Towards the Synthesis of the Ajudazols

Ben A Egan

MSc

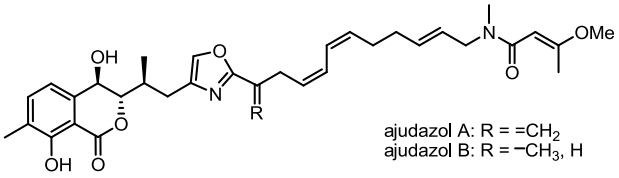
Thesis submitted in part fulfilment of the requirements for the Degree of Doctor of Philosophy

School of Chemistry
University of Glasgow
Glasgow G12 8QQ

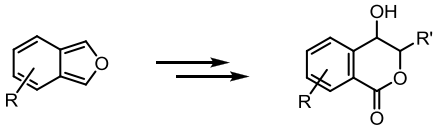
September 2012

Abstract

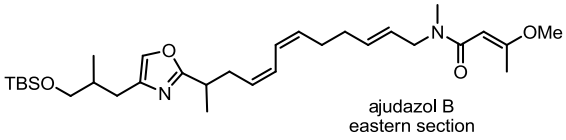
The Ajudazols A and B are secondary metabolites, isolated in 2004, that exhibit anti-fungal and cytotoxic activity.



The primary objective of the work presented in this thesis was to expand and develop our novel isobenzofuran oxidative rearrangement methodology for generation of isochromanones, and to apply this methodology towards the total synthesis of the ajudazols.



An efficient, high yielding, regio- and diastereoselective oxidative rearrangement sequence has been developed, allowing for the generation of elaborately-functionalised isochromanone structures, from transient isobenzofuran intermediates.



A flexible route to the synthesis of the ajudazol B eastern section was achieved, and this research culminated in the synthesis of *ent*-8-*epi*-ajudazol B.

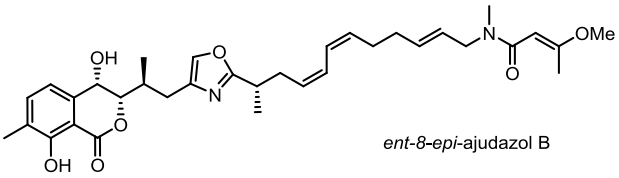


Table of Contents

Acknowledgements 5
Author Declaration 6
List of Abbreviations 7
1 Introduction 11
1.1 Total Synthesis of Natural Products 11
1.2 Ajudazol A and B 13
1.3 4-Hydroxyisochromanones 15
1.3.1 Danishefsky's Approach to 4-Hydroxyisochromanones 16
1.3.2 Yeung's Approach to 4-Hydroxyisochromanones 16
1.3.3 Fujita's Approach to 4-Hydroxyisochromanones 17
1.4 Biosynthesis of the Ajudazols 19
1.5 Approaches Towards the Total Synthesis of the Ajudazols 23
1.5.1 Taylor's Synthesis of Ajudazol Eastern Section 52 23
1.5.2 Rizzacasa's Synthesis of Ajudazol A & B C9-C29 Eastern Fragments 26
1.5.3 Rizzacasa's Synthesis of 8-Deshydroxyajudazol B 49 29
1.5.4 Preliminary Work within the Marquez Group 32
1.6 Summary and Outlook 38
2 Retrosynthetic Analysis of the Ajudazols 39
2.1 Ajudazol A 39
2.2 Ajudazol B 40
3 Regiochemistry of the IBF Oxidative Rearrangement 41
3.1 Investigation of Methoxy Substituent 41
3.2 Steric Control 43
3.3 Optimisation of the Keto-Lactol Oxidation and Keto-Lactone Reduction Conditions 46
3.4 Chelation Control 47
3.5 IBF Oxidative Rearrangement with Regioisomeric Phthalan Precursors 50
3.6 Summary and Outlook 52
4 The Ajudazol Western Section 53
4.1 Ajudazol Isochromanone Moiety 53
4.2 Ajudazol Western Section Model System 55
4.3 Synthesis of Ajudazol Western Section 58
4.4 Accessing Anti-Isochromanones 59
4.4.1 Keto-Lactone Reduction 59
4.4.2 Reduction of α-Anomeric Intermediates 61
4.5 Summary and Outlook 64
5 Ajudazol C14-C15 Bond Construction 65
5.1 Oxazole C-H Activation 65

5.1.1 Direct C2 Alkenylation of Oxazoles 67
5.2 Oxazole C2 Stille Coupling 69
5.3 Nucleophilic Aromatic Substitution of 2-Halo Oxazoles 73
5.4 2-Silyl Oxazoles as Oxazolyl Anion Equivalents 74
5.5 Summary and Outlook 75
6 Studies Towards the Synthesis of Ajudazol A 76
6.1 Revised Stille Route Towards Ajudazol A 76
6.1.1 *Bis*-alkyne Synthesis and Functionalisation 77
6.1.2 Double Stille Route Towards Ajudazol A 81
6.2 Summary and Outlook 83
7 Synthesis of the C9-C29 Section of Ajudazol B 84
7.1 Late-Stage Stille Route Towards Ajudazol B 84
7.2 Stille Approach Towards the Synthesis of the Ajudazol B C9-C29 Unit 390 85
7.3 Enyne Reduction Route for the Synthesis of the Ajudazol B C9-C29 Unit 390 87
7.4 Reverse Enyne Reduction Route for the Synthesis of the Ajudazol B C9-C29 Unit 390 . 88
7.5 Summary and Outlook 89
8 Towards the Synthesis of Ajudazol B 90
8.1 Synthesis of Aldehydes 408a and 408b 91
8.2 Oxidative Rearrangement Sequence Towards Ajudazol B 94
8.3 Towards Late-Stage Aldehyde 431 96
8.4 Ajudazol B End-Game Strategy 100
8.5 Summary and Outlook 103
9 Conclusion 104
10 Future Work 107
10.1 Chelation Controlled Route to 5-Substituted Isochromanones 107
10.2 Enhancing *Anti*-Felkin IBF Anion Alkylation 107
11 Addendum 110
12 Experimental 111
12.1 Apparatus 111
12.2 Chromatography 111
12.3 Solvents, Reagents and Reaction Conditions 111
12.4 Experimental Details 111
13 X-Ray Crystallographic Data 212
14 References 221

Acknowledgements

I would like to firstly thank Rudi for accepting me into his research group, and providing me with a challenging, yet rewarding research project, together with being a great mentor and friend. I appreciate all the support and advice you have given me over the past 4 years – it looks like you've succeeded in keeping me in the chemistry world.

A big thanks also to my industrial supervisors, Michael Paradowski and Alan Nadin, for showing such an interest in my chemistry and providing me with interesting thoughts, tips and suggestions. My (often brief) visits into industry have been vital to the successful outcomes of crucial areas of my research – so thank you for accommodating me (and my requests) so readily.

A thank you goes out to the helping hands in the chemistry department: Jim Tweedie, David Adam, Ted Easdon, Shaun Maidwell and of course a massive thank you to Lynne Thomas for always providing me with nice X-ray structures (Wilson Group, Bath).

Finally I would like to thank Dr. Anna Hansen for her help and to everyone on the Marquez group, past and present, who have made Glasgow an enjoyable place to live out my final tax free years.

Author Declaration

This thesis represents the original work of Ben. A. Egan unless explicitly stated otherwise in the text. The research upon which this thesis is based was carried out in the Cooke Laboratory (October 2008-April 2009) and the Raphael Laboratory (April 2009-July 2012), at the University of Glasgow, under the supervision of Dr. Rudi Marquez. Additional PhD traineeship and research was carried out at Pfizer Global R&D, Sandwich (May-June 2010), under the guidance of Michael Paradowski and at GlaxoSmithKline, Stevenage (June 2012), under the guidance of Dr. Alan Nadin.

Portions of this thesis have been adapted from the following articles co-written by the author:

"Regiocontrolled Rearrangement of Isobenzofurans." Egan, B. A.; Paradowski, M.; Thomas, L. H.; Marquez, R., *Organic Letters* 2011, *13*, 2086-2089.

"Synthesis of the C1-C16 fragment of the ajudazols." Egan, B. A.; Paradowski, M.; Thomas, L. H.; Marquez, R., *Tetrahedron* 2011, *67*, 9700-9707.

Ben Egan, September 2012

List of Abbreviations

Å	angstrom
Ac	acetyl
Aju	protein encoded by *aju* gene
aju	gene encoding an Aju protein
app.	apparent
aq.	aqueous
BAIB	bis(acetoxy)iodobenzene
9-BBN	9-borabicyclo[3.3.1]nonane
BOM	benzyoxymethyl acetal
br.	broad
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
CBS	Corey-Bakshi-Shibata catalyst
CDI	1,1-carbonyldiimidazole
CI	chemical Ionisation
conc.	concentrated
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylidenacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCAD	di-(4-chlorobenzyl)azodicarboxylate
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereoisomeric excess
DEPT	distortionless enhancement by polarisation transfer
DHP	2,3-dihydropyran
DIAD	di*iso*propyl azodicarboxylate
DIBAL	di*iso*butylaluminium hydride
DIPEA	di*iso*propyl ethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*'-dimethyl propylene urea
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
d	doublet
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-*tert*-butylpyridine
EDA	ethylenediamine
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
EI	electron impact
Et	ethyl
EtO	ethoxy
EtOAc	ethyl acetate
equiv.	equivalent(s)
FAB	fast atom bombardment
g	gram(s)
h	hours
HBTU	*o*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	iso
IBF	isobenzofuran
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibition concentration
IMDA	intramolecular Diels-Alder
Imid.	imidazole
LDA	lithium di*iso*propylamide
LiHMDS	lithium bis(trimethylsilyl)amide
L_n	ligand
LUMO	lowest unoccupied molecular orbital
m	multiplet
m	*meta*
M	molar
MAD	methylaluminium bis(2,6-di-*tert*butyl-4-methylphenoxide)
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MEM	methoxyethyoxymethyl
MHz	megahertz

min	minutes
mL	millilitres
mmol	millimoles
MOM	methoxymethyl
Ms	methanesulfonyl
MTM	methylthiomethyl
NaHMDS	sodium bis(trimethylsilyl)amide
MP	melting point
MPEG	methylpolyethylene glycol
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nM	nanomolar
NMP	*N*-methyl-2-pyrrolidone
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOBA	3-nitrobenzyl alcohol
N*O*e	nuclear Overhauser effect
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
PMBA	phosphomolybdic acid hydrate solution
PNB	*p*-nitrobenzoyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Py.	pyridine
q	quartet
quint	quintet
RT	room temperature
s	singlet
sat'd	saturated
SCX	strong cation exchange
sept	septet
sext	sextet
TBAF	tetra-*n*-butylammonium fluoride

TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Temp	temperature
TEMPO	2,2,6,6-tetramethyl-piperidinyloxyl radical
tert	tertiary
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	trifuran-2-yl-phosphine
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TosMIC	toluenesulfonylmethyl isocyanide
TPAP	tetra-*n*-propylammonium perruthenate
t	triplet
Ts	4-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
µL	microlitres
µM	micromolar
)))	sonication

1 Introduction

1.1 Total Synthesis of Natural Products

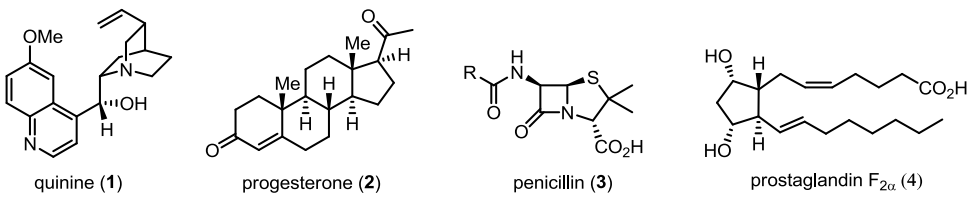
"The synthesis of a complicated molecule is, however, a very difficult task; every group, every atom must be placed in its proper position and this should be taken in its most literal sense. It is sometimes said that organic synthesis is at the same time an exact science and a fine art."

A. Fredga (Nobel Prize Committee, 1965)[1]

Total synthesis is regarded as the complete chemical synthesis of a complex organic molecule, constructed from smaller fragments, without the aid of biological processes. The birth of total synthesis can ultimately be traced back to Wöhler's synthesis of urea in 1828. Although rendered somewhat trivial by today's standards, this milestone event served as the gateway for future endeavours in total synthesis.[2]

There are various motives for one to undertake the total synthesis of a natural product. Embarking on the challenge of a total synthesis is often undertaken to showcase recently developed chemical methodology, with total synthesis providing the ultimate testing ground for new methodology and synthetic strategies. Conversely, total synthesis can be justified as a stimulus for the development of new chemical reactivity, thereby adding to the toolkit of the organic chemist. Total synthesis is also often pursued for the purpose of checking the correctness of a newly isolated compound. Furthermore, if a compound is of practical importance, in particular, having notable biological activity, obtaining the substance by synthetic methods may offer a cost advantage over isolation method and may provide a more accessible route to the natural product, especially if it has a low abundance in nature.[1,2]

The early 20th century saw efforts towards the synthesis of the naturally occurring antimalarial agent, quinine (**1**), which prompted research into the synthesis of heteroaromatic systems and led to the discovery of the unique properties of quinoline and piperidine rings (Figure 1). In more recent times, the structure of quinine has served as the foundation for new classes of antimalarials. Similarly, efforts towards the synthesis of steroids, for example, progesterone (**2**), led to a greater understanding of how to synthesise and cleave carbon-carbon bonds. The ability to synthesise partial and fully-steroidal frameworks in meaningful quantities allowed for the development of new drugs, notably the birth control pill, used by millions of women worldwide.[2]



quinine (**1**) progesterone (**2**) penicillin (**3**) prostaglandin $F_{2\alpha}$ (**4**)

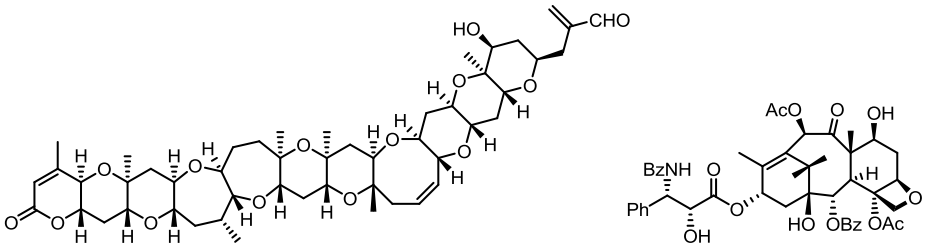
Figure 1 Milestones in Total Synthesis

In the 1950s the highly sensitive β-lactam of penicillin (**3**) acted as a driver for John Sheehan as he developed carbodiimide reagents for the synthesis of peptide bonds.[3] This methodology revolutionised the field of peptide synthesis, and to this day it receives widespread use. This

breakthrough allowed for the first total synthesis of penicillin and opened the door for the synthesis of antibiotic derivatives with biological activity superior to the parental natural product.[2]

The work of Corey in the 1960s and 1970s into the synthesis of many of the eicosanoid family of natural products, such as prostaglandin $F_{2\alpha}$ (**4**), resulted in the development of the first catalysts capable of effecting asymmetric Diels-Alder reactions. This work also inspired the now ubiquitous silyl-based protecting groups, together with the catalytic asymmetric reduction of ketones (Corey-Bakshi-Shibata reduction): inventions that have become the bread and butter of the modern day synthetic chemist.[2]

The latter part of the 20th century saw researchers pushing the boundaries of total synthesis. Notably, the prolific work of Nicolaou has highlighted the feasibility of synthesising highly complex natural products, for example, the brevetoxins A and B (**5**) and taxol (**6**) (Figure 2).[4] Taxol was discovered in 1962 and has become an important drug for cancer treatment but unfortunately it is harvested in insufficient quantities from a scarce resource, the pacific yew tree. Due to its limited availability, taxol is incredibly expensive and therefore a synthetic route to this densely functionalised polycyclic natural product has generated great interest from the chemical community. The first successful total synthesis of a popular molecule is a huge honour and achievement, a philosophy no better exemplified than by the taxol case. The total synthesis of taxol was hotly contested, with no less than 30 competing research groups by 1992. A close finish in 1994 saw the Holton group narrowly beat the efforts of K.C.Nicolaou.[5,6] With other masters in total synthesis, including Mukaiyama[7] and Danishefsky[8] publishing their respective total synthesis, together with the fact that there are still numerous research groups actively working on taxol, it is great testament to the significance of this natural product.[9]



brevetoxin B (**5**) taxol (**6**)

Figure 2 Highly Complex Natural Product Targets

Regardless of the motives to embark on a total synthesis, they all serve as a vehicle for discovery, perhaps unparalleled, in the realm of chemical synthesis; every natural product isolated from the vast chemical diversity in nature provides a unique challenge and numerous research opportunities that originate from the unique three-dimensional architecture and associated biological activity.[1,2]

Modern day total synthesis concerns the selection of structurally challenging and preferably, biologically significant, target molecules. Powerful tools have allowed for the isolation and structural elucidation of novel natural products, thereby rendering nature a seemingly limitless source of chemical targets for total synthesis.[1,2]

The total synthesis of complex natural products is increasingly perceived as an artform, an issue first addressed by Hendrickson in 1975 when he described the concept of an "ideal" synthesis as one which "…creates a complex molecule… in a sequence of only construction reactions involving no intermediary refunctionalisations, and leading directly to the target, not only its skeleton but also its correctly placed functionality."

Hendrickson's concept of an ideal synthesis epitomises the desire to design a total synthesis with high atom efficiency, minimal synthetic steps and good redox-economy, ensures that the role of the synthetic chemist is akin to that of an inventor.[10]

1.2 Ajudazol A and B

Ajudazols A (**7**) and B (**8**) are biologically active metabolites isolated from the *Chondromyces crocatus* strain of myxobacteria (Figure 3).[11] Myxobacteria lives preferentially in areas of high microbial life and organic matter, typically temperate topsoil, animal dung, rotting plant material and tree bark. Myxobacteria are present in all climatic regions but are particularly prevalent in warm, semi-arid climatic regions, for example, Egypt and northern India.[12]

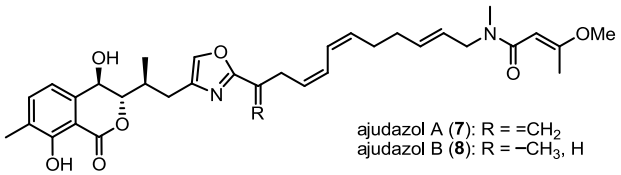


Figure 3 **The Ajudazols**

The *Chondromyces crocatus* strain of myxobacteria is renowned for exhibiting high cytotoxic and antifungal activities. This activity has been ascribed to several structurally diverse groups of secondary metabolites, which are simultaneously produced by *Chondromyces crocatus*. *Chondromyces crocatus* strains have long been recognised as an important source of biologically active natural products notably, the crocacins A-D and the chondramides A-D (Figure 4). Crocacin A, the most abundant member of the crocacin family of *N*-acyl dipeptides, effectively inhibits the growth of yeasts and fungi. Chondromides A-D are new cyclo-depsipeptides that exhibit high cytostatic activity against mammalian cell lines.[13,14]

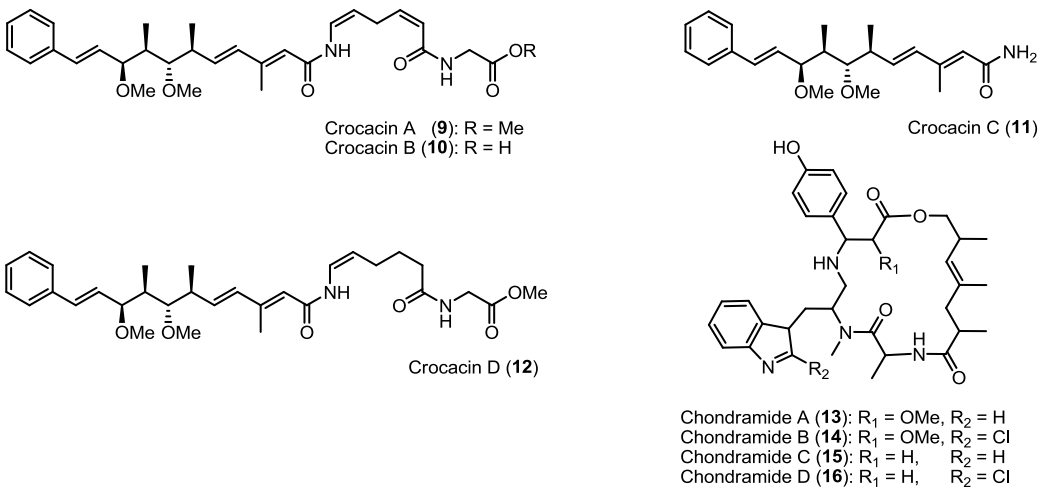


Figure 4 **Notable Secondary Metabolites Isolated From *Chondromyces Crocatus***

Ajudazols A and B were isolated in 2003 as a result of screening of myxobacteria for new biologically active compounds. Advanced analysis of crude extracts of *Chondromyces crocatus* cultures led to the discovery of the ajudazols, together with the isolation of new β-amino styrenes, the chondrochlorens.[11]

The antifungal activity of the ajudazols has been partly assessed. Ajudazol A, the major metabolite, showed only minor activity against a few fungi and Gram-positive bacteria. However ajudazol B inhibited the growth of several important fungi: *Botrytis cinerea*, *Trichoderma koningii*, *Giberella fujikuroi* and *Ustilago maydis*.[13] It also exhibited weak activity against several Gram-positive bacteria. *Botrytis cinerea* is a fungus that causes grey rot which, although welcomed in the wine industry, can have a severe effect on many plant species. Furthermore, *Ustilago maydis* (corn smut) causes smut disease on maize and, if untreated, can ruin entire harvests.

The ajudazols have been identified as inhibitors of the bacterial mitochondrial electron transport chain at low nanomolar concentrations; the ajudazols showed inhibition of nicotinamide adenine dinucleotide oxidation in submitochondrial particles with an IC_{50} of 13.0 ng/mL (22.0 nM) for ajudazol A. Ajudazol B was marginally more potent at 10.9 ng/mL (18.4 nM).

Structurally, the ajudazols showcase a number of highly unusual features. The most notable feature is the isochroman-1-one core: a fused phenol-lactone bicyclic unit (Figure 5). The bi-cycle possesses hydroxyl functionality at the C8 position and an alkyl chain extending out from the C9 position.

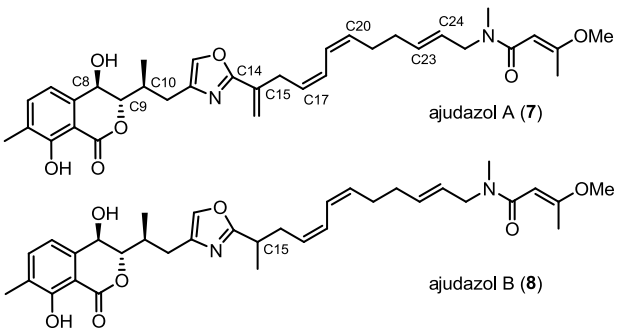


Figure 5 **The Structure of the Ajudazols**

Other than the isochromanone core, the ajudazols boast an extended side chain containing a 2,5-substituted oxazole (C12-C14), a *Z*,*Z*-diene (C17-C20) and an *E*-olefin (C23-C24), together with a *(E)*-3-methoxy-*N*-methylbut-2-enamide moiety, previously unprecedented in natural product synthesis. The ajudazols A and B differ only at the C15 position: ajudazol A has an *exo*-methylene olefin whereas ajudazol B bears a fully saturated methyl group, the stereochemistry of which is unassigned.

Extensive NMR studies have been carried out to assign the stereochemistry of ajudazols A and B. The C8, C9 and C10 protons have a *trans*-stereochemical relationship with one another and this relative stereochemical configuration of the isochromanone core unit, together with the *Z,Z,E*-triene, were assigned on the basis of NOESY and ^{1}H–^{1}H coupling constant analysis; however, the stereochemistry of the C15 methyl group of ajudazol B could not be assigned. Likewise, the absolute stereochemistry of the ajudazols remains to be determined.[11]

1.3 4-Hydroxyisochromanones

The 4-hydroxyisochromanone motif is a biologically relevant building block that is present in a number of biologically active compounds including the ajudazols A (**7**) & B (**8**), 4-hydroxymellein (**17**), (4*R*)-hydroxyochratoxin A (**18**),[15] acetoxy-geranyloxymellein (**19**),[16] thailandolide B (**20**),[17] bergenin (**21**),[18] and the *Helminthosporium monoceras* antifungal metabolite monocerin (**22**) (Figure 6).[19]

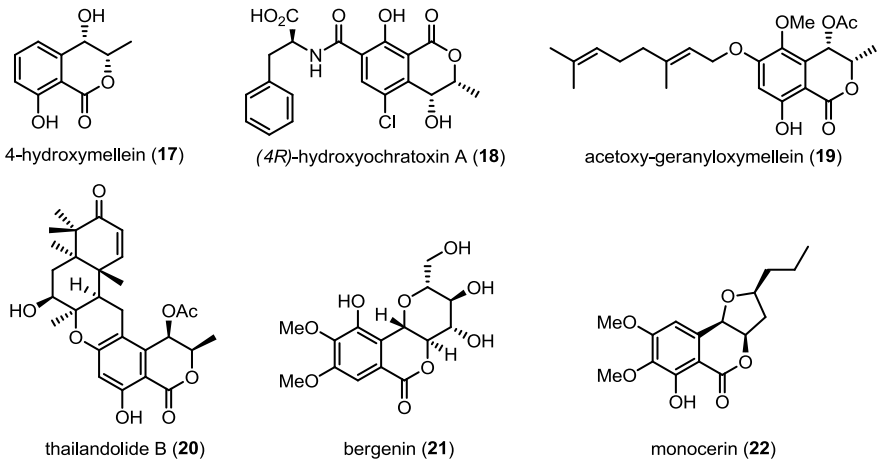
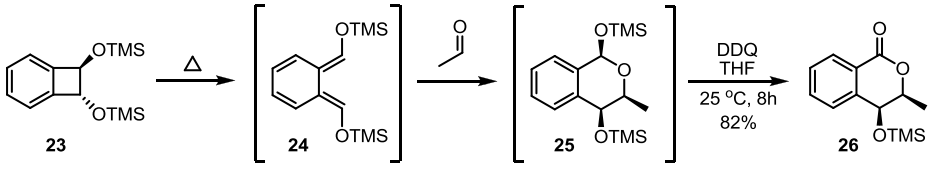


Figure 6 **Hydroxyisochromanone Containing Natural products**

Synthetically, 4-hydroxyisochromanones have been approached via four distinct methods, with one approach coming from within our research group *(vide infra)* and two novel approaches appearing within the past year. The recent interest towards the synthesis of 4-hydroxyisochromanones from within the chemical community highlights their importance, due to their presence in structurally interesting natural products, coupled with their biological and pharmacological potential.

1.3.1 Danishefsky's Approach to 4-Hydroxyisochromanones

In 2000, Danishefsky reported an approach for the synthesis of 4-hydroxyisochromanones, utilizing *ortho*-quinone dimethides in intermolecular hetero-Diels-Alder cycloadditions (Scheme 1).[20] Under thermal conditions, 1,2-*trans*-benzyloxycyclobutane **23** undergoes facile ring opening to generate ortho-quinone dimethide **24**, an intermediate that can then function as a diene in Diels-Alder reactions. Diene **23** reacts with ethanal to generate the hetero-Diels-Alder intermediate **25**, which is oxidized *in situ* to afford 4-silyloxyisochromanone **26** in excellent yield under mild reaction conditions.



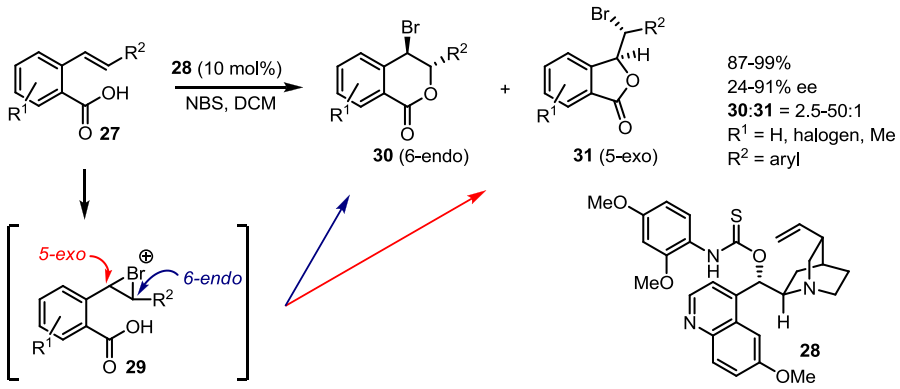
Scheme 1 **4-Hydroxyisochromanones from 1,2-*Trans*-Benzyloxycyclobutanes**

This ground-breaking methodology constituted the first completely stereodefined [4+2] intermolecular Diels-Alder cycloaddition of dienes with unactivated aldehydes, in the absence of catalytic activation.[21]

1.3.2 Yeung's Approach to 4-Hydroxyisochromanones

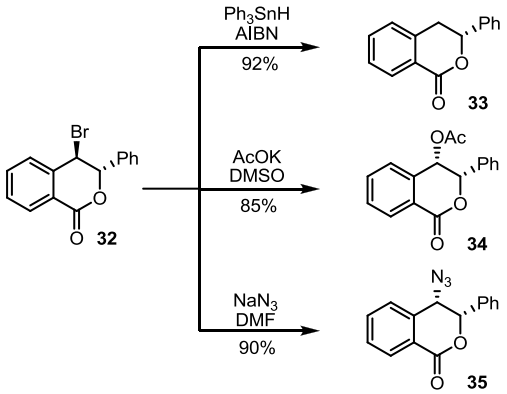
In late 2011, Yeung reported an enantioselective approach towards 4-hydroxyisochromanone synthesis through the bromocyclisation of styrene-type carboxylic acids.[21] The synthetic route allows for the synthesis of various 4-functionalised-isochromanone derivatives, accessible from a common late-stage intermediate (Scheme 2).

Mechanistically, the styrene-type carboxylic acid **27** undergoes an enantioselective bromocyclisation, using NBS as stoichiometric oxidant, in the presence of the chiral amino-thiocarbamate catalyst **28**, to generate the bromonium species **29**. The 4-bromoisochromanone product **30**, the result of 6-*endo* cyclisation, is formed in strong preference to the phthalide (5-*exo*) species **31**. In general, high yields, together with excellent levels of enantioselectivity are achieved (Scheme 2).



Scheme 2 **Yeung's Bromocyclisation Route to 4-Bromoisochromanones**

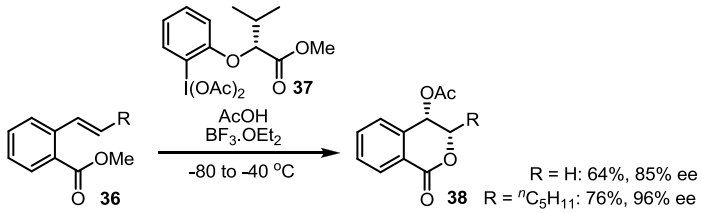
Yeung then showed that the 4-bromoisochromanone moiety **32** could be used to access various isochromanone building blocks (Scheme 3). Radical debromination of 4-bromoisochromanone **32**, allowed access to the deshydroxyisochromanone **33**. Alternatively the bromide could be displaced by nucleophilic acetate displacement to generate the oxygenated core **34**, while azide displacement allowed entry to the nitrogen substituted core **35**. Inversion of stereochemistry of the 4-bromo-isochromanone ensured that the oxygen and nitrogen analogues **34** and **35**, displayed *syn* stereochemistry (C3-C4).[21]



Scheme 3 **4-Bromoisochromanone Functionalisation**

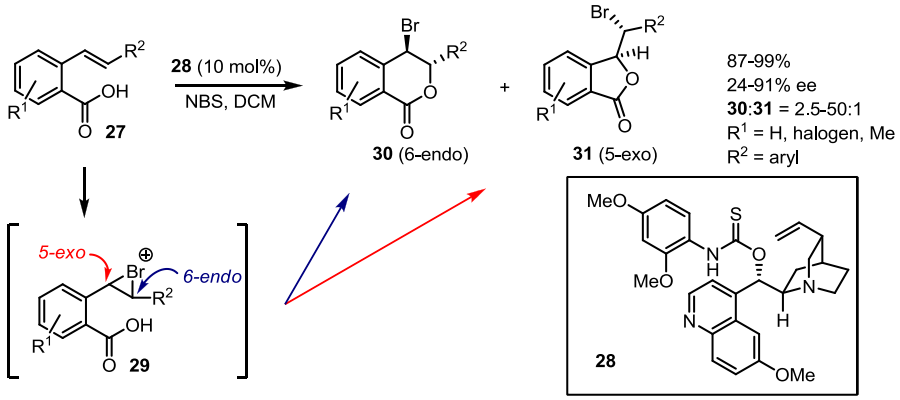
1.3.3 Fujita's Approach to 4-Hydroxyisochromanones

A month after Yeung's report, Fujita reported methodology for the asymmetric synthesis of 4-hydroxyisochromanones *ortho*-alkenylbenzoate substrates.[22] The stereoselective oxylactonisation of *ortho*-alkenylbenzoate **36** proceeds in the presence of the chiral hypervalent iodine oxidant **37**, to afford, almost exclusively, the 6-*endo* cyclisation product **38** in good yield and enantioselectivity (Scheme 4).



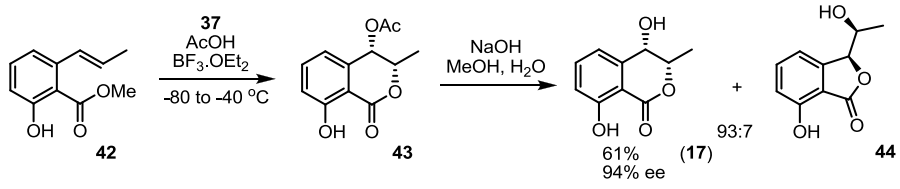
Scheme 4 **Fujita's Oxylactonisation Route to 4-Hydroxyisochromanones**

Based on the *syn* selectivities observed, mechanistically, it was proposed that the (diacetoxyiodo)arene is activated by the Lewis acid, followed by asymmetric electrophilic addition of the activated iodine(III) reagent **37** to the alkene substrate **36**. From intermediate **39**, two consecutive nucleophilic displacements lead to the 4-acetoxyisochromanone product **38**. Mechanistically, two possible pathways may exist. The initial nucleophilic displacement of **39** may occur via Path A where the acetate counterion acts as a nucleophile at the benzylic position, where the building positive charge can be delocalised, to generate intermediate **40**. The ensuing participation of the internal carboxylate leads to the departure of the aryliodonio group and this second nucleophilic displacement with inversion generates the 4-acetoxyisochromanone product **38**. Fujita believed that reaction pathway B is unlikely because substrates of type **41** gave similar regioselectivity independent of the nucleophilicity of the internal carboxylate. If the reaction proceeded via **41**, the stereochemical purity of product **38** would have decreased, owing to facile elimination of the aryliodonio group at the benzyl position of intermediate **39** in an S_N1 fashion (Scheme 5). [22,23]



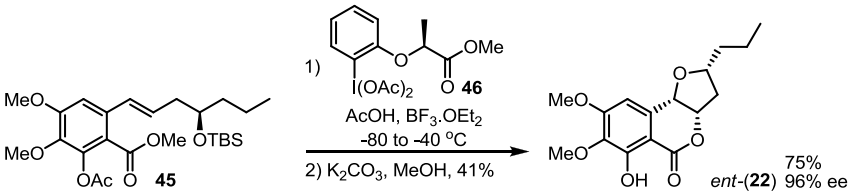
Scheme 5 **Mechanism for Fujita's Oxylactonisation Route to 4-Hydroxyisochromanones**

Fujita applied this methodology towards the synthesis of 4-hydroxyisochromanone polyketide derivatives. Hydroxymellein (**17**) was accessed via the asymmetric oxylactonisation of *ortho*-alkenylbenzoate **42**, via hydrolysis of the acetylated intermediate **43** (Scheme 6).



Scheme 6 **Fujita's Synthesis of Hydroxymellein**

The antipodal enantiomer of monocerin *ent*-(**22**) was generated from *ortho*-alkenylbenzoate **45** via hypervalent iodine oxylactonisation, with the silyloxy tether acting as an internal nucleophile to afford the tricyclic product in good yield and excellent enantiocontrol (Scheme 7).[22]

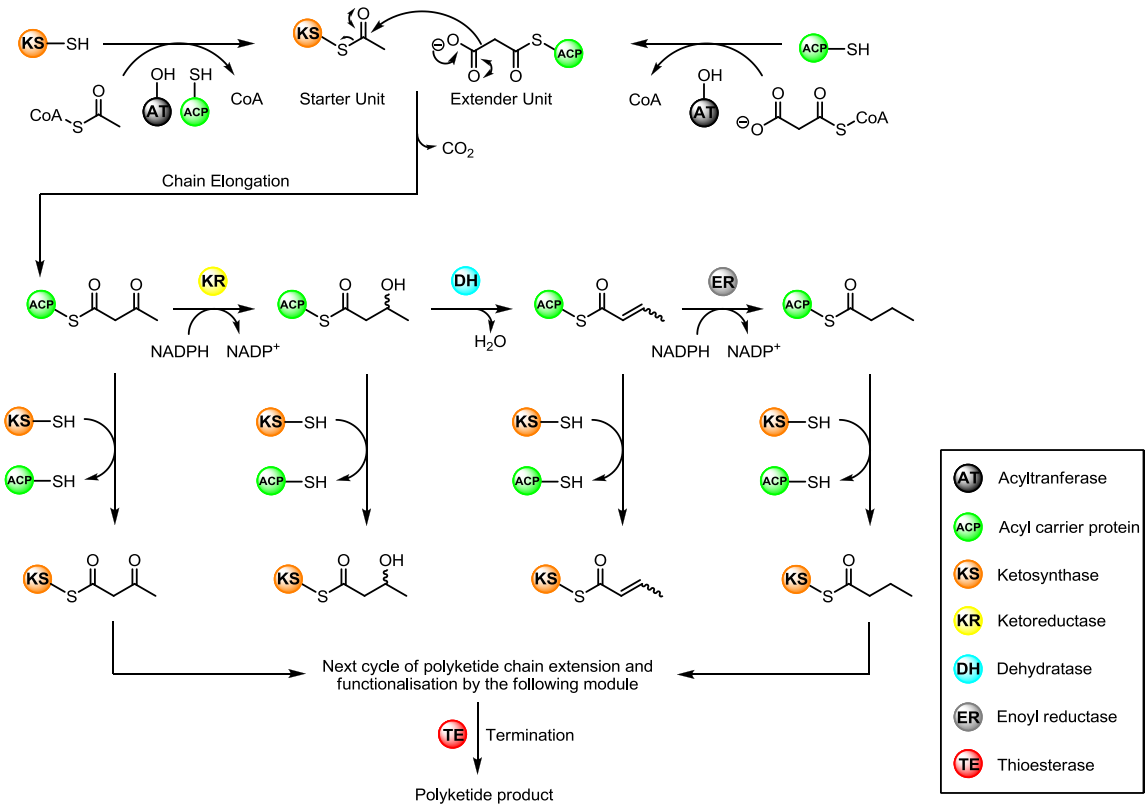


Scheme 7 **Fujita's Synthesis of Monocerin *ent*-(22)**

1.4 Biosynthesis of the Ajudazols

Polyketides are a large class of secondary metabolites that are found in bacteria, plants, fungi and animals. Type I polyketide synthases (PKSs) are large, covalently bound multienzyme complexes which are responsible for the biosynthesis of a plethora of polyketide natural products. Biosynthetically, polyketide formation occurs by the catalytic action of PKS multienzymes in a highly co-ordinated assembly-line, wherein each catalytic step is attributable to a specific domain. The organisation of modules within a specific domain, together with the catalytic activities present in each module ultimately determines the structure of the polyketide chain. Thus, polyketides are generated in a fashion analogous to fatty acid biosynthesis.[24]

In modular PKSs, the polyketide chain is assembled by the stepwise condensation of activated carboxylic acid-derived units. The growth of the polyketide carbon chain is initiated by the condensation of a starter unit with an extender unit. The starter and extender units are present in the host as CoA thioesters. The starter units are derived from acetyl-CoA or propionyl-CoA, while malonyl-CoA and methylmalonyl-CoA are the typical extender units; however, various acetyl-CoA derivatives that are activated by carboxylation at the α-position may also be used. The CoA-bound starter group is loaded onto the acyl carrier protein (ACP) domain of the PKS starter module, a process catalysed by the acyltranferase (AT) domain. The starter group is then transferred to the ketosynthase (KS) domain of the current module, whilst the extender group is loaded onto the ACP domain. Decarboxylation of the ACP-bound elongation group then promotes a Claisen condensation with the KS-bound starter group, under CO_2 evolution, to furnish a free KS domain and the ACP-bound elongated chain (Scheme 8).[24]

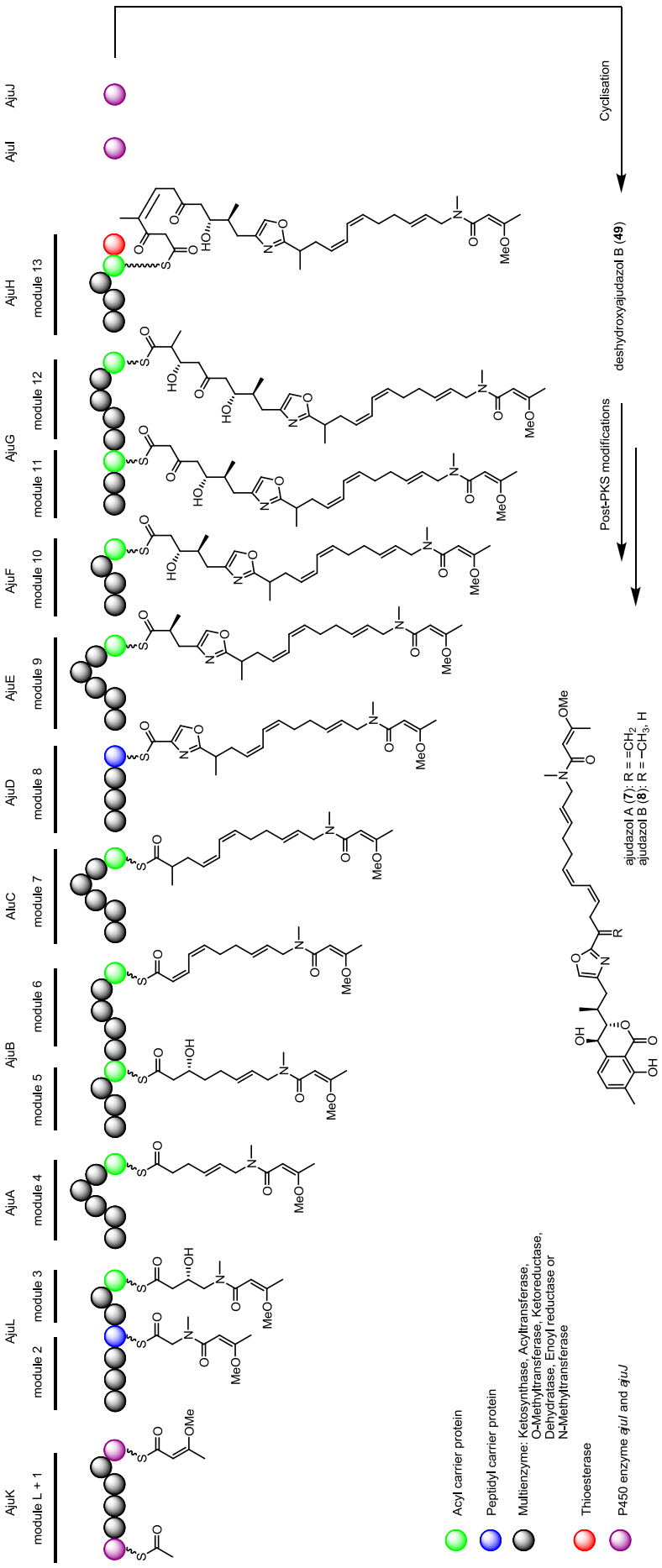


Scheme 8 Polyketide Biosynthesis

The fate of the resultant elongated diketide depends on whether post-ketosynthase modifications are present in the module. Functional ketoreductase (KR), dehydratase (DH) or enoylreductase (ER) can act to promote one or more of the sequential reactions of ketoreduction, dehydration and enoylreduction, to generate compounds containing a hydroxyl group, unsaturated double bond or fully reduced carbon. Therefore the variety of extender units available, together with multiple post-KS modifications available, provides great potential to introduce structural diversity, with asymmetric reduction introducing chirality. Following post-KS modification, the elongated chain is transferred to the KS domain of subsequent modules, allowing for further chain elongation as it passes through each domain of the assembly line (Scheme 8).

