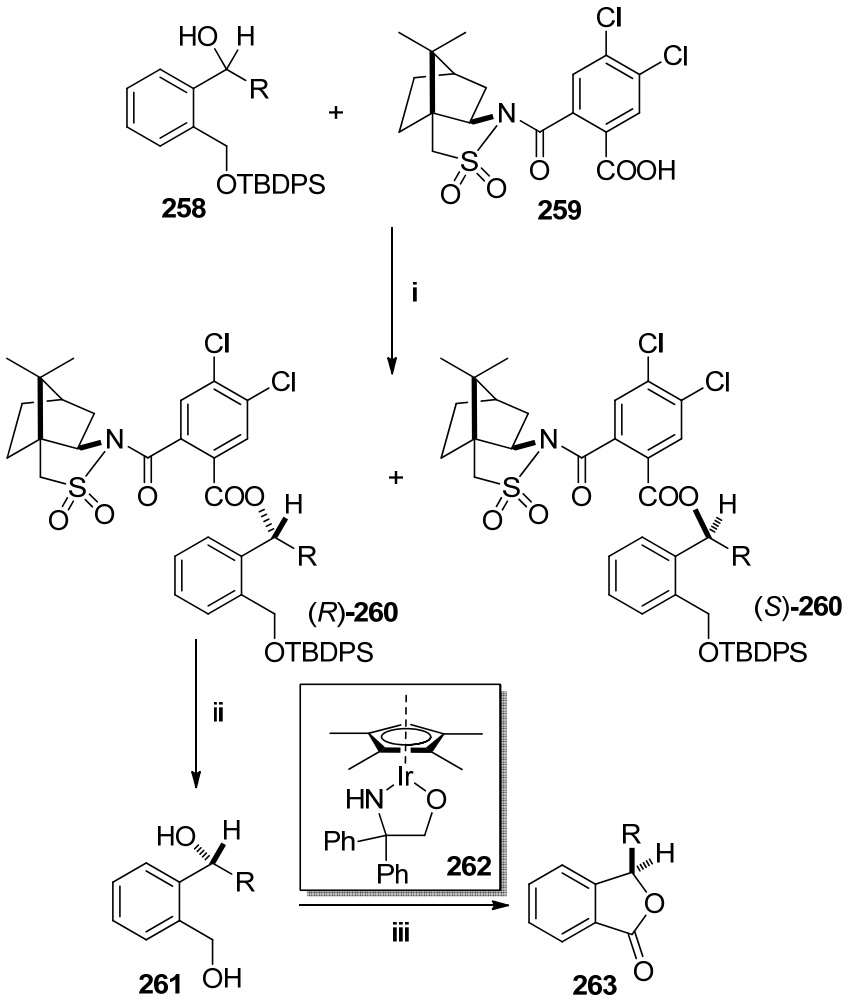
Significant effort has been directed toward the synthesis of phthalides bearing 3-alkyl substituents. Existing asymmetric methods primarily involve the use of chiral auxiliaries and chiral organometallics,[129-137] but recently reported organocatalytic[138] and hydroacylation[139, 140] methodologies have provided elegant additions to the synthetic repertoire. Representative examples of such reactions are summarised in the following section.

4.2 Previous Synthetic Studies of Chiral 3-Substituted Phthalides

4.2.1 Synthesis of Chiral 3-Substituted Phthalides using Chiral Auxiliaries

A. Use of Camphorsultam Dichlorophthalic Acid, (1*S*,2*R*,4*R*)-(−)-CSDP Acid

Hiroi *et al*.[137] have synthesised enantiopure phthalides via resolution of racemic alcohols using the chiral auxiliary camphorsultam dichlorophthalic acid, (1*S*,2*R*,4*R*)-(−)-CSDP acid. Racemic alcohols **258** were esterified with (1*S*,2*R*,4*R*)-(−)-CSDP acid **259**, yielding a diastereomeric mixture of esters (*R*)-**260** and (*S*)-**260**. Treatment of (*R*)-**260** with potassium hydroxide and methanol gave enantiopure diol **261** which was subsequently oxidised with iridium complex **262**, giving the desired phthalide **263** in good yields (Scheme 74).



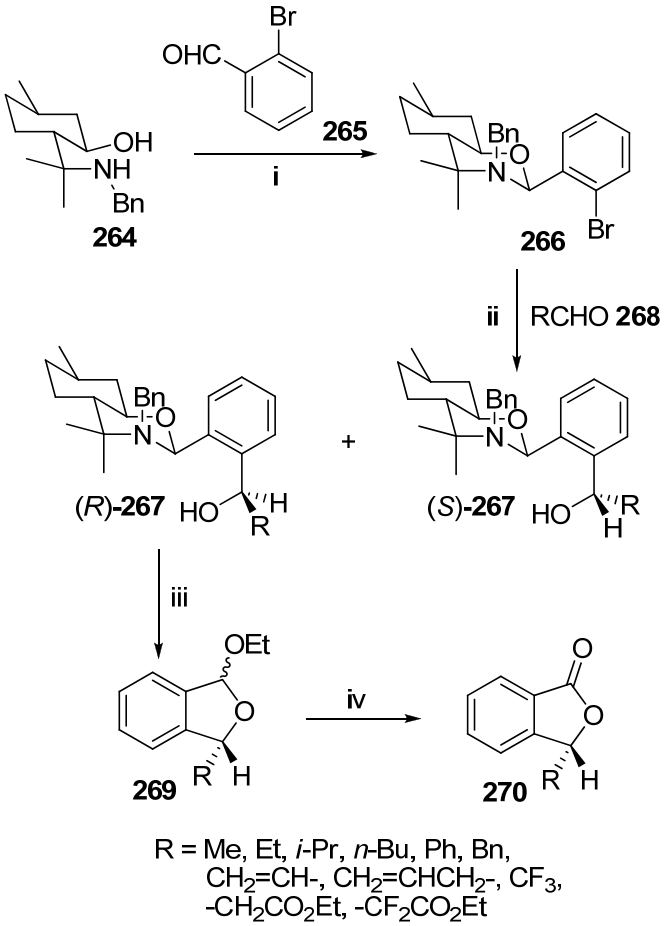
Reagents and conditions: i. DCC, DMAP/CH_2Cl_2, r.t., (*R*)-**260**, 33-46%, (*S*)-**260**, 39-50%; ii. KOH, CH_3OH, 87-91%; iii. Ir catalyst **262**, acetone, r.t., 80-99%.

Scheme 74. Synthesis of chiral phthalide **263** by Hiroi *et al*.[137]

B. Use of Perhydro-1,3-benzoxazine

Pedrosa *et al*.[141] have synthesised chiral phthalides using perhydro-1,3-benzoxazine **264** as the chiral auxiliary. Intermediate **266** was formed by reacting aminol **264** and *o*-bromobenzaldehyde **265** in 65% yield. This was converted to chiral alcohols (*R*)-**267** and (*S*)-**267** by the treatment of *t*-butyllithium at -90 °C in THF followed by addition of the appropriate aldehyde **268**. The major alcohol (*R*)-**267** was treated with 2% HCl solution in ethanol which

facilitated hydrolytic cleavage of the *N*,*O*-ketal, thereby allowing for the regeneration of the carbonyl group and the formation of acetal **269**. Treatment of **269** with *m*-CPBA and $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature gave the desired phthalide **270** in good to excellent yields (Scheme 75).

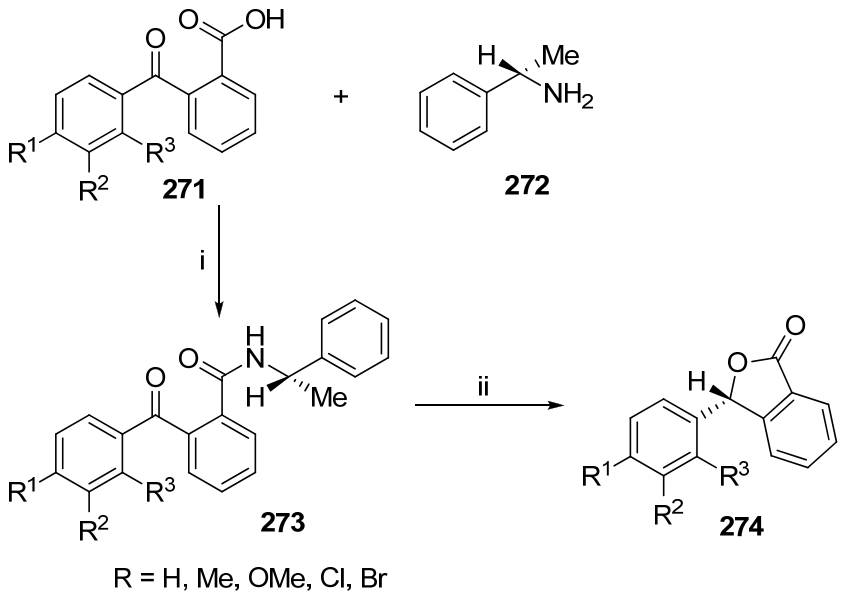


Reagents and conditions: i. CH_2Cl_2, 120 °C, 120 h, sealed tube, 65%; ii. a) *t*-BuLi, THF, -90 °C; b) **268**, 67-89%, (*R*)-**267**:(*S*)-**267** = ~3:1; iii. 2% HCl, EtOH, 62-97%; iv. *m*-CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, r.t., 52-90%, >99% e.e.

Scheme 75. Synthesis of chiral phthalide **270** by Pedrosa *et al*.[141]

C. Use of (*S*)-1-Phenylethylamine 272 as a Chiral Auxiliary

Karnik *et al.*[142] have synthesised chiral 3-substituted phthalides using (*S*)-1-phenylethylamine **272** as the chiral auxiliary. Benzamides **273** were prepared from benzoic acid **271** and (*S*)-1-phenylethylamine **272** using DCC as the coupling reagent. The synthesis of enantiopure 3-substituted phthalides was achieved in a one-pot reaction by sodium borohydride reduction of **273** followed by acid catalysed lactonisation (Scheme 76).



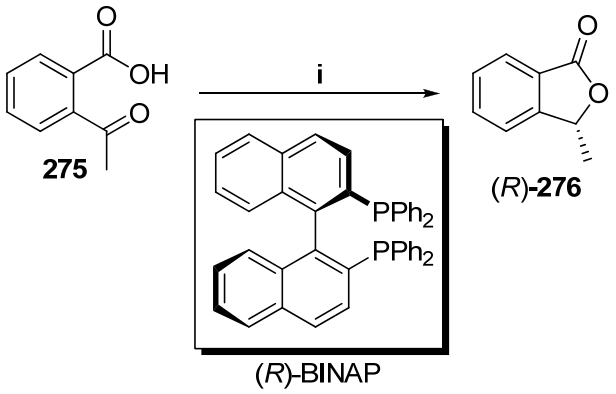
Reagents and conditions: i. DCC, DMAP, DMAP·HCl, CH_2Cl_2, 0 °C to r.t.; ii. a) $NaBH_4$, MeOH, 0 °C; b) aq. HCl, 0 °C, 75-85%.

Scheme 76. Synthesis of chiral phthalide **274** by Karnik *et al.*[142]

4.2.2 Synthesis of Chiral 3-Substituted Phthalides using Organometallic Reagents

A. Asymmetric Hydrogenation using BINAP-Ru(II) Complexes

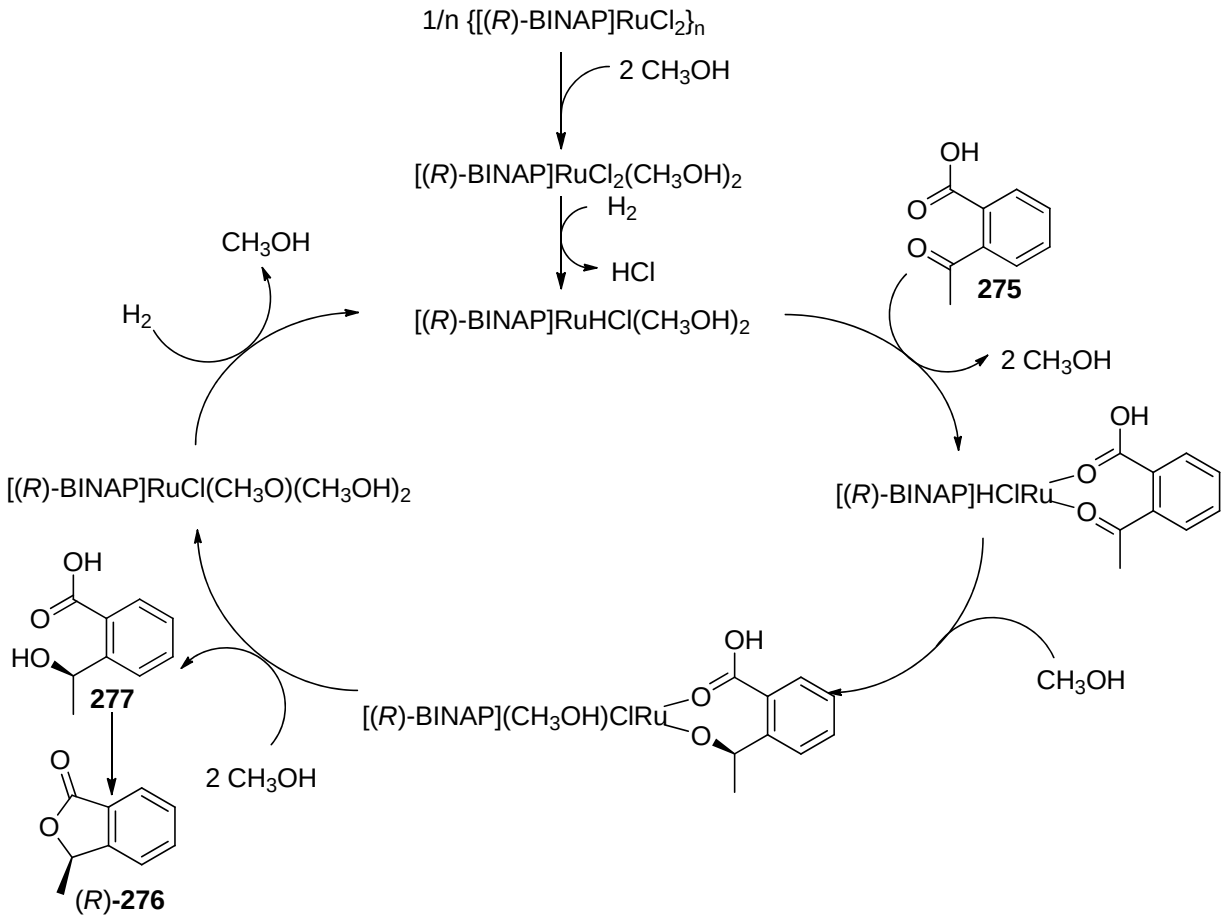
Noyori *et al*.[130] have synthesised chiral phthalide (*R*)-**276** starting from *o*-acetylbenzoic acid **275** which was hydrogenated in the presence of a (*R*)-BINAP-Ru complex. The phthalide (*R*)-**276** was obtained in 92% e.e. and quantitative yield (Scheme 77).



Reagents and conditions: i H_2, $RuCl_2$[(*R*)-BINAP], methanol, 20 °C, >99%, 92% e.e.

Scheme 77. Synthesis of chiral phthalide **276** by Noyori *et al*.[130]

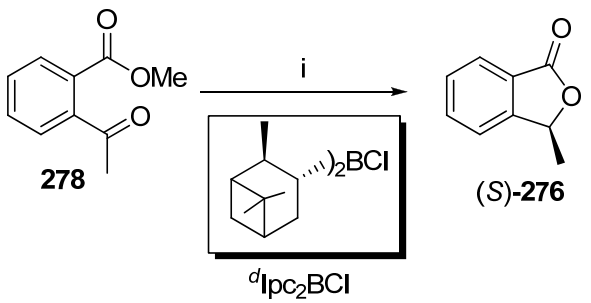
The mechanism of the reaction is outlined in Scheme 78. Hydrogen is first inserted in to the (*R*)-BINAP-Ru complex followed by the coordination of *o*-acetylbenzoic acid **275**. The complex selectively directs the addition of hydrogen across a single enantiotopic face of the carbonyl double bond, yielding chiral alcohol **277**. Alcohol **277** then undergoes lactonisation to the desired phthalide **276**.



Scheme 78. Asymmetric Hydrogenation mechanism[143]

B. Asymmetric Reduction using *B*-Chlorodiisopinocampheylborane

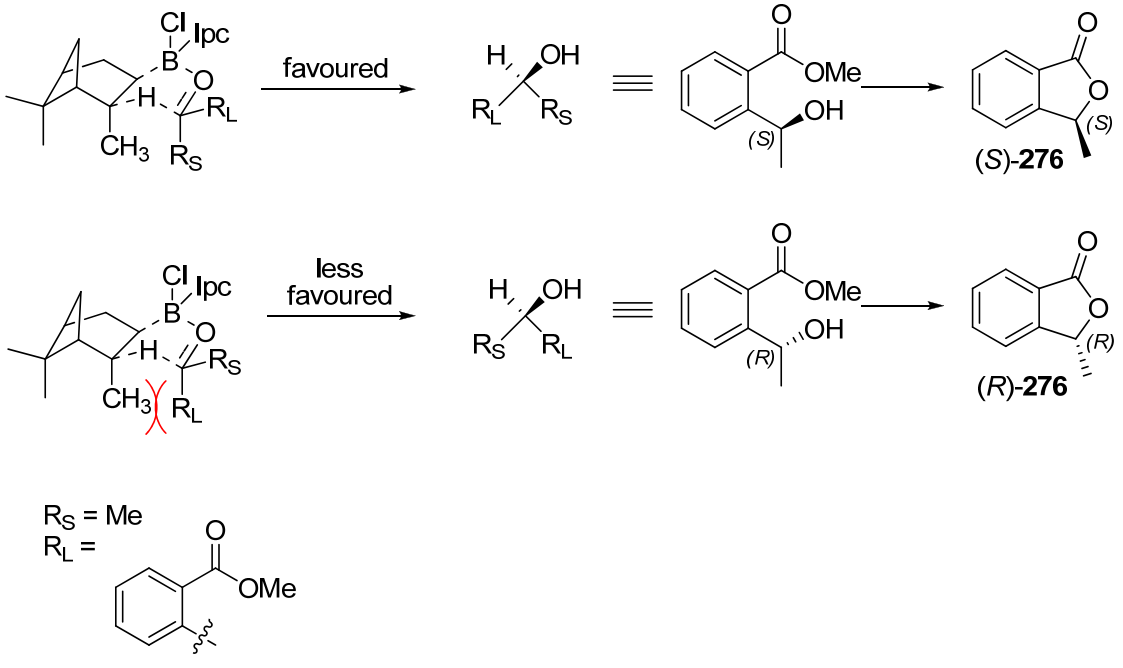
Brown *et al.*[129] have installed the chirality in 3-substituted phthalides by intermolecular asymmetric reduction of ketones using *B*-chlorodiisopinocampheylborane. Treatment of ketone **278** with *B*-chlorodiisopinocampheylborane in diethyl ether at -25 °C for 8 h followed by workup provided the desired phthalide **279** in good yield (Scheme 79).



Reagents and conditions: i $^{d}Ipc_2BCl$, Et_2O, -25 °C, 8 h, 87%, 97% e.e.

Scheme 79. Synthesis of chiral phthalide **276** by Brown *et al*.[129]

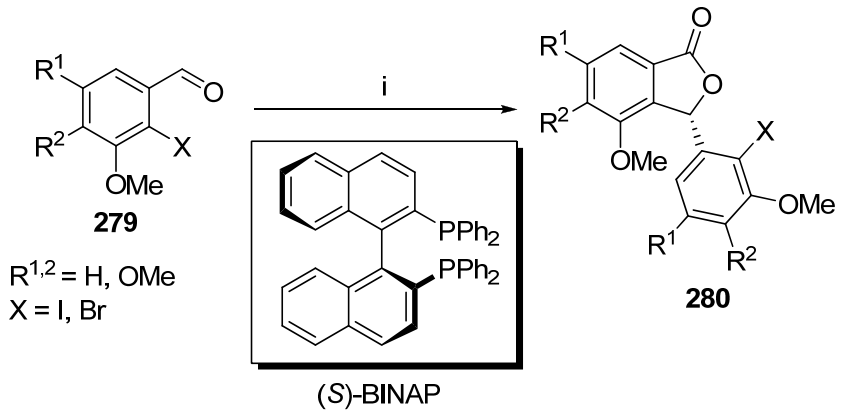
The mechanism of the reaction is depicted in Scheme 80. *B*-chlorodiisopinocampheylborane coordinates to the carbonyl group in **278**. Due to steric interations between the methyl group at the 2-position of α-pinene with ketone **278**, alcohol formation with less steric bulk near the methyl group at the 2-position is favoured. In this case, it favours the formation of the (*S*)-alcohol hence affording phthalide (*S*)-**276**.[144]



Scheme 80. Mechanism of Ipc_2BCl reductions

C. Nickel-catalysed Tandem Reactions

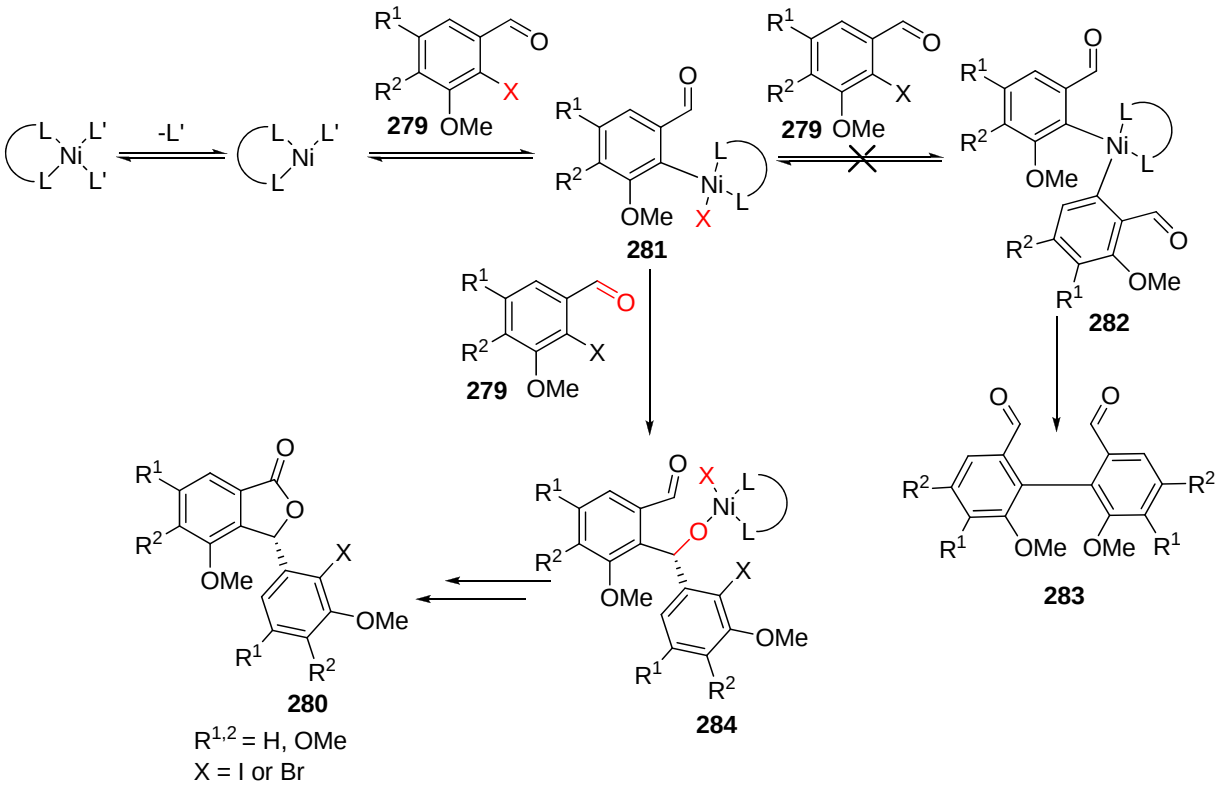
Lin *et al.*[131] have reported a nickel-catalysed tandem (addition-cyclisation) reaction to synthesise optically active phthalides. Aryl halide **279** was treated with $NiCl_2(PPh_3)_2$/(*S*)-BINAP in toluene at 90 °C to form the desired phthalide **280**. The choice of the bidentate ligand in the nickel-catalysed reaction was critical to the formation of the phthalides in good yield and high e.e. (Scheme 81).



Reagents and conditions: i. $NiCl_2(PPh_3)_2$/(*S*)-BINAP, zinc, toluene, 90 °C, 48-97%, 43-98% e.e.

Scheme 81. Synthesis of chiral phthalide **280** by Lin *et al.*[131]

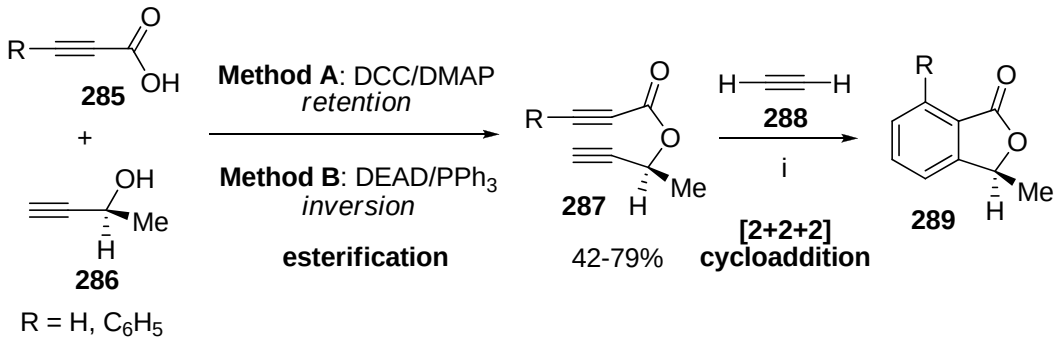
The $NiCl_2(PPh_3)_2$/(*S*)-BINAP complex first inserts into aryl halide **279** forming arylnickel complex **281**. The steric hinderence caused by the bidentate ligand ((*S*)-BINAP) makes transmetallation of arylnickel complex **281** to diarylnickel **282** difficult. The arylnickel complex **281** instead inserts into the C=O bond of a second molecule of **279** to form the diarylcarbinol complex **284**. Subsequent lactonisation and β-hydride elimination furnishes phthalide **280** (Scheme 82).



Scheme 82. Proposed pathway for the synthesis of chiral phthalide **280** by Lin *et al.*[131]

D. Rhodium (I)-Catalysed Crossed Alkyne Cyclotrimerisation

Witulski *et al.*[145] synthesised various chiral 3-substituted phthalides by crossed alkyne cyclotrimerisations with Wilkinson's catalyst [$RuCl(PPh_3)_3$] (Scheme 83). Esterification of propiolic acids **285** with chiral propargylic alcohols **286** under DCC/DMAP (Method A) or Mitsunobu conditions (Method B) allowed the synthesis of both enantiomeric forms of the diyne esters **287**. Subsequent alkyne cyclotrimerisations with acetylene **288** provided 3-substituted phthalides **289** in moderate to good yields (Scheme 83).

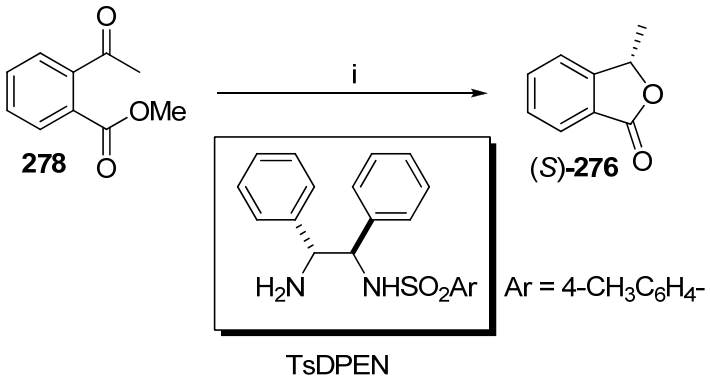


Reagents and conditions: i. $RhCl(PPh_3)_3$, toluene, r.t., 40 °C, 68-89%.

Scheme 83. Synthesis of chiral phthalide **289** by Witulski *et al*.[145]

E. Ruthenium (II)-catalysed Asymmetric Transfer Hydrogenation of Carbonyl Compounds

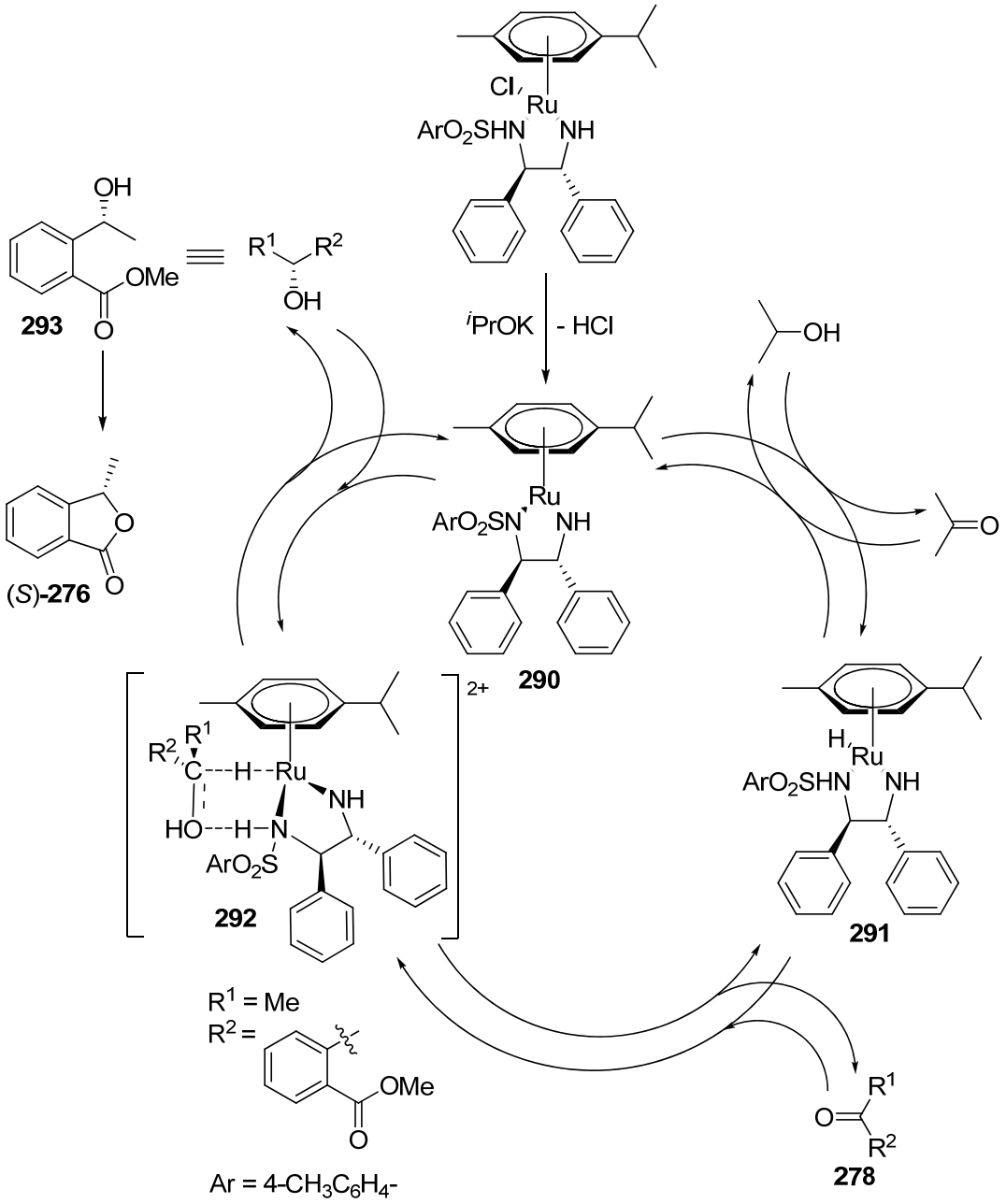
Catalytic asymmetric transfer of hydrogenation of ketones using 2-propanol has emerged as a viable means of synthesising chiral alcohols. Everaere *et al*.[136] applied the transfer hydrogenation of 2-propanol to prochiral ketones to synthesise various chiral phthalides. The catalytic asymmetric reduction of ketones was attempted on ketone **278** which was transformed into chiral phthalide **276**. The transfer hydrogenation of ketone **278** using [Ru(*p*-cymene)(TsDPEN)] in isopropanol gave the desired phthalide (*S*)-**276** in high yields and e.e. (Scheme 84).



Reagents and conditions: i. [Ru(*p*-cymene)(TsDPEN)], ^{i}PrOH, ^{i}PrOK, 20 °C, 99%, 91% e.e.; TsDPEN = (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine.

Scheme 84. Synthesis of chiral phthalide **276** by Everaere *et al*.[136]

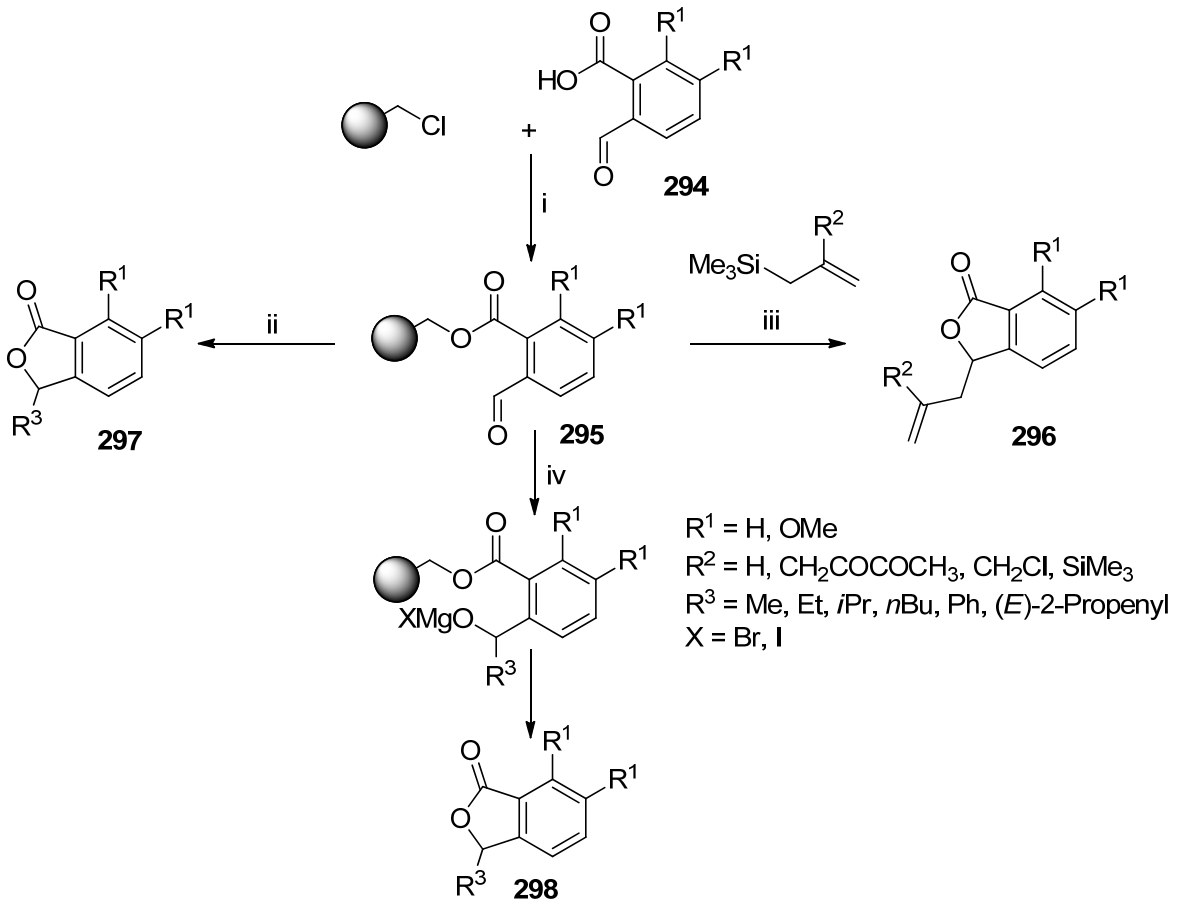
The reaction mechanism is depicted in Scheme 85. The reaction involves the preliminary formation of Ru complex **290** in the presence of a base. Addition of 2-propanol then affords Ru hydride **291**, the reducing intermediate. Reduction of ketone **278** occurs via a stable six-membered cyclic transition state **292** which is stabilised by hydrogen bonding between Ru-N-H and the carbonyl oxygen atom. Hydrogen transfer follows affording chiral alcohol **293** which undergoes subsequent lactonisation to the desired phthalide **276**.



Scheme 85. Proposed pathway for the synthesis of chiral phthalide **276** by Everaere *et al*.[136]

F. Solid-phase Synthesis of Chiral 3-Substituted Phthalides

Knepper *et al.*[133] have synthesised various phthalides by installing the chirality at the C-3 position using solid-phase synthesis. Commercially available 2-formylbenzoic acid **294** was first immobilised on Merrifield resin **295** (Scheme 86). By reacting immobilised 2-formylbenzoic acid **295** with different organometallic reagents (zinc reagents, allyl silanes *via* Sakurai type reactions or Grignard reagents) secondary alcohols were furnished and lactonised to give the desired phthalides **296-298**.

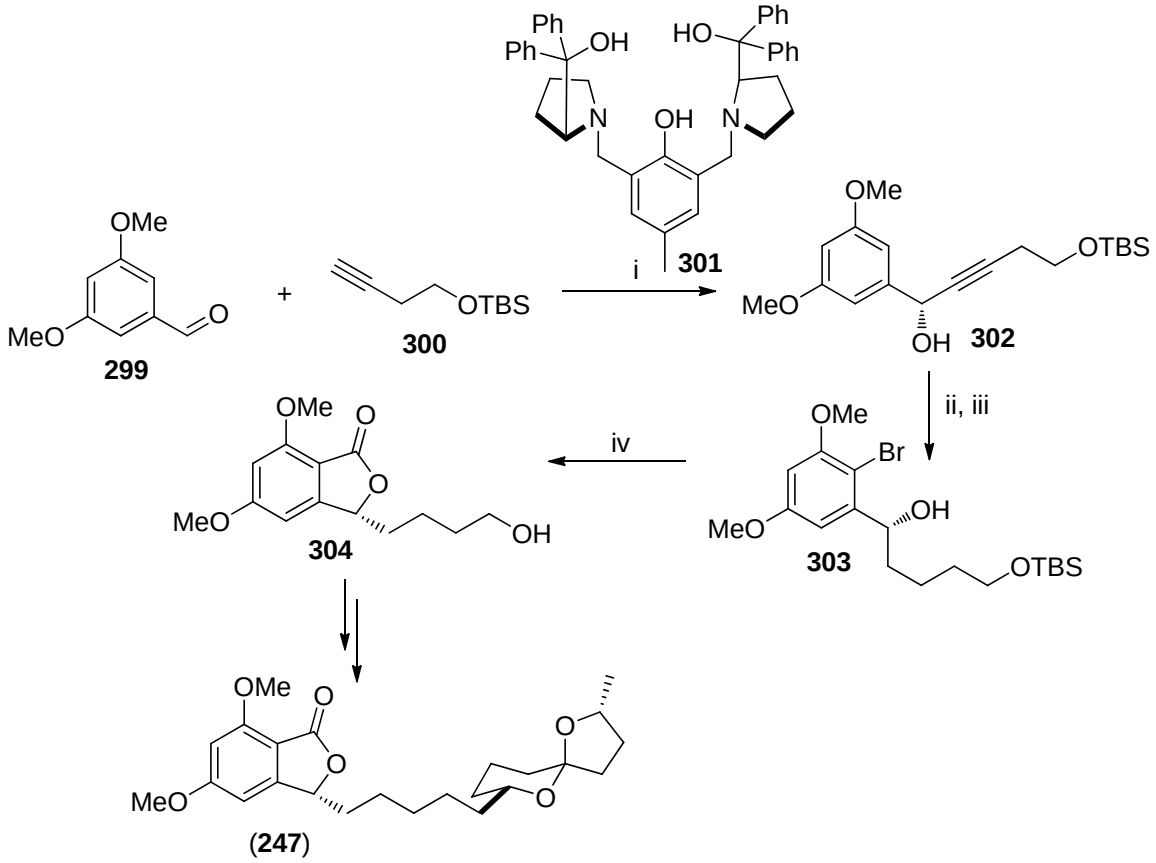


Reagents and conditions: i. Cs_2CO_3, DMF, 50 °C, 24 h; ii. $R^3{}_2Zn$, ligand, THF/toluene (3:1), 40 h, 0 °C, 80-88%, 0-60% e.e.; iii. $TiCl_4$, THF/CH_2Cl_2 (1:1), r.t. 40 h, 24-73% 75-95% e.e.; iv. R^3-MgX, THF, 20 h, 13-17%, 74-89% e.e.

Scheme 86. Synthesis of chiral phthalides **296-298** by Knepper *et al.*[133]

G. ProPhenol-catalysed Addition of Acetylenes

Trost *et al*.[132] in their work towards the synthesis towards the (+)-spirolaxine methyl ether (**247**), have utilised asymmetric alkyne additions using ProPhenol as the catalyst. TBDMS protected butyne **300** was added to 3,5-dimethoxybenzaldehyde **299** with 10 mol% of (*R*,*R*)-ProPhenol **301** in toluene, resulting in the formation of the desired propargylic alcohol **302** in 82% yield and 90% e.e. Mild hydrogenation of alkyne **302** in the presence of Adams' catalyst furnished the saturated alkane **303** without reduction of the benzylic alcohol. *Ortho* bromination of the benzyl alcohol **303** followed and subsequent trapping with CO_2 led to phthalide **304** in high yield (Scheme 87).

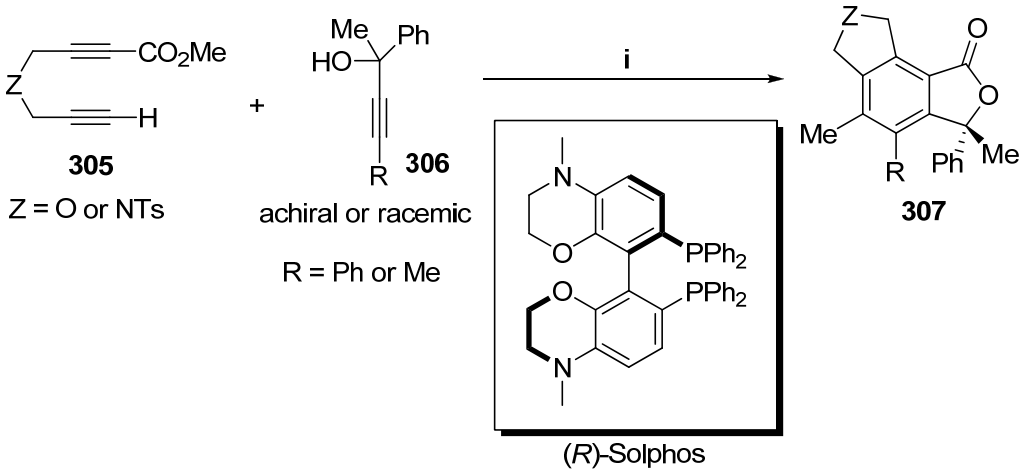


Reagents and conditions: i. (*R*,*R*)-ProPhenol **301**, Me_2Zn, toluene, 82%, 90% e.e.; ii. H_2, PtO_2, EtOAc, quant.; iii. NBS, $CHCl_3$, 99%; iv. *n*-BuLi (1 min), THF, -78 °C then CO_2, HCl/H_2O, 90%.

Scheme 87. Synthesis of chiral phthalide **304** by Trost *et al*.[132]

H. Rhodium-catalysed Asymmetric Transesterification and [2+2+2] Cycloaddition

Tanaka *et al*.[134] have successfully used a Rodium(I)/(*R*)-Solphos ligand complex in an asymmetric one-pot transesterification and [2+2+2] cycloaddition. A mixture of 1,6-diyne ester **305** and tertiary propargylic alcohol **306** in dichloromethane led to the formation of enantioenriched tricyclic 3,3-disubstituted phthalides **307** (Scheme 88). The procedure uses achiral or racemic propargylic alcohols providing readily access to coupling partners. The procedure reported by Witulski *et al*.[145] (Scheme 83) required the preparation of optically active tertiary propargylic alcohols.

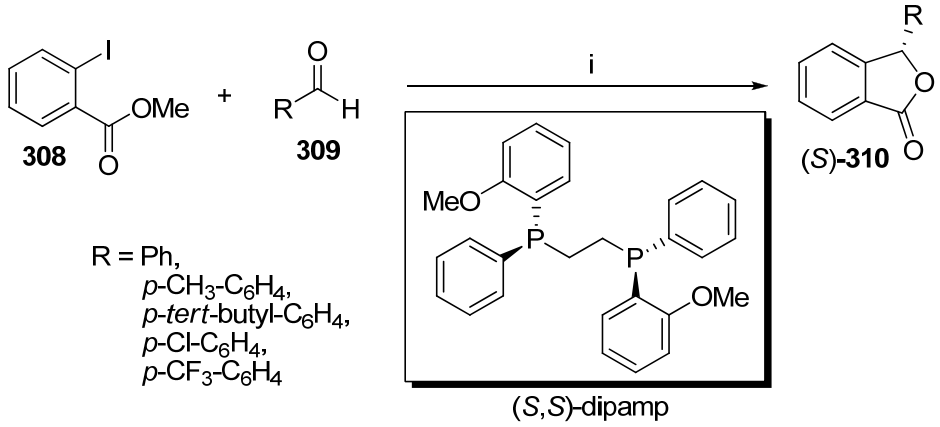


Reagents and conditions: i. 5% $[Rh(cod)_2]BF_4$/(*R*)-Solphos, CH_2Cl_2, r.t., 1 h, 55-89%, 86-94% e.e.

Scheme 88. Synthesis of chiral phthalide **307** by Tanaka *et al*.[134]

I. Cobalt Bidentate Phosphine Catalysed Synthesis of Chiral 3-Substituted Phthalides

Cheng *et al.*[135] have synthesised chiral phthalides **310** using a cobalt bidentate phosphine complex as the catalyst. Methyl-2-iodobenzoate **308** underwent cyclisation reactions with various aromatic aldehydes **309** with cobalt catalyst, [CoI_2((*S*,*S*)-dipamp)] and zinc powder in tetrahydrofuran at 75 °C for 24 h. The corresponding phthalides (*S*)-**310** were isolated in 80-87% yields and 70-98% e.e. (Scheme 89).



Reagents and conditions: i. [CoI_2]((*S*,*S*)-dipamp)], Zn, THF, 75 °C, 24 h, 80-87%, 70-98% e.e.;

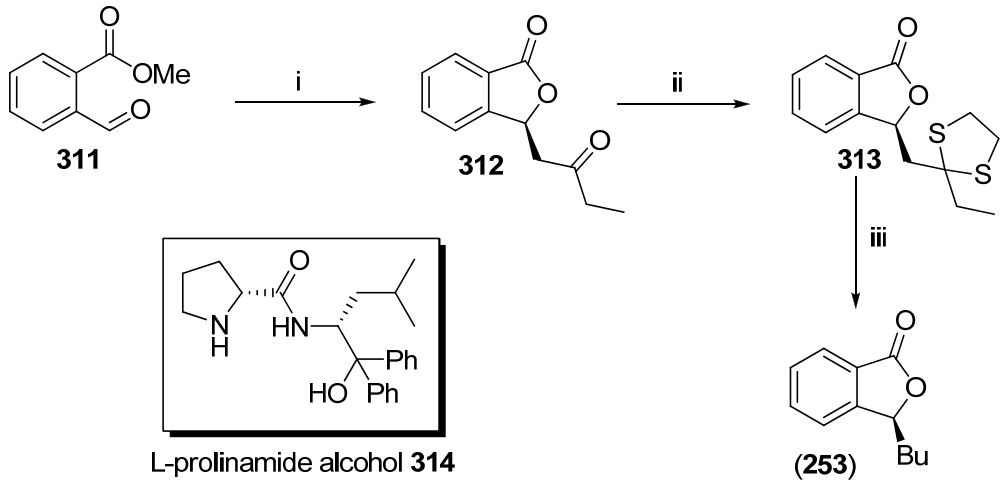
(*S*,*S*)-dipamp = (1*S*,2*S*)-(+)-bis[2-methoxyphenyl]phenylphoshino)ethane).

Scheme 89. Synthesis of chiral phthalide **310** by Cheng *et al.*[135]

4.2.3 Synthesis of Chiral 3-Substituted Phthalides using Organocatalyst

A. Use of an Organocatalytic Enantioselective Aldol-Lactonisation Reaction

Zhang *et al*.[138] used an organocatalytic asymmetric aldol-lactonisation reaction of 2-formylbenzoic esters with ketones/aldehydes for the convenient construction of chiral phthalides. The optimum conditions were achieved using the catalyst L-prolinamide alcohol **314** with benzoic acid as an additive. Moreover, due to the sensitivity of the reaction conditions towards a sequential aldol-lactonisation process which potentially could affect the enantioselectivity, it was crucial to remove the catalyst for the subsequent lactonisation reaction by adding potassium carbonate. This procedure was applied to the synthesis of natural product (*S*)-(−)-3-butylphthalide (**253**) in three steps. Phthalide intermediate **312** was obtained in good yield and excellent e.e. from **311** by a catalysed aldol-lactonisation reaction (Scheme 90). The phthalide intermediate **312** then underwent thioacetalisation to form **313** followed by desulfurisation to yield (*S*)-(−)-3-butylphthalide (**253**) in 66% yield over two steps.



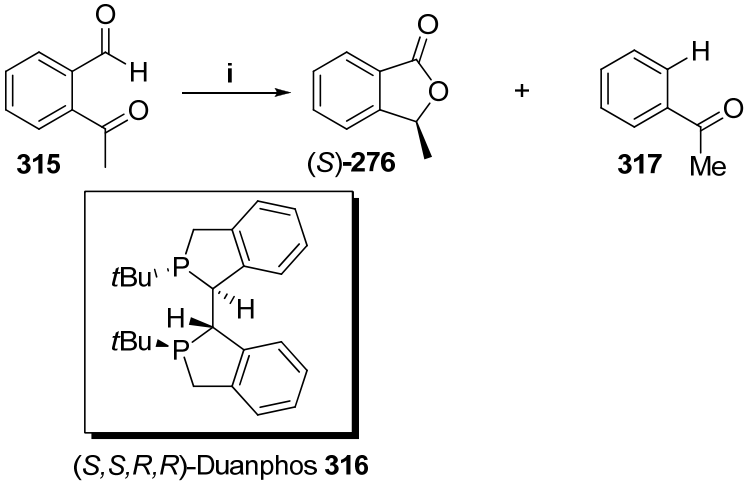
Reagents and conditions: i. a) butanone, catalyst **314**, $PhCO_2H$, -40 °C; b) K_2CO_3, 72% yield, 96% e.e.; ii. ethane-1,2-dithiol, $TiCl_4$, $CHCl_3$, r.t., 12 h; iii. Raney-Ni, EtOH, reflux, 4 h, 66% over two steps.