The growing polyketide chain can pass through numerous elongation and functionalisation stages in a pre-determined order, as determined by the PKS multienzyme. Once complete, the polyketide chain enters the termination stage. The thioesterase (TE) domain releases the completed polyketide from the PKS multienzyme via either hydrolysis or cyclisation (alcoholysis or aminolysis) (Scheme 8).

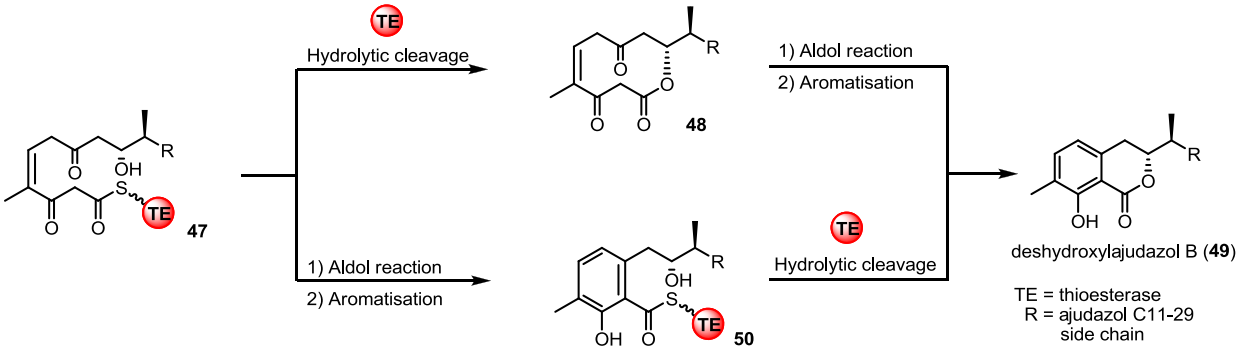
As far as the ajudazols are concerned, the gene cluster in *Chondromyces crocatus* Cm c5 that is responsible for their biosynthesis, was identified by Buntin and co-workers.[25] Although the shared backbone of both ajudazols could be predicted to arise from a mixed system of type I PKS and non-ribosomal polyketide synthase (NRPS), the origins of the isochromanone unit and the *exo*-methylene of ajudazol B are not clear, as neither of these units are obvious products of classical assembly-line biosynthesis.



Scheme 9 **Biosynthesis of the Ajudazols**

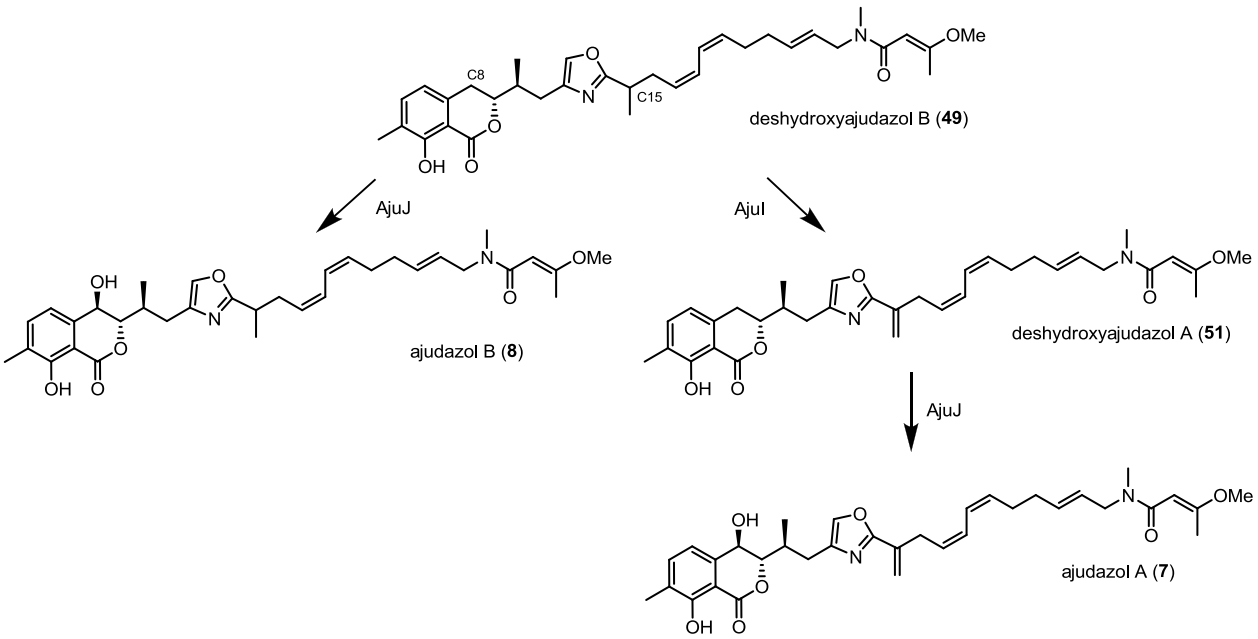
Biosynthetically, ajudazol formation requires the growing chain to pass through a total of 13 modules, with various PKS and NRPKS domains introducing the necessary functionality, until the termination stage is reached. Importantly, the biosynthetic machinery does not incorporate a terminal cyclase, but a variant thioesterase (TE) domain. Upon reaching the end of the PKS-NRPS assembly line, the elongated ajudazol chain is transacylated onto the serine active site of the terminal TE domain (Scheme 9).[25]

Two mechanisms have been postulated for TE catalysed chain release and isochromanone ring formation. Mechanism A involves TE catalysed lactonisation between the C9Hydroxyl group and the acyl terminus to generate the 10-membered lactone **48**, with chain release from the protein. Subsequent intramolecular aldol condensation and aromatisation affords the isochromanone ring of deshydroxyajudazol B (**49**). Alternatively, for mechanism B, aromatisation occurs whilst the chain is still bound to TE, to generate intermediate **50**, followed by TE catalysed lactonisation and chain release, to generate the lactone ring of deshydroxyajudazol B (**49**) (Scheme 10).



Scheme 10 **Thioesterase Catalysed Chain Release in Ajudazol Biosynthesis**

Biosynthetically, ajudazols A and B share a common PKS-NRPS assembly line, followed by TE catalysed isochromanone generation and chain release, resulting in the common metabolite, deshydroxyajudazol B (**49**). Following release from the protein cluster, deshydroxyajudazol B (**49**) undergoes several post-PKS modifications in order to generate the hydroxyl functionality at C8 and the C15 *exo*-methylene of ajudazol A. The enzymes *ajuI* and *ajuJ*, are responsible for these late stage post PKS modifications. *AjuI* is responsible for C15 dehydrogenation while *ajuJ* is responsible for C8Hydroxylation. Again, two possible pathways have been proposed. If deshydroxyajudazol B (**49**) acts first with *ajuJ*, the product, ajudazol B (**8**), is no longer a substrate for *ajuI*. However, if deshydroxyajudazol B (**49**) acts first as a substrate for AjuI then the resulting deshydroxyajudazol A (**51**) can then react with *ajuJ* to generate ajudazol A (**7**). The fact that ajudazol A is the major metabolite isolated from *Chondromyces crocatus,* would suggest that *ajuI* is the more efficient enzyme, and hence, the second route is the preferred pathway (Scheme 11).[25,26]



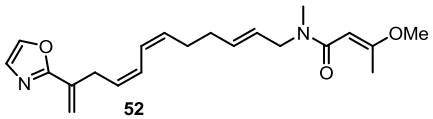
Scheme 11 Post-PKS Modifications in Ajudazol Biosynthesis

1.5 Approaches Towards the Total Synthesis of the Ajudazols

The combination of unusual structural features, coupled with their biological activity makes the ajudazols highly attractive synthetic targets. As such, they have received notable interest from the chemical community. To date, a complete total synthesis of either ajudazol A or B is yet to be reported; however, two research groups besides our own have published their respective approaches and progress towards the total synthesis of the ajudazols.[27-29]

1.5.1 Taylor's Synthesis of Ajudazol Eastern Section 52

In 2004, Taylor reported his approach to the synthesis of the C12-C29 fragment of ajudazol A **52**, showcasing a one-pot double acetylene carbocupration to efficiently generate the internal *Z,Z*-diene (Figure 7).[29]

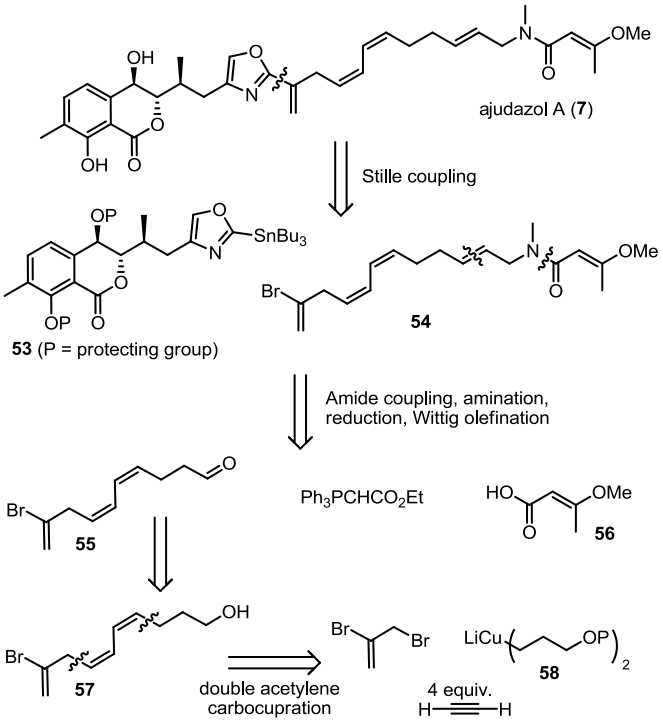


52

Figure 7 Taylors Ajudazol A Eastern Section 52

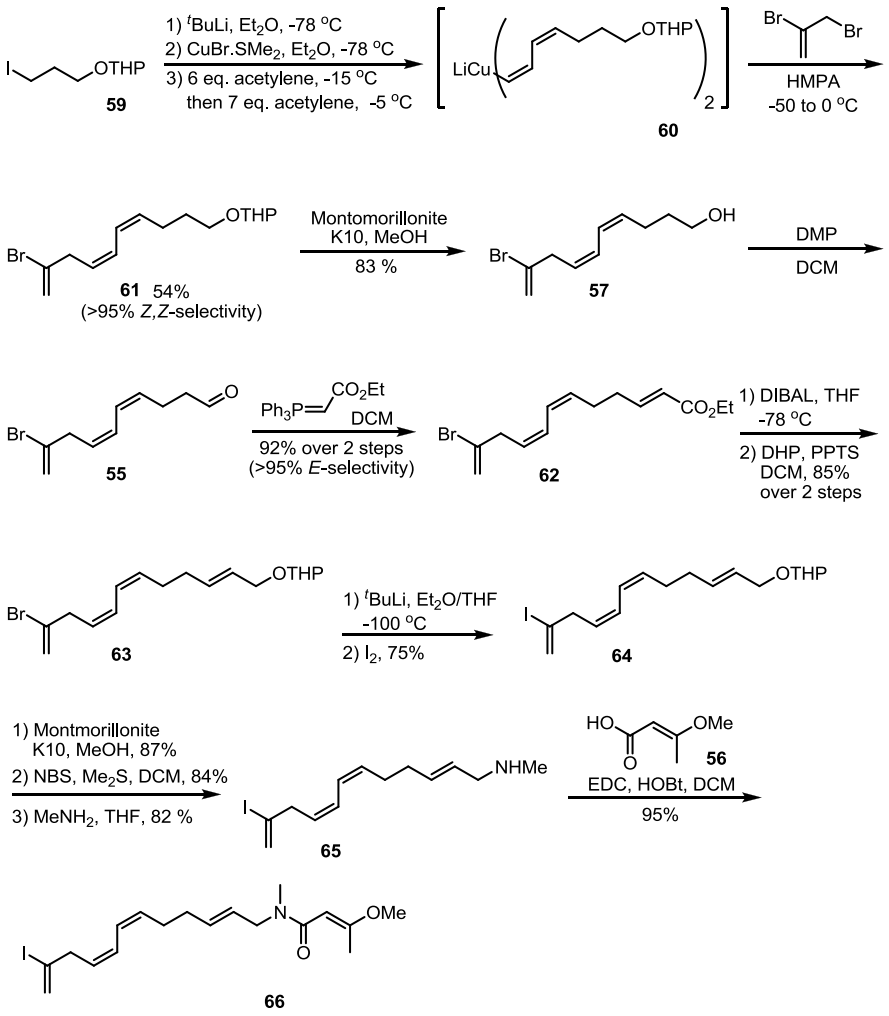
Taylor's retrosynthetic approach towards ajudazol A relied on the key Stille disconnection to generate the 2-stannyl-oxazole **53** and vinyl bromide **54,** comprising the eastern side-chain unit (Scheme 12). This convergent route, involving the introduction of the eastern side-chain **15**, as a late stage intermediate, was specifically devised to circumvent any potential side reactions that could occur between the oxazole or isochromanone portions of the molecule and reactive intermediates that would be required to otherwise construct the polyene side chain. Retrosynthetic analysis of the side-chain **54** suggested an amide coupling with 3-methoxybutenoic acid **56** as the final step, preceded by an amination and *E*-selective Wittig olefination to suggest the polyene-aldehyde **55** as a suitable precursor. Aldehyde **55** would be accessible from alcohol **57** which, in turn, could be constructed via the key double acetylene

carbo-cupration reaction of propoxylithium cuprate **58**, followed by trapping with 2,3-dibromopropene.



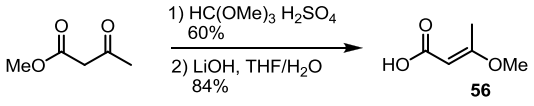
Scheme 12 **Taylor's Retrosynthesis of Ajudazol A**

Taylor's synthesis commenced with the stereocontrolled double acetylene carbocupration of the readily available THP-protected 3-iodopropanol **59**, to generate the *Z,Z*-dienyl cuprate intermediate **60** (Scheme 13). This was quenched with 2,3-dibromopropene to afford the desired diene **61** in 54% yield and excellent *Z,Z*-selectivity (>95%). The highly efficient double acetylene carbocupration is a variant of the Normant reaction: the nucleophilic addition of organocuprate reagents to acetylene or terminal alkynes to yield alkenyl copper compounds.[30] Taylor had previously utilized this double acetylene carbocupration methodology in his syntheses of navel orangeworm pheromone and leukotriene B_4 analogues.[31]



Scheme 13 **Taylor's Synthesis of Polyene Eastern Fragment 66**

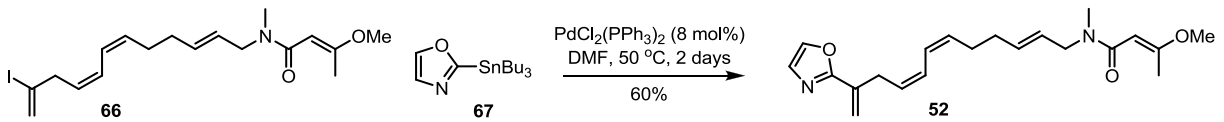
The THP-protected diene **61** was deprotected and the resulting alcohol **57** was oxidized to the corresponding aldehyde **55**, under Dess-Martin conditions. Wittig olefination yielded the desired *E*-configured α,β-unsaturated ester **62** in excellent yield. Ester reduction followed by THP protection of the resulting alcohol occured in 85% yield. Vinyl bromide **63** was then converted to the corresponding vinyl iodide **65** in 75% yield, via lithium-halogen exchange with ^{t}BuLi and iodine. This halogen interconversion was necessary because their studies revealed that the vinyl bromide species **54** was insufficiently reactive as a Stille coupling partner. Compound **64** was then deprotected and the resulting alcohol was converted to the corresponding bromide which was displaced with methylamine to generate the desired allylic amine **65**. Peptide coupling with 3-methoxybutenoic acid **56** afforded amide **66** in excellent yield (Scheme 13). 3-Methoxybutenoic acid **56** was synthesized from methyl acetoacetate in two steps following literature procedure (Scheme 14).[32]



Scheme 14 **Synthesis of 3-Methoxybutenoic Acid 56**

The key and final step to Taylor's synthesis of the C12-C29 eastern fragment of ajudazol A **52** involved the convergent Stille cross-coupling between vinyl iodide **66** and stannyl oxazole **67**. Unfortunately, polyene **66** proved to be unstable under high temperatures (>100 °C). After

extensive optimisation, the C12-C29 fragment **52** was best achieved using $PdCl_2(PPh_3)_2$ in DMF. The relatively low reaction temperature was vital in order to avoid any substantial product degradation (Scheme 15).

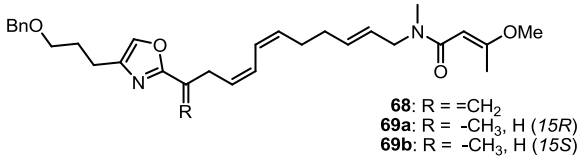


66 67 52

Scheme 15 **Stille Coupling to Access C12-C29 Ajudazol A Fragment 52**

1.5.2 Rizzacasa's Synthesis of Ajudazol A & B C9-C29 Eastern Fragments

Rizzacasa reported his approach to the synthesis of the C9-C29 fragment of both ajudazols A **68** and B **69** in 2007. The ajudazol fragment generated by the Rizzacasa group differs from Taylor's only by way of an additional alkoxy tether at the oxazole C4 position (Figure 8).[27]

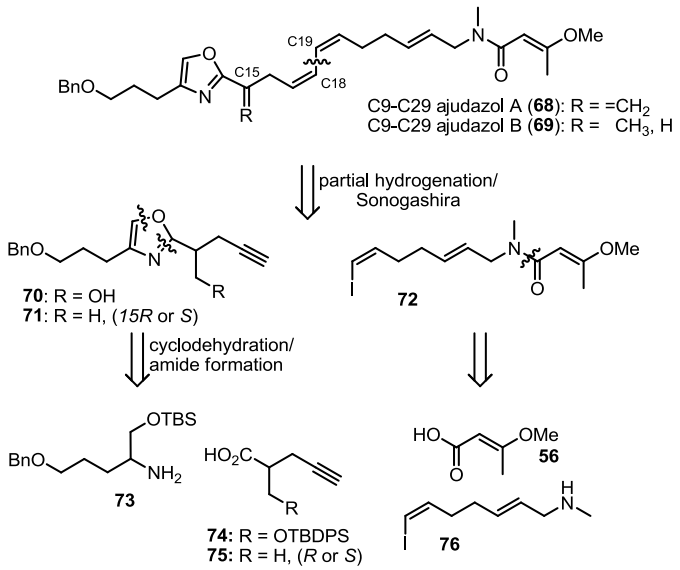


68: R = =CH_2
69a: R = -CH_3, H (*15R*)
69b: R = -CH_3, H (*15S*)

Figure 8 **Rizzacasa's C9-C29 Eastern Fragments of Ajudazol A & B**

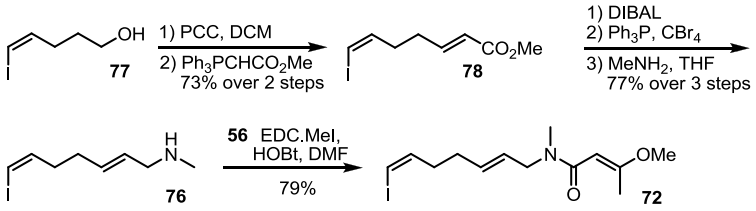
Rizzacasa envisaged a convergent approach in which both ajudazol A and B model systems could arise from common late stage intermediates. For Ajudazol A, the key Sonogashira reaction between alkyne fragment **70** and vinyl iodide **72** would generate the C18-C19 bond of the ajudazol A C9-C29 fragment **68**, in a convergent manner. Partial hydrogenation would then yield the desired *Z,Z*-diene functionality in a stereoselective fashion, followed by dehydration to generate the C15-olefin and complete the synthesis of the ajudazol A C9-C29 fragment **68**. It was envisioned that the ajudazol B system **69** would be accessed via the coupling of the same late-stage fragment **72** with either enantiomer of the chiral acetylene **71*R*** or **71*S***, followed by stereoselective enyne reduction to generate either enantiomer of the ajudazol B C9-C29 fragment **69a** and **69b** (Scheme 16).

The vinyl iodide fragment **72** could be accessed via the amide coupling between 3-methoxybutenoic acid **56** and amine **76.** Oxazole units **70** and **71*R*/*S*** would be obtained by the cyclodehydration of the amide generated from condensation of amine **73** and either acid **74** (for C9-C29 ajudazol A fragment **68**) or enantiopure acids **75*R*** and **75*S*** (for C9-C19 ajudazol B diastereoisomers **69a** and **69b**) (Scheme 16).



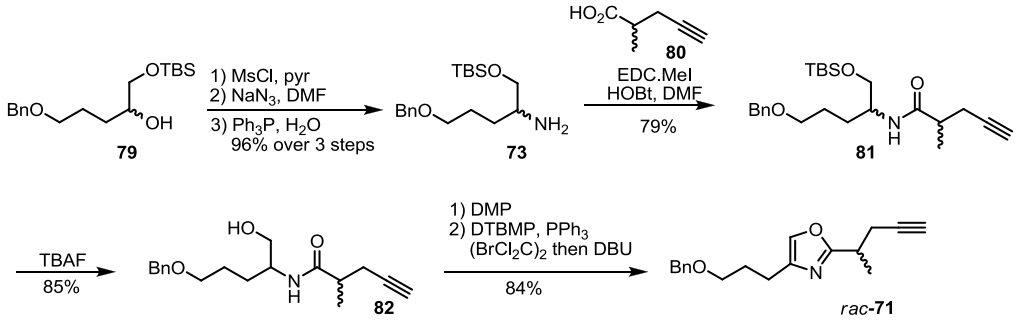
Scheme 16 **Rizzacasa's Retrosynthesis of C9-C29 Ajudazol A & B Fragments**

Rizzacasa's synthesis of the C9-C29 fragments of ajudazol A **68** and B **69** commenced with the known alcohol **77**, which was oxidized to the corresponding aldehyde and subjected to *E*-selective Wittig olefination to generate diene **78**. Ester reduction, followed by bromination of the resulting alcohol and displacement with methylamine, afforded the secondary amine **76**. Amide coupling with 3-methoxybutenoic acid **56** generated the key vinyl iodide **72** (Scheme 17).



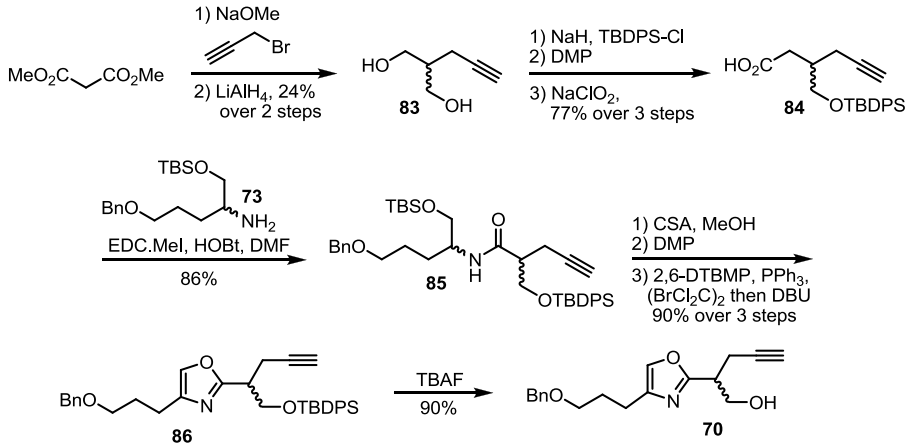
Scheme 17 **Synthesis of Vinyl Iodide 72**

The synthesis of the ajudazol B acetylene fragment *rac*-**71** began from the known racemic alcohol **79**, which was converted into amine **73** in a 3-step sequence in excellent yield. Amine **73** then underwent peptide coupling with the racemic carboxylic acid **80** to afford amide **81** as a mixture of diastereoisomers. Silyl deprotection followed by oxidation of the subsequent alcohol **82**, afforded the aldehyde intermediate, which upon cyclodehydration, generated the racemic oxazole *rac*-**71**, in excellent yield (Scheme 18).



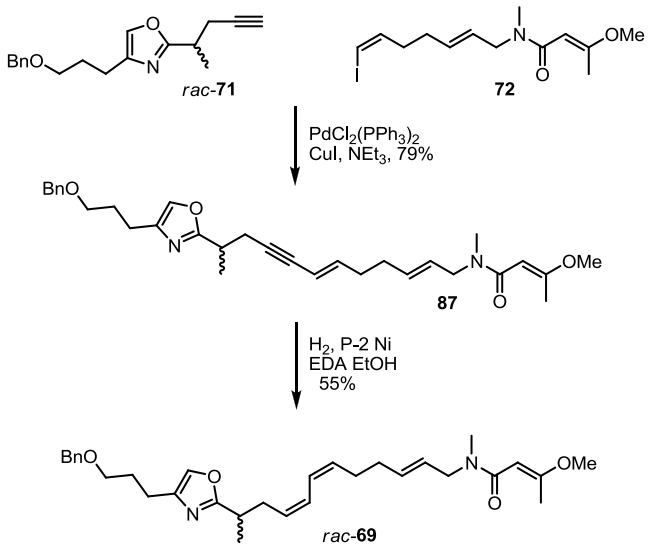
Scheme 18 **Synthesis of the Ajudazol B Acetylene Fragment *rac*-71**

On the other hand, the synthesis of the oxazole unit **70**, present in ajudazol B C9-C29 fragment **69**, commenced with the alkylation of dimethyl malonate with propargyl bromide, followed by reduction to the corresponding diol **83** in low overall yield. The diol **83** was mono-protected and the resultant alcohol was oxidised to afford racemic acid **84** in good yield. Subsequent peptide coupling with amine **73** generated amide **85**. Regioselective deprotection followed by oxidation of the newly obtained alcohol, afforded the aldehyde intermediate that underwent cyclodehydration to generate the racemic oxazole **86** in high yield. Deprotection afforded primary alcohol **70** (Scheme 19).



Scheme 19 **Synthesis of the Ajudazol A Acetylene Fragment 70**

Having synthesized the common vinyl iodide side chain **72**, together with the oxazole-alkyne unit *rac*-**71**, Rizzacasa sought to attempt the crucial C18-C19 coupling reaction. Sonogashira cross-coupling between acetylene *rac*-**71** and vinyl iodide **72** proceeded in good yield to generate enyne **87**. Subsequent stereoselective partial hydrogenation using P-2 nickel catalysis afforded the racemic ajudazol B C9-C29 fragment *rac*-**69** in 55% yield (Scheme 20).

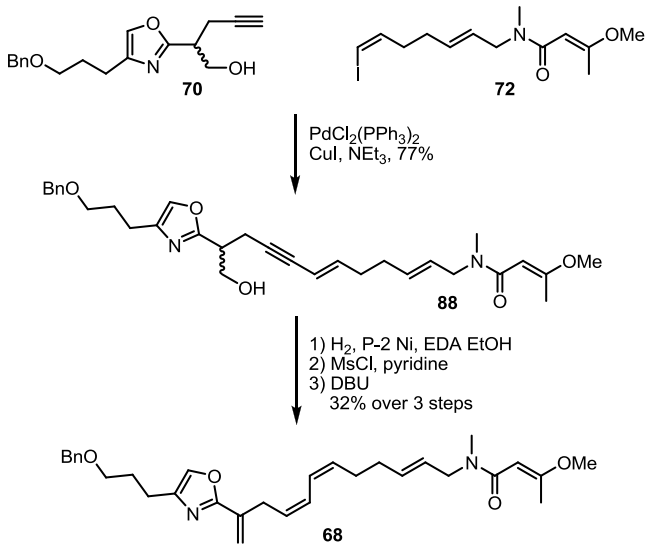


Scheme 20 **Synthesis of C9-C29 Ajudazol B Fragment *rac*-69**

Rizzacasa also demonstrated that this route could be modified to allow for the enantioselective synthesis of ajudazol B. Both enantiomers of acid **75** were synthesized and used to generate both enantiomers of oxazole-aldehyde **71**. This enantioselective approach would allow for either enantiomer of the ajudazol B C9-C29 fragment to be synthesized,

[33]merely by selecting the appropriate acid coupling partner. However, despite this, no enantioselective synthesis of the ajudazol B C9-C19 fragment **69** was reported.

On the other hand, Sonogashira coupling between acetylene **70** and vinyl iodide **72** proceeded in good yield to generate enyne **88**. Partial hydrogenation of the enyne unit followed by dehydration yielded the ajudazol A C9-C19 fragment **68** (Scheme 21).

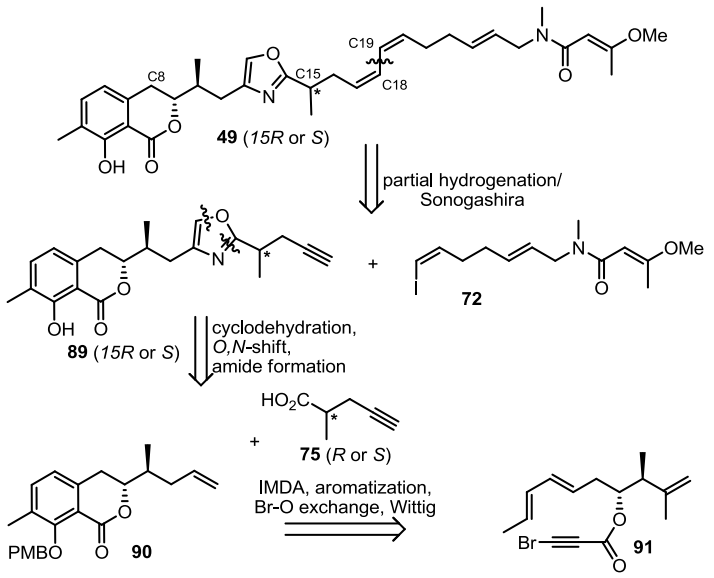


Scheme 21 Synthesis of C9-C29 Ajudazol A Fragment 68

1.5.3 Rizzacasa's Synthesis of 8-Deshydroxyajudazol B 49

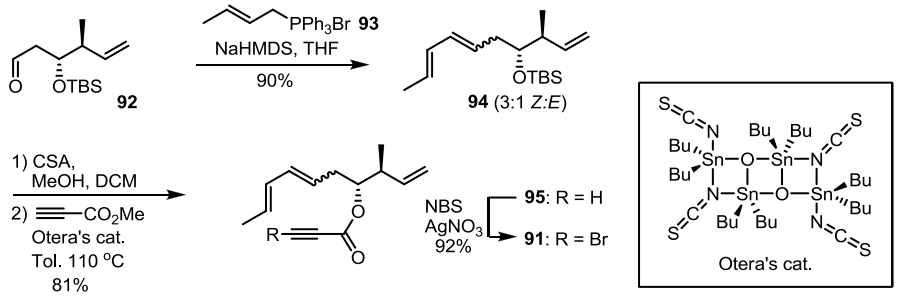
In 2011, Rizzacasa reported the synthesis of the *15R*-isomer of deshydroxyajudazol B **49**, a compound that is believed to be a putative intermediate in the biosynthesis of both ajudazol A and B (Scheme 11). The route took advantage of an intramolecular Diels-Alder reaction to generate the deshydroxyisochromanone unit, cyclodehydration chemistry to generate the oxazole and the previously reported Sonogashira/reduction protocol to synthesize the polyene side chain.[28]

Retrosynthetic analysis of the deshydroxyajudazol B **49** utilizes the Sonogashira coupling between terminal acetylene **89** and vinyl iodide **72**, followed by partial reduction, to secure the *Z,Z*-diene. It was predicted that the 2,4-substituted oxazole of **89** could be accessed via cyclodehydration of a β-formylamide, which in turn could be accessed from terminal olefin **90** and either enantiomer of carboxylic acid **75**, thereby allowing for the synthesis of both C15 stereoisomers of deshydroxyajudazol B **49**, in an efficient manner. It was envisioned that deshydroxyisochromanone **90** could be accessed via an intramolecular Diels-Alder reaction of the tethered dienyne **91** followed by subsequent aromatization, bromide-oxygen exchange, and Wittig extension (Scheme 22).



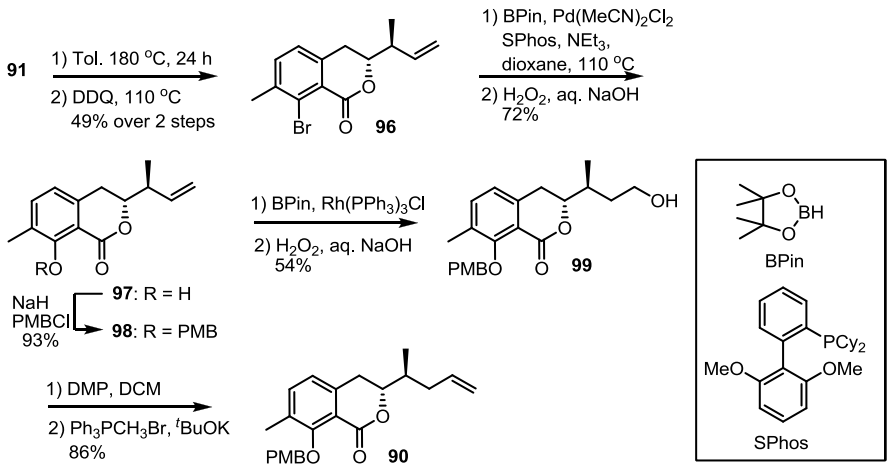
Scheme 22 **Retrosynthetic Analysis of 8-Deshydroxyajudazol B**

Synthesis of the intramolecular Diels-Alder precursor **91** began with the known enantiopure aldehyde **92**, which underwent Wittig olefination to yield diene **94**, as a 3:1 mixture of isomers, with the *E,Z*-diene being favoured. Silyl deprotection, followed by transesterification with methyl propynoate, generated ester **95**. Bromination of the acetylene moiety afforded the dienyne intramolecular Diels-Alder precursor **91** (Scheme 23).



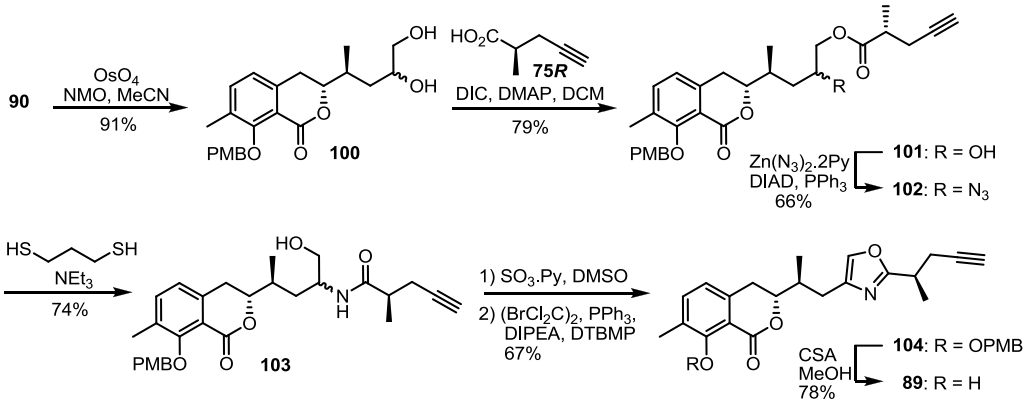
Scheme 23 **Synthesis of Intramolecular Diels-Alder Precursor 91**

The intramolecular Diels-Alder reaction of dienyne **91**, followed by oxidation of the Diels-Alder product, generated isochromanone **96** in 49% yield. Br-O exchange was achieved via a Miyaura borylation/oxidation sequence, generating phenol **97**, which was protected as PMB ether **98**. Hydroboration/oxidation of the terminal olefin **98** proved troublesome and required rhodium catalysis to obtain the terminal alcohol **99**. Oxidation followed by Wittig methylenation generated olefin **90** (Scheme 24).



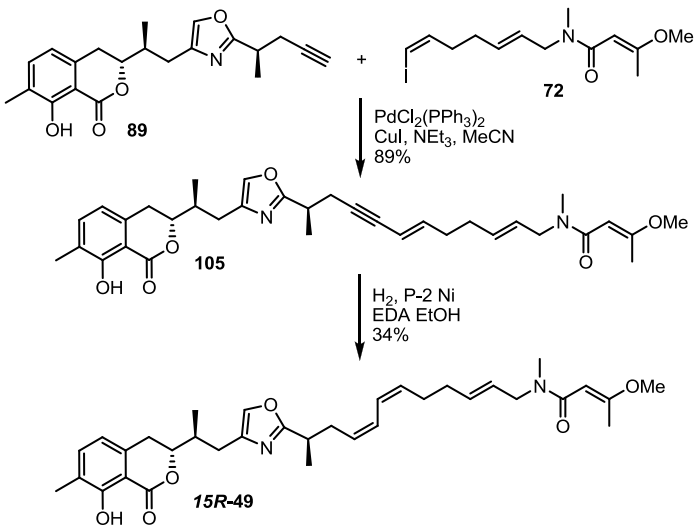
Scheme 24 Synthesis of Terminal Olefin 90

Upjohn dihydroxylation of olefin **90** afforded diol **100** as a mixture of diastereoisomers. Chemoselective esterification of diol **100** with enantiomerically pure **75*R*** yielded ester **101**. Mitsunobu conditions successfully generated the azide **102**. A one-pot azide reduction, followed by an *O,N*-acyl shift yielded β-hydroxyamide **103**. Finally, oxidation and cyclodehydration generated the *15R*-deshydroxyajudazol B western section **89** (Scheme 25).



Scheme 25 Synthesis of Terminal Acetylene 89

Sonogashira coupling between acetylene **89** and vinyl iodide **72** generated enyne **105**, generating the key C18-C19 bond. Partial hydrogenation, previously optimized on the earlier studies towards the ajudazol eastern fragment synthesis, was implemented on enyne **105** to afford the *15R*-isomer of deshydroxyajudazol B **49** in 34% yield (Scheme 26).

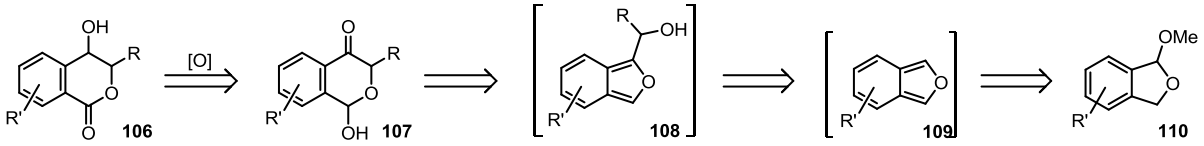


Scheme 26 **Rizzacasa's End-Game Route to *15R*-Deshydroxyajudazol B 49**

1.5.4 Preliminary Work within the Marquez Group

Until the most recent letter published by Rizzacasa, all synthetic efforts towards the synthesis of the ajudazols focussed on the oxazole-linked polyene eastern side-chain. On the contrary, research efforts within the Marquez group focussed on the synthesis of the western section of the ajudazols, with particular emphasis on the isochromanone core. In the Marquez approach, it was envisioned that the isochromanone functionality could be accessed via a modified Achmatowicz rearrangement, utilising the high reactivity of isobenzofurans (IBFs) as synthetic intermediates.

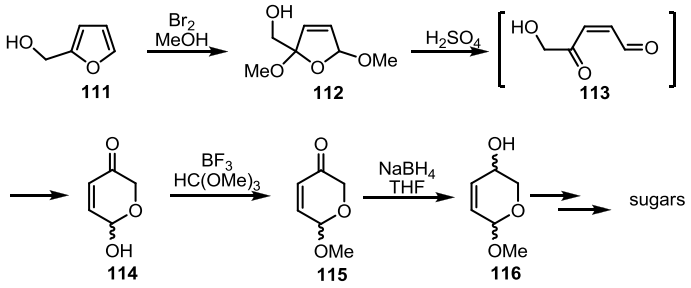
Retrosynthetically, it was hypothesised that isochromanone **106** could be accessed via oxidation and chemoselective reduction of keto-lactol **107**, which in turn could be generated via an Achmatowicz-type rearrangement of α-hydroxyisobenzofuran **108**. It was hypothesised that α-hydroxy-IBF **108** could be obtained by the lithiation and alkylation of IBF intermediate **109**, which could be generated from phthalan precursor **110** (Scheme 27).[33]



Scheme 27 **Retrosynthetic Analysis of Isochromanones via IBF Intermediates**

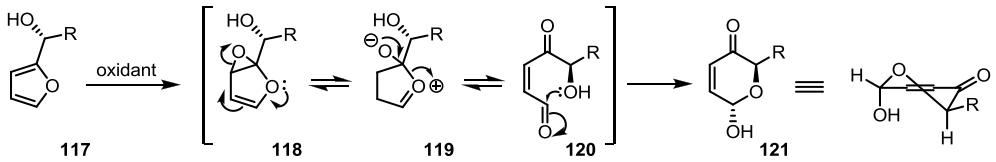
1.5.4.1 The Achmatowicz Rearrangement

The Achmatowicz rearrangement, first reported in 1971, involves the generation of α,β-unsaturated pyranones via the oxidative treatment of α-hydroxyfurans.[35] In the original publication, furfuryl alcohol **111** was treated with bromine in methanol to give the dihydrofuran derivative **112**, that in acidic conditions, underwent acetal cleavage to give the dicarbonyl species **113**, that immediately cyclised to afford the hydroxypyranone **114**. Alcohol protection, followed by ketone reduction, afforded the dihydropyran intermediate **116**, from which a variety of monosaccharides were synthesized (Scheme 28).



Scheme 28 **Original Achmatowicz Rearrangement of Furfuryl Alcohol 111**

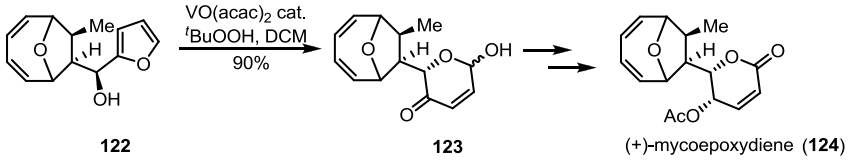
The accepted mechanism for the Achmatowicz rearrangement involves hydroxyl directed allylic epoxidation of furfuryl alcohol **117**, followed by ring opening to generate the transient 1,4-dicarbonyl species **120** via an initial zwitterionic intermediate **119**. Nucleophilic attack of the free hydroxyl onto the aldehyde functionality then generates the lactol product **121**, favouring the α-anomeric product (Scheme 29).



Scheme 29 **Mechanism of the Achmatowicz Rearrangement**

Various one-pot conditions for the generation of α,β-unsaturated pyranones from furfuryl alcohols have been developed since the original Achmatowicz report: NBS/H_2O,[36,37] peroxyacids, (in particular, *m*CPBA)[38-41] and $VO(acac)_2$/^{t}BuOOH has proved popular for this transformation.

The Achmatowicz rearrangement initially found widespread use in organic synthesis in the field of carbohydrate chemistry; [32,42,35] however, more recently it has been utilised in natural product synthesis for the generation of substituted pyran rings. The Achmatowicz rearrangement was implemented as the key step in the synthesis of (+)-mycoepoxydiene (**124**) by Tadano,[43] where $VO(acac)_2$/^{t}BuOOH was used to effectively generate the pyranone product **123** as a 2:1 mixture of anomers (Scheme 30).



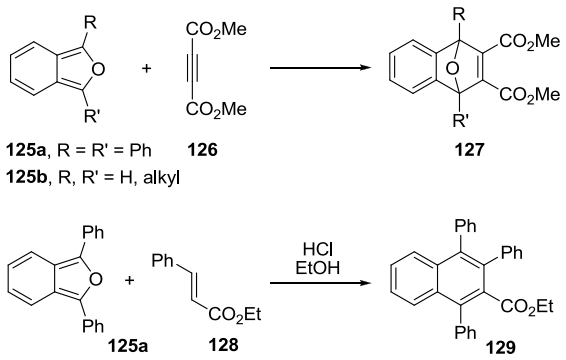
Scheme 30 **Utility of Achmatowicz Rearrangement in the Synthesis of (+)-Mycoepoxydiene (124)**

1.5.4.2 Isobenzofurans

IBFs are highly reactive 10π heteroaromatic compounds that readily polymerise at room temperature. The extreme reactivity of IBF is in contrast to the stable benzofuran which differs only in the placement of the heteroatom (Figure 9).[44]

Figure 9 **Benzofuran and Isobenzofuran**

A number of theoretical studies have been published to account for the instability of IBF.[45-49] The accumulation of these studies concluded that the resonance stabilisation and aromaticity in IBF is confined to the 5-membered heteroaromatic ring with two continuous, but virtually non-interacting π-systems. Hence, the extreme reactivity is believed to be attributable to the adjacent diene moiety. This structural feature allows synchronous disruption of the π-system in the 5-membered heterocyclic ring and formation of the more stable benzene ring during dienophile addition, resulting in the observed hyper-reactivity.[46] Therefore, due to the high instability of IBFs, they have been synthesized as transient intermediates and reacted *in situ*. IBFs have been used in both inter- and intramolecular Diels-Alder cycloadditions. For example, IBF **125** reacts with alkyne **126** to generate oxabicyclo adduct **127**. Similarly, IBF **125a** also reacts with olefin **128**, followed by acid treatment, to generate naphthalene **129** (Scheme 31).[44]



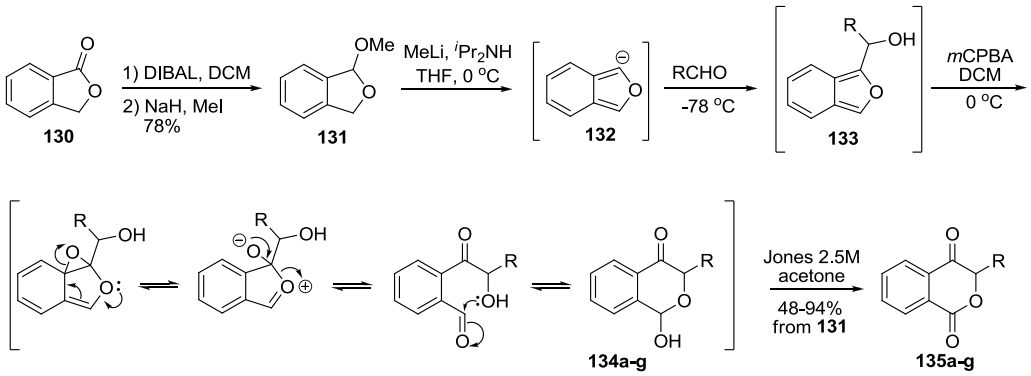
Scheme 31 **Utility of Isobenzofurans in Diels-Alder Chemistry**

Deprotonation of IBF and related systems has been reported in which the lithiated species can be intercepted by a variety of electrophiles.[50] Sequential lithiation and alkylation can be achieved to generate alkyl- and 1,3-dialkyl-IBF derivatives. However such derivatives have only ever been generated *in situ* and consequently, have only been used in Diels-Alder chemistry.[44,49] Therefore, at the time when the Marquez group sought to access isochromanones from IBFs, their synthetic utility was restricted, almost exclusively, to Diels-Alder chemistry.

1.5.4.3 Marquez' Synthesis of Ajudazol Western Section

Preliminary work on the ajudazols within the Marquez group focussed on the development of an efficient approach to isochroman-1-one **136**, starting from simple phthalide **130**.[33] In the initial approach, phthalide **130** was efficiently converted to phthalan **131,** which upon treatment with 2 equivalents of LDA, proceeded to generate the putative IBF anion **132**. Mechanistically, the first equivalent of base promotes the elimination of methanol to induce aromatization, before the second equivalent of base directly deprotonates the IBF intermediate. The highly reactive IBF anion **132** was trapped with a variety of simple aldehydes to afford the corresponding alcohol **133**. Oxidative treatment of the crude α-hydroxy-IBF **133** then generated the keto-lactols **134a**-**g**, believed to be through a mechanism analogous to that of the Achmatowicz rearrangement. Lactol oxidation then afforded the desired keto-lactones

135a-**g**. A variety of keto-lactone species were generated in excellent yield (Scheme 32, Table 1).

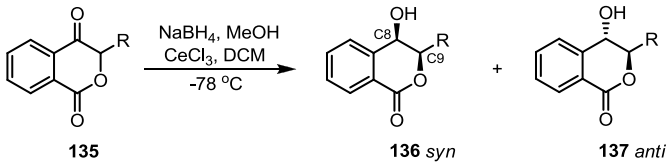


Scheme 32 **Isobenzofuran Alkylation and Oxidative Rearrangement Sequence**

Table 1 **Isobenzofuran Alkylation and Oxidative Rearrangement Sequence**

Entry	Aldehyde	Keto-lactone	Yield / %
1	MeCHO	**135a**	94
2	^{c}hexCH$_2$CHO	**135b**	67
3	EtCHO	**135c**	84
4	BuCHO	**135d**	72
5	^{i}BuCHO	**135e**	82
6	^{i}PrCHO	**135f**	85
7	^{c}hexCHO	**135g**	57
8	PhCHO	**135h**	67

Chemoselective reduction of keto-lactones **135a**-**g** under Luche conditions generated the desired isochroman-1-one species **136a**-**g** (Scheme 33, Table 2).



Scheme 33 **Keto-Lactone Reduction to Afford Isochromanones**

Table 2 **Keto-Lactone Reduction to Afford Isochromanones**

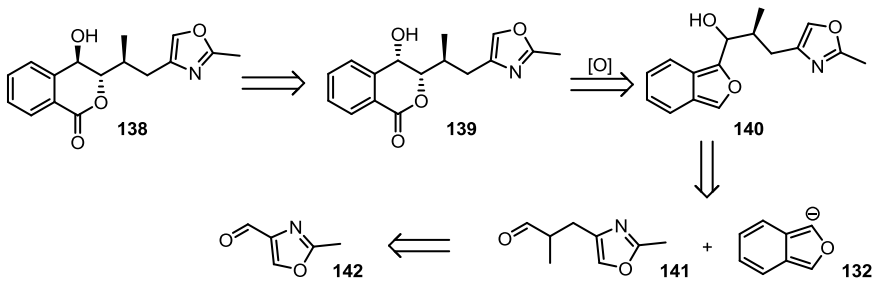
Entry	R group	Isochromanone	Yield / %	**136** : **137**
1	Me	**a**	90	50 : 50
2	^{c}hexCH$_2$	**b**	58	50 : 50
3	Et	**c**	56	60 : 40
4	Bu	**d**	80	75 : 25
5	^{i}Bu	**e**	56	90 : 10
6	^{i}Pr	**f**	96	100 : 0
7	^{c}hex	**g**	82	100 : 0
8	Ph	**h**	48	100 : 0

This approach was used to efficiently generate a number of isochroman-1-ones in excellent yields. The *syn*-stereochemistry observed during the Luche reduction step was attributable to the nature of the alkyl side chain. For sterically bulky side chains for example, isopropyl, cyclohexyl and phenyl groups (Table 2, entries 6-8), complete facial selectivity in the reduction was observed to exclusively obtain the C8-C9 *syn*-products **136f**-**h**.

The entire 5-step protocol could be carried out in the space of 48h and allowed for the synthesis of isochromanones from phthalan precursors, with complete diastereoselectivity and in high yields. Furthermore, isolation of any of the intermediate species was unnecessary which avoided the need for unnecessary purification. The methodology radically expanded the use and scope of IBFs as useful synthetic intermediates.

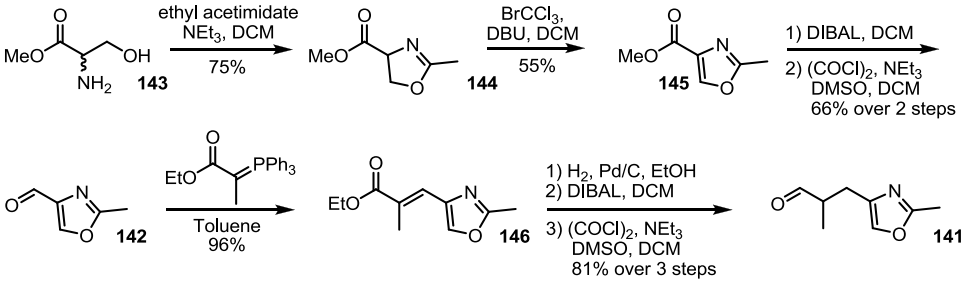
In order to investigate the compatibility of the newly developed α-hydroxy-IBF oxidative rearrangement with more complex aldehyde systems and test its applicability in natural product synthesis, the synthesis of a model system of ajudazol A was undertaken.

Retrosynthetically, it was envisioned that the ajudazol western section model system **138** could be accessed via stereochemical inversion of isochromanone **139**, which in turn could be accessed by the oxidative rearrangement of IBF anion **132** with aldehyde **141**. The known formyl-oxazole **142** would provide easy access to aldehyde **141**.



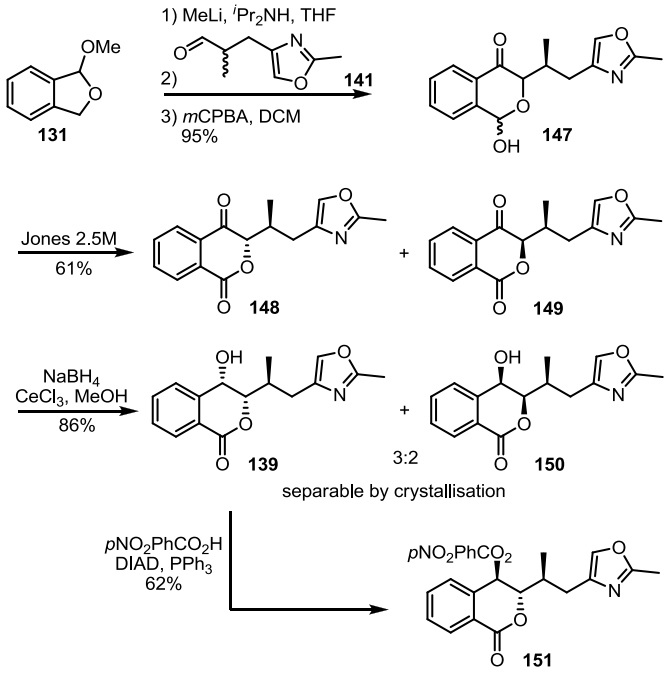
Scheme 34 **Retrosynthetic Analysis of Ajudazol A Model System 138**

Formyl oxazole **142** was accessed via a 4-step sequence, starting from serine methyl ester **143**. Conversion to the oxazolidine **144**, followed by aromatization, afforded oxazole **145**. DIBAL reduction to the alcohol followed by Swern oxidation generated aldehyde **142**. *E*-selective Wittig olefination then produced acrylate **146**, which upon a reduction, hydrogenation and Swern oxidation sequence, yielded the racemic oxazole-aldehyde **141** (Scheme 35).[33]



Scheme 35 **Synthesis of Oxazole-Aldehyde 141**

With the functionalised aldehyde **141** in hand, the oxidative rearrangement sequence was undertaken. The IBF anion **132**, generated from treatment of phthalan **131** with LDA, was trapped with aldehyde **141**, affording the transient α-hydroxy-IBF intermediate, which was subjected to the oxidative rearrangement conditions to generate the keto-lactol intermediate **147**. Oxidative rearrangement and Jones oxidation of the keto-lactol intermediate gave the desired keto-lactones **148** and **149** as a 3:2 mixture of diastereoisomers. Luche reduction of the diastereoisomeric mixture afforded the isochromanones **139** and **150** with complete facial selectivity. The major diastereoisomer **139**, possessing a *syn,anti*-C8-C10 stereochemical relationship, was separable by crystallization. Isochromanone **139** was subjected to Mitsunobu conditions to yield the benzoate ester **151**, in which the C8 stereochemistry has been inverted to match that of the ajudazols (Scheme 36).[33]



Scheme 36 **Synthesis of the Ajudazol Western Section Model System**

1.6 Summary and Outlook

The ajudazols, secondary metabolites isolated from the myxobacterial *Chondromyces crocatus*, exhibit interesting biological activity and possess interesting structural features. As such, the chemical community has taken an interest in the total synthesis of Ajudazols A (**7**) and B (**8**), with Taylor (2004) and Rizzacasa (2007) reporting their respective approaches to the oxazole-linked polyene eastern section sections of the ajudazols **52**, **68** and **69**. More recently, in 2011, Rizzacasa reported his approach towards the *15R*-deshydroxyajudazol metabolite **49**. Recent work within the Marquez group has focussed on the synthesis of the isochromanone containing ajudazol western section **151**. As such, a novel oxidative rearrangement sequence for the efficient synthesis of isochromanone units has been developed, utilising putative isobenzofurans as reactive intermediates.

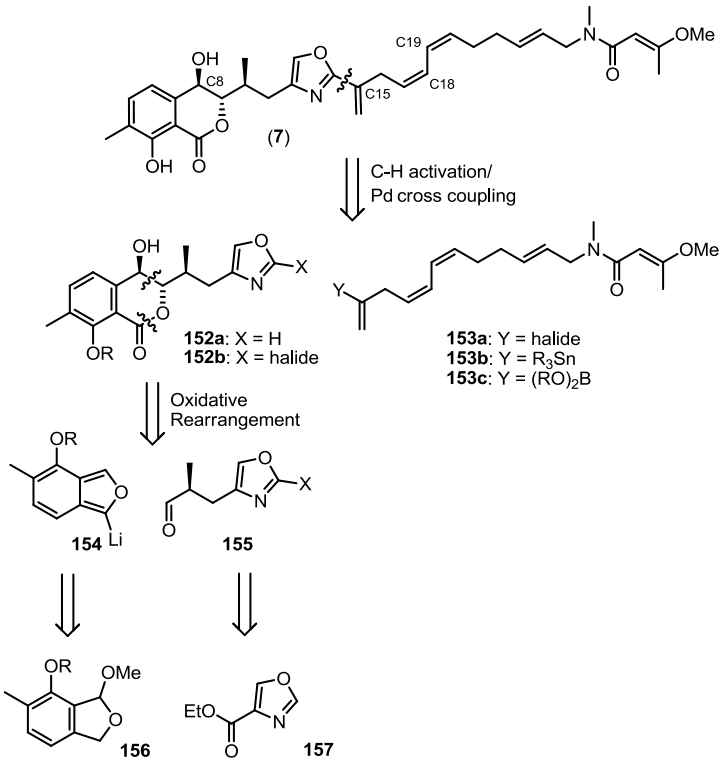
2 Retrosynthetic Analysis of the Ajudazols

The main aim of this project was to complete the total synthesis of ajudazols A (**7**) and B (**8**), utilising the IBF oxidative rearrangement methodology for the synthesis of isochromanones, recently developed within the Marquez group.[33]

Upon embarking on this project in late 2008, at least two other research groups, those of Taylor and Rizzacasa, were known to be actively pursuing the ajudazols as synthetic targets, having respectively reported their partial syntheses of ajudazols A and B.[29,27,3427]

2.1 Ajudazol A

Retrosynthetically, ajudazol A was envisioned as originating from a convergent, late-stage coupling between the oxazole-linked isochromanone western section **152** and the polyene eastern section **153** (Scheme 37). The strategic coupling was based on the C-H activation of unfunctionalised oxazole **152a** with vinyl fragment **153a.**[29] Alternatively, the key C14-C15 bond was also thought as originating through the more conventional palladium catalysed cross-coupling between western section **152b** and eastern sections **153b** or **153c** (or their reverse coupling counterparts). The oxazole-linked hydroxyisochroman-1-one unit **152**, in turn, would be obtained via the coupling of IBF anion **154** and aldehyde **155**, followed by an IBF oxidative rearrangement sequence. IBF anion **154** could be generated from phthalan precursor **156**, while oxazole-aldehyde **155** would originate from oxazole-ester **157**.



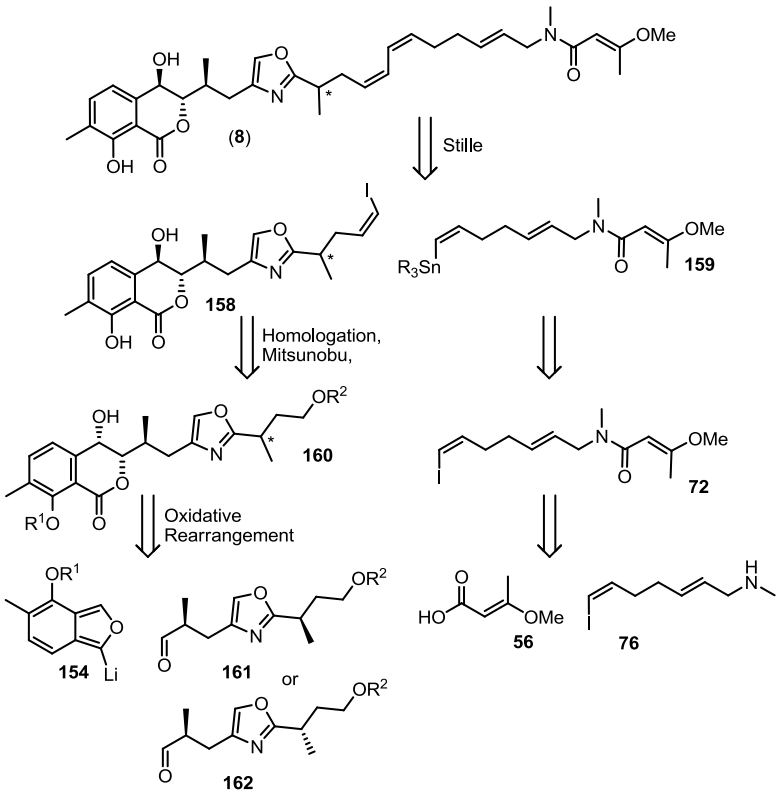
Scheme 37 **Retrosynthetic Analysis of Ajudazol A**

Upon pursuing the total synthesis of related natural products, it is often advantageous to utilise a late stage intermediate from which more than one synthetic target can be generated. Unfortunately, in the case of the ajudazols, it is unlikely that ajudazol B could be accessed via a late stage reduction of the C15 olefin of ajudazol A, which would have to be both stereo- and

chemoselective, due to the presence of numerous other olefin functionalities. Therefore, any proposed retrosynthesis of ajudazol B would require that the saturated C15 methyl group be installed early on in the synthesis and therefore, the approach taken to each of the respective eastern sections would differ.

2.2 Ajudazol B

Thus, ajudazol B was thought as being accessed via the late-stage Stille cross-coupling between vinyl-iodide **158** and vinyl-stannane **159** (Scheme 38). Stannane **159** could be generated from vinyl iodide **72**, which in turn could be obtained via the amide condensation between 3-methoxybutenoic acid **56** and simple allylic amine **76**.[27] The isochromanone-containing vinyl iodide intermediate **158** was envisioned as originating from ether **160**. Isochromanone fragment **160** being the product of the IBF oxidative rearrangement sequence, originating from IBF anion **154** and either aldehyde **161** or **162**. Utilising aldehyde **161** would provide *15R*-diastereoisomer of ajudazol B, whilst aldehyde **162** would provide the *15S*-diastereoisomer of ajudazol B.

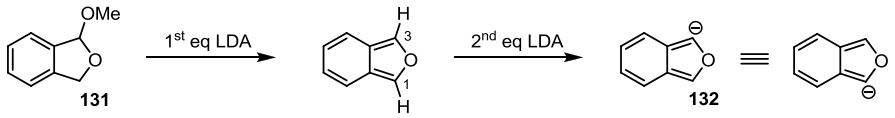


Scheme 38 Retrosynthetic Analysis of Ajudazol B

3 Regiochemistry of the IBF Oxidative Rearrangement

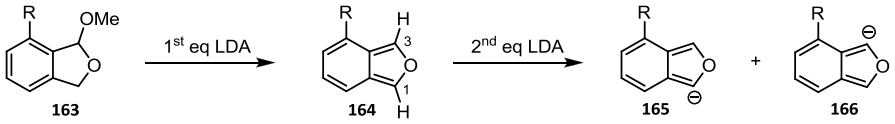
In order to achieve the ultimate goal of completing the total synthesis of ajudazols A and B, it was necessary to adapt the IBF oxidative rearrangement methodology, so to be able to incorporate the aromatic substitution pattern present in the isochromanone aromatic framework of the ajudazols.

Prior to the start of this work, all of the IBF anion alkylations and oxidative rearrangements previously undertaken within the Marquez group utilised unsubstituted phthalan precursors. Regioselectivity of the alkylation step was not an issue as deprotonation of unsubstituted IBF at either C1 or C3 resulted in the generation of equivalent IBF anions **132** (Scheme 39).[33]



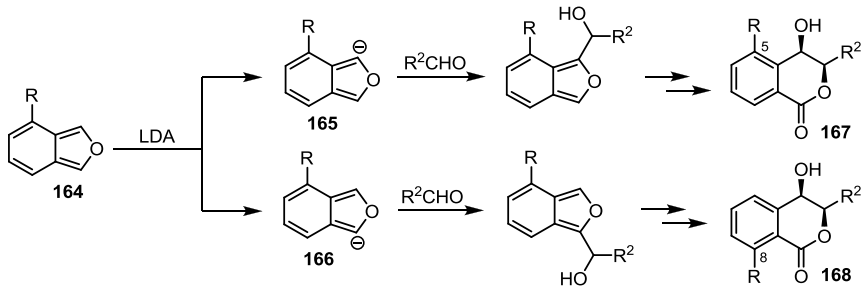
Scheme 39 **IBF Anion Generation**

This would no longer be the case when substituted IBFs are used. For instance, while treatment of C7-substituted phthalan **163** with LDA would generate the key IBF intermediate **164**, the second equivalent of LDA could potentially deprotonate at either C1 or C3, resulting in the generation of regioisomeric IBF anions **165** and **166** (Scheme 40).



Scheme 40 **Generation of Non-Equivalent IBF Anions**

It was postulated that if a suitable C4 substituted IBF unit **164** could be generated, then it would be possible to use the chemical nature of the C4 group to influence the second deprotonation step. A regioselective deprotonation would allow for the selective formation of either the C5 or C8-substituted isochromanone **167** or **168** (Scheme 41). The ability to control the regiochemistry of the deprotonation step was crucial if the 4-hydroxy-isochromanone substitution pattern present in the ajudazols was to be accessed using this methodology.



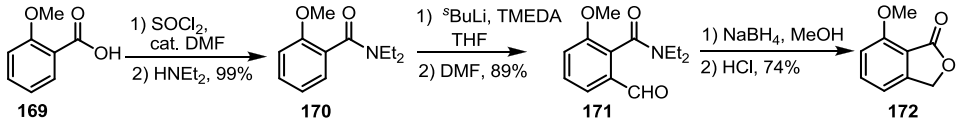
Scheme 41 **Regioselective Approach Towards Isochromanone Synthesis**

3.1 Investigation of Methoxy Substituent

Initial studies on the influence that a C4-IBF substituent may have on the regiochemistry of IBF anion alkylation, and hence, the regiochemical outcome of the isochromanone product of the

subsequent oxidative rearrangement, were focussed on the alkylation and oxidative rearrangement sequence of 4-methoxy-IBF (**164** when R = MeO). The methoxy group was chosen due to its likely ability to withtand the reaction conditions whilst simultaneously allowing the assessment of the reliability and flexibility of the oxidative rearrangement sequence in the presence of a potentially competing highly activated olefin.

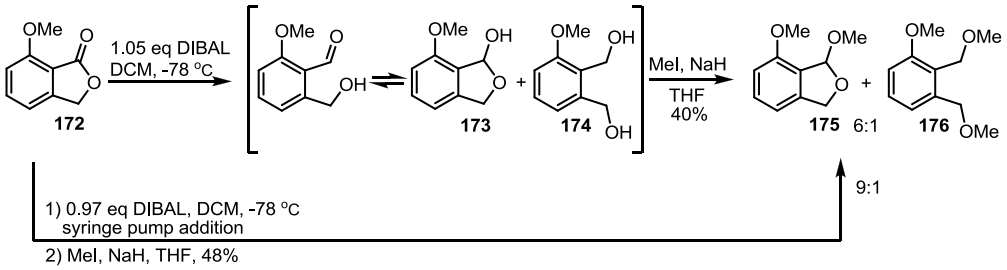
The synthesis of 7-methoxyphthalide **172** began with commercially available *o*-anisic acid **169**, which was converted into benzamide **170** in excellent yield. Directed *ortho*-formylation using Snieckus' conditions yielded the benzaldehyde **171**, which upon reduction, followed by acid catalysed cyclisation, generated 7-methoxyphthalide **172** in good yield.[51] The robust, high yielding route was attractive as it was reproducible on a multi-gram scale (>20 g) and required minimal purification (Scheme 42).



169 **170** **171** **172**

Scheme 42 **7-Methoxyphthalan Synthesis 75**

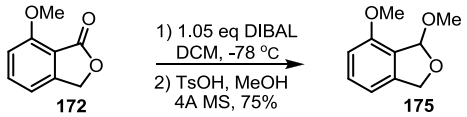
Initial attempts to reduce 7-methoxyphthalide **172** using DIBAL, followed by methylation, generated 7-methoxyphthalan **175** in a modest 40% yield, with significant amounts of by-product **176**. The problem of over-reduction of phthalide **172** to diol **174** was observed and methylation of intermediates **173** and **174** with NaH/MeI resulted in the formation of the desired phthalan **175**, together with the undesired *bis*-methoxy ether **176**, in an inseparable 6:1 ratio. Attempts to suppress the over-reduction by the carefully controlled addition of DIBAL, together with a reduction in the quantity of the reducing agent from 1.05 to 0.97 equivalents, increased the yield of the phthalan product to 48% (Scheme 43). However, due to the still unavoidable presence of the *bis*-methoxy ether by-product **176**, alternative reaction conditions were desired.



172 **173** **174** **175** **176**

Scheme 43 **Synthesis of 7-Methoxyphthalan 175**

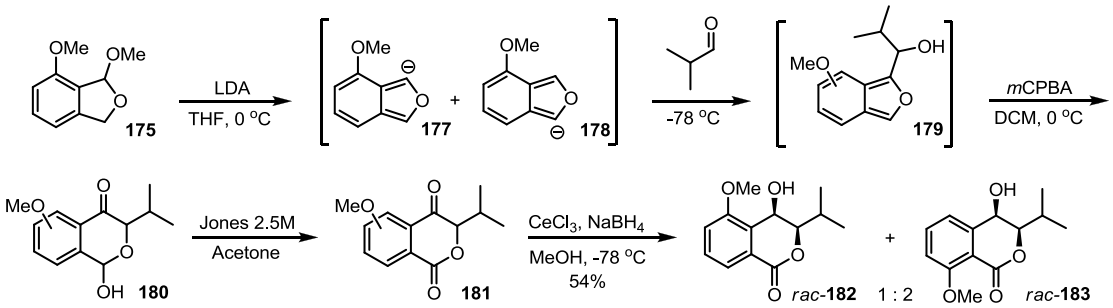
In our modified approach, the lactol methylation was attempted using tosic acid in methanol, which resulted in a much improved yield of 75%, under mild conditions and avoided the use of toxic MeI.[52,53] Furthermore, the chemoselective methylation conditions allowed for a drastically easier purification (Scheme 44).



172 **175**

Scheme 44 **Improved Synthesis of 7-Methoxyphthalan 175**

With the 7-methoxyphthalan **175** to hand, the regiochemistry of the IBF anion alkylation was investigated. This was achieved by undertaking the entire IBF oxidative rearrangement sequence, as reported previously within the Marquez group, to afford the isochromanone products(s). Due to the instabilities of the α-hydroxy-IBF, keto-lactol and keto-lactone intermediates, the regiochemical outcome of the IBF anion alkylation would be identified from the isochromanone products obtained. The decision to use isobutyraldehyde as the alkylating species emanated from the fact that the isopropyl group had previously shown complete diastereocontrol in the Luche reduction step and therefore, would simplify characterization of the isochromanone products.



Scheme 45 **IBF Oxidative Rearrangement Sequence with Methoxy Substituent**

Treatment of 7-methoxyphthalan **175** with LDA resulted in the formation of the corresponding IBF anions **177** and **178** before trapping with isobutyraldehyde, to access the putative α-hydroxy-IBF intermediate **179**. Oxidative rearrangement using *m*CPBA to generate keto-lactol **180**, followed by Jones oxidation yielded the crude keto-lactone **181**, which upon Luche reduction gave the isochromanone species in 54% and as a 1:2 mixture of the two regioisomers **182** and **183** (Scheme 45). The product ratio was determined to be 1:2 via ^{1}H NMR analysis of the crude mixture. Fortunately, the two regiosiomers could be separated and X-ray crystallographic studies revealed their regiochemistry (Figure 10). The major isochromanone **183**, the C8-methoxy substituted isochromanone, is the result of alkylation occuring at the C1 position of IBF **178**. This initial moderate selectivity is likely due to the steric hindrance provided by the methoxy group which forces IBF anion formation on the opposite side of the molecule. X-ray crystallographic structures also confirmed that, as expected, the use of isobutyraldehyde as an alkylating agent resulted in complete diastereocontrol during the Luche reduction, yielding the *syn*-isochromanone products **182** and **183** as single diastereoisomers.

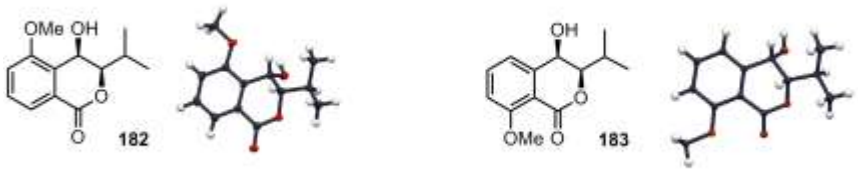
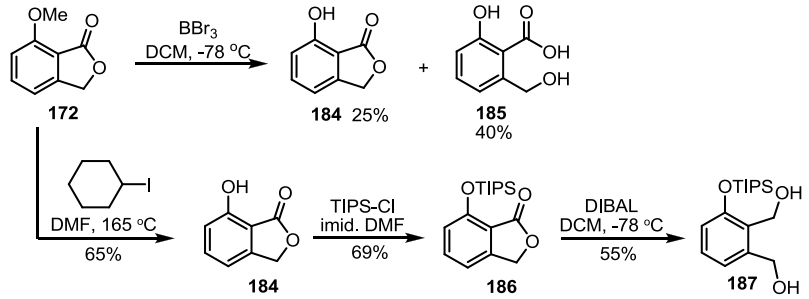


Figure 10 **X-ray Crystallographic Structures of Isochromanones *rac*-182 and *rac*-183**

3.2 Steric Control

This promising initial result made us hopeful that complete regiocontrol could be achieved through the use of large, sterically demanding groups. In order to test this hypothesis, 7-

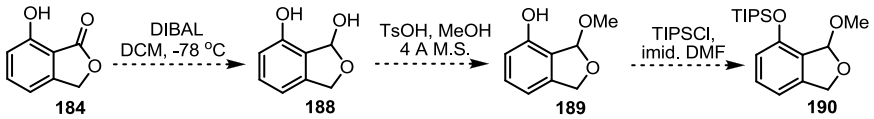
hydroxyphthalide **184H**ad to be generated as a platform from which an array of 7-substituted compounds could easily be accessed. Initially, it was envisioned that 7-hydroxyphthalide **184** could be easily accessed via the demethylation of 7-methoxyphthalide **172**, which had been synthesized with ease. Initial attempts of deprotection using BBr_3 afforded the desired product, but in a poor yield of 25%, together with large amounts of benzoic acid by-product **185**.[54] Interestingly, when the demethylation of 7-methoxyphthalide **172** was attempted using iodocyclohexane in DMF, the desired phenol **184** was obtained in good yield.[55] It has been postulated that iodocyclohexane in DMF acts as a mild form of HI. In this case, it not only increased the yield of the desired product, but it also suppressed formation of benzoic acid **185**.



Scheme 46 **Synthesis of 7-Methoxyphthalide and Functionalisation**

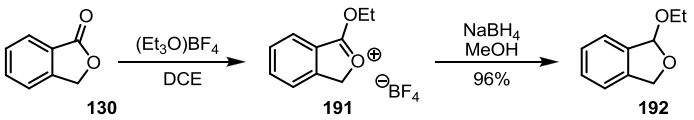
In an attempt to introduce a large, bulky and stable group at C7, 7-hydroxyphthalide **184** was protected as the TIPS-ether **186**.[56] Unfortunately however, reduction of 7-TIPS-phthalide **186** proved unsuccessful, yielding only the over-reduced diol **187**. Unfortunately, despite extensive experimentation: modifying the reaction solvent (DCM, Et_2O, THF), temperature (-100 °C, –78 °C, -20°C) and reducing the equivalents of DIBAL, the over-reduction was unable to be suppressed.

An alternative approach for the synthesis of 7-TIPS-phthalan **190** was then attempted. It was envisioned that 7-hydroxyphthalide **184** could undergo DIBAL reduction to give the lactol **188**, which followed by acid-catalysed methylation, would give phthalan **189**. TIPS protection of phenol **189** would then yield the desired silyl-ether **190** (Scheme 47). Unfortunately, 7-hydroxyphthalide **184** failed to undergo reduction to the lactol **188**. When the reduction was performed with DIBAL, a bright yellow precipitate, believed to be a chelate, resulted instead.



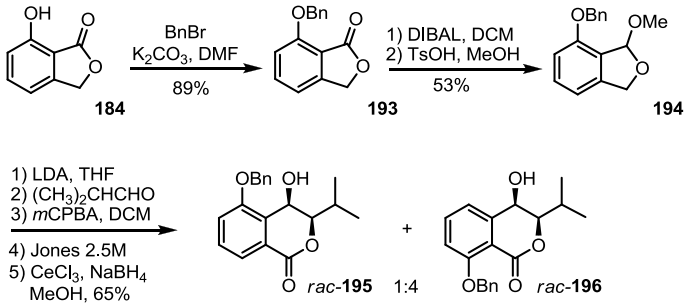
Scheme 47 **Alternative Approach to the Synthesis of Phthalan 190**

As an alternative approach to the conversion of phthalides to phthalans, the conditions used by Meerwein for the synthesis of ethoxyphthalans, were trialled.[57,58] Meerwein reported that treatment of phthalide **130** with triethoxy fluoroborate generated oxonium salt **191** that could then be reduced to the ethoxyphthalan **192** with $NaBH_4$ (Scheme 48). However, in our hands, Meerwein's conditions were found to be irreproducible, and thus it was decided to continue with the well-established DIBAL/TsOH/MeOH protocol for the conversion of phthalides to phthalans.



Scheme 48 **Meerwein's Phthalan Synthesis**

As a result of the inability to access 7-TIPS pthalan **190**, the next logical step was to synthesize other C7-substituted phthalides stable enough to undergo DIBAL reduction with minimal over-reduction to the diol by-product, yet be bulky enough to influence the regiochemical outcome of the IBF anion alkylation. Hence, it was decided to investigate 7-benzyloxyphthalan **194** as a suitable substrate. Alkylation of 7-hydroxyphthalide **184** cleanly generated 7-benzyloxyphthalide **193**, which upon DIBAL reduction and methylation, yielded phthalan **194** in good overall yield (Scheme 49).[59]



Scheme 49 **IBF Oxidative Rearrangement Sequence with Benzyloxy Substituent**

Subjecting 7-benzyloxyphthalan **194** to our oxidative rearrangement sequence afforded two regioisomeric isochromanone products, **195** and **196**, in excellent overall yield and in a 1:4 ratio (Scheme 49). X-ray crystallographic analysis of the major product **196** confirmed its identity as the sterically directed regioisomer (Figure 11). The change from a methoxy to benzloxy group increased the regioselectivity in the IBF anion alkylation from 1:2 to 1:4. This small change is consistent with the similar size of the two groups.

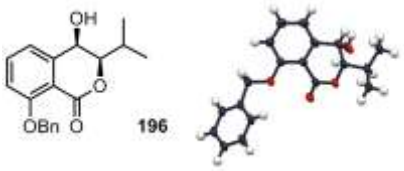
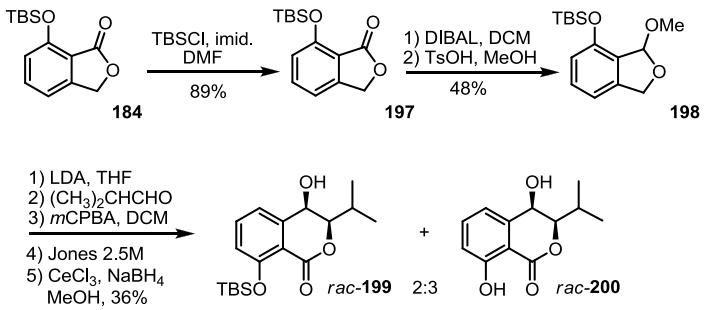


Figure 11 **X-ray Crystallographic Structure of Isochromanones *rac*-196**

Encouraged by this result, it was hoped that the use of a TBS group would further increase the regioselectivity of IBF anion alkylation. 7-TBS-phthalan **198** was synthesised from 7-hydroxyphthalide **184** and subjected to our oxidative rearrangement sequence (Scheme 50).

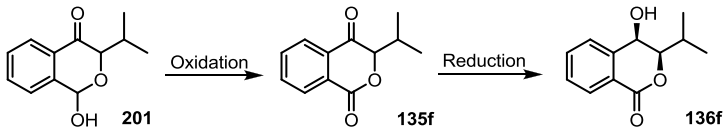


Scheme 50 IBF Oxidative Rearrangement Sequence with Silyloxy Substituent

Excitingly, isochromanone **199** was obtained as a single regioisomeric product, together with the TBS-deprotected isochromanone **200**, in good overall yield (Scheme 50). It was reasoned that the TBS cleavage was likely to have taken place during the Jones oxidation stage of the rearrangement sequence. The unwanted deprotection made it clear that the reaction conditions had to be optimised if the rearrangement sequence was to accommodate, and be able to handle, sensitive substrates.

3.3 Optimisation of the Keto-Lactol Oxidation and Keto-Lactone Reduction Conditions

Hypervalent periodinane reagents such as IBX and DMP are known for their mildness and selectivity.[60] We hypothesised that IBX and DMP might be able to selectively oxidise the keto-lactol **201** to the keto-lactone **135f** whilst avoiding loss of sensitive functionalities, should they be present. Unfortunately both IBX and DMP failed to react with the keto-lactol **201** at ambient temperature. Although disappointing, this was not surprising considering that all previous reported instances of lactol oxidation with periodinane reagents have required refluxing conditions in order to achieve reaction completion.[61] However, efficient lactol oxidations at room temperature in the presence of acetal and TBS ether groups had been reported using PCC, PDC and TPAP/NMO.[62,63] Replacing the Jones oxidation step in our sequence with PCC, PDC or TEMPO/BAIB promoted oxidation of the keto-lactol **201** to the keto-lactone **135f** (Scheme 51, Table 3). Rewardingly, the TEMPO oxidation conditions provided a high yielding alternative to the Jones oxidation and eliminated the need for heavy metal-based, toxic reagents.



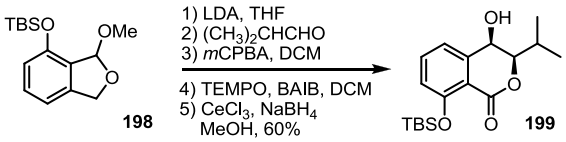
Scheme 51 Optimisation of Oxidation and Reduction Conditions

Table 3 **Oxidation of Keto-Lactol 201 to Keto-Lactone 135f**

Entry	Oxidant	Reaction Time	Yield / %
1	2.5 M Jones	45 min	96
2	TEMPO, BAIB	6H	84
3	PCC	24H	82
4	PDC	24H	80
5	PDC, Py.TFA	12H	80

Having found a mild, non-toxic, viable alternative to the Jones oxidation, we decided to focus on the reduction step of our rearrangement sequence. It was desirable to achieve the keto-lactone reduction under non-Luche conditions so that, again, sensitive functionalities could be tolerated, and our synthetic sequence simplified. To our satisfaction, reduction of the keto-lactone **135f** was successfully carried out under standard $NaBH_4$ conditions to afford the *syn*-isochromanone **136f** in 89% yield, exceeding the 82% yield obtained under Luche conditions (Scheme 51).