Scheme 90. Synthesis of (*S*)-(−)-3-butylphthalide (**253**) by Zhang *et al*.[138]

4.2.4 Synthesis of Chiral 3-Substituted Phthalides using Hydroacylation

A. Use of Rhodium-Catalysed Ketone Hydroacylation

Phan *et al*.[139] have reported a catalytic enantioselective synthesis of chiral phthalide compounds. The enantiomerically enriched phthalide **276** was furnished *via* ketone hydroacylation reaction starting from ketobenzaldehyde **315**. As with the majority of transition-metal-catalysed hydroacylation reactions, the formation of by-products originating from decarbonylation, in this case ketone **317**, was a competing process. After careful experimentations, the combination of rhodium chloride catalyst $[Rh(cod)Cl_2]_2$, phosphine ligand (*S*,*S*,*R*,*R*)-Duanphos **316** and silver nitrate as a counterion were found to be optimal (Scheme 91).

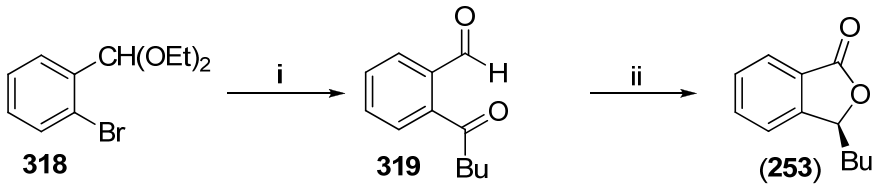


Reagents and conditions: i. $[(Rh(cod))Cl_2]_2$, (*S*,*S*,*R*,*R*)-Duanphos **316**, $AgNO_3$, toluene, 90 °C, >95%, 97% e.e.

Scheme 91. Synthesis of chiral phthalide **276** by Phan *et al*.[139]

This procedure was also applied to the synthesis of the natural product (*S*)-(−)-3-butylphthalide (**253**) (Scheme 92). Commercially available acetal **318** was converted to ketoaldehyde **319** in

71% in one pot. In the presence of [Rh((*S*,*S*,*R*,*R*)-Duanphos)]NO_3, **319** cyclised to phthalide (**253**) in 93% yield and 97% e.e.



Reagents and conditions: i. MeN(OMe)(C=O)*n*-Bu, *n*-BuLi, THF, -78 °C to r.t., overnight then aq. HCl (2 M), r.t., 3 h, 71%; ii. 5 mol% $[(Rh(cod))Cl_2]_2$, 10 mol% (*S*,*S*,*R*,*R*)-Duanphos **316**, 10 mol % $AgNO_3$, toluene, 75 °C, 3 days, 93%, 97% e.e.

Scheme 92. Synthesis of (*S*)-(−)-3-butylphthalide (**253**) by Phan *et al*.[139]

4.3 Conclusion

The importance of chiral 3-substituted phthalide frameworks is highlighted by their broad, potent and significant biological activities. Significant effort has been directed toward the synthesis of chiral phthalides bearing 3-alkyl substituents. Nonetheless, efficient new methods for the asymmetric synthesis of the medicinally important chiral 3-substituted phthalides are highly sought after.

We wish to examine the synthesis of chiral 3-substituted phthalide containing natural products. In particular the execution of the planned synthesis of (+)-aigialospirol (**256**) and (−)-herbaric acid (**255**) and the various challenges encountered will be discussed in the following chapter.

Chapter Five

Discussion

5.1 Synthetic Studies Towards (+)-Aigialospirol (256)

5.1.1 Aigialospirol – Overview

Aigialospirol (**256**) was isolated from the mangrove fungus *Aigialus parvus* BCC 5311 by Vongvilai *et al.*[146] Previous fermentation studies of the fungus BCC 5311 led to the isolation of five resorcylic macrolides, aigialomycins A-E **320-324** and the major biometabolite hypothemycin (**257**) (Figure 25).[124]

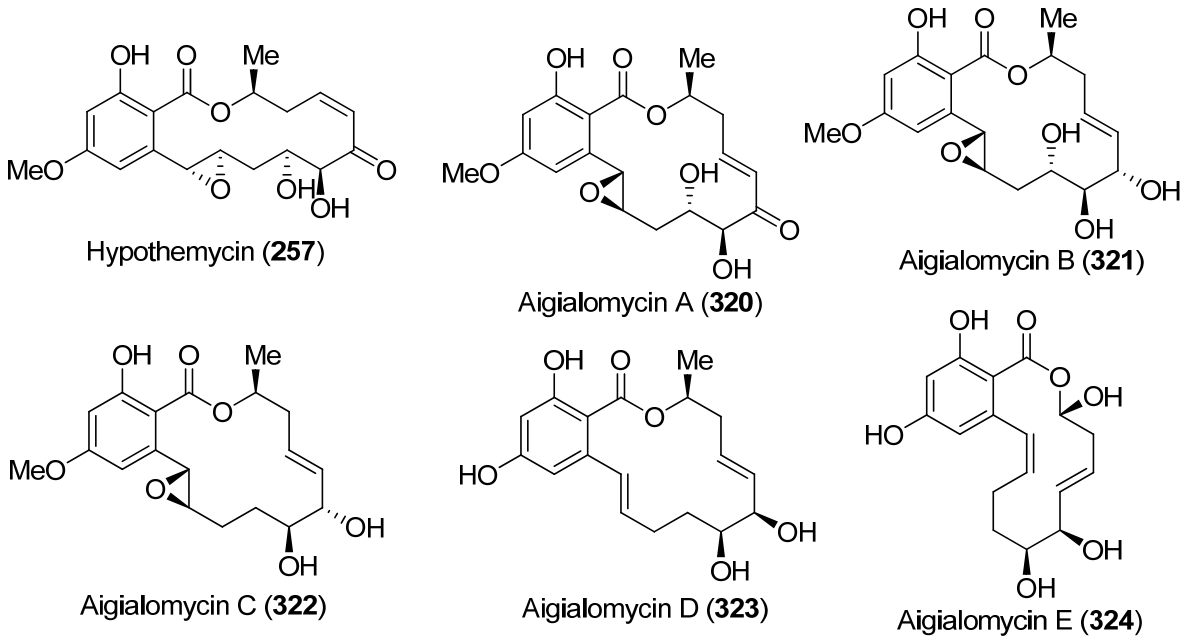


Figure 25: Natural products of the marine mangrove fungus *Aigialus parvus.*

Extension of the incubation period from 35 to 80 days resulted in the isolation of two new compounds, aigialone (**325**) and aigialospirol (**256**) (Figure 26).[146]

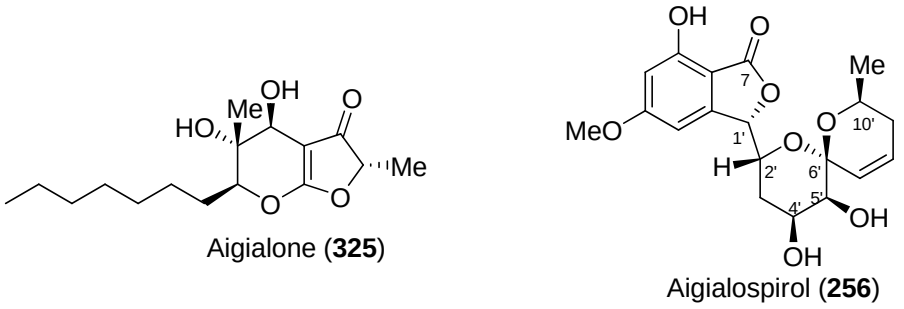


Figure 26: Products of extended fermentation of *Aigialus parvus*.

More recently, in a reinvestigation of the secondary metabolites from *Aigialus parvus*, Isaka *et al*.[147] have isolated six new nonaketide metabolites from the ethyl acetate extract of the 80 day culture broth. The six new derivatives isolated were; aigialomycins F (**328**) and G (**329**), 7′,8′-dihydroaigialospirol (**326**), 4′-deoxy-7′,8′-dihydroaigialospirol (**327**), and the rearranged macrolides (**330**) and (**331**) (Figure 27). Compound (**332**) was recently isolated by Wee *et al*.[148] from *Hypomyces subiculosus* DSM 11931 and DSM 11932 as a minor co-metabolite with (**257**).

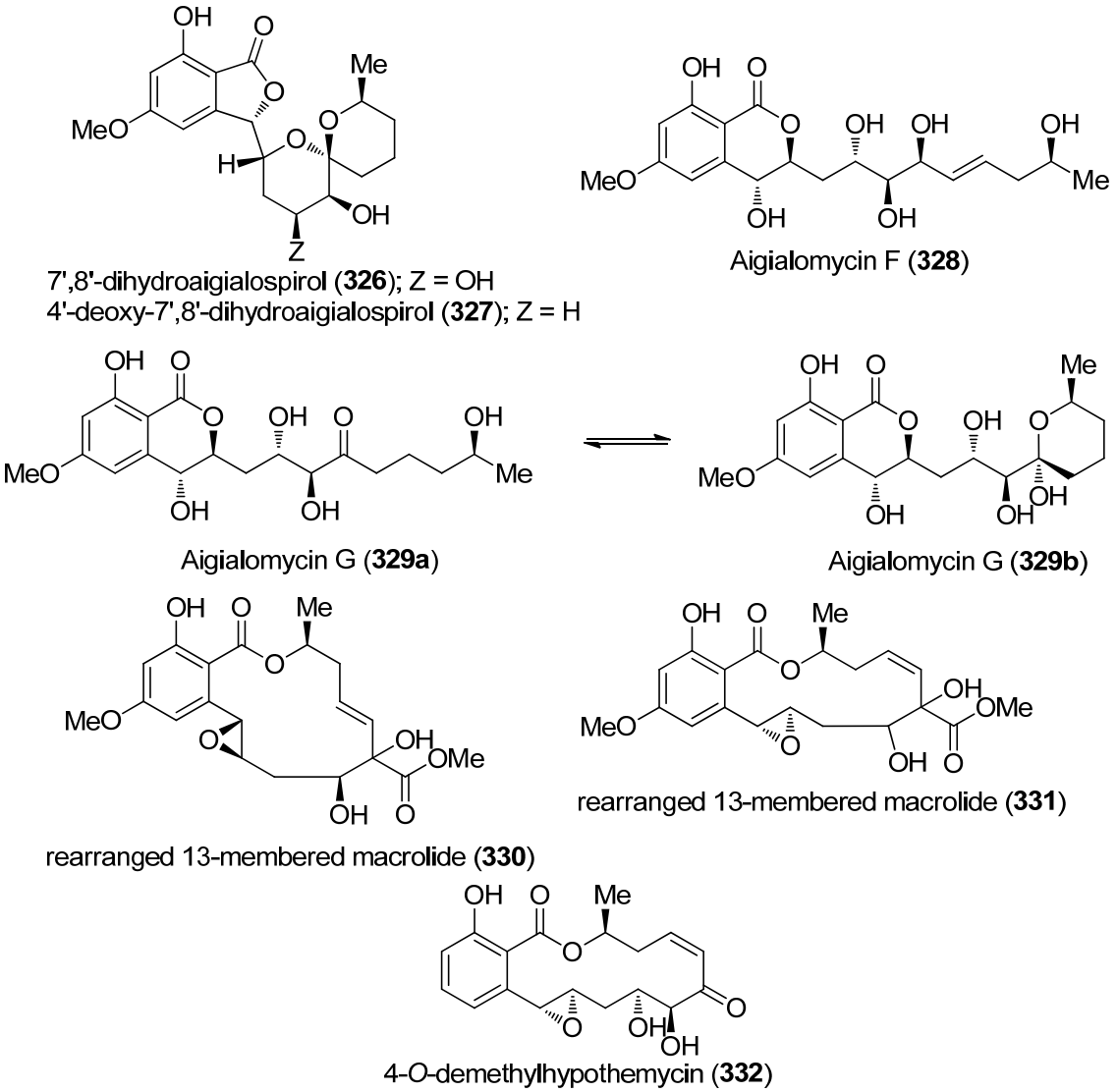
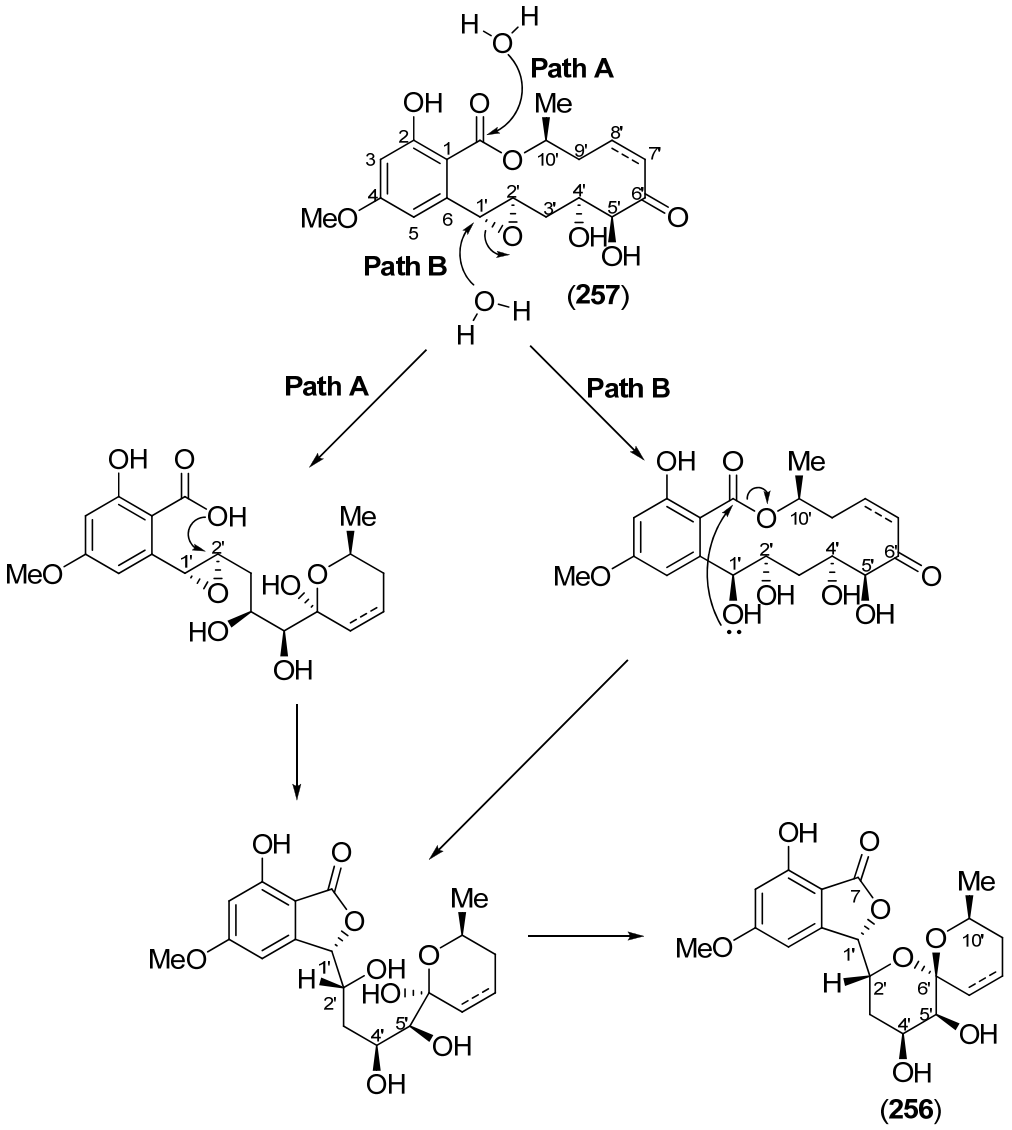


Figure 27: Six new products of extended fermentation of *Aigialus parvus* and 4-*O*-demethylhypothemycin (**332**).

X-ray analysis of aigialospirol (**256**) indicated a structural similarity to hypothemycin (**257**) and the aigialomycins. Key structural components of the above molecules include a resorcylic ester connected to an aliphatic polyketide chain. Aigialospirol (**256**) was found to possess a dihydroisobenzofuranone structure and a 6,6-spiroketal functionality, rather than the 14-membered macrocycle seen in hypothemycin (**257**) and the aigialomycins. 2-D NMR analysis indicated that aigialospirol (**256**) possessed identical relative stereochemistry to hypothemycin (**257**) at all stereocentres except C-1′ hence it was proposed to be a metabolite of hypothemycin (**257**).[146]

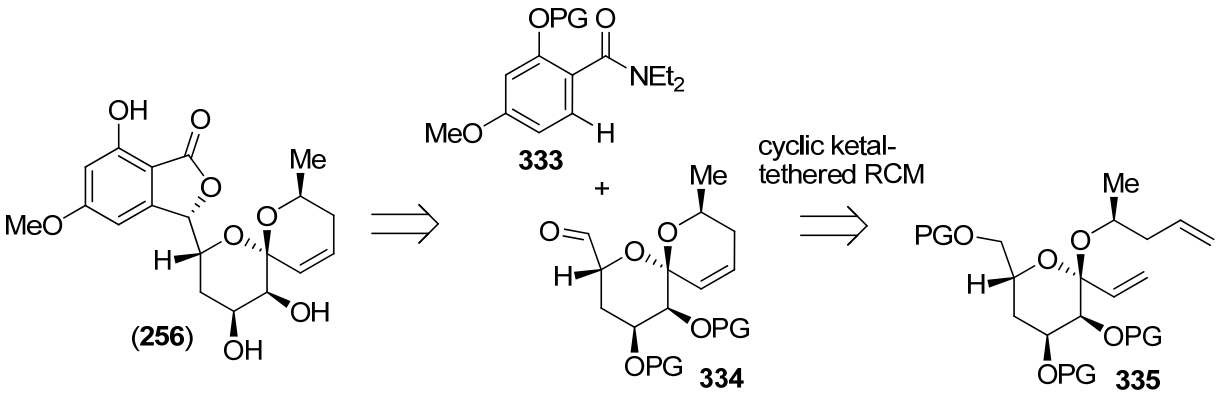
Two routes for the conversion of hypothemycin (**257**) to aigialospirol (**256**) are possible. Path A consists of hydroxyl promoted epoxide opening with concomitant (S_N2) stereoinversion at C-1′ followed by attack at the ester carbonyl to form a γ-lactone. The resulting polyhydroxylated chain is readily setup for spiroketal formation (Scheme 93).[146, 149] The other possible mechanism involves hydrolysis of the ester linkage (Path B) and subsequent attack at the epoxide (C-1′) to give the same final precursor as Path A. As for the newly isolated 7′,8′-dihydroaigialospirol (**326**) and 4′-deoxy-7′,8′-dihydroaigialospirol (**327**), the likely precursors are dihydrohypothemycin[150] and 4′-deoxy-dihydrohypothemycin, respectively, although these presursors were not isolated in extracts of *Aigialus parvus* BCC 5311.[147]



Scheme 93: Proposed route for the biosynthesis of aigialospirol (**256**) from hypothemycin (**257**).

5.1.2 Enantioselective Total Synthesis of (+)-Aigialospirol (256) by Hsung *et al.*[149]

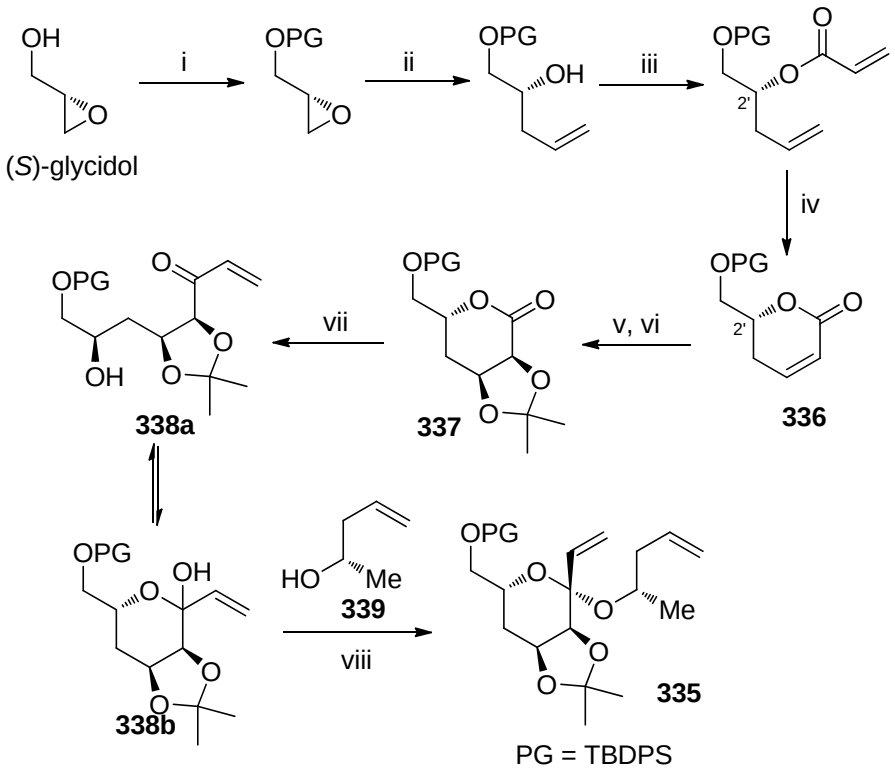
The isolation and structural elucidation of aigialospirol (**256**) was reported in 2004 and to date, there has been only one total synthesis of this natural product which was reported in 2007 by Hsung *et al*.[149]



Scheme 94. Retrosynthetic analysis of (+)-aigialospirol (**256**).

Hsung and coworkers reported the synthesis of (+)-aigialospirol using a cyclic ketal tethered ring-closing metathesis (RCM) strategy.[151] The retrosynthetic analysis is shown in Scheme 94 dipicting that the synthesis of unit **334** is the key step in the total synthesis.

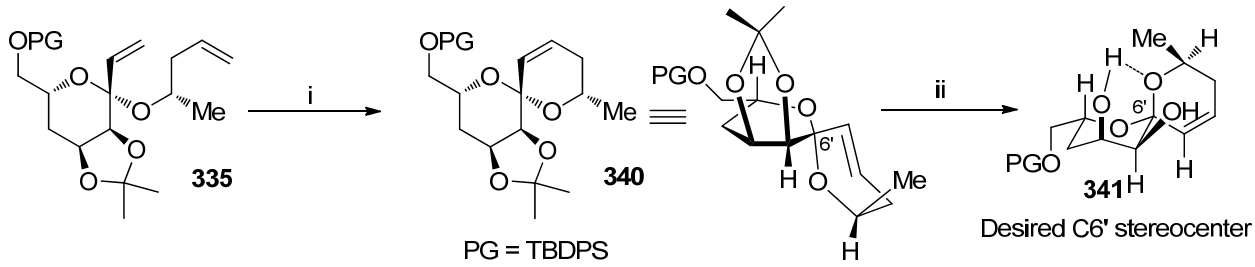
The dihydro-α-pyrone intermediate required for the synthesis of the key intermediate is prepared from *(S)*-glycidol, which provides the required stereochemistry at C-2′ in 62% yield over four steps (Scheme 95).[152] The compound **336** then undergoes dihydroxylation[153] followed by acetonide formation giving δ-lactone **337**, which upon treatment with vinyl Grignard gives an equilibrating mixture of vinyl ketone **338a** and lactol **338b**. The key intermediate **335** is then obtained by treatment of the lactol-ketone mixture and chiral homoallylic alcohol **339** with trifluoromethanesulfonimide (Scheme 95).



Reagents and conditions: i. TBDPSCl, imidazole, DMF, 95%; ii. a) CuCN, THF, −78 °C; b) $CH_2CHMgCl$, −78 to −20 °C, 80%; iii. Et_3N, acryloyl chloride, THF, 0 °C, 89%; iv. $Ru{=}CHPhCl_2(PCy_3)_2$, CH_2Cl_2, Δ, 75%; v. 6.0 mol% OsO_4, NMO, Me_2CO/H_2O, r.t.; vi. *p*-TsOH, $(CH_3)_2C(OMe)_2$; Me_2CO, r.t., 68% over 2 steps; vii. $CH_2{=}CHMgBr$, Et_2O, -78 °C, 88%; viii. **339**, Tf_2NH, 4 Å, CH_2Cl_2, -78 °C, 76%.

Scheme 95. Synthesis of key cyclic ketal **335**.

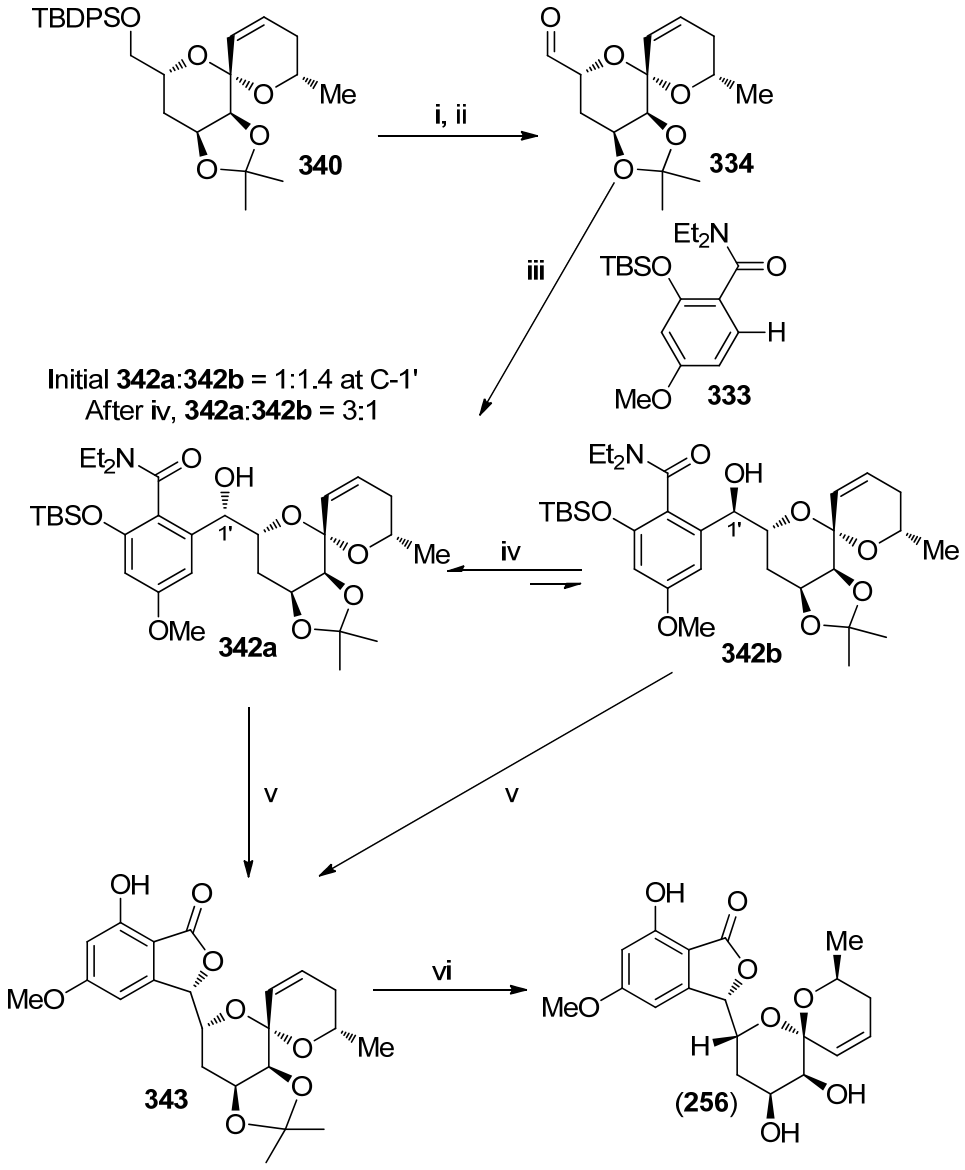
The cyclic ketal **335** was subjected to ring-closing metathesis employing Grubb's first generation catalyst to give **340**[151] which possessed the wrong stereochemistry at the C-6′ position. However, when the acetonide group was removed under acidic conditions, epimerisation of the spiroketal centre took place to establish the desired C-6′ stereocenter, as confirmed by NOE structure and an X-ray structure of diol **341** (Scheme 96).



Reagents and conditions: i. Grubbs' Gen-1, toluene, 86%; ii. *p*-TsOH, MeOH, r.t., 81%.

Scheme 96. Cyclic ketal-tethered RCM and C-6′ epimerisation.

To complete the total synthesis, the authors used spiroketal **340** rather than **341** and carried out the epimerisation at C-6′ in the spiroketal center in the last step. Desilylation and oxidation of **340** gave aldehyde **334** and subsequent addition of the aryllithium intermediate, generated via a Snieckus' directed *ortho*-metallation[154] of amide **333**,[155] afforded a readily separable (1:1.4) mixture of alcohols **342a** and **342b**. Both **342a** and **342b** led to the same lactone **343** (with loss of the TBDMS group) (Scheme 97). Finally, the acetal group in lactone **343** was hydrolysed to give (+)-aigialospirol (**256**) in which concomitant C-6′ epimerisation took place.



Reagents and conditions: i. TBAF, THF, r.t.; ii. TEMPO, BAIB, CH_2Cl_2, r.t., 76% over 2 steps; iii. *s*-BuLi, TMEDA, THF, -78 °C, 50%; iv. in C_6D_6 at r.t. or at -10 °C or w/ silica gel; v. KOH, MeOH/H_2O/THF, r.t., 71%; vi. *p*-TsOH, MeOH, r.t., 53%.

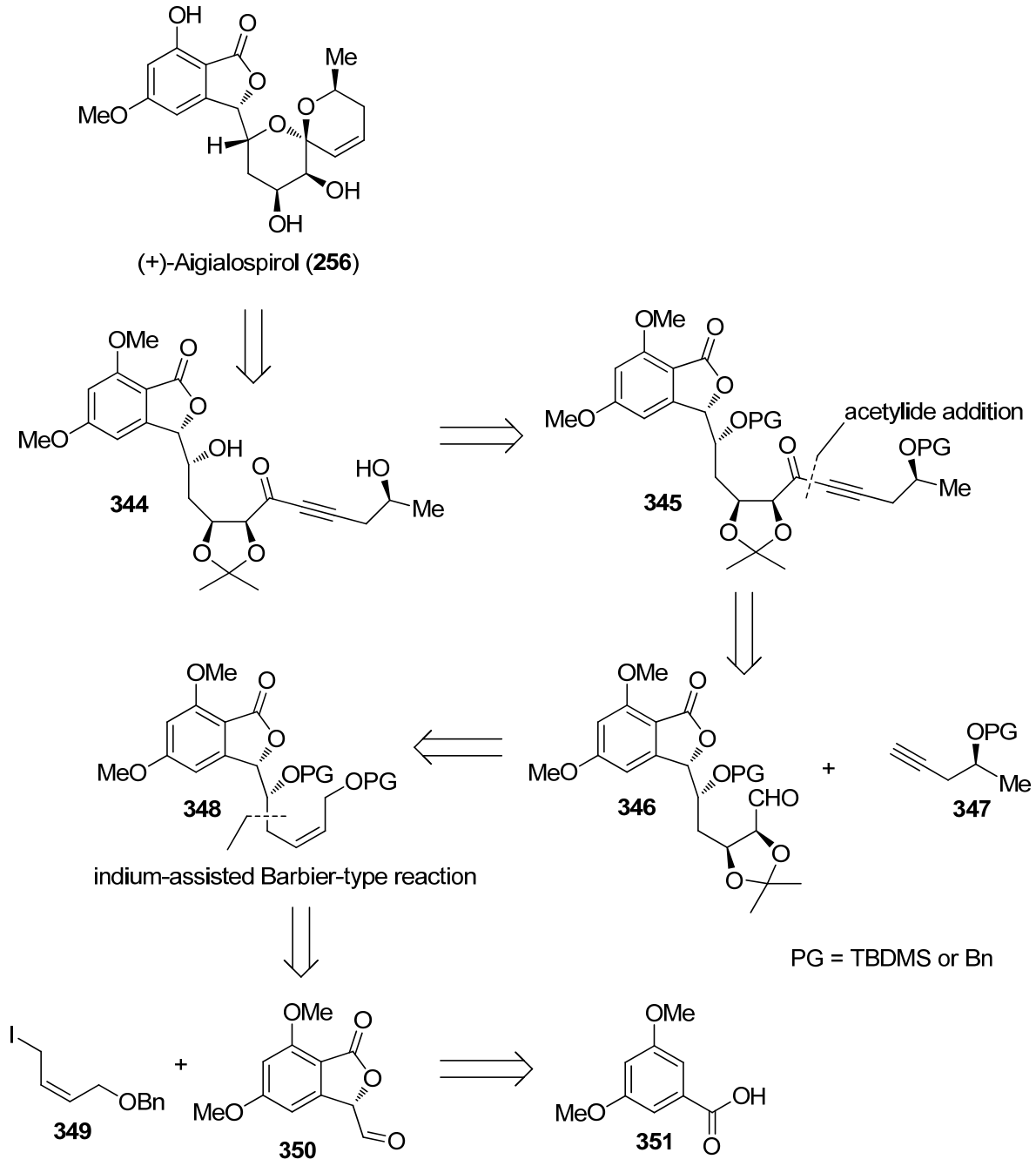
Scheme 97. Total synthesis of (+)-aigialospirol (**256**) by Hsung *et al*.[149]

5.1.3 Proposed Synthetic Route

The aim of the present research is to develop a synthetic route to the natural product aigialospirol (**256**). Aigialospirol (**256**), like hypothemycin (**257**), possesses a resorcylic ester connected at C-6 to an aliphatic polyketide chain. Unlike the 14-membered macrolide hypothemycin (**257**), aigialospirol (**256**) possesses a dihydroisobenzofuranone structure linked to an unsaturated dihydroxyspiroketal ring system. The synthesis of novel phthalide-containing spiroketals based on the aigialospirol structure provides an exciting new heterocyclic template to explore for potential new antitumour agents thus providing the main impetus for the present work.

5.1.3.1 Retrosynthetic Analysis of (+)-Aigialospirol (256)

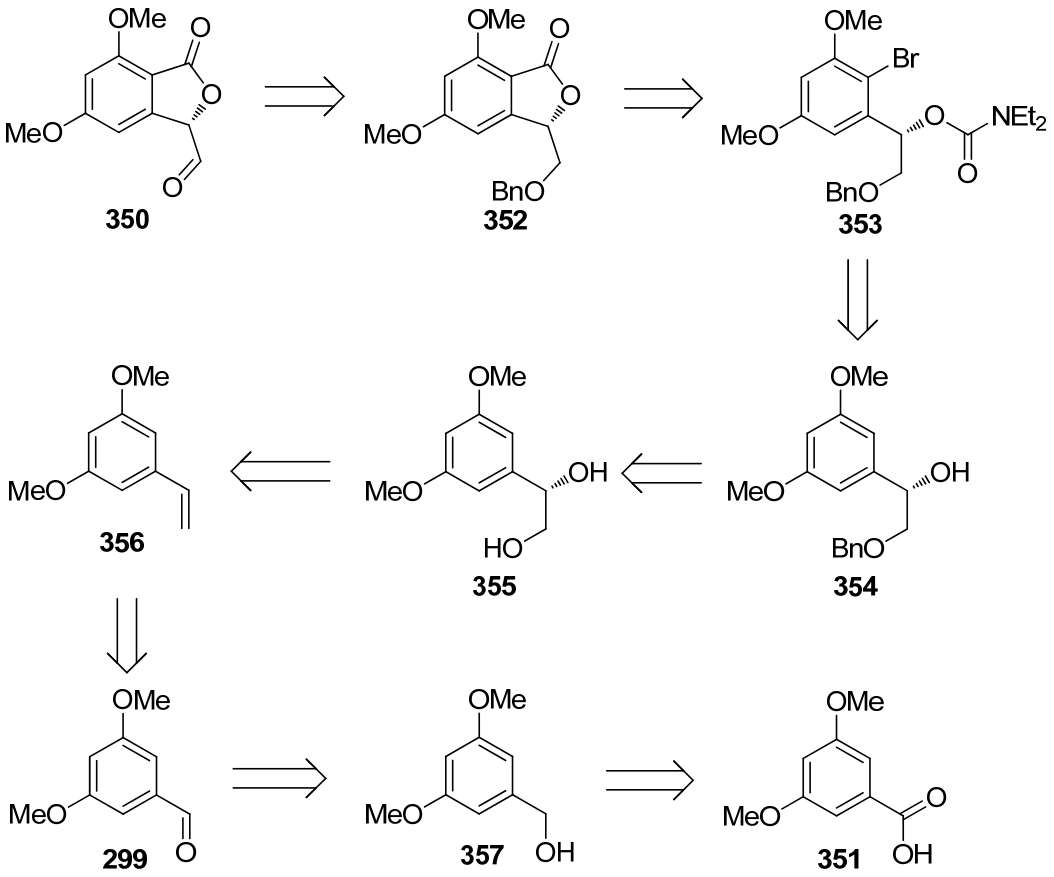
The retrosynthesis adopted is shown in Scheme 98 and involves acid catalysed cyclisation of dihydroxyketone **344** as the final step. It was envisaged that dihydroxyketone **344** would be available from **345** that in turn is available from addition of the acetylide derived from homochiral protected acetylenic alcohol **347** to aldehyde **346**. The initial synthesis of aldehyde **346** via unsaturated alcohol **348** involves the addition of the iodide fragment **349** to the phthalide-aldehyde **350** which undergoes Sharpless asymmetric dihydroxylation and oxidation to give the aldehyde **346**. Phthalide-aldehyde **350**, in turn would be accessible from the commercially available 3,5-dimethoxybenzoic acid **351**.



Scheme 98. Initial retrosynthesis of aigialospirol (**256**).

5.1.4 Synthesis of Phthalide-aldehyde 350

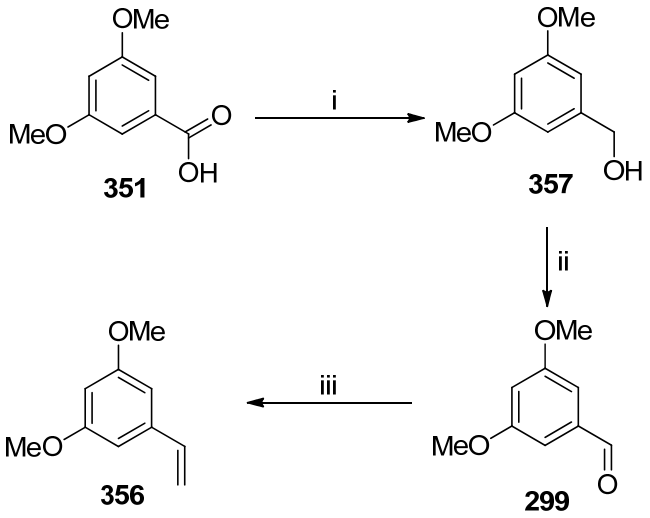
The strategy for the synthesis of phthalide-aldehyde **350** is outlined in Scheme 99 and initially involved the reduction of commercially available 3,5-dimethoxybenzoic acid **351** to give alcohol **357** which is oxidised to 3,5-dimethoxybenzaldehyde **299**. After Wittig reaction to yield dimethoxystyrene **356**, Sharpless dihydroxylation would give chiral diol **355**. After selective protection of the primary alcohol to give **254**, α-bromination followed by addition of diethyl carbamoyl chloride gives carbamate **353**. Bromide **353** then undergoes halogen/metal exchange followed by intramolecular cyclisation to give phthalide-alcohol **352**. Subsequent oxidation of the primary alcohol liberated after deprotection of the benzyl ether then gives phthalide-aldehyde **350** (Scheme 99).



Scheme 99. Strategy for the synthesis of phthalide-aldehyde **350**.

Protected benzyl diol **354** has been synthesised in high yields by the Nicolaou group to give the (*R*) enantiomer of **354**.[156] The synthetic route employed involved Wittig olefination of benzaldehyde **299** to afford styrene **356** followed by a Sharpless asymmetric dihydroxylation using AD-mix β. The resultant diol **355** was selectively protected using dibutyltin oxide and benzyl bromide, a method commonly chosen in carbohydrate chemistry for the selective protection of primary alcohols.[156]

3,5-Dimethoxybenzaldehyde **299** was synthesised from the readily available 3,5-dimethoxybenzoic acid **351**. Reduction of acid **351** to alcohol **357** using lithium aluminium hydride was achieved in high yield and could be used with no additional purification in the following Swern oxidation to afford benzaldehyde **299** in 84% yield over two steps (Scheme 100).



Reagents and conditions: i. $LiAlH_4$, THF, reflux; ii. oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, r.t., 84% over 2 steps; iii. Zn, DMF, acetyl chloride, CH_2Br_2, 74%.

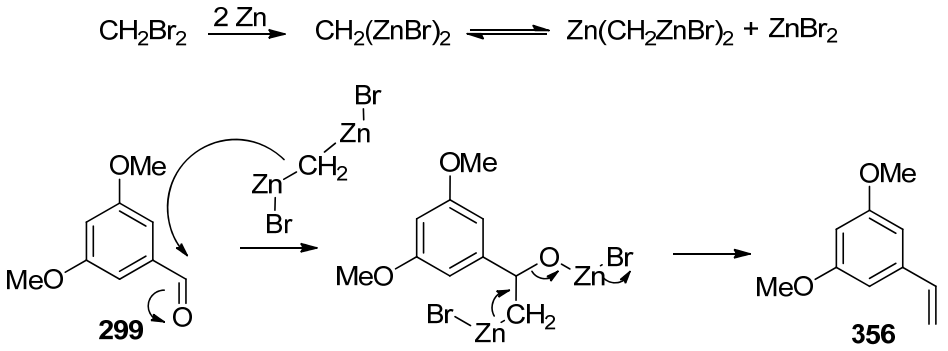
Scheme 100. Synthesis of 3,5-dimethoxystyrene **356**.

Next, the carbonyl group methylenation was attempted. The initial approach employed was based on that used by the Nicolaou group, namely Wittig olefination.[156] Methyl

triphenylphosphonium iodide was used rather than the bromide salt previously employed. However, only moderate yields of the olefin were obtained. Both commercial and freshly prepared methyl triphenylphosphonium iodide were used, with an optimum 61% yield of **356** being obtained using freshly recrystallised, phosphonium salt.

The Wittig reaction has some limitations, one of which is the formation of large amounts of triphenylphosphine oxide which is difficult to remove from the product. Therefore, in an effort to improve the yield of the carbonyl methylenation step an alternative route was sought. A less common alternative to the Wittig reaction, namely the zinc promoted Wittig type carbonyl methylenation was employed by Tsujihara *et al*.[157] and application of this method yielded the desired styrene **356** in 74% yield.

The Wittig type carbonyl methylenation was first reported by Fried *et al*.[158] in 1966 as "an unusual example of methylenation with a modified Simmons-Smith reagent." In the Simmons-Smith cyclopropanation, diiodomethane reacts with a zinc-copper couple (Zn-Cu) to form an organozinc complex thought to be in the form of "I-CH_2-ZnI". This undergoes a concerted reaction with olefins to stereoselectively form a cyclopropane ring. A number of groups have reported that, in the presence of excess zinc, the organozinc complex rather than reacting at the olefin, replaces carbonyl functionalities with a methylene.[158-160] It has been found that the choice of solvent in the formation of the Simmons-Smith reagent (I-CH_2-ZnI) is important with formation of the "I-CH_2-ZnI" species alone in ether whereas in tetrahydrofuran *gem*-dizinc species (IZn-CH_2-ZnI) are also formed.[161] The Simmons-Smith reagent reacts as an electrophile with olefins but does not attack carbonyl compounds. However, double substitution of the carbon atom with electropositive zinc, increases the nucleophilicity of the *gem*-dizinc species, promoting nucleophilic attack of this species at the carbonyl carbon (Scheme 101).[161]

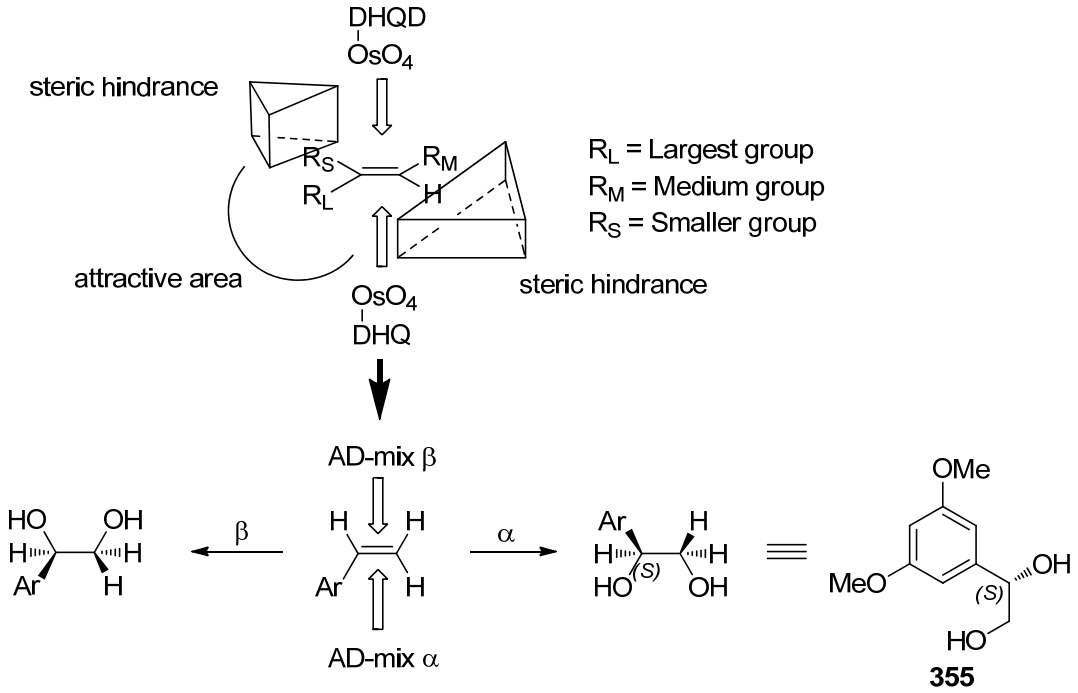


Scheme 101. Proposed mechanism for Wittig-type carbonyl methylenation.[158-161]

With styrene **356** in hand, introduction of the stereocentre at C-1′ could be carried out using a Sharpless dihydroxylation.[162]

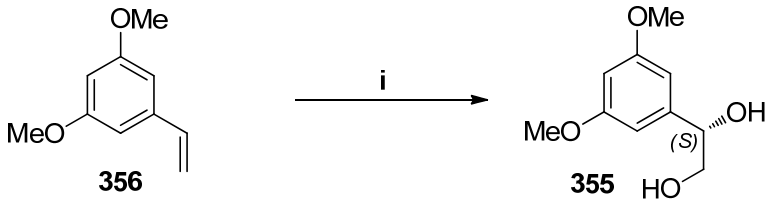
The selectivity of the Sharpless dihydroxylation reaction can be determined using Scheme 102. With the substrate arranged as shown, with the largest group (R_L) positioned bottom left, the next largest group (R_M) positioned top right. AD-mix α with DHQD-based ligands will direct osmium tetroxide to dihydroxylate from the top face of the double bond while AD-mix β with DHQ-based ligands will direct it to the bottom. This is due to the ligand-osmium complex forming a 'chiral pocket' which forces approaching alkenes to the correct orientation.

Using the Sharpless mnemonic it was determined that AD-mix α or $(DHQ)_2PHAL$ would be required in order to achieve the desired stereochemistry.



Scheme 102. Determination of Sharpless catalyst needed to achieve desired stereochemistry.

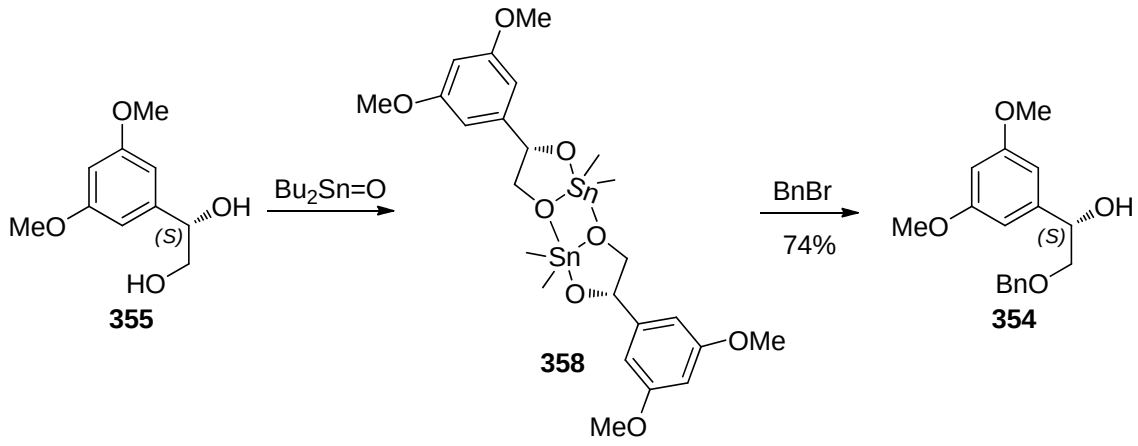
To a mixture of potassium ferricyanide, potassium carbonate, $(DHQ)_2PHAL$, methanesulfonamide, osmium tetroxide in a 1:1 mixture of *t*-butanol/water was added styrene **356** at 0 °C. The Sharpless dihydroxylation was carried out on a large scale with a pleasing 96% yield and >96% e.e. (Scheme 19).



Reagents and conditions: i. K_3FeCN_6, K_2CO_3, $(DHQ)_2PHAL$, OsO_4, methanesulfonamide, *t*-BuOH:H_2O (1:1), 96%, e.e. >96%.

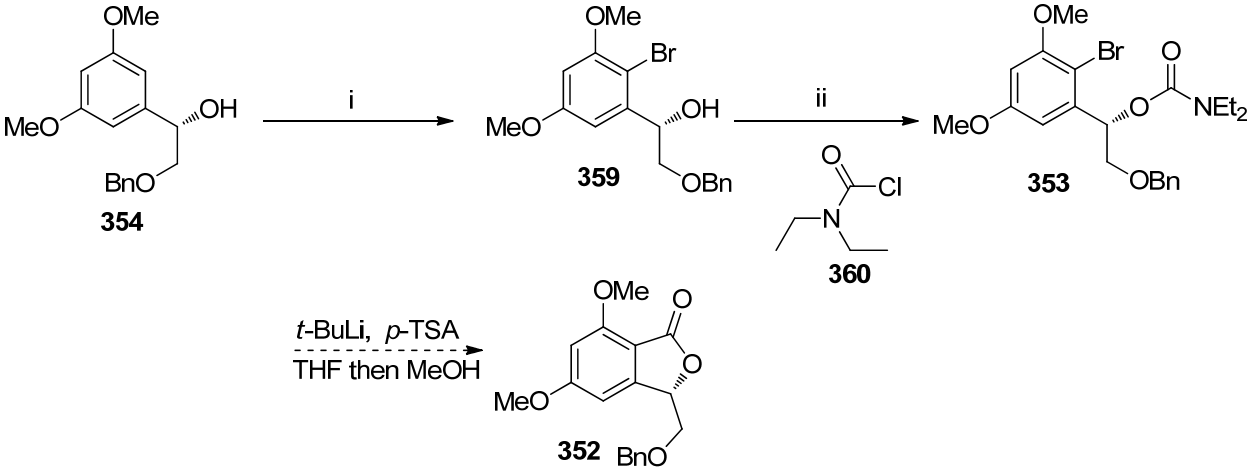
Scheme 103. Synthesis of diol **355**.

Selective protection of the primary alcohol followed. In order to selectively protect the primary alcohol, a carbohydrate protection protocol was adopted which uses dibutyltin oxide to form a cyclic intermediate which is then cleaved upon introduction of benzyl bromide.[156, 163] Upon refluxing the diol **355** in the presence of dibutyltin oxide a stannylene derivative **358** forms.[163] The origin of selectivity is not understood but it is proposed that the oxygens in the ring are more nucleophilic hence they are more readily alkylated thus selectively protecting the primary alcohol. Structural studies of the stannylene intermediates suggest that they adopt a dimeric structure and this may contribute to the regioselectively by protecting the oxygen atoms in the Sn_2O_2 ring system as well as by changing the electronics of the two different oxygen atoms.[163] Treatment of benzyl bromide to diol **355** gave the mono benzyl ether **354** in 74% yield (Scheme 104).



Scheme 104. Selective protection of the primary alcohol *via* the proposed stannylene dimer.

Once the primary alcohol was protected, selective α-bromination and carbamate formation was required to setup the precursor for a halogen-lithium exchange followed by cyclisation to give the phthalide intermediate **353** (Scheme 105). Selective bromination at C-2 proceeded in 97% yield, using the procedure reported by Tanemura *et al.*[164] which has been used successfully for the synthesis of similar phthalides by the Brimble group.[165-167] Formation of carbamate **353** presented some minor difficulties, however, it was finally achieved in 92% yield by treating the protected diol **359** with NaH followed by *N,N*-diethylcarbamyl chloride **360**.[165-167] It was found that use of DMF instead of tetrahydrofuran as the reaction solvent gave better yields. Due to hindered rotation around the C-N bond, broad peaks were observed for the N*CH*$_2$CH$_3$ and NCH$_2$*CH*$_3$ groups in both the ^{1}H and ^{13}C NMR spectra. Temperature controlled NMR at 60 ^{o}C in DMSO gave better resolution of these peaks to unequivocally facilitate characterisation of **353**.



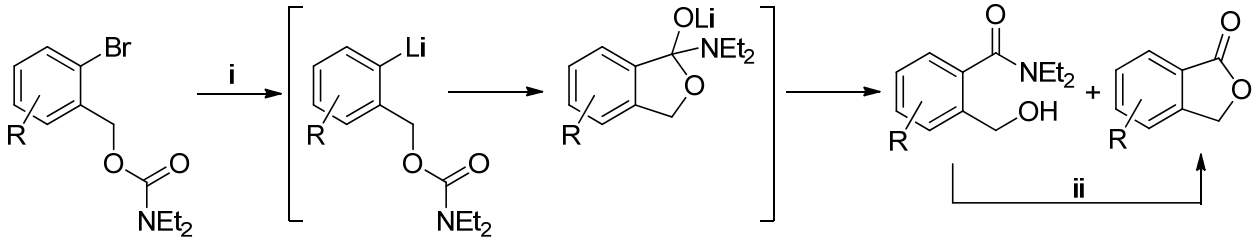
Reagents and conditions: i. NBS, NH_4OAc, Et_2O, 97%; ii. NaH, DMF, 92%.

Scheme 105. Selective α-bromination and carbamate formation followed by proposed cyclisation to give phthalide **352**.

5.1.4.1 Intramolecular Acylation of 353 to 352

Parham *et al*.[168, 169] have reported the intramolecular annulations of *ortho*-lithiated aromatics, generated *via* lithium halogen exchange, with electrophiles resident in the anion precursor. In an extension of this methodology, Castedo *et al.*[170] have synthesised a number of phthalides

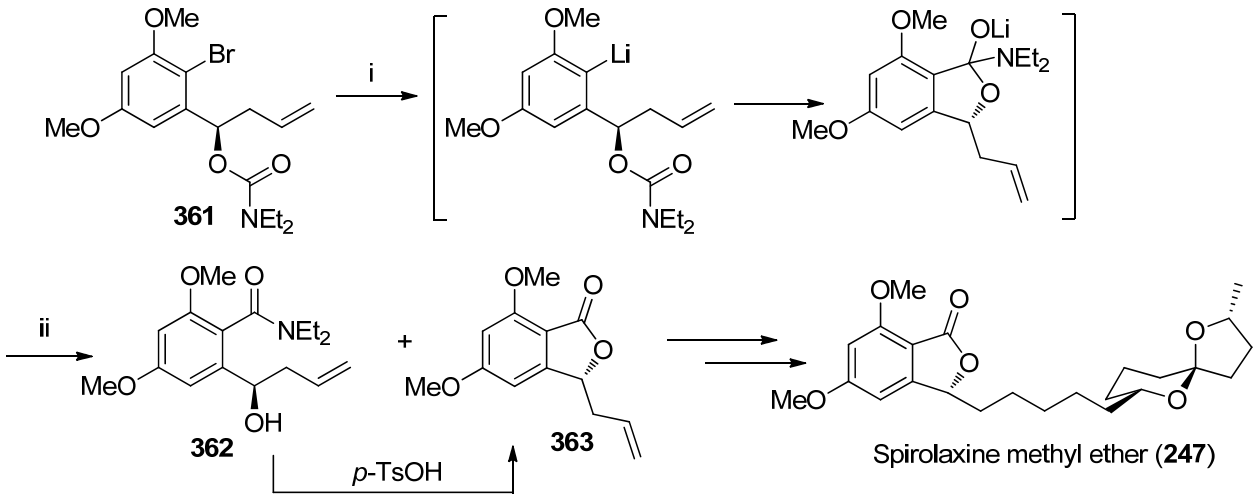
via the internal trapping of carbamates derived from benzylic alcohols (Scheme 106) in high yields.



Reagents and conditions: i. *t*-BuLi, THF, -78 °C then MeOH; ii. TFA, r.t.

Scheme 106: Synthesis of phthalides *via* carbamates by Castedo *et al*.[170]

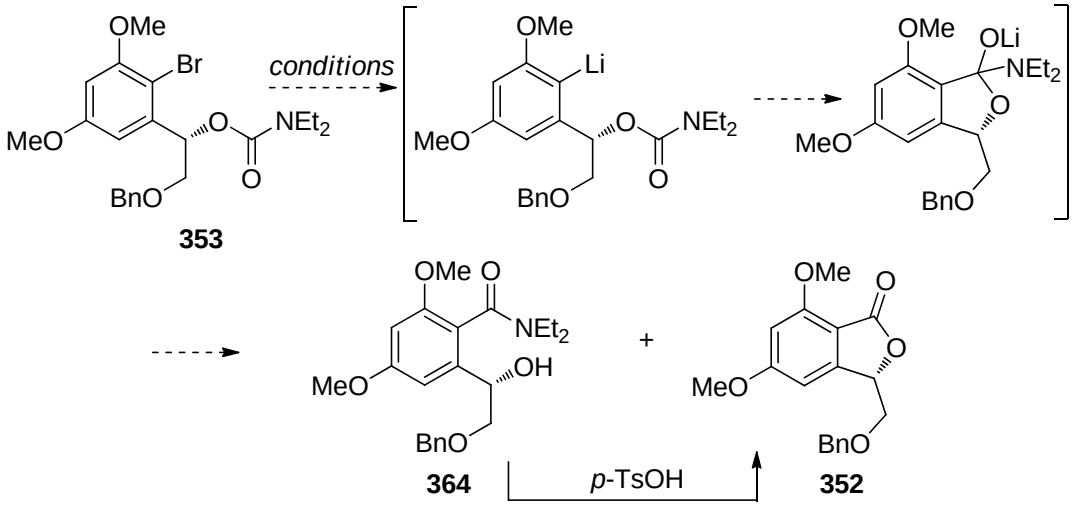
More recently, the Brimble group[165, 166] have utilised the intramolecular acylation for the synthesis of a phthalide **363** in the total synthesis of (+)-spirolaxine methyl ether (**247**). Lithium-halogen exchange of **361**, with *tert*-butyllithium (2.2 equiv.) in tetrahydrofuran at -78 °C, provided a mixture of the desired phthalide **363** and diethylamide **362**. Diethylamide **362** was then underwent lactonisation to the desired phthalide **363** using *p*-toluenesulfonic acid in 71% yield (Scheme 107).



Reagents and conditions: i. *t*-BuLi, THF, -78 °C, 45 min then MeOH; ii. *p*-TsOH, r.t., 12 h., 71% over 2 steps.

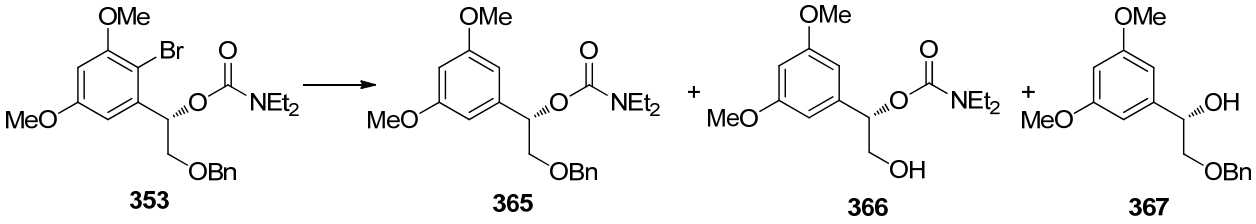
Scheme 107: Synthesis of phthalide **363** *via* intramolecular acylation by Brimble *et al*.[165, 166]

With this idea in mind and with carbamate **353** in hand, the intramolecular acylation could next be attempted (Scheme 108).



Scheme 108: Proposed intramolecular acylation of carbamate **353**.

A number of attempts were made to cyclise the resultant carbamate **353** (Table 11).



Entry	Base	Conditions	Yield 365 (%)	Yield 366 (%)	Yield 367 (%)
1	*t*-BuLi (2.2 eq)	-78 °C add base, stir for 45 min. Add methanol, *p*-TsOH and stir for 12 h, r.t.	<10%	35%	<10%
2	*t*-BuLi (2.2 eq)	-78 °C add base, stir for 15 min. Add methanol, *p*-TsOH and stir for	<10%	41%	<10%

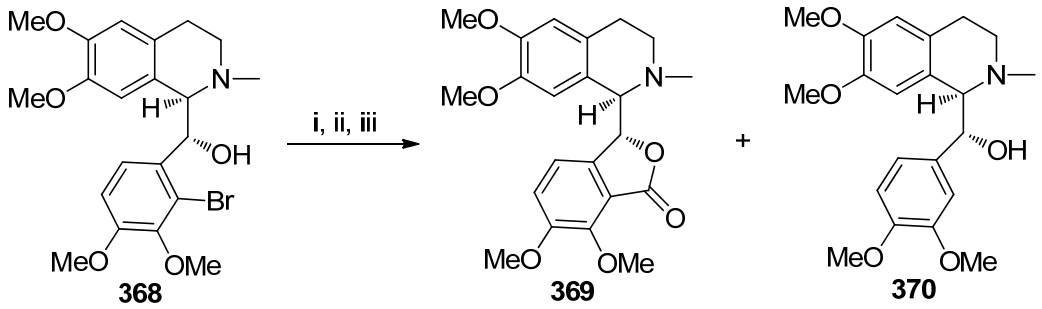
		12 h, r.t.			
3	*t*-BuLi (2.5 eq)	-78 °C add base, stir for 1 min. Add methanol, *p*-TsOH and stir for 12 h, r.t.	<10%	51%	<10%
4	*t*-BuLi (2.5 eq)	-78 °C add base, warm to -40°C and stir for 1 h. Add methanol, *p*-TsOH and stir for 12 h, r.t.	<10%	34%	<10%
5	*n*-BuLi (2.5 eq)	-78 °C add base, stir for 1 h. Add methanol, *p*-TsOH and stir for 12 h, r.t.	<10%	20%	<10%

Table 11: Intramolecular acylation of carbamate **353**

The reaction involved a halogen-lithium exchange to give a lithium anion at C-2. This anion can then react *via* intramolecular attack at the carbonyl group and loss of the diethylamino group to give phthalide **352**. Based on the work carried out by the Brimble group,[165, 166] *p*-toluenesulfonic acid was used as the catalyst for the acid catalysed lactonisation.

Entries 1 to 4 used *tert*-butyllithium (2.2 equiv.) in tetrahydrofuran at -78 °C, with various reaction times and adding catalytic amounts of *p*-toluenesulfonic acid. However the reaction gave a mixture of unwanted sideproducts. Debrominated product **365** was produced as confirmed by the 2:1 integration ratio for the aromatic hydrogen atoms H-6 (and H-2) and H-4 in the ^{1}H NMR spectrum. The product with the loss of a diethylamine group **367** and the debenzylated product **366** were isolated as major sideproducts. Using a slightly weaker base *n*-butyllithium (Entry 5), also gave similar results. The halogen-lithium exchange proceeded well as evidenced by the colour change from colourless to dark orange. The sideproducts clearly indicate that the anion was being protonated before cyclisation could take place.

Work reported by Orito *et al*.[171] attracted our attention as they reported similar problems using halogen-lithium exchange reaction for the synthesis of phthalide-isoquinoline **369** (Scheme 109).



Entry	Reaction time of 368 with *t*-BuLi	Product yield (%) 369 : 370
1	1 min	99 : trace
2	5 min	95 : 5
3	30 min	64 : 36

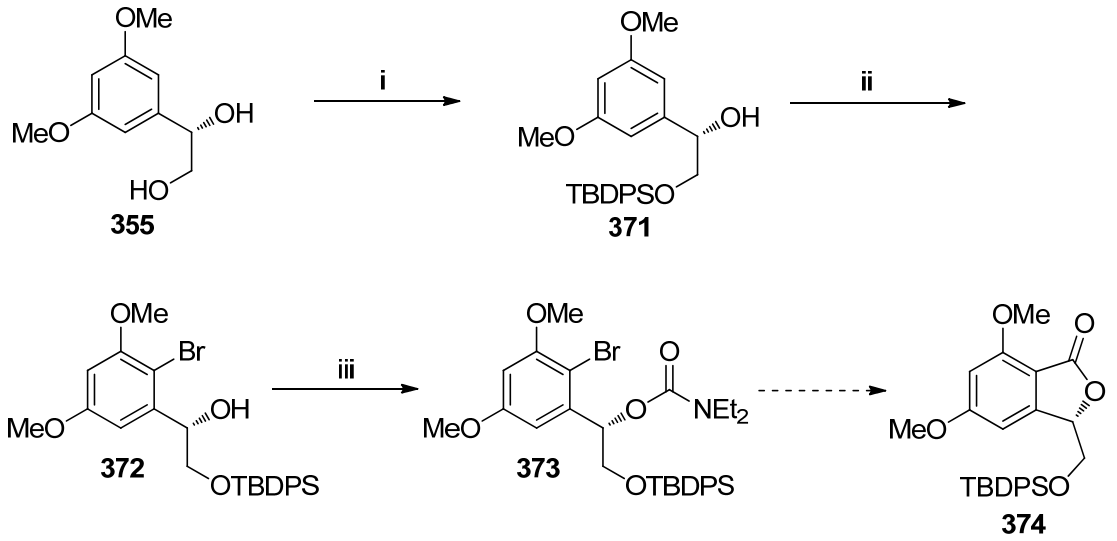
Reagents and conditions: i. *t*-BuLi, THF, -78°C, 1 min; ii. CO_2, 30 min; iii. HCl (2 M), 3 h, 99%.

Scheme 109: Synthesis of phthalide-isoquinoline **369** *via* halogen-lithium exchange

The authors reported that prolonged exposure of precursor **368** to *t*-BuLi (Entry 3) increased the amount of the debrominated **370** being formed. By decreasing exposure time to *t*-BuLi to 1 min then adding CO_2 followed by 2 M HCl formed the desired product **369** in quantitative yields. These results suggested the 2′-aryllithium is initially formed by a rapid halogen-lithium exchange and this then reacts with acidic hydrogen of the benzylic OH group.

For substrate **353**, even when the reaction time was reduced to 1 min before being quenched (Entry 3), there was still no sign of phthalide **352** being formed. Having isolated the debenzylated product **366** as the major byproduct, it was proposed that the hydrogen from the OH group would quench the anion hence prevent intramolecular acylation from occurring.

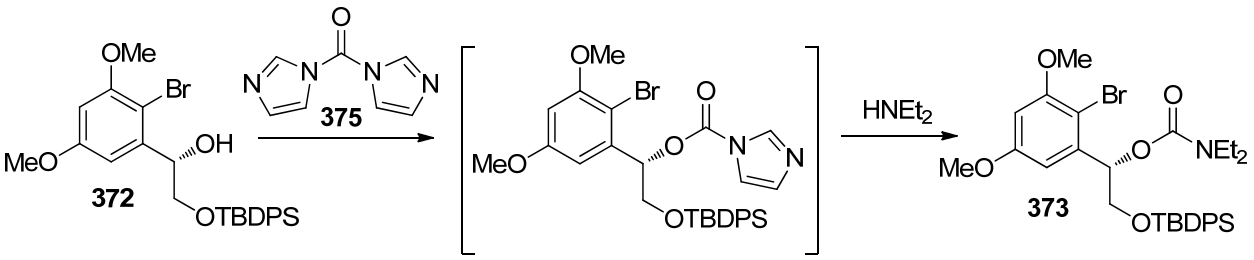
It was therefore envisaged that by changing the protecting group to a more base labile protecting group, the substrate would withstand the conditions required for this reaction. A *tert*-butyldiphenylsilyl (TBDPS) group was therefore used instead of the benzyl ether protecting group. (Scheme 110)



Reagents and conditions: i. TBDPSCl, imidazole, THF, r.t., 12 h, 89%; ii.NBS, NH_4OAc, Et_2O, r.t., 36 h, 97%, iii. CDI, $HNEt_2$, CH_2Cl_2, 50 h, 92%.

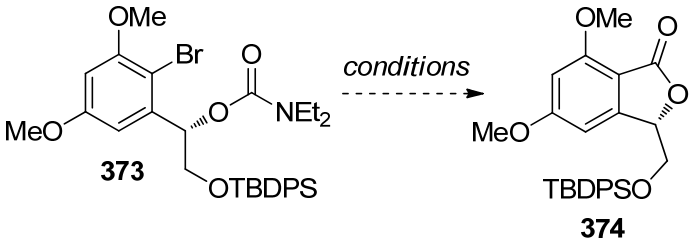
Scheme 110. Revised synthesis of phthalide **374** with a new protecting group.

The selective primary protection of the primary alcohol in **355** proceeded smoothly giving *tert*-butyldiphenylsilyl protected diol **371** in 89% yield. α-Bromination at the C-2 position was carried out to give **372** in 97% yield. Formation of carbamate **373** with NaH followed by *N,N*-diethylcarbamoyl chloride in DMF proceeded in 60% yield. However, use of *N,N*'-carbonyldiimidazole (CDI) **375** in dichloromethane with diethylamine gave the desired carbamate **373** in 92% yield. Despite the long reaction time, the ease of purification and high yields made it a favourable method over using the harsh conditions of NaH and DMF (Scheme 111).



Scheme 111. Formation of carbamate **373** using *N*,*N*'-carbonyldiimidazole and diethylamine.

With carbamate **373** in hand, intramolecular acylations were next attempted (Table 12).



Entry	Base	Conditions	Yield 376 (%)	Yield 377 (%)	Yield 378 (%)
1	*t*-BuLi (2.2 eq)	-78 °C add base, stir for 45 min. Add methanol, *p*-TsOH and stir for 12 h, r.t	<10%	35%	<10%
2	*t*-BuLi (2.2 eq)	-78 °C add base, stir for 15 min. Add methanol, *p*-TsOH and stir for 12 h, r.t.	<10%	25%	<10%
3	*t*-BuLi (2.5 eq)	-78 °C add base, stir for 1 min. Add methanol, *p*-TsOH and stir for 12 h, r.t	<10%	28%	<10%
4	*t*-BuLi (2.5 eq)	-78 °C add base, warm to -40°C and stir for 1 h. Add methanol, *p*-TsOH and stir for 12 h, r.t	<10%	20%	<10%

5	*n*-BuLi (2.5 eq)	-78 °C add base, stir for 1 h. Add methanol, *p*-TsOH and stir for 12 h, r.t	<10%	35%	<10%

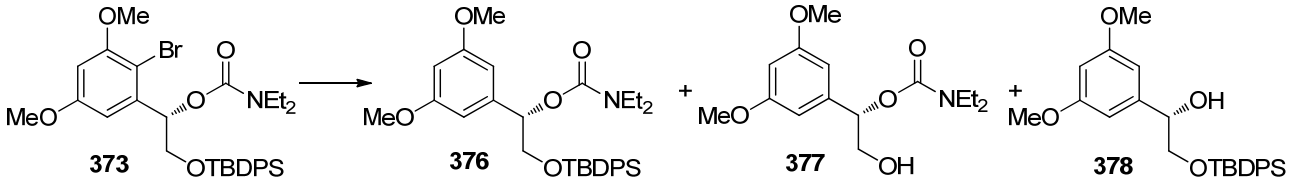
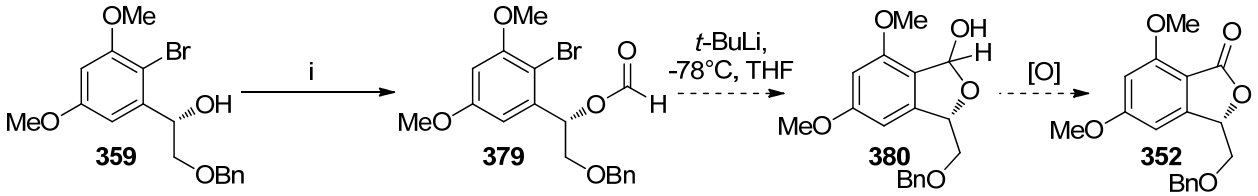


Table 12. Intramolecular acylation conditions and byproducts from the reaction.

Unfortunately, attempted intramolecular acylation of TBDPS protected substrate **373** failed to afford any of the desired phthalide **374** with only mixtures of the three byproducts **376-378** being afforded using *t*-BuLi and *n*-BuLi in a range of conditions (Table 12).

5.1.4.2 Alternative Synthetic Pathway to Phthalide 352

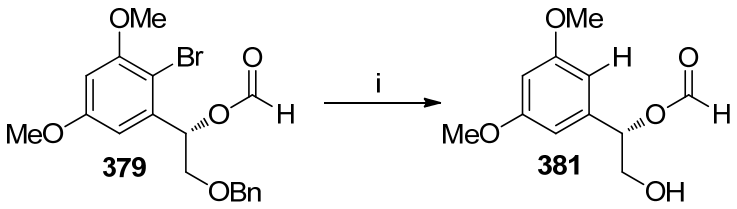
It was hoped that an alternative route may improve the production of the phthalide intermediate **352**. An alternative method used a procedure used previously by the Brimble group[172] involving formylation of the free secondary alcohol followed by halogen-lithium exchange and attack of the anion at the carbonyl carbon to give the alcohol derivative **380** (Scheme 112).



Reagents and conditions: i. formic acid, DCC, DMAP, 0 °C to r.t., 24 h, 64%.

Scheme 112. Intramolecular acylation of **379**.

Formate **379** readily formed in 64% yield upon treatment of **359** with formic acid followed by DCC and catalytic DMAP in a classic esterification reaction.[172] Treatment of the resultant formate **379** with 2 equivalents of *t*-BuLi followed by quenching with water after stirring at -78 ^{o}C for 1.5 h gave a spot to spot conversion as seen *via* TLC. However, NMR analysis of the products obtained indicated that protonation of the lithium anion had occurred, as established by the introduction of symmetry into the aromatic ring giving a 2:1 integration for the aromatic hydrogen atoms in the ^{1}H NMR spectrum (Scheme 113).

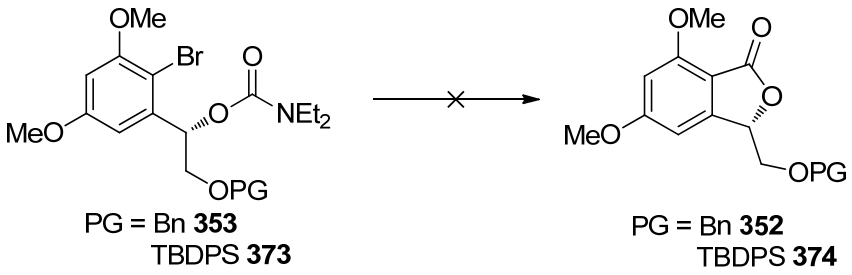


Reagents and conditions: i. *t*-BuLi, THF, -78 °C, 45 min then MeOH; ii. *p*-TsOH, r.t., 12 h., 21%.

Scheme 113. Alternative cyclisation route towards phthalide intermediate **352**.

Again, formation of the anion was considered to be achieved due to the deep orange-red colour the solution turned when *t*-BuLi was added. All precautions had been carried out to ensure exclusion of water from the reaction, including vacuum drying the formate overnight, heat and vacuum drying the glassware and use of freshly distilled tetrahydrofuran.

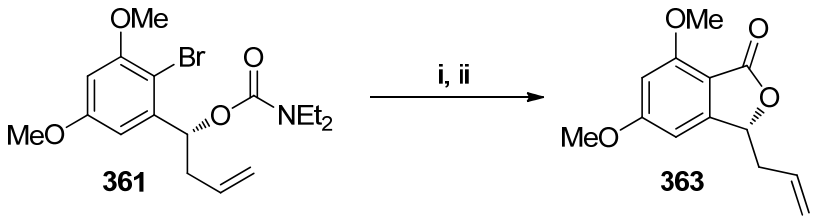
5.1.4.3 Conclusion



Scheme 114. Failed intramolecular acylation on carbamate **353** and **377** to phthalide **352** and **374**.

Intramolecular acylation of carbmates **353** and **373** failed to provide any of the desired phthalides **352** and **374** (Scheme 114). After analysing the byproducts of the reaction it was concluded that the halogen-lithium exchange was proceeding well (evident by the colour change from colourless to dark orange). However, the aryllithium was being quenched by a proton source before it could undergo intramolecular acylation to form the diethylamide intermediate which would be lactonised to the desired phthalide.

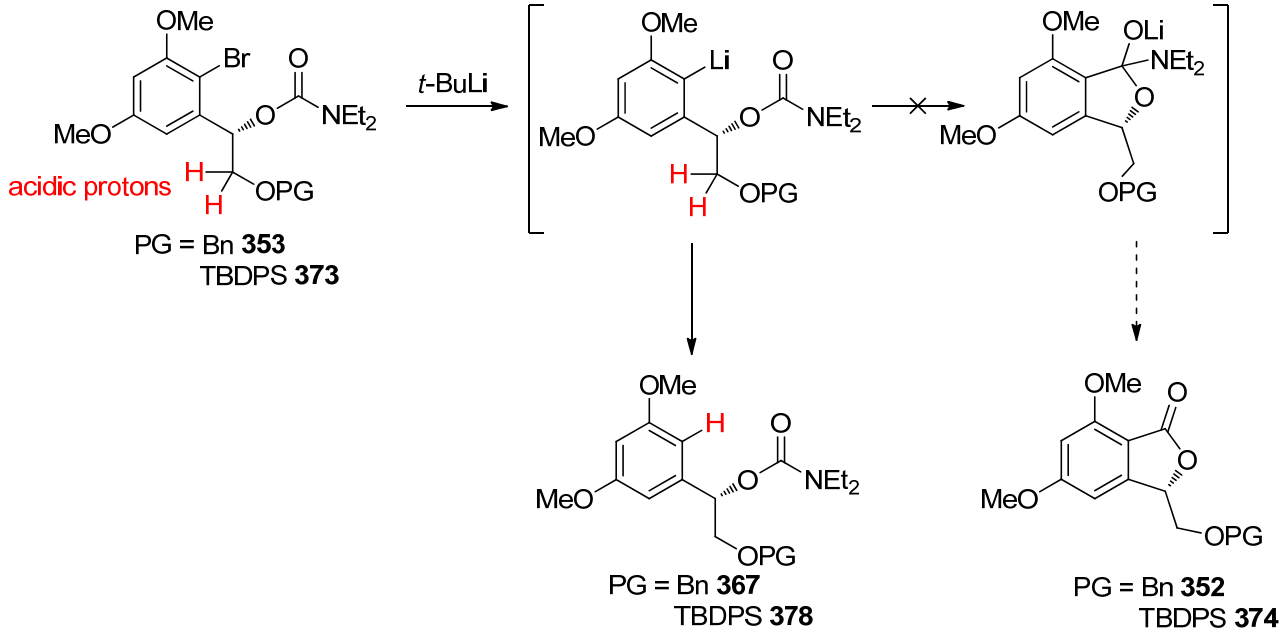
Similar intramolecular acylations by Brimble *et al*.[165, 166] had been successful using a very similar substrate in high yields (Scheme 115). This reaction did prove reproducible in our hands with the desired phthalide **363** forming in a pleasing 74% yield by the treatment of **361** with *t*-BuLi at -78 °C and using *p*-toluenesulfonic acid as the catalyst.



Reagents and conditions: i. *t*-BuLi, THF, -78 °C, 45 min, then MeOH; ii. *p*-TsOH, r.t., 12 h, 74% over 2 steps.

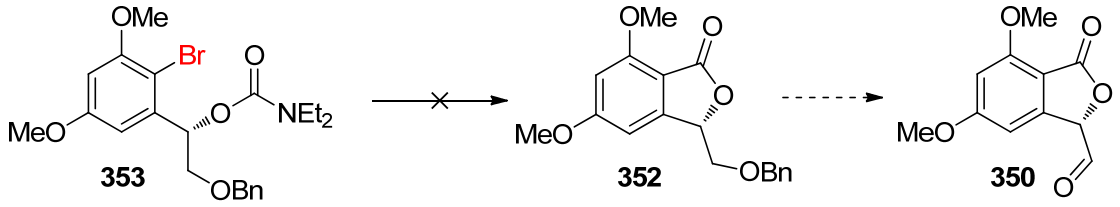
Scheme 115. Successful intramolecular acylation from carbamate **361** to phthalide **363** by Brimble *et al*.[165, 166]

The main differences between substrates **353**, **373** and substrate **361** is the presence of a protected oxygen group which could render the hydrogen next to the oxygen group more acidic therefore encouraging Li-proton exchange which prevents formation of the desired phthalides **352** and **376** (Scheme 116).



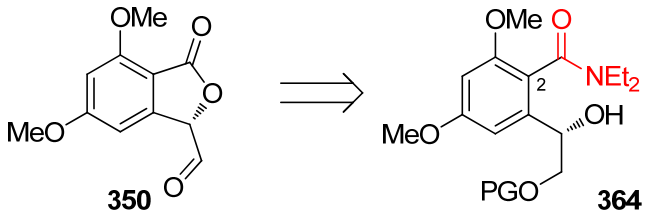
Scheme 116: Failed intermolecular acylation of carbamate **353** and **377** to phthalide **352** and **374**.

5.1.5 Revised Synthesis of Phthalide-aldehyde 350



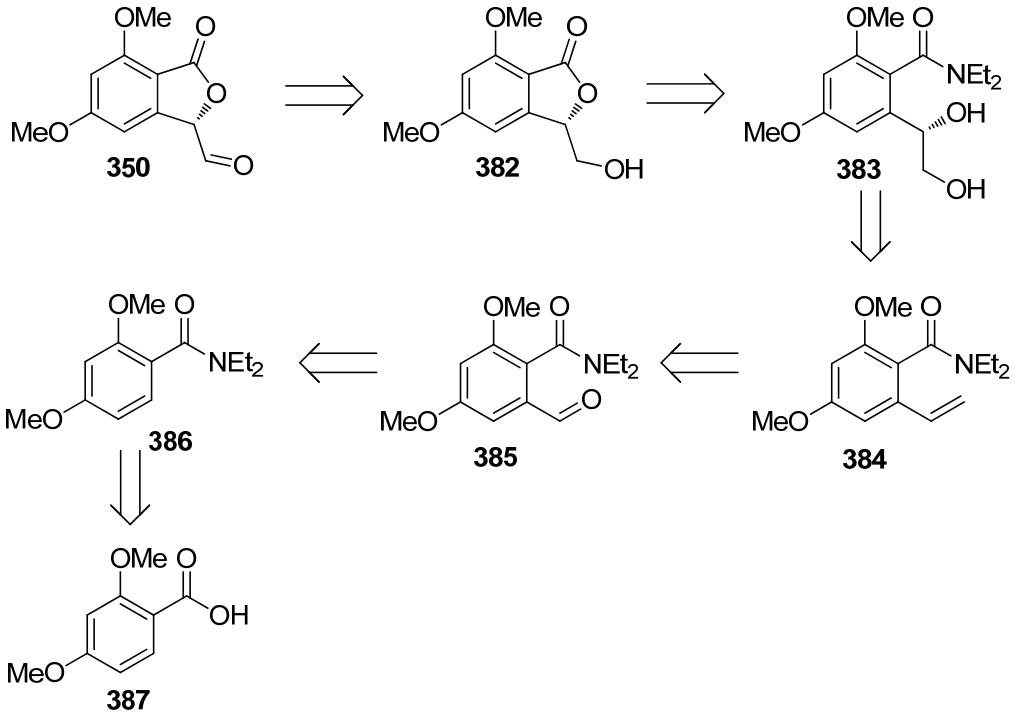
Scheme 117. Failed intramolecular cyclisation from substrate **353**.

With the intramolecular acylation at the C-2 position being unsuccessful (Scheme 117), it was next decided to modify our approach to phthalide-aldehyde **350** by starting the synthesis with the C-2 position already occupied with the desired amide functionality (Scheme 118).



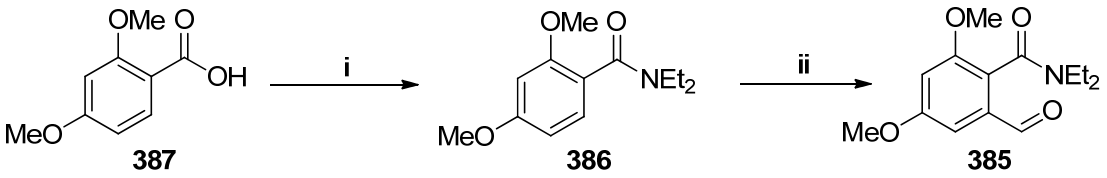
Scheme 118. Retrosynthesis of phthalide-aldehyde **350** from precursor **364**.

The revised strategy for the synthesis of phthalide-aldehyde **350** is outlined in Scheme 119 and initially involved the conversion of commercially available 2,4-dimethoxybenzoic acid **387** to the corresponding amide **386** followed by *ortho*-lithiation and formylation to give aldehyde **385**. After a modified Wittig reaction to yield dimethoxystyrene **284**, Sharpless dihydroxylation would give chiral diol **383**. The chiral diol **383** would undergo lactonisation to yield phthalide-alcohol **382** which would then be oxidised to give the desired phthalide-aldehyde **350** (Scheme 119).



Scheme 119. Proposed synthesis of the phthalide-aldehyde **350**.

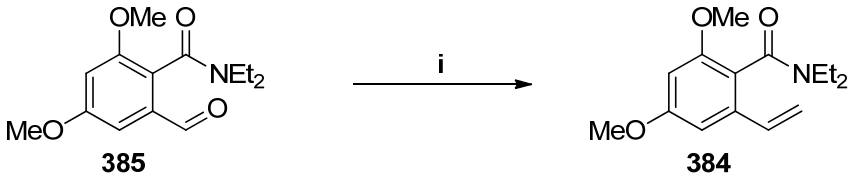
Applying the procedure used by the Brimble group,[173] aldehyde **385** was synthesised smoothly from commercially available 2,4-dimethoxybenzoic acid **387** which was subsequently converted to amide **386**, followed by *ortho*-lithiation then formylation which gave the desired aldehyde **385** in 90% yield (Scheme 120).



Reagents and conditions: i. $SOCl_2$, reflux, 2.5 h, then Et_2NH, CH_2Cl_2, r.t., 12 h, 96%; ii. *t*-BuLi, THF,-78 °C, 15 min, then DMF, r.t., 16 h, 90%.

Scheme 120. Synthesis of aldehyde **385**.

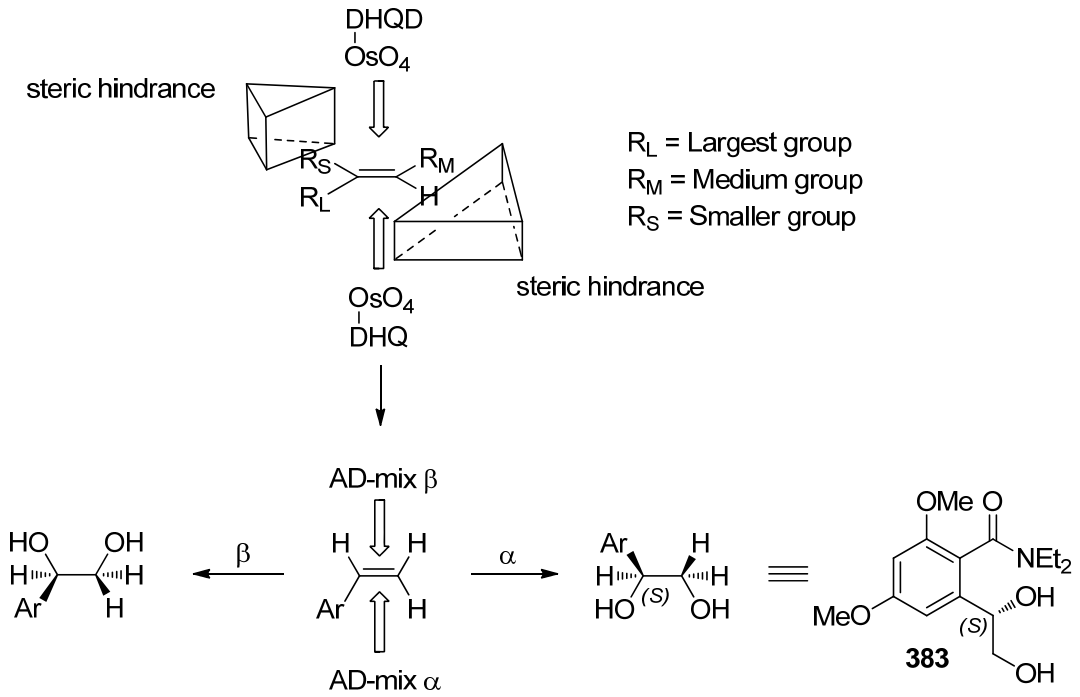
Styrene **384** was synthesised using the Wittig type carbonyl methylenation as described previously (Scheme 101) in good 82% yield. (Scheme 121)



Reagents and conditions: i. Zn, DMF, acetyl chloride, CH_2Br_2, 82%.

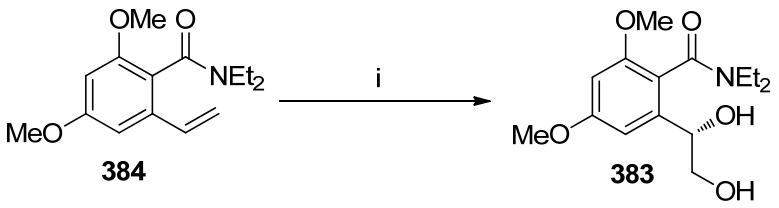
Scheme 121: Carbonyl methylenation for the formation of 3,5-dimethoxystyrene **384**.

With styrene **384** in hand, introduction of the stereocentre at C-1′ was carried out using a Sharpless asymmetric dihydroxylation. Using the Sharpless mnemonic it was determined that AD-mix α or $(DHQ)_2PHAL$ would be required in order to achieve the desired (*S*) stereochemistry (Scheme 122).



Scheme 122. Determination of Sharpless catalyst needed to achieve desired stereochemistry.

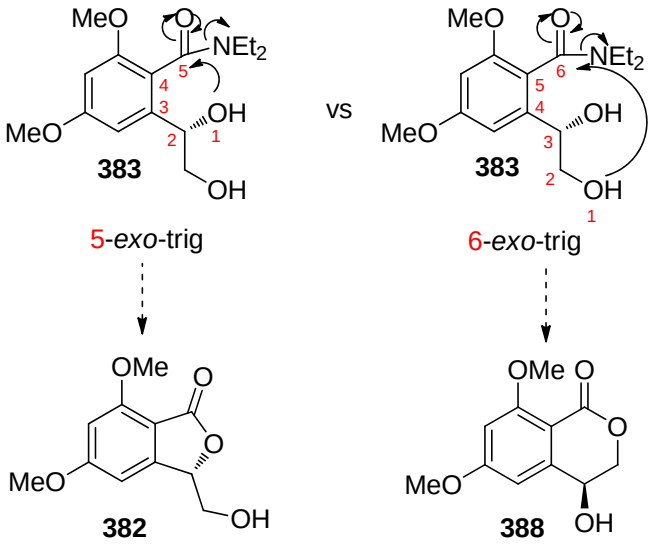
The Sharpless dihydroxylation was affected to afford **383** in a pleasing 84% yield with an e.e. of 85% (Scheme 123).



Reagents and conditions: i. K_3FeCN_6, K_2CO_3, $(DHQ)_2PHAL$, OsO_4, methanesulfonamide, *t*-BuOH:H_2O (1:1), 84%, 85% e.e.

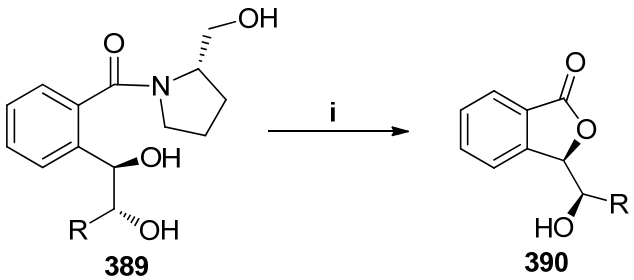
Scheme 123. Synthesis of diol **383**.

The next step in our synthesis was the lactonisation of diol **383**. It was envisaged that diol **383** would undergo selective lactonisation of the secondary alcohol without the need to protect the primary alcohol. However, following the Baldwin's rules,[174, 175] 5-*exo*-trig and 6-*exo*-trig cyclisations are both favorable pathways (Scheme 124).



Scheme 124. Possible lactonisation pathways for diol **383**.

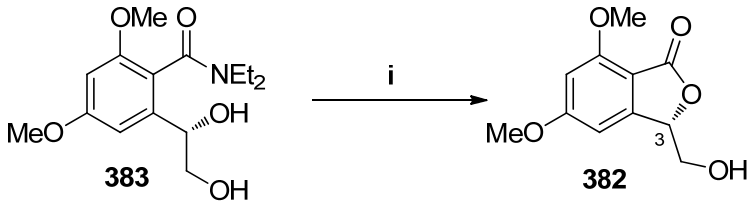
Annunziata *et al*.[176] have reported the successful synthesis of various phthalides **390** yielding exclusively the five membered lactones on a similar substrate **389** (Scheme 125).



Reagents and conditions: i. *p*-TSA, THF, r.t., 15 h, 77-93%, 75-84% e.e.

Scheme 125. Successful five membered lactonisations by Annunziata *et al*.[176]

Encouraged by the literature, diol **383** was treated with potassium hydroxide in a mixture of methanol, water and tetrahydrofuran. After stirring at room temperature for 24 h, the desired 5 membered phthalide-alcohol **382** was obtained in 64% yield (Scheme 126).



Reagents and conditions: i. KOH, MeOH, H_2O, THF, r.t., 24 h, 64%.

Scheme 126. Lactonisation of diol **383**.

The ^{1}H NMR spectrum of the product indicated the successful formation of phthalide-alcohol **382** with the characteristic 3-H proton resonating as a triplet at δ_H 5.35 ppm. The ^{1}H NMR spectra was compared to a similar phthalide-alcohol **391** (Figure 28)[177, 178] and it was indeed confirmed as the 5 membered, not the 6 membered lactone.

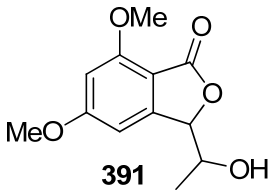
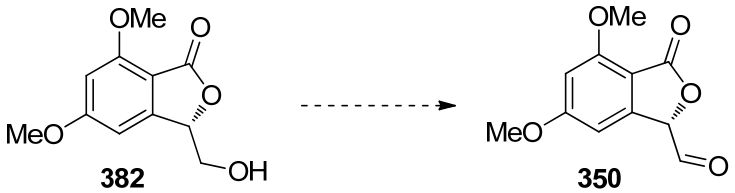


Figure 28. Phthalide alcohol **391**.

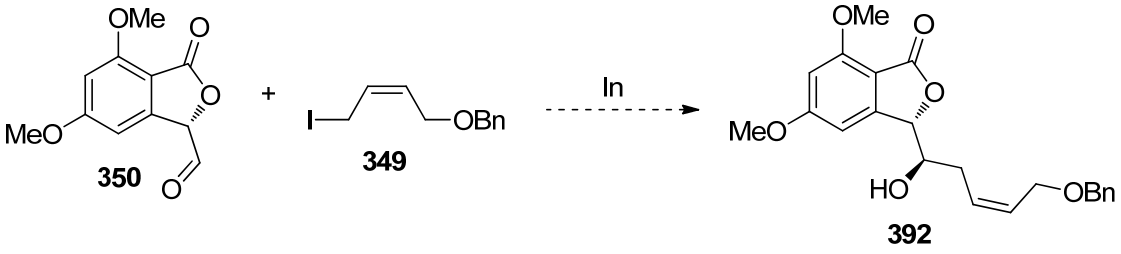
The next step required the oxidation of the primary alcohol to the desired aldehyde. The various conditions attempted to effect this transformation are summarised in Table 13.



Entry	Reagents and Conditions	Results
1	TPAP, NMO, 4Å MS, CH_2Cl_2, r.t., 2 h.	No reaction
2	PCC, Celite®, CH_2Cl_2, r.t., 2 h.	No reaction
3	Dess-Martin periodinane, CH_2Cl_2, r.t., 1h.	Unstable product formed
4	IBX, DMSO, 40° C, 2 h	No reaction

Table 13: Attempted oxidation of phthalide-alcohol **382**.

Several oxidation methods (Entries 1, 2 and 4) all afforded recovered starting material, while Dess-Martin periodinane (Entry 3) gave a new spot by TLC analysis, however it was not stable enough to be isolated for characterisation. Rather than screen many different oxidation methods, it was decided to investigate the next step in the synthesis, namely the indium mediated Barbier-type reaction (Scheme 127).

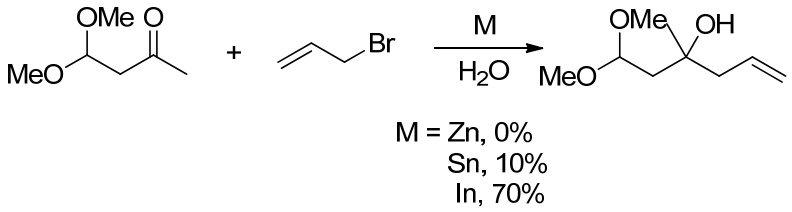


Scheme 127. Proposed indium mediated Barbier-type reaction.

5.1.5.1 Barbier-type Reactions- Indium Mediated Additions to Aldehydes and Ketones

The term 'Barbier-type reaction' is used whenever the organometallic species used for nucleophilic addition to a carbonyl compound is generated *in situ*. Indium was found to be an ideal metal for promoting Barbier-type reactions.[179, 180] This is because when using indium, there is no need for acidic catalysis, heat or sonication which is necessory for activation when

using other metals such as tin or zinc (Scheme 128).[181] It was hence possible to react very acid sensitive compounds with organoindiums.[182]



Scheme 128. Allyl addition to ketones mediated by various metals[181]

Other appealing properties of indium are its relatively low reduction potential compared to other elements (Table 14).[183] If aqueous organometallic reactions proceed by a single electron transfer (SET) mechanism as previously proposed,[184] indium may well be a very effective metal for organometallic reactions. Furthermore, indium does not readily form oxides when exposed to air. Indium is also non toxic and is even found in dental alloys.[180]

Redox Equation	**ε_0 (V)**
$Mg \rightleftharpoons Mg^{2+} + 2\ e^-$	-2.356
$Al \rightleftharpoons Al^{3+} + 3\ e^-$	-1.676
$Zn \rightleftharpoons Zn^{2+} + 2\ e^-$	-0.763
$Sn \rightleftharpoons Sn^{4+} + 4\ e^-$	-0.136
$In \rightleftharpoons In^{3+} + 3\ e^-$	**-0.338[B]**

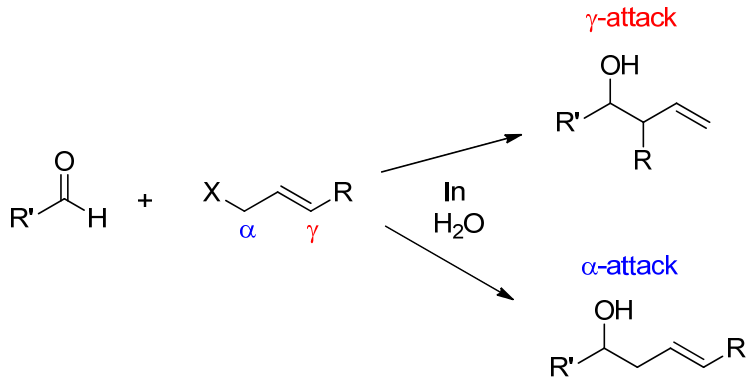
[A] As measured against the standard hydrogen electrode at 25 °C

[B] Determined in dilute solution of indium chloride

Table 14. Reduction potential of common metals[A]

5.1.5.2 Regioselectivity in Indium-Mediated Reactions

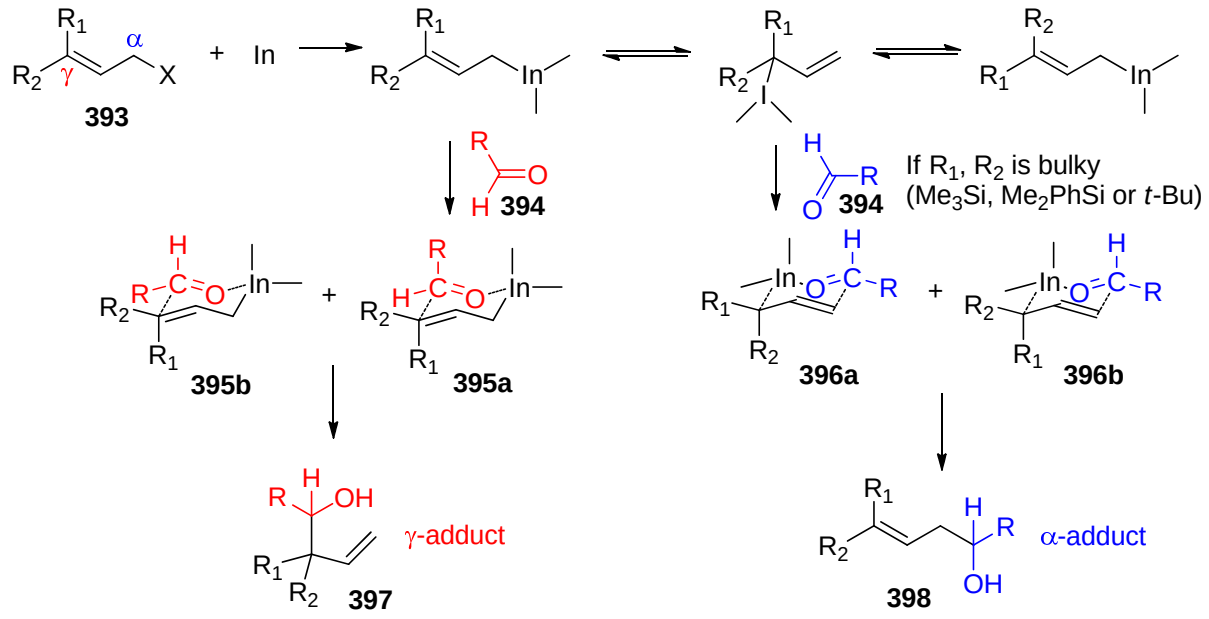
The addition of allyl halides in indium-mediated reactions can take two different pathways. Attack at the α-position bearing the halogen can take place while γ-attack can also proceed via reaction to the double bond. (Scheme 129).