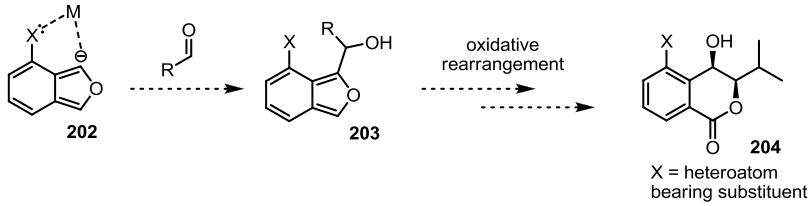
Having developed a set of optimised conditions, 7-TBS-phthalan **198** was subjected to the IBF alkylation and oxidative rearrangement sequence. Rewardingly 7-TBS-phthalan **198** was converted to the desired isochroman-1-one **199** in an improved overall yield of 60%, once again, with complete regiocontrol and with no desilylated product **200** observed (Scheme 52).



Scheme 52 **Synthesis of Isochromanone *rac*-199 Under Optimised Conditions**

3.4 Chelation Control

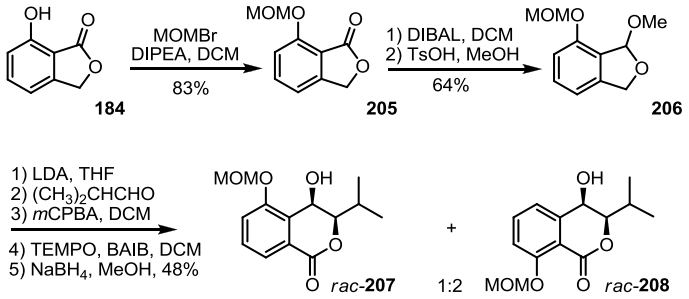
After successfully demonstrating that IBF anion alkylation can be controlled to give exclusively the sterically directed product, we then set out to investigate whether this regiocontrol could be reversed. It was postulated that by having a chelating functional group in the C4-position of the IBF intermediate, addition of the second equivalent of base to generate the IBF anion **202** could be directed to the C3-position (i.e. on the same side of the IBF framework). In a process analogous to *ortho*-lithiation, it was hypothesised that the presence of heteroatoms, namely nitrogen or oxygen, could form a stabilised chelate with the IBF anion and metal ion of the organometallic base. This chelate would in turn allow for the generation of regioisomeric isochroman-1-one **204** (Scheme 53).



Scheme 53 **Chelation Controlled IBF Anion Alkylation and Rearrangement**

It was envisioned that by incorporating functionality akin to the already well established chelating groups implemented in directed *ortho*-metallation chemistry, chelation controlled IBF anion alkylation could be achievable.[51] Groups with the ability to promote chelation; MOM, MEM, MTM and *N,N*-diethylcarbamate were seen as attractive functionalities that could be attached to the phthalan precursors and used in the oxidative rearrangement sequence, in order to investigate whether chelation controlled IBF anion alkylation is achievable.

The first chelating group that was investigated was the MOM group. The 7-MOM-phthalan **206** was readily synthesized via simple alkylation of 7-hydroxyphthalide **184** with MOM-Br followed by reduction and methylation, in reasonable yields. The oxidative rearrangement sequence was carried out on phthalan **206** using LDA and isobutyraldehyde, followed by *m*CPBA promoted rearrangement, TEMPO oxidation and $NaBH_4$ reduction. The two regioisomeric isochroman-1-ones **207** and **208** were obtained in a 1:2 ratio in favour of the sterically directed product **208**, and in good overall yield (Scheme 54). The structure of regiosiomer **208** was subsequently confirmed by X-ray crystallographic analysis (Figure 12).



Scheme 54 **IBF Oxidative Rearrangement Sequence with MOM Substituent**

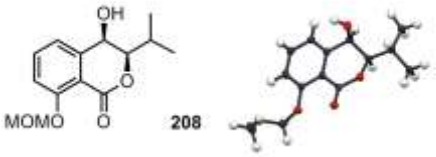
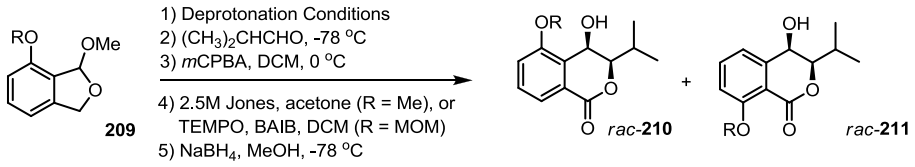


Figure 12 **X-ray Crystallographic Structure of Isochromanone *rac*-208**

Although disappointing, the results are consistent with a lack of chelation and suggest a slight steric bias akin to that observed with the methoxy group. Our initial set-back prompted us to suggest that chelation control would be achieved by modification of the deprotonation conditions (Scheme 55, Table 4).



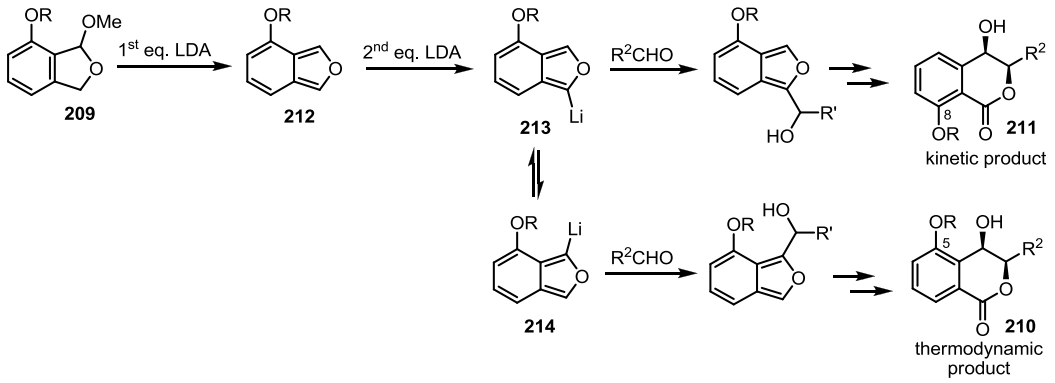
Scheme 55 **Alternative Conditions to Access Chelation Controlled IBF Anion Alkylation**

Table 4 Alternative Conditions for IBF Anion Generation

Entry	R	Deprotonation Conditions	**210** : **211**	Yield / %
1	Me	MeLi (2.1eq), $^{i}Pr_2NH$ (0.1eq), 0 ^{o}C	1:2	54
2	Me	MeLi (2.1eq), $^{i}Pr_2NH$ (2.1eq), 0 ^{o}C	1:2	58
3	Me	MeLi (2.1eq), Me_2NH (0.1eq), 0 ^{o}C	1:1.3	52
4	Me	MeLi (2.1eq), 2,2,6,6-TMP (0.1eq), 0 ^{o}C	1:1.1	47
5	Me	MeLi (2.1eq), 0 ^{o}C	1:1	18
6	Me	^{s}BuLi (2.1eq), TMEDA (2.1eq), 0 ^{o}C	1:3	36
7	Me	MeMgBr (2.1 eq), 0 ^{o}C	-	-
8	Me	LiHMDS (2.1 eq), 0 ^{o}C	-	-
9	Me	NaHMDS (2.1 eq), 0 ^{o}C	-	-
10	MOM	MeLi (2.1eq), $^{i}Pr_2NH$ (0.1eq), 0 ^{o}C	1:2	48
11	MOM	MeLi (2.1eq), 2,2,6,6-TMP (0.1eq), 0 ^{o}C	1:1.2	54
12	MOM	^{s}BuLi (2.1eq), TMEDA (2.1eq), 0 ^{o}C	1:3	66
13	Me	MeLi (2.1eq), $^{i}Pr_2NH$ (2.1eq), r.t.	1:2	21
14	MOM	MeLi (2.1eq), $^{i}Pr_2NH$ (2.1eq), 45 ^{o}C.	-	-

Disappointingly, the effect of varying the choice of base failed to have a profound effect on regiochemistry of the IBF anion alkylation. The regiochemical outcome was independent of whether stoichiometric or catalytic LDA was used (Table 4, entries 1 and 2). The use of a lithium-amine base appears crucial to promote IBF anion formation, as MeMgBr, NaHMDS and LiHMDS failed to generate the IBF anion (entries 7-9). MeLi in the absence of a secondary amine, reacted slowly and incompletely to generate isochromanone products in poor yield with no regiochemical bias (entry 5). ^{s}BuLi in combination with TMEDA, the optimal conditions for directed *ortho*-metalation chemistry, afforded isochromanones in good yield, however still promoting steric control (entries 6 and 12). The use of lithum dimethylamine or lithium-2,2,6,6-tetramethylpiperidine generated an almost equal amount of both regioisomers (entries 3, 4, 10 and 11). Although this could be viewed optimistically as an inverse in terms of chelation control, it could also be seen as an erosion of overall selectivity.

At this stage it was hypothesised whether the steric bias achieved to this point was a result of kinetic control. For the IBF anion formation and subsequent alkylation, deprotonation has been performed at 0 ^{o}C before cooling to –78 ^{o}C, followed by addition of aldehyde. It would not be unreasonable to envisage that at low temperature, under kinetic control, sterics would predominate and trapping with aldehyde at low temperature would lock the regiochemistry to generate sterically directed isochromanone **211**. Alternatively, should the phthalan-base reaction mixture be allowed to warm, and assuming the second deprotonation to generate the IBF anion **213** is reversible, equilibration between the steric and chelation controlled anions **213** and **214** could occur, of which subsequent oxidative rearrangement could afford the chelation-directed isochromanone product **210** (Scheme 56).



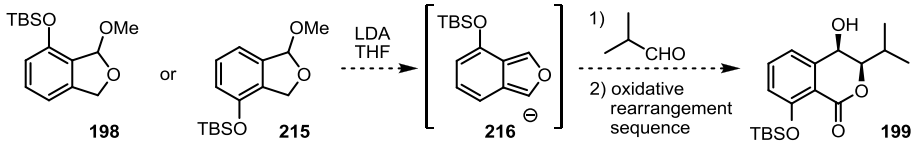
Scheme 56 Kinetic Versus Thermodynamic Control

However, the difficulty in investigating kinetic vs thermodynamic control with this particular reaction is the great instability of the IBF intermediates which needs the reaction to be kept at suppressed temperatures to avoid polymerisation and degradation. This severely limits the temperature to which the IBF anion can be warmed before degradation becomes the prevalent pathway. When the IBF anion generation reaction was warmed to room temperature, no change in the isochromanone product ratios were observed. However, as a consequence of warming to room temperature, drastically reduced product yields were obtained (Table 4, entry 13). Furthermore, heating to 45 ^{o}C resulted in complete degradation (entry 14). Faced with such instability, it was decided that temperature control was not a viable way to alter the regiochemical outcome of the reaction.

At this point, due to time constraints, it was decided to stop our investigation into chelation control, although interesting and potentially very useful.

3.5 IBF Oxidative Rearrangement with Regioisomeric Phthalan Precursors

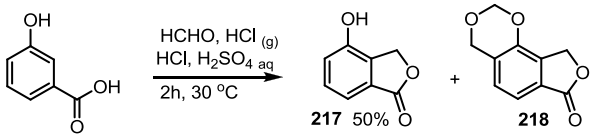
It has been demonstrated that complete regiocontrol can be achieved in the IBF oxidative rearrangement sequence through the use of C7 phthalan substituents. It was hypothesised that isochromanone **199**, previously accessed from 7-TBS phthalan **198**, could be synthesized under analogous oxidative rearrangement conditions starting from the regioisomeric 4-TBS phthalan **215**. Obtaining the identical isochroman-1-one product **199** from either the 7- or 4-TBS-phthalan precursor would prove that the reaction proceded via the common IBF intermediate **216**. (Scheme 57).



Scheme 57 Rearrangement with Regiosiomeric Phthalan Precursors

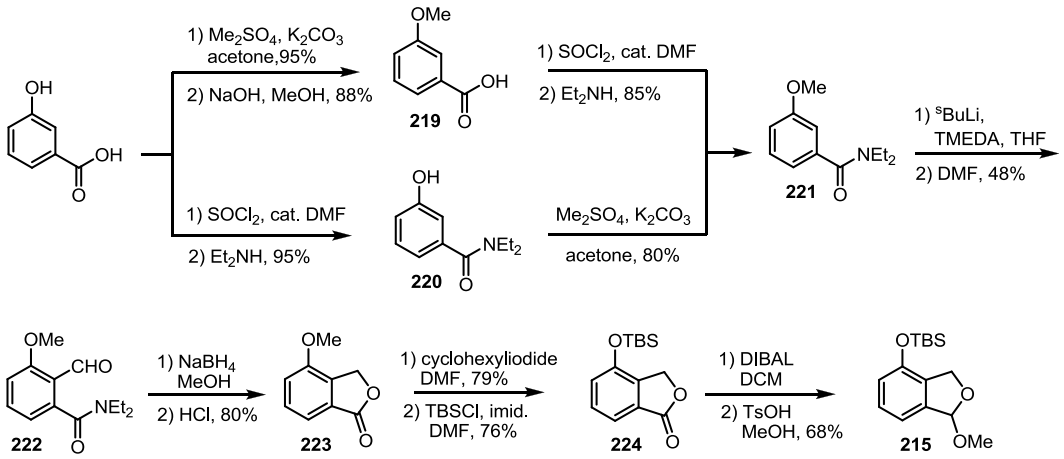
The chemical literature is sparsely populated with approaches to the synthesis of 4-hydroxyphthalide **217**. The single example was reported by O'Doherty, who takes advantage of a one-step procedure in which 3-hydroxybenzoic acid is condensed with formaldehyde in the

presence of sulfuric and hydrochloric acid.[64] Unfortunately, in our hands, O'Doherty's procedure gave an inseparable mixture of products (Scheme 58).



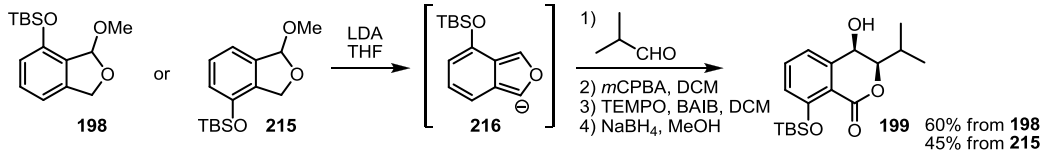
Scheme 58 **O'Doherty's Synthesis of 4-Hydroxyphthalide 217**

The lack of success with the O'Doherty protocol meant that an approach to 4-TBS-phthalan **215**, analogous to our 7-TBS phthalan synthesis, was carried out. Thus, commercially available 3-hydroxybenzoic acid was converted to the 3-methoxybenzoic acid **219** in high yield via a two-step dimethylation/hydrolysis procedure (Scheme 59). Acid **219** was converted into the benzamide **221**, proceeding via the acid chloride, in good overall yield. Alternatively, benzamide **221** was also obtained through reversal of the methylation and amidation steps, proceeding via the 3-hydroxybenzamide intermediate **220**. Benzamide **221** was *ortho*-formylated using Snieckus's conditions in satisfactory yield to afford benzaldehyde **222**.[51] Reduction, followed by lactonisation of the resulting alcohol, generated 4-methoxyphthalide **223** in good yield. The entire process was reproducible on a multi-gram scale. Demethylation of methyl ether **223** with iodocyclohexane in DMF afforded 4-hydroxyphthalide **217**, which was reprotected as the TBS-ether **224**. Reduction and methylation afforded the desired 4-TBS-phthalan **215** in excellent yield (Scheme 59).



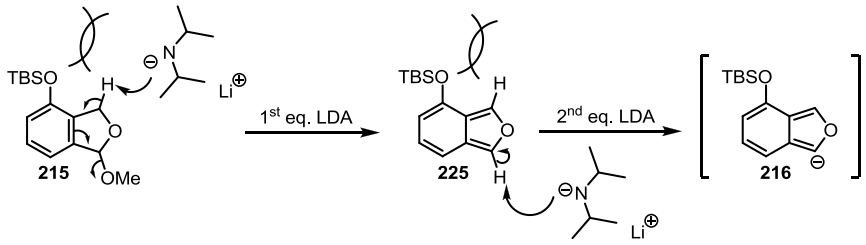
Scheme 59 **Synthesis of 4-TBS Phthalan 215**

The alkylation and oxidative rearrangement sequence was carried out with 4-TBSO-phthalan **215** using our standard conditions, to afford exclusively the sterically directed isochroman-1-one **199** in 45% yield (Scheme 60).



Scheme 60 **Rearrangement with Regiosiomeric Phthalan Precursors**

This demonstrated that the rearrangement does in fact proceed via identical IBF anion intermediates, regardless of whether the 7-TBS-phthalan **198** or 4-TBS-phthalan **215**, is used. Mechanistically, the hindered C3 position of 4-TBS-phthalan **215** is first deprotonated by the first equivalent of LDA to generate IBF **225**, while the second equivalent of LDA deprotonates exclusively at the C1 position, at the expense of the hindered C3 position (Scheme 61). Therefore this methodology allows for the use of either C4 or C7-substituted phthalans to access 8-hydroxyisochromanones.



Scheme 61 **Generation of IBF Anion 216**

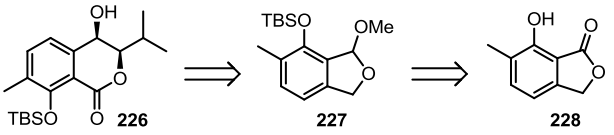
3.6 Summary and Outlook

In summary, the IBF oxidative rearrangement sequence for the diastereoselective synthesis of *anti*-isochromanones has been extended by achieving complete regiocontrol to access C8 oxygenated isochromanones in excellent yield. The 7-substituted phthalan precursors were synthesised efficiently in high yield from *o*-anisic acid. The reaction conditions for the oxidative rearrangement sequence were optimised to accommodate acid sensitive functionalities. It was demonstrated that C8 oxygenated isochromanones could be generated from regiosiomeric 4-substituted phthalan precursors, showing that both pathways proceed via a common IBF anion intermediate. Chelation-controlled IBF anion alkylation to access C5-substituted isochromanones, as yet, could not be achieved and requires further investigation.

4 The Ajudazol Western Section

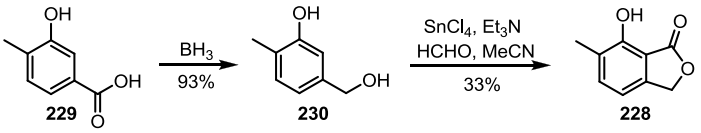
4.1 Ajudazol Isochromanone Moiety

After demonstrating that complete regiocontrol can be achieved in the IBF oxidative rearrangement, we sought to implement this methodology to generate a simple model system of the ajudazol isochromanone moiety. We were keen to evaluate the oxidative rearrangement's ability to tolerate the additional methyl substituent on the aromatic ring. Retrosynthetically, the ajudazol isochromanone fragment **226** was envisioned as originating via the sterically directed IBF alkylation and oxidative rearrangement sequence of functionalised phthalan **227**. In turn, phthalan **227** would be accessible from hydroxyphthalide **228** (Scheme 62).

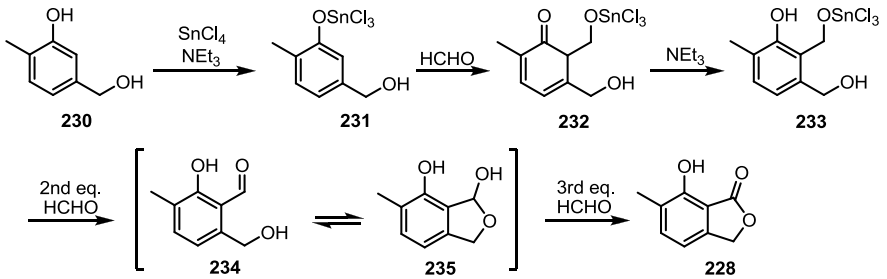


Scheme 62 **Retrosynthetic Ananlysis of Ajudazol Isochromanone Moiety 226**

To date there have been two examples where 7-hydroxy-6-methylphthalide **228H**as been synthesised. M^{c}Nab reported the synthesis of phthalide **228**; however, it involved low yielding, unattractive pyrolysis chemistry.[65] Toney published a highly regioselective, moderate yielding, one-pot synthesis of phthalide **228** from 3-hydroxy-4-methylbenzylalcohol **230** in an acid-catalysed Friedel-Crafts acylation reaction.[66] Mechanistically, the formation of phthalide **228** involves *ortho*-formylation followed by hemiacetal formation and oxidation (Scheme 63).

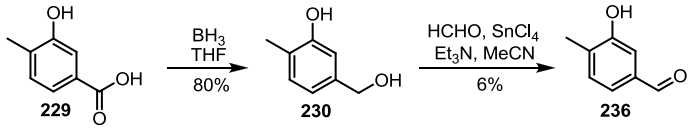


Proposed Mechanism:



Scheme 63 **Toney's $SnCl_4$ Catalysed Friedel-Crafts Acylation to Afford Phthalide 228**

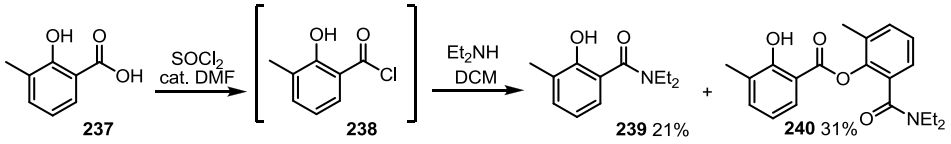
Following Toney's procedure, borane reduction of benzoic acid **229** was performed successfully to yield alcohol **230** in good yield. However, the key Friedel-Crafts reaction failed to afford any of the desired 7-hydroxy-6-methylphthalide **228**. All that was recovered from the reaction was benzaldehyde **236** in 6% yield (Scheme 64). This was a side-product that was reported in Toney's original publication; however, its abundance was not reported. The failure of the Friedel-Crafts reaction coupled with the low yield reported in the original publication, meant that an alternative route to access 7-hydroxy-6-methylphthalide **228H**ad to be found.



Scheme 64 Repetition of Toney's Synthesis of 7-hydroxy-6-methylphthalide 228

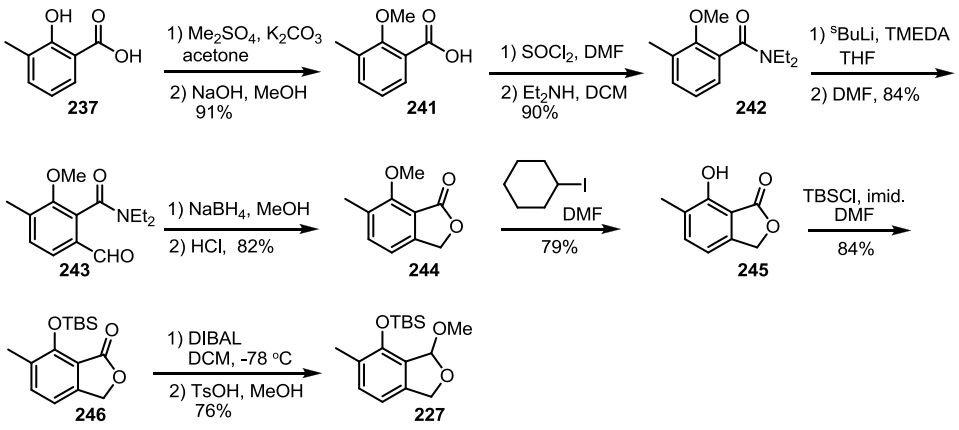
Thus, it was decided to attempt to access 7-hydroxy-6-methylphthalide **228** via a synthetic route analogous to our already well-established protocol for the synthesis of 4- and 7-hydroxyphthalides.

In our new approach, commercially available benzoic acid **237** was converted to the acid chloride **238** and then treated with diethylamine to afford the desired benzamide **239**, together with significant amounts of the dimeric species **240** (Scheme 65). This result was unexpected because previously, in the synthesis of 4-TBS-phthalan **215** (Scheme 59), 3-hydroxybenzoic acid underwent smooth amidation with no by-product formation. In this case, on steric grounds, one would expect acid **237** to disfavour dimerization due to the increased steric bulk around the phenol functionality, as opposed to the more accessible phenol functionality in 3-hydroxybenzoic acid, which proceeded without dimerisation. However, it is possible that dimerisation may have occurred due to the increased nucleophilic character of the phenol group due to activation by the *ortho*-methyl group.



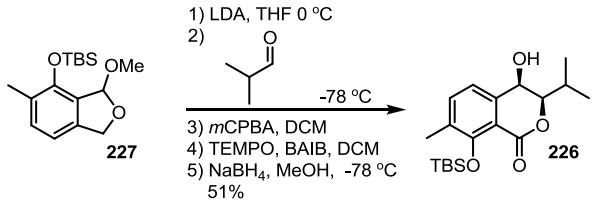
Scheme 65 Synthesis of Benzamide 239

It was decided that the dimerization problem could be easily avoided through methylation of the phenol functionality prior to amidation. Hence, benzoic acid **237** was converted to 2-methoxy-3-methylbenzoic acid **241** in excellent yield, followed by clean conversion to the benzamide **242**. *Ortho*-formylation of amide **242** afforded benzaldehyde **243**, which upon reduction and lactonisation, yielded phthalide **244** in excellent yield. Demethylation of methyl ether **244** gave phenol **245**, which was protected as the TBS ether **246**, before being converted into the phthalan **227** in high yield (Scheme 66). The entire synthetic route to phthalan **247** was robust and was easily scaled up to provide over 30 g of the target compound.



Scheme 66 Synthesis of Phthalan 227

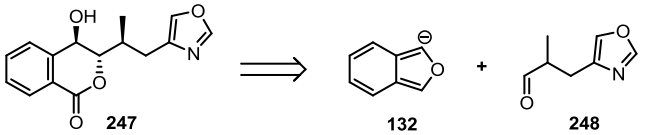
The IBF oxidative rearrangement sequence was carried out with functionalised phthalan **227**, using our optimised conditions, to generate isochromanone **226** in good yield over the entire protocol and as a single regioisomer (Scheme 67). This result demonstrated that functionalised phthalan **227** is well-tolerated in the oxidative rearrangement sequence and should be applicable towards the total synthesis of the ajudazols.



Scheme 67 **Synthesis of Ajudazol Isochromanone Moiety 226**

4.2 Ajudazol Western Section Model System

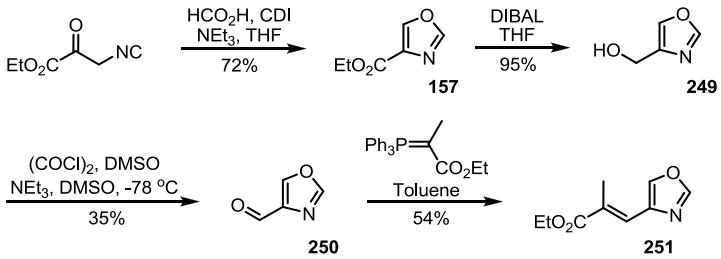
Having demonstrated that the oxidative rearrangement sequence can be used to efficiently access the isochromanone moieties present in the ajudazols, with complete regio- and diastereocontrol, we sought to generate the oxazole-linked isochromanone moiety **247**, based on the IBF alkylation and oxidative rearrangement with IBF anion **132** and aldehyde **248** (Scheme 68).



Scheme 68 **Retrosynthetic Analysis of Ajudazol Western Section Model System**

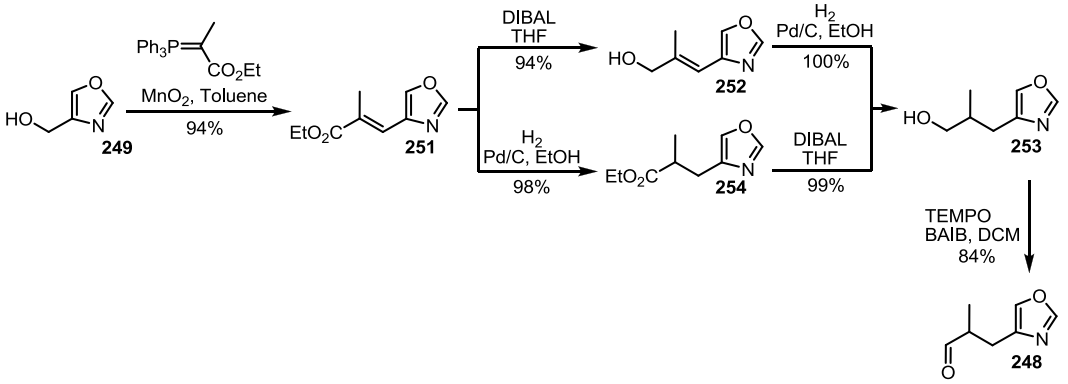
It was hypothesised that the unsubstituted oxazole C2 position may have a profound effect on the IBF alkylation and rearrangement due to its relatively acidic nature (pK_a 20-25), and therefore, we were eager to test whether it could be tolerated in the oxidative rearrangement sequence.[67] The decision for using a C2 unsubstituted oxazole emanated from the hope that direct C-H activation chemistry could be implemented to provide a convergent, late-stage coupling in the total synthesis of the ajudazols (Scheme 37).

The synthesis of oxazole-linked aldehyde **248** commenced with the cyclodehydration between ethyl isocyanoacetate, formic acid and CDI to generate oxazole-ester **157**. Reeves claimed a 64% yield for the partial reduction of ethyl oxazole-4-carboxylate **157** to aldehyde **250**; however, like most partial DIBAL reductions reported in the literature, we found the conditions irreproducible.[68] In our hands, DIBAL reduction of ester **157** afforded alcohol **249** in excellent yield. Frustratingly, oxidation of alcohol **249** to aldehyde **250** proved troublesome, with Swern conditions resulting in only a 35% yield. Furthermore, aldehyde **250** proved to be both thermally unstable and volatile. On the other hand, Wittig olefination of aldehyde **250** afforded exclusively the desired *E*-olefin **251** in 54% yield (Scheme 69).



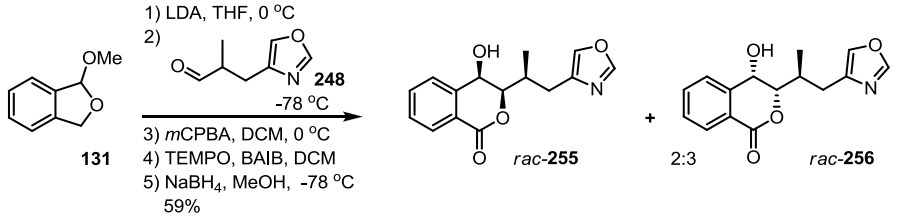
Scheme 69 Synthesis of Ester 251

However, due to the unacceptably poor yielding oxidation and olefination steps, an alternative method for the synthesis of ester **251** was sought. Taylor's tandem oxidation Wittig olefination methodology for the one-pot oxidation and olefination of allylic and benzylic alcohols was implemented.[69] Gratifyingly, alcohol **249** readily reacted with MnO_2 in the presence of stabilised ylid, to afford *E*-olefin **251** in excellent yield and with complete *E*-selectivity (Scheme 70). Ester **251** was then reduced to the allylic alcohol **252** in excellent yield, followed by hydrogenation using Pd/C, to afford the desired alcohol **253**. Alternatively, alcohol **253** was also accessed by a reversal of the reduction and hydrogenation steps, with no overall drop in yield. Oxidation of alcohol **253** to the racemic aldehyde **248** was achieved with TEMPO in high yield (Scheme 70).



Scheme 70 Synthesis of Aldehyde 248

With racemic aldehyde **248** in hand, the oxidative rearrangement was then carried out using the unfunctionalised phthalan **131** in the first instance. Rewardingly, a 2:3 mixture of two diastereoisomeric isochromanones, **255** and **256**, were obtained in good overall yield (Scheme 71). The identity of both diastereoisomers was corroborated by X-ray crystallographic analysis, which confirmed the relative C8-C9 stereochemistry of the major diastereoisomer **256** as *syn,anti* (Figure 13).



Scheme 71 IBF Oxidative Rearrangement Sequence with Aldehyde 248

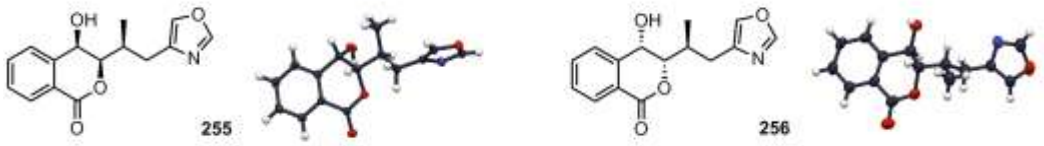


Figure 13 **X-ray Crystal Structures of Isochromanones *rac*-255 and *rac*-256**

The Felkin-Anh model can be used to explain the stereochemical outcome of nucleophilic additions to aldehydes. The model predicts that the two lowest energy, non-eclipsing, conformations result from the largest group (R_L = CH_2-oxazole) on the α-stereocentre, being orientated perpendicular to the carbonyl. As the nucleophile (IBF anion) will attack the aldehyde at 107° along the Bürgi-Dunitz trajectory, then the lowest energy conformation arises when the nucleophile "passes" over the small group (R_S = H), conformation **A**, as opposed to the medium group (R_M = CH_3), conformation **B**. Conformation **A** encounters less steric hindrance and is expected to be the favoured Felkin addition product **255**, over the *anti*-Felkin product **256** (Figure 14)**.**

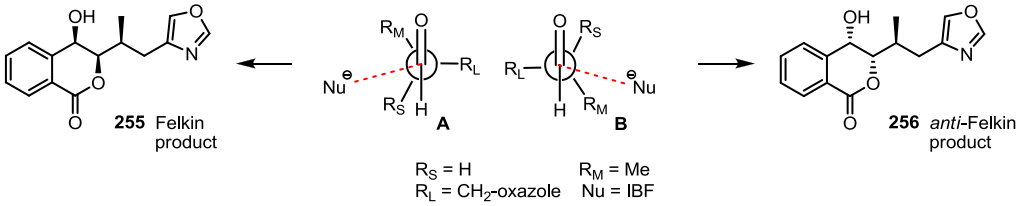
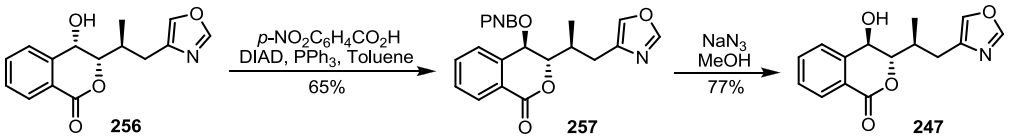


Figure 14 **Felkin-Anh Model**

However, in the addition to aldehyde **248** in the synthesis of the *syn,syn* and *syn,anti* diastereoisomers **255** and **256**, both diastereoisomers were obtained in near-equal proportions, with a marginal bias (3:2) for the *anti*-Felkin product **256** in this case. It is hypothesized that the marginal preference for the *anti*-Felkin product is because the substituents R_S and R_M (H and Me respectively) are not sufficiently size differentiated for there to be full steric control over the addition.

Gratifyingly, the *syn,anti*-diastereoisomer **256** underwent Mitsunobu inversion with 4-nitrobenzoic acid to afford the *para*-nitrobenzoate ester **257** in reasonable yield (Scheme 72). However, purification of the Mitsunobu product proved troublesome due to the presence of phosphine and azodicarboxylate by-products and impurities. Forcing conditions (reflux in toluene) were necessary to invert the hindered benzylic 2° alcohol **256**. Chemoselective cleavage of the *para*-nitrobenzoate group was achieved in the presence of the lactone functionality under extremely mild conditions, using NaN_3 in MeOH, to afford isochromanone **247** in good yield (Scheme 72). The C8-C10 *anti,anti* stereochemistry of isochromanone **247** reflecting that of the ajudazols was confirmed via NMR analysis, and was further corroborated via X-ray crystallographic analysis (Figure 15).



Scheme 72 **Stereochemical Inversion to Access Western Section Model System *rac*-247**

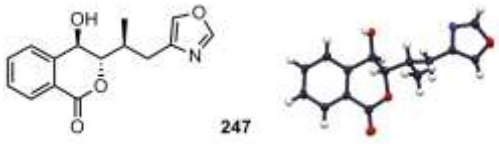
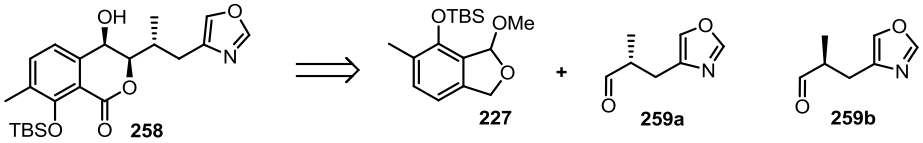


Figure 15 **X-Ray Crystallographic Structure of Western Section Model System *rac*-247**

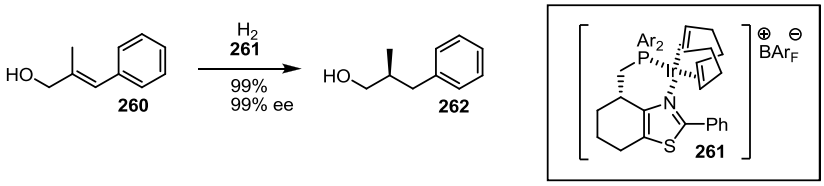
4.3 Synthesis of Ajudazol Western Section

Having demonstrated that the oxidative rearrangement sequence can be used to efficiently access the western section model system **247**, the synthesis of a true western section was then undertaken. Our synthesis of western section **258** would be based on oxidative rearrangement sequence between the functionalised phthalan precursor **227** and enantiopure aldehyde **259a** or **b** (Scheme 73).



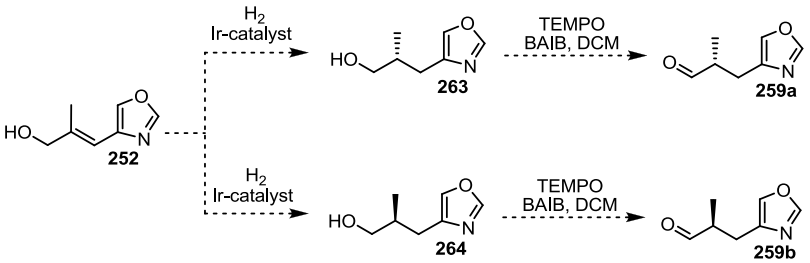
Scheme 73 **Retrosynthetic Analysis of Ajudazol Western Section 258**

The main challenge of this target was to access and use the enantiopure oxazole-linked aldehydes **259a** and **259b**, having to this stage, only carried out the oxidative rearrangement with racemic aldehydes. Furthermore, since only the relative stereochemistry of the ajudazols is known, it would be desirable to access both aldehydes **259a** and **259b** in enantio-enriched form**.** Pfaltz has show that olefins of type **260** can be asymmetrically reduced under iridium catalysis to afford alcohol **262** with complete enatioselectivity (Scheme 74).[70]



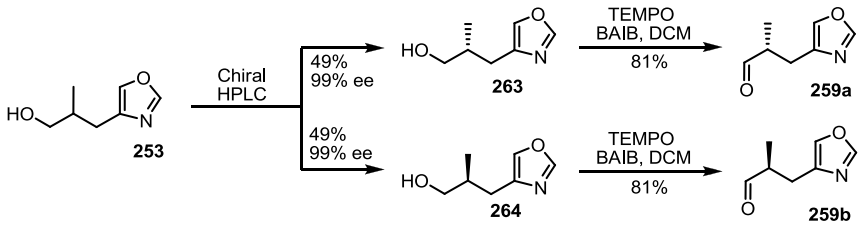
Scheme 74 **Pfaltz's Asymmetric Iridium Catalysed Hydrogenation**

Although Pfaltz's chemistry could hopefully be applied to oxazole-linked allylic alcohol **252**, from which both aldehydes **259a** and **259b** could be accessed in enantio-enriched form, the time and resources that optimising such a step would require, could not be justified at this stage in the project (Scheme 75).



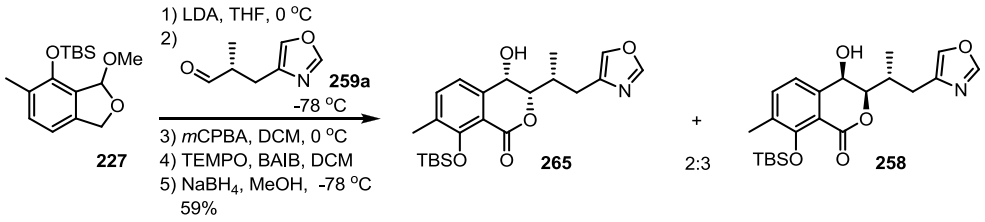
Scheme 75 **Asymmetric Hydrogenation Route Towards Aldehydes 259a and 259b**

Therefore, as part of our first generation synthesis, enantiopure aldehydes **259a** and **259b** were accessed via chiral separation of the racemic alcohol **253**, followed by TEMPO oxidation, in good yields (Scheme 76). At this stage, the stereochemical identity of aldehydes **259a** and **259b** was arbitrarily assigned.



Scheme 76 **Synthesis of Enantiopure Aldehydes 259a and 259b**

With the enantiopure aldehydes to hand, the IBF oxidative rearrangement protocol was carried out with functionalised phthalan **227** and *R*-aldehyde **259a**, to generate the *syn,syn* and *syn,anti*-isochromanones **265** and **258**, in 59% overall yield (Scheme 77).



Scheme 77 **IBF Oxidative Rearrangement Sequence with Enantiopure Aldehyde 259a**

Fortunately, an X-ray crystal structure of the major *syn,anti*-diastereoisomer **258** was obtained, which allowed for the absolute stereochemistry of our western section to be elucidated, and hence, the absolute stereochemistry of aldehydes **259a** and **259b**.

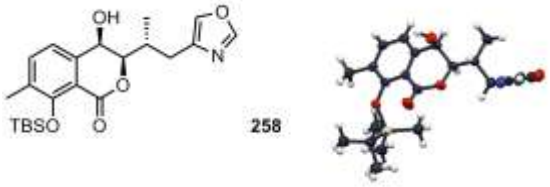


Figure 16 **X-Ray Crystallographic Structure of Ajudazol Western Section 258**

4.4 Accessing Anti-Isochromanones

4.4.1 Keto-Lactone Reduction

One of the major limitations of the current route towards accessing *anti*-isochromanones was the need to invert the stereochemistry of *syn*-isochromanones, the direct products of the IBF oxidative rearrangement sequence. The ability to directly access *anti*-isochromanones via the reduction of the keto-lactone intermediates would be far more efficient as it would avoid the need for the troublesome, poor yielding Mitsunobu inversion/hydrolysis steps.