Scheme 129. Regioselectivity in indium mediated Barbier-type reactions with α- and γ-substituted allyl halides.[185]

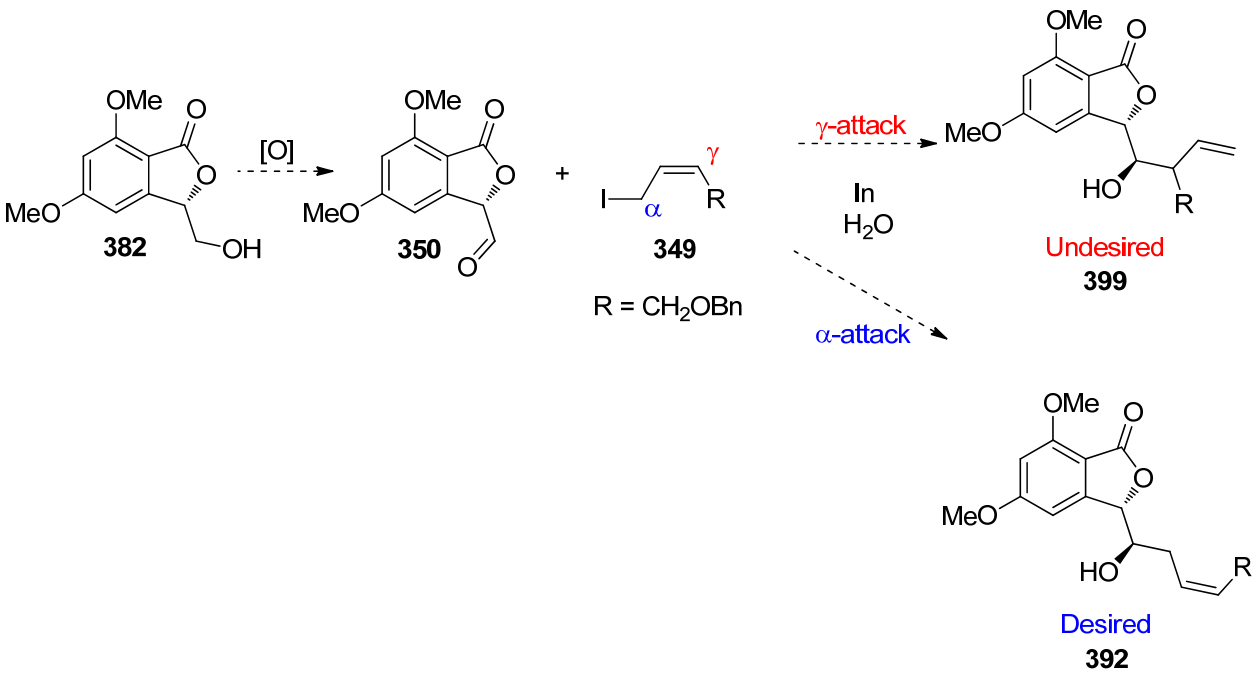
In a detailed investigation by Isaac *et al.*,[185] γ-attack was exclusively observed in most cases except when substrates with very bulky substituents such as Me_3Si, Me_2PhSi or *t*-Bu in the γ-position (Scheme 130).

In a coupling reaction between aldehydes **394** and allyl halides **393**, the reaction proceeds through several possible cyclic transition states. In cases where the γ-substituent is bulky, the cyclic transition states **396a** and **396b** are the preferred pathway giving rise to a mixture of α-adducts **398**. In other cases, the cyclic transition states **395a** and **395b** are favoured giving rise to mainly γ-adducts **397**.



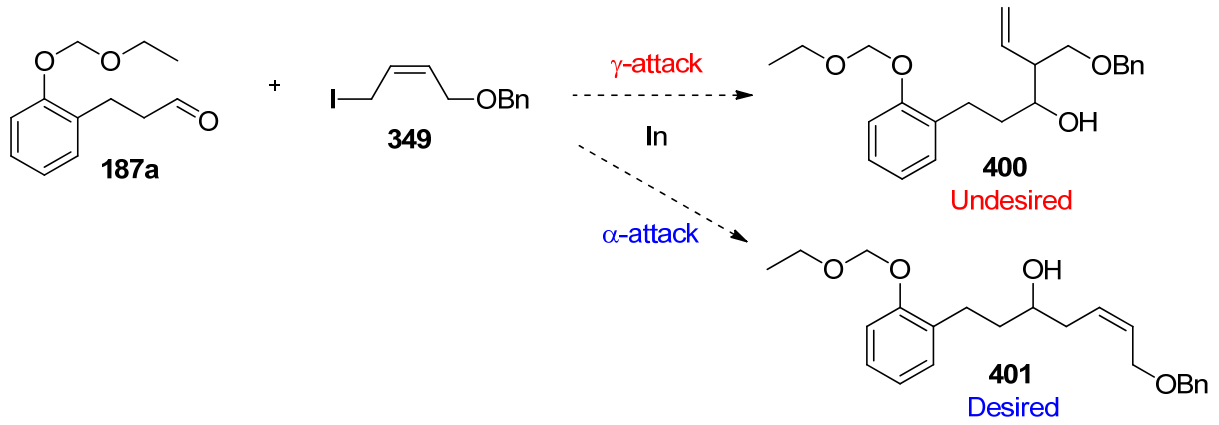
Scheme 130. Possible reaction pathways for the indium mediated Barbier-type reactions.

Applying this mechanism to allyl halide substrate **349** which has a CH_2OBn group at the γ-position, it was unclear whether the reaction would take place via the desired α- or the undesired γ-attack. (Scheme 131)



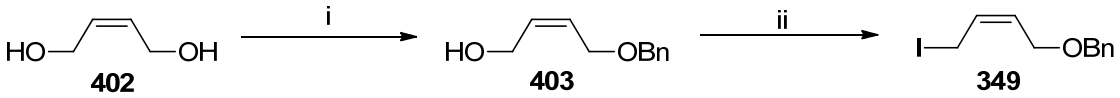
Scheme 131. Possible pathways for Barbier-type reaction between phthalide **350** and iodide **349**.

In order to test the regioselectivity of this reaction, a simple model study was carried out (Scheme 132).



Scheme 132. Proposed model study between aldehyde **187a** and iodide **349**.

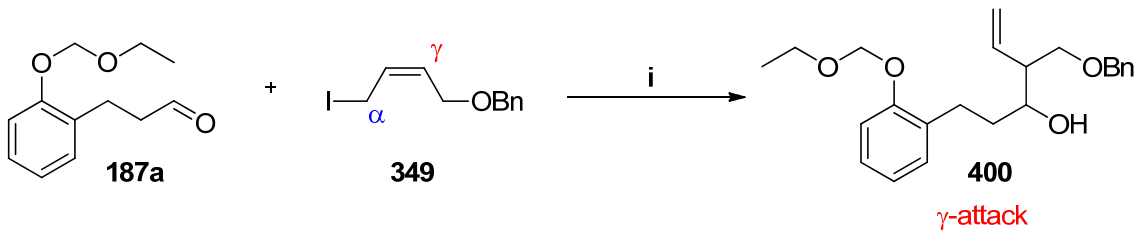
The allyl iodide fragment **349** was synthesised from *cis*-butene-1,4-diol **402** which underwent mono-benzylation followed by Appel reaction[186] to give the desired iodide fragment **349**. (Scheme 133)



Reagents and conditions: i. NaH, BnBr, THF, r.t. to 75 °C, 2 h, 79%; ii. PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C, 30 min, 65%.

Scheme 133. Synthesis of the iodide fragment **349**.

The iodide fragment was then subjected to indium-mediated Barbier-type reaction with a simple aromatic aldehyde **187a** (Scheme 134).[187] Disappointingly, the iodide fragment underwent exclusive γ-attack to give the undesired product **400** in 55% yield. It was postulated that the steric bulk of the CH_2OBn group on the alkyl halide **349** was not bulky enough to induce α-attack hence γ-adduct was produced as the sole product.

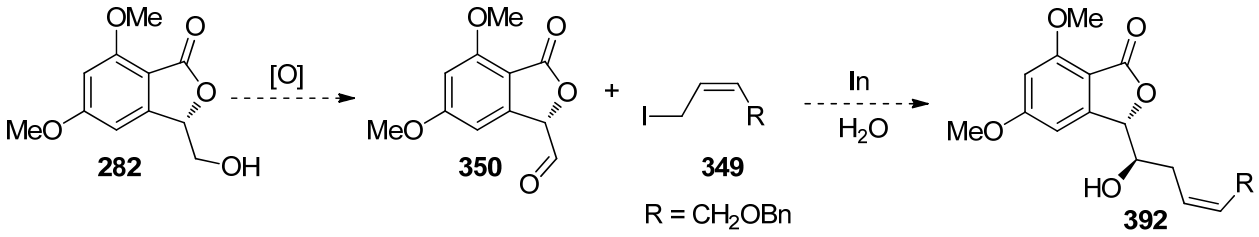


Reagents and conditions: i. In, r.t., 24 h, 55%

Scheme 134. Indium mediated Barbier-type reaction on aldehyde **187a**.

These results led to the conclusion that, the Barbier-type reaction of phthalide-aldehyde **350** with iodide fragment **349** would also undergo exclusively γ-attack thereby rendering the phthalide-aldehyde **350** intermediate inappropriate for the synthetic approach adopted (Scheme 135).

Rather than investigating more oxidation conditions to convert alcohol **282** to phthalide-aldehyde **350**, a new synthetic strategy was proposed.

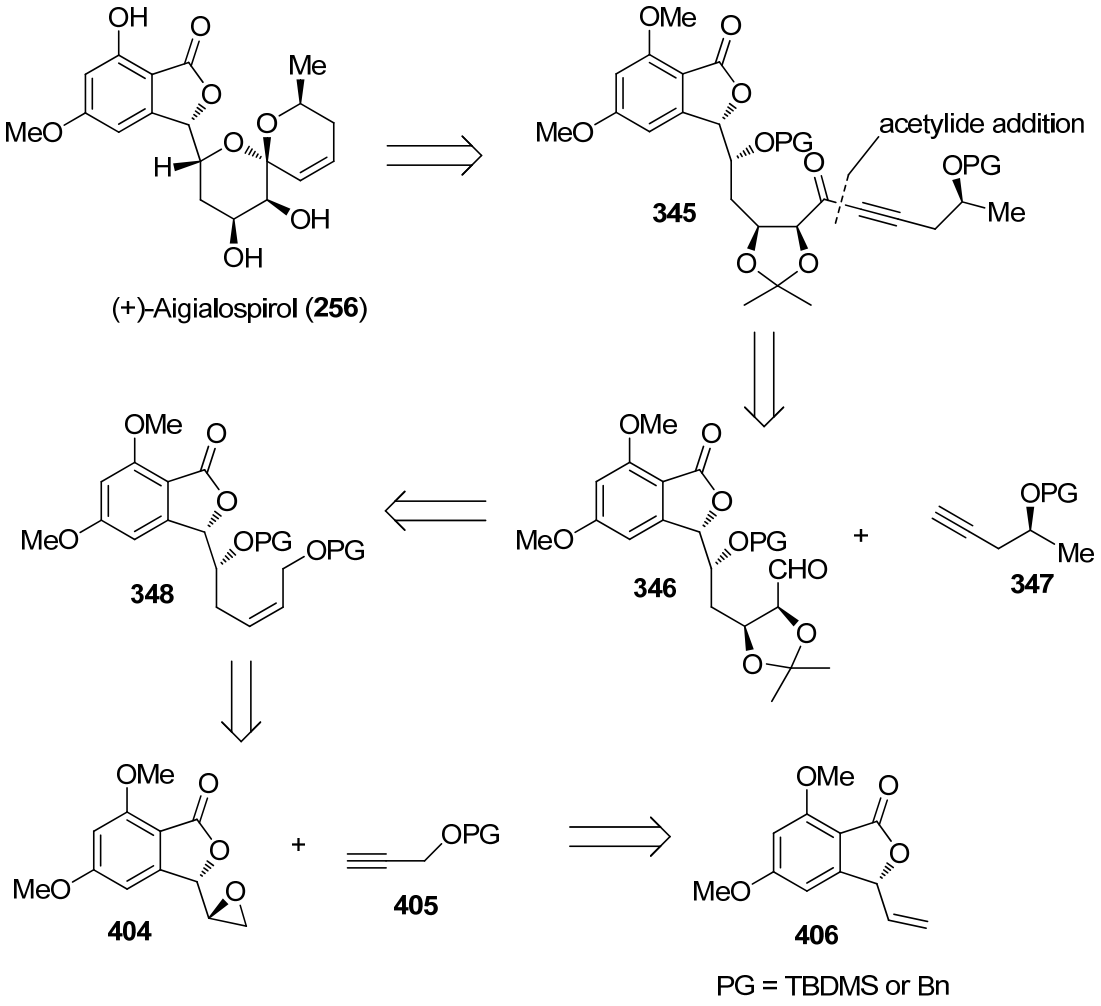


Scheme 135. Proposed synthesis of intermediate **392**.

5.1.6 Revised Synthesis: Synthesis of Vinylphthalide 406

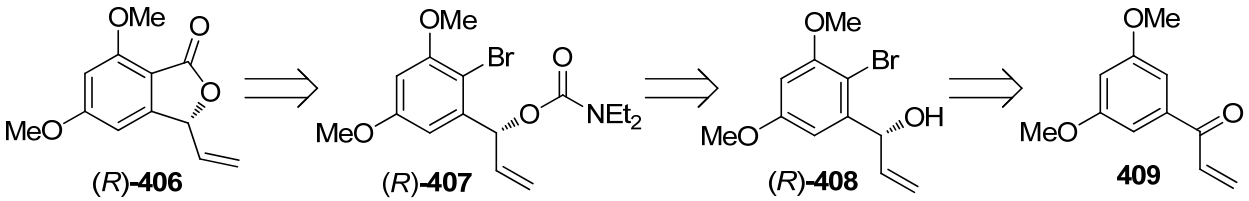
The original synthetic target, phthalide-aldehyde **350** proved to be an inadequate intermediate for the synthesis of (+)-aigialospirol (**256**) hence a new phthalide target was revised. It was envisaged that the vinyl group in phthalide **406** could be converted a chiral epoxide **404** which in turn would undergo an acetylide anion addition of the protected propargyl alcohol **405**.

Lindlar reduction would then give the desired *cis*-alkene **348** and subsequent Sharpless asymmetric dihydroxylation and protection would afford aldehyde **346** (Scheme 136).



Scheme 136. Proposed synthesis of spiroketal moiety to give aigialospirol (**256**).

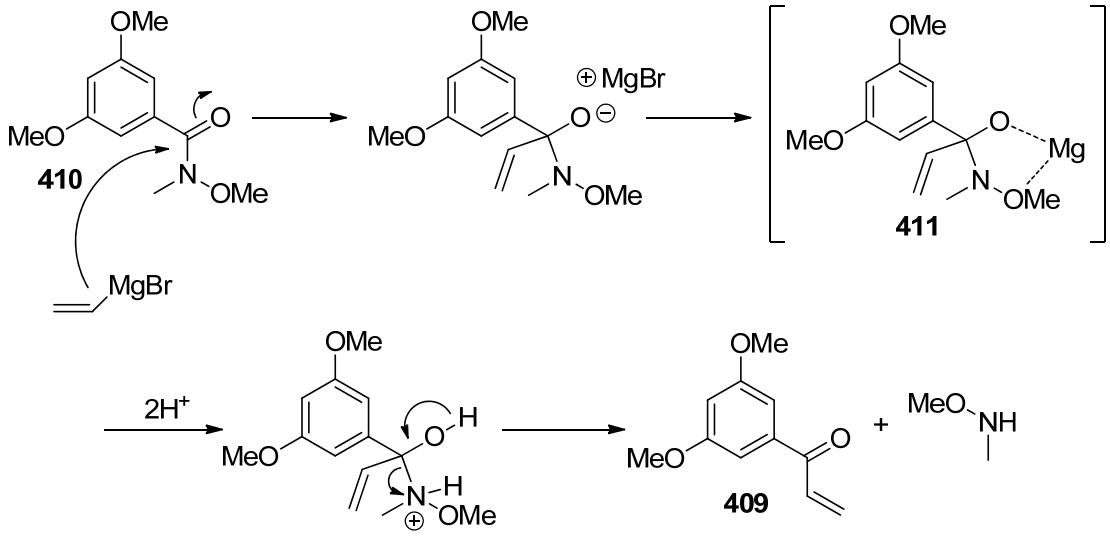
For the synthesis of the key phthalide epoxide **404** it was necessary to prepare vinylphthalide **406**. It was envisaged that this could be accomplished via the synthesis of carbamate **407** which in turn could be prepared from 3,5-dimethoxyketone **409** (Scheme 137).



Scheme 137. Retrosynthesis of vinylphthalide **406**.

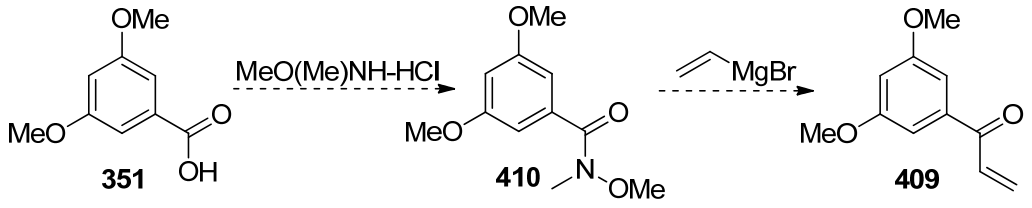
5.1.6.1 Synthesis of 3,5-Dimethoxyketone 409

Since their discovery by Weinreb in 1981,[188] the use of the so-called Weinreb amides for the synthesis of ketones is commonplace. Before the discovery that *N*-methoxy-*N*-methylamides (Weinreb amides) underwent reaction with Grignard or organolithium reagents to exclusively form ketones, ketone synthesis from carboxylic acids and their derivatives was problematic. The biggest problem faced was double addition of the organometallic component to give a tertiary alcohol.[188] Weinreb found that the *N*-methoxy-*N*-methylamides formed a stable, metal-chelated tetrahedral intermediate **411** upon reaction with Grignard or organolithium reagents, which only collapses upon introduction of acid (Scheme 138).[188] This chelation effect effectively prevents further addition of the organometallic reagent even when used in large excess.[188]



Scheme 138. Mechanism of Grignard addition to give α,β-unsaturated ketone **409**.

It was envisaged that the α,β-unsaturated ketone **409** could be synthesised from the Weinreb ketone **410** which was available from the cheap 3,5-dimethoxybenzoic acid **351** and vinyl magnesium bromide (Scheme 139).

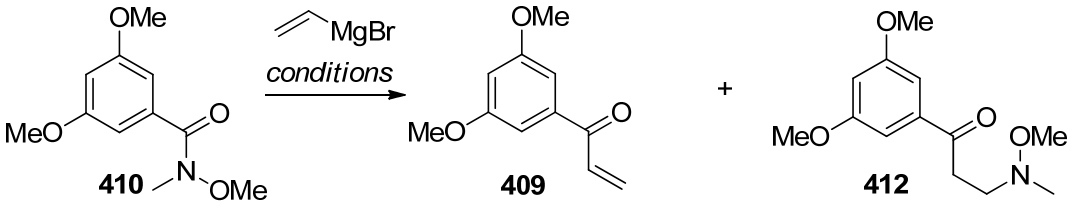


Scheme 139. Proposed synthesis of starting material **409**.

The synthesis of Weinreb amides from carboxylic acids has been well documented in the literature. Conversion of the carboxylic acid to a more reactive acid derivative, such as acid halides, allows rapid and easy conversion to the Weinreb amide.[189] However, some functional groups can be incompatible with this method, therefore alternative methods utilising lactones and esters have been developed.[190] An appealing alternative is the direct conversion of an acid to an amide using a variety of peptide coupling reagents,[191, 192] allowing the formation of a reactive intermediate followed by amide formation in one-pot, eliminating the necessity to isolate intermediates.

Harrington *et al*.[193] report the synthesis of **410** from **351** *via* the crude acid chloride in 96% yield. However, removal of the excess oxalyl chloride *via* distillation followed by a second distillation of the amide was required.[193] A one-pot method with a single isolation step was therefore more preferable. Many of the peptide coupling reagents such as DCC, BOP and chloroformates are expensive and removal of excess reagent and byproducts can be difficult.[194] De Luca and coworkers[194] reported a simple, high yielding synthesis utilising the readily available coupling reagent 2-chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT). Workup involving washing with water, aq. Na_2CO_3, 1 M HCl and brine was all that was required to give the pure Weinreb amide **410**, 72% yield.[194] The coupling reagent, CDMT, was readily synthesised from cyanuric chloride and methanol in the presence of 3 equivalents of sodium bicarbonate.[195]

With amide **410** in hand, reaction with the organometallic agent, vinylmagnesium bromide could be investigated. The initial reaction was carried out in diethyl ether resulting in unsatisfactory yields after reaction for 1 h at 0 ^{o}C. Changing the solvent to tetrahydrofuran gave a cleaner reaction, while increasing the reaction time to 3 h improved the yield 3-fold. However, even longer reaction times or increasing reaction temperature to room temperature was detrimental to the yield. Extensive investigation of the reaction time at 0 ^{o}C indicated that at this temperature, 1.5 h was the optimal reaction time (Table 15).



Entry	Solvent	Time (h)	Temperature (°C)	Yield 409 (%)	Amine 412 Yield (%)
1	Et_2O	1	0	23	nd
2	THF	3	0	60	nd
3	THF	3.5	r.t.	43	nd
4	THF	5	0	21	nd
5	THF	5	r.t.	10	nd
6	THF	3	0	13	nd
7	THF	3.5	0	18	nd
8	THF	o/n	r.t.	3	nd
9	THF	10 min	0	51	nd
10	THF	0.5	0	57	nd
11	THF	1.5	0	66	nd
12	THF	2.5	0	43	nd
13	THF	1.5	-20	57	32

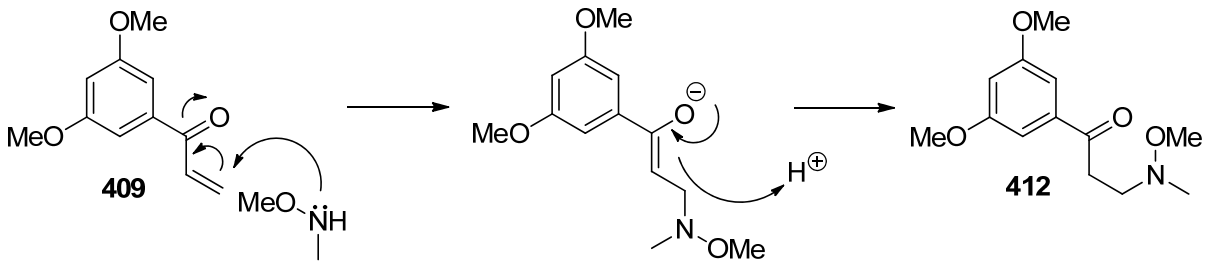
14	THF	3	-20	68	20
15	THF	15	-78	23	-
16	**THF**	**15**	**-50**	**74**	**-**

nd= yield not determined

Table 15. Conditions attempted for Grignard addition of **41**.

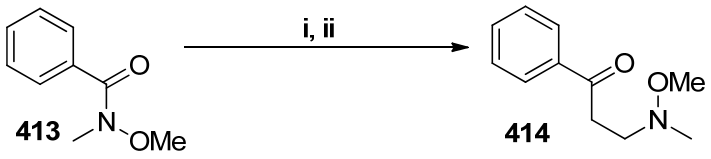
Entries 1-5 were carried out using a commercial solution of vinylmagnesium bromide (1 M in THF). These conditions resulted in a messy reaction mixture which was difficult to purify and the maximum yield achieved was only 60%. It was thought that use of freshly synthesised vinylmagnesium bromide may give better results. Vinylmagnesium bromide was therefore synthesised by reacting vinyl bromide with magnesium in tetrahydrofuran. As vinyl bromide is a gas at room temperature this required condensing the reagent into a measuring cylinder and slowly transferring the vinyl bromide into the reaction vessel.

The use of freshly prepared vinylmagnesium bromide (Table 15, Entries 6-16) gave superior results in terms of the cleanliness of the reaction, however an unknown byproduct was formed, which appeared to be adversely affecting the yield of the desired product **409**. Flushing the column after collection of the fractions containing the desired product and NMR analysis of the resulting brown oil indicated that the undesired side product resulted from Michael addition of the liberated amine to enone **409** to give **412** (Scheme 140).



Scheme 140. Side reaction to give **412**.

The use of Weinreb amides for the synthesis of ketones is reported to prevent side-reactions by forming a stable metal chelate which is only broken down upon work-up. However, it appears that at higher temperatures this metal chelate is broken prematurely liberating a free amine which can then attack the α,β-unsaturated ketone **409**, in a Michael addition to give **412** (Table 15, Entries 13 and 14). Similar results were observed by Gomtsyan *et al*.[196] where various *β*-aminoketones were synthesised from amides by sequential nucleophilic substitution at the carbonyl group by vinylmagnesium bromide followed by Michael reaction after quenching the first reaction by water. (Scheme 141)



Reagents and conditions: i. vinylmagnesium bromide, THF, r.t.; ii. H_2O, 77%.

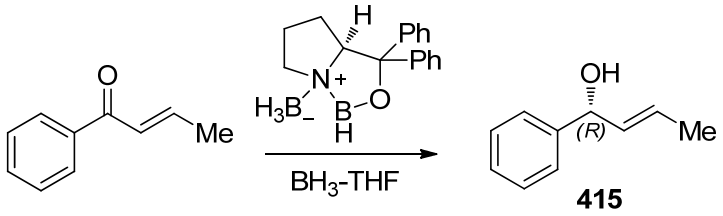
Scheme 141. Formation of *β*-aminoketone **414** from amide **413** by Gomtsyan[196]

Lowering the temperature to -78 ^{o}C suppressed the reaction of the Grignard reagent giving only a poor 23% yield of **409** after 15 h (Table 15, Entry 15). It was found that by strictly maintaining the temperature at -50 ^{o}C, a 74% yield of the desired product **409** could be achieved after 15 h with negligible amine production (Table 15, Entry 16).

5.1.6.2 Asymmetric Ketone Reduction

With α,β-unsaturated ketone **409** in hand, asymmetric reduction of the ketone was next attempted. There have been many developments in the asymmetric reduction of ketones in the past few decades.[197, 198] The CBS catalyst and BINAL-H catalysts being among those most commonly reported in the literature. BINAL-H has shown good selectivity for the reduction of ketones with one substituent containing unsaturation.[199] Extensive mechanistic studies have suggested that the stereoselectivity comes from a 6-membered transition state with the

unsataturated group sitting equatorial in order to avoid unfavourable interactions with the 'O' lone pair, whereas the CBS reagent shows selectivity based on the bulk of the substituents.[199] According to these studies, the α,β-unsaturated ketone **409**, containing unsaturation in both of its substituents with similar bulk. Therefore, it was unsure as to whether the reduction could be carried out with suitable selectivity for the desired enantiomer. An extensive literature search indicated that asymmetric reduction of ketones with similar substitution patterns had only be carried out once using the CBS reagent to give the alcohol **415** with a 71% e.e. as determined by HPLC (Scheme 142).[200] No yield was recorded for this reduction and the reduction had been carried out in a mixture of ketones.

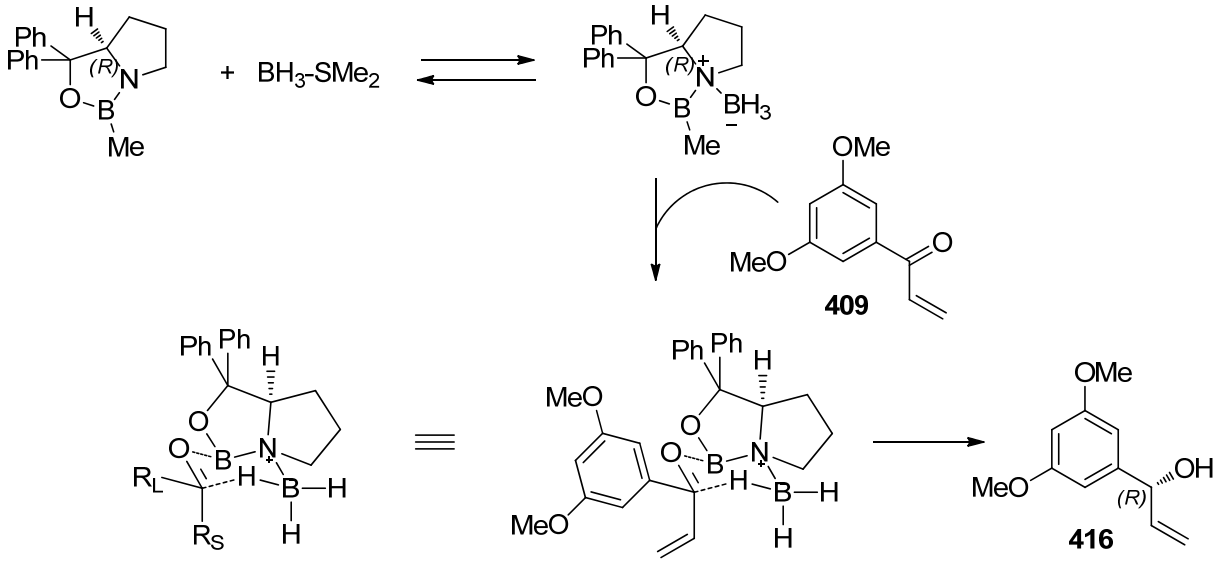


Scheme 142. Asymmetric reduction of ketones with similar substitution pattern to ketone **409**.[200]

A. CBS Reduction

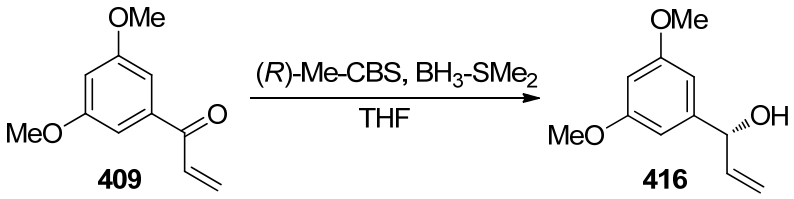
Based on this result, it was hoped that α,β-unsaturated ketone **409** used in the present study could be reduced with similar levels of selectivity. The Me-CBS reagent was used as this is reported to be both easier to handle due to its decreased air sensitivity and to result in higher stereoselectivity. The hydride source used was BH_3-DMS.[167, 201, 202]

Upon analysis of the ketone using the CBS mnemonic it was determined that the (*R*)-Me-CBS catalyst was required to achieve the desired (*R*)-stereochemistry in the desired alcohol **416** (Scheme 143).



Scheme 143. Catalyst determination for desired stereochemistry.

Ketone **409** was added to a stirred solution of (*R*)-Me-CBS and the hydride source at -20 ^{o}C and the reaction was stirred at this temperature for a further 3 hours before quenching with the addition of methanol. The desired alcohol **416** was obtained in 28% yield. Mosher's ester analysis indicated 69% e.e. with an $[\alpha]_D^{20}$ of +3.46 (Table 16, Entry 1). Mosher's ester analysis confirmed the desired stereochemistry was the enantiomer depicted.[203] Although the e.e. was acceptable, the yield was poor. Therefore with the aim of improving the yield of this initial key step in the synthesis of aigialospirol (**256**) the reaction was repeated at room temperature with a reaction time of 2 h. It was hoped that the warmer temperature would promote the reduction reaction without any major adverse effect on the e.e. It is well known that cooler temperatures results in greater selectivity for asymmetric reactions, however the optimum temperature for CBS reduction is reported to be 0-20 ^{o}C.[199] Unfortunately, the warmer temperature gave a lower yield of **416** in only 23% and as expected the e.e was negatively affected as indicated by the $[\alpha]_D^{20}$ of +0.61 (Table 16, Entry 2). Increasing the temperature further proved to adversely effect the reaction with no product being observed (Table 16, Entry 3).



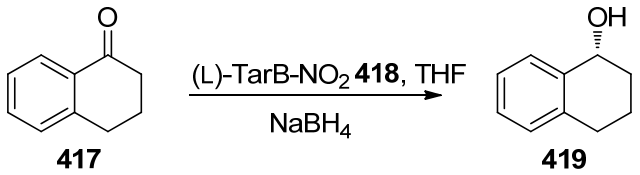
Entry	Time (h)	Temperature (^{o}C)	Yield (%)	e.e. (%)
1	3	-20	28	69
2	2	0	23	<69
3	2	r.t.	0	-

Table 16. Conditions for CBS reduction of ketone **409**.

B. TarB-NO_2 Reduction

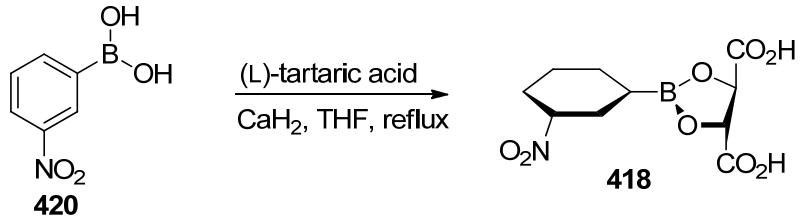
It came to our attention that a relatively recent addition to the asymmetric ketone reduction arsenal was the use of the stoichiometric asymmetric catalyst known as TarB.[204-206] This catalyst is attractive in that, either *R* or *S* selective catalysts can be made from the same boronic acid starting material by altering the stereochemistry of the tartaric acid component of the catalyst from L to D. Extensive studies on the utility of this catalyst found that substitution at C-3 of the boronic acid with NO_2 gave the best results.[206, 207] Although, studies investigating the utility of TarB-NO_2 were only carried out on relatively simple ketones which had significantly different substituents in terms of bulk and electron density, we were interested to see how this catalyst would perform on more challenging substrates.

In order to assess the reaction, a literature reduction was first carried out using α-tetralone **417** and (L)-TarB-NO_2 **418** to give alcohol **419** (Scheme 144).



Scheme 144. Asymmetric reduction of α-tetralone **417** using (L)-TarB-NO_2 **418**.

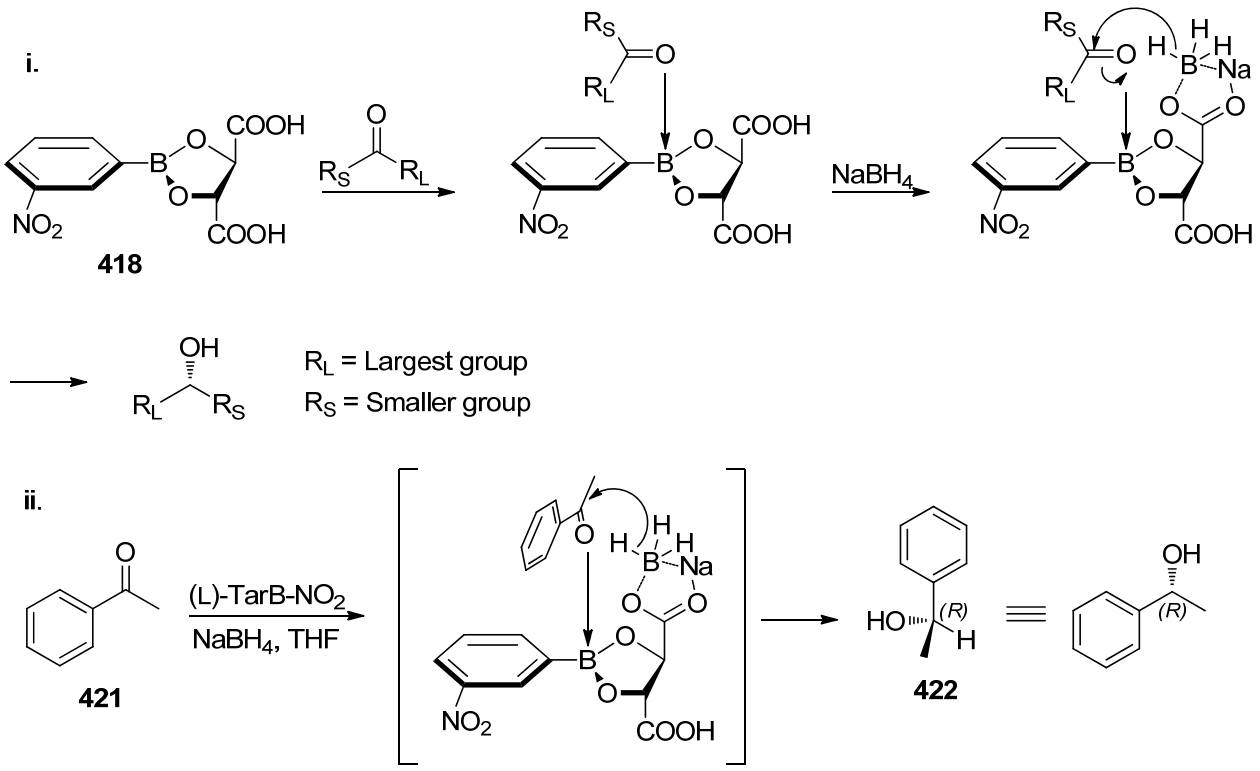
The catalyst, (L)-TarB-NO_2 **418** was easily prepared by heating 3-nitrophenylboronic acid **420** and (L)-tartaric acid under reflux in tetrahydrofuran, in the presence of the drying agent calcium hydride (Scheme 145). The literature preparation reported by Cordes *et. al.*[207] filtered off the calcium hydride after the reflux, however, as (L)-TarB-NO_2 **418** is highly water sensitive, it was found that better yields were achieved when the filtration step was omitted. It has been reported that the catalyst can be stored as a solution in tetrahydrofuran, protected from light for up to a year, and it was found that storing the catalyst for a few days before use did not adversely affect the reaction. The boronic acid **420** can be recovered for future use either using a basic work-up, followed by acidification of the aqueous layer and cooling to recrystallise the acid, or acidification of the aqueous layer followed by extraction with diethyl ether.[206, 207] The recrystallisation method gave variable results and was highly dependent on the volume of water use to effect dissolution. It is therefore thought that extraction of the aqueous layer with diethyl ether would give more reproducible yields and higher quality product.



Scheme 145. Preparation of (L)-TarB-NO_2 **418**.

Both lithium aluminium hydride and sodium borohydride have been used successfully for the asymmetric reduction of ketones.[204, 205] Pleasingly, the reduction of α-tetralone **417** proved reproducible in our hands with a 98% yield of **419** obtained with an e.e. of >96%.[208, 209]

It is known that borohydrides form acyloxyborohydride intermediates in the presence of carboxylic acids.[207] It was therefore proposed that the mechanism for TarB-NO_2 asymmetric reduction proceeds *via* coordination of the carbonyl oxygen to the boron of TarB-NO_2, which is Lewis acidic. Computational studies indicated that the carbonyl carbon was in the lowest energy when it was stacked in the same plane as the carbonyl oxygen with the carbon closest to the carboxylic acid. This holds the carbonyl group in a defined orientation for hydride delivery. Introduction of $NaBH_4$ results in the formation of the acyloxyborohydride intermediate and liberation of H_2. Formation of this intermediate increases the solubility of the borohydride and also brings the hydride into close proximity to the carbonyl carbon allowing efficient delivery of the hydride to a specific face (Scheme 146).[207]



Scheme 146. i. Proposed mechanism for TarB-NO_2 **418** mediated asymmetric ketone reduction; ii. example of asymmetric reduction of acetophenone **421**.[207]

Based on the studies carried out using (L)-TarB-NO_2 **418**, a prediction of the stereochemical outcome of the reduction of **409** can be made based on the bulk of the two substituents.[207] Using formaldehyde as the carbonyl component of the reaction further computational studies were carried out which showed that the two substituents were situated back into the plane one above the other (Figure 29). It was therefore predicted that the larger substituent would be furthest away from the catalyst, thus determining facial selectivty.[207]

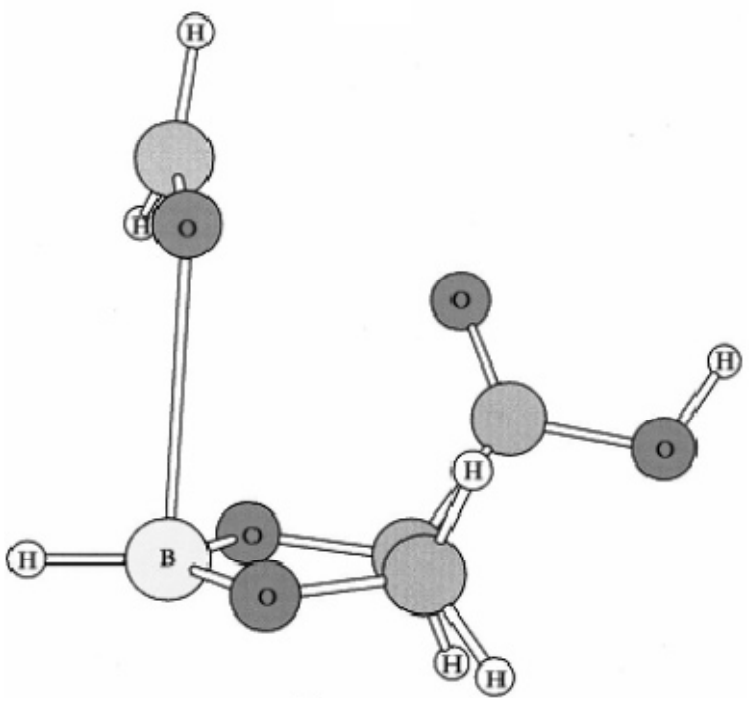
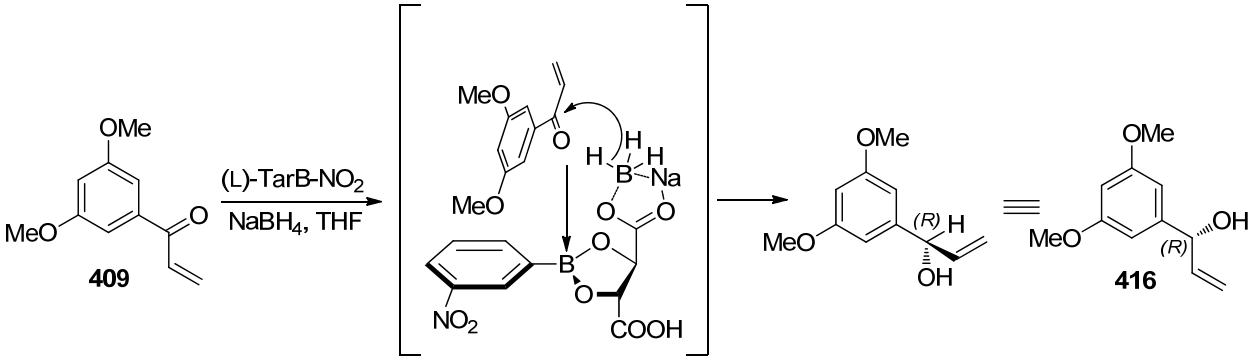


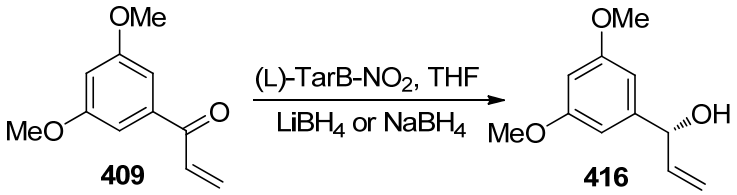
Figure 29. Computer model for formaldehyde coordinated to an acyloxyborohydride.[207]

Based on this model, the catalyst required to give the required *R* stereochemistry was determined to be (L)-TarB-NO_2 **418** (Scheme 147). As this had already been synthesised, the solution used for the reduction of α-tetralone **417** was used for the attempted reduction of ketone **409**.



Scheme 147. Determination of catalyst required to achieve desired stereochemistry.

Unfortunately, reductions carried out using both $LiBH_4$ and $NaBH_4$, while giving improved yields over those achieved using the CBS reagent, only gave a modest e.e. of 53% at best (Table 17, Entry 3). Mosher's ester analysis indicated that the undesired enantiomer was the predominant one, therefore to obtain the desired enantiomer, (D)-TarB-NO_2 would be required. This is readily synthesised from the common starting material, 3-nitrophenylboronic acid, using the unnatural (D)-tartaric acid.



Entry	Hydride source	Time (h)	Yield 416 (%)	$[\alpha]_D$
1	$LiBH_4$	0.5	28	0.6
2	$LiBH_4$	0.5	74	0.7
3	$NaBH_4$	3.5	80	54.6

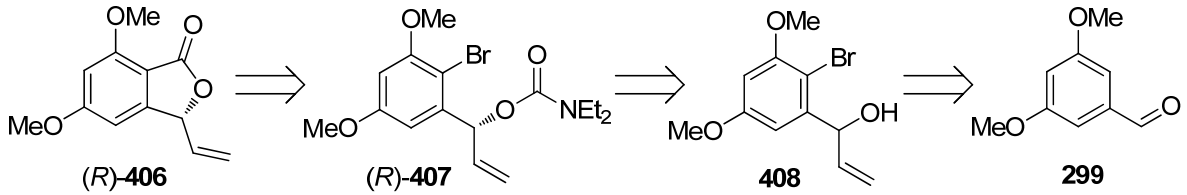
Table 17. Conditions used for (L)-TarB-NO_2 **418** mediated ketone reduction.

It has been demonstrated that the original route to the phthalide moiety **406** was not ideal as the asymmetric reduction either gave poor yields or poor selectivity. The poor selectivity may be a result of relative similarity in bulk of the two R groups (aryl and olefin) shielding the carbonyl group.

In order to try to improve the e.e. an alternative method to install the chiral centre was proposed based on previous work carried out in our research group.

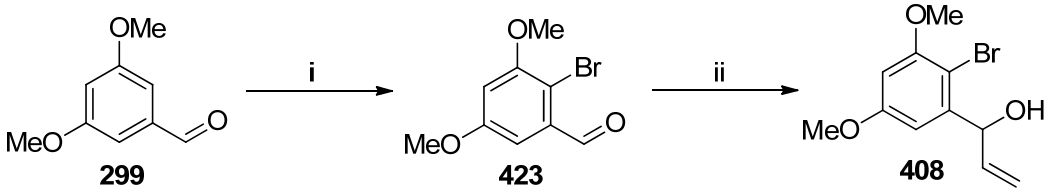
5.1.7 Alternative Approach to Vinylphthalide 406

With the chiral reduction of ketone **409** giving disappointing e.e.'s and yields, a revised pathway was envisaged to install the chirality at the C-3 position. It was envisaged the alcohol (*R*)-**407** could be synthesised *via* enzymatic resolution of racemic alcohol **408** which in turn could be synthesised from 3,5-dimethoxybenzaldehyde **299**. (Scheme 147)



Scheme 147. Revised retrosynthesis of vinylphthalide **406**.

3,5-Dimethoxybenzaldehyde **299** was prepared as before (Scheme 100) which underwent α-bromination to **423** in 74% yield. (Scheme 148)



Reagents and conditions: i. Br_2, AcOH, 5 min, 74%; ii. vinylmagnesium bromide, THF, -78 °C, 12 h, 85%.

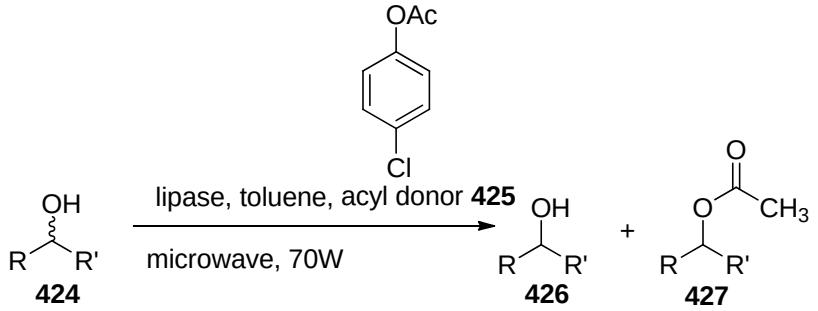
Scheme 148. Formation of racemic alcohol **408**.

The next step requires Grignard reaction with vinylmagnesium bromide (Scheme 148). After various optimisations, the best yield was obtained using excess vinylmagnesium bromide (3.5 equiv.) at -78 °C in tetrahydrofuran for 12 h. As a rough guide, it was also important to have volume of tetrahydrofuran roughly the same volume as the volume of vinylmagnesium bromide being added.

5.1.7.1 Enzymatic Resolution

Biocatalysts are an attractive alternative to conventional methods for effecting asymmetric organic transformations, offering unique characteristics when compared to chemical (homogeneous and heterogeneous) catalysts. Very high enantio-, regio- and chemoselectivities can be achieved using biocatalysts due to the strict recognition of the substrate by the enzyme. Biocatalytic reactions are also generally safe and the reaction conditions are mild. The kinetic resolution of secondary alcohols *via* esterification or hydrolysis has been extensively studied with different lipases, where the enzyme selectively acetylates one alcohol enantiomer faster than the other allowing separation of the two alcohol enantiomers present in a racemic mixture. The alcohol enantiomer that is acetylated faster can be predicted by Kazlauskas' Rule.[210]

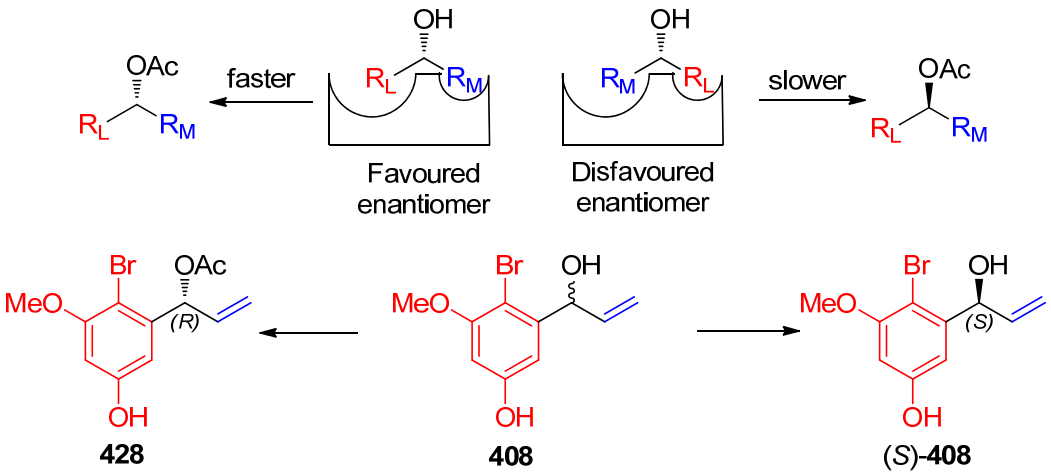
Brimble *et al*.[211] have successfully used kinetic resolution to resolve secondary alcohols with different functional groups with high enantiomeric excess. (Scheme 149)



Scheme 149. Lipase-catalysed kinetic resolution of racemic secondary alcohols by Brimble *et al*.[211]

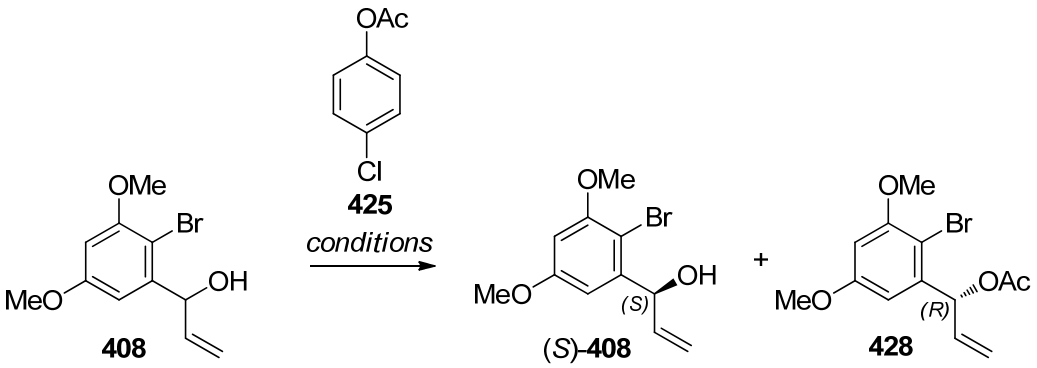
Novozyme 435® (*Candida antarctica* lipase) and *p*-chlorophenyl acetate **425** (used as an acyl donor) were added to racemic alcohol **424** in toluene and the mixture was subjected to microwave irradiation at 60 °C at 70 W to afford the resultant alcohol **426** in 90~ >99 e.e.'s.

With racemic alcohol **408** in hand, Kazlauskas' rule[210, 212] was applied establishing that the (*R*)-alcohol would undergo acetylation faster than the (*S*)-alcohol (Scheme 150).



Scheme 150. Kazlauskas' rule for resolution of secondary alcohols.[210, 212]

Having established that (*R*)-alcohol would react faster than the (*S*)-alcohol, we set out to find the optimum conditions required for the enzymatic resolution (Table 18).



Entry	Heating	Temp (°C)	Time (h)	(*S*)-408: yield, e.e.	(*R*)-428: yield, e.e.
1	Conventional	55	24	62%, 50% e.e.	24%, 91% e.e.
2	Microwave – open vessel	55	24	54%, 59% e.e.	34%, 93% e.e.
3	Microwave – closed vessel	55	24	46%, 74% e.e.	36%, 99% e.e.
4	**Microwave – closed vessel**	**55**	**48**	**50%, 84% e.e.**	**45%, 99% e.e.**
5	Microwave – closed vessel	55	60	40%, 66% e.e.	42, 99% e.e.

Conditions: Novozyme 435®, *p*-chlorophenyl acetate **425**, toluene

* All microwave reactions were conducted at 300 W

* Enantiomeric excess calculated by HPLC [Chiralcel OD-H, hexanes : *i*-PrOH (93:7)]

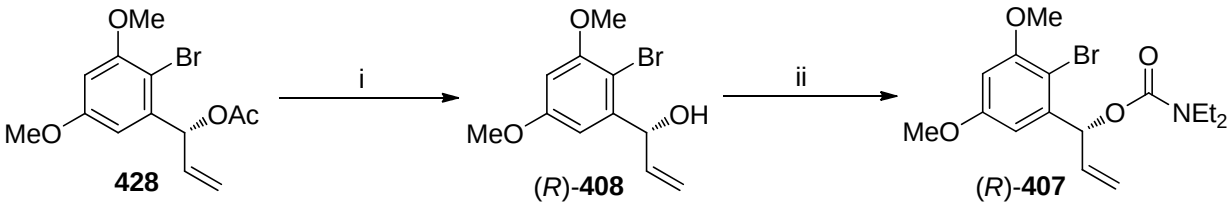
Table 18. Chemoenzymatic resolution of (±)-**408**.

Previous experience in our laboratory has established that the optimum conditions for this microwave assisted chemoenzymatic resolution used toluene as the solvent with *para*-chlorophenyl acetate **425** as the acyl donor.[211] Preliminary screening of the conversion of (±)-**408** to (*S*)-**408** and (*R*)-**428** using several solvents and acyl donors confirmed these conditions as the most promising and further optimisation of these baseline conditions is shown in Table 1.

Entries 1, 2 and 3 use different methods of heating for the enzymatic resolution. Brimble *et al*.[211] have previously established that use of closed vessel microwave heating was crucial to obtain high enantiomeric excess during the resolution process. Indeed, the enantiomeric excess obtained for (*S*)-**408** were the highest when heating was carried out using microwave irradiation in a closed vessel (Entry 3) compared to conventional heating (Entry 1) and the use

of microwave in an open vessel (Entry 2). The reaction times used were crucial in obtaining optimum yields of (*S*)-**408** and (*R*)-**428**. Gratifyingly, conducting the resolution for 48 hours led to a quantitative yield of (*S*)-**408** in 84% e.e. and 45% of (*R*)-**428** in 99% e.e. (Entry 4). The resolution showed no appreciable drop in yield or enantioselectivity upon scale up and was routinely conducted on a two gram scale.

With the desired (*R*) acetate **428** obtained in high e.e., it was subjected to hydrolysis using potassium carbonate in methanol at room temperature for 30 min to give (*R*) alcohol **408** in 87% yield and in 99% e.e. (Scheme 151). (*R*)-**408** was then converted to carbamate **407** using *N*,*N*'-carbonyldiimidazole (CDI) in dichloromethane with diethylamine in 90% yield (Scheme 151).

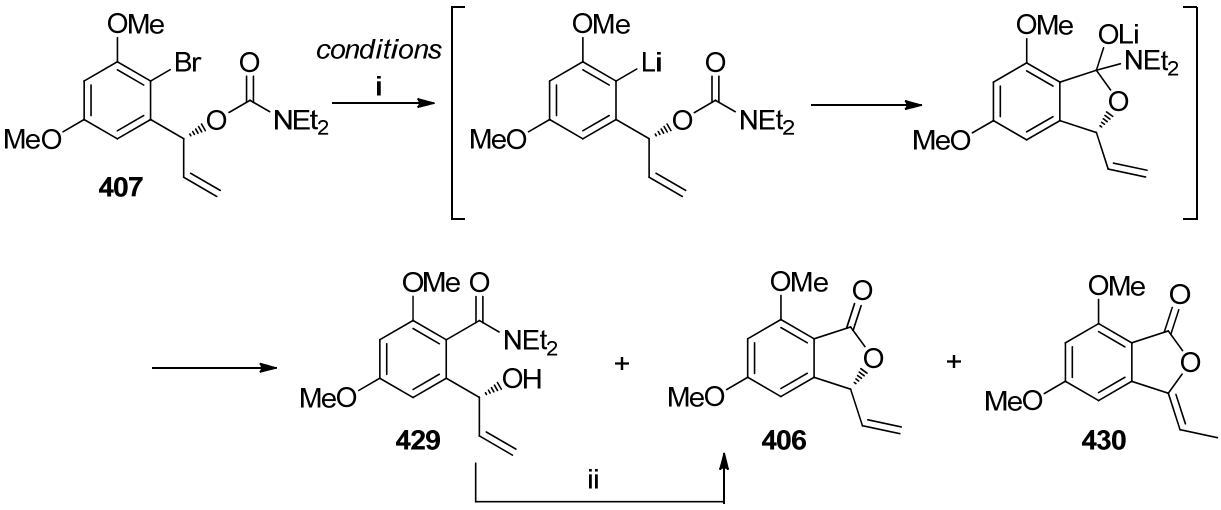


Reagents and conditions: i. KOH, MeOH, r.t., 87%; ii. CDI, $HNEt_2$, CH_2Cl_2, r.t., 90%.

Scheme 151. Formation of carbamate **407**.

5.1.7.2 Intramolecular Acylation on Carbamate 407

With carbamate **407** in hand, intramolecular acylation was next attempted (Scheme 152).



Scheme 152. Intramolecular acylation of carbamate **407**.

Entry	Base	Temp °C	Conditions		Yield (%)		
			i	ii	429	406	430
1	*t*-BuLi (2.2 eq)	-78 °C	Add base, stir for 45 min	add methanol, *p*-TsOH and stir for 12 h, r.t	7	3	2
2	*t*-BuLi (2.2 eq)	-78 °C	Add base, stir for 45 min	Aqueous work up, add anhydrous HCl (1 M) in dioxane and stir for 12 h, r.t	-	67	6
3	*n*-BuLi (2.2 eq)	-78 °C	Add base, stir for 45 min	Aqueous work up, add anhydrous HCl (1 M) in dioxane and stir for 12 h, r.t	-	74	-
4	*n*-BuLi	-78 °C	Add base,	Aqueous work up, add anhydrous HCl (1 M) in	-	71	-

(2.5 eq)	stir for 45 min	dioxane and stir for 12 h, r.t	

Table 19. Intramolecular acylation conditions.

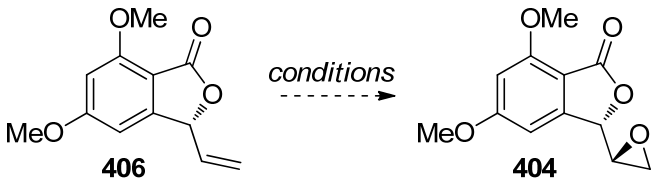
tert-Butyllithium was the initial base of choice as it had previously been used successfully by our research group (Table 19, Entries 1 and 2).[165, 166] *tert*-Butyllithium was added at -78 °C to carbamate **407** in tetrahydrofuran and halogen-metal exchange was evident by the distinct colour change from colourless to yellow. After stirring the reaction for 45 min, the reaction was allowed to warm to room temperature before it was quenched with methanol and a catalytic amount of *p*-toluenesulfonic acid was added. The desired phthalide **406** was obtained in 43% yield along with diethylamide intermediate **429** in 27% yield and the byproduct **430** in 12% yield. The byproduct **430** was established to be the isomer of the desired phthalide **406**. The strong basic conditions used for the intramolecular acylation led to isomerisation of the vinylic double bond thus affording byproduct **430**. It was essential to avoid formation of this byproduct **430** as it has lost the chirality at the C-3 position.

Given the fact that the diethylamide intermediate **429** was isolated in 27% yield, it was possible that the *p*-toluenesulfonic acid was not strong enough to effect the acid catalysed intramolecular acylation hence anhydrous HCl (1 M) in dioxane was tried next (Entry 2). Treatment of **407** with HCl (1 M) in dioxane for 12 h gave a better 67% yield of the desired phthalide **406** and none of the diethylamide intermediate **429** was observed. However, the undesired byproduct **430** was still formed.

The problem was overcome by changing the base to *n*-butyllithium which is less basic compared to *tert*-butyllithium (Entry 3). Using *n*-butyllithium, the intramolecular acylation yielded the desired phthalide **406** in a pleasing 74% yield with no byproduct **430** or diethylamide intermediate **429** being observed. Increasing the *n*-butyllithium stoichiometry to 2.5 eq. did not increase the overall yield of the vinylphthalide **406** (Entry 4).

5.1.8 Epoxidation of Vinylphthalide 406

Having successfully synthesised vinylphthalide **406**, epoxidation of vinylphthalide **406** was next investigated (Table 20).



Entry	Reagent	Solvent	Buffer /Additive	Conditions	Comment
1	*m*-CPBA	CH_2Cl_2	$NaHCO_3$	0 °C for 2 h, warm to r.t., stir for 48 h	Epoxide formation 3%
2	*m*-CPBA	CH_2Cl_2	$NaHCO_3$	0 °C for 2 h, warm to r.t., stir for 48 h then reflux for 24 h	Epoxide formation 4%
3	*m*-CPBA	DCE	NaOAc	0 °C for 2 h, warm to r.t., stir for 3 h then reflux for 24 h	3%
4	*m*-CPBA	DCE	NaOAc	0 °C for 2 h, reflux in sealed tube at 140 °C for 6 h	4%
5	DMDO distilled	acetone	$NaHCO_3$	Stir at r.t. for 48 h	No reaction
6	DMDO (*in situ*)	CH_2Cl_2, acetone	$NaHCO_3$	0 °C for 30 min, warm to r.t., stir for 12 h	No reaction
7	$MnSO_4$, H_2O_2	*t*-BuOH	$NaHCO_3$	Stir at r.t. for 48 h	Complex mixture, degradation
8	$MnSO_4$, H_2O_2	DMF	$NaHCO_3$	Stir at r.t. for 48 h	Complex mixture, degradation

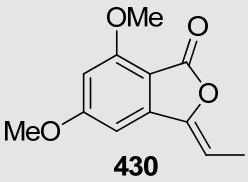
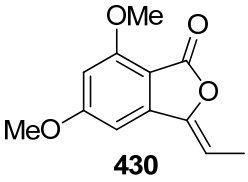
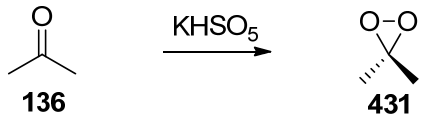
9	MTO, H_2O_2			Stir at r.t. for 48 h	No reaction
10	trifluoro DMDO *(in situ)*	CH_2Cl_2/ Trifluro-acetone	$NaHCO_3$	0 °C for 30 min, warm to r.t. for 12 h	No reaction
11	Iodosyl-benzene	$CHCl_3$		Stir at r.t. for 48 h	No reaction
12	H_2O_2, Bu_4NF	CH_2Cl_2	NaOAc	Stir at r.t. for 48 h	 **430**
13	TBHP, DBU	DCE		Stir at r.t. for 48 h	 **430**

Table 20. Epoxidation conditions.

It was envisaged that the chiral epoxide could be installed by a substrate directed epoxidation using *m*-chloroperbenzoic acid (*m*-CPBA).[213] (Entries 1 to 5) Treatment of *m*-CPBA in dichloromethane using sodium bicarbonate as buffer did effect formation of the desired epoxide **404** in trace amounts (Entry 1). The temperature of the reaction was increased to 50 °C (Entry 2), however this procedure did not afford an increase in yield of the desired epoxide **404**. The temperature of the reaction was increased further to 80 °C by changing the solvent to dichloroethane, however this also did not improve the yield (Entry 3). The reaction was then carried out in a sealed tube and increasing the temperature to 140 °C only yielded the epoxide **404** in 4% yield (Entry 4).

The use of mild dioxirane reagent to affect epoxidation was next attempted. The reactive dimethyldioxirane (DMDO) **431** species is formed upon reaction of Oxone® (potassium

peroxymonosulfate) with acetone (Scheme 153).[214] Use of a simplified procedure by Adam *et al*.[215] to give distilled DMDO **431** in ca. 0.10 M, however, failed to afford any of the desired epoxide **404** (Entry 5).



Scheme 153. Formation of DMDO using acetone and Oxone®.[214]

Dondoni *et al*.[216] have reported a method for the *in situ* generation of DMDO **431** which avoids the need to distill the potentially explosive DMDO **431**. Accordingly, a solution of vinylphthalide **406** in dichloromethane, acetone and saturated sodium bicarbonate solution was treated with an aqueous solution of Oxone® at 0 °C for 2.5 h. Unfortunately, these conditions also failed to give any of the desired epoxide **404**.

Hydrogen peroxide is another common oxidant of choice for terminal olefins. Lane *et al*.[217] have reported the use of manganese-catalysed epoxidations of alkenes using hydrogen peroxide as the terminal oxidant and using catalytic amounts of manganese (II) salts. It was reported, the use of bicarbonate buffer along with dimethylformamide or *tert*-butanol gave the best results. Accordingly, hydrogen peroxide (2 equiv.), manganese sulfate (1 mol %), sodium bicarbonate (0.2 M buffer at pH 8.0), in *tert*-butanol was added vinylphthalide **406** and stirred at room temperature for 48 h (Entry 7). However, TLC analysis showed degradation of the starting material **406** and none of the desired epoxide **404** was isolated. Similar results were obtained when dimethylformamide was used instead of *tert*-butanol (Entry 8). Using methyltrioxorhenium (MTO)[218] as catalyst for the epoxidation also failed to give any positive results (Entry 9). Peroxytrifluoroacetic acid[219], one of the strongest epoxidation reagents known, also failed to give any of the desired epoxide **404** (Entry 10).

Epoxidation of electron-rich olefins is generally achieved using electrophilic oxidants such as peroxy acids (*m*-CPBA). The double bond in vinylphthalide **406** is electron-deficient through a strong inductive effect, as the double bond bears an electron-withdrawing group in this case an ester functionality (Figure 30).

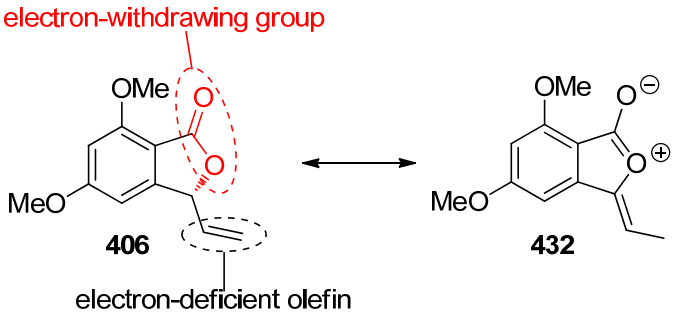
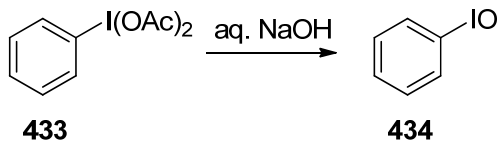


Figure 30. Vinylphthalide **406**.

Electron-deficient olefins generally require the use of nucleophilic oxidants under basic condition to affect epoxidation. Use of hydrogen peroxide with tetra-*n*-butylammonium fluoride (Entry 12)[220] and *tert*-butyl hydroperoxide with 1,8-diazabicyclo[5.4.0]undec-7-ene (Entry 13)[221] are examples of nucleophilic oxidants. When these conditions were screened, the strong basic nature of the reaction led to isomerisation of double bond forming phthalide **430** as observed previously (Scheme 152). However, the epoxidation of electron-deficient olefins as used by Pettus *et al*.[222] using iodosyl benzene under neutral condition were attractive. Iodosylbenzene is widely used as an oxygen source and can be synthesised by treating iodosobenzene diacetate with sodium hydroxide (Scheme 154).[223]

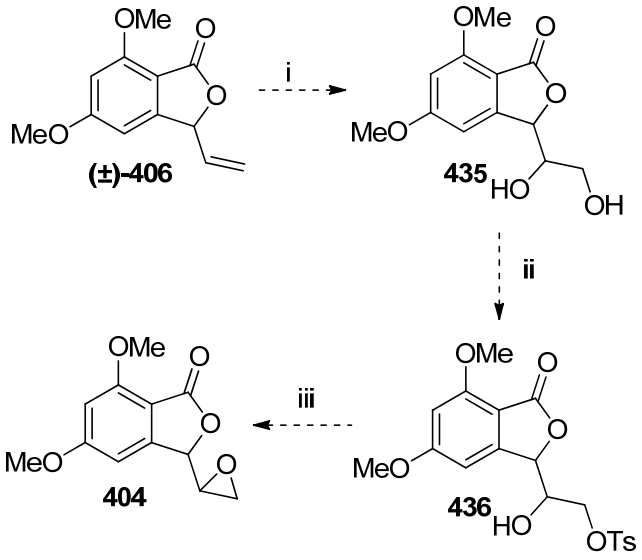


Scheme 154. Synthesis of iodosylbenzene.[223]

Finely ground iodosobenzene diacetate **433** was added sodium hydroxide to yield iodosylbenzene **434** as a yellow solid. Iodosylbenzene was then added to a solution of vinylphthalide **406** in chloroform and the mixture stirred at room temperature for 48 h. Disappointingly, no reaction took place and only starting material **406** was recovered.

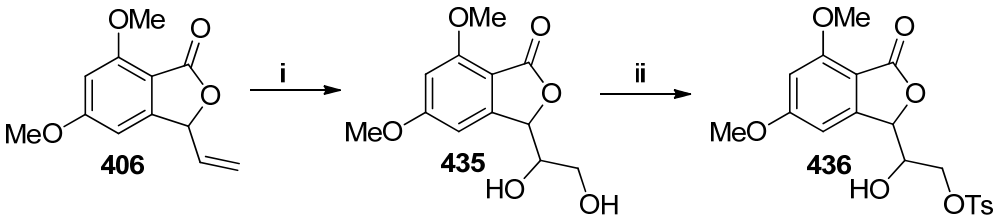
5.1.9 An Alternative Approach to Epoxide 404

With the synthesis of epoxide **404** proving unexpectedly problematic, an alternative approach to epoxide **404** was sought. (Scheme 155). It was envisaged, that vinylphthalide **406** would undergo dihydroxylation to diol **435**, which would undergo selective tosylation on the primary alcohol to give **436**. By using base to encourage tosylate elimination, the desired epoxide **404** would then be formed. The viability of this revised synthetic strategy was first explored using racemic material (±)-**406**.



Scheme 155. Revised synthetic route to epoxide **404**.

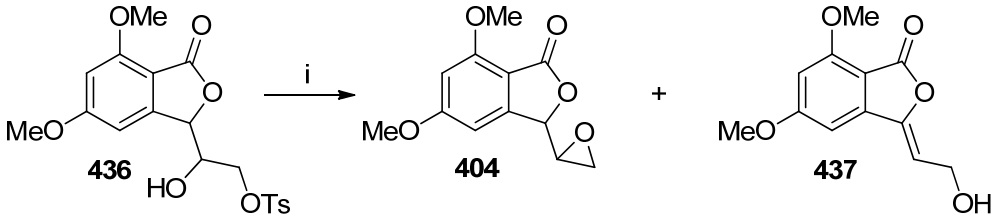
Vinylphthalide **406** was treated with *N*-methylmorpholine-*N*-oxide and osmium tetroxide to give diol **435**, which provided tosylate **436** upon subsequent monotosylation using dibutyltin oxide[163] and *p*-toluenesulfonyl chloride (Scheme 156).



Reagents and conditions: i. NMO, OsO_4, acetone, 0 °C to r.t., 24 h., 85%; ii. TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 2 h., 74%.

Scheme 156. Formation of tosylate **436**.

With the tosylate **436** in hand, elimination of the leaving group using base was investigated (Scheme 157). A solution of tosylate **436** in dichloromethane was added 1,8-diazabicyclo[5.4.0]undec-7-ene at 0 °C and was stirred for 4 h. TLC analysis showed formation of two new products and after 4 h, complete consumption of starting material **436** was observed.

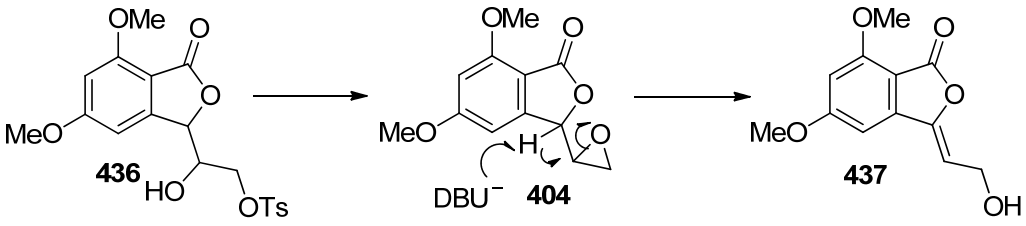


Reagents and conditions: i. DBU, CH_2Cl_2, 0 °C, 4 h, **404**, 34%; **437**, 58%.

Scheme 157. Formation of epoxide **404**.

Isolation of the new products established that the desired epoxide **404** has formed in 34% yield. The other major spot proved to be byproduct **437** which was isolated in 58% yield. Decreasing the reaction time by stopping the reaction after 2 h showed no increase in the yield

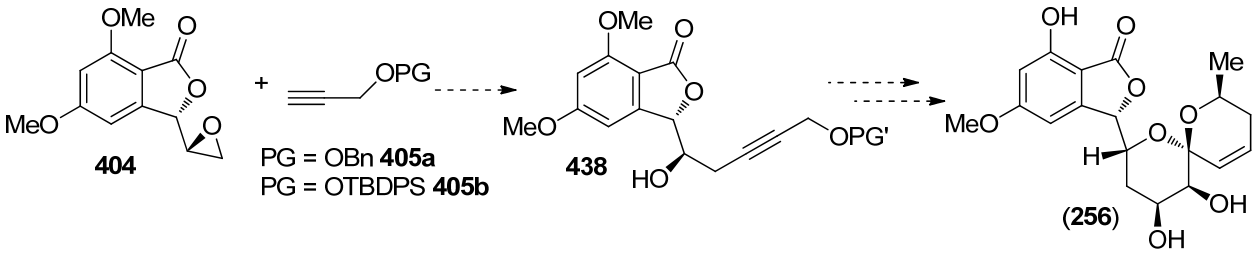
of epoxide **404** and unreacted starting material was still visible by TLC analysis. Increasing the reaction time to 6 h led to complete consumption of epoxide **404** and only byproduct **437** was present suggesting that prolonged exposure of epoxide **404** to base led to decomposition. It was proposed the basic nature of the reaction resulted in conversion of epoxide **404** to byproduct **437** (Scheme 158).



Scheme 158. Possible mechanism for the formation of byproduct **437**.

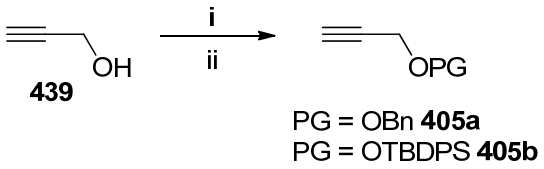
Despite the undesired formation of byproduct **437**, epoxide **404** was able to be isolated in a respectable yield such that enough material was available to investigate the crucial acetylide anion addition step.

5.1.10 Acetylide Anion Addition to Epoxide 404



Scheme 159. Proposed acetylide anion addition on epoxide **404**.

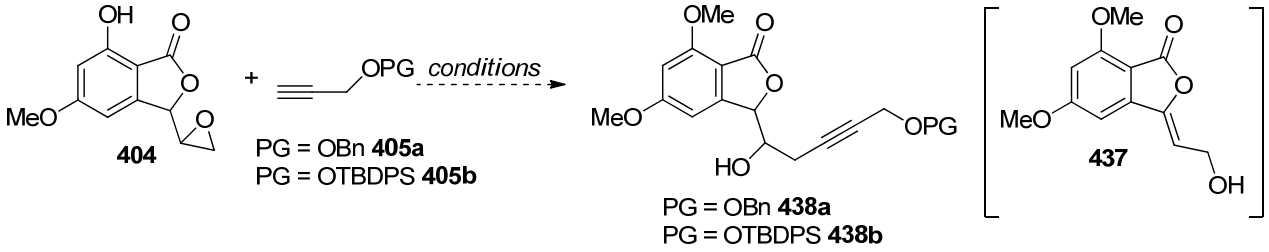
With epoxide **404** in hand, addition of protected propargyl alcohol **405a** and **405b** was investigated. The protection of propargyl alcohol **439** went smoothly, giving the desired products **405a** and **405b** in 71% and 96% yields respectively (Scheme 160).



Reagents and conditions: i. NaH, BnBr, DMF, 0 °C, 24 h., 71%; ii. TBDPSCl, imidazole, CH_2Cl_2, 14 h, 96%.

Scheme 160. Synthesis of protected propargyl alcohols **405a** and **405b**.

With protected propargyl alcohols **405a** and **405b** in hand, the acetylide anion addition was attempted (Table 21).



Entry	Alcohol	Base	Temp °C	Conditions	Yield (%)		
					438a	**438b**	**437**
1	**405a**	*n*-BuLi (1.2 eq)	-78 °C	Add base, stir for 30 min, add epoxide **404**, stir for 1 h, r.t	0	-	nd
2	**405a**	*n*-BuLi (1.2 eq)	-78 °C	Add base, stir for 30 min, add epoxide **404**, stir for 30 min, r.t	0	-	nd
3	**405a**	*n*-BuLi (1.2 eq)	-78 °C	Add base, stir for 1 min, add epoxide **404**, stir for 1 h, r.t	0	-	nd
4	**405a**	*t*-BuLi (1.2 eq)	-78 °C	Add base, stir for 30 min, add epoxide **404**, stir for 1 h, r.t	0	-	nd
5	**405b**	*n*-BuLi	-78 °C	Add base, stir for 30 min, add epoxide **404**, stir for 1 h,	-	0	nd

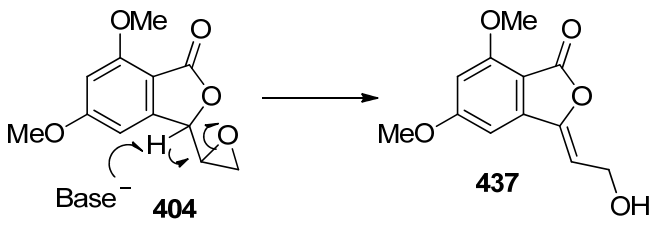
		(1.2 eq)		r.t			
6	**405b**	*n*-BuLi (1.2 eq)	-78 °C	Add base, stir for 30 min, add epoxide **404**, stir for 30 min, r.t	-	0	nd
7	**405b**	*n*-BuLi (1.2 eq)	-78 °C	Add base, stir for 1 min, add epoxide **404**, stir for 1 h, r.t	-	0	nd
8	**405b**	*t*-BuLi (1.2 eq)	-78 °C	Add base, stir for 30 min, add epoxide **404**, stir for 1 h, r.t	-	0	nd

nd = yield not determined

Table 21. Attempted acetylide anion addition to epoxide **404**.

The conditions used to effect conversion of **404** to **438** are outlined in Table 21. The first conditions screened involved use of *n*-BuLi as the base and adding dropwise to a solution solution of propargyl alcohol benzyl ether **405a** at -78 °C and stirring for 30 min to allow for the formation of the acetylide anion. Epoxide **404** was then added dropwise via syringe. The solution was stirred for 1 h before being quenched and purified. Disappointingly, none of the coupled product **438a** was observed, and the byproduct **437** also formed in basic conditions (Entry 1). Changing the reaction times (Entries 2, 3) or changing the base to *t*-BuLi (Entry 4) was unsuccessful with none of the desired product **438a** being obtained. The use of TBDPS protected propargyl alcohol (Entries 5 to 8) also failed to undergo the acetylide anion addition, only returning the undesired byproduct **437**.

It was thought that epoxide **404** was undergoing base induced epoxide opening to form byproduct **437** (Scheme 161).

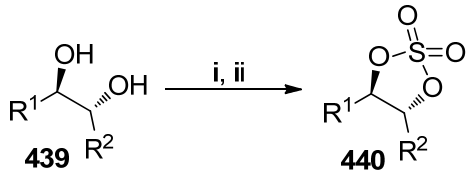


Scheme 161. Possible mechanism for the formation of byproduct **437**.

With this undesired reaction taking place, an alternative synthetic route to (+)-aigialospirol (**256**) was needed.

5.1.11 Cyclic Sulfites and Cyclic Sulfates

The use of organic cyclic esters of sulfurous and sulfuric acids known as cyclic sulfites and sulfates have been known since 1932.[224] The lack of an efficient method for preparing cyclic sulfates limited their applications until Sharpless *et al*.[225] reported facile conversion of 1,2-diols **439** to cyclic sulfites then oxidising to cyclic sulfates **440** with sodium periodate catalysed by ruthenium tetraoxide (Scheme 162).



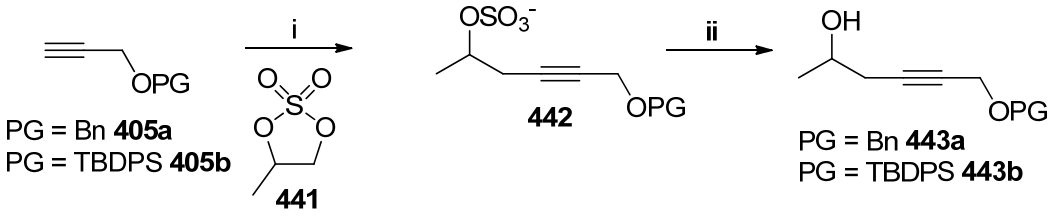
R^1 = CO_2*i*-Pr, CO_2Et, CO_2Me, *n*-C_8H_{17}, *c*-C_6H_{11}, *n*-C_4H_9, *n*-$C_{15}H_{31}$, *c*-C_6H_{11}, H
R^2 = CO_2*i*-Pr, CO_2Et, CO_2Me, *n*-C_4H_9, CO_2*c*-C_6H_{11}, $CONHCH_2Ph$, H

Reagents and conditions: i. $SOCl_2$, CCl_4, 60 °C; ii. $NaIO_4$, $RuCl_3 \cdot 3H_2O$, CH_3CN/H_2O, 25 °C, 63-97% over 2 steps.

Scheme 162. Synthesis of cyclic sulfates **440** by Sharpless *et al*.[225]

Several properties render cyclic sulfites and sulfates favourable intermediates in organic synthesis. Firstly, they have high reactivity towards various nucleophiles and are more reactive than epoxides. Secondly, they can activate nucleophilic attack at one position while serving as a protecting group at a second position. Thirdly, the reactions of five-membered cyclic sulfates with nucleophiles provide two adjacent stereocenters. Finally, since the intermediate of nucleophilic substitution is generally the salt form of a monosulfate ester, separation/purification of the product is typically a facile process.

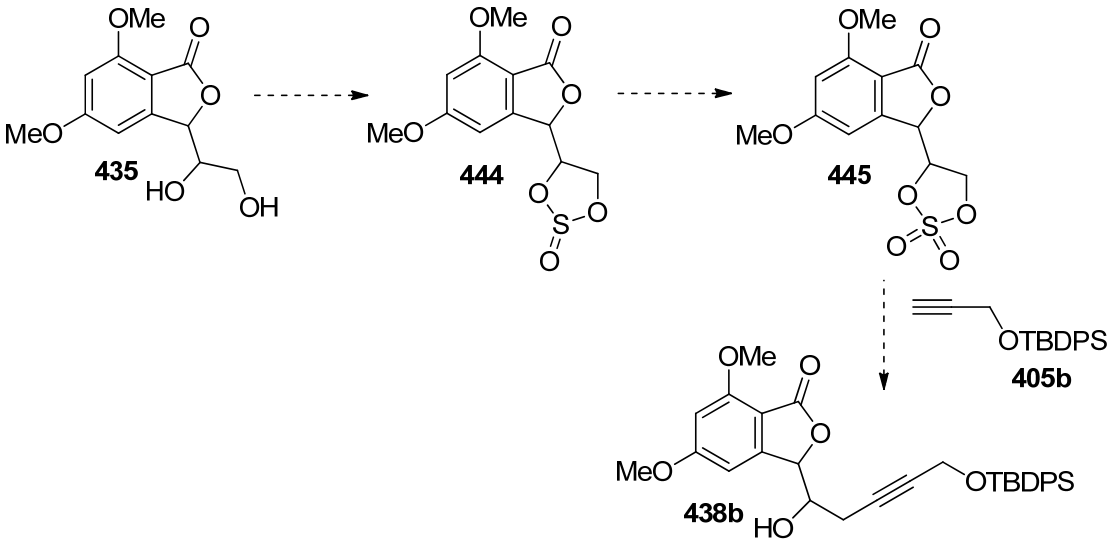
Bates *et al*.[226] have successfully coupled various cyclic sulfates with lithium acetylides (Scheme 163). The reaction between cyclic sulfate **441** and lithium acetylides **405a**, **405b** afforded products **443a**, **443b** arising from attack at the less substituted carbon of the cyclic sulfate. The lithium acetylides, generated by treatment of the acetylenes **405a**, **405b** in tetrahydrofuran with *n*-BuLi at -78 °C under N_2 reacted with cyclic sulfate **441** to give hemisulfate **442** which was then hydrolysed under acidic conditions to give the homopropargyl alcohols **443a**, **443b**. The TBDPS protected acetylene **405a** and benzyl ether protected acetylene **405b** gave the best yields with other common protecting groups being too labile.



Reagents and conditions: i. *n*-BuLi, -78 °C, cyclic sulfate, r.t. 1 h; ii. H_2O, H_2SO_4, **443a**, 79%; **443b**, 90%.

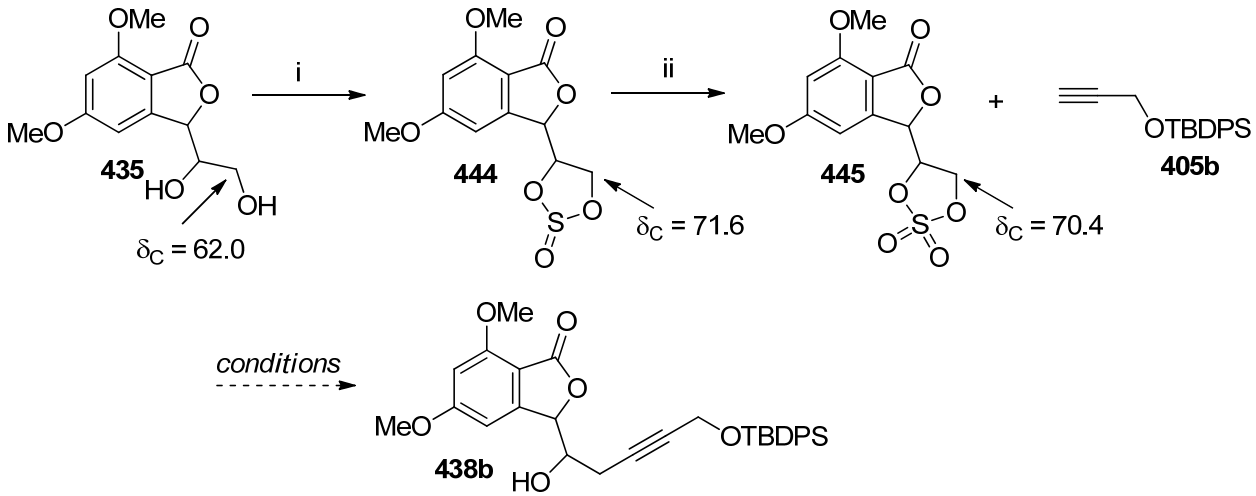
Scheme 163. Acetylide anion addition to propylene glycol cyclic sulfate **441** by Bates *et al*.[226]

In the present work, it was envisaged that cyclic sulfate **445** would undergo acetylide anion addition with protected propargyl alcohol **405b** (Scheme 164). The cyclic sulfate **445** would be synthesised from facile conversion of diol **435** to cyclic sulfite **444** then effecting oxidation to cyclic sulfate **445** with sodium periodate catalysed by ruthenium tetroxide. Given that cyclic sulfates are known to be more reactive than epoxides, it was hoped that the use of cyclic sulfates would avoid the formation of the undesired byproduct **437**.



Scheme 164. Proposed synthesis of cyclic sulfate **445** and acetylide anion addition.

Triethylamine and thionyl chloride were added to a solution of diol **435** in dichloromethane to give the desired cyclic sulfite **444** in 71% yield. Cyclic sulfite **444** was then oxidised to cyclic sulfate **445** using sodium periodate and ruthenium tetraoxide in 83% yield. The ^{13}C NMR spectrum of the product obtained indicated the successful formation of cyclic sulfite **444** and sulfate **445**, respectively with the hydroxymethylene carbon shifting from δ_C 62.0 ppm to 71.6 ppm and 70.4 ppm, respectively (Scheme 165).



Reagents and conditions: i. Et_3N, $SOCl_2$, CH_2Cl_2, r.t., 20 min, 71%; ii. $RuCl_3.H_2O$, $NaIO_4$, CCl_4, CH_3CN, r.t., 10 h, 83%.

Scheme 165. Synthesis of cyclic sulfate **445** and attempted acetylide anion addition

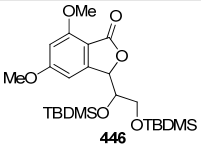
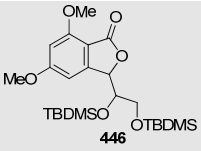
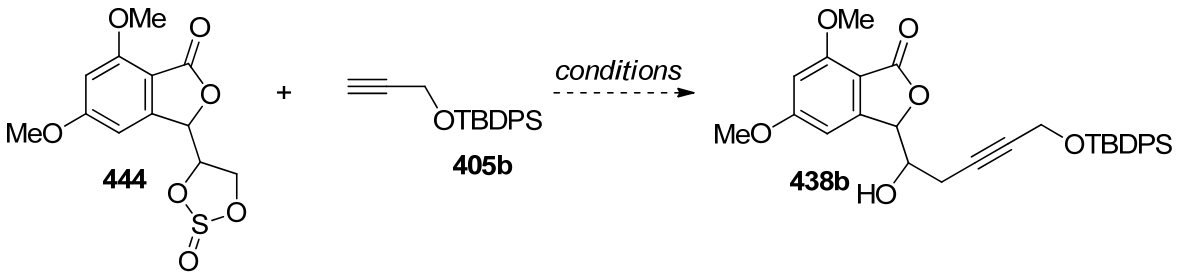
Entry	Base	Temp (°C)	Conditions	Yield (%)
1	*n*-BuLi (2.2 eq)	-78 °C	Add base, stir for 30 min, add cyclic sulfate **445**, stir for 1 h, r.t.	degradation
2	*t*-BuLi (2.2 eq)	-78 °C	Add base, stir for 30 min, add cyclic sulfate **445**, stir for 1 h, r.t.	degradation
3	*n*-BuLi (2.2 eq)	-78 °C	Add base, stir for 5 min, add cyclic sulfate **445**, stir for 1 h, r.t, add 2,6-lutidine and TBDMSOTf.	 **446**
4	*n*-BuLi (2.2 eq)	-78 °C	Add base, stir for 30 min, add cyclic sulfate **445**, stir for 1 h, r.t, , add imidazole, TBDMSCl	 **446**

Table 22. Conditions for acetylide anion addition

With cyclic sulfate **445** in hand, the key acetylide anion addition was investigated (Table 22). The TBDPS group was the most stable protecting group for the acetylide anion addition step for Bates *et al*.,[226] hence TBDPS propargyl alcohol **405b** was used. The reaction was carried out by adding base to acetylene **405b** at -78 °C and the anion was allowed to form for 30 min. Cyclic sulfate **445** in tetrahydrofuran was added dropwise to the mixture and left to stir for 1 h at room temperature. Use of *n*-BuLi (Entry 1) and *t*-BuLi (Entry 2) resulted in degradation of **445** by TLC analysis and no products were isolated. The possible unstable nature of the proposed product **438b** prompted us to effect *in situ* protection of the alcohol with the hope of isolating the desired coupled product. After 1 h, the reaction was quenched with 2,6-lutidine and TBDMSOTf (Entry 3) however, the only product isolated was the bis-protected TBDMS diol **446**. Use of imidazole and TBDMSCl returned similar results, only affording bis-protected TBDMS diol **446**. It was postulated, the cyclic sulfate was falling off during the reaction, liberating the two hydroxyl groups in diol **435** which were then protected *in situ* as TBDMS ether.

The enhanced reactivity of cyclic sulfates relative to an acyclic sulfate may originate from the partial double bond character between the ring oxygen atoms and the sulfur atom. With cyclic sulfites, the presence of an unshared pair of electrons on sulfur partially represses the double-bond character of the sulfur atom and the ring oxygen atoms.[227] Therefore cyclic sulfites and cyclic sulfates are expected to show different reactivities. With cyclic sulfate **445** failing to give the anticipated product, acetylide anion addition between acetylene **405b** and cyclic sulfite **444** was next considered (Table 23).



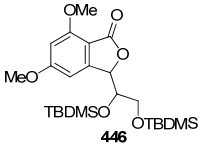
Entry	Base	Temp (°C)	Conditions	Yield (%)
1	*n*-BuLi (2.2 eq)	-78 °C	Add base, stir for 30 min, add cyclic sulfite **444**, stir for 1 h, r.t.	degradation
2	*t*-BuLi (2.2 eq)	-78 °C	Add base, stir for 30 min, add cyclic sulfite **444**, stir for 1 h, r.t.	degradation
3	*n*-BuLi (2.2 eq)	-78 °C	Add base, stir for 5 min, add cyclic sulfite **444**, stir for 30 min, r.t, add 2,6-lutidine and TBDMSOTf.	 **446**

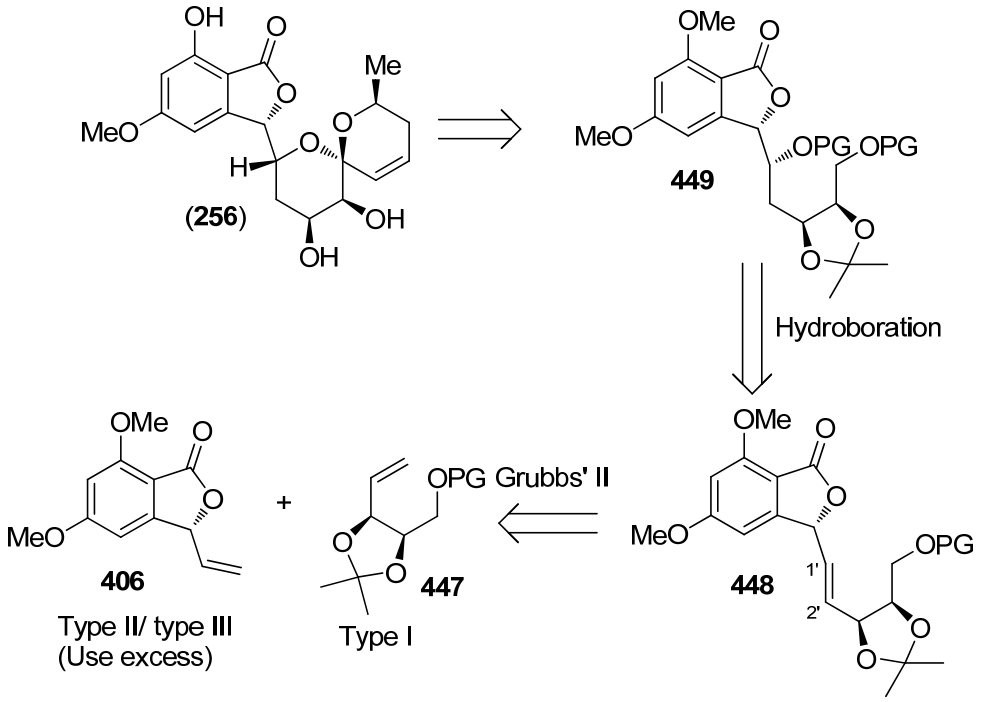
Table 23. Conditions for acetylide anion addition.

Following the procedure used for cyclic sulfate **445**, *tert* or *n*-butyllithium was added to acetylene **405b** at -78 °C and the reaction mixture stirred for 30 min. Cyclic sulfite **444** was added dropwise to the reaction mixture and the mixture left the stir for 1 h at r.t. TLC analysis

showed degradation (Entry 1 and 2) and attempts to trap the product **438b** by addition of TBDMSOTf (Entry 3) only returned bis-protected diol **446**. Given that both cyclic sulfate **445** and sulfite **444** failed to undergo acetylide anion addition, an alternative synthetic route was required.

5.1.12 Grubbs' Cross Metathesis Approach to Aigialospirol (256)

The intermediate epoxide **404**, cyclic sulfate **445**, cyclic sulfite **444**, proved to be inadequate to advance the synthesis of aigialospirol (**256**). A new approach was therefore proposed that hinged on the use of vinylphthalide **406** which would undergo a Grubbs' cross metathesis reaction with protected diol **447** (Scheme 166). Asymmetric hydroboration would then give the desired alcohol functionality on the double bond which can be further elaborated to give aigialospirol (**256**). The regioselectivity of the hydroboration step can be predicted as the secondary alcohol arising from the C-B oxidation is preferentially formed adjacent to the more electron-deficient carbon.[228] It was proposed the ester functionality on phthalide **447** would be electron withdrawing which would favour the C-B oxidation on the C-1′ position.



Scheme 166. Revised synthesis of spiroketal moiety to give aigialospirol (**256**).

5.1.12.1 Background to Olefin Metathesis

Grubbs' olefin cross metathesis (CM) is an intermolecular exchange of alkylidene groups between two olefins that is catalysed by a transition metal.[229-231] One of the most common catalysts for the ring closing metathesis are ruthenium catalysts developed in the 1990's. Ruthenium catalyst is a perfect metal for olefin metathesis due to their preferential reactivity towards olefins than most other functional groups. In addition, ruthenium catalysts are moisture and air stable and they are tolerant towards a wide variety of functional groups.[151, 229, 232] The structures of the Grubbs' first generation **450**, second generation **451** and Hoveyda-Grubbs' second generation **452** catalysts are shown in Figure 31.

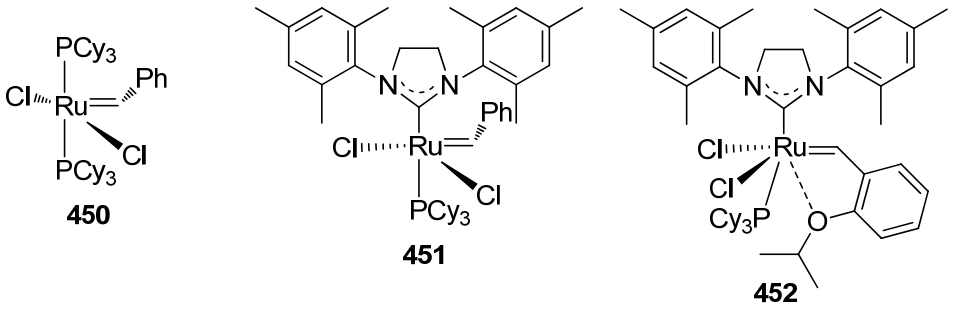
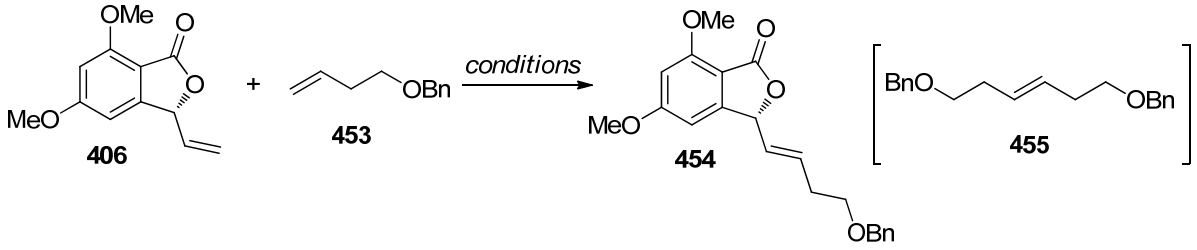


Figure 31. Structures of the Grubbs' first generation **450** and second generation **451** and Hoveyda-Grubbs' second generation **452** catalysts.

Grubbs and co-workers[233] examined the ability of different olefins to homodimerise as well as the susceptibility of their homodimers to take part in further metathesis. Their analyses provided them with a suitable model that consisted of four different olefin types. Type I olefins are the most reactive which are able to undergo homodimerisation rapidly. Generally, electron-rich and sterically unhindered olefins are classified in this category. Type II olefins are less reactive than type I olefins but can still undergo homodimerisation. Type III olefins cannot form homodimers and are less reactive than type I or type II. Type IV olefins are the least reactive, with no CM occurring between these olefins. Overall, there is a decrease in olefin

reactivity from type I (most reactive) to type IV (least reactive). The general model here could be used for the design of CM reactions that are selective for the desired heterodimer.