For the reduction of the conformationally locked 4-*t*ert-butylcyclohexanone, the reducing agent can potentially attack from either the axial or equatorial position, to afford either the *cis*-**266** or *trans*-diastereoisomer **267** (Figure 17). Equatorial attack is favoured for sterically large nucleophiles because it minimises unfavourable 1,3-diaxial interactions. L-Selectride reduces 4-tert-butylcyclohexanone to afford the *cis*-product **266** in a 19:1 ratio.

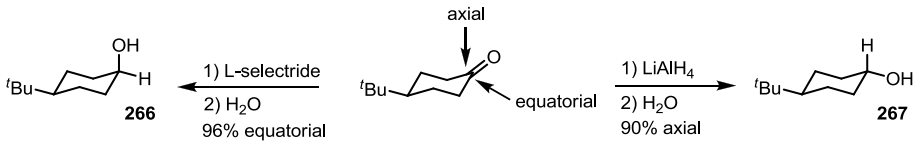


Figure 17 Reduction of 4-Tert-Butylcyclohexanone

However, for smaller nucleophiles there is a reversal in selectivity as axial attack is favoured, even though this is a more sterically restricted approach than the equatorial trajectory, to afford predominately the *trans*-product **267** (Scheme 17). $LiAlH_4$ reduction of 4-*t*ert-butylcyclohexanone generates, almost exclusively, the *trans*-diastereoisomer **267**, in a 9:1 ratio. Various theories have been put forward to try to explain the preference for axial attack of unhindered cyclohexanones by small nucleophiles. Felkin proposed that the preference for axial attack was due to greater torsional strain in the transition state for equatorial attack. On the cyclohexanone substrate, the C2 and C6 C-H bonds almost eclipse the carbonyl and this torsional strain is relieved by axial attack, but equatorial attack increases it somewhat because the oxygen must move through a fully eclipsed arrangement.[71,72] Anh further expressed the importance of an electronic effect in which flattening of the carbonyl bond resulted in the C2 and C6 C-H bonds becoming almost anti-periplanar with the incoming axial nucleophile. This would allow delocalisation of electron density from the approaching axial nucleophile to the σ* orbital of the vicinal C-H bonds.[73,74]

The keto-lactones of type **135f**, generated via the IBF oxidative rearrangement sequence, are more complex than simple cyclohexanones as they incorporate an aromatic ring, lactone unit and an ^{i}Pr group α-to the ketone carbonyl. The keto-lactone **135f** is believed to adopt a *pseudo*-half chair conformation (Figure 18). Due to this additional complexity, together with the added degree of steric bulk on either side of the ketone carbonyl, it was perhaps unsurprising that complete selectivity to generate the *syn*-isochromanone **136f** was achieved under Luche conditions and with $NaBH_4$ (Table 5, entries 1 and 2), the result of equatorial attack at the sterically hindered ketone carbonyl. Increasing the reaction temperature from –78 ^{o}C to room temperature failed to alter the selectivity. Similarly $Na(CN)BH_3/ZnI_2$ exclusively gave *syn*-product **136f** in a modest 52% yield (entry 3). Because the small reducing agent ($NaBH_4$), attacked exclusively from the equatorial position, then it would have been very unlikely that a bulky reducing agent would do anything else. L-selectride failed to react with keto-lactone **135f**, presumably due to the clash of a hindered ketone environment and a sterically bulky nucleophile (entry 4).

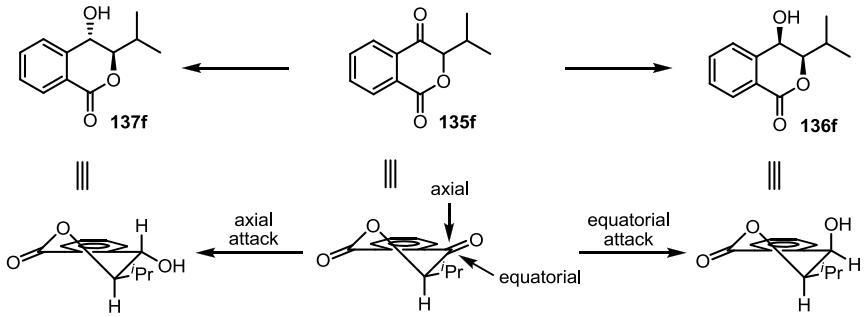


Figure 18 Reduction of Keto-Lactone 135f

It was hypothesised that the *anti*-isochromanone **137f**, with the hydroxyl group in the equatorial position, would be more thermodynamically stable than the *syn*-isochromanone **136f**, where such hydroxyl is axial. It was hoped that by utilising reversible reaction conditions, equilibration could yield the *anti*-isochromanone **137f**. The reversible Meerwein-Ponndorf-Verley reduction failed to show any evidence of the *anti*-diastereoisomer **137f** (entry 5).[75] A $Sm(O^iPr)_3$ variant of the Meerwein-Ponndorf-Verley reduction also exclusively afforded the *syn*-isochromanone **136f** in reasonable yield (entry 6).[76] It is believed that the energy barrier to reach the *anti*-isochromanone **137f** was too high.

Table 5 Reduction of Keto-Lactone 135f

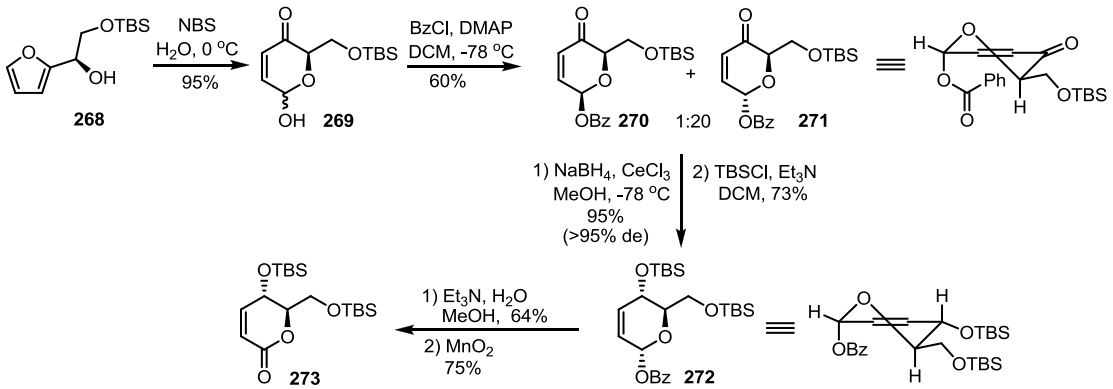
Entry	Reaction conditions	**136f**:**137f**	Yield / %
1	$NaBH_4$, $CeCl_3$, MeOH, DCM, –78 °C	100:0	82
2	$NaBH_4$, MeOH, –78 °C	100:0	89
3	$Na(CN)BH_3$, ZnI_2, DCE, reflux, 16H	100:0	52
4	L-selectride, THF, 0 °C	-	-
5	Me_2AlCl, ^{i}PrOH, Tolune, reflux, 50 h	100:0	71 (85% brsm)
6	$Sm(O^iPr)_3$, ^{i}PrOH, Tolune, RT, 50 h	100:0	64%
7	BH_3, THF, –78 °C	12:1	40%
8	9-BBN, THF, 0 °C	-	-
9	Alpine borane, THF, 0 °C	-	-
10	*(R)*-CBS, BH_3, THF, 0 °C	12:1	45%
11	*(S)*-CBS, BH_3, THF, 0 °C	12:1	45%

Borane reductions were then investigated. The use of BH_3/THF showed glimpses of the *anti*-product **137f**, albeit in a very low 1:12 ratio of **137f**:**136f**, and in low yield (entry 7). Varying the reaction temperature (–78°C, 0 °C, RT) failed to improve either the selectivity or yield. 9-BBN failed to react with keto-lactone **135f**, as did alpine borane (entries 8 and 9). The use of CBS with BH_3, failed to show any improvements on the selectivity achieved with BH_3 alone (entry 10).[77]

4.4.2 Reduction of α-Anomeric Intermediates

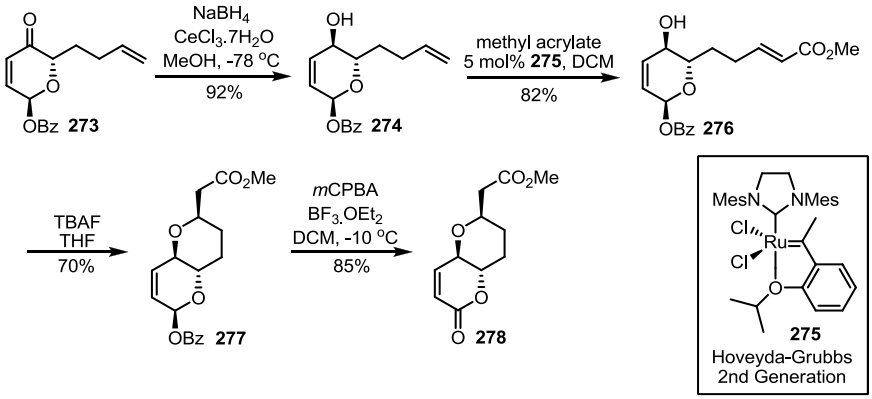
Due to the inability to generate the *anti*-isochromanone **137f** via the direct reduction of keto-lactone **135f**, an alternative strategy was investigated. Through O'Doherty's efforts towards the diastereoselective synthesis of sugar molecules, he has shown that pyranones can be diastereoselectively reduced to furnish allylic alcohols with 1,2-*anti* stereoselectivity (Scheme 78).[78-80] The Achmatowicz rearrangement of furfuryl alcohol **268**, promoted by NBS/H_2O,

yielded hemiacetal **269** as an equilibrating mixture of diastereoisomers. However, O'Doherty took advantage of the difference in reactivities of axial and equatorial anomeric alcohols to selectively protect the axial anomer. Benzoylation afforded pyranone **271** in >20:1 diastereoselectivity. Luche reduction of pyranone **271** proceeded with complete diastereocontrol to afford allylic alcohol **272**. Benzoylated pyranone **271** was believed to adopt a half-chair conformation, with the steric bulk of the axial benzoyl group hindering attack of $NaBH_4$ from the equatorial trajectory of the carbonyl, forcing it to attack via the axial trajectory on the top face, resulting in the generation of the *trans,trans*-diastereosiomer **272**. O'Doherty then deprotected anomeric benzoyl-lactol **272** with NH_3/MeOH, and re-oxidised with MnO_2 to afford lactone **273** (Scheme 78).[78]



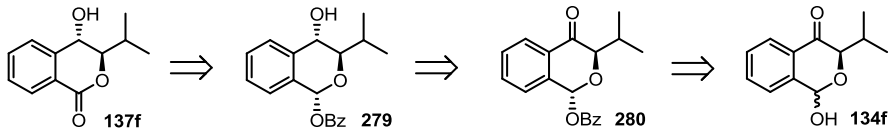
Scheme 78 **O'Doherty's Route to *5,6-Anti*-Pyranones**

Phillips then used O'Doherty's approach in efforts towards the synthesis of halichondrins. Allylic alcohol **274** was generated with complete diastereocontrol from α-benzoylated pyranone **273**.[81] After olefin metathesis and cyclisation to generate pyropyran **277**, Phillips employed a Grieco oxidation to convert benzoyl alcohol **277** to lactone **278** in a single step, an improvement to O'Doherty's troublesome two-step procedure (Scheme 79).[81,82]



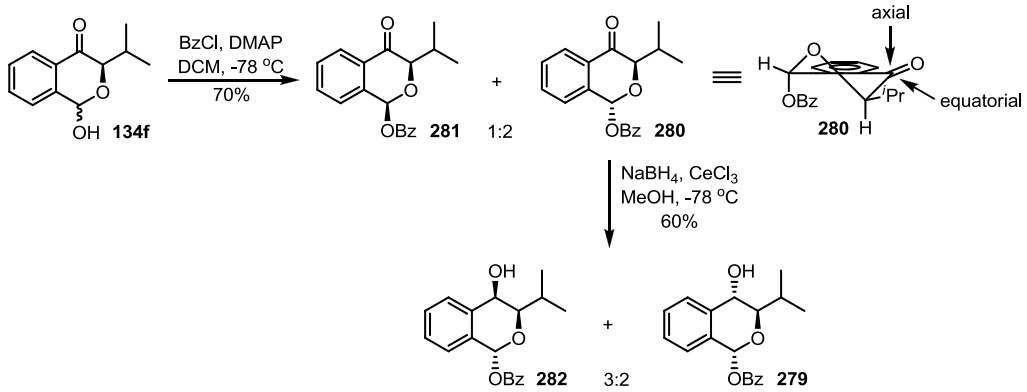
Scheme 79 **Phillips' Route to *5,6-Anti*-Pyranones**

It was hoped that O'Doherty's α-anomer benzoylation/reduction approach could be incorporated into the oxidative rearrangement sequence to allow access to *anti*-isochromanones. Retrosynthetically, the highly sought after *anti*-isochromanone **137f** could be accessed via Grieco oxidation of benzoyl acetal **279**, which in turn could originate from the diastereoselective reduction of ketone **280**.[78,81] Ketone **280** could be generated via the diastereoselective benzoylation of lactol **134f**, the initial product from the IBF oxidative rearrangement sequence (Scheme 80).



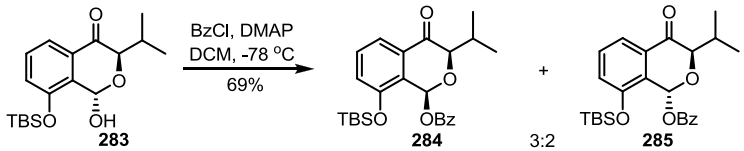
Scheme 80 **Retrosynthetic Analysis of *Anti*-Isochromanones Via O'Doherty Approach**

Benzoylation of keto-lactol intermediate **134f**, according to O'Doherty's conditions, failed to provide the benzolyated product **280** as a single diastereoisomer. Instead, a poor 2:1 ratio in favor of the α-benzoylated species **280** resulted. Varying the reaction temperature failed to improve the product ratios. The diastereoisomers could be separated after careful chromatography to afford α-benzoylated lactol **280**, in modest yield. However, Luche reduction of **280** failed to give a single diastereoisomeric product and instead an inseparable 3:2 mixture in favour of the *syn*-product **282** was observed (Scheme 81). It was apparent that the axial trajectory was still too inaccessible even with the axial-benzoyl group which would have been acting against equatorial attack.



Scheme 81 **α-Anomer Benzoylation/Reduction Route to *Anti*-Isochromanoes**

For the unfunctionalised keto-lactol **134f**, a dynamic equilibrium of anomers existed, which was evident in ^{1}H NMR; however, for the TBS protected phenolic species **283**, only the α-anomer was observed (Scheme 82). It was hoped that this conformational anchor would allow for complete axial benzoylation, unlike the situation for unfunctionalised lactol **134f**. However, this was not the case, with similar ratios of unseparable benzoylated species **284** and **285** being observed.



Scheme 82 **α-Anomer Benzoylation/Reduction Route Using Keto-Lactol 283**

Due to these shortcomings, together with the inability to obtain diastereocontrol in the reduction of the α-diastereosiomer **285**, this route towards the synthesis of *anti*-isochromanones was abandoned.

4.5 Summary and Outlook

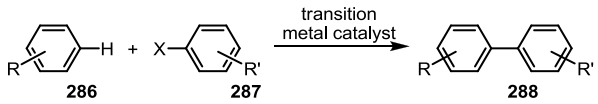
In summary, the functionalised phthalan **227** was efficiently generated in excellent yield and multi-gram scale from 3-methylsalicylic acid and was implemented in the IBF oxidative rearrangement sequence to generate the ajudazol isochromanone moiety **226**. The C2 unsubstituted oxazole-linked aldehyde **248**, efficiently generated from ethylisocyanoacetate, was used to synthesise the western section model system **256**, for which the C8-stereochemistry could be inverted, generating the *anti,anti*-isochromanone **247**, akin to that observed in the ajudazols. Furthermore, the true ajudazol C1-C14 western section framework **258** was accessed via the IBF oxidative rearrangement sequence between functionalised phthalan **227** and enantiopure aldehyde **259a**. Methods to access *anti*-isochromanones, via methods other than the inversion of *syn*-isochromanones, proved unsuccessful.

5 Ajudazol C14-C15 Bond Construction

5.1 Oxazole C-H Activation

Over recent years, the preparation of (hetero)-biaryl, (hetero)-aryl alkenyl units has been dominated by transition metal-catalysed processes, whereby an organometallic species is cross-coupled with a (hetero)aromatic halide. Such chemistry, namely Suzuki, Stille and Negishi cross-coupling, has become fundamental to the pharmaceutical industry to allow rapid access to bioactive (hetero)biaryl species.[83] Such transformations can be typically achieved in excellent yields, with good selectivity and functional group tolerance. However, the major drawback to such chemistry is the need to pre-functionalise one of the coupling partners, which can be time-consuming and atom-inefficient. There are few heteroaryl halides and metallated coupling partners commercially available and their synthesis can often be difficult, often further compounded with stability issues.[84] Furthermore, the need to dispose of stoichiometric by-products is a major concern to industry.[85]

Therefore, unsurprisingly, there has been considerable interest in transition metal-catalysed direct C-C (sp^2-sp^2) bond formation, in which one of the coupling partners, typically the organometallic component, is replaced by a simple unactivated (hetero)aromatic **286**, which upon transition metal catalysed coupling with halide **287**, generates (hetero)biaryl species **288** (Scheme 83). A streamlined synthesis would provide major time and atom economies once the need to prepare a suitably activated coupling partner has been eliminated. Direct C-H activation, as a replacement for conventional transition metal cross-coupling chemistry, would provide environmental benefits, with less waste, in particular, toxic by-products.[85]

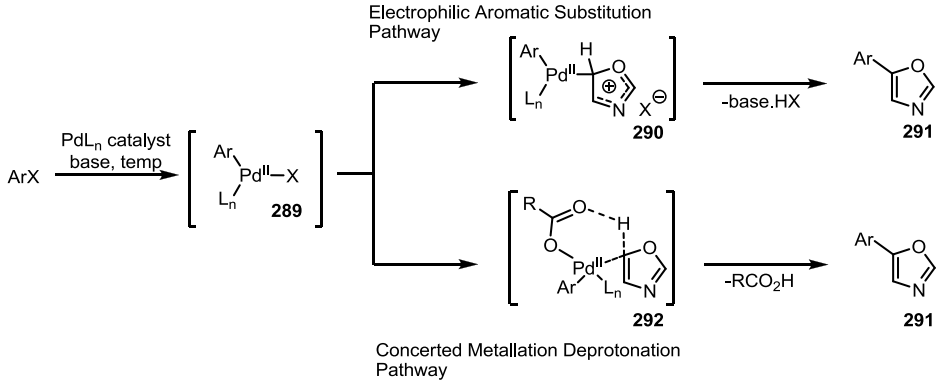


286 **287** **288**

Scheme 83 **Direct C-H Arylation**

Palladium catalysed direct C-H activation has received the most widespread attention; however other second-row transition metals: rhodium, ruthenium, copper and nickel have also been shown to participate in such processes. The ligands used in C-H activation processes depend on the nature of the aryl-halide component **287**. Although the more reactive (hetero)aryl iodides have been used predominately, bromides and chlorides have been shown to participate in direct C-H arylation processes. However, to obtain satisfactory conversions and yields, they have been used in conjunction with more sterically bulky and electron rich phosphine ligands. Direct C-H activation reactions usually require the presence of a base, although the exact role of the base can remain unclear. A wide variety of bases have been reported, and typically the inorganic bases K_2CO_3, Cs_2CO_3,KOAc, ^{t}BuOK and CsOPiv are employed. Typically, polar, aprotic solvents have been used most frequently for direct C-H activation processes.[85]

Direct C-H activation chemistry is believed to occur via several possible mechanisms, strongly dependent on the substrates, catalytic systems and bases. For 1,3-azoles in particular, direct arylation is proposed to occur via oxidative addition of the transition metal into the aryl halide followed by, predominately, one of two C-C bond forming pathways: electrophilic aromatic substitution (S_EAr) or concerted metallation-deprotonation (CMD) (Scheme 84).[85-87]

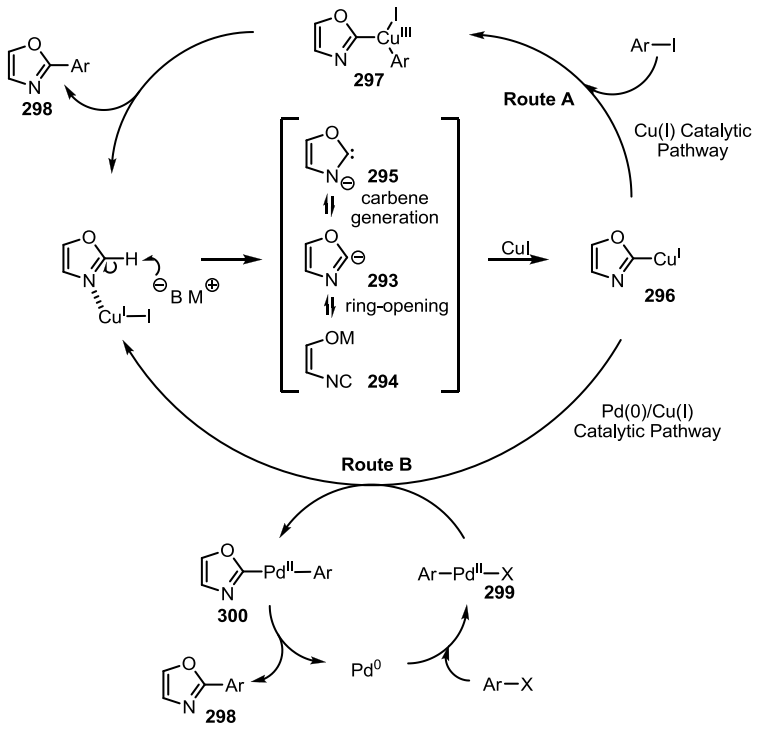


Scheme 84 **S_EAr and CMD Direct Pathways for Direct C5 Arylation of Oxazole**

It was initially believed that electron rich 1,3-azoles reacted via an S_EAr mechanism, whereby electropalladation of the azole onto the Pd^{II} intermediate **289** occurred, which, followed by re-aromatisation from the Wheland intermediate **290** and reductive elimination, afforded the hetero(biaryl) species **291**.[85] However, Fagnou has shown that π-excessive heteroaromatics, commonly proposed to react via electrophilic aromatic substitution pathways (S_EAr), can operate via the CMD pathway, whereby the acetate/pivalate serves as a soluble proton transfer agent to facilitate metal insertion into the C-H bond, via a six-membered transition state **292** (Scheme 84).[86]

In the case of azoles, and more particularly oxazoles, *ab initio* calculations have revealed that the HOMO, indicating the most electron rich site, resides on C2 and C5 carbons of the oxazole ring.[88] Arylation should then occur at these two positions. It is believed that the C5 direct activation of oxazoles proceeds via S_EAr and/or CMD mechanistic pathways; however, the exact nature of the mechanism for C2 direct arylation of oxazoles has received considerably more debate. Together with support of S_EAr and CMD mechanistic pathways for the direct C2 arylation of oxazoles, anionic cross-coupling mechanisms have also been mooted.

Initially Miura rationalised that the C2 selectivity observed in a Pd(0)/Cu(I) system was suspected to arise from a proton-metal exchange of the most acidic position (C2>C5>C4), leading to the C2-oxazolylcopper species **296,** which acts as a transmetallating agent, reacting with Pd(II) species **299** to generate intermediate **300**, followed by reductive elimination to afford aryl-oxazole **298** (Scheme 85, Route B).[89] Daugulis reported the first rationalised route for the direct C2 arylation of azoles, including oxazoles, using a strong base under Cu(I) catalysis.[90] The C2-oxazolylcopper species **296** was believed to undergo a subsequent oxidative addition step with aryl iodide, before reductive elimination of the Cu(III) species **297**, to afford the arylated-oxazole **298** (Route A).



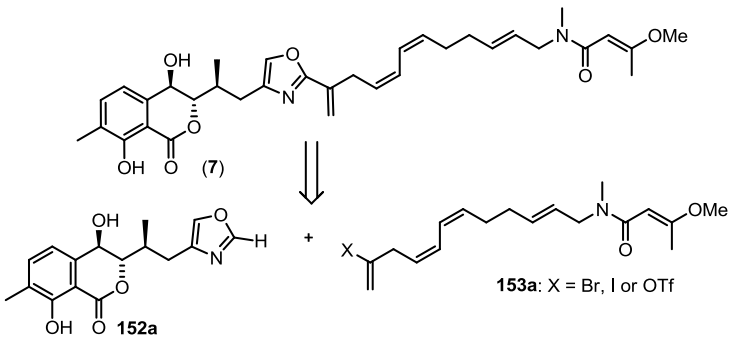
Scheme 85 **Catalytic Cycles for Cu(I) and Pd(0)/Cu(I)-Catalysed Direct Arylation of Oxazoles**

However Bellina and Rossi argued that the formation of C2-oxazolylcopper species **296** remained unclear.[91] They proposed that copper coordination to the oxazole could induce C2 deprotonation by a mild base, to generate C2-deprotonated species **293**. They stressed that the subsequent transmetallation step may be further complicated by the well-known equilibrium of the 2-metallated oxazole **293** and its ring opened tautomer **294** (Scheme 85).

Furthermore, under copper-free palladium(0) catalysis, Zhuralev and co-workers have disclosed mechanistic studies on the C2 phenylation of the related benzoxazole system, believed to take place via an anionic mechanism, proceeding via a ring-opened species akin to **294**.[92]

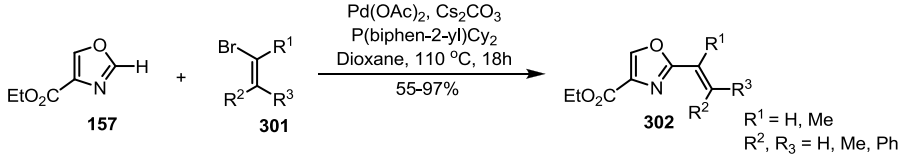
5.1.1 Direct C2 Alkenylation of Oxazoles

Having demonstrated that the ajudazol C1-C14 framework can be generated, the ability to directly activate and react the oxazole C2 position in a late-stage coupling would be highly desirable as it would allow for a highly efficient and convergent synthesis of ajudazol A, from the oxazole-containing western section **152a** and eastern section vinyl halide **153a** (Scheme 86).



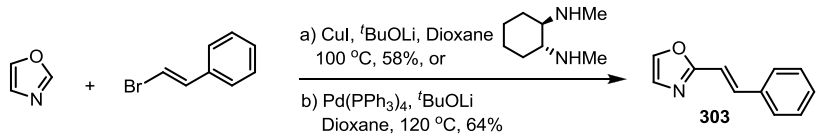
Scheme 86 Direct C-H Activation Route Towards Ajudazol A

Although there were emerging methods for the C2 or C5-selective direct arylation of oxazoles, very few reports for C2-alkenylation were reported. Moreover, of these, most were only applicable to activated oxazoles, such as oxazole-ethyl ester **157**, where C-H alkenylation with vinyl bromide **301**, under palladium catalysis, to generate alkenylated species **302** (Scheme 87).[93] Although there have been reports of regioselective C2 or C5 direct C-H arylation of oxazoles, most examples had one of the reactive positions (C2 or C5) blocked off.



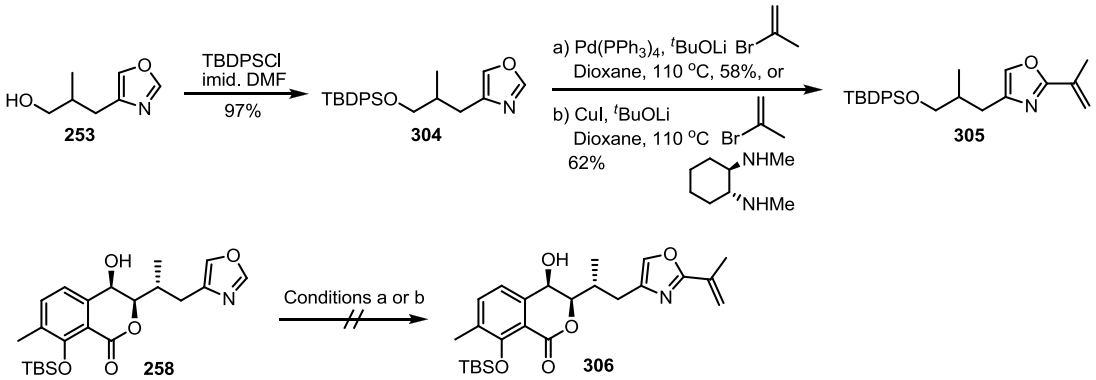
Scheme 87 Hoarau's Direct C2 Alkenylation of Oxazle Ethyl Ester

However, encouragingly, the work of Piguel showed that unsubstituted 1,3-oxazole could be alkenylated exclusively at the C2 position in 58% yield, under copper catalysis, to generate alkenyl oxazole **303**.[94] In a closely related publication, Piguel showed that the same transformation could be realised under palladium catalysis (Scheme 88).[95]



Scheme 88 Piguel's Direct C2 Alkenylation of Oxazle

Pleasingly, applying Piguel's conditions to the oxazole model system **304** resulted in C2 selective C-H alkenylation, under both palladium and copper mediated conditions, to generate the desired sp^2-sp^2 coupled product **305** (Scheme 89).[94,95]



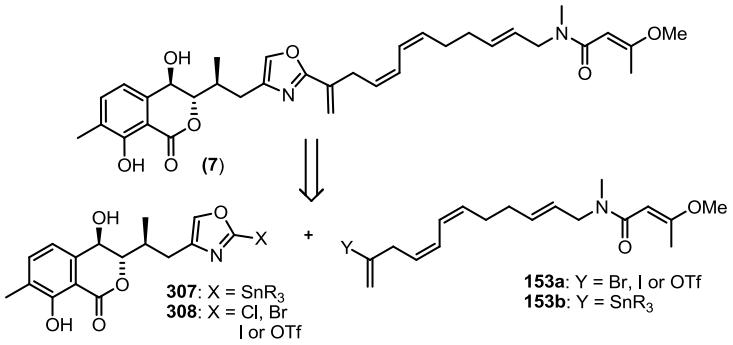
Scheme 89 Direct C-H Alkenylation of Oxazole 304

Unfortunately, to our disappointment, the reaction conditions used to generate alkene **305** could not be applied successfully to the oxazole-containing western section **258**. Modification of the C-H activation conditions proved fruitless with isochromanone ring degradation being the predominant pathway, rather than generation of alkenyl oxazole **306**. It's believed that this degradation is due to the strong base and high temperatures used. Attempts to improve the coupling conditions by using K_2CO_3 in dioxane at 70 °C proved unsuccessful and resulted in complete substrate degradation. Although various other catalytic conditions reported in the

literature may have been successfully applied to oxazole **304**, the inability of the isochromanone unit to withtand even mild base at elevated temperatures meant that C-H activation chemistry would not be applicable towards the total synthesis of ajudazol A.[87]

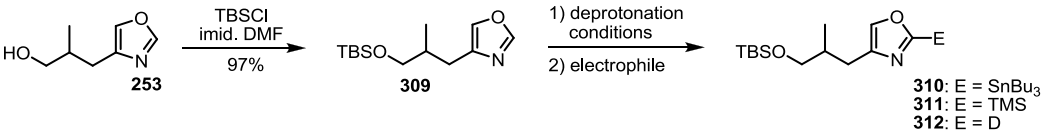
5.2 Oxazole C2 Stille Coupling

Faced with the failure of C-H activation chemistry to achieve the desired C14-C15 coupling, conventional cross-coupling reactions were considered. Suzuki, Negishi and Heck couplings, however, were ruled out due to their dependency of base, usually in combination with elevated reaction conditions, which we believe would result in isochromanone decomposition. However, it was possible a Stille reaction could be suitable for achieving the C14-C15 coupling as Stille reactions proceed under neutral conditions, and importantly, in the absence of base. However, a Stille coupling would require the oxazole C2 position to be activated as either the trialkylstannane **307** or halide **308**. The C2 functionality would have to be installed prior to the IBF oxidative rearrangement sequence as any conditions requiring strong base to deprotonate on the oxazole ring to introduce the necessary functionality would result in isochromanone ring degradation. Initial studies on the Stille strategy focussed on the introduction of a trialkylstannane prior to the oxidative rearrangement sequence. A successful rearrangement would then provide us with an advanced intermediate (**307** or **308**) which could be used in cross-coupling with vinyl halide **153a** or vinyl stannane **153b**, akin to that employed by Taylor in his ajudazol A eastern section (Scheme 90).



Scheme 90 **Late-Stage Stille Route Towards Ajudazol A**

The synthesis of stannane **310** began with oxazole **253** which was protected as the TBS ether **309**. Deprotonation of **309** with ^{n}BuLi, followed by treatment with Bu_3SnCl, failed to yield any of the desired stannane **310** (Scheme 91, Table 6, entry 1). Replacing LDA with ^{n}BuLi as base failed to improve matters (entry 3). Trapping the oxazole anion with TMSCl failed to generate the silyl oxazole **311** (entry 5). There was concern that the lack of success might be due to competing deprotonation at the C5 position. However, quenching with D_2O yielded exclusively the C2 deuterated species **312**, showing that complete C2 deprotonation did indeed take place (entry 6).



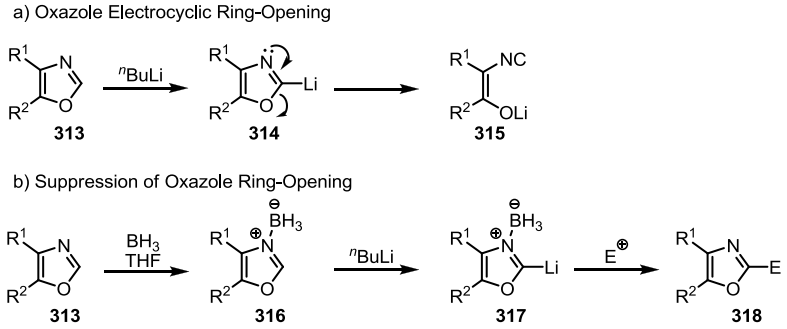
Scheme 91 **Oxazole C2 Functionalisation**

Table 6 Oxazole C2 Functionalisation

Entry	Deprotonation Conditions	Electrophile	E	Yield
1	^{n}BuLi, THF, –78 °C	Bu_3SnCl	$SnBu_3$	-
2	^{t}BuLi, THF, –78 °C	Bu_3SnCl	$SnBu_3$	-
3	LDA, THF, –78 °C	Bu_3SnCl	$SnBu_3$	-
4	^{n}BuLi, THF, 0 °C	Bu_3SnCl	$SnBu_3$	-
5	^{n}BuLi, THF, –78 °C	TMSCl	TMS	-
6	^{n}BuLi, THF, –78 °C	D_2O	D	83%

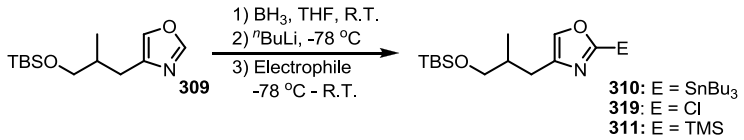
The lack of reactivity is believed to be attributable to the well known phenomenon of electrocyclic ring opening of C2 lithio-oxazoles. Studies have shown that the C2-lithiated oxazole **314** is in equilibrium with the acyclic lithium enolate tautomer **315**.[96,97] This equilibrium, together with the choice of electrophile, has been shown to dictate the product distribution between C2-functionalised oxazole **318** and acyclic side-products. NMR studies by Hughes and co-workers showed that the acyclic species tend to predominate; however, transmetallation with $ZnCl_{2H}$as been shown to shift the equilibrium from the acyclic species to predominately cyclic 2-zincated oxazole species.[98]

Vedejs and co-workers reported a practical solution to the problem of electrocyclic ring-opening of 2-lithiooxazoles.[99] Vedejs discovered that the ring-opening pathway could be suppressed via Lewis Acid complexation, in particular, with BH_3. Mechanistically, complexation of the oxazole **313** with BH_3, prior to organolithium addition, suppressed C2 ring-opening by locking the oxazole nitrogen lone pair in place (**316**), preventing it from participating in ring-opening, avoiding generation of the acyclic isonitrile species **315**. Complexation also enhanced the acidity of the C2 position and ensured that only the C2 substituted product **318** was obtained (Scheme 92).



Scheme 92 Vedejs' Oxazole C2 Functionalisation Via BH_3 Complexation

Following Vedejs' complexation protocol, the 2-stannyl oxazole **310**, chloride **319** and trimethylsilane **311** were all successfully generated in good yields (Scheme 93 and Table 7, entries 1,2 and 8). [100,99] Attempts to introduce further halides (entries 4-7), and sterically bulkier silanes (entry 9) proved fruitless.

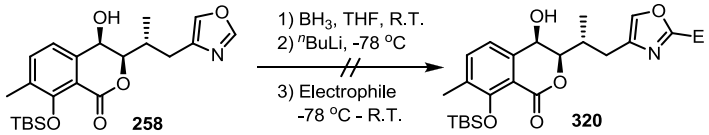


Scheme 93 Oxazole C2 Functionalisation Via BH_3 Complexation

Table 7 **Oxazole C2 Functionalisation Via BH_3 Complexation**

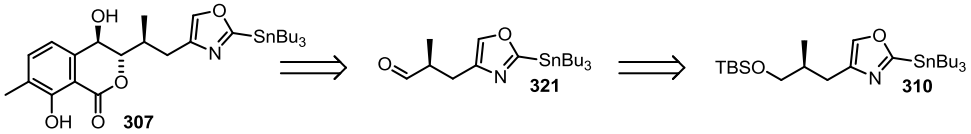
Entry	Electrophile	E	Yield / %
1	Bu_3SnCl	$SnBu_3$	71
2	C_2Cl_6	Cl	87
3	NCS	Cl	-
4	NBS	Br	-
5	Br_2	Br	-
6	NIS	I	-
7	I_2	I	-
8	TMSCl	TMS	81
9	TIPSCl	TIPS	-

However, attempts at functionalising the C2 oxazole position of western section model system **258**, using this methodology resulted only in substrate degradation (Scheme 94). This was disappointing as the ability to directly functionalise the western section **258** would have been very desirable as it would have meant that oxazole functionalisation would have taken place at a later-stage intermediate, and thus minimising the number of functional group and protecting group manipulations required.



Scheme 94 **Attempted Functionalisation of Western Section 258**

The failure to stannylate isochromanone **258** meant that the pre-functionalised oxazole **321** would have to be carried through the IBF oxidative rearrangement sequence, in order to access stannyl oxazole western section **307** (Scheme 95). However, attempts to convert 2-stannyl oxazole **310** to the aldehyde **321** failed due to the inability to desilylate **310** without competing protodestannylation, under TBAF, CSA/MeOH or even HF.Py conditions.[101]

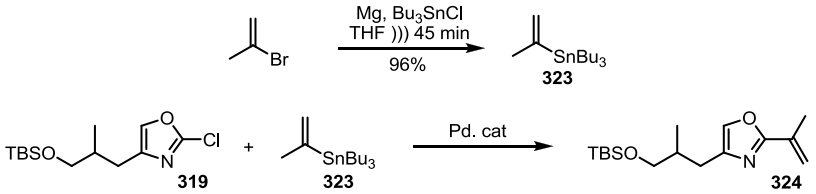


Scheme 95 **Revised Retrosynthetic Analysis of Stannylated Western Section 307**

Attempts to bypass the need to access aldehyde **321** by undertaking the C14-C15 Stille coupling prior to the oxidative rearrangement was trialled on the system with stannyl-oxazole **310** and 2-bromopropene. However, the instability of stannyl-oxazole **310**, coupled with its poor reactivity meant that the Stille coupling to generate vinyl-oxazole **324** failed (Scheme 96). Ultimately, the inability to utilise 2-stannyl oxazoles towards the synthesis of ajudazol A forced this route to be abandoned.

Scheme 96 **Attempted Stille Coupling of Stannyl-Oxazole 310**

However, despite our initial Stille setbacks, it was postulated that a 2-chloro-oxazole unit (the only halo-oxazole that could be generated using Vedejs procedure (Scheme 93, Table 7), could be used in a reverse Stille coupling between western section **308a** (X=Cl) and vinyl stannane eastern section **153b** (Scheme 90). In order to test whether such a coupling would be feasible, a simple model Stille coupling was investigated. 2-Bromopropene was thus stannylated under Barbier conditions, with sonication, to access the 2-stannylpropene coupling partner **323** in excellent yield (Scheme 97).[102]



Scheme 97 **Stille Cross-Coupling with Chloro-Oxazole 319**

Table 8 **Stille Cross-Coupling Conditions**

Heat Source	Temp / °C	Time / h	Catalyst	Yield / %
Thermal	60	72	$Pd(PPh_3)_2Cl_2$ (8%)	10 *(25)*
MW	75	48	$Pd(PPh_3)_2Cl_2$ (8 %)	17 (47)
MW	120	12	$Pd(PPh_3)_2Cl_2$ (8 %)	80
MW	120	12	$Pd(PPh_3)_4$ (8 %)	86
MW	120	6	$Pd(PPh_3)_4$, TFP (20 %)	78 (87)
MW	120	2	$Pd_2(dba)_3$ (8 %)	-
MW	120	12	$Pd(PPh_3)_2Cl_2$ (8 %), CuI (20 %)	70
MW	80	24	$Pd_2(dba)_3$ (1.5%), P^tBu_3 (6%) & CsF (220%) in THF	8 *(22)*

N.B Stille reactions carried out in anhydrous, degassed DMF (0.1M) with 1.10 eq of stannane 323, unless stated otherwise. Yields in parenthesis are based on recovered starting material. All reactions performed on scale specified in general procedure.