Using these guidelines, it was predicted that vinylphthalide **406** would be classified as type II or type III. In order to test the reactivity of vinylphthalide **406**, a model study was undertaken by subjecting **406** to CM with a readily available simple benzyl alcohol **453**[234] which is classified as a type I olefin (Table 23).



Entry	Vinylphthalide 406 (equiv)	Benzyl alcohol 453 (equiv)	Catalyst/ Loading (mol%)	Solvent	Conditions	Yield 454 (%)
1	5	1	2nd / 10	CH_2Cl_2	r.t., 6 h	nr
2	5	1	2nd / 10	CH_2Cl_2	Reflux, 50 °C, 10 h	nr
3	5	1	2nd / 15	CH_2Cl_2	MWI, 40 °C, 100 W, 3 h	nr
4	10	1	Hoveyda-Grubbs' / 10	CH_2Cl_2	Reflux, 50 °C, 5.5 h	Homodimer **455**, 23%
5	10	1	Hoveyda-Grubbs' / 15	CH_2Cl_2	Reflux, 55 °C, 4 h then 80 °C, 20 h	Homodimer **455**, 21%

Table 23. Cross Metathesis between vinylphthalide **406** and benzyl alcohol **453**.

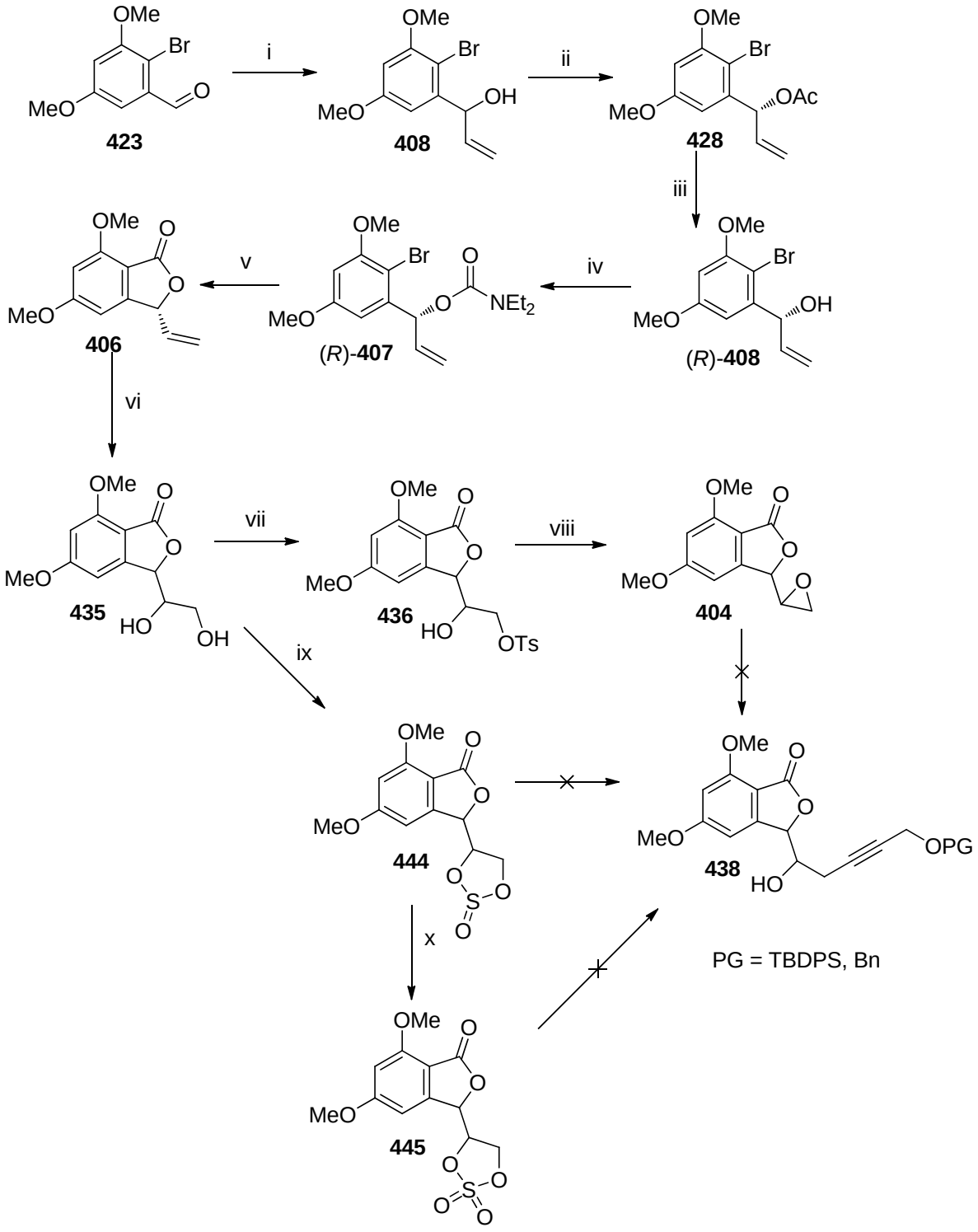
With vinylphthalide **406** and benzyl alcohol **453** in hand, attention turned to CM between the two starting materials using Grubbs' second generation **451** catalyst and Hoveyda-Grubbs'

catalyst **452**. Vinylphthalide **406** was added in excess as it has lower reactivity (type II or III) than benzyl alcohol **453** (type I) to minimise the homodimer formation of benzyl alcohol. As recorded in Table 23, the reaction was first trialled using Grubbs' second generation catalyst **451** in dichloromethane at room temperature and under reflux (Entries 1 and 2). An attempt was also made to effect the reaction in dichloromethane using Grubbs' second generation catalyst **451** in a CEM Discover microwave reactor using the conditions reported by Zerrouki *et al*.[235] (Entry 3). Disappointingly, no cross products were produced when Grubbs' second generation catalyst **451** was used, hence Hoveyda-Grubbs' catalyst **452** was next employed. Use of Hoveyda-Grubbs' catalyst **452** in dichloromethane under reflux (Entry 4 and 5) also gave none of the desired heterodimer. Instead, only homodimer **455** was isolated.

The lack of formation of cross metathesis between vinylphthalide **406** and benzyl alcohol **453** suggested the reactivity of vinylphthalide **406** during CM is very low. It was therefore proposed that vinylphthalide **406** would not undergo CM with alkene **447** hence an alternative approach was needed.

5.1.13 Summary of Synthetic Approach to Vinylphthalide 406

Vinylphthalide **406** was synthesised using a novel chemoenzymatic resolution using microwave irradiation. Use of the closed vessel system and the correct reaction time was vital for the success of this reaction (Scheme 167). The synthesis of epoxide **404** from vinylphthalide **406** proved problematic. Epoxide **404** was prepared by forming diol **435** from vinylphthalide **406**, followed by selective tosylation then subsequent elimination to form the desired epoxide **404**. Epoxide **404** however underwent ring opening to form olefin **437** when exposed to base, hence attempted acetylide anion addition to epoxide **404** was unsuccessful. Other epoxide synthons such as cyclic sulfite **444** and cyclic sulfate **445** were investigated however, the desired coupled product **438** was not observed. An alternative Grubbs' cross metathesis route also failed to afford the desired vinylphthalide **406** (Scheme 167).



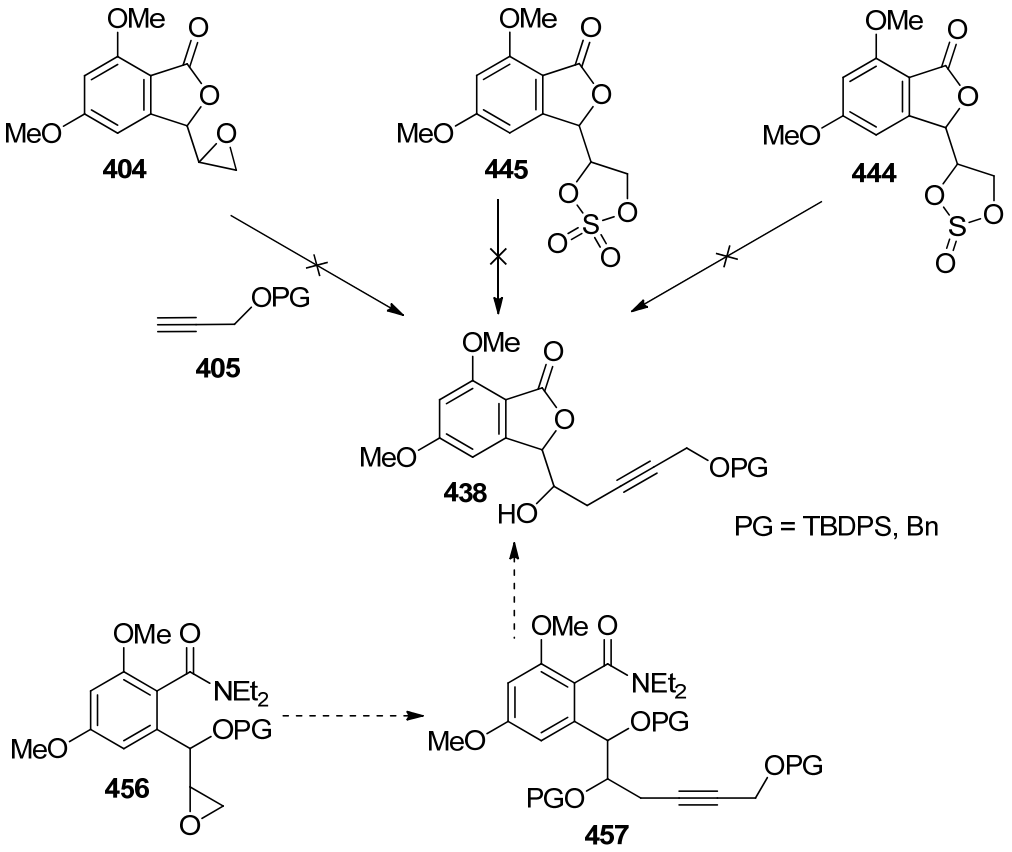
Reagents and conditions: i. vinylmagnesium bromide, THF, -78 °C, 12 h., 85%; ii. *p*-chlorophenyl acetate, Novozyme 435®, toluene, 55 °C, 48 h, 48%, 99% e.e; iii. KOH, MeOH, 30 min, 87%; iv. CDI, $HNEt_2$, CH_2Cl_2, 24 h, 90%; v. a) *n*-BuLi, THF, -78 °C, 1 h; b) anhydrous HCl (1 M), dioxane, 12 h, 74% over two steps; vi. NMO, OsO_4, acetone, H_2O, 90%; vii. TsCl, Bu_2SnO, CH_2Cl_2, 2 h,

71%; viii. DBU, CH_2Cl_2, 4 h, 34%; ix. Et_3N, $SOCl_2$, CH_2Cl_2, 20 min, 71%; x. $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, 10 h, 83%

Scheme 167. Summary of synthesis of vinylphthalide **406**.

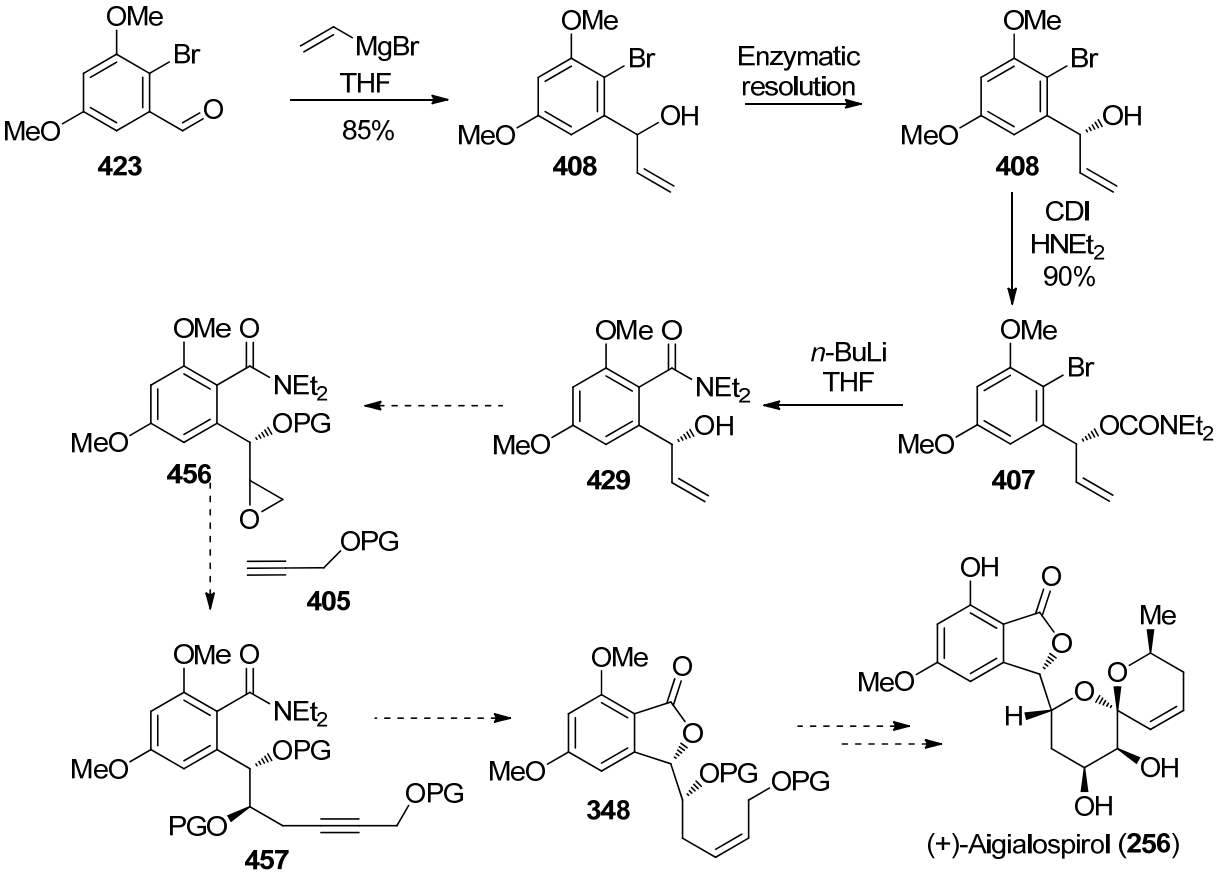
5.1.14 Future Directions

Future work will focus on the problematic acetylide anion addition step which will provide a platform for accessing aigialospirol (**256**). This problem maybe overcome by attempting the addition of acetylide anion before the phthalide moiety is formed. Our initial synthetic approach focused on the synthesis of various phthalide intermediates **404**, **444**, **445** which was followed by unsuccessful elaboration of carbon frame-work to intermediate **438**. The new approach would focus on the initial acetylide anion addition of protected propargyl alcohol **405** to epoxide **456** followed by phthalide formation to afford intermediate **457** (Scheme 168).



Scheme 168. Proposed synthesis of key intermediate **438**.

Using the protocol developed, carbamate **407** can be prepared as described previously (Scheme 152). Subjecting carbamate **407** to halogen-metal exchange with *n*-BuLi would provide amide intermediate **429** which was previously lactonised *in situ* with acid to afford vinylphthalide **406**. However, in the present proposed synthesis, amide intermediate **429** would be isolated, whereby subsequent protection of the alcohol and epoxidation would afford epoxide **456**. Acetylide anion addition of protected propargyl alcohol **405** to epoxide **456** will follow affording intermediate **457**. Intermediate **457** would be lactonised to yield phthalide intermediate **348** which would be further elaborated to the target compound aigialospirol (**256**) (Scheme 169).



Scheme 169. Proposed synthesis of aigialospirol (**256**).

5.2 Synthesis of Herbaric Acid (255)

Faced with the problems elaborating vinylphthalide **406** to the desired (+)-aigialospirol (**256**), the fungal metabolite herbaric acid (**255**) was noticed in the literature. Herbaric acid (**255**) was isolated from the fungus *Cladosporium herbarum* which was isolated from the sponge *Callyspongia aerizusa* in 2002 by Proksch *et al*.[128] (Figure 32). The stereochemistry at the C-3 position was unassigned in the isolation paper.

Herbaric acid (**255**) is the 5-hydroxyl derivative of the known toxin iso-ochracinic acid (**458**) previously isolated from *Alternaria kikuchiana*, a parasite responsible for the black spot disease on Japanese pears.[236] It is also related to acetophthalidin (**459**), a cytotoxic metabolite produced by *Aspergillus fumigatus*, isolated from a sea sediment, which has an acetyl group at the C-7 position.[237] Herbaric acid (**255**) was tested against *A.salina* and human leukemia cell line HL-60 however, it showed no activity.[128]

With chiral vinylphthalide **406** being a potential precursor to herbaric acid (**255**) and no synthesis of herbaric acid (**255**) being reported, the synthesis of this natural product was initiated.

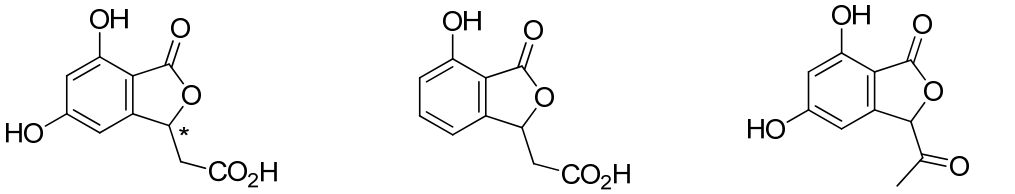
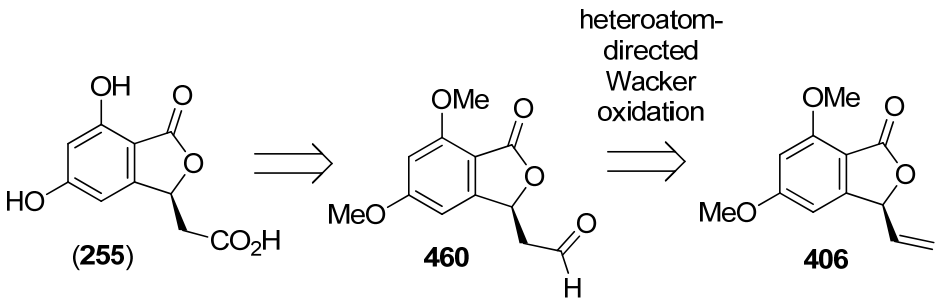


Figure 32. Structures of herbaric acid (**255**), iso-ochracinic acid (**458**) and acetophthalidin (**459**).

Our initially planned retrosynthesis of herbaric acid (**255**) is shown in Scheme 170 involving oxidation and deprotection of aldehyde **460**. It was envisaged that upon subjecting

vinylphthalide **406** to Wacker oxidation conditions, the bridging oxygen present in the lactone would provide an anchor enabling chelation to palladium, thereby facilitating delivery of water to the methylene carbon affording the desired aldehyde **460**. The successful realisation of this heteroatom-directed Wacker oxidation would provide a basis for a convenient and mild alternative to hydroboration/oxidation, a harsh procedure traditionally used for the synthesis of aldehydes from terminal alkenes.[238] Although the stereochemistry at the C-3 position was unknown, both forms of vinylphthalide **406** were available from the enzymatic resolution (Table 18). However with the (*R*)-vinylphthalide **406** already consumed in the synthetic studies towards aigialospirol, it was decided to use (*S*)-vinylphthalide **406** for the synthesis of herbaric acid (**255**).



Scheme 170. Retrosynthetic analysis of herbaric acid (**255**).

With vinylphthalide **406** in hand, attention turned to the pivotal heteroatom-directed Wacker oxidation step.

5.2.1 Reverse Wacker Oxidations

5.2.1.1 Background to Reverse Wacker Oxidations

The Wacker oxidation refers to Pd^{II}-catalysed oxidation of alkenes to carbonyl compounds.[239, 240] Wacker oxidation is one of the most well-known reactions mediated by palladium which has extensive synthetic applications.[241-243] This process involves coordination of the alkene to Pd^{II} and reaction of the η^2-Pd-alkene complex with water to yield methyl ketones.[241, 242, 244] Upon Wacker oxidation, terminal alkenes principally form methylketones, suggesting that

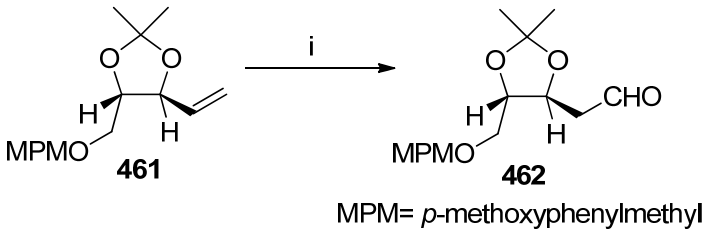
hydroxypalladation take place following Markovnikov's rules.[241] However, there are cases of aldehyde formation known as "reverse" Wacker oxidations. A few papers report the formation of the aldehyde with fair to high selectivity but in most cases mixtures of aldehyde and methyl ketone were observed.[245-247] A reliable procedure for the anti-Markovnikov addition of nucleophiles during the Wacker oxidation of terminal alkenes would provides a mild alternative to hydroboration/oxidation protocols that are traditionally used for terminal alkenes and greatly enhance the synthetic utility of this widely employed reaction.

Currently, the few successful examples of so-called "reverse" Wacker transformations are controlled by substrates having a second chelating fragment in the form of either a heteroatoms[248-251] or by π-complexation.[252] This reaction has not found any use in natural product synthesis, primarily due to the rarely observed[248, 253] total reversal of regioselectivity.

5.2.1.2 Heteratom-directed Wacker Oxidations

A. 1-Alkenes with an Oxygen Atom in the β-Position

Previous work by Kang *et al*.[248] have selectively obtained aldehyde **462** from allylic acetonide **461** depicted in Scheme 171. The anti-Markovnikov attack of water was induced by simultaneous chelation of palladium with the two adjacent oxygen atoms.

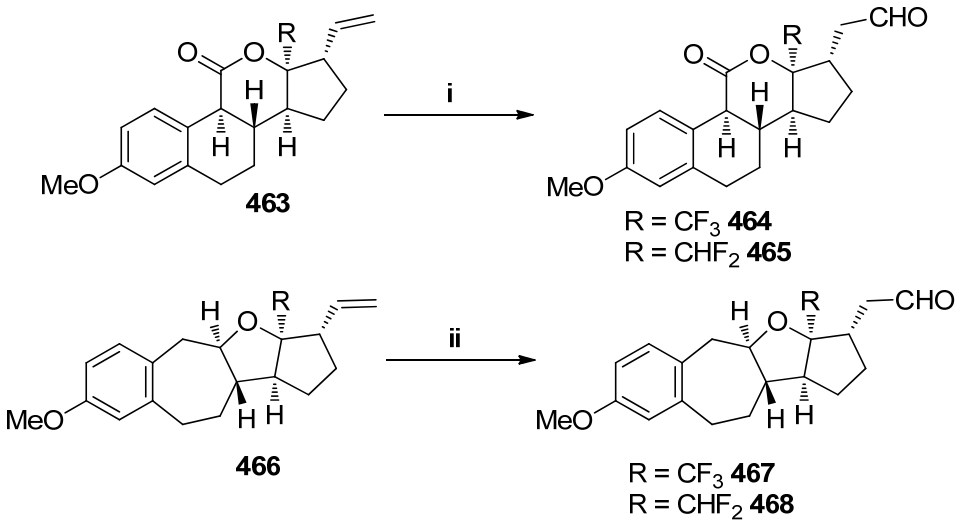


Reagents and conditions: i. $PdCl_2$, CuCl, O_2, DMF/H_2O, 60 °C, 6 h, 93%.

Scheme 171. Heteroatom-directed Wacker oxidation by Kang *et al*.[248]

B. 1-Alkenes with an Oxygen Atom in the γ-Position

Santelli *et al*.[250, 251] have reported the Wacker type oxidation of a range of steroids bearing a vinyl group which has various neighbouring oxygen groups (Scheme 172). Both steroids **463** and **466** underwent Wacker oxidations to give aldehydes **464**, **465** and **467**, **468** selectively in high yields. The selectivity towards aldehyde formation was rationalised by intramolecular coordination between the lactone/ether functionality and the palladium atom.

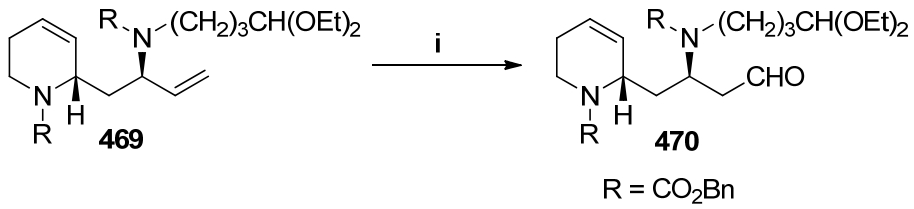


Reagents and conditions: i. $Pd(OAc)_2$, benzoquinone, $HClO_4$, $MeCN/H_2O$, r.t., 1 h, **464**, 80%; **465**, 85%; ii. $Pd(OAc)_2$, benzoquinone, $HClO_4$, $MeCN/H_2O$, r.t., 1 h, **467**, 74%; **468**, 82%.

Scheme 172. Heteroatom-directed Wacker oxidation by Santelli *et al*.[250, 251]

C. 1-Alkenes with a Nitrogen Atom in the β-Position

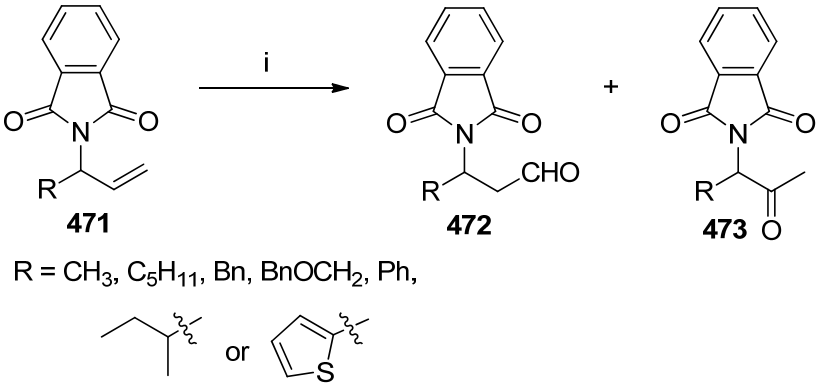
More recently, Stragies *et al*.[249] have used Wacker oxidation to selectively convert allylic amines **469** exclusively into the β-amino aldehydes **470** (Scheme 173) in good yields.



Reagents and conditions: i. $PdCl_2$, CuCl, O_2, DMF/H_2O, 60 °C, 6 h, 76%.

Scheme 173. Heteroatom-directed Wacker oxidation by Stragies *et al*.[249]

Feringa *et al*.[254] have used catalytic Wacker-type oxidations on allylic phthalimides **471** to produce aldehydes **472** in high yields and selectivity. Coordination of the nitrogen and carbonyl group to the palladium accounts for the aldehyde product selectivity.



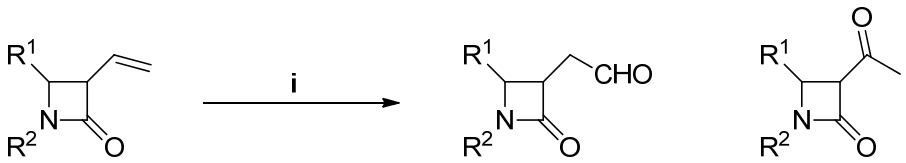
Reagents and conditions: i. $Pd(MeCN)_2Cl(NO_2)$, $CuCl_2$, *t*-BuOH, O_2, 16 h or $PdCl_2$, CuCl, O_2, DMF/H_2O (7:1), 3 days, 77-94%, **472**:**473** = >99:1.

Scheme 174. Heteroatom-directed Wacker oxidation by Feringa *et al*.[249]

D. 1-Alkenes with a C=O Fragment

Bose *et al*.[255] have reported the formation of aldehydes **476** in fair yields from the oxidation of 3-vinyl-4-substituted-2-azetidinones **474** under Wacker conditions (Scheme 175). The

regioselectivity is influenced by coordination of the carbonyl group of the β-lactam to the palladium atom.



474 **475** **476**

$R^{1,2}$ = Ph:	65 %	5 %
R^1 = PhCH=C(Me)CH_2, R^2 = *p*-$MeOC_6H_4$:	60 %	4 %
$R^{1,2}$ = *p*-$MeOC_6H_4$:	60 %	5 %
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$:	60 %	5 %
R^1 = COPh, R^2 = *p*-$MeOC_6H_4$:	70 %	0 %

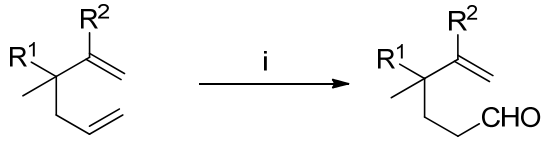
Reagents and conditions: i. $PdCl_2$, CuCl, O_2, DMF/H_2O (23:1), r.t., overnight.

Scheme 175. Heteroatom-directed Wacker oxidation by Bose *et al*.[255]

5.2.1.3 π-Complexation

A. 1-Alkenes with C=C Fragment

The second method to obtain aldehyde selectively via 'reverse' Wacker oxidation is via coordination of a C=C bond to the palladium atom. Ho *et al*.[252] obtained aldehydes **478**, **479**, **480** in good-to-high yields from substituted 1,5-dienes **477** (Scheme 176).



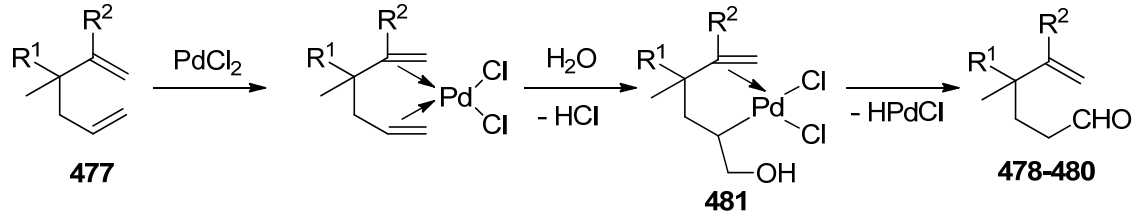
477

478 R^1 = Me, R^2 = *p*-tol
479 $R^{1,2}$ = Me
480 R^1 = Me, R^2 = *n*-C_8H_{17}

Reagents and conditions: i. $PdCl_2$, CuCl, O_2, DMF/H_2O, r.t., 24 h, **478**, 73%; **479**, 99%; **480**, 75%.

Scheme 176. π-Complexation-directed Wacker oxidation by Ho *et al*.[252]

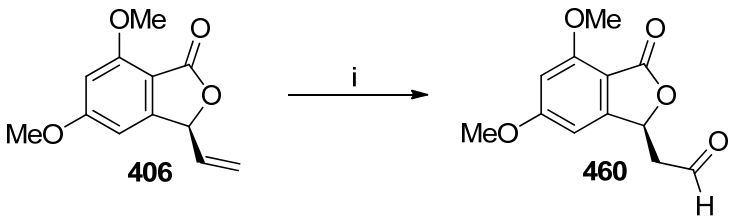
A possible mechanism for the reaction is depicted in Scheme 177. The palladium complex chelates with both the double bonds. Water attacks the double bond in an *anti*-Markovnikov fashion giving palladium intermediate **481**. Elimination of the palladium complex give aldehyde **478-480** selectively.



Scheme 177. Possible reaction pathway for π-complexation directed Wacker oxidations.[253]

5.2.2 Heteroatom-directed Reverse Wacker Oxidation of Vinylphthalide 406

Given the neighboring oxygen heteroatoms present in vinylphthalide **406**, it was anticipated that a heteroatom-directed Wacker oxidation would take place to give the desired aldehyde **460**. Upon exposing **406** to standard Wacker oxidation conditions, TLC analysis indicated clean consumption of the starting material within two hours (Scheme 178).



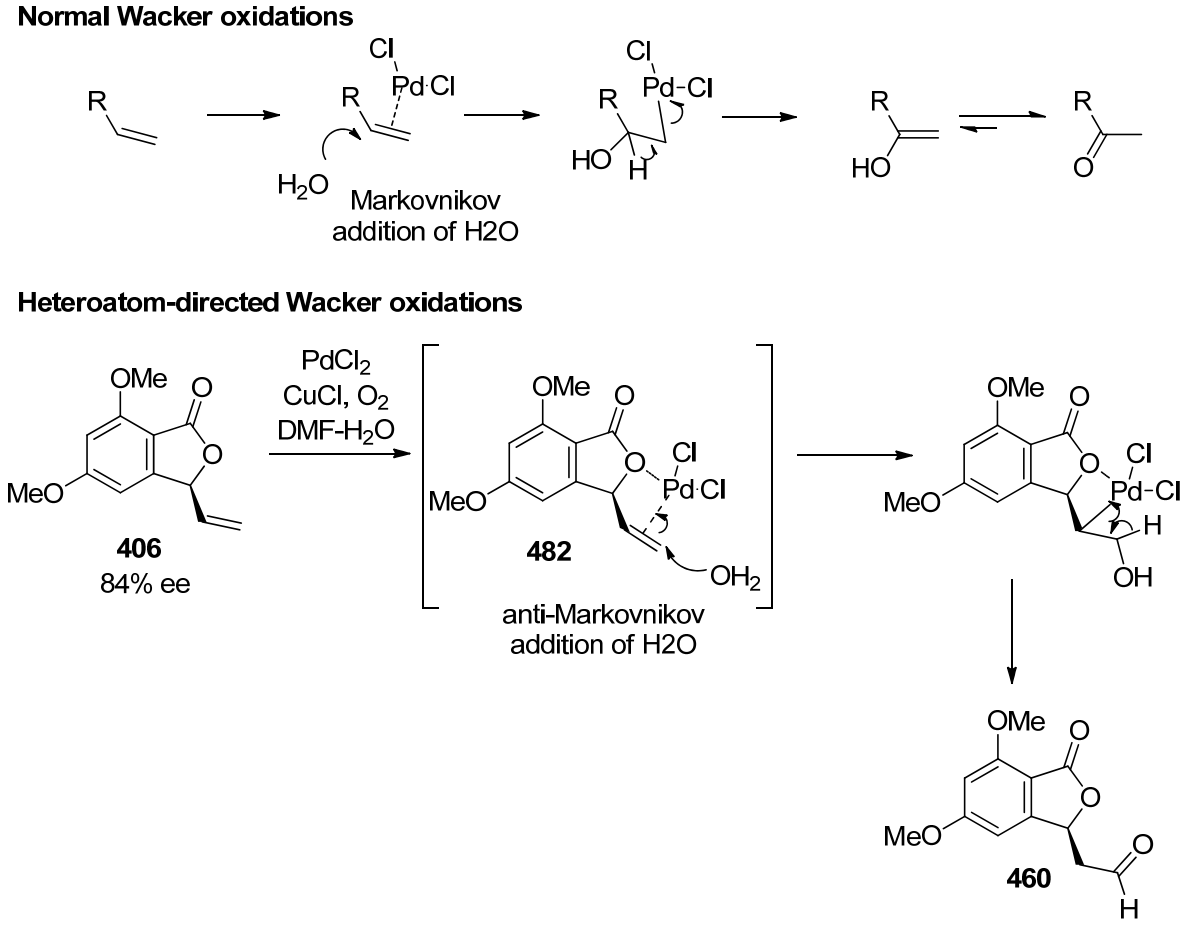
Reagents and conditions: i. $PdCl_2$, CuCl, O_2, DMF/H_2O (3:1), r.t., 2 h, 86%.

Scheme 178. Reverse Wacker oxidation of vinylphthalide **406**.

Pleasingly, the sole product obtained from this reaction was the desired aldehyde **460** in excellent yield, with no methyl ketone observed in the ^{1}H NMR spectrum of the crude reaction

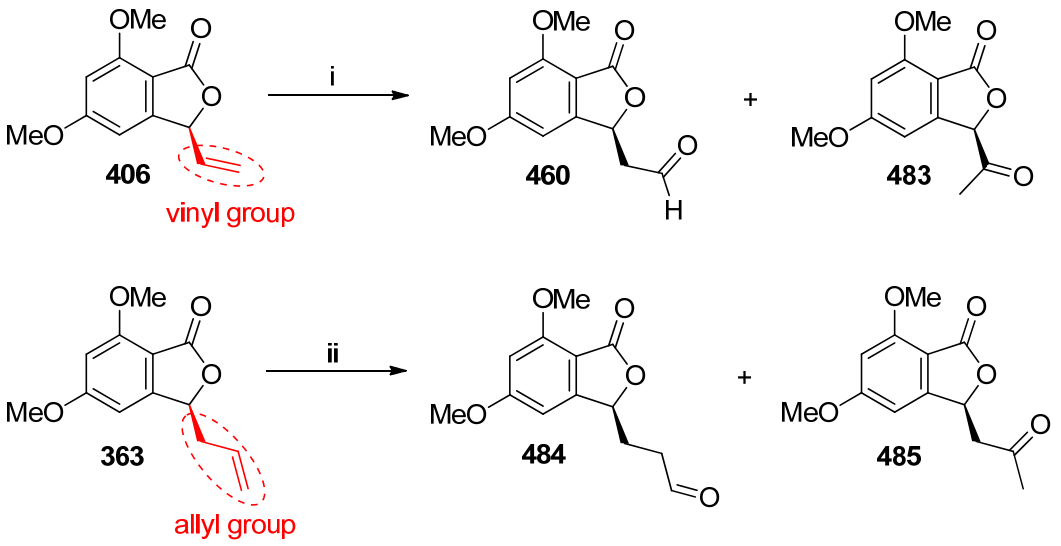
mixture. The ^{1}H NMR spectrum of the product indicated the successful formation of aldehyde **460** by the characteristic aldehyde proton that resonated as a triplet at δ 9.81.

This remarkable regioselectivity has been rationalised to result from intramolecular coordination of the lactone oxygen to the palladium that polarizes the palladium to the central vinylic carbon, thereby encouraging nucleophilic attack of water exclusively at the methylene carbon (Scheme 179). The regioselectivity is reversed compared to normal Wacker oxidations where the water is added according to the Markovnikov's rules.



Scheme 179. Normal Wacker oxidation and the reverse Wacker oxidation.

Intrigued by the exclusive formation of aldehyde **460**, the same Wacker oxidation conditions were applied to a similar substrate **363** which has an allyl group instead of a vinyl group (Scheme 180). The Wacker oxidation proceeded smoothly and to our surprise the product being isolated was an inseparable mixture of aldehyde **484** and methyl ketone **485** in a 1:1.6 ratio favouring the methyl ketone **485**. With the only difference between substrates **406** and **363** being an extra carbon atom, this was sufficient to change the regioselectivity of the Wacker oxidation. It was therefore concluded that the position of the heteroatom relative to the double bond was important in determining the regioselectivity of the Wacker oxidations.

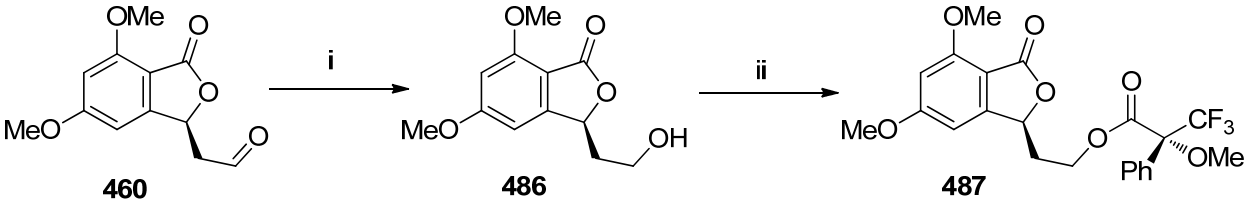


Reagents and conditions: i. $PdCl_2$, CuCl, O_2, DMF/H_2O (3:1), r.t., 2 h, **460**:**483** = 100:0, 86%; ii. $PdCl_2$, CuCl, O_2, DMF/H_2O (3:1), r.t., 2 h, **484**:**485** = 1:1.6, 56%.

Scheme 180. Reverse Wacker oxidation on substrate **363**.

To verify whether the chirality at the C-3 position was retained during the Wacker oxidation process, a Mosher ester analysis was undertaken (Scheme 181). A sample of aldehyde **460** was reduced to alcohol **486** using sodium borohydride in ethanol in 74% yield. Alcohol **486** was converted to its corresponding Mosher ester[256] by reaction with (*R*)-(+)-*α*-methoxytrifluorophenylacetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide and *N*,*N*-dimethyl-4-aminopyridine. Analysis of the resulting Mosher ester deivative by ^{19}F NMR spectroscopy revealed a major peak and a minor peak which showed the enantiomeric excess

to 84%, thus confirming that the stereochemical integrity of the substrate was retained during the reverse-Wacker oxidation (Figure 33).



Reagents and conditions: i. $NaBH_4$, EtOH, 0 °C, 30 min, 74%; ii. (*R*)-(+)-MTPA, DCC, DMAP, CH_2Cl_2, r.t., 84 % e.e.

Scheme 181. Formation of Mosher ester derivative **487** from alcohol **486**.

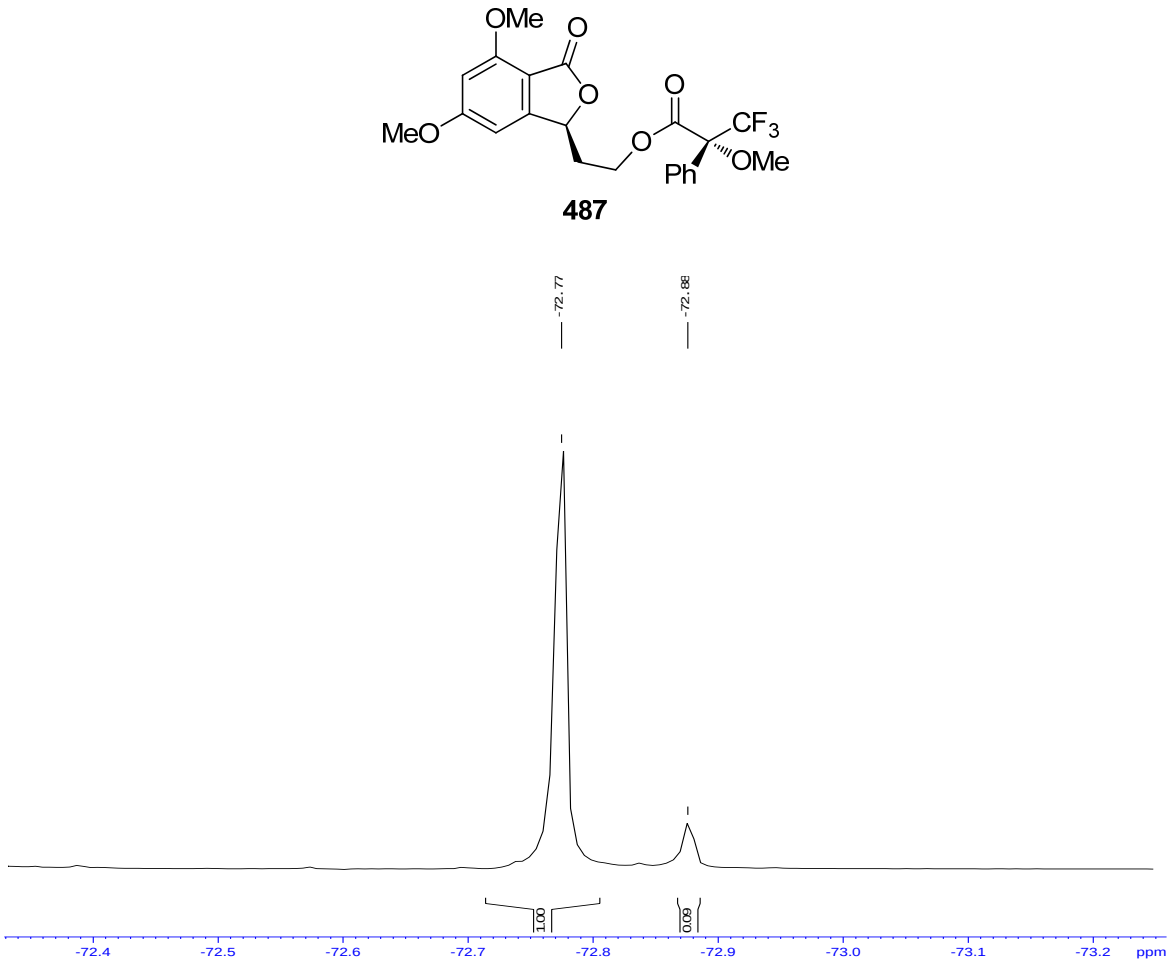
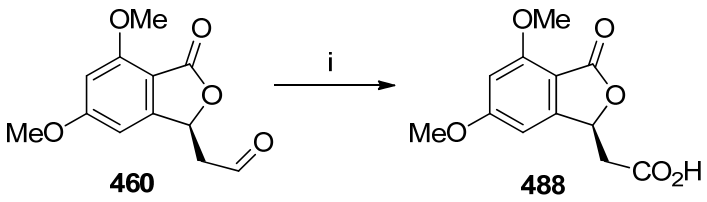


Figure 33. ^{19}F NMR analysis of the Mosher ester **487** showing 84% e.e.

5.2.3 Synthesis of (−)-Herbaric Acid (255)

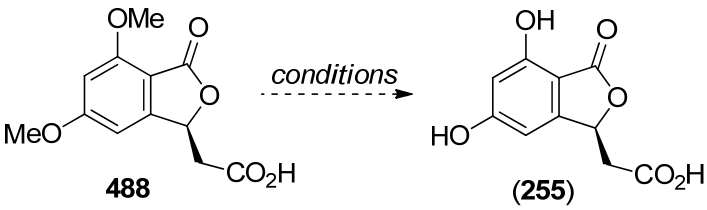
With the stereochemical integrity present in alkene **406** completely retained during the oxidation process, the final stages of the synthesis of herbaric acid (**255**) were initiated. Aldehyde **460** underwent smooth oxidation with Oxone® affording acid **488** in 89% yield (Scheme 182).



Reagents and conditions: i. Oxone, DMF, r.t., 6 h, 89%.

Scheme 182. Formation of acid **488** from aldehyde **460**.

With acid **488** in hand, various demethylation conditions were screened (Table 24).

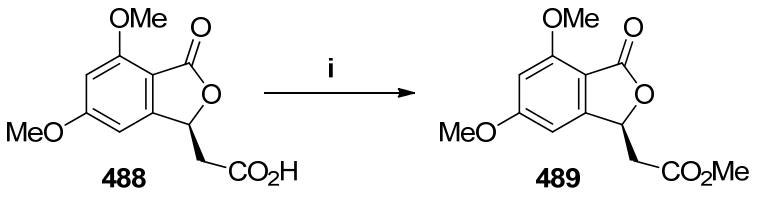


Entry	Reagents	Solvent	Conditions	Product
1	BBr_3	CH_2Cl_2	0°C then r.t for 48 h	Complex mixture
2	$AlCl_3$, NaI	-	Stir at r.t for 48 h	Complex mixture
3	iodocyclohexane	DMF	150°C for 72 h	No reaction
4	TMSI, quinoline	-	Stir at r.t for 48 h	No reaction

Table 24. Attempted demethylation conditions.

Use of boron tribromide in dichloromethane (Entry 1) gave a complex mixture upon TLC analysis. Use of aluminium trichloride with sodium iodide[257] (Entry 2) also gave a complex mixture. Use of iodocyclohexane[258] (Entry 3) which acts as a mild source of HI *in situ* also failed to give any results. TMSI in quinoline[259] (Entry 4) also gave no reaction.

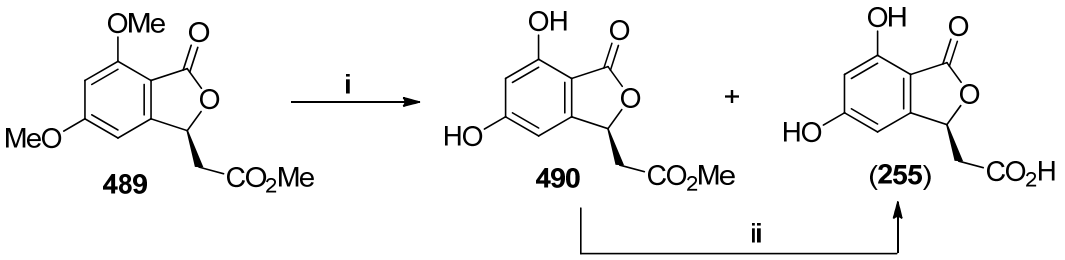
During the reaction, demethylation of two methoxy groups takes place liberating two polar phenolic groups in addition to the existing carboxylic acid group that renders the product (**255**) very polar. In order to facilitate purification and with the hope of monitoring the reaction easier, acid **488** was converted to methyl ester **489** (Scheme 183) using conc. sulfuric acid in methanol. The ^{1}H NMR spectrum of the product indicated the successful formation of methyl ester **489** as demonstrated by the additional OCH_3 group that resonated as a singlet at δ 3.74.



Reagents and conditions: i. H_2SO_4, MeOH, r.t., 12 h, 82%.

Scheme 183. Formation of methyl ester **489** from acid **488**.

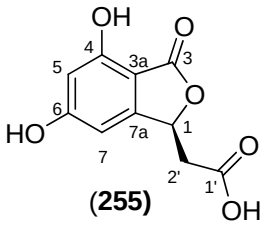
With methyl ester **489** in hand, it was exposed to boron tribromide in dichloromethane at 0 °C for 2 h. With no signs of products forming by TLC analysis, the temperature was raised to room temperature and the mixture stirred for a further 72 hours. Gratifyingly, demethylation with concomitant ester hydrolysis occurred delivering (−)-herbaric acid (**255**) in excellent overall yield along with a small quantity of herbaric acid methyl ester **490** in a 5:1 ratio favouring (**255**). The latter ester underwent facile saponification to provide further amounts of (**255**) (Scheme 184).



Reagents and conditions: i. BBr_3, CH_2Cl_2, 0 C, 2 h, then r.t. 72 h. (**255**):**490** = 5:1, 77%; ii. NaOH, MeOH·H_2O, 12 h, 85%.

Scheme 184. Synthesis of the reported structure of (−)-herbaric acid (**255**).

Comparison of the ^{1}H and ^{13}C spectra of synthetic (**255**) (d_6-DMSO) with the spectroscopic data supplied[128] for natural herbaric acid clearly showed several significant differences (Table 25).



Assignment	Natural Herbaric Acid ^{13}C-NMR [ppm] 400 MHz in d_4-methanol	Synthesised Herbaric Acid (**255**) ^{13}C-NMR [ppm] 400 MHz in d_6-DMSO
C-1′	173.0	172.1
C-3	171.4	168.2
C-4	167.1	165.3
C-6	159.7	158.6
C-7a	154.8	154.6
C-3a	104.5	103.2

C-5	103.9	103.0
C-7	101.7	101.0
C-1	78.2	77.0
C-2′	40.4	obscured by d_6-DMSO

Table 25. Comparison of ^{1}C-NMR for natural herbaric acid and synthetic herbaric acid (**255**) prepared herein.

After some initial confusion, communication with the authors of the isolation paper confirmed that the solvent used to collect the NMR data of natural herbaric acid was in fact d_4-methanol and not d_6-DMSO as stated in the original report.[128] Disappointingly, our synthetic sample of (**255**) was not sufficiently soluble in d_4-methanol to obtain anything other than a poor quality ^{1}H NMR spectrum.

Nevertheless, we were confident our synthetic sample was indeed (−)-herbaric acid (**255**) and there is a subtle difference between the synthetic and natural samples that is contributing to their respective solubility. Unfortunately, the researchers who isolated herbaric acid (**255**) no longer have any natural material remaining for direct comparison with our synthetic material.

Next we set out to assign the absolute configuration of (−)-herbaric acid (**255**). The optical rotations of our synthetic sample (84% e.e.) $[\alpha]_D^{20}$ –21.7 (*c* 0.18, MeOH) and the reported value[128] for natural (**255**) $[\alpha]_D^{20}$ –27.0 (*c* 0.18, MeOH) were in good agreement (Table 26). It was therefore concluded the (−)-herbaric acid possesses (*S*)-stereochemistry.

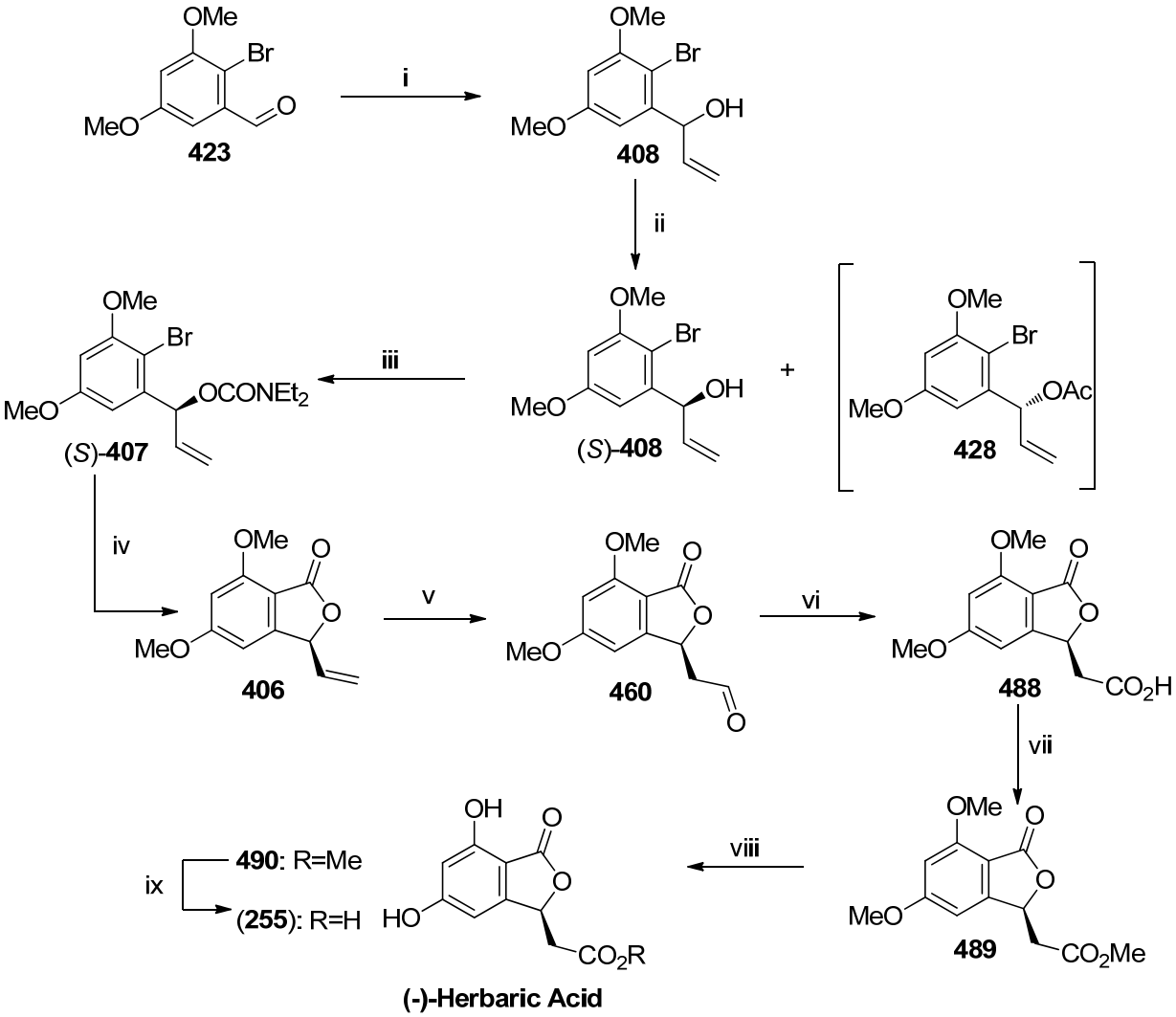
	Synthesised Herbaric Acid	**Natural Herbaric**

	(255) (84% e.e.)	**Acid**
$[\alpha]_D^{20}$	–21.7 (*c* 0.18, MeOH)	–27.0 (*c* 0.18, MeOH)

Table 26. Comparison of optical rotations for synthetic herbaric acid (**255**) prepared herein and natural herbaric acid.

5.2.4 Summary and Conclusions

The first synthesis and the structural assignment of (−)-herbaric acid (**255**) was accomplished. This was achieved *via* heteroatom-directed Wacker oxidation on vinylphthalide **406** to form aldehyde **460**. Aldehyde **460** underwent smooth oxidation with Oxone® affording acid **488** which underwent facile methyl ester formation to facilitate purification, thus delivering enantioenriched lactone ester **489**. Smooth demethylation with concomitant ester hydrolysis was effected by boron tribromide to give (−)-herbaric acid (**255**) (Scheme 185). The realisation of this entirely regioselective anti-Markovnikov addition of water during the Wacker oxidation provides a mild alternative to hydroboration/oxidation protocols that are traditionally used for terminal alkenes.



Reagents and conditions: i. vinylmagnesium bromide, THF, -78 °C, 12 h., 85%; ii. *p*-chlorophenyl acetate, Novozyme 435®, toluene, 55 °C, 48 h, 50%, 84% e.e; iii. CDI, $HNEt_2$, CH_2Cl_2, 24 h, 90%; iv. a) *n*-BuLi, THF, -78 °C, 1 h; b) anhydrous HCl (1 M), dioxane, 12 h, 74% over two steps; v. $PdCl_2$, CuCl, O_2, DMF/H_2O (3:1), r.t., 2 h, 86%; vi. Oxone, DMF, r.t., 6 h, 89%; vii. H_2SO_4, MeOH, r.t., 12 h, 82%; viii. BBr_3, CH_2Cl_2, 0 °C, 2 h, then r.t. 72 h. (**255**):**490** = 5:1, 77%; ix. NaOH, MeOH·H_2O, 12 h, 85%.

Scheme 185. Synthesis of (−)-herbaric Acid (**255**).

Chapter Six

Experimental

6.1 General Details

All reactions were carried out in flame or oven dried glassware under a dry nitrogen or argon atmosphere. Diethyl ether (Et_2O), dioxane and tetrahydrofuran (THF) were freshly distilled over sodium/benzophenone. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2), ethanol (EtOH) and toluene were freshly distilled from calcium hydride. Acetone ($(CH_3)_2CO$) was freshly distilled from calcium chloride. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were freshly distilled from molecular sieves (Linde type 4 Å). Reactions performed at low temperature were either cooled with an acetone–dry ice bath to reach –78 °C or using a water–ice bath to reach 0 °C. Flash chromatography was carried out using 0.063 – 0.1 mm Riedel-de-Häen silica gel with the denoted solvent.

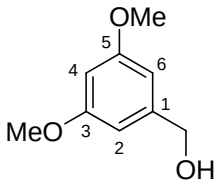
Thin-layer chromatography (TLC) was carried out using E. Merck silica gel plates using UV light as the visualising agent and/or developed using an ethanolic solution of vanillin or ammonium molybdate and cerium sulfate in aqueous sulfuric acid. Optical rotations were measured with a Perkin Elmer 341 polarimeter, using the sodium-D line (589 nm), with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum 1000 FT-IR spectrometer with the absorption peaks expressed in wavenumbers (cm^{-1}) and recorded using a range of 450 to 4000 cm^{-1}. NMR spectra were recorded in $CDCl_3$ on either a Bruker BRX300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei or a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported as parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the solvent in which the sample was analysed ($CDCl_3$: δ 7.26 for ^1H NMR, δ 77.0 for ^{13}C NMR) and coupling constants (J) are reported in hertz (Hz) to the nearest 0.1 ppm. ^1H NMR data is reported as chemical shift in ppm, followed by multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad), relative integral, coupling

constants where applicable, and assignment. Infrared (IR) spectra were recorded as a thin film between NaCl plates or a composite of zinc selenide and diamond crystal on a FT-IR System transform spectrometer. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained using a VG70SE spectrometer operating at a nominal accelerating voltage of 70 eV.

6.2 Experimental Procedures

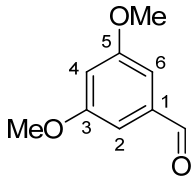
6.2.1 Synthesis of Phthalide-alcohol 352

3,5-Dimethoxybenzyl alcohol 357



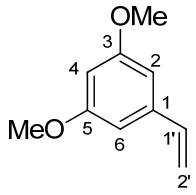
A mixture of 3,5-dimethoxybenzoic acid **351** (20 g, 0.11 mol) in THF (250 mL) was added dropwise to a suspension of $LiAlH_4$ (6.27 g, 0.17 mol) in THF (150 mL) at r.t. After addition was complete the mixture was refluxed for 5 h. The reaction mixture was cooled to 0 ^oC and quenched with H_2O (160 mL). After H_2 generation was complete the precipitate was dissolved in 33% H_2SO_4 (400 mL). Brine (600 mL) and CH_2Cl_2 (900 mL) were added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 600 mL) and the combined organic layers were washed with brine (400 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield the crude *title compound* **357** as a brown solid. This was used without further purification in the synthesis of compound **36**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.64 (1 H, br s, O*H*), 3.80 (6 H, s, OCH_3), 4.64 (2 H, s, CH_2OH), 6.39 (1 H, t, *J* 2.3 Hz, 4-H), 6.53 (2 H, d, *J* 2.3 Hz, 2-H and 6-H). The ^{1}H NMR data were in agreement with the literature.[260]

3,5-Dimethoxybenzaldehyde 299



DMSO (15.6 mL, 220 mmol) in CH_2Cl_2 (17 mL) was added to a solution of oxalyl chloride (9.4 mL, 110 mmol) in CH_2Cl_2 (350 mL) cooled to -78 ^oC. The reaction mixture was stirred for 30 min before alcohol **357** (16.8 g, 100 mmol) was added. After 1 h, triethylamine (69.2 mL, 500 mmol) was added. The reaction was warmed to r.t. and stirred for 5 h. H_2O (450 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 200 mL). The combined organic layers were washed with 1 M aq. HCl (2 × 100 mL), sat. aq. $NaHCO_3$ (2 × 100 mL), brine (80 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo*. The product was purified by recrystallisation from hexanes/Et_2O (3:4) at 4 ^oC to yield the *title compound* **299** (15.32 g, 84% over 2 steps) as an off-white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.84 (6 H, s, OC*H*$_3$), 6.70 (1 H, t, *J* 2.4 Hz, 4-H), 7.01 (2 H, d, *J* 2.4 Hz, 2-H and 6-H), 9.90 (1 H, s, C*H*O). The ^{1}H NMR data were in agreement with the literature.[260]

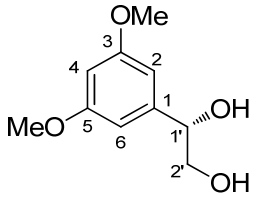
3,5-Dimethoxystyrene 356



Acetyl chloride (0.97 mL, 13.5 mmol) was added dropwise to a stirred suspension of zinc powder (15.0 g, 229 mmol) in DMF (50 mL) heated to 50 ^oC. The yellow/green suspension was stirred for a further 15 min before a solution of recrystallised 3,5-dimethoxybenzaldehyde **299** (10 g, 60.2 mmol) in dibromomethane (15.7 g, 90.3 mmol) was added dropwise over 20 min. The mixture was stirred at 50 ^oC for 30 min before cooling to 0 ^oC. A solution of sat. aq. NH_4Cl (50 mL) and Et_2O (50 mL) was added. The insoluble material was removed by filtration and washed well with Et_2O. The layers of the filtrate were separated and the aqueous

layer extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 10% aq. HCl (100 mL), H_2O (100 mL), 1 M NaOH (10 mL), brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resultant brown oil was purified by flash column chromatography using hexanes/CH_2Cl_2 (7:3) as eluent to yield the *title compound* **356** (7.26 g, 74%) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.82 (6 H, s, OCH_3), 5.27 (1 H, d, *J* 10.8 Hz, 2′-H_α), 5.75 (1 H, d, *J* 17.7 Hz, 2′H-$_\beta$), 6.41 (1 H, t, *J* 2.4, 4-H), 6.59 (2 H, d, *J* 2.4, 2-H and 6-H), 6.67 (1 H, dd, *J* 17.7, 10.8, 1′-H). The ^{1}H NMR data were in agreement with the literature.[157]

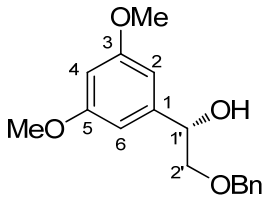
(*S*)-1′-(3,5-Dimethoxyphenyl)ethane-1′,2′-diol 355



A solution of K_3FeCN_6 (31.7 g, 96.3 mmol), K_2CO_3 (13.3 g, 96.3 mmol), $(DHQ)_2PHAL$ (500 mg, 0.6 mmol), methanesulfonamide (3.05 g, 32.1 mmol) and OsO_4 (3.26 g, 2.5% wt in *t*-BuOH, 0.3 mmol) in *t*-BuOH:H_2O (1:1, 300 mL) was stirred for 2 h at r.t. The mixture was cooled to 0 ^{o}C before addition of styrene **356** (5.27 g, 32.1 mmol). The reaction mixture was stirred for a further 4.5 h, slowly warming to r.t. The reaction was quenched with the addition of solid sodium sulfite (4 g) before extracting with EtOAc (3 × 150 mL). The combined organic layers were washed with H_2O (150 mL), brine (150 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was flashed through a short plug of silica using hexanes/EtOAc (30% EtOAc → 90%) in order to remove the $(DHQ)_2PHAL$, which was recovered from the silica by flushing the plug of silica using 10% NH_3 in MeOH as eluent. The solvent was removed *in vacuo* and the residue purified *via* flash column chromatography, using hexanes/EtOAc (1:1) as eluent to yield the *title compound* **355** (6.30 g, 99%, >96% e.e.) as a yellow oil. $\mathbf{[\alpha]_D}^{20}$ = +32.6 (*c* = 6.2, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.64 (1 H, br s, O*H*), 3.11 (1 H, br s, O*H*), 3.63-3.70 (2 H, m, 2′-H), 3.77 (6 H, s, OCH_3), 4.72 (1 H, dd, *J*

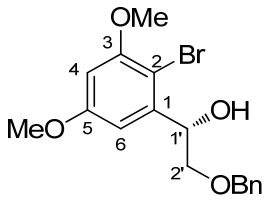
8.1, 3.3 Hz, 1′-H), 6.38 (1 H, t, *J* 2.1 Hz, 4-H), 6.50 (2 H, d, *J* 2.1 Hz, 2-H and 6-H). The ^{1}H NMR data were in agreement with the literature.[156]

(*S*)-2′-(Benzyloxy)-1′-(3,5-dimethoxyphenyl)ethanol 354



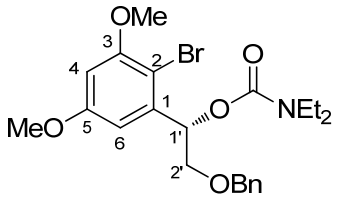
A solution of diol **355** (4 g, 20.2 mmol) in toluene (160 mL) was treated with *n*Bu_2SnO (5.03 g, 20.2 mmol) and the mixture was heated to reflux for 3 h with removal of H_2O *via* a Dean-Stark apparatus. The mixture was cooled to 70 ^{o}C and benzyl bromide (3.6 mL, 30.3 mmol) followed by tetrabutylammonium iodide (3.73 g, 10.1 mmol) was added and the mixture stirred at 70 ^{o}C for 2 h. The mixture was cooled to r.t., washed with H_2O (2 × 100 mL), brine (200 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash column chromatography using hexanes/EtOAc (3:1) as eluent to yield the *title compound* **354** (4.28 g, 74%) as a yellow oil. **$[\alpha]_D^{20}$** = +30.8 (*c* = 7.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.86 (1 H, br d, *J* 6.7 Hz, O*H*), 3.49 (1 H, t, *J* 8.8 Hz, 2′-H_α), 3.63 (1 H, dd, *J* 10.0, 2.9 Hz, 2′-H_β), 3.77 (6 H, s, OCH_3), 4.59 (2 H, d, *J* 3.0 Hz, OCH_2Ph), 4.86 (1 H, dt, *J* 8.8, 2.9 Hz, 1′-H), 6.39 (1 H, t, *J* 4.7 Hz, 4-H), 6.54 (2 H, d, *J* 2.3 Hz, 2-H and 6-H), 7.30-7.31 (5 H, m, Ar-*H*). The ^{1}H NMR data were in agreement with the literature.[156]

(*S*)-2-(Benzyloxy)-1-(2-bromo-3,5-dimethoxyphenyl)ethanol 359



To a stirred solution of protected diol **354** (1 g, 3.5 mmol) in Et_2O (20 mL) was added *N*-bromosuccinimide (680 mg, 3.8 mmol) and ammonium acetate (27 mg, 0.35 mmol) and the mixture was stirred at r.t. for 36 h. The solution was filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to yield the *title compound* **359** (1.23 g, 97%) as a pale yellow oil. $[\alpha]_D^{20}$ = +43.4 (*c* = 6.8, $CHCl_3$); **IR:** ν_{max}(neat) 3454, 2938, 1734, 1587, 1453, 1324, 1240, 1198, 1159, 1045 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.97 (1 H, br s, O*H*), 3.36 (1 H, dd, *J* 10.1, 8.9 Hz, 2′-H_α), 3.79 (1 H, dd, *J* 10.1, 2.6 Hz, 2′-H_β), 3.81 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.62 (2 H, d, *J* 8.9 Hz, OCH_2Ph), 5.34 (1 H, dd, *J* 8.9, 2.7 Hz, 1′-H), 6.42 (1 H, d, *J* 2.7 Hz, 4-H), 6.83 (1 H, d, *J* 2.7 Hz, 6-H), 7.29-7.36 (5 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.5 (CH_3, OCH_3), 56.3 (CH_3, OCH_3), 71.9 (CH, C-1′), 73.2 (CH_2, OCH_2Ph), 73.8 (CH_2, C-2′), 99.3 (CH, C-4), 102.2 (C, C-2), 103.6 (CH, C-6), 127.8, 128.0, 128.5 (CH, Ar-*C*H), 137.8 (C, Bn), 141.2 (C, C-1), 156.3 (C, C-3), 160.0 (C, C-5); ***m/z*** (EI, %) 366 (M^+, 6), 335 (2), 245, (18), 179 (12), 166 (15), 138 (24), 91 (100), 77 (18), 65 (19); **HRMS** Found (EI): M^+, 366.0463, $C_{17}H_{19}BrO_4$ requires 366.0467.

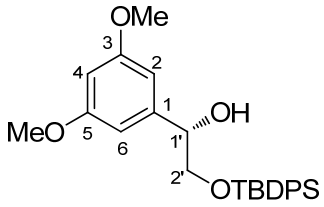
(*S*)-2-(Benzyloxy)-1-(2-bromo-3,5-dimethoxyphenyl)ethyl diethylcarbamate 353



NaH (504 mg, 60% dispersion in mineral oil, 12.6 mmol) was washed under argon with distilled hexanes (2 × 7 mL) and DMF (7 mL) before suspending in DMF (20 mL) and cooling to 0 ^oC. A solution of the bromoalcohol **359** (1.85 g, 5.04 mmol) in DMF (20 mL) was added dropwise and the mixture stirred for 20 min to ensure H_2 evolution had ceased. *N,N*-diethylcarbamyl chloride (1.0 mL, 7.56 mmol) was added and the mixture was warmed to r.t. and stirred overnight. The reaction mixture was cooled to 0 ^oC and MeOH (ca. 6 mL) (enough for the cloudy solution to go transparent) was added slowly. The reaction was diluted with CH_2Cl_2 (40 mL), washed with H_2O (3 × 40 mL) and brine (40 mL) and dried over

$MgSO_4$. The solvent was removed *in vacuo* and the resultant orange oil was purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to yield the *title compound* **353** (2.16 g, 92%) as a colourless oil. $[\alpha]_D^{20}$ = +13.8 (*c* = 6.5, $CHCl_3$); **IR:** ν_{max}(neat) 2971, 1697, 1585, 1453, 1419, 1325, 1270, 1200, 1061 cm^{-1}; **^{1}H NMR** (300 MHz, DMSO-$_{d6}$; 60 ^oC): δ 1.11 (6 H, m, $N(CH_2CH_3)_2$), 3.29 (4 H, t, m, $N(CH_2CH_3)_2$), 3.77 (2 H, m, 2′-H), 3.78 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.56 (2 H, d, *J* 6.5 Hz, OCH_2Ph), 6.15 (1 H, dd, *J* 6.5, 2.7 Hz, 1′-H), 6.58 (1 H, d, *J* 2.7 Hz, 4-H), 6.65 (1 H, d, *J* 2.7 Hz, 6-H), 7.27-7.33 (5 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, DMSO-$_{d6}$; 60 ^oC): 13.3 (2 × CH_3, NCH_2CH_3), 40.8 (2 × CH_2, NCH_2CH_3), 55.1 (CH_3, OCH_3), 56.2 (CH_3, OCH_3), 70.9 (CH, C-1′), 71.8 (CH_2, OCH_2Ph), 73.7 (CH_2, C-2′), 99.0 (CH, C-4), 101.3 (C, C-2), 104.6 (CH, C-6), 126.9, 126.9, 127.7 (CH, Ar-*C*H), 137.8 (C, Bn), 139.0 (C, C-1), 153.6 (C, C=O), 156.0 (C, C-3), 159.4 (C, C-5); ***m/z*** (EI, %) 465 (M^+, 2), 386 (23), 280 (2), 242 (8), 179 (2), 164 (5), 118 (6), 105 (9), 100 (75), 91 (100), 77 (11), 72 (16), 65 (13); **HRMS** Found (EI): M^+, 465.1149, $C_{22}H_{28}BrNO_5$ requires 465.1151.

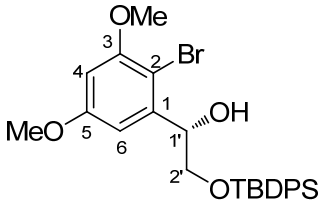
(*S*)-2′-(*tert*-Butyldiphenylsilyloxy)-1′-(3,5-dimethoxyphenyl)ethanol 371



To a stirred solution of diol **355** (2.0 g, 10.1 mmol) in THF (100 mL) was added imidazole (0.83 g, 12.1 mmol) and *t*-butyldiphenylsilyl chloride (2.78 mL, 10.1 mmol) and the mixture stirred overnight at r.t. The reaction mixture was diluted with H_2O (300 mL) and Et_2O (300 mL) and organic phase was separated. The aqueous phase was further extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed *in vacuo* and purified by flash chromatography hexanes/EtOAc (1:1) to afford the title compound **371** (3.9 g, 89%) as a yellow oil. $[\alpha]_D^{20}$ = -7.89 (*c* = 0.38, $CHCl_3$); **IR:** ν_{max}(neat): 3460, 2932, 2858, 2248, 1597, 1462, 1427, 1204, 1153, 1110, 1062, 908 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.08 (9 H, s, $SiC(CH_3)_3$, 3.11 (1 H, br s, O*H*), 3.69 (6 H, s, OCH_3), 3.81 (2 H, m, 2′-

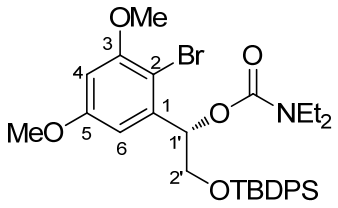
H), 4.73 (1 H, t, *J* 2.7 Hz, 1′-H), 6.34 (1 H, t, *J* 2.4 Hz, 4-H), 6.44 (2 H, d, *J* 2.4 Hz, 2-H and 6-H), 7.31-7.67 (10 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.1 (CH_3, SiC(CH_3)$_3$), 26.7 (C, SiC(CH_3)$_3$), 55.1 (CH_3 × 2, OCH_3), 69.4 (CH_2, C-2′), 74.3 (CH, C-1′), 99.7 (CH, C-4), 103.9 (CH × 2, C-2 and C-6), 133.0 (C, Si-*C*), 132.8 (C, Si-*C*), 127.7, 127.7, 129.7, 129.8, 135.4 (CH, Ar-*C*H), 142.8 (C, C-1), 160.6 (C × 2, C-3 and C-5); ***m/z*** (EI, %) 459 (M^+ + Na, 100), 419 (30), 319 (3), 202 (5); **HRMS** Found (EI): $(M + Na)^+$, 459.1969, $C_{26}H_{32}NaO_4Si$ requires 459.1962.

(*S*)-1-(2-Bromo-3,5-dimethoxyphenyl)-2′-((*tert*-butyldiphenylsilyl)oxy)ethanol 372



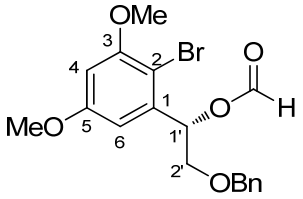
To a stirred solution of protected diol **371** (1.0 g, 3.5 mmol), in Et_2O (20 mL) was added *N*-bromosuccinimide (680 mg, 3.8 mmol) and ammonium acetate (27 mg, 0.35 mmol) and the mixture was stirred at r.t. for 36 h. The solution was filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to yield the *title compound* **372** (1.23 g, 97%) as a pale yellow oil. $[\alpha]_D^{20}$ = +3.70 (*c* = 0.54, $CHCl_3$); **IR** ν_{max}(neat): 3564, 2931, 2857, 2248, 1588, 1454, 1427, 1327, 1160, 1112, 1055, 906, 730, 701 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (9 H, s, SiC(CH_3)$_3$), 3.34 (1 H, br s, O*H*), 3.82 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.12 (2 H, m, 2′-H), 5.30 (1 H, t, *J* 5.4 Hz, 1′-H), 6.48 (1 H, d, *J* 3.0 Hz, 4-H), 6.90 (1 H, d, *J* 3.0 Hz, 6-H), 7.26-7.69 (5 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.3 (CH_3, SiC(CH_3)$_3$), 27.0 (C, SiC(CH_3)$_3$), 55.5 (CH_3, OCH_3), 56.3 (CH_3, OCH_3), 67.5 (CH_2, C-2′), 73.6 (CH, C-1′), 99.4 (CH, C-4), 102.3 (CH, C-2), 103.8 (CH, C-6), 133.0 (C, Si-*C*), 133.1 (C, Si-*C*), 127.9, 127.9, 129.9, 130.0, 135.6, 135.7 (CH, Ar-*C*H), 141.3 (C, C-1), 156.3 (C, C-3), 159.9 (C, C-5); ***m/z*** (EI, %) 537 (M^+ + Na, 100), 534 (74), 532, (72), 497 (32), 439 (28), 360 (8), 277 (6), 202 (16), 130 (2); **HRMS** Found (EI): $(M + Na)^+$, 537.1050, $C_{26}H_{31}BrNaO_4Si$ requires 537.1067.

(*S*)-1′-(2-Bromo-3,5-dimethoxyphenyl)-2′-(*tert*-butyldiphenylsilyloxy)ethyl diethylcarbamate 373



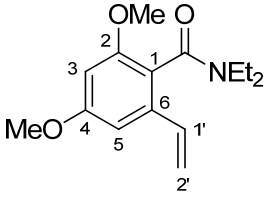
A solution of bromoalcohol **372** (1.0 g, 1.95 mmol) in CH_2Cl_2 (50 mL) was added *N*,*N*'-carbonyldiimidazole (1.14 g, 7.0 mmol) and stirred at r.t. for 2 h. Diethylamine (0.40 mL, 3.9 mmol) was added dropwise to the mixture and was stirred for 48 h. The reaction was diluted with CH_2Cl_2 (40 mL), washed with NH_4Cl (3 × 40 mL) and brine (40 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resultant orange oil was purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to yield the *title compound* **373** (1.1 g, 1.79 mmol, 92%) as a colourless oil. $[\alpha]_D^{20}$ = -19.1 (*c* = 1.10, $CHCl_3$); **IR** ν_{max}(neat): 2862, 1580, 1482, 1448, 1350, 1056, 971, 745, 695 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, 60 °C): δ 1.04 (9 H, s, SiC(CH_3)$_3$, 1.15 (6 H, s br, N(CH_2CH_3)$_2$), 3.42 (4 H, s br, N(CH_2CH_3)$_2$), 3.76 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.00 (2 H, m, 2′-H), 6.27 (1 H, dd, *J* 3.0, 3.3 Hz, 1′-H), 6.42 (1 H, d, *J* 2.7 Hz, 4-H), 6.63 (1 H, d, *J* 2.7 Hz, 6-H), 7.31-7.56 (10 H, m, Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$, 60 °C): δ 13.5 (CH_3, NCH_2CH_3), 14.3 (CH_3, NCH_2CH_3), 19.1 (C, SiC(CH_3)$_3$), 26.6 (CH_3, SiC(CH_3)$_3$), 41.3 (CH_2, NCH_2CH_3), 41.9 (CH_2, NCH_2CH_3), 55.2 (CH_3, OCH_3), 56.2 (CH_3, OCH_3), 65.2 (CH_2, C-2′), 76.3 (CH, C-1′), 98.9 (CH, C-4), 102.6 (CH, C-2), 104.5 (CH, C-6), 133.1 (C, Si-*C*), 133.3 (C, Si-*C*), 127.5, 127.6, 129.5, 129.6, 135.4, 135.6 (CH, Ar-*C*H), 139.7 (C, C-1), 154.9 (C, C=O), 156.4 (C, C-3), 159.5 (C, C-5); ***m/z*** (EI, %) 614 (MH^+, 45), 499 (18); **HRMS** Found (EI): MH^+, 614.1917, $C_{31}H_{41}BrNO_5Si$ requires 614.1917.

(*S*)-2′-(Benzyloxy)-1′-(2-bromo-3,5-dimethoxyphenyl)ethyl formate 379



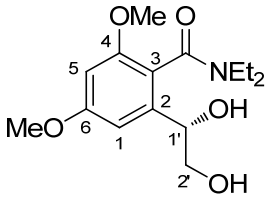
To a solution of bromoalcohol **359** (100 mg, 0.27 mmol) in CH_2Cl_2 (9 mL) was added formic acid (0.07 mL, 1.76 mmol). The reaction mixture was cooled to 0 ^oC under nitrogen. DMAP (5 mg, 0.04 mmol) was added and the reaction stirred for 2 min before DCC (72.2 mg, 0.35 mmol) was added. The reaction mixture at 0 ^oC for 15 min before warming to r.t. and stirring for a further 24 h. TLC analysis of the reaction mixture indicated that only starting material was present therefore the above procedure was repeated (addition of formic acid (0.07 mL), cooling to 0 ^oC followed by addition of DMAP and DCC). The reaction was stirred for a further 24 h at r.t. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography using hexanes/EtOAc (3:1) as eluent to yield the *title compound* **379** (68.3 mg, 64%) as a colourless oil. **IR:** ν_{max}(neat) 2937, 1723, 1588, 1453, 1353, 1326, 1201, 1159, 1074, 1021 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.70 (1 H, d, *J* 7.8 Hz, 2′-H_α), 3.73 (1 H, d, *J* 8.4 Hz, 2′-H_β), 3.79 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.60 (2 H, m, OCH_2Ph), 6.44 (1 H, d, *J* 2.7 Hz, 4-H), 6.49 (1 H, dd, *J* 10.9, 2.8 Hz, 1′-H), 6.61 (1 H, d, *J* 3.0 Hz, 6-H), 7.29-7.33 (5 H, m, Ar-*H*), 8.01 (1 H s, C*H*O); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.6 (CH_3, OCH_3), 56.4 (CH_3, OCH_3), 71.2 (CH, C-1′), 73.0 (CH_2, OCH_2Ph), 73.8 (CH_2, C-2′), 99.5 (CH, C-4), 102.5 (C, C-2), 104.1 (CH, C-6), 127.7, 127.7, 128.4 (CH, Ar-*C*H), 137.7 (C, Bn), 137.7 (C, C-1), 156.6 (C, C-3), 160.0 (C, C-5), 162.5 (C, C=O); ***m/z*** (EI, %) 394 (M^+, 5), 269 (15), 247 (26), 245 (30), 241 (18), 239 (8), 209 (16), 181 (15), 166 (21), 138 (36), 91 (100); **HRMS** Found (EI): M^+, 394.0415, $C_{18}H_{19}BrO_5$ requires 394.0411.

***N,N*-Diethyl-2,4-dimethoxy-6-vinylbenzamide 384**



Acetyl chloride (0.03 mL, 0.428 mmol) was added dropwise to a stirred suspension of zinc powder (0.47 g, 7.23 mmol) in DMF (5 mL) heated to 50 °C. The yellow/green suspension was stirred for a further 15 min before a solution of recrystallised 3,5-dimethoxybenzaldehyde **385** (0.5 g, 1.9 mmol) in dibromomethane (0.50 g, 2.85 mmol) was added dropwise over ca. 20 min. The mixture was stirred at 50 °C for 30 min before cooling to 0 °C. A solution of sat. aq. NH_4Cl (10 mL) and Et_2O (10 mL) was added. The insoluble material was removed by filtration and washed with Et_2O. The layers of the filtrate were separated and the aqueous layer extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with 10% HCl (10 mL), H_2O (10 mL), 1 M NaOH (5 mL), brine (5 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resultant brown oil was purified by flash column chromatography using hexanes/EtOAc (1:1) as eluent to yield the *title compound* **384** (0.41 g, 82%) as a colourless oil. **IR** ν_{max}(neat): 2972, 2935, 1622, 1598, 1573, 1425, 1315, 1201, 1153, 1084, 922, 833 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.98 (3 H, t, *J* 7.2 Hz, NCH_2CH_3), 1.24 (3 H, t, *J* 7.2 Hz, NCH_2CH_3), 3.07 (2 H, m, NCH_2CH_3), 3.46 (1 H, m, $NCH_{2\alpha}CH_3$), 3.65 (1 H, m, $NCH_{2\beta}CH_3$), 3.76 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 5.29 (1 H, d, *J* 10.8 Hz, 2′-H_α), 5.71 (1 H, d, *J* 17.2 Hz, 2′-H_β), 6.39 (1 H, d, *J* 2.0 Hz, 3-H), 6.63 (1 H, m, 1′-H), 6.68 (1 H, d, *J* 2.0 Hz, 5-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 12.3 (CH_3, NCH_2CH_3), 13.3 (CH_3, NCH_2CH_3), 38.3 (CH_2, NCH_2CH_3), 42.3 (CH_2, NCH_2CH_3), 54.9 (CH_3, OCH_3), 55.1 (CH_3, OCH_3), 97.6 (CH, C-3), 100.4 (CH, C-5), 115.9 (CH_2, C-2′), 118.5 (C, C-1), 133.2 (CH, C-1′), 135.7 (C, C-6), 156.2 (C, C-2), 160.2 (C, C-4), 167.3 (C, C=O); ***m/z*** (EI, %) 264 (MH^+, 86), 172 (12); **HRMS** Found (EI): MH^+, 264.1609, $C_{15}H_{22}NO_3$ requires 264.1594.

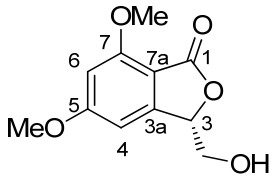
(*S*)-2-(1′,2′-Dihydroxyethyl)-*N*,*N*-diethyl-4,6-dimethoxybenzamide 383



A solution of K_3FeCN_6 (5.6 g, 17.1 mmol), K_2CO_3 (2.36 g, 17.1 mmol), $(DHQ)_2PHAL$ (0.084 mg, 0.11 mmol), methanesulfonamide (0.54 g, 5.7 mmol) and OsO_4 (0.014 g, 2.5% wt in *t*-

BuOH, 0.05 mmol) in *t*-BuOH:H_2O (1:1, 200 mL) was stirred for 2 h at rt. The mixture was cooled to 0 ^oC before addition of styrene **384** (1.5 g, 5.7 mmol). The reaction mixture was stirred for a further 4.5 h, slowly warming to r.t. The reaction was quenched with the addition of solid sodium sulfite (3.0 g) before extracting with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was flashed through a short plug of silica using hexanes/EtOAc (30% EtOAc → 90%) in order to remove the $(DHQ)_2PHAL$, which was recovered from the silica by flushing the plug of silica using 10% NH_3 in MeOH as eluent. The solvent was removed *in vacuo* and the crude residue was carried on to the next step without further purification.

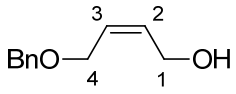
(*S*)-3-(Hydroxymethyl)-5,7-dimethoxyisobenzofuran-1(3H)-one 382



To a crude solution of alcohol **383** (0.3 g, 1.01 mmol) in a mixture of MeOH (10 mL), THF (3.3 mL), H_2O (1 mL) was added potassium hydroxide (0.06 g, 1.01 mmol). Mixture was stirred at r.t for 24h. The solvent was removed *in vacuo* and the residue purified *via* flash column chromatography, using hexanes/EtOAc (1:1) as eluent to yield the *title compound* **382** (0.13 g, 56% over 2 steps, 85% e.e.) as a white solid. **IR** ν_{max}(film): 3480, 2880, 1731, 1598, 1493, 1466, 1431, 1366, 1327, 1217, 1196, 1155, 1067, 1025, 994, 829, 770, 689, 689 cm^{-1}; **M.p.** = 164-166 ^oC; $[\alpha]_D^{20}$ = +5.95 (*c* = 0.84, $CHCl_3$, 85% ee); **^{1}H NMR** (400 MHz, DMSO-$_{d6}$): δ 3.65 (1 H, m, C$H_{2\alpha}$OH), 3.88 (1 H, m, C$H_{2\beta}$OH), 3.85 (6 H, s, 5-H and 7-H), 5.09 (1 H, t, *J* 5.7 Hz, O*H*), 5.35 (1 H, t, *J* 3.9 Hz, 3-H), 6.57 (1 H, d, *J* 1.8 Hz, 6-H), 6.73 (1 H, d, *J* 1.5 Hz, 4-H); **^{13}C NMR** (100 MHz, DMSO-$_{d6}$): δ 56.2 (CH_3, O*C*H_3), 56.5 (CH_3, O*C*H_3), 62.6 (CH_2, CH_2OH), 80.8 (CH, C-3), 99.3 (2 × CH, C-4 and C-6), 106.9 (C, C-7a), 153.0 (C, C-3a), 159.3 (C, C-7), 166.6 (C, C-5), 167.8 (C, C-1); ***m/z*** (EI, %) 224 (MH^+, 46%), 202 (58), 179 (4), 157 (3), 102 (7); **HRMS** Found (EI): MH^+, 225.0763, $C_{11}H_{13}O_5$ requires 225.0757.

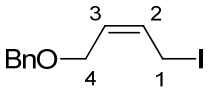
6.2.2 Model Study- Barbier-type Reaction (5.1.5.1)

(*Z*)-4-(Benzyloxy)but-2-en-1-ol 403



To a stirred solution of *cis*-butene-1,4-diol **402** (3.2 g, 36.5 mmol) in THF (20 mL) was carefully added sodium hydride (0.31 g, 12.8 mmol) at 0 °C. After being stirred for 1 h at r.t., benzyl bromide (1.47 mL, 12.2 mmol) was added, and the resulting mixture was stirred at 75 °C for 1 h. The reaction was then quenched at r.t. by the addition of sat. aq. NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography using hexanes/EtOAc 10:1 to 5:1 to 1:1 to afforded the *title compound* **403** (1.44 g, 79%) as pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.18 (2 H, d, *J* 4.2 Hz, 4-H), 4.23 (2 H, d, *J* 5.9 Hz, 1-H), 4.53 (2 H, s, C*H*$_2$OBn), 5.74-5.89 (2 H, m, 2-H and 3-H), 7.29-7.35 (5 H, m, Ar-*H*). The ^{1}H NMR data were in agreement with the literature.[261]

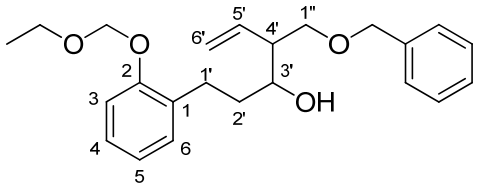
(*Z*)-((1-Iodobut-2-enyloxy)methyl)benzene 349



A solution of PPh_3 (0.98 g, 3.73 mmol) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C. To the resulting solution were added sequentially: imidazole (0.32 g, 4.75 mmol), iodine (1.03 g, 4.07 mmol), and a solution of alcohol **403** (0.51 g, 3.39 mmol) in CH_2Cl_2 (2.5 mL). The reaction was stirred at 0 °C, protected from light, for 30 min. The reaction was quenched by addition of 20% aq. $Na_2S_2O_3$ (15 mL) and CH_2Cl_2 (15 mL). The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using hexanes/EtOAc (2:1) as eluent to yield the *title compound* **349** (0.63 g, 65%) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.95 (2 H, d, *J* 4.2 Hz, 1-H), 3.99 (2 H, d, *J* 5.9 Hz, 4-H), 4.50 (2 H, s, C*H*$_2$OBn), 5.80-5.88 (1

H, m, 3-H), 5.98-6.09 (1 H, m, 2-H), 7.27-7.40 (5 H, m, Ar-*H*). The ^{1}H NMR data were in agreement with the literature.[262]

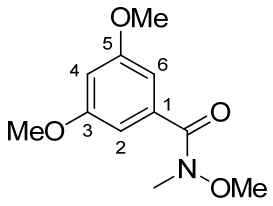
4'-(Benzyloxymethyl)-1′-(2-(ethoxymethoxy)phenyl)hex-5'-en-3'-ol 400



Indium (0.016 g, 0.14 mmol) was added to a vigorously stirred mixture of aldehyde **187a** (0.013 g, 0.06 mmol) and iodide **349** (0.04 g, 0.14 mmol) in DMF (0.6 mL) and H_2O (0.4 mL) at r.t. The reaction mixture was stirred for 3 days at r.t. H_2O (1 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL) and the organic extracts were washed with brine (2 × 5 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude products were purified by flash chromatography using hexane/EtOAc (7:3) as eluent to afford the *title compound* **400** (0.013 g, 55%) as a colourless oil. **IR** ν_{max}(film): 2862, 1586, 1491, 1226, 1099, 995, 917, 750, 696, 526 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.20 (3 H, t, *J* 7.2 Hz, OCH_2CH_3), 1.73 (2 H, m, 2′-H), 2.45 (1 H, m, 3′-H), 2.81 (2 H, m, 1′-H), 3.60 (2 H, m, 1′′-H), 3.65 (1 H, m, 4′-H), 3.70 (2 H, m, OCH_2CH_3), 4.89 (2 H, d, *J* 3.6 Hz, OCH_2Ph), 5.09 (2 H, m, 6′-H), 5.21 (2 H, s, OCH_2O), 5.57 (1H, m, 5′-H), 6.91-7.15 (4 H, Ar-*H*), 7.26-7.33 (5 H, OCH_2Ar-*H*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.2 (CH_3, OCH_2CH_3), 26.8 (CH_2, C-1′), 35.1 (CH_2, C-2′), 49.0 (CH, C-3′), 64.3 (CH_2, CH_3CH_2O), 71.8 (CH, C-4′), 72.4 (CH_2, C-1′′), 73.5 (CH_2, OCH_2Ph), 93.1 (CH_2, OCH_2O), 114.0 (CH, C-5), 118.0 (CH_2, C-6′), 121.7 (CH, C-3), 127.0, 127.6, 127.8 (CH, Ar-*C*H), 128.5 (CH, C-4), 130.2 (CH, C-6), 131.1 (C, C-1), 136.3 (CH, C-5′), 137.9 (C, OCH_2Ph), 155.1 (C, C-2); ***m/z*** (EI) 371 (M^+, 36%), 307 (3), 289 (2), 223 (19), 193 (5), 157 (2) and 133 (2); **HRMS** Found (EI): M^+, 371.2217, $C_{23}H_{31}O_4$ requires 371.2196.

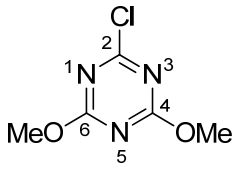
6.2.3 Revised Synthesis of Vinylphthalide 406 (5.1.6)

_N_-3,5-trimethoxy-_N_-methylbenzamide 410



To an ice cold solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (20.5 g, 0.12 mol) in THF (200 mL) was added *N*-methylmorpholine (30 mL, 0.27 mol) and 3,5-dimethoxybenzoic acid **351** (16.4 g, 0.09 mol). The mixture was warmed to r.t. and stirred for 5 h. *N,O*-dimethylhydroxylamine hydrochloride (8.78 g, 0.09 mol) was added and the reaction mixture was stirred for a further 15 h. The reaction was quenched with H_2O (150 mL) and extracted with Et_2O (2 × 400 mL). The combined organic layers were washed with sat. sodium carbonate solution (2 × 400 mL), 1M HCl (400 mL) and brine (300 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the *title compound* **410** (14.4 g, 72%) as a brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.32 (3 H, s, NC*H*$_3$), 3.57 (3 H, s, NOC*H*$_3$), 3.78 (6 H, s, OC*H*$_3$), 6.52 (1 H, t, *J* 2.4 Hz, 4-H), 6.77 (2 H, d, *J* 2.4 Hz, 2-H and 6-H). The ^{1}H NMR data were in agreement with the literature.[193]

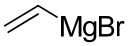
2 –Chloro-4,6-dimethoxy-1,3,5-triazine



To suspension of $NaHCO_3$ (86.5 g, 1.03 mol) in MeOH (170 mL) and H_2O (17 mL) cooled to 0 ^oC was added cyanuric chloride (62.7 mg, 0.34 mol). The mixture was heated to 35 ^oC and stirred for 21 h. H_2O (300 mL) was added and the mixture stirred for a further 30 min. The mixture was filtered and the filter cake washed with deionised H_2O before drying under vacuum at 35 ^oC to give the *title compound* (48.2 g, 80%) as a white solid. **M.p.** = 75-77 ^oC

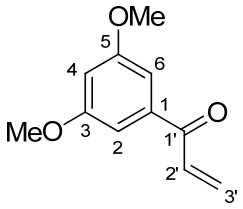
(lit.[263] 75-76 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.24 (6 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 56.0 (CH_3 × 2, O*C*H_3), 172.5 (C × 2, C-4 and C-6), 172.6 (C, C-2).

Vinylmagnesium bromide



Heat dried, mechanically activated magnesium turnings (4.71 g, 0.19 mol) were placed in a 3-necked flask equipped with stirrer bar, dry ice condenser, septum and a gas inlet adaptor connected to a measuring cylinder and dry ice condenser. THF (200 mL) was added to the flask with a crystal of iodine and the mixture was heated to 60 °C. Vinyl magnesium bromide (14.1 mL, 0.20 mol) was slowly added to the flask by controlled evaporation from the measuring cylinder (through the gas inlet adaptor). Once the reflux was complete the mixture was heated for a further 30 minutes before cooling to r.t.

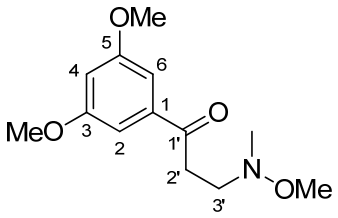
1-(3,5-Dimethoxyphenyl)prop-2-en-1-one 409



A solution of vinylmagnesium bromide (91.1 mL, 1 M in THF, 91.1 mol) was added dropwise to a solution of *N*-3,5-trimethoxy-*N*-methylbenzamide **410** (5.9 g, 26.0 mol) in THF (100 mL) cooled to -50 °C. The mixture was stirred at -50 °C overnight before quenching *via* the slow addition of 1M HCl (300 mL). The reaction mixture was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (150 mL), brine (150 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash column chromatography using hexanes/EtOAc (5:1) as eluent to afford the *title compound* **409** (3.69 g, 74%) as a yellow oil. **IR** ν_{max}(neat): 2925, 1673, 1609, 1447, 1403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.82 (6 H, s, OCH_3), 5.89 (1 H, dd, *J* 10.8, 1.8 Hz, 3′-H_α),

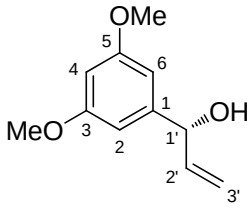
6.41 (1 H, dd, *J* 17.3, 1.8 Hz, 3′-H_β), 6.64 (1 H, t, *J* 2.4 Hz, 4-H), 7.06 (2 H, d, *J* 2.4 Hz, 2-H and 6-H), 7.08 (1 H, dd, *J* 17.3, 10.8 Hz, 2′-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.5 (2 × CH_3, O*C*H_3), 105.3 (CH, C-4), 106.4 (2 × CH, C-2 and C-6), 130.1 (*C*H_2, C-3′), 132.3 (CH, C-2′), 139.1 (C, C-1), 160.8 (2 × C, C-3 and C-5), 190.5 (C, C-1′); ***m/z*** (EI, %): 192 (M^+, 100), 165 (85), 161 (12), 149 (28), 137 (39), 122 (40), 107 (15), 77 (17), 63 (21), 55 (29); **HRMS** Found (EI): M^+, 192.0782, $C_{11}H_{12}O_3$ requires 192.0786.

1′-(3,5-Dimethoxyphenyl)-3′-(methoxy(methyl)amino)propan-1′-one 412



Side product from Grignard addition of **410**. **IR** ν_{max}(neat): 2910, 1633, 1619, 1540, 1447, 1403, 1046 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.59 (3 H, s, NCH_3), 3.03 (2 H, t, *J* 6.6 Hz, 3′-H), 3.17 (2 H, t, *J* 6.6 Hz, 2′-H), 3.45 (3 H, s, NOCH_3), 3.80 (6 H, s, OCH_3), 6.62 (1 H, t, *J* 2.1 Hz, 4-H), 7.08 (2 H, d, *J* 2.1 Hz, 2-H and 6-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 36.3 (CH_2, C-2′), 45.0 (CH_3, N*C*H_3), 55.5 (2 × CH_3, OCH_3), 55.5 (CH_2, C-3′), 60.0 (CH_3, NOCH_3), 105.1 (CH, C-4), 105.8 (2 × CH, C-2 and C-6), 138.9 (C, C-1), 160.8 (2 × C, C-3 and C-5), 198.6 (C, C-1′); ***m/z*** (EI, %): 253 (M^+, 3), 222 (23), 193 (11), 180 (15), 165 (100), 151 (4), 137 (16), 122 (15), 74 (72), 42 (26); **HRMS** Found (EI): M^+, 253.1309, $C_{13}H_{19}NO_4$ requires 253.1314.