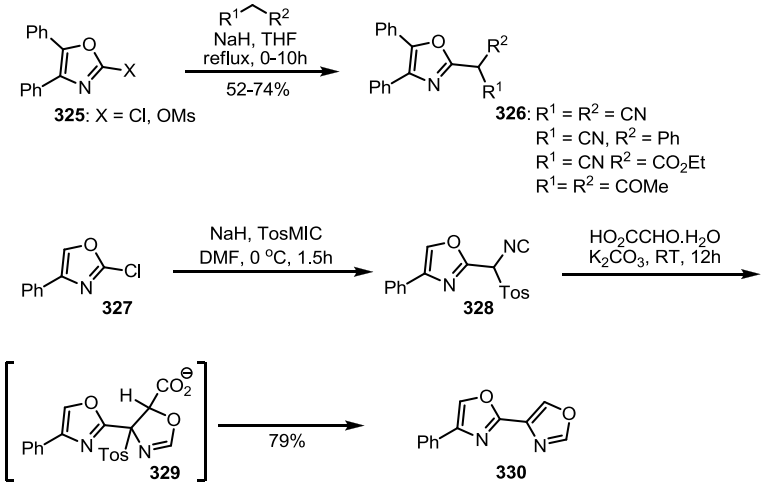
Initially the Stille coupling was trialled at 60 °C with convential heating, in the presence of $Pd(PPh_3)_2Cl_2$ catalyst in DMF (Table 8, entry 1). However, these conditions yielded only 10% of the desired cross-coupled product **324** after 72h. Switching to microwave irradiation at 75 °C failed to improve the product yield. It was not until temperatures in excess of 120 °C were used that complete conversion to the alkenyl-oxazole product **324** was observed, in good yield with $Pd(PPh_3)_2Cl_2$ (entry 3). The yields were marginally improved by using $Pd(PPh_3)_4$ as the catalyst (entry 4). Unfortunately, all other catalyst combinations failed to allow the reaction to proceed at lower temperatures, not even Fu's conditions that have been reported for the successful coupling of aryl-chlorides at ambient temperatures (entry 8).[103]

In conclusion, although 2-chloro oxazole **319H**as been shown to successfully undergo Stille cross-coupling in excellent yield, the high temperatures necessary for reaction (120 ^{o}C), would not be tolerated by an eastern section coupling partner bearing the thermally unstable *Z,Z*-diene moiety.

5.3 Nucleophilic Aromatic Substitution of 2-Halo Oxazoles

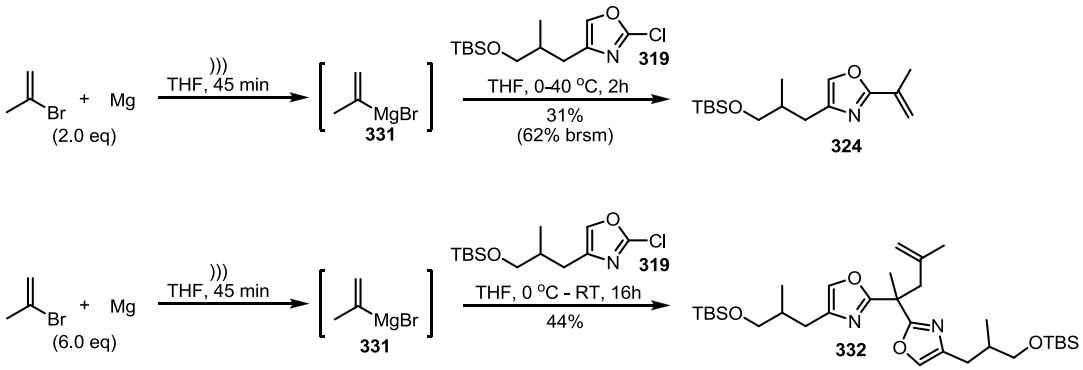
Faced with the limitations of the Stille coupling approach, it was hypothesised that 2-chloro oxazole **319** could participate in nucleophilic aromatic substitution chemistry (S_NAr).[100] This method could potentially provide an alternative late-stage coupling method, utilising the same chloro-oxazole western section **308a** (X=Cl) and vinyl-halide eastern section **153a** coupling partners to the previously investigated Stille route (Scheme 90).

Yamanaka demonstrated that 2-chloro and 2-mesyl oxazoles **325** could readily undergo displacement with carbanions of active methylene compounds, generating alkylated oxazoles **326**.[104] Vedejs utilised this chemistry to synthesize *bis*-oxazole **330** in a one-pot procedure from 2-chloro-oxazole **327** (Scheme 98).[100] The TosMIC anion and chloro-oxazole **327** participate in an S_NAr reaction and the resultant substituted oxazole **328** is treated with glyoxylic acid monohydrate and K_2CO_3 to generate *bis*-oxazole **330**, via fragmentation of the oxazoline intermediate **329**.



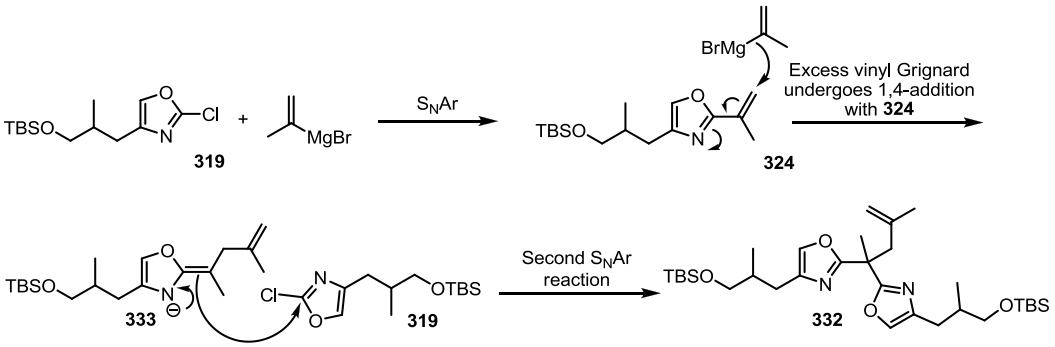
Scheme 98 Nucleophilic Aromatic Substitution of Chloro-Oxazoles

Although there were no specific reports of S_NAr chemistry of 2-halo oxazoles with vinylic nucleophiles, we were hopeful of its feasibility. To test this hypothesis, propenylmagnesium bromide **331**, generated *in situ* from 2-bromopropene and magnesium turnings, was trialled as a nucleophile in an S_NAr reaction with 2-chloro-oxazole **319**. The reaction showed promise, with a yield of 31% (62% based on recovered starting material). In an attempt to push the reaction to completion, a further three-fold excess of nucleophile was added. This modification resulted in complete consumption of starting material; however, none of the desired vinyl oxazole **324** was obtained. Instead, dimeric species **332** was isolated in high yield (Scheme 99).



Scheme 99 **Nucleophilic Aromatic Substitution of Chloro Oxazole 319**

Mechanistically, it would appear that the reaction undergoes the desired S_NAr process and then undergoes 1,4-addition with excess Grignard reagent to yield **333**. The resulting intermediate **333** then acts as a nucleophile to undergo a second S_NAr reaction with 2-chloro oxazole **319**, to generate dimeric species **332** (Scheme 100).

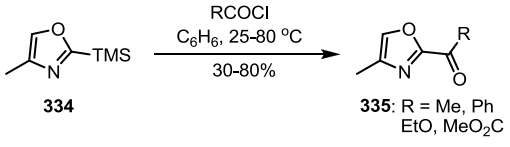


Scheme 100 **Proposed Mechanism for Generation of Dimeric Species 332**

Although disappointing, these results are consistent with recent reports by Lam which demonstrate the reactivity of 2-alkenyl oxazoles as they have been shown to be ideal substrates for asymmetric conjugate addition reactions. [105] The use of 2-lithiopropene as the nucleophile resulted only in unreacted starting material. Although the use of a 2-fluoro oxazole substrate may increase the rate of reaction, it would be unlikely to completely suppress the undesirable dimerisation.

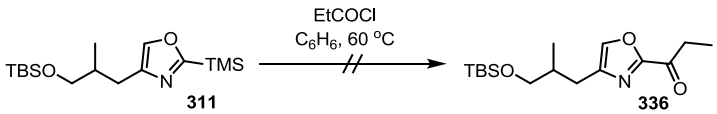
5.4 2-Silyl Oxazoles as Oxazolyl Anion Equivalents

Pedrini has shown that 2-silyl-oxazoles can behave as stable 2-oxazolyl anion equivalents toward various carbon electrophiles, including aldehydes and acid chlorides, to yield the corresponding C2-substituted-oxazoles. In Pedrini's work, 2-TMS-oxazole **334** was converted to the corresponding 2-acyl-oxazole **335**, in modest to good yields, and provides an alternative to the lithiation of oxazoles and all the problems associated with it (Scheme 101).[106]



Scheme 101 **Silyl-Oxazole Acylation**

It was hoped that 2-acyl oxazoles could be methylenated to generate the C15 methylene functionality of ajudazol A. However, Pedrini's 2-sily oxazole acylation methodology was not reproducible with 2-TMS-oxazole **311**, with only protodesilylation taking place, rather than acylation to generate oxazole **336** (Scheme 102).



Scheme 102 Attempted Acylation of Silyl-Oxazole 311

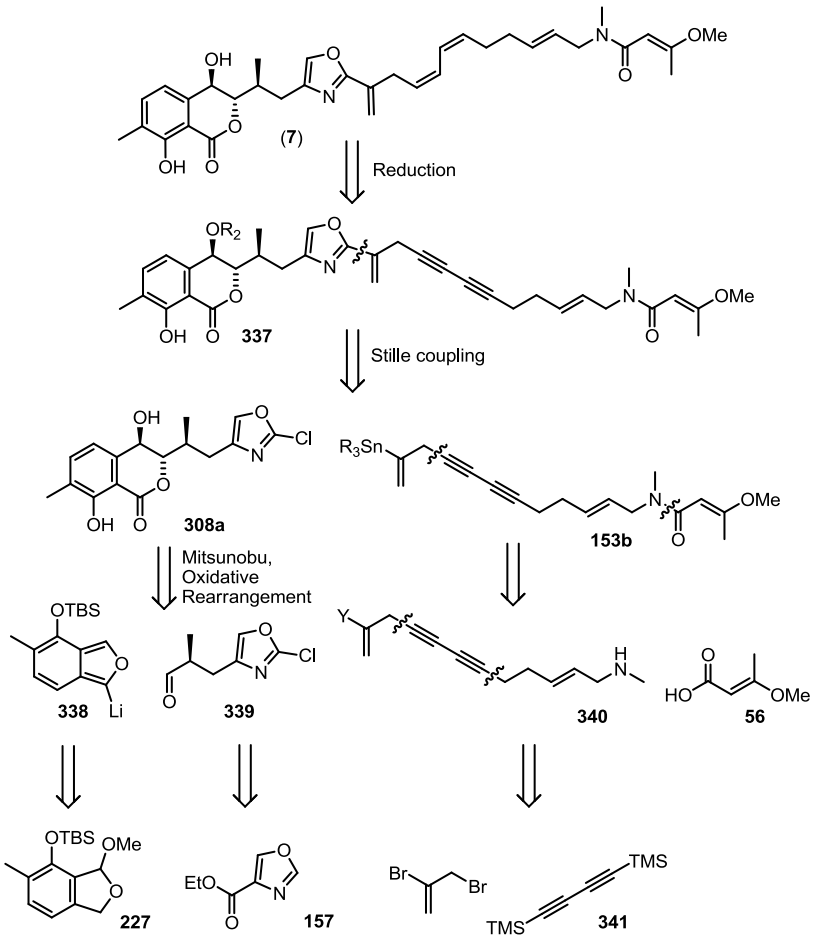
5.5 Summary and Outlook

In order to access the key C14-C15 oxazole-olefin bond of ajudazol A, various methods to investigate oxazole C2 alkenylation were investigated. C-H activation chemistry was used to alkenylate the simple model oxazole **304**; however, the harsh, basic reaction conditions could not be tolerated by isochromanone-containing systems. After much investigation, model oxazole **309** was functionalised as the 2-chloro oxazole **319**, which was shown to undergo Stille alkenylation, to access vinyl oxazole **324** in excellent yield. Unfortunately, the high temperatures necessary for the coupling would not be tolerated by an eastern section coupling partner bearing the thermally unstable *Z,Z*-diene moiety. Alternative methods to access 2-alkenyl oxazoles from 2-chloro oxazoles were investigated: S_NAr chemistry was utilised to generate alkenyl oxazole **324**; however the reaction was capricious, whilst the investigation of using silyl-oxazoles as oxazolyl anion equivalents, proved fruitless.

6 Studies Towards the Synthesis of Ajudazol A

6.1 Revised Stille Route Towards Ajudazol A

Due to the unsuitability of the S_NAr and 2-silyl oxazole approaches towards the ajudazol C14-C15 coupling, efforts were diverted back towards the Stille coupling of 2-chloro oxazoles. It was researched that a Stille approach might still be successful in a total synthesis of ajudazol A, provided that the unstable *Z,Z*-diene functionality is only introduced after the Stille cross-coupling has been achieved. Hence, in our revised retrosynthetic analysis, ajudazol A was envisioned as originating from the stereospecific reduction of *bis*-alkyne **337**, generated via the Stille cross-coupling between 2-chloro oxazole **308a** and vinyl stannane **153b** (Scheme 103). It was hoped that the *bis*-alkyne unit would be thermally robust enough to survive the elevated temperatures required for the Stille cross-coupling. The vinyl stannane eastern fragment **153b** could be obtained from the amide condensation of 3-methoxybutenoic acid **56** and amine **340**. Amine **340** could be accessed via double alkylation of *bis*-TMS-diyne **341**. The 2-chloro-oxazole-linked isochromanone unit **308a**, on the other hand, could be obtained via coupling of IBF anion **338** and aldehyde **339**, followed by oxidative rearrangement and Mitsunobu inversion. IBF anion **338** could be generated from phthalan precursor **227**, while oxazole-aldehyde **339** would originate from oxazole-ester **157**.

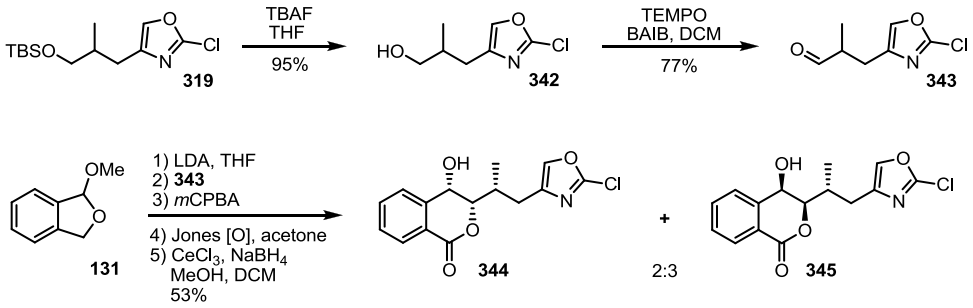


Scheme 103 Revised Retrosynthetic Analysis of Ajudazol A

Although this new approach had the potential to provide a very efficient synthesis of ajudazol A, there were a number of potential pit-falls as well. The main one involved the potential for

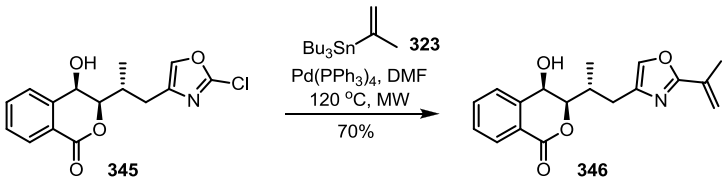
the 2-chloro oxazole unit to participate in nucleophilic aromatic substitution, together with potential transmetallation issues, under the IBF alkylation conditions.

Hence, to test whether the chloro-oxazole moiety could tolerate such conditions, an ajudazol western section, comprising a 2-chloro oxazole-linked isochromanone **345**, was synthesised (Scheme 104). Our synthesis began with 2-chloro oxazole **319** which was desilylated, and the resultant alcohol **342** was oxidised to aldehyde **343** in good yield. Aldehyde **343** was then subjected to the IBF oxidative rearrangement sequence with simple phthalan **131**. Gratifyingly, the sequence proceeded to generate the *syn,syn* and *syn,anti* isochromanone products **344** and **345** respectively, in good overall yield. More importantly, the 2-chloro oxazole functionality remained intact after the entire sequence (Scheme 104).



Scheme 104 **Synthesis of Chloro Oxazole-Containing Western Section Model 345**

Furthermore, the key Stille coupling between chloro oxazole **345** and vinyl stannane **323** provided the desired C14-C15 linked species **346** in excellent yield (Scheme 105). Moreover, the isochromanone ring was stable under the Stille reaction conditions.

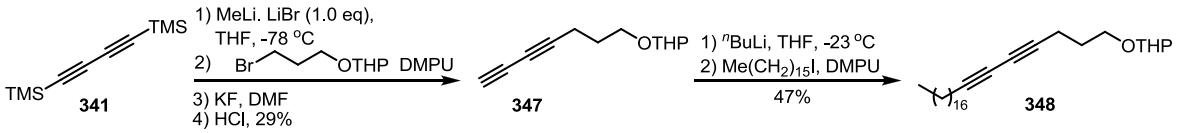


Scheme 105 **Stille Coupling of Ajudazol Western Section System 345**

6.1.1 *Bis*-alkyne Synthesis and Functionalisation

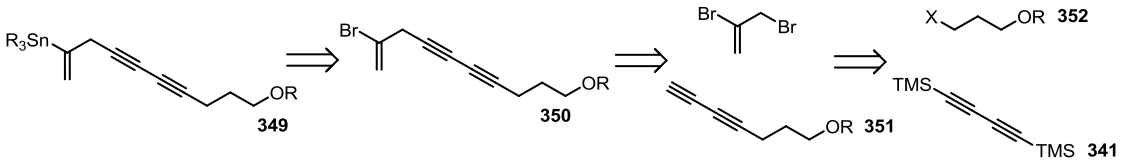
Faced with such encouraging preliminary results, a more representative test of the late-stage Stille coupling, in which a *bis*-alkyne unit was present within the vinyl-stannane coupling partner, was developed.

In natural product synthesis unsymmetrical diynes are frequently constructed linearly, often starting from a terminal alkyne.[107] Seeking a more direct approach to the synthesis of eastern section **153b**, we looked at literature reports in which sequential alkylation of 1,4- *bis*-TMS-diyne **341H**ad been used *en route* to the synthesis of diacetylinic fatty acids.[108] In this procedure, *bis*-TMS-diyne **341** was mono-desilylated, alkylated and the second silyl group cleaved, to generate the mono-alkylated *bis*-alkyne **347**, in reasonable yield. A second alkylation then proceeded in moderate yield to afford the internal diyne **348** (Scheme 106).



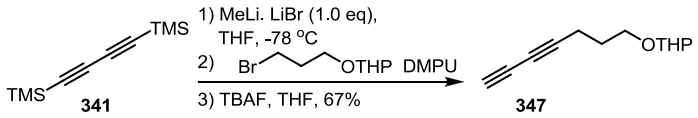
Scheme 106 Correia's Route to Diynes

Therefore, based on this approach, eastern section model system **349** could potentially be accessed via stannylation of the vinyl bromide-linked diyne **350**. In turn, diyne **350** could potentially be generated via the sequential alkylation of *bis*-TMS-diyne **341** with alkyl halide **352** and 2,3-dibromopropene respectively (Scheme 107).



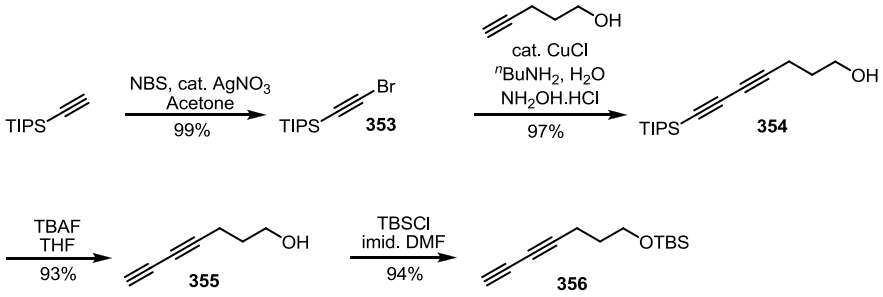
Scheme 107 Retrosynthetic Analysis of Eastern Section Model 349

Unfortunately, following Correia's procedure, although the mono-alkylation of *bis*-TMS-diyne **341**, to generate diyne **347** could be reproduced in slightly improved yields, severe difficulties in purification meant that an alternative method for the synthesis of alkylated *bis*-alkynes was required (Scheme 108).



Scheme 108 Attempted Synthesis of *Bis*-Alkynes via Correia's Procedure

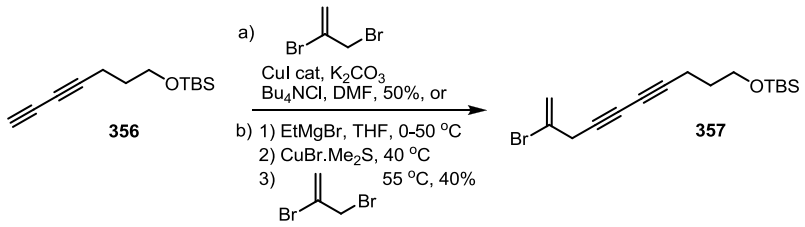
Our alternative route towards the synthesis of mono-alkylated diyne **351** commenced with the bromination of TIPS-acetylene to generate bromo-acetylene **353** in quantitative yield (Scheme 109).[109] Bromo-acetylene **353** participated in a copper-catalyzed Cadiot-Chodkiewicz coupling to yield the *bis*-alkyne **354** in excellent yield and in a very short reaction time.[110] TIPS-acetylene deprotection, followed by protection of the resultant alcohol **355**, generated the terminal *bis*-alkyne **356** in very high yield over 4 steps.



Scheme 109 Cadiot-Chodkiewicz Route Towards *Bis*-Alkyne 356

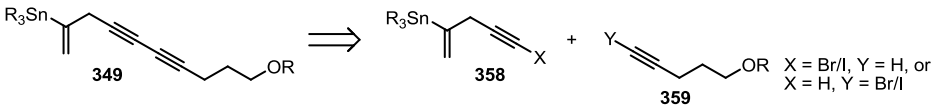
Having generated the desired diyne core, the next step was to alkylate diyne **356** with 2,3-dibromopropene, in order to generate vinyl bromide **357**, from which the vinyl-stannane eastern section model system **349** could potentially be accessed (Scheme 107). Unfortunately, despite extensive literature precedent for the allylation of terminal alkynes under copper catalysis, reaction of diyne **356** with 2,3-dibromopropene failed to proceed to completion

(Scheme 110).[111-113] The most successful conditions using Cu(I)-catalysed phase transfer conditions gave only 50% conversion, with more forcing conditions leading to product degradation. Moreover, the allylated product **357** could not be separated from the unreacted terminal alkyne **356**. Similar conversion problems were encountered when direct deprotonation and transmetallation to generate the copper-acetylide intermediate were attempted.



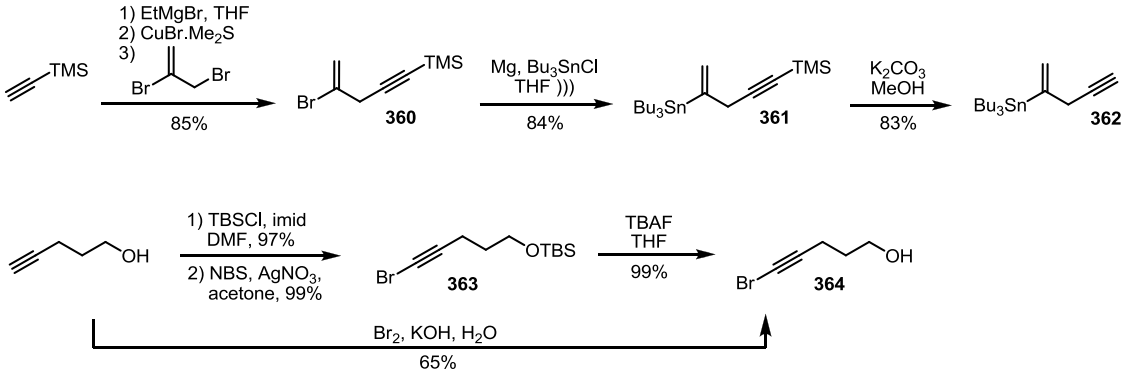
Scheme 110 **Attempted Allylation of Terminal Diyne 356**

Faced with such a low conversion step, combined with the purification issues, a new approach was sought in which the bis-alkyne **349** could be accessed via the convergent coupling of two asymmetric acetylene units, **358** and **359** (Scheme 111).



Scheme 111 **Revised Retrosynthetic Analysis of Eastern Section Model 349**

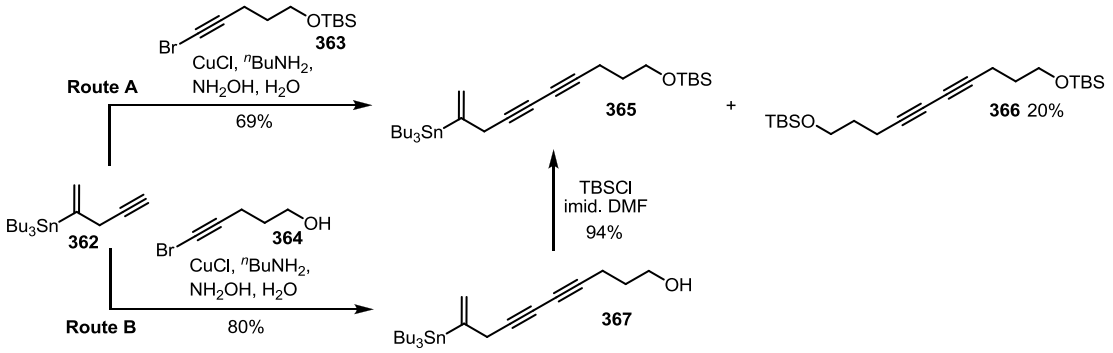
TMS-acetylene underwent efficient allylation with 2,3-dibromopropene to afford vinyl bromide **360** in excellent yield (Scheme 112). Metallation and stannylation, under Barbier conditions, provided vinyl stannane **361**, which upon desilylation under mild conditions, generated terminal alkyne **362**.[114,102] The second alkyne coupling partner **363** was readily accessible from 4-pentyn-1-ol, through silyl protection, followed by alkyne bromination.



Scheme 112 **Synthesis of Cadiot-Chodkiewicz Coupling partners**

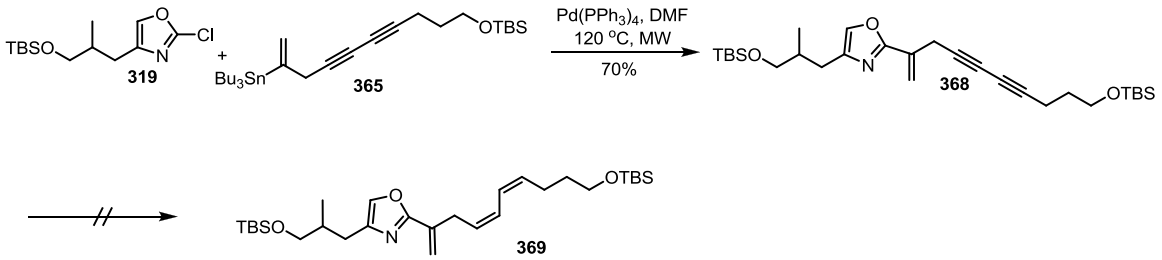
Cadiot-Chodkiewicz coupling between acetylene **362** and silyl-protected bromo-pentynol **363** afforded *bis*-alkyne **365** in good yield (Scheme 113, Route A). However, the symmetrical diyne side-product **366**, the result of the homo-coupling of bromo-acetylene **363**, was obtained in significant amounts and therefore purification of *bis*-alkyne **365** proved difficult**.** Unfortunately, the inability to brominate alkyne **362** with $AgNO_3$/NBS or Br_2/KOH, meant that the analagous coupling, but with reverse coupling partners, could not be attempted.

Despite this initial setback, we decided to persist and modify the nature of the coupling partners. Cadiot-Chodkiewicz chemistry has been shown to work best when the acetylene and 1-haloacetylene units are dissimilar, for example, alkyl vs. aryl or functionalised vs. unfunctionalised.[115] Gratifyingly, Cadiot-Chodkiewicz coupling between acetylene **362** and bromo-acetylene **364**, provided diyne **367** in excellent yield and with drastically suppressed homo-coupling (Scheme 113, Route B). Silylation provided the desired diyne **365** in excellent yield.



Scheme 113 **Cadiot-Chodkiewicz Routes Towards Diyne 365**

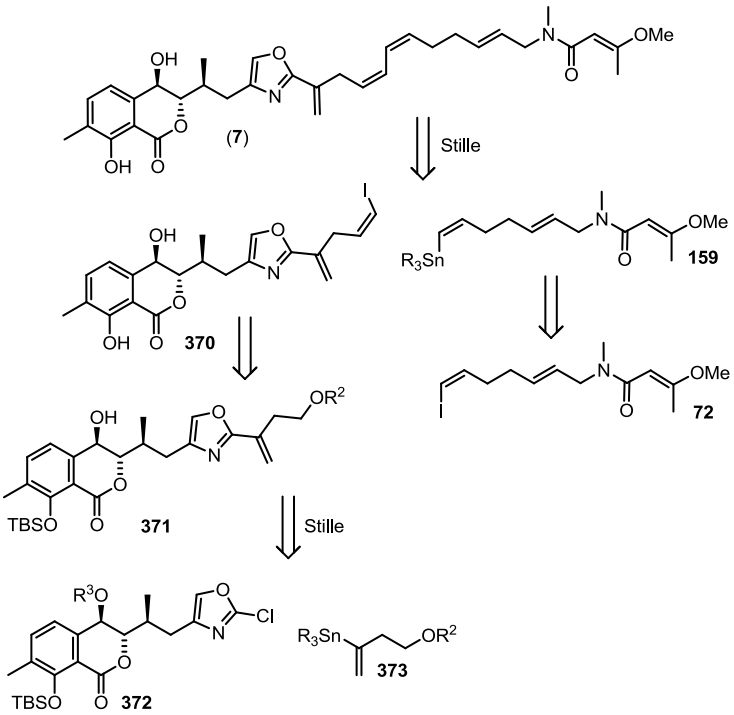
With the diyne-linked vinyl stannane **365** in hand, the more elaborate Stille coupling with 2-chloro-oxazole **319** was attempted. Gratifyingly, the Stille coupling proceeded under microwave irradiation to generate the ene-diyne unit **368** in good yield (Scheme 114). Having achieved the synthesis of the eastern section framework, ene-diyne **368** was used as a model system to test whether the stereoselective reduction to generate *Z,Z*-diene **369** could be achieved. There was literature evidence showing the stereoselective reduction of diynes to *Z,Z*-dienes. However, despite extensive experimentation under a variety of conditions, no such conditions were able to afford *Z,Z*-diene **369**. Hydroboration-protonolysis (dicyclohexylborate then HCl),[116] Lindlar hydrogenation (5% Pd/$CaCO_3$/Pb, quinoline, H_2),[117] transfer hydrogenation (HCO_2H-NEt_3, [$Pd_2(dba)_3$]-P^{t}Bu$_3$, THF)[118] and Strykers' reagent ([$(Ph_3P)CuH]_6$, C_6H_6) failed.[119] Finally, the P2-Nickel conditions employed by Rizzacasa also failed to give the desired *Z,Z*-diene **369**.[27,28] In general, the only observable products appeared to be those of over-reduction of diyne to alkane and/or reduction of the C15 exo-alkene (Scheme 114).



Scheme 114 **Synthesis and Attempted Reduction of Ene-Diyne 368**

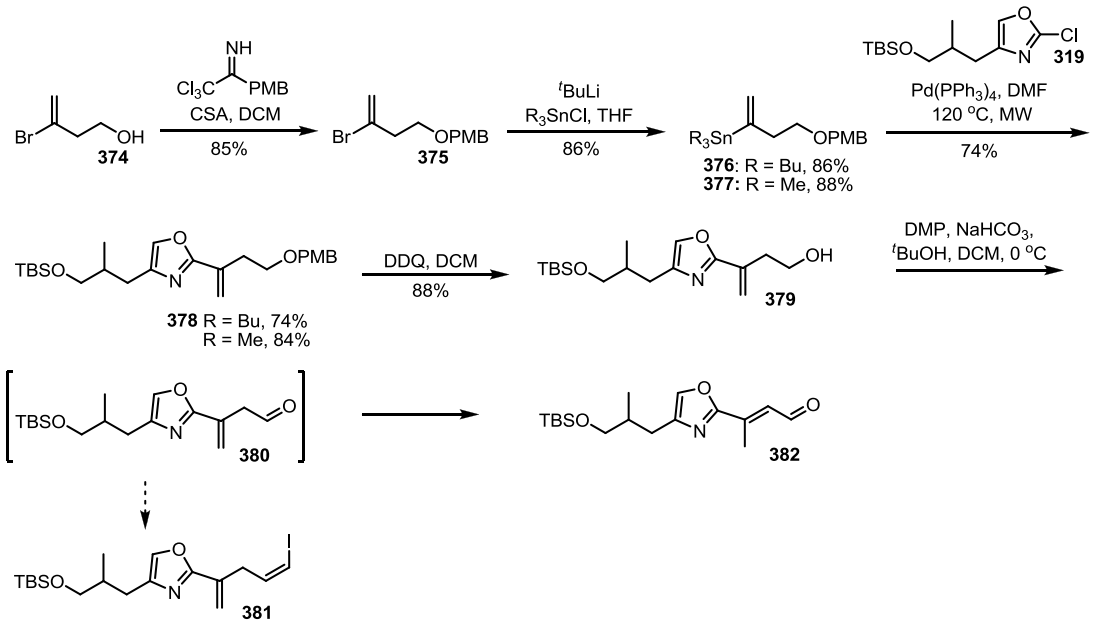
6.1.2 Double Stille Route Towards Ajudazol A

Due to this setback, an alternative approach towards the synthesis of the key *Z,Z*-diene of ajudazol A was devised. In our newly modified retrosynthesis, it was proposed that the *Z,Z*-diene functionality, as in previous approaches, would be introduced as the last step of the synthesis and would be accessed via the late stage Stille coupling between the western section vinyl iodide **370** and the eastern section vinyl stannane **159**.[120] Stannane **159** would originate from vinyl iodide **72**. The western coupling partner **370** was envisioned to be generated from protected alcohol **371**, which in turn could be accessed from the Stille coupling between vinyl stannane **373** and chloro-oxazole **372** (Scheme 115).



Scheme 115 Retrosynthetic Analysis of Ajudazol A via Double Stille Approach

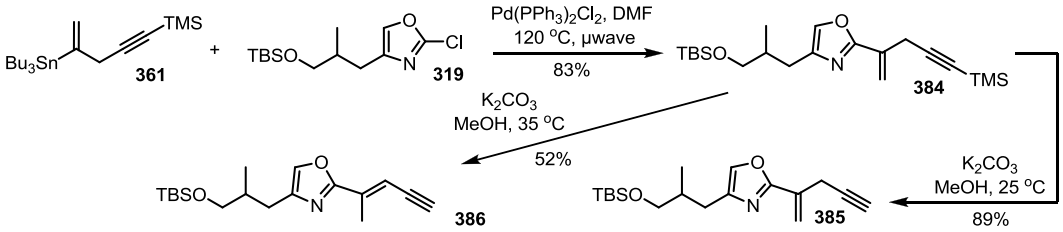
To test the feasibility of the latest proposed route, the simple chloro-oxazole **319** was used as a model for the ajudazol western section **372**. Our synthesis began with bromobutenol, which was protected as the PMB ether **375** (Scheme 116). Treatment of bromide **375,** under the Barbier stannylation conditions previously employed to synthesise stannanes **323** and **361** (Schemes 97 and 112), failed in this instance.[102] However, metallation using ^{t}BuLi and anion trapping with Bu_3SnCl afforded vinyl stannane **376** in excellent yield.[121] The use of Me_3SnCl in place of Bu_3SnCl afforded stannane **377** in comparable yield. The model Stille coupling between stannane **376** with chloro-oxazole **319** proceeded smoothly to provide vinyl oxazole **378**. Using trimethyl stannane **377** in the Stille coupling in place of tributyl stannane **376** resulted in a slight improvement in yield; however it allowed for a considerably more straight-forward purification, despite having similar reaction conditions.



Scheme 116 Synthetic Route Towards Vinyl Iodide 381

Deprotection of PMB ether **378** gave alcohol **379**, which it was hoped could be oxidised to the corresponding aldehyde **380** *en route* to accessing the *Z*-vinyl iodide **381**, via Stork-Zhao olefination chemistry.[122] Unfortunately, aldehyde **380** could not be isolated in pure form as it readily underwent alkene isomerisation to generate the thermodynamically stable enal **382**, in which the double bond is in full conjugation with both the carbonyl and oxazole ring. Modification of the oxidation conditions (Dess-Martin, Tempo/BAIB, Swern) failed to suppress the alkene isomerisation.

In an attempt to bypass the isomerisation issues, the stannane cross-coupling partner was modified. In our modified approach, Stille coupling between chloro oxazole **319** and vinyl stannane **361** generated the desired alkenyl oxazole **384** (Scheme 117). TMS removal proceeded cleanly to provide acetylene **385**; however, isomerisation was evident at prolonged reaction times. Furthermore, complete conversion of TMS acetylene to enyne by-product **386** occurred by merely increasing the reaction temperature from 25 to 35 °C.



Scheme 117 Revised Synthetic Route Towards Vinyl Iodide 381

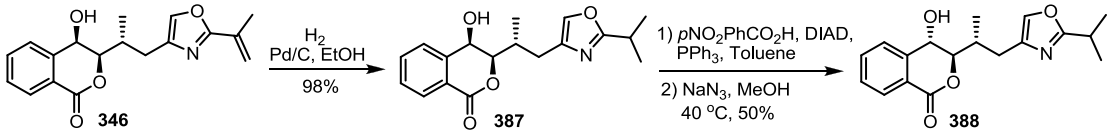
These results demonstrated the inherent instability of the ajudazol C15 olefin and this factor could well have been a reason for the reported instability of ajudazol A (**7**) upon characterisation.[11]

6.2 Summary and Outlook

The chloro oxazole-linked western section **345** was shown to successfully undergo Stille alkenylation and was very tolerant of the sensitive isochromanone functionality, demonstrating that this methodology could be applicable in the total synthesis of ajudazol A. The model diyne of ajudazol A, **368**, was accessed using the Stille alkenylation and a Cadiot-Chodkiewicz coupling to efficiently generate the bis-alkyne functionality. Efforts towards the total synthesis of ajudazol A were thwarted by the inability to chemoselectively reduce the model diyne **368** in the presence of the C15 olefin functionality, and were further hampered by the tendancy of the C15-olefin to undergo isomerisation. Therefore, as a result, all further efforts were directed towards the total synthesis of ajudazol B, where the C15 position is fully saturated (Figure 3).

7 Synthesis of the C9-C29 Section of Ajudazol B

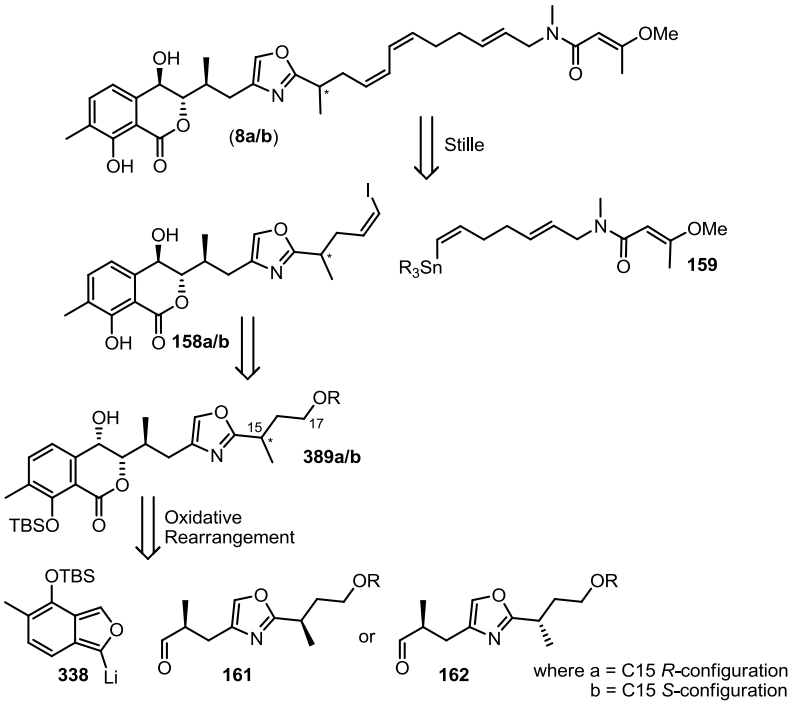
Upon focussing our attention exclusively towards ajudazol B (**8**), it was noted that the ajudazol A vinyl-oxazole model **346** could potentially be further manipulated to resemble the ajudazol B system. Thus, olefin hydrogenation of alkene **346** proceeded in excellent yield, before Mitsunobu inversion and cleavage of the *para*-nitrobenzoate intermediate afforded the desired *anti,anti*-isochromanone species **388** (Scheme 118). It is noteworthy that Mitsunobu inversion did not proceed on either the chloro-oxazole **345** or vinyl olefin **346.**



Scheme 118 **Synthesis of *Anti,anti*-Ajudazol B Model Western Section 388**

7.1 Late-Stage Stille Route Towards Ajudazol B

Although efforts to access ajudazol A (**7**) via the double Stille route were ultimately abandoned, it was believed that an analogous strategy could be successfully applied towards the synthesis of ajudazol B (**8**), where it was expected that the aliphatic C15 position would be chemically inert, unlike the ajudazol A counterpart.



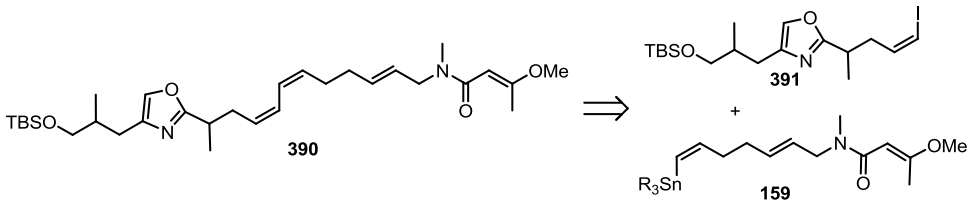
Scheme 119 **Retrosynthetic Analysis of Ajudazol B**

Retrosyntetically, ajudazol B (**8a**) was thought as being accessed via the late-stage Stille coupling between vinyl iodide **158a** and vinyl stannane **159**. The western vinyl iodide **158a**, generated from protected alcohol **389a**, in turn could be obtained from the alkylation and oxidative rearrangement sequence between IBF anion **338** and enantiopure aldehyde **161**. This route would differ from our previous strategies towards the ajudazols as the C15-C17 framework would already be installed prior to the oxidative rearrangement sequence, thereby

bypassing the need for functionalisation and cross-coupling at the oxazole C2 position. It is noteworthy that the C15 stereochemistry of ajudazol B is unknown, and therefore by carrying out the oxidative rearrangement with the alternative C15 aldehyde diastereoisomer **182**, the corresponding ajudazol B C15-epimer (**8b**) could potentially be accessed. It was hoped that this flexible approach would be able to provide access to both possible ajudazol B diastereoisomers and help to deduce the absolute stereochemistry of ajudazol B.