(*R*)-1-(3,5-Dimethoxyphenyl)prop-2′-en-1′-ol 416



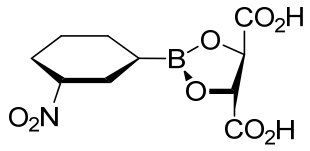
CBS Reduction

(*R*)-2-Metyl-CBS-oxazaborolidine reagent (714 mg, 2.57 mmol) in THF (4 mL) was added to BH_3-DMS (0.25 mL, 2.57 mmol) and stirred for 15 min at r.t. under nitrogen. The mixture was cooled to -20 ^oC and a solution of α,β-unsaturated ketone **409** (494 mg, 2.57 mmol) in THF (7.5 mL) was added dropwise. The solution was stirred at -20 ^oC, for 3 h then quenched by slow addition of MeOH (8.5 mL) and warmed to r.t. over 1 h. The solvent was removed *in vacuo* and the resultant yellow oil was purified by flash column chromatography using hexanes/EtOAc (3:1) as eluent to yield the *title compound* **416** (139 mg, 28%, e.e. 70%) as a yellow oil. $[\alpha]_D^{20}$ = +3.5 (*c* = 10.4, $CHCl_3$); **IR** ν_{max}(neat): 3431, 2961, 1594, 1457, 1427, 1293, 1202, 1149, 1057 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.35 (1 H, br s, O*H*), 3.77 (6 H, s OCH_3), 5.10 (1 H, d, *J* 6.0 Hz, 1′-H), 5.18 (1 H, dt, *J* 10.2, 1.2 Hz, 3′-H_α), 5.34 (1 H, dt, *J* 17.1, 1.2 Hz, 3′-H_β), 6.00 (1 H, m, 2′-H), 6.37 (1 H, t, *J* 2.3 Hz, 4-H), 6.52 (2 H, d, *J* 2.3 Hz, 2-H and 6-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.4 (2 × CH_3, O*C*H_3), 75.3 (CH, C-1′), 99.7 (CH, C-4), 104.1 (2 × CH, C-2 and C-6), 115.3 (CH_2, C-3′), 140.0 (C, C-2′), 145.2 (C, C-1), 160.9 (2 × C, C-3 and C-5); ***m/z*** (EI, %) 194 (M^+, 100), 177 (79), 165 (46), 163 (26), 151 (16), 139 (47), 91 (17), 77 (24), 55 (39) ; **HRMS** Found (EI): 194.0945, $C_{11}H_{14}O_3$ requires 194.0943.

(L)-TarB-NO_2 reduction

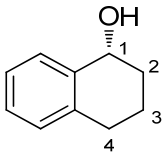
To a solution of (L)-TarB-NO_2 (2.6 mL, 0.4 M in THF, 1.04 mmol) was added to α,β-unsaturated ketone **409** (100 mg, 0.52 mmol) and the mixture was stirred for 30 min at r.t. $NaBH_4$ (39.3 mg, 1.04 mmol) was added and the mixture stirred for a further 3.5 h. The reaction was quenched with 10% aq. HCl (3 mL) until no further gas evolution was observed. The pH was adjusted to pH 12 using 2 M aq. NaOH solution and the mixture extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography using hexanes/EtOAc (3:1) as eluent yielding the *title compound* **416** (80.9 mg, 80%, 53% e.e.) as a yellow oil. $[\alpha]_D^{20}$ = -54.6 (*c* = 4.6, $CHCl_3$).

(L)-TarB-NO_2 418



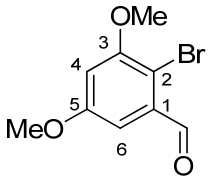
3-Nitrophenylboronic acid (1 g, 5.99 mmol), (L)-tartaric acid (900 mg, 5.99 mmol) and CaH_2 (49 mg, 1.20 mmol (should use excess CaH_2)) were dissolved in THF (15 mL). The reaction mixture was heated to reflux for 1 h before cooling to r.t., protecting from light and putting aside for future use.

(*R*)-1,2,3,4-Tetrahydronaphthalen-1-ol 419



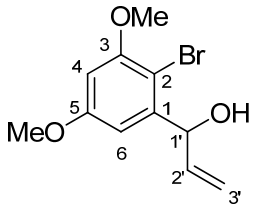
To a solution of (L)-TarB-NO_2 (6.85 mL, 0.4 M in THF, 2.74 mmol) was added α-tetralone **417** (200 mg, 1.37 mmol) and the mixture stirred at r.t. for 30 min. $NaBH_4$ (104 g, 2.74 mmol) was added and the mixture stirred for a further 3.5 h. The reaction was quenched with 1M aq. HCl (3 mL) until no further gas evolution was observed. Th pH was adjusted to pH 12 using 2 M aq. NaOH and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to yield the *title compound* **419** (200 mg, 98%, e.e. >96%) as a colourless oil. $\mathbf{[\alpha]_D^{20}}$ = -42.1 (*c* = 5.7, $CHCl_3$) (lit.[209] 96% e.e., $\mathbf{[\alpha]_D^{20}}$ = -37.0); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.27-2.05 (5 H, m, H-2, H-3 and O*H*), 2.70-2.87 (2 H, m, 4-H), 4.79 (1 H, t, *J* 5.1 Hz, 1-H), 7.09-7.13 (1 H, m, 5-H), 7.18-7.26 (2 H, m, 6-H and 7-H), 7.42-7.45 (1 H, m, 8-H). The ^{1}H NMR data were in agreement with the literature.[208, 209]

2-Bromo-3,5-dimethoxybenzaldehyde 423



3,5-dimethoxybenzaldehyde **299** (1.0 g, 6.02 mmol) was added acetic acid (5 mL) at 0 °C. A solution of bromine (320 μL, 6.25 mmol) in acetic acid (2 mL) was added dropwise to the cool reaction mixture. Once the addition was complete the ice bath was removed. After 5 min, the reaction had solidified and H_2O (10 mL) was added. The solid was collected by vacuum filtration and rinsed with H_2O. The solid was then dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and filtered through a plug of silica gel using CH_2Cl_2 as the eluent. The filtrate was concentrated *in vacuo* to afford a white solid consisting of both mono and dibrominated aldehydes. EtOAc (5 mL) was added to dissolve the solid. After standing at 5 °C, a white solid (the dibrominated aldehyde) had precipitated. The solid was separated from the liquid by vacuum filitration and the filtrate was concentrated *in vacuo* to yield the *title compound* **423** (1.09 g, 74%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.87 (3 H, s, OC*H*$_3$), 3.93 (3 H, s, OC*H*$_3$), 6.73 (1 H, d, *J* 2.7 Hz, 4-H), 7.06 (1 H, d, *J* 2.7 Hz, 6-H), 10.43 (1 H, s, C*H*O). The ^{1}H NMR data were in agreement with the literature.[264]

1′-(2-Bromo-3,5-dimethoxyphenyl)prop-2′-en-1′-ol 408

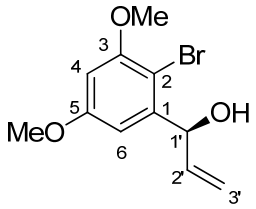


A solution of vinylmagnesium bromide (9.1 mL, 1 M in THF, 91.1 mmol) was added dropwise to a solution of **423** (5.9 g, 26.0 mol) in THF (10 mL) cooled to -78 ^{o}C. The mixture was

stirred at -78 °C overnight before quenching *via* the slow addition of 1M HCl (300 mL). The reaction mixture was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (150 mL) and brine (150 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash column chromatography using hexanes/EtOAc (5:1) as eluent to afford the *title compound* **408** (3.69 g, 74%) as a yellow oil; **IR** ν_{max}(film): 3398, 2938, 2839, 1584, 1452, 1417, 1321, 1198, 1157, 1019, 927, 836, 601 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.72 (1 H, br s, O*H*), 3.76 (3 H, s, OC*H*$_3$), 3.86 (3 H, s, OC*H*$_3$), 5.15 (1 H, dt, *J* 10.5, 1.5 Hz, 3′-H$_\alpha$), 5.34 (1 H, dt, *J* 17.4, 1.5 Hz, 3′-H$_\beta$), 5.59 (1 H, t, *J* 1.5 Hz, 1′-H), 5.96 (1 H, m, 2′-H), 6.36 (1 H, d, *J* 3.0 Hz, 4-H), 6.68 (1 H, d, *J* 3.0 Hz, 6-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.4 (CH_3, O*C*H$_3$), 56.2 (CH_3, O*C*H$_3$), 73.2 (CH, C-1′), 99.0 (CH, C-4), 102.7 (C, C-2), 103.5 (CH, C-6), 115.4 (CH_2, C-3′), 138.1 (CH, C-2′), 143.5 (C, C-1), 156.3 (C, C-3), 159.8 (C, C-5); ***m/z*** (EI) 295 (M^+, 21%), 273 (4), 257 (21), 190 (1), 176 (100),161 (2); **HRMS** Found (EI): M^+, 294.9927, $C_{11}H_{13}BrNaO_3$ requires 294.9940.

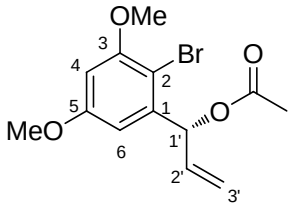
(*S*)-1′-(2-Bromo-3,5-dimethoxyphenyl)prop-2′-en-1′-ol 408 and

(*R*)-1′-(2-bromo-3,5-dimethoxyphenyl)allyl acetate 428



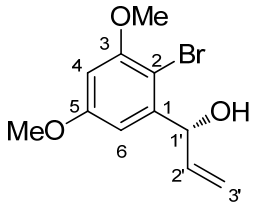
A mixture of alcohol **408** (2.0 g, 7.35 mmol) and *p*-chlorophenyl acetate **425** (2.5 g, 14.7 mmol) in toluene (50 mL) was flushed with argon for 1 min followed by the addition of Novozyme 435® (Sigma-Aldrich) (100 mg). The resulting mixture was stirred at 55 °C in a microwave reactor (single mode CEM Discover® Focused Microwave Synthesis System) at 300 W for 48 h. When the reaction was complete (as indicated by TLC analysis) the mixture was filtered through cotton wool to remove the enzyme and washed with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were concentrated *in vacuo* and the residue purified by flash chromatography using hexanes/EtOAc (9:1) as eluent to afford the *title compound* (*S*)-**408** (1.0

g, 50%, 84% e.e.) as a colourless oil. $[\alpha]_D^{19}$ = -33.3 (*c* 1.2, CH_2Cl_2); (spectroscopic data as described for **408**) and *title compound* **428** (1.04 g, 45%, 99% e.e.) as a yellow oil.



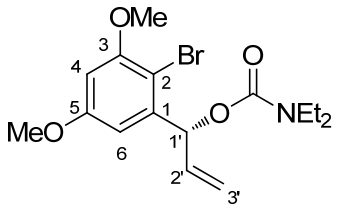
$[\alpha]_D^{19}$ = +17.7 (*c* 2.7, CH_2Cl_2); **IR** ν_{max}(film): 2941, 1740, 1586, 1454, 1323, 1223, 1161, 1020, 980, 605 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.12 (3 H, s, C*H*$_3$CO), 3.80 (3 H, s, OC*H*$_3$), 3.85 (3 H, s, OC*H*$_3$), 5.25 (2 H, m, 3′-H), 5.95 (1 H, m, 2′-H), 6.42 (1 H, d, *J* 2.8 Hz, 4-H), 6.58 (1 H, d, *J* 2.8 Hz, 6-H), 6.61 (1H, d, *J* 5.6 Hz, 1′-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 21.1 (CH_3, *C*H$_3$CO), 55.5 (CH_3, OC*H*$_3$), 56.4 (CH_3, OC*H*$_3$), 74.9 (CH, C-1′), 99.0 (CH, C-4), 103.4 (C, C-2), 104.4 (CH, C-6), 117.3 (CH_2, C-3′), 134.5 (CH, C-2′), 140.2 (C, C-1), 156.7 (C, C-3), 160.0 (C, C-5), 169.5 (C, C=O); ***m/z*** (EI) 315 (M^+, 34%), 257 (50), 257 (21), 176 (100), 161 (2); **HRMS** found (EI): M^+, 315.0226, $C_{13}H_{16}BrO_4$ requires 315.0219.

(*R*)-1′-(2-Bromo-3,5-dimethoxyphenyl)prop-2′-en-1′-ol 408



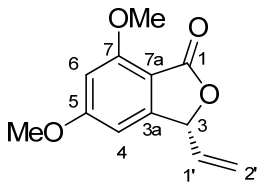
A solution of **428** (2.0 g, 6.37 mmol) in MeOH (10 mL) was added potassium hydroxide (0.43 g, 7.64 mmol). The resulting mixture was stirred at r.t. for 12 h for 48 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography using hexanes/EtOAc (9:1) as eluent to afford the *title compounds* (*R*)-**408** (1.6 g, 87%) as a colourless oil. $[\alpha]_D^{19}$ = +35.6 (*c* 1.1, CH_2Cl_2); spectroscopic data as described for (*S*)-**408**.

(*R*)-1′-(2-Bromo-3,5-dimethoxyphenyl)allyl diethylcarbamate 407



Solution of alcohol (*R*)-**408** (0.75 g, 2.76 mmol) in CH_2Cl_2 (100 mL) was added *N*,*N*'-carbonyldiimidazole (1.64 g, 10.1 mmol). The mixture was stirred at r.t. for 1 h, then diethylamine (0.57 mL, 5.51 mmol) was added dropwise. The reaction was stirred for a further 24 h. The reaction mixture was washed with H_2O (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using hexane/EtOAc (4:1) as eluent to give the *title compound* (*R*)-**407** as a colourless oil (0.92 g, 90%). $[\alpha]_D^{19}$ = +6.41 (*c* 1.5, CH_2Cl_2); **IR** ν_{max}(neat): 2972, 1698, 1587, 1454, 1418, 1323, 1269, 1200, 1058, 995, 766 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.01 (3 H, br s, NCH_2CH_3), 1.11 (3 H, br s, NCH_2CH_3), 3.22 (2 H, br s, NCH_2CH_3), 3.26 (2 H, br s, NCH_2CH_3), 3.68 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 5.15 (2 H, m, 3′-H), 5.91 (1 H, m, 2′-H), 6.32 (1 H, d, *J* 2.8 Hz, 4-H), 6.47 (1 H, d, *J* 1.6 Hz, 1′-H), 6.49 (1 H, t, *J* 2.8 Hz, 6-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.0 (CH_3, NCH_2CH_3), 13.8 (CH_3, NCH_2CH_3), 40.9 (CH_2, NCH_2CH_3), 41.5 (CH_2, NCH_2CH_3), 54.9 (CH_3, OCH_3), 55.8 (CH_3, OCH_3), 75.0 (CH, C-1′), 98.3 (CH, C-4), 102.4 (C, C-2), 103.6 (CH, C-6), 115.8 (CH_2, C-3′), 135.0 (CH, C-2′), 140.7 (C, C-1), 154.0 (C, C=O), 156.2 (C, C-3), 159.5 (C, C-5); ***m/z*** (EI) 394 (100%, M^+ + Na), 350 (6), 318 (3), 140 (2); **HRMS** Found (EI): $(M + Na)^+$, 394.0624, $C_{16}H_{22}BrNNaO_4$ requires 394.0623.

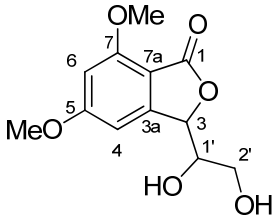
(*R*)-5,7-Dimethoxy-3-vinylisobenzofuran-1(3*H*)-one 406



Carbamate (*R*)-**407** (1.0 g, 2.69 mmol) was dissolved in THF (8 mL). The solution was cooled to -78 ^{o}C and *n*-BuLi (3.71 mL, 1.6 M in hexanes, 5.93 mmol) was added dropwise. The yellow solution was stirred at -78 ^{o}C for 1 h and warmed to r.t. The reaction was quenched with H_2O (10 mL), extracted with EtOAc (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was dissolved in dioxane (15 mL) and added anhydrous HCl (5 mL, 4 M in dioxane, 20 mmol) dropwise. The solution was stirred for 12 h and concentrated *in vacuo*. The residue was purified by flash column chromatography using hexane/EtOAc (7:3) as eluent to give the *title compound* (*R*)-**406** as a colourless solid (0.44 g, 74%). **M.p.** = 84 ^{o}C; $[\alpha]_D^{19}$ = -24.1 (*c* 0.57, CH_2Cl_2); **IR** ν_{max}(neat): 3093, 2951, 2842, 1751, 1596, 1417, 1461, 1330, 1213, 1156, 1050, 837, 690 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.86 (3 H, s, OC*H*$_3$), 3.92 (3 H, s, OC*H*$_3$), 5.36 (2 H, dt, *J* 10.2, 1.2 Hz, 2′-H), 5.61 (1 H, d, *J* 7.2 Hz, 3-H), 5.79 (1 H, m, 1′-H), 6.37 (1 H, s, 6-H), 6.40 (1 H, s, 4-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.9 (CH_3, O*C*H$_3$), 55.9 (CH_3, O*C*H$_3$), 80.6 (CH, C-3), 98.0 (CH, C-4), 99.0 (CH, C-6), 106.1 (C, C-7a), 119.4 (CH_2, C-2′), 133.6 (CH, C-1′), 153.5 (C, C-3a), 159.5 (C, C-7), 166.8 (C, C-5), 167.9 (C, C=O); ***m/z*** (EI) 221 (22%, MH$^+$), 178 (8), 162 (9); **HRMS** Found (EI): MH$^+$, 221.0805, $C_{12}H_{13}O_4$ requires 221.0808.

6.2.4 Synthesis of Epoxide 404 (5.1.9)

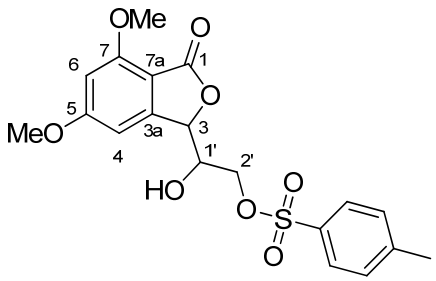
3-(1′,2′-Dihydroxyethyl)-5,7-dimethoxyisobenzofuran-1(3H)-one 435



To a solution of vinylphthalide **406** (0.1 g, 0.45 mmol) in acetone (15 mL) and H_2O (3 mL) was added *N*-methylmorpholine-*N*-oxide (0.08 mg, 0.66 mmol) and the mixture was cooled to 0 ^{o}C. After 5 min stirring, a solution of osmium tetroxide (0.008 mL, 0.018 mmol) was added and the mixture was gradually warmed to r.t. The reaction mixture was stirred for 24 h then 33% aq. Na_2SO_3 (5 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL) and

the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL). After drying over anhydrous Na_2SO_4, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography using hexanes/EtOAc (1:1) as eluent to afford the *title compound* **435** (0.098 g, 85%) as a colourless solid. **M.p.** = 168-170 ^oC; **IR** ν_{max}(film): 3431, 3318, 2953, 1733, 1600, 1466, 1332, 1229, 1167, 1089, 1064, 1015, 899, 834, 685 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.51 (2 H, d, *J* 6.0 Hz, 2′-H), 3.75 (1 H, m, 1′-H), 3.86 (6 H, s, OC*H*$_3$), 4.59 (1 H, br s, O*H*), 5.09 (1 H, br s, OH), 5.34 (1 H, d, *J* 6.0 Hz, 3-H), 6.61 (1 H, d, *J* 3.0 Hz, 4-H), 6.71 (1 H, d, *J* 3.0 Hz, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.7 (CH_3, O*C*H$_3$), 56.0 (CH_3, O*C*H$_3$), 62.0 (CH_2, C-2′), 72.1 (CH, C-1′), 79.3 (CH, C-3), 98.6 (CH, C-4), 100.0 (CH, C-6), 106.3 (C, C-7a), 152.3 (C, C-3a), 158.9 (C, C-7), 165.9 (C, C-5), 167.3 (C, C=O); ***m/z*** (EI) 255 (MH^+, 55%), 237 (64), 219 (52), 207 (80), 193 (100), 179 (25), 165 (12), 151 (4), 135 (2), 121 (1); **HRMS** Found (EI): MH^+, 255.0856, $C_{12}H_{15}O_6$ requires 255.0863.

3-(1′-Hydroxyethyl 4″-methylbenzenesulfonate)- 5,7-dimethoxyisobenzofuran-1(3H)-one 436



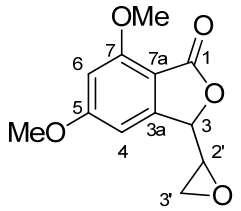
Bu_2SnO (4 mg, 0.01 mmol), *p*-toluenesulfonyl chloride (57 mg, 0.29 mmol) and Et_3N (0.04 mL, 0.29 mmol) were added sequentially to a solution of diol **435** (40 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) at r.t. and the resulting solution stirred for 2 h. The reaction was then diluted with H_2O (3 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic fractions were washed with brine (5 mL), organic layer dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to afford the *title compound* **436** (3.69 g, 74%) as a colourless solid. **M.p.** = 157 - 159 ^oC; **IR** ν_{max}(film): 3488, 2932, 1746, 1601, 1457, 1335, 1220, 1175, 1157, 978, 931, 819, 668 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46 (3 H, s,

PhCH_3), 3.89 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 4.15 (2 H, m, 2′-H), 4.29 (1 H, m, 1′-H), 5.38 (1 H, d, *J* 3.0 Hz, 3-H), 6.44 (1 H, s, 4-H), 6.62 (1 H, s, 6-H), 7.36-7.79 (4 H, m, Ar-*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.7 (CH_3, Ph*C*H_3), 56.0 (CH_3 × 2, O*C*H_3), 70.8 (CH_2, C-2′), 71.1 (CH, C-1′), 78.2 (CH, C-3), 98.0 (CH, C-4), 99.5 (C, C-7a), 99.7 (CH, C-6), 145.5 (C, *C*-CH_3), 150.9 (C, *C*-S), 151.9 (C, C-3a), 159.7 (C, C-7), 167.0 (C, C-5), 167.9 (C, C=O); ***m/z*** (EI) 355 (M^+ + Na, 100%), 333 (43), 284 (2), 259 (2), 251 (7), 149 (4); **HRMS** Found (EI): (M + Na)$^+$, 355.0446, $C_{13}H_{16}NaO_8S$ requires 355.0458.

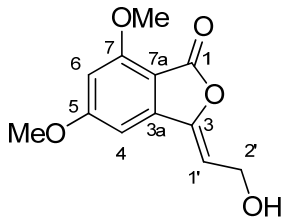
5,7-Dimethoxy-3-(oxiran-2′-yl)isobenzofuran-1(3H)-one 404 and

(*Z*)-3-(2′-Hydroxyethylidene)-5,7-dimethoxyisobenzofuran-1(3H)-one 437

DBU (0.06 mL, 0.42 mmol) was added to a solution of **436** (0.17 g, 0.42 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C and stirred for 4 h. The solution was then concentrated *in vacuo* and the resulting crude residue was purified by flash chromatography using hexanes/EtOAc (1:1) as eluent to give the *title compounds* **404** (0.03 g, 34%); as a colourless oil followed by **437** as a colourless oil (0.06 g, 61%).

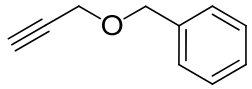


IR ν_{max}(film): 2924, 1754, 1612, 1468, 1335, 1215, 1158, 1050, 1023, 839, 692 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.90 (2 H, m, 3′-H), 3.03 (1 H, m, 2′-H), 3.90 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 4.84 (1 H, d, *J* 6.0 Hz, 3-H), 6.46 (1 H, s, 4-H), 6.64 (1 H, s, 6-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 45.9 (CH_2, C-3′), 52.2 (CH, C-2′), 56.0 (CH_3 × 2, O*C*H_3), 79.2 (CH, C-3), 98.3 (CH, C-6), 99.8 (CH, C-4), 106.2 (C, C-7a), 152.3 (C, C-3a), 159.7 (C, C-7), 162.3 (C, C-5), 167.1 (C, C-1); ***m/z*** (EI) 237 (MH^+, 100%), 207 (14), 191 (4), 165 (3); **HRMS** Found (EI): MH^+, 237.0758, $C_{12}H_{13}O_5$ requires 237.0757.



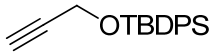
IR ν_{max}(film): 3434, 2927, 1751, 1690, 1600, 1496, 1449, 1343, 1206, 1159, 1082, 1018, 820, 699, 517 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.94 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.54 (2 H, d, *J* 6.8 Hz, 2′-H), 5.71 (1 H, t, *J* 6.8 Hz, 1′-H), 6.44 (1 H, d, *J* 1.6 Hz, 4-H), 6.62 (1 H, d, *J* 1.6 Hz, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 56.0 (CH_3, O*C*H$_3$), 56.1 (CH_3, O*C*H$_3$), 57.1 (CH_2, C-2′), 95.4 (CH, C-4), 100.4 (CH, C-6), 105.5 (C, C-7a), 106.8 (CH, C-1′), 141.3 (C, C-3a), 146.0 (C, C-3), 159.4 (C, C-7), 164.3 (C, C=O), 167.1 (C, C-5); ***m/z*** (EI) 237 (MH^+, 100%), 219 (19), 207 (4), 191 (2), 165 (2); **HRMS** Found (EI): MH^+, 237.0767, $C_{12}H_{13}O_5$ requires 237.0757.

((Prop-2-ynyloxy)methyl)benzene 405a



Propargyl alcohol **439** (3.48 mL, 60 mmol) was added in portions to a suspension of NaH (2.4 g, 60% in mineral oil, 60 mmol) in DMF (50 mL) at 0 °C. After stirring for 30 min at r.t., the solution was cooled to 0 °C and benzyl bromide (7.2 mL, 60 mmol) was added. The solution was stirred for 30 min at r.t., then a solution of 20% aq. ammonia (20 mL) was added and stirred overnight. The reaction mixture was added H_2O (20 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with H_2O (3 × 10 mL) and 1 M HCl (20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash column chromatography using hexanes/EtOAc (3:1) as eluent to yield the *title compound* **405a** (6.2 g, 71%) as a yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.55 (1 H, t, *J* 4.0 Hz, C*H*), 4.23 (2 H, d, *J* 4.0 Hz, CH_2), 4.68 (2 H, s, OCH_2Bn), 7.36-7.46 (5 H, m, Ar-*H*). The ^{1}H NMR data were in agreement with the literature.[265]

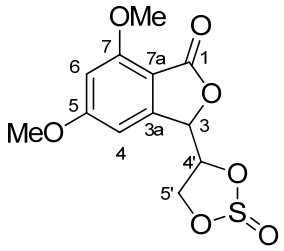
tert-Butyldiphenyl(prop-2-ynyloxy)silane 405b



Propargyl alcohol **439** (10.0 g, 178 mmol), *t*-$BuPh_2SiCl$ (53.9 g, 196 mmol) and imidazole (13.4 g, 196 mmol) in CH_2Cl_2 (100 mL) were stirred at r.t. 14 h. After this time, the reaction mixture was diluted with Et_2O (100 mL) and washed with brine (2 × 50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The resulting white solid was recrystallised from hexanes and Et_2O to afford *title compound* **405b** (50.7 g, 96%) as a white solid. **M.p.** = 58–60 °C; **IR** ν_{max}(film): 3309, 1587, 1426, 1370 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.11 (9 H, s, C(CH_3)$_3$), 2.41 (1 H, t, *J* 4.0 Hz, C*H*), 4.35 (2 H, d, *J* 4.0 Hz, CH_2), 7.41-7.77 (10 H, m, Ar-*H*); The ^{1}H NMR data were in agreement with the literature.[266]

6.2.5 Synthesis of Cyclic Sulfite 444 and Cyclic Sulfate 445 (5.1.11)

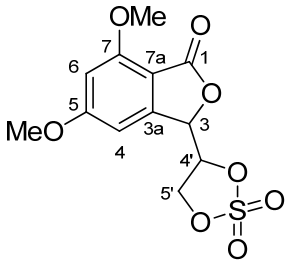
5,7-Dimethoxy-3-(2-oxido-1,3,2-dioxathiolan-4-yl)isobenzofuran-1(3H)-one 444



To an ice cooled stirring solution of diol **435** (0.6 g, 2.4 mmol) in CH_2Cl_2 (15 mL) and anhydrous Et_3N (1.3 mL, 9.6 mmol), was added thionyl chloride (0.26 mL, 3.6 mmol) dropwise. The reaction mixture was stirred for 20 min and then quenched by adding H_2O (10 mL). The phases were separated and aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue purified by flash column chromatography using hexanes/EtOAc (4:1) as eluent to afford the *title compound* **444** (0.51 g, 71%) as a yellow oil; **IR** ν_{max}(film): 2929, 1760, 1613, 1462, 1432, 1341, 1266, 1211, 1160, 1053, 1024,843, 736 cm^{-1}: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 4.33 (1 H, m, 4′-H), 4.72 (1 H, dd, *J* 9.2, 6.8 Hz, 5′-H_α), 4.95 (1

H, dd, *J* 9.2, 6.8 Hz, 5′-H_β), 5.48 (1 H, s, 3-H), 6.47 (1 H, d, *J* 2.0 Hz, 4-H), 6.73 (1 H, d, *J* 1.2 Hz, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 56.1 ($CH_3 \times 2$, O*C*H_3), 71.6 (CH_2, C-5′), 78.7 (CH, C-3), 81.1 (CH, C-4′), 99.5 (CH, C-6), 100.0 (CH, C-4), 105.9 (C, C-7a), 151.4 (C, C-3a), 159.7 (C, C-7), 166.8 (C, C-5), 167.1 (C, C-1); ***m/z*** (EI) 301 (MH^+, 8%), 237 (38), 219 (26), 207 (100), 193 (90), 178 (18), 165 (24), 150 (5); **HRMS** Found (EI): MH^+, 301.0374, $C_{12}H_{13}O_7S$ requires 301.0376.

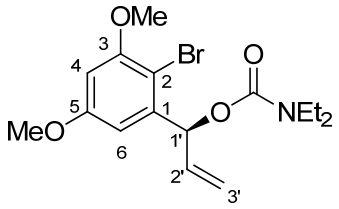
3-(2,2-Dioxido-1,3,2-dioxathiolan-4-yl)-5,7-dimethoxyisobenzofuran-1(3H)-one 445



To an ice cooled solution of cyclic sulfite **444** (0.4 g, 1.3 mmol) in CH_3CN (5 mL) were added CCl_4 (5 mL), $RuCl_3 \cdot H_2O$ (5 mg, 0.02 mmol), $NaIO_4$ (0.58 g, 2.7 mmol) and H_2O (5 mL). The resulting orange mixture was stirred at r.t. for 10 h. The mixture was diluted with ether (20 mL), and the two phases separated. The organic layer was washed with H_2O (20 mL), sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue purified by flash column chromatography using hexanes/EtOAc (5:1) as eluent to afford the *title compound* **445** (0.34 g, 83%) as a colourless solid. **M.p.** = 166 ^oC; **IR** ν_{max}(film): 2947, 1755, 1607, 1477, 1387, 1330, 1208, 1155, 1092, 991, 972, 943, 831, 749, 653 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.92 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 4.71 (1 H, m, 4′-H), 4.88 (2 H, m, 5′-H), 5.46 (1 H, d, *J* 9.0 Hz, 3-H), 6.49 (1 H, d, *J* 3.0 Hz, 4-H), 6.65 (1 H, d, *J* 3.0 Hz, 6-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 56.1 (CH_3, O*C*H_3), 56.2 (CH_3, O*C*H_3), 70.4 (CH_2, C-5′), 75.5 (CH, C-4′), 79.8 (CH, C-3), 99.1 (CH, C-6), 100.4 (CH, C-4), 105.6 (C, C-7a), 149.9 (C, C-3a), 160.0 (C, C-7), 166.2 (C, C-5), 167.6 (C, C-1); ***m/z*** (EI) 317 (MH^+, 82%), 310 (37), 298 (1), 291 (3), 267 (4), 208 (4); **HRMS** Found (EI): MH^+, 317.0325, $C_{12}H_{13}O_8S$ requires 317.0326.

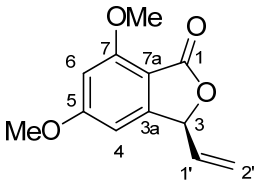
6.2.6 Synthesis of (−)-Herbaric Acid (255) (5.2)

(*S*)-1′-(2-Bromo-3,5-dimethoxyphenyl)allyl diethylcarbamate 407



Solution of alcohol (*S*)-**408** (0.75 g, 2.76 mmol) in CH_2Cl_2 (100 mL) was added *N*,*N*'-carbonyldiimidazole (1.64 g, 10.1 mmol). The mixture was stirred at r.t. for 1 h, then diethylamine (0.57 mL, 5.51 mmol) was added dropwise. The reaction was stirred for a further 24 h. The reaction mixture was washed with H_2O (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using hexane/EtOAc (4:1) as eluent to give the *title compound* (*S*)-**407** as a colourless oil (0.92 g, 90%). $[\alpha]_D^{19}$ = -5.71 (*c* 1.4, CH_2Cl_2); spectroscopic data as described for (*R*)-**407**.

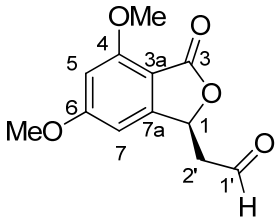
(*S*)-5,7-Dimethoxy-3-vinylisobenzofuran-1(3*H*)-one 406



Carbamate (*S*)-**407** (1.0 g, 2.69 mmol) was dissolved in THF (8 mL). The solution was cooled to -78 ^oC and *n*-BuLi (3.71 mL, 1.6 M in hexanes, 5.93 mmol) was added dropwise. The yellow solution was stirred at -78 ^oC for 1 h and warmed to r.t. The reaction was quenched with H_2O (10 mL), extracted with EtOAc (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was dissolved in dioxane (15 mL) and added anhydrous HCl (5 mL, 4 M in dioxane, 20 mmol) dropwise. The solution was stirred for 12 h and concentrated *in vacuo*. The residue was purified by flash column chromatography

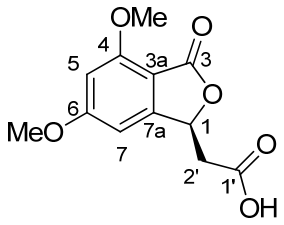
using hexane/EtOAc (7:3) as eluent to give the *title compound* (*S*)-**406** as a colourless solid (0.44 g, 74%). $[\alpha]_D^{19}$ = +21.1 (*c* 0.57, CH_2Cl_2); spectroscopic data as described for (*R*)-**406**.

(*S*)-2-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetaldehyde 460



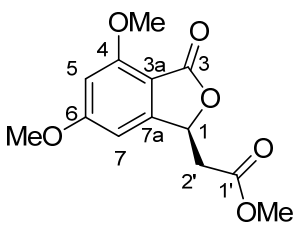
A solution of vinylphthalide **406** (100 mg, 0.454 mmol) in DMF (3 mL) was added to a mixture of palladium(II) chloride (40 mg, 0.227 mmol), copper(I) chloride (58 mg, 0.59 mmol) in DMF (3 mL) and H_2O (1 mL). Oxygen gas was bubbled through the solution for 2 h. The reaction mixture was filtered through silica and the residue washed with EtOAc (100 mL) and hexanes (50 mL). The volatile solvents were removed in vacuo and DMF was removed under high vacuum at 40 °C. The residue was purified by flash column chromatography using CH_2Cl_2/MeOH (50:1) as eluent to give the *title compound* **460** as a colourless oil (92 mg, 86%). $[\alpha]_D^{19}$ = -9.09 (*c* 0.44, CH_2Cl_2); **IR** ν_{max}(film): 2929, 2848, 1749, 1601, 1334, 1212, 1200, 1158, 1026, 839, 731, 699 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 2.97 (2 H, m, 2′-H) 3.85 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 5.74 (1 H, t, *J* 6.0 Hz, 1-H), 6.40 (1 H, d, *J* 3.0 Hz, 5-H), 6.44 (1 H, d, *J* 3.0 Hz, 7-H), 9.81 (1 H, t, *J* 3.0 Hz, C*H*O); ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 48.2 (CH_2, C-2′), 55.9 (CH_3, O*C*H_3), 56.0 (CH_3, O*C*H_3), 74.1 (CH, C-1), 97.8 (CH, C-5), 99.1 (CH, C-7), 106.2 (C, C-3a), 153.8 (C, C-7a), 159.7 (C, C-4), 167.0 (C, C-6), 167.5 (C, C-3), 198.0 (C, C-1′); ***m/z*** (EI) 259 (M^+ + Na, 18%), 237 (2), 193 (9), 172 (7), 135 (2); **HRMS** Found (EI): $(M + Na)^+$, 259.0581, $C_{12}H_{12}NaO_5$ requires 259.0577.

(*S*)-2′-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid 488



Aldehyde **460** (100 mg, 0.42 mmol) in DMF (5 mL) was added Oxone® (260 mg, 0.42 mmol) and the reaction mixture stirred at r.t. for 6 h. The reaction mixture was washed with 1M HCl (15 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using CH_2Cl_2/MeOH (10:1) as eluent to give the *title compound* **488** as a colourless solid (95 mg, 89%). **M.p.** = 201 °C; $[\alpha]_D^{19}$ = -14.3 (*c* 0.21, EtOH); **IR** ν_{max}(film): 3171, 2983, 1738, 1711, 1601, 1330, 1225, 1204, 1164, 1060, 1009, 836, 694 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.57 (1 H, dd, *J* 16.8, 8.4 Hz, 2′-H_α), 3.07 (1 H, dd, *J* 16.8, 3.6 Hz, 2′-H_β), 3.84 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 5.61 (1 H, q, *J* 4.0 Hz, 1-H), 6.57 (1 H, d, *J* 1.6 Hz, 5-H), 6.78 (1 H, t, *J* 1.2 Hz, 7-H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 39.5 (CH_2, C-2′), 56.3 (CH_3, OCH_3), 56.5 (CH_3, OCH_3), 76.2 (CH, C-1), 99.2 (CH, C-5), 99.3 (CH, C-7), 106.1 (C, C-3a), 154.5 (C, C-7a), 159.4 (C, C-4), 166.8 (C, C-6), 167.3 (C, C-3), 171.3 (C, C-1′); ***m/z*** (EI) 253 (MH^+, 41%), 235 (5), 227 (2), 193 (10); **HRMS** Found (EI): MH^+, 253.0708, $C_{12}H_{13}O_6$ requires 253.0707.

(*S*)-Methyl 2′-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate 489



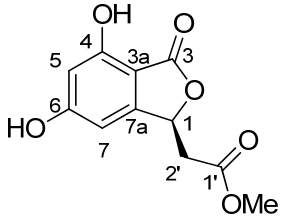
A solution of acid **488** (200 mg, 0.793 mmol) in MeOH (10 mL) was added concentrated H_2SO_4 (1 mL). The solution was stirred at r.t for 12 h and concentrated *in vacuo*. The residue

was purified by flash column chromatography using CH_2Cl_2/MeOH (20:1) as eluent to give the *title compound* **489** as a colourless solid (173 mg, 82%). **M.p.** = 145 °C; $[\alpha]_D^{19}$ = -13.0 (*c* 0.23, EtOH); **IR** ν_{max}(film): 2952, 2848, 1736, 1601, 1434, 1336, 1200, 1156, 1054, 1012, 838, 733, 689 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.83 (2 H, m, 2′-H), 3.74 (3H, s, COOCH_3), 3.86 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 5.69 (1 H, t, *J* 6.8 Hz, 1-H), 6.42 (1 H, d, *J* 2.0 Hz, 5-H), 6.46 (1 H, t, *J* 0.8 Hz, 7-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 39.6 (CH_2, C-2′), 52.1 (CH_3, COO*C*H_3), 55.9 (CH_3, O*C*H_3), 56.0 (CH_3, O*C*H_3), 75.5 (CH, C-1), 97.8 (CH, C-5), 99.1 (CH, C-7), 106.5 (C, C-3a), 153.7 (C, C-7a), 159.7 (C, C-4), 166.9 (C, C-6), 167.6 (C, C-3), 169.8 (C, C-1′); ***m/z*** (EI) 267 (MH^+, 70%), 226 (5), 193 (18), 149 (2), 130 (4); **HRMS** Found (EI): MH^+, 267.0858, $C_{13}H_{15}O_6$ requires 267.0863.

(*S*)-Methyl 2′-(4,6-dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate 490 and

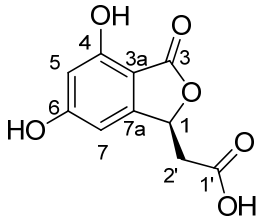
(*S*)-2′-(4,6-Dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid (255)

To a solution of methyl ester **489** (11 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) was added BBr_3 (0.04 mL, 0.41 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h, then to r.t. and stirred for 72 h. The reaction mixture was quenched with 1M HCl (3 × 5 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using CH_2Cl_2/MeOH (5:1) as eluent to give the *title compound* **490** (5 mg, 12%) as a colourless solid followed by (**255**) (6 mg, 65%) as a colourless solid .



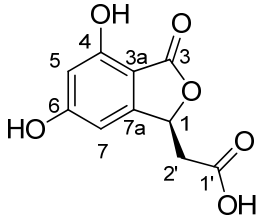
M.p. = 164-166 °C; $[\alpha]_D^{19}$ = -10.53 (*c* 0.19, MeOH); **IR** ν_{max}(film): 3265, 1720, 1614, 1477, 1440, 1336, 1216, 1163, 1071, 1016, 850, 692, 656 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.75

(1 H, dd, *J* 16.5, 8.0 Hz, 2′-H_α), 2.97 (1 H, dd, *J* 16.5, 3.8 Hz, 2′-H_β), 3.71 (3 H, s, COOCH_3), 5.68 (1 H, t, *J* 8.0 Hz, 1-H), 6.29 (1 H, s, 5-H), 6.39 (1 H, s, 7-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 40.3 (CH_2, C-2′), 52.5 (CH_3, OCH_3), 78.0 (CH, C-1), 101.7 (CH, C-5), 103.8 (CH, C-7), 104.5 (C, C-3a), 154.5 (C, C-7a), 159.8 (C, C-6), 167.1 (C, C-4), 171.4 (C, C-3), 171.7 (C, C-1′); ***m/z*** (EI) 239 (MH^+, 100%), 225 (10), 207 (2), 179 (7), 165 (35), 149 (4); **HRMS** Found (EI): MH^+, 239.0544, $C_{11}H_{11}O_6$ requires 239.0550.



M.p. = 190 °C; **$[\alpha]_D^{19}$** = -21.7 (*c* 0.184, MeOH); **IR** ν_{max}(film): 3201, 2959, 1707, 1612, 1474, 1399, 1366, 1336, 1251, 1216, 1160, 1076, 1012, 823, 737, 693 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-$_{d6}$): δ 2.65 (1 H, br s, 2′-H_α), 2.73 (1 H, br s, 2′-H_β), 5.55 (1 H, br s, 1-H), 6.30 (1 H, br s, 5-H), 6.44 (1 H, br s, 7-H); **^{13}C NMR** (100 MHz, DMSO-$_{d6}$): δ ~40.0 (CH_2, C-2′), 77.0 (CH, C-1), 101.0 (C, C-3a), 103.0 (CH, C-5), 103.2 (CH, C-7), 154.6 (C, C-7a), 158.6 (C, C-6), 165.3 (C, C-4), 168.2 (C, C-3), 172.1 (C, C-1′); ***m/z*** (EI) 225 (MH^+, 86%), 207 (3), 165 (56), 149 (12); **HRMS** Found (EI): MH^+, 225.0400, $C_{10}H_9O_6$ requires 225.0394.

(*S*)-2′-(4,6-Dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid (255)



Methyl ester **490** (5 mg, 0.02 mmol) was added 2 M NaOH (3 mL) and the resulting mixture was stirred at r.t. for 2 h. The reaction mixture was acidifed with 1M HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using CH_2Cl_2/MeOH (5:1)

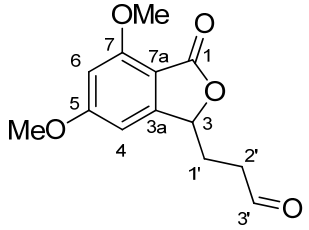
as eluent to give the *title compound* **255** as a colourless solid (4 mg, 85%). Spectroscopic data as described previously.

6.2.6.1 Reverse Wacker Oxidation of Alkene 363 (5.2.2)

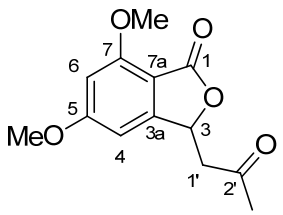
5,7-Dimethoxy-3-(2′-oxopropyl)isobenzofuran-1(3H)-one 484 and

3-(3′-Oxopropyl)-5,7-dimethoxy-3*H*-isobenzofuran-1-one 485

A solution of alkene **363** (20 mg, 0.09 mmol) in DMF (2 mL) was added to a mixture of palladium(II) chloride (7 mg, 0.04 mmol), copper(I) chloride (11 mg, 0.11 mmol) in DMF (3 mL) and H_2O (1 mL). Oxygen gas was bubbled through the solution for 2 h. The reaction mixture was filtered through silica and the residue washed with EtOAc (100 mL) and hexanes (50 mL). The volatile solvents were removed *in vacuo* and DMF was removed under high vacuum at 40 °C. The solution was then concentrated *in vacuo* and the resulting crude residue was purified by flash chromatography using hexanes/EtOAc (1:1) as eluent to give inseparable mixtures of *title compounds* **484** and **485** (ratio 1:1.6, 12 mg) as a colourless oil.



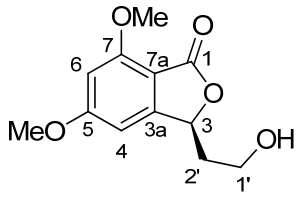
IR ν_{max}(film): 2928, 2951, 1755, 1602, 1463, 1338, 1218, 1158, 1028, 837, 734 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.88 (1 H, dddd, *J* 14.1, 8.3, 8.3, 5.1 Hz, 1′-H_α), 2.44 (1 H, dddd, *J* 14.4, 7.4, 7.4, 3.2 Hz, 1′-H_β), 2.54 (1 H, ddd, *J* 18.7, 8.3, 5.1 Hz, 2′-H_α), 2.75 (1 H, dd, *J* 18.7, 7.4, 7.4 Hz, 2′-H_β), 3.88 (3 H, s, OC*H*$_3$), 3.94 (3 H, s, OC*H*$_3$), 5.34 (1 H, dd, *J* 8.3, 3.2 Hz, 3-H), 6.42 (1 H, s, 4-H), 6.43 (1 H, s, 6-H), 9.80 (1 H, s, 3′-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 26.9 (CH_2, C-1′), 38.9 (CH_2, C-2′), 56.0 (CH_3 × 2, O*C*H$_3$), 78.4 (CH, C-3), 97.4 (CH, C-6), 99.1 (CH, C-4), 106.7 (C, C-7a), 154.3 (C, C-3a), 159.7 (C, C-7), 167.0 (C, C-5), 168.0 (C, C-1), 200.7 (CH, C-3′); ***m/z*** (EI) 251 (M^+, 30%), 206 (61), 193 (100), 165 (21), 135 (20), 77 (10); **HRMS** Found (EI): M^+, 250.0833, $C_{13}H_{14}O_5$ requires 250.0841.



IR ν_{max}(film): 2931, 1749, 1604, 1466, 1338, 1218, 1159, 1028, 981, 840 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.25 (3 H, CH_3C=O), 2.83 (1 H, dd, *J* 17.4, 6.3 Hz, 1′-H_α), 3.07 (1 H, dd, *J* 17.4, 6.6 Hz, 1′-H_β), 3.86 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 5.74 (1 H, t, *J* 6.6 Hz, 3-H), 6.44 (1 H, s, 4-H), 6.45 (1 H, s, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 30.8 (CH_2, C-1′), 48.4 (CH_3, C-3′), 56.0 (CH_3 × 2, OCH_3), 75.3 (CH, C-3), 97.9 (CH, C-4), 99.1 (CH, C-6), 106.5 (CH, C-7a), 128.6 (C, C-3a), 130.9 (C, C-7), 154.5 (C, C-5), 167.8 (C, C-1), 204.8 (C, C-2′); ***m/z*** (EI) 251 (MH^+, 5%), 233 (28), 205 (100), 191 (59), 177 (23), 163 (8), 158 (2); **HRMS** Found (EI): MH^+, 251.0912, $C_{13}H_{15}O_5$ requires 251.0914.

6.2.6.2 Mosher Ester Analysis of Alcohol 486 (5.2.2)

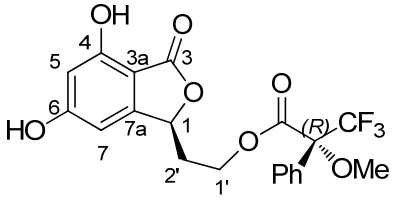
(*S*)-3-(1′-Hydroxyethyl)-5,7-dimethoxyisobenzofuran-1(3H)-one 486



To a stirred solution of aldehyde **460** (4 mg, 0.02 mmol) in ethanol (3 mL) cooled to 0 ^oC was added sodium borohydride (2 mg, 0.05 mmol). The cooling bath was removed after 5 min and the solution was warmed to r.t. and stirred for 30 min. Ethanol was removed *in vacuo* and the resultant residue was taken up in EtOAc (2 mL) then washed with H_2O (1 mL) and brine (1 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using CH_2Cl_2/MeOH (20:1) as eluent to give the *title compound* **486** as a yellow oil (3 mg, 74%). **$[\alpha]_D^{19}$** = +10.471 (*c* 0.19, CH_2Cl_2); **IR** ν_{max}(film): 3216, 2927, 1737, 1608, 1460, 1198, 1160, 1042, 762 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.85 (1 H, m, 2′-H_α), 2.25 (1 H, m, 2′-H_β), 3.80 (2 H, m, 1′-H), 3.88 (3 H, s, OCH_3), 3.94 (3 H,

s, OC*H*$_3$), 5.49 (1 H, dd, *J* 9.5, 3.1 Hz 3-H), 6.42 (1 H, s, 6-H), 6.43 (1 H, s, 4-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 37.8 (CH_2, C-2′), 55.9 (CH_3, O*C*H$_3$), 56.0 (CH_3, O*C*H$_3$), 59.1 (CH_2, C-1′), 77.4 (CH, C-3), 97.4 (CH, C-4), 98.9 (CH, C-6), 106.5 (C, C-7a), 155.1 (C, C-3a), 159.8 (C, C-7), 166.9 (C, C-5), 168.2 (C, C-1); ***m/z*** (EI) 261 (M^+ + Na, 100%), 239 (42), 209 (14), 191 (7), 177 (5), 142 (3); **HRMS** Found (EI): $(M + Na)^+$, 261.0728, $C_{12}H_{14}NaO_5$ requires 261.0733.

(*R*)-2′-((*S*)-4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 487



To a stirred solution of alcohol **486** (3 mg, 0.013 mmol) in CH_2Cl_2 (0.8 mL) was added (*R*)-(+)-*α*-methoxytrifluorophenylacetic acid (5 mg, 0.021 mmol), *N*,*N*′-dicyclohexylcarbodiimide (5 mg, 0.24 mmol) and DMAP (2 mg, 0.02 mmol) and the mixture stirred at r.t. overnight. The mixture was filtered, the filtrate concentrated and the oily residue dissolved in Et_2O (2mL), then filtered and concentrated *in vacuo*. This crude material was analysed by ^{19}F NMR to determine the diastereomeric purity of *title compound* **487**.

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