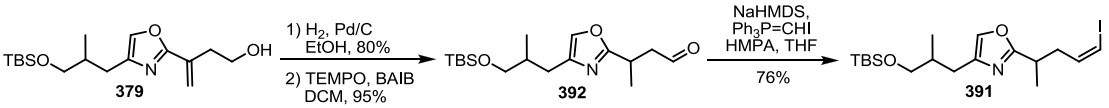
7.2 Stille Approach Towards the Synthesis of the Ajudazol B C9-C29 Unit 390

Initially, to test the feasibility of the Stille route towards the synthesis of ajudazol B, a model system of the key Stille coupling was developed. Ajudazol B C9-C29 unit **390** would be accessed via Stille coupling between vinyl iodide **391** and vinyl stannane **159** (Scheme 120).



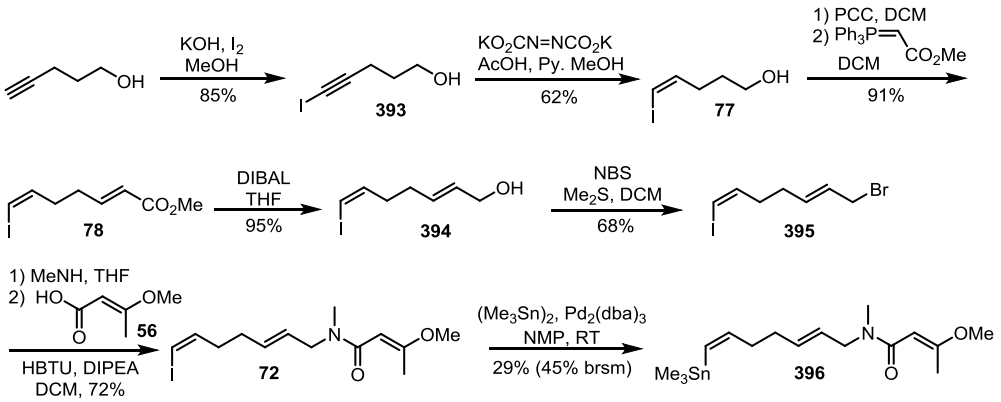
Scheme 120 Key Stille Disconnection of Ajudazol B C9-C29 Unit

Our synthesis of the ajudazol B C9-C29 fragment **390** began with vinyl oxazole **379**, which was hydrogenated and then oxidised to afford aldehyde **392** (Scheme 121). The fact that aldehyde **392** was obtained as a racemic mixture of diastereoisomers was not deemed to be a hindrance as the diastereoisomers appeared indistinguishable on both flash chromatography and $^{1}H/^{13}C$ NMR. Moreover, in the true ajudazol B synthesis, the C10 and C15 stereochemistries would be set early in the synthesis rather than being generated via olefin hydrogenation. Stork-Zhao olefination of aldehyde **392** afforded *Z*-vinyl iodide **391** in good yield and as a single double bond isomer.[123]



Scheme 121 Synthesis of *Z*-Vinyl Iodide 391

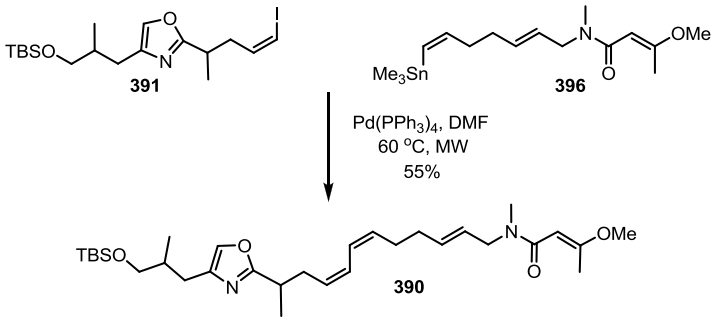
Synthesis of the *Z*-vinyl stannane coupling partner **396** commenced with commercially available 4-pentyn-1-ol, which was efficiently converted into iodoalkyne **393** in good yield. Diimide reduction of iodoalkyne **393** gave exclusively the *Z*-vinyl iodide **77** in satisfactory yield. Oxidation was optimised using PCC, and the resulting aldehyde intermediate underwent Wittig olefination to yield the *E*-conjugated ester **78**, in excellent yield over the two steps. DIBAL reduction generated the allylic alcohol **394** which was then used to generate the allylic bromide **395**. Treatment of allylic bromide **395** with methylamine afforded the corresponding secondary amine intermediate which was then coupled with acid **56** to afford amide **72** (Scheme 122).[27,29,32]



Scheme 122 Synthesis of Vinyl Stannane 396

Unfortunately, the desired conversion of *Z*-vinyl iodide **72** into a suitable *Z*-vinyl stannane **159** proved troublesome. Treatment with ^{t}BuLi followed by Bu_3SnCl or Me_3SnCl failed to generate the required stannane, with only unreacted starting material or the terminal olefin by-product being observed. After much optimisation, trimethylstannane **396** was obtained, albeit in 29% yield via transmetallation with $(Me_3Sn)_2$ under Pd catalysis (Scheme 122).[124] The low yield being partially due to the isolation of the stannane **396** from the unreacted starting material. Increasing the temperature either under conventional or microwave heating failed to achieve complete conversion. Moreover, the more active catalyst systems reported for vinyl stannane synthesis: $Pd(TFP)_2$ and $Pd(PAs_3)_2$ failed to improve the reaction yield.[125]

Nevertheless, having achieved the synthesis of the vinyl stannane unit **396**, the key Stille cross-coupling was attempted. Gratifyingly, the desired coupling between *Z*-vinyl iodide **391** and *Z*-vinyl stannane **396** proceeded cleanly to afford the *Z,Z*-diene **390** (Scheme 123). Importantly, the reaction took place at 60 ^{o}C, ensuring that the integrity of the thermally unstable *Z,Z*-diene was not compromised. More active catalyst systems failed to allow the reaction to proceed at lower temperatures.

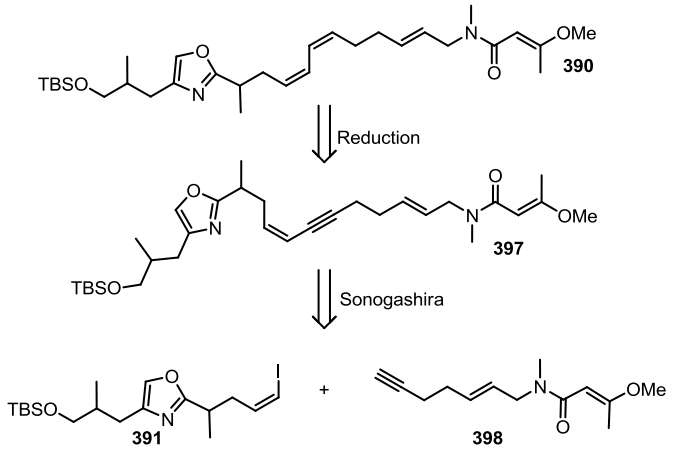


Scheme 123 Stille Coupling to Afford Ajudazol B C9-C29 Unit 390

Although the synthesis of model system **390** demonstrated the viability of the Stille route towards the total synthesis of ajudazol B (**8**), the modest yield obtained, combined with the failure to optimise the conditions for the generation of *Z*-vinylstannane **396** meant that alternative routes for the synthesis of the *Z,Z*-diene unit of ajudazol B had to be sought.

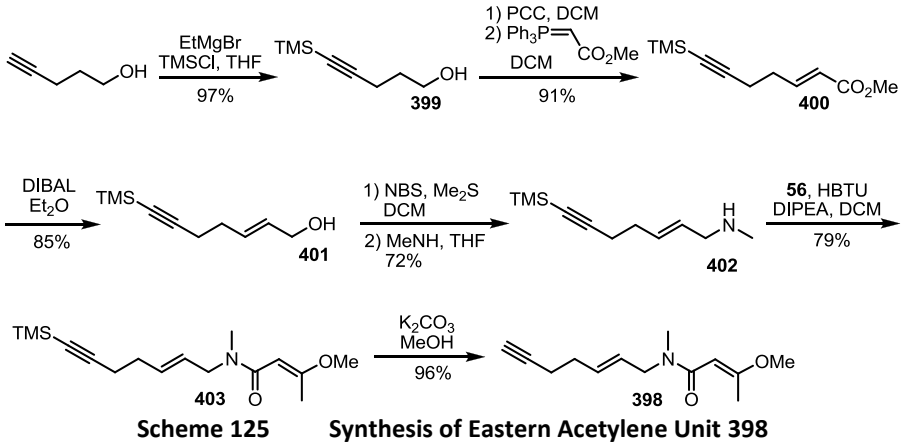
7.3 Enyne Reduction Route for the Synthesis of the Ajudazol B C9-C29 Unit 390

It was envisioned that ajudazol B C9-C29 unit **390** could be accessed via the chemoselective reduction of enyne **397** (Scheme 124). It was postulated that this reduction would be an improvement on the previously attempted reduction of ajudazol A model diyne **368** (Scheme 114) as the C15 olefin would no longer be an issue. Enyne **397** was thought as being accessed via a late-stage Sonogashira coupling between vinyl iodide **391** and acetylene **398**.



Scheme 124 **Sonogashira/Reduction Route Towards the Ajudazol C9-C29 Unit 390**

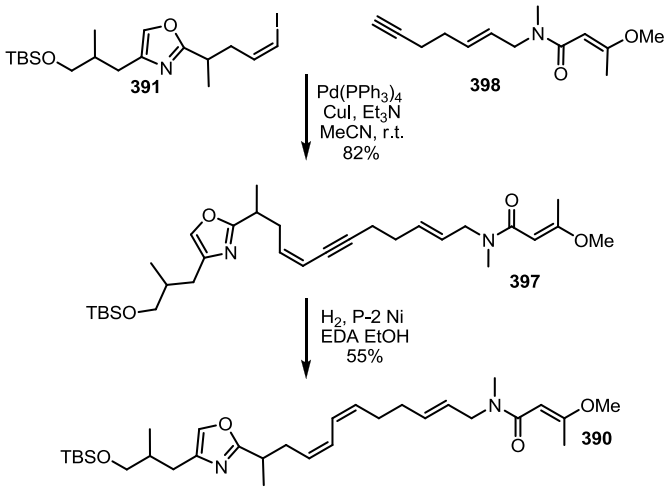
The synthesis of acetylene **399** began with 4-pentyn-1-ol, which was converted to the TMS-acetylene **399** in excellent yield (Scheme 125). Oxidation of alcohol **399**, followed by Wittig olefination, yielded the *E*-conjugated ester **400**, in very high yield over the two steps. DIBAL reduction generated the allylic alcohol **401**, which upon bromination, followed by amination, generated the secondary amine **402**. Amide condensation with acid **56** provided access to amide **403**, while desilylation provided the terminal acetylene **398** in excellent yield.



Scheme 125 **Synthesis of Eastern Acetylene Unit 398**

The Sonogashira coupling between vinyl iodide **391** and acetylene **398** proceeded in high yield to generate enyne **397** (Scheme 126). With the enyne **397** in hand, the key reduction was attempted. Pleasingly, the reduction proceeded cleanly to afford the desired *Z,Z*-diene **390**, together with an over-reduced side-product in a 3:2 mixture. The side-product corresponded to either a C17-C18 or C19-C20 bond over-reduction. Despite careful monitoring of the reaction, suppression of side-product formation could not be achieved. Despite this, the

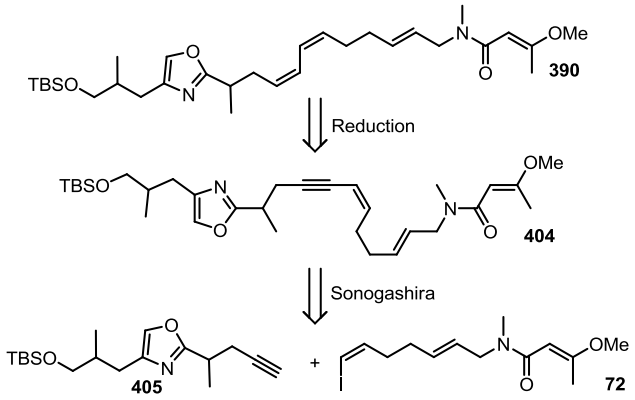
ajudazol B C9-C29 unit **390** was obtained in a reasonable yield of 55% after careful chromatographic purification.



Scheme 126 **Sonogashira Coupling and Reduction to Afford Ajudazol B C9-C29 Unit 390**

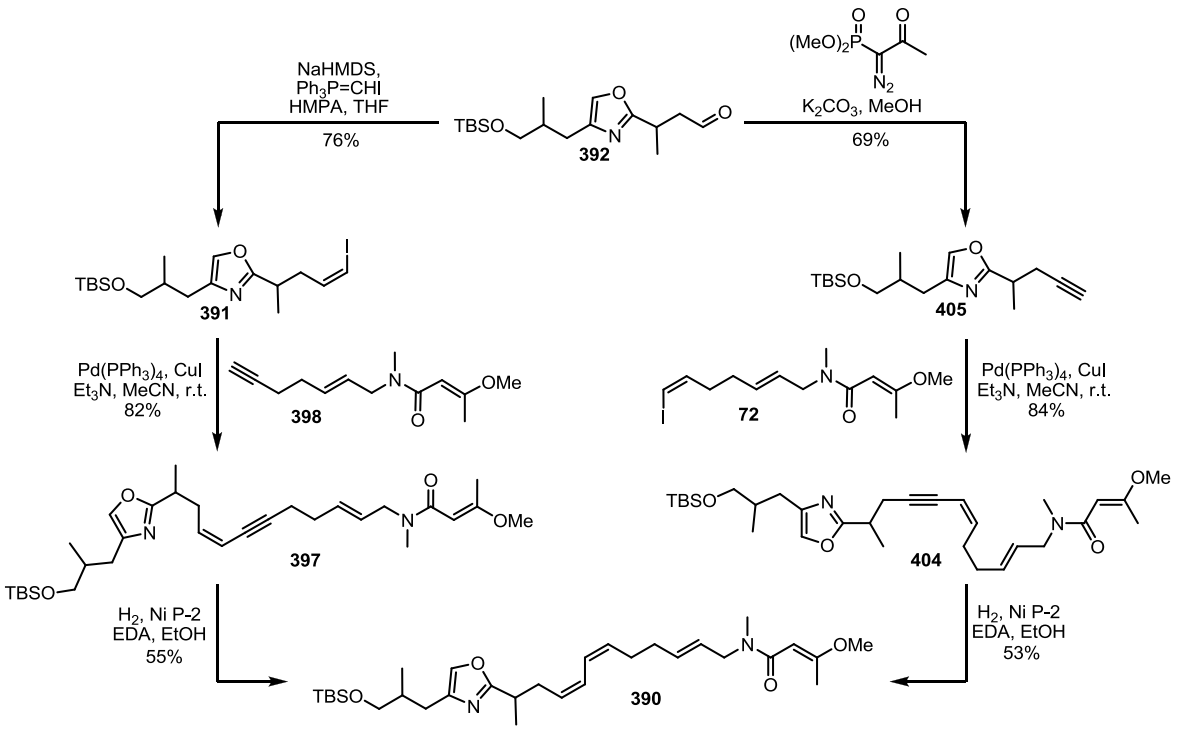
7.4 Reverse Enyne Reduction Route for the Synthesis of the Ajudazol B C9-C29 Unit 390

Having demonstrated that the enyne reduction route could be applicable towards the synthesis of ajudazol B, a final complementary route for accessing the key *Z,Z*-diene **390** was investigated. It was hypothesised that the *Z,Z*-diene **390** could also be accessible via the stereoselective reduction of enyne **404**, which would be the reverse enyne to **397** (Scheme 127). Reverse enyne **404** was thought as originating from the acetylene western section **405** and vinyl iodide eastern section **72**.



Scheme 127 **Reverse Sonogashira/Reduction Route Towards *Z,Z*-diene 390**

The synthesis of alkyne **405** began with aldehyde **392**, which was successfully converted to terminal acetylene **405** via an Ohira-Bestmann reaction (Scheme 128). Gratifyingly, acetylene **405** participated in the Sonogashira coupling with vinyl iodide **72** to afford the reverse enyne **404** in excellent yield.[34] Encouragingly, the P2-Ni enyne reduction proceeded in analogous fashion to the previously observed reduction, affording *Z,Z*-diene **390**, with a similar proportion of over-reduction product.



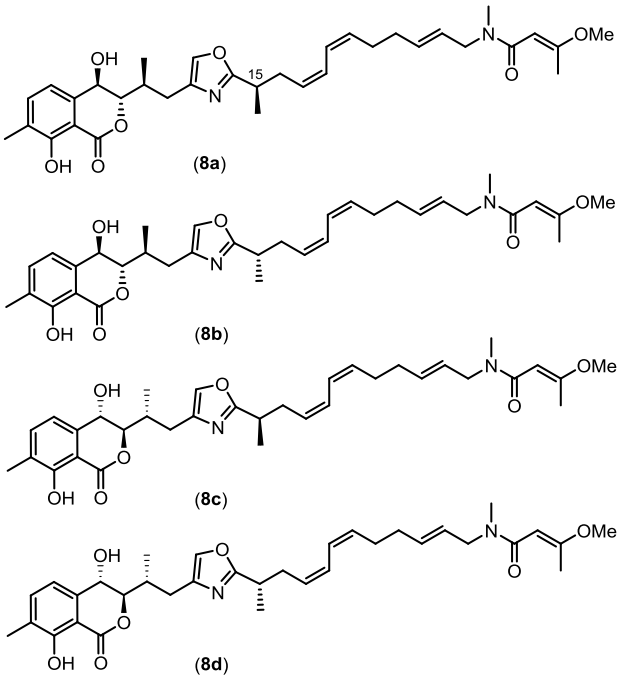
Scheme 128 **Sonogashira and Reverse Sonogashira Routes Towards *Z,Z*-Diene 390**

7.5 Summary and Outlook

Upon focussing exclusively on the total synthesis of ajudazol B (**8**), various end-game approaches were developed to achieve the key C17-C20 *Z,Z*-diene functionality, from a single late-stage intermediate. The ajudazol B eastern section **390** was synthesised via the Stille coupling between *Z*-vinyl olefin **391** and *Z*-vinyl stannane **396**. Alternatively, acetylene **398** and *Z*-vinyl olefin **391** participated in a high yielding Sonogashira coupling to generate enyne **397**, which was chemoselectively reduced to provide the ajudazol B C9-C29 unit **390**. Finally, *Z*-vinyl olefin **72** was utilised in a reverse Sonogashira/reduction sequence with acetylene **405** to access the ajudazol B eastern section **390**. In turn, these synthetic strategies would then be applied towards the total synthesis of ajudazol B (**8**).

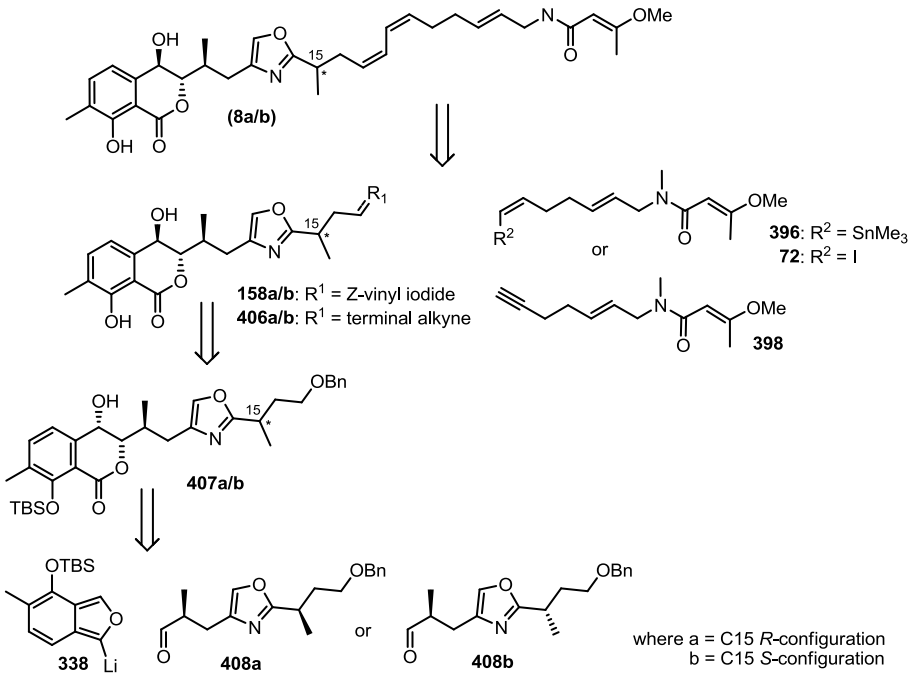
8 Towards the Synthesis of Ajudazol B

Due to the fact that only the C8-C10 relative stereochemistry of the ajudazols is known, for our first generation synthesis of ajudazol B, the absolute stereochemistry will be arbitrarily set. Commencing from the *R*-Roche ester (Scheme 132) would allow us to access the ajudazol B isomers **8a** and **8b**, which have the absolute stereochemistry that has been presented so far within this thesis. Therefore, upon completion of the synthesis of the C15-epimers of ajudazol B (**8a** and **8b**), an analagous synthesis, commencing from *S*-Roche ester, would generate the final two ajudazol B isomers (**8c** and **8d**). It was hoped that by synthesising all four possible ajudazol B isomers (**8a**-**8d**) could the absolute stereochemistry of the natural product be assigned (Scheme 129).[11]



Scheme 129 Four Possible Ajudazol B Isomers

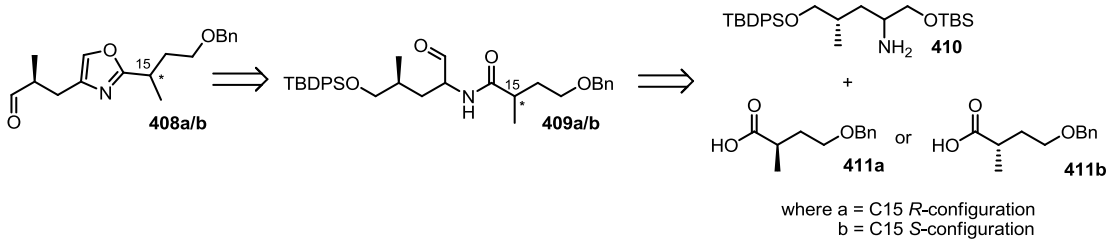
Having developed the end-game methodology required for the synthesis of ajudazol B (**8**), a flexible approach to the synthesis of ajudazol B was designed. Based on recent results, ajudazol B was envisioned as being accessed via the late-stage Stille coupling between vinyl iodide **158a/b** and vinyl stannane **396**. Alternatively, vinyl iodide **158a**/**b** could undergo Sonogashira couping with acetylene **398**, followed by chemoselective reduction, to generate ajudazol B (**8a**/**b**). As a third option, the western acetylene section **406a**/**b** could undergo Sonogashira coupling with the vinyl iodide eastern section **72**, followed by enyne reduction, to provide access to ajudazol B (**8a**/**b**). The late stage western section intermediates, **158a**/**b** and **406a**/**b**, could be accessed from protected alcohol **407a**/**b**, the species that could be generated from the alkylation and oxidative rearrangement between IBF anion **338** and either one of the diastereoisomeric aldehydes **408a** or **408b** (Scheme 130).



Scheme 130 **Retrosynthetic Analysis of Ajudazol B**

8.1 Synthesis of Aldehydes 408a and 408b

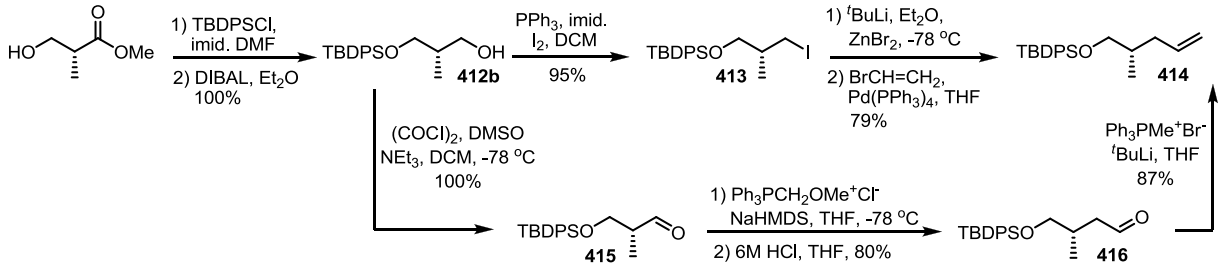
The three possible eastern section coupling partners, vinyl stannane **396**, vinyl iodide **72** and acetylene **398**, have been synthesised, together with the functionalised phthalan precursor to IBF anion **338**. Hence, attention was focussed on the synthesis of the C9-C17 aldehydes **408a** and **408b**.



Scheme 131 **Retrosynthetic Analysis of Oxazole Aldehydes 408a and 408b**

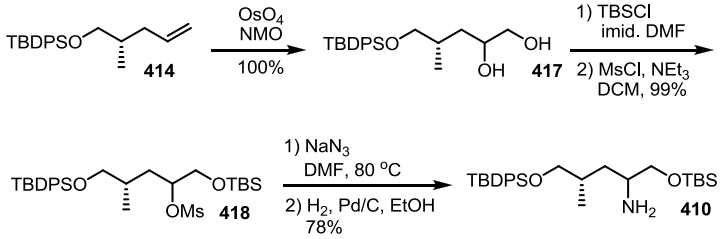
Retrosynthetically, diastereoisomeric aldehydes **408a** and **408b** could be accessed via the cyclodehydration of β-formyl amides **409a/b**, which could be generated via the amide condensation between secondary amine **410** and enantiopure acids **411a** or **411b** (Scheme 131).

Our synthesis began with *R*-Roche ester which was TBS protected and then reduced to yield alcohol **412b** in quantitative yield.[126-128] Iodination of alcohol **412b** afforded alkyl iodide **413** in excellent yield.[129] Negishi coupling of iodide **413** with vinyl bromide afforded terminal olefin **414** in good yield.[128,130] This four step sequence to generate olefin **414** was efficient and high yielding; however, on scale-up, the yield of the Negishi coupling step suffered significantly. Therefore, on larger scales, it became more efficient to generate olefin **414** via an alternative synthetic sequence. Thus, alcohol **412b** was oxidised to aldehyde **415**,[131,132] which upon homologation to give aldehyde **416**,[133] followed by a second Wittig olefination, generated terminal alkene **414** in good overall yield (Scheme 132). [132,134]



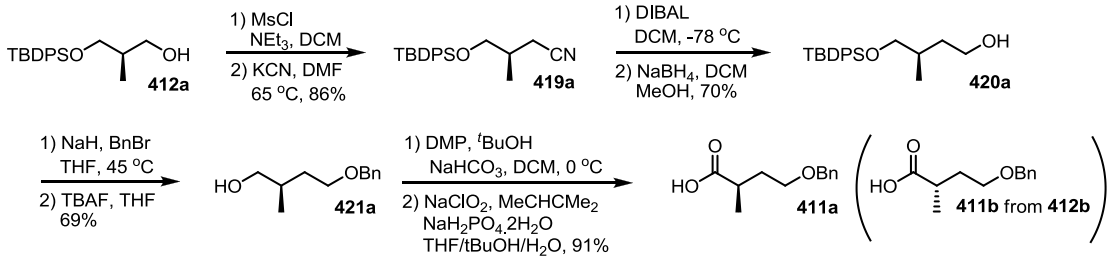
Scheme 132 Synthesis of Terminal Olefin 414

The terminal olefin **414** was then dihydroxylated to afford diol **417** in quantitative yield.[135] Regioselective silylation of the primary alcohol **417**, followed by mesylation of the remaining secondary alcohol, generated mesylate **418** in quantitative yield. The mesylate **418** was displaced with NaN_3, and the resulting azide intermediate was reduced to give the secondary amine **410** in high yield over two steps. It must be noted that although the dihydroxylation step afforded diol **417** as a 3:2 mixture of diastereoisomers, carrying forward the diastereoisomeric mixture was not problematic as the diastereoisomers coalesced into a single spot during flash chromatography. In this situation, asymmetric dihydroxylation would have been wasteful as the chiral centre was to be lost during the oxazole cyclodehydration step, becoming an sp^2 centre (Scheme 131).[136]



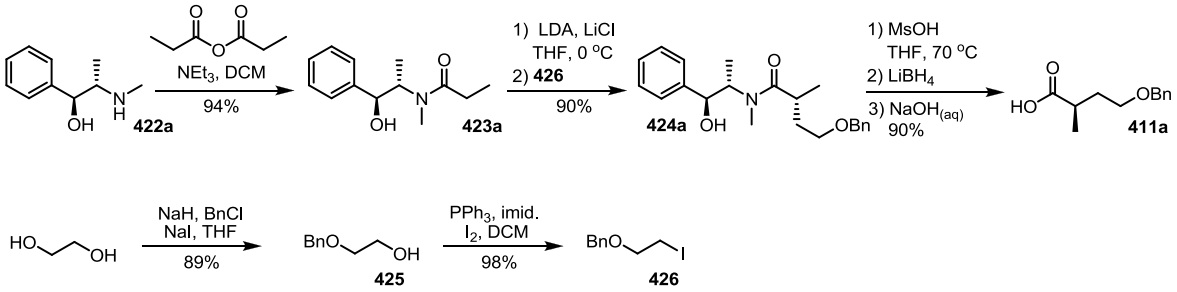
Scheme 133 Synthesis of Secondary Amine 410

With the secondary amine **410** in hand, the synthesis of chiral acids **408a** and **408b** was embarked upon. In our initial approach, the enantiopure acid **411a** was accessed, starting from alcohol intermediate **412a**. Mesylation of alcohol **412a**, followed by displacement with KCN afforded nitrile **419a** in excellent yield.[137] DIBAL reduction to the aldehyde, followed by $NaBH_4$ reduction, afforded alcohol **420a**. Protecting group interconversion then generated alcohol **421a**. A number of different conditions were attempted to achieve the transformation of alcohol **421a** into acid **411a**. The one-step oxidation of alcohol **421a** with PDC/DMF afforded acid **411a** in a reasonable yield of 69%; however the reaction was sluggish and troublesome to purify.[138] Unfortunately, other one-step oxidations such as TPAP/NMO/MeCN/H_2O and TEMPO/NaOCl failed to give efficient conversion.[139,140] Thus, two-step oxidation procedures were explored. Oxidation of alcohol **421a** to the corresponding aldehyde intermediate was best performed under Dess-Martin conditions, as TEMPO/BAIB, TPAP/NMO and Swern oxidation conditions gave inferior results. Pinnick oxidation of the aldehyde intermediate then afforded the enantiopure acid **411a** in excellent yield and with no detectable epimerisation of the α-stereocentre (*vide infra*). The *S*-enantiomer, **411b** was obtained in identical yield and purity, starting from the corresponding *S*-alcohol **412b** (Scheme 134).



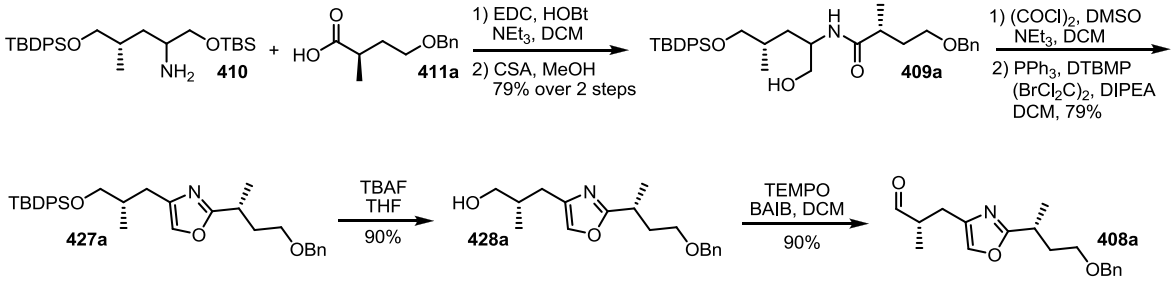
Scheme 134 **Synthesis of Enantiopure Acids 411a and 411b**

Faced with such a long-winded synthesis of such a simple fragment, an improved synthesis was sought. Our second generation synthesis of enantiomerically pure acid **411a** began with (+)-pseudoephedrine (**422a**), which was propionylated in excellent yield to afford amide **423a**.[141] Meanwhile, alkyl iodide **426** was generated from ethylene glycol in a two step benzylation/iodination procedure in excellent yield.[142] Pseudoephedrine amide then underwent diastereoselective enolate alkylation with alkyl iodide **426** in excellent yield and >99% de (*vide infra*).[143,144] Amide hydrolysis was achieved through *N* - *O* acyl transfer, followed by borane complexation and ester saponification to afford the enantiopure acid **411a** in superb overall yield (Scheme 135).[143] The mild hydrolysis conditions ensured that the stereochemical integrity of the α-stereocentre was maintained (*vide infra*). The *S*-enantiomer **411b** was obtained in identical yield and purity, starting from (-)-pseudoephedrine (**422b**).



Scheme 135 **Second Generation Synthesis of Enantiopure Acids 411a and 411b**

With amine **410** and the enantiomerically pure acids **411a** and **411b** in hand, the synthesis of the oxazole-aldehydes **408a** and **408b** was undertaken. Condensation of amine **410** and acid **411a,** followed by desilylation, afforded β-hydroxyamide **409a** in high yield.[145] The oxidation of β-hydroxyamide **409a** to the β-formylamide intermediate proved sluggish and was best performed under Swern conditions. Cyclodehydration of the β-formylamide intermediate under Wipf's conditions, generated oxazole **427a**, in good yield.[146,34] Desilylation to oxazole **428a**, followed by oxidation of the resulting alcohol **428a** provided aldehyde **408a** in excellent yield (Scheme 136). Commencing with the *S*-acid **411b** provided the diastereoisomeric aldehyde **408b** in identical yield and purity to aldehyde **408a**.



Scheme 136 Synthesis of Oxazole-Aldehyde 408a

Inspection of the NMR spectra of both β-hydroxyamide intermediates **409a** and **409b** showed that no epimerisation had occurred over the entire synthetic route (Schemes 132-136) as there was zero evidence of cross-over products. The NMR analysis showed that the asymmetric alkylation of pseudoephedrine amides **423a** and **423b** occurred with complete diastereocontrol.

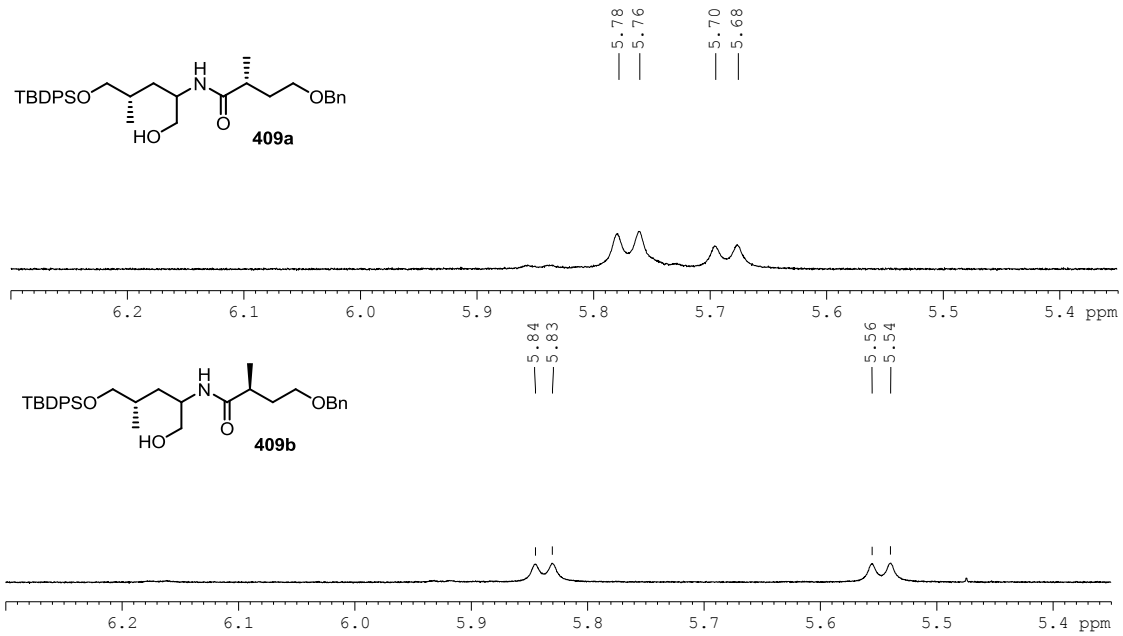
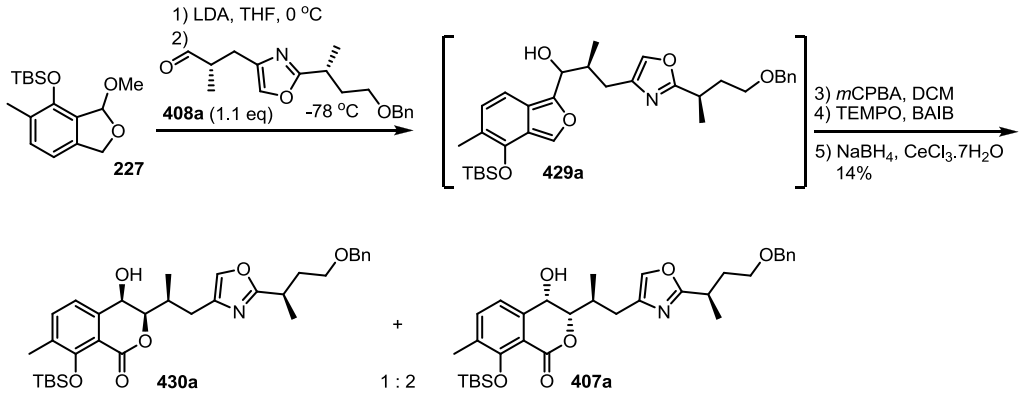


Figure 19 NMR Analysis of β-Hydroxyamide Intermediates 409a and 409b

8.2 Oxidative Rearrangement Sequence Towards Ajudazol B

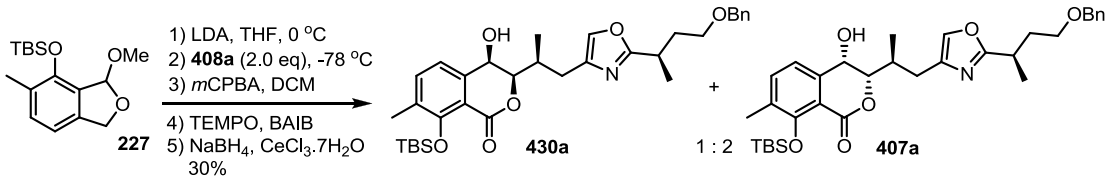
With the aldehydes **408a** and **408b** in hand, the crucial oxidative rearrangement sequence to generate the ajudazol B western section, was trialled. Disappointingly, the oxidative rearrangement sequence between functionalised phthalan **227** and oxazole-aldehyde **408a**, under our standard conditions afforded the expected isochromanones **430a** and **407a**, in a very poor yield of 14% (Scheme 137).



Scheme 137 **Oxidative Rearrangement Sequence of Phthalan 227 and Aldehyde 408a**

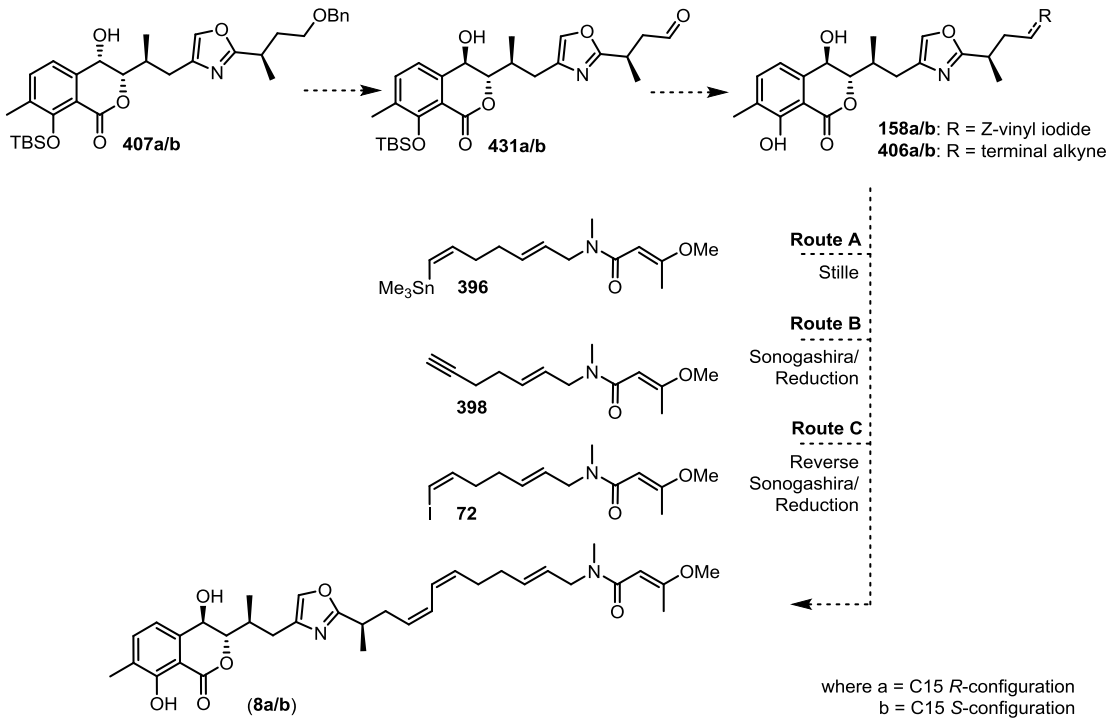
However, it was evident that significant levels of unreacted aldehyde **408a** were still present after quenching, which seriously hindered purification. NMR analysis of the alkylated IBF intermediate showed a 2:1 mixture of unreacted aldehyde **408a** to alkylated IBF intermediate **429a**. It was evident that the initial ratios of unreacted aldehyde **408a** to IBF intermediate **429a** were far from optimal and this had a detrimental effect on the purification. While keeping in mind that aldehyde **408a** was the more valuable substrate, efforts to improve the alkylation step were undertaken. Initial attempts to increase the yield by means of extended reaction times and carefully elevated reaction temperatures, failed to improve the degree of alkylation. Furthermore, it appeared that these two factors may have contributed to degradation of the transient IBF intermediate **429a**. Interestingly, the use of HMPA and TMEDA additives, designed to enhance the nucleophilicy of IBF anion **338**, resulted in complete suppression of the alkylation.

Complete consumption of aldehyde **408a** was achieved however, by using 2.0 equivalents of phthalan **227** relative to aldehyde **408a**. This modification afforded the *syn,syn* and *syn,anti*-isochromanones **430a** and **407a**, in a much improved yield over the entire sequence (Scheme 138). The C15 epimer **407b** was obtained, starting from aldehyde **408b**, in analogous yield and in a similar diastereoisomeric ratio.



Scheme 138 **Improved Oxidative Rearrangement Conditions to Access Isochromanone 407a**

Having obtained the complete western section framework **407a**, it was hoped that a C9 Mitsunobu inversion, followed by homogation, could provide access to the late-stage aldehyde intermediate **431a**. Aldehyde **431a**, in turn, could provide access to either vinyl-iodide **158a** or acetylene **406a** in a single step. From these key intermediates, potentially either of the three end-game couplings that had been developed could be employed to generate the ajudazol B diastereoisomer (**8b**) (Scheme 139).



Scheme 139 End-game Routes Towards Ajudazol B

8.3 Towards Late-Stage Aldehyde 431

The first step in the proposed synthesis of aldehyde **431a** from the *syn,anti*-isochromanone **407a** involved Mitsunobu inversion of the C9Hydroxyl group to access the *anti,anti*-C9-C11 stereochemistry of the ajudazols. Significant difficulties were associated with the harsh Mitsunobu conditions employed previously, which resulted in complex mixtures, from which the desired products could only be isolated after careful purification. Therefore, alternative Mitsunobu conditions were sought.

Para-nitrobenzoic acid has been shown to be the nucleophile of choice for Mitsunobu reactions on hindered secondary positions (i.e. as in the case of our isochromanone substrates).[147] This factor, combined with our previous results showing the ability to chemoselectively cleave the *para*-nitrobenzoate moiety in the presence of the lactone ring of isochromanones, meant that varying the choice of nucleophile was not a desirable option in this case.[148] Furthermore, the apparent difficulty experienced during the Mitsunobu inversions on isochromanone substrates was the problem of purification. Numerous azodicarboxylate reagents have been recently developed to aid purification.

Methyl polyethylene glycol (MPEG)-supported DEAD and PPh_{3H}as been shown to greatly aid purification as the reaction side-products can be easily removed by simple filtration (Figure 20).[149] Unfortunately, MPEG-DEAD and MPEG-PPh_3 failed to react even with simple isochromanones. Further experimentation using *para*-nitrobenzoic acid in combination with polystyrene bound reagents: PS-DEAD/PPh_3, DEAD/PS-PPh_3 and PS-DEAD/PS-PPh_3, either in THF or toluene, at room temperature or reflux, failed to improve the success of the transformation. Use of the Lipshutz DCAD reagent, which had been shown to aid purification as the hydrazine by-product (DCAD-H_2) is insoluble in DCM, failed to react with isochromanone **136f** (Figure 20).[150]

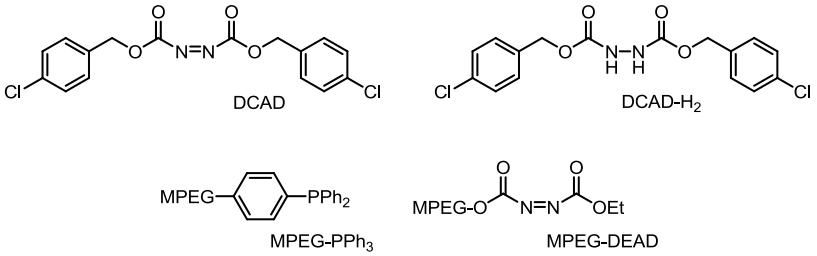


Figure 20 Recently Developed Mitsunobu Reagents

Whitten reported a solution to the often tedious separation of reaction product from Mitsunobu byproducts.[151] Whitten used a combination of a basic triarylphosphine (2-$PyPPh_2$ **432**), together with the acid labile azodicarboxylate (DTBAD **434**). This meant that a simple acid workup of the reaction crude mixture would remove the phosphine derived species **432** and **433**, while DTBAD **434** and DTBAD-H_2 **435** degraded into gaseous isobutene, CO_2 and N_2/N_2H_2 respectively, thus alleviating the need for column chromatography (Figure 21).[151]

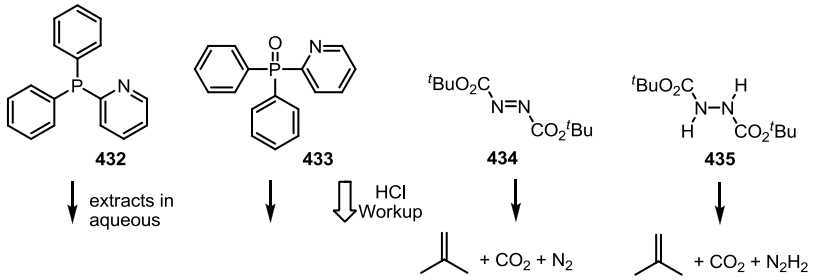
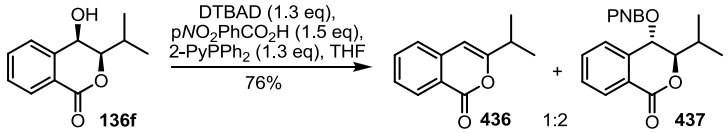


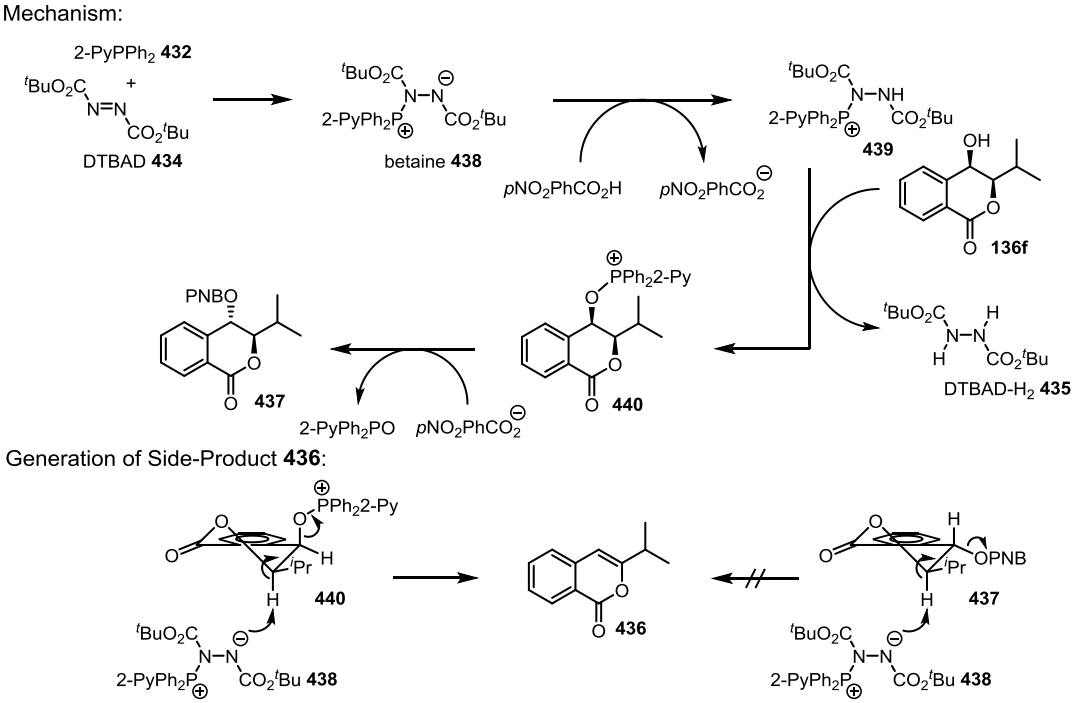
Figure 21 Whitten's DTBAD/2-$PyPPh_2$ Mitsunobu Work-Up Procedure

Gratifyingly, the combination of DTBAD/2-$PyPPh_2$/*para*-nitrobenzoic acid in THF reacted with the simple isochromanone **136f** to afford *para*-nitrobenzoate **437**, albeit in a moderate 51% yield (Scheme 138). Importantly, the reaction achieved complete consumption of the starting material at room temperature. However, closer inspection of the reaction mixture showed the presence of by-product **436**, in a significant yield of 25%. We believe that side-product **436** is the result of β-elimination occurring during the Mitsunobu reaction.



Scheme 140 Mitsunobu Reactions of Isochromanones Using DTBAD/2-$PyPPh_2$

Mechanistically, the first step of the Mitsunobu reaction is irreversible formation of the betaine intermediate **438** (Scheme 141). Betaine **438** then deprotonates the *para*-nitrobenzoic acid to generate the ionic species **439**, which upon reaction with the alcohol substrate **136f** forms the key alkoxyphosphonium salt **440** and DTBAD-H_2**435**. Alkoxyphosphonium **440** can then either undergo S_N2 inversion to generate the desired *anti*-adduct **437**, or an alternative E2 reaction to yield by-product **436**. Elimination must proceed via intermediate **440** and not from the *para*-nitrobenzoate product **437**, as once inversion has taken place, it is no longer possible to achieve the *anti*-periplanar arrangement necessary for elimination (Scheme 141).

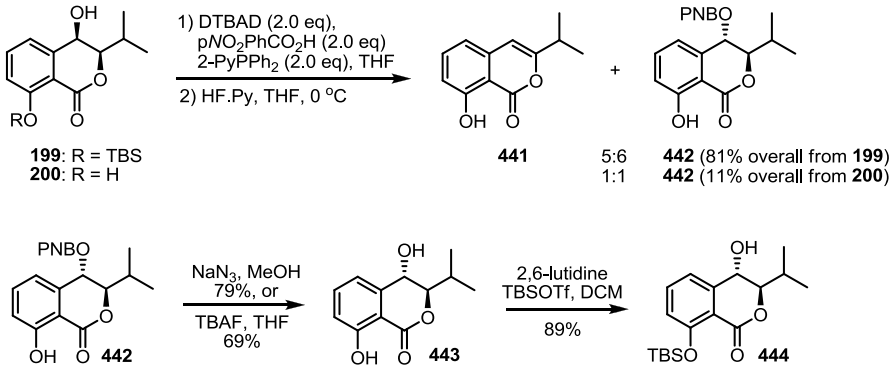


Scheme 141 Mitsunobu Mechanism to Generate *Anti*-Adduct 437 and Side-Product 436

Hence, it would appear that the basicity of betaine intermediate **438** may have been responsible for the undesired β-elimination. Unfortunately, attempts to suppress the elimination by careful addition of DTBAD, failed to improve the product to by-product ratio. Evidence to support our mechanistic hypothesis was provided by close monitoring of the course of the reaction, as it was evident that by-product **436** formed long before starting material consumption. Furthermore, pre-forming betaine **438** prior to the addition of alcohol **136f** also failed to suppress β-elimination and merely resulted in incomplete consumption of starting material.

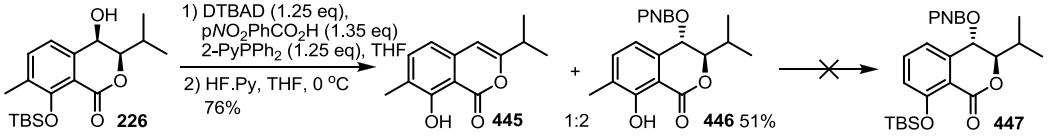
Closer inspection of previous Mitsunobu reactions with DIAD/PPh_3 also showed evidence of β-elimination products. We believe that the β-elimination pathway is able to compete with the traditional Mitsunobu inversion due to the increase in aromatisation, and hence stability, which results upon elimination. Therefore, it was deemed unlikely that this side-reaction could be completely suppressed.

Nevertheless, having worked out an improved Mitsunobu procedure for the key inversion, a more realistic model system was employed. Mitsunobu reaction of silyl phenol **199**, under DTBAD/2-$PyPPh_2$/*para*-nitrobenzoate conditions afforded the *para*-nitrobenzoate, together with by-product. Substantial silyl cleavage was observed during the reaction, and therefore HF.Py was used in a second step to access the fully deprotected product **442** and side-product **441** (Scheme 142). Interestingly, the Mitsunobu reaction of protecting-group-free phenol **200** proceeded to give products **442** and **441** with minimal drop off in yield. *Para*-nitrobenzoate cleavage to afford *anti*-isochromanone **443** was achieved using either NaN_3/MeOH or TBAF. [148] Reprotection of the phenol proved troublesome, as isochromanone **443** failed to react with TBSCl/imid/DMF; however, the slightly more forcing conditions of TBSOTf/2,6-lutidine/DCM generated the protected phenol **444** in excellent yield (Scheme 142).



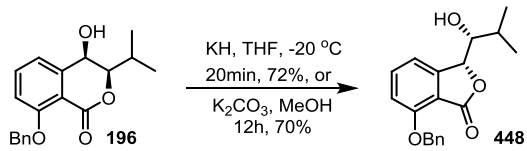
Scheme 142 **Mitsunobu Reaction with Phenolic Isochromanones**

Isochromanone **226**, more representative of the isochromanone moiety present in the ajudazols, was subjected to our improved Mitsunobu conditions, to yield the desired *para*-nitrobenzoate **446**, together with side-product **445**, in a 2:1 mixture. Disappointingly, the more hindered 7-hydroxy-8-methyl isochromanone **446** could not be reprotected. Attempts to reprotect phenol **446** as the TMS ether using TMSCl/imid/DMF or TMSCl/$(Me_3Si)_2NH$/pyridine proved fruitless as the resultant products were too labile (Scheme 143).



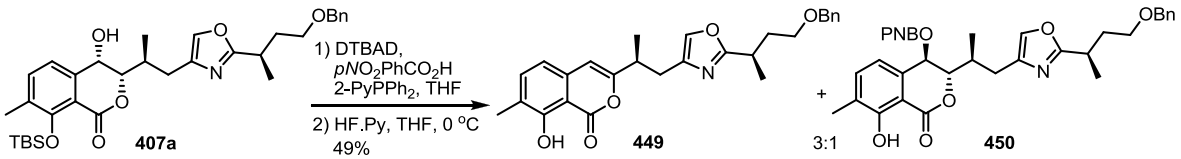
Scheme 143 **Mitsunobu Reaction With Functionalised Isochromanone 226**

More forcing conditions for re-protection using stronger bases resulted in substrate degradation. However, it was observed that treatment of simple isochromanones with KH or even K_2CO_3 over prolonged reaction times, resulted in a 5-exo-trig cyclisation to generate phthalide **448** (Scheme 144).



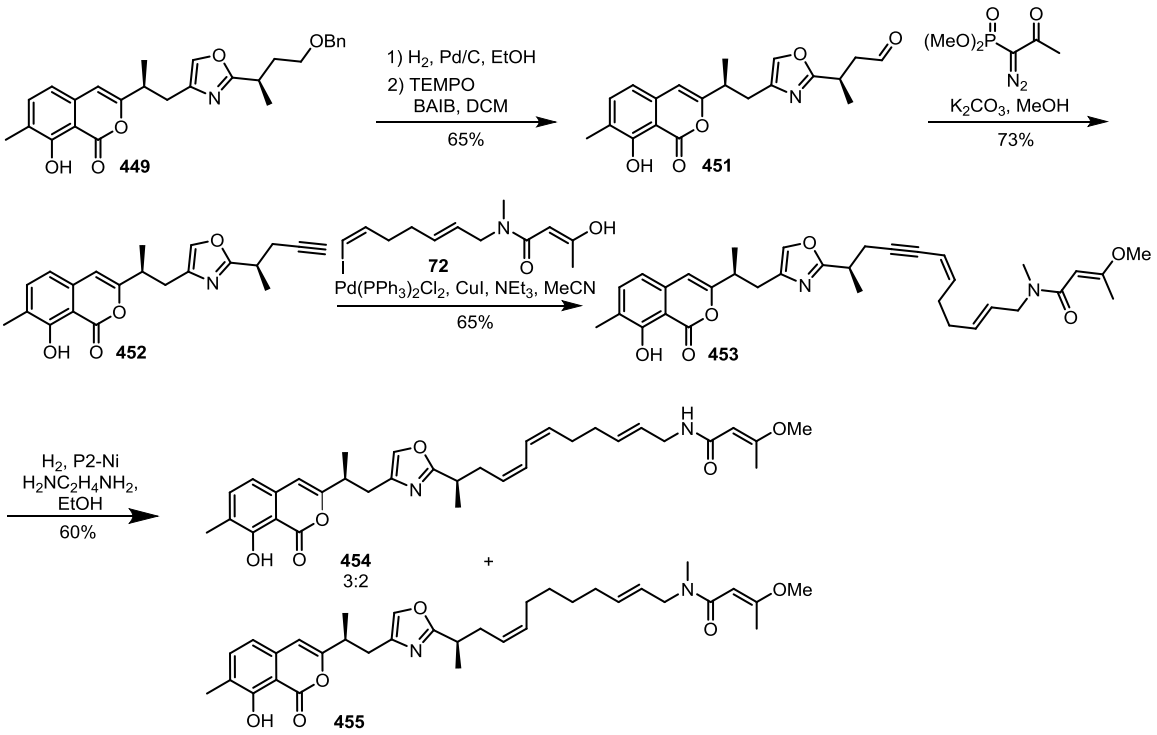
Scheme 144 **Isochromanone Ring Degradation**

Faced with all of the protecting group stability issues, it was decided that a protecting group-free synthesis would be necessary. Thus, isochromanone **407a** was subjected to the DTBAD/2-$PyPPh_2$ Mitsunobu conditions followed by desilylation, to afford the unwanted elimination product **449** as the major product, together with the Mitsunobu adduct **450**, in modest yields (Scheme 145). Unfortunately, efforts to separate Mitsunobu product **450** from the elimination product **449** proved fruitless, and resulted in partial product degradation. Hence, it was decided that in order to access ajudazol B, the Mitsunobu step would have to be undertaken later in the synthesis.



Scheme 145 **Mitsunobu Inversion of Isochromanone 407a**

Nevertheless, the elimination product **449** that could be isolated, was debenzylated and the resultant alcohol was oxidised to aldehyde **451** in 65% overall yield. The oxidation proceeded surprisingly slowly with DMP and TPAP/NMO: mild oxidation conditions that have become synonymous with application in complex natural product synthesis.[152,153] Aldehyde **451** would not provide access to ajudazol B without considerable difficulty and optimisation for which there was certainly not enough material; however, such a system would provide a model for which to trial the late stage coupling between eastern and western sections. Due to the apparent instabilities of the ajudazol B late-stage intermediates, it was decided that the Sonogashira/enyne reduction route (akin to Scheme 139, Route C), proceeding via acetylene **406**, would provide the mildest conditions. Therefore, although it was hopeful that the reverse Sonogashira/enyne reduction (Route B) and the Stille route (Route A) could work, when faced with the prospect of a very limited quantity of material, route C was investigated initially, as the preferred option. Thus, Ohira-Bestmann homologation provided access to acetylene **452**, which was used in the Sonogashira coupling with the eastern section vinyl iodide **72**, to generate enyne **453**. Finally, P2-Ni reduction of enyne **453** generated the desired *Z,Z*-diene **454**, together with the over-reduced side-product **455** (Scheme 146). In accessing *Z,Z*-diene **454**, it gave us confidence that the this end-game strategy, proceeding via a western section aldehyde species, followed by Sonogashira coupling and chemoselective reduction, should allow us to access ajudazol B. However, obtaining the anti-isochromanone **450** in large enough quantity and purity remained a significant drawback.

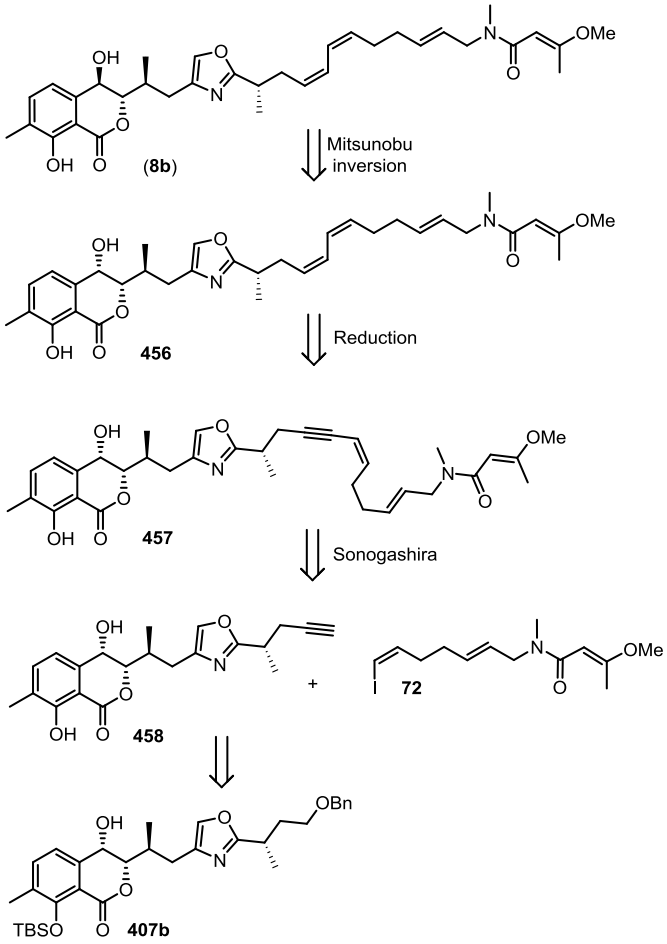


Scheme 146 Sonogashira/Reduction Route to *Z,Z*-diene 454

8.4 Ajudazol B End-Game Strategy

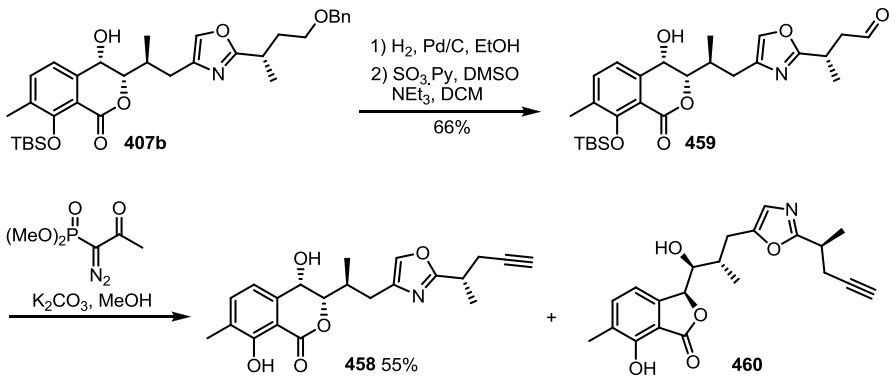
Our final effort towards the synthesis of ajudazol B involved attempting to firstly access the C8-epi-ajudazol B isomer **456** via the reduction of enyne **457**, generated from acetylene **458**, and then attempt to invert the C9Hydroxyl stereochemistry as the final step of the synthesis (Scheme 147). Although it was more risky to attempt the audacious inversion as the final step with the entire ajudazol B skeleton in place, notably the *Z,Z*-diene, all other options had been

exhausted. N.B. Due to minimal quantity of the western section **407a** (which would be used to access the ajudazol B isomer (**8a**), the first generation synthesis was attempted with western section **408b**, to provide access to ajudazol B isomer (**8b**).



Scheme 147 Final Retrosynthetic Analysis of Ajudazol B

The *syn,anti*-isochromanone **407b** was debenzylated and the resultant alcohol intermediate was oxidised to generate aldehyde **459** (Scheme 148). Parikh-Doering conditions proved optimal to afford chemoselective oxidation in the presence of the benzylic alcohol functionality.[154] Aldehyde **459** was subjected to Ohira-Bestmann conditions to afford the desired acetylene **458**. However, together with the welcomed phenol desilylation, the K_2CO_3 necessary to generate the active Ohira-Bestman species, generated noticeable levels of the 5-membered cyclisation side-product **460**. Unfortunately, the undesired cyclisation was unavoidable as it proceeded at such a rate that side-product formation was evident long before complete consumption of starting material. After optimisation, acetylene could be isolated in a modest 55% yield, based on a 2:1 ratio of product **458**:side-product **460** (Table 9). Extreme care was necessary during flash chromatography as the acidity of the silica was also enough to promote cyclisation to the 5-membered side-product **460** (Scheme 148).

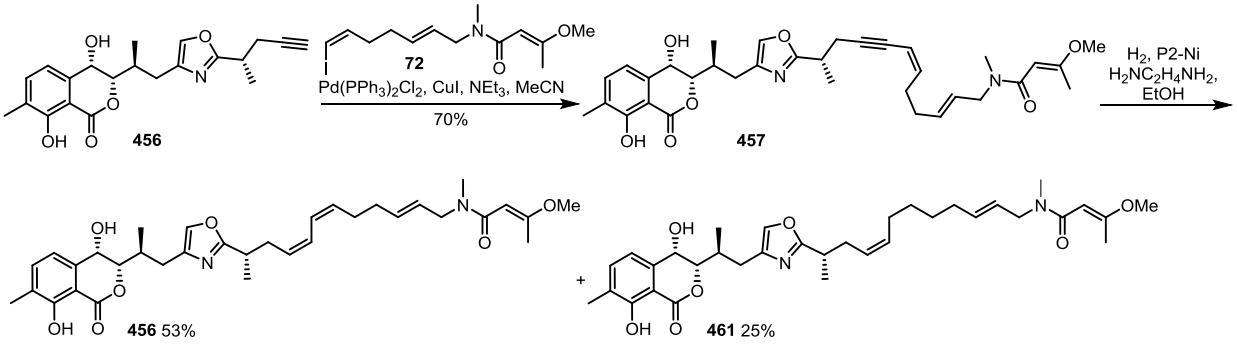


Scheme 148 **Synthesis of Late-Stage Acetylene 458**

Table 9 **Ohira-Bestmann Conditions**

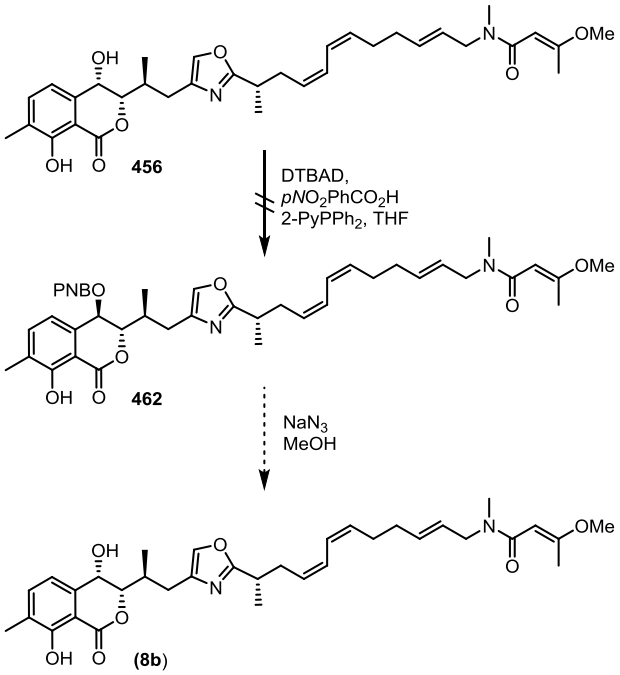
Equiv. of K_2CO_3	Ratio of acetylene **458:** side-product **460**	Yield of **458** isolated /%
5.0	1:4	17
3.0	2:1	55

Due to its instability, acetylene **458** was immediately coupled with eastern section vinyl iodide **72**, under Sonogashira conditions, to afford enyne **457** in good yield. Enyne **457** was then reduced under P-2 Ni conditions, with the crude product mixture showing that *epi*-ajudazol B **456** was present in a 2:1 ratio, together with the over-reduced species **461**. HPLC chromatography provided C8-*epi*-ajudazol B **456** in 53%, and allowed isolation of the over-reduced species **461**, in 25% from enyne **457** (Scheme 149).



Scheme 149 **Synthesis of *Epi*-Ajudazol B 456**

The C8-*epi*-ajudazol B isomer **456** represents the first example of the synthesis of the entire ajudazol C1-C29 framework, albeit with the opposite stereochemistry at C8, with respect to the desired ajudazol B isomer (**8b**). Unfortunately, all attempts to invert the C8 stereochemistry of **456** failed. Although the Mitsunobu inversion of free phenol **200** proceeded in a similar yield to the analogous protected substrate **199** (Scheme 142), such conditions failed to react with the more elaborate C8-*epi*-ajudazol B isomer **456**. Addition of excess reagents or increasing the reaction temperature only led to degradation of starting material (Scheme 150).



Scheme 150 **Attempted Mitsunobu Inversion of C8-*Epi*-Ajudazol B Analogue 456**

8.5 Summary and Outlook

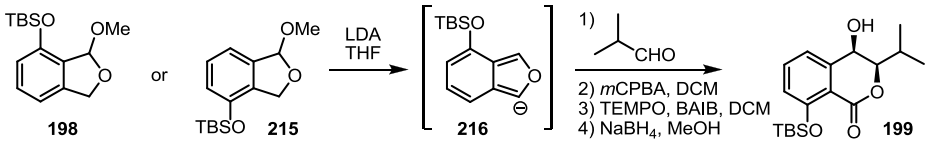
The enantiopure aldehydes **408a** and **408b**, necessary to access both C15-epimers of Ajudazol B, were accessed via a convergent route, from Roche ester and pseudoephedrine precursors. The ajudazol B western section framework **407a/b** was accessed via the IBF oxidative rearrangement sequence from phthalan **227** and aldehydes **408a** and **408b**. Ultimately, after much investigation, ajudazol B could not be accessed, inherently due to instabilities of the isochromanone ring.

Although we were unable to complete the total synthesis of ajudazol B, we managed to deliver the total synthesis of the C8-epimer of ajudazol B **456**, via a convergent synthetic route. C8-*Epi*-ajudazol B analogue **456** represents the first example of the synthesis of the entire ajudazol C1-C29 framework.

9 Conclusion

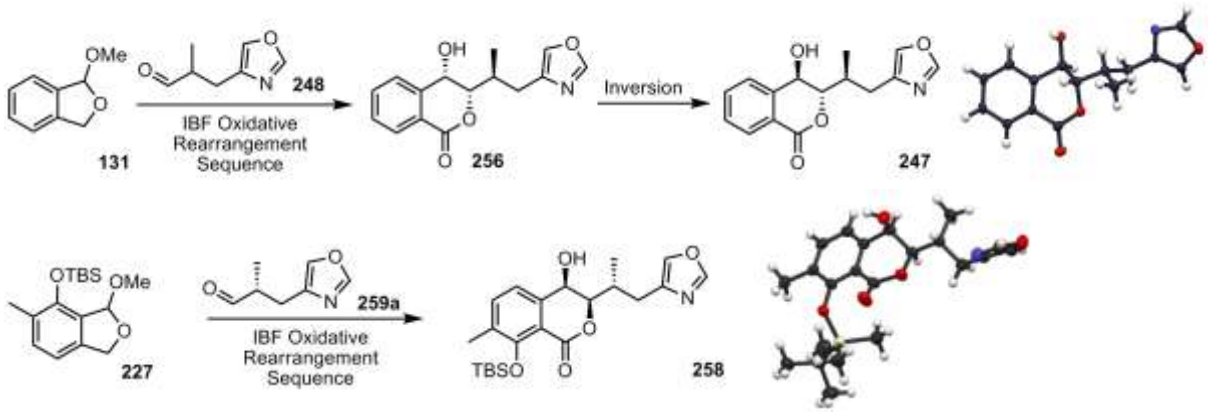
The initial objective of the work presented in this thesis was to expand and develop the isobenzofuran oxidative rearrangement methodology, recently developed within the Marquez group for generation of isochromanones, and to apply this methodology towards the total synthesis of the ajudazols.[33]

Our IBF alkylation and oxidative rearrangement sequence has been developed to efficiently generate C8-substituted isochromanones, of type **199**, with complete regio- and diastereocontrol, in excellent yield and requiring minimal purification. C8-substituted isochromanone **199** can be accessed from either the C7 or C4-substituted phthalan precursor **198** or **215** (Scheme 151).[155]



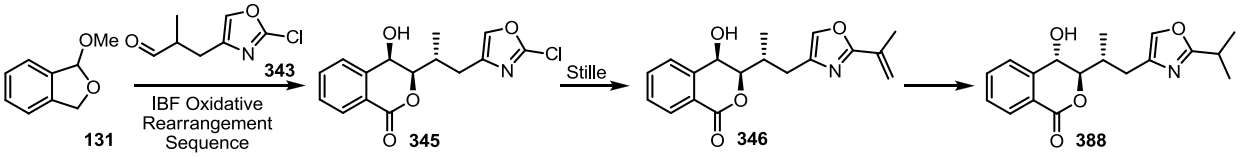
Scheme 151 **Regiocontrolled IBF Oxidative Rearrangement Sequence**

The oxazole-linked aldehyde **248** was compatible with the IBF alkylation and oxidative rearrangement conditions to generate isochromanone **256**, *en route* to the *anti,anti*-adduct **247**, the C8-C10 stereochemistry matching that of the ajudazols. The functionalised phthalan **227** and enantiopure aldehyde **259a** were utilised in the IBF oxidative rearrangement sequence to successfully access the ajudazol C1-C14 western section framework **258** (Scheme 152).[156]



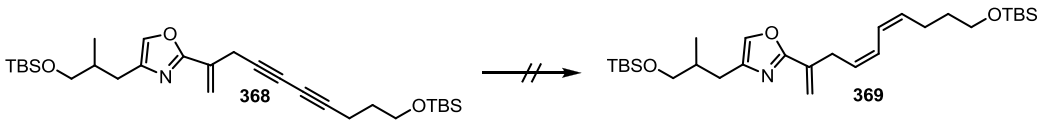
Scheme 152 **Synthesis of the Ajudazol Western Systems 258**

After applying our methodology towards the ajudazol western section, attention was focussed on achieving a coupling that would allow us to bring together the eastern and western ajudazol sections in a convergent manner. In order to access the key C14-C15 bond of ajudazol A, various methods to investigate oxazole C2 alkenylation were investigated, including C-H activation and S_NAr chemistry, and although said chemistry worked on model systems, it was not tolerated by isochromanone systems. However, Stille coupling, utilising 2-chloro oxazoles, was very tolerant of the sensitive isochromanone functionality. The chloro-oxazole containing western section **345** was shown to undergo Stille alkenylation to generate alkenyl oxazole **346**, *en route* to the *anti,anti*-adduct **388** (Scheme 153).



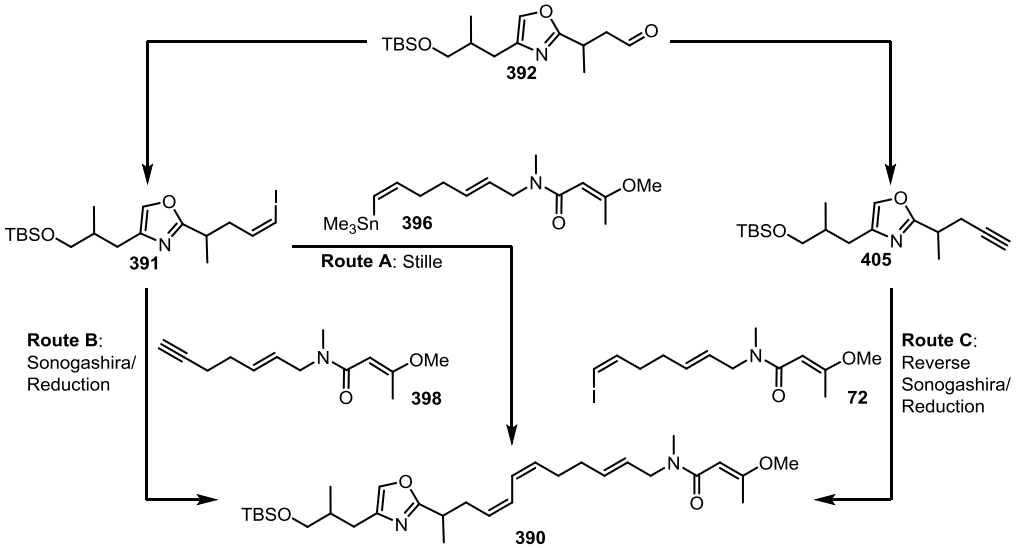
Scheme 153 Stille Route Towards Ajudazol C14-C15 Bond Synthesis

Ultimately, efforts towards the total synthesis of ajudazol A were thwarted by the inability to chemoselectively reduce the model diyne **368** in the presence of the C15 olefin functionality, and were further hampered by the tendancy of the C15-olefin to undergo isomerisation (Scheme 154).



Scheme 154 Attempt to Access the *Z,Z*-Diene of Ajudazol A

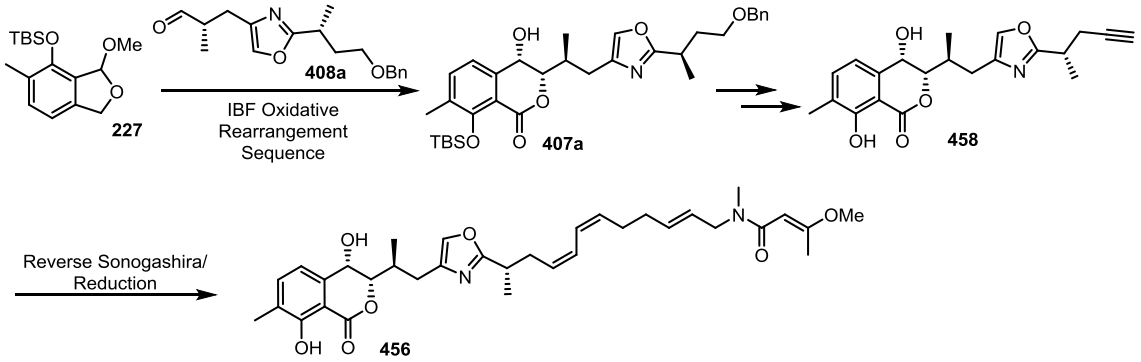
Upon focussing our efforts exclusively on the total synthesis of ajudazol B (**8**), various end-game approaches were developed to achieve the key C17-C20 *Z,Z*-diene functionality, from a single late-stage intermediate **392**. Stille coupling, Sonogashira coupling/chemoselective reduction and reverse-Sonogashira/reduction methodologies were utilised in the synthesis of the ajudazol B eastern section **390** (Scheme 155). This would allow for a flexible synthesis of ajudazol B.



Scheme 155 Accessing the Ajudazol B Eastern Section 390

The enantiopure aldehydes **408a** and **408b**, necessary to access the C15-epimers of Ajudazol B, were accessed via a convergent route, from Roche ester and pseudoephedrine precursors. The ajudazol B western section framework **407a**/**b** was accessed via the IBF oxidative rearrangement sequence from phthalan **227** and aldehydes **408a** and **408b**. Ultimately, after much investigation, ajudazol B could not be accessed, inherently due to instabilities of the isochromanone ring.

Although we were unable to complete the total synthesis of ajudazol B, we managed to deliver the total synthesis of *ent*-C8-epimer of ajudazol B **456** (refer to addendum), via a convergent synthetic route, utilising our novel IBF oxidative rearrangement sequence to efficiently generate the isochromanone-containing western section. *Ent*-C8-*epi*-ajudazol B **456** represents the first example of the synthesis of the entire ajudazol C1-C29 framework (Scheme 156).



Scheme 156 **Synthesis of C8-*Epi*-Ajudazol B Isomer 456**

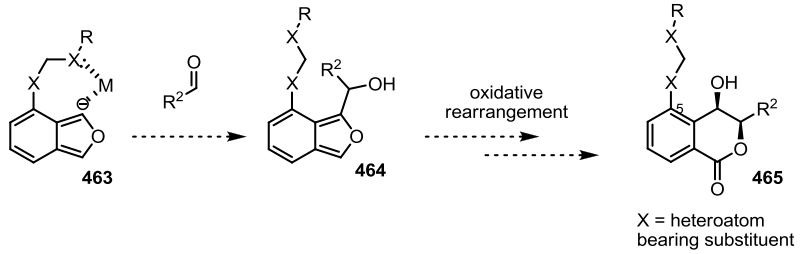
We believe that the work carried out during the course of this project will provide a meaningful contribution to both the field of synthetic chemistry and the art of total synthesis.

10 Future Work

Should there have been more time during the course of this doctorate research, there are a few areas of research that we would have liked to dedicate some time to. Time spent researching these areas would lead to a more complete research project.

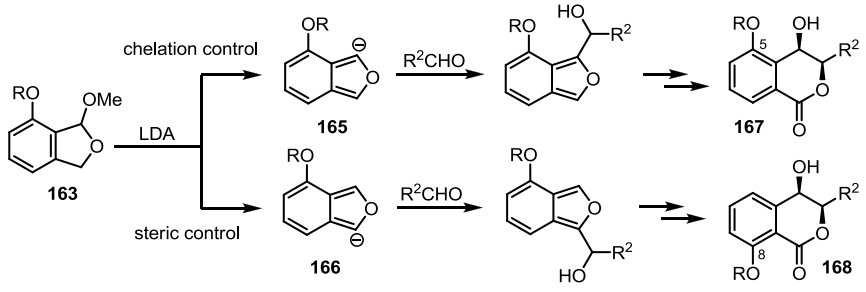
10.1 Chelation Controlled Route to 5-Substituted Isochromanones

The IBF alkylation and oxidative rearrangement with MOM-substituted phthalan **206** gave the 8-substituted isochromanone **208** as the major product (Scheme 157). Attempts to optimise reaction conditions to favour chelation control, failed to overturn the selectivity. It is hypothesized that by using chelating groups that have heteroatoms fixed at different positions away from the aromatic framework, this may help to create more optimal chelation conditions between the heteroatom, metal ion and proximal anion **456**. MEM, SEM, MTM and BOM ethers, or the diethylcarbamate, may help to access the chelation controlled C5-substituted isochromanones **465**.[51]



Scheme 157 Accessing 5-Substituted Isochromanones Via Chelation Control

The ability to achieve both steric and chelation controlled IBF anion alkylation would enhance our methodology, whereby simply altering the nature of phenol protecting group on the phthalan precursor **163**, would allow for the selective synthesis of either 5 or 8-substituted isochromanone products **167** or **186** (Scheme 158).



Scheme 158 Accessing Either 5- or 8-Substituted Isochromanones

10.2 Enhancing *Anti*-Felkin IBF Anion Alkylation

During the course of this project, the IBF anion alkylation with aldehydes possessing an α-stereocenter, resulted in a 3:2 ratio of isochromanone products, with a marginal bias in favour of the *syn,anti*-product. The *syn,anti* product appeared to be the result of *anti*-Felkin addition.

Therefore, the synthetic route towards *syn,anti*-isochromanones and thus, *anti,anti*-isochromanones could be greatly improved if the *anti*-Felkin selectivity could be enhanced.

Designer Lewis acid ligands have proven to be versatile reagents for the control of regio-, sterio- and chemoselective transformations. One such example is the sterically hindered aluminium aryloxide ligand, MAD (methylaluminium *bis*(2,6-di-*tert*-butyl-4-methylphenoxide)), developed by Yamamoto.[157] The high oxophilicity of monomeric MAD results in the formation of stable Lewis acid complexes with the carbonyl oxygen (**467**). This complexion leads to steric protection of the initially less hindered substrate positions and has been used to enhance selectivities in nucleophiic addition reactions, often reversing the regio- or stereospecificity of reactions, to generate the *anti*-Felkin product **469** (Figure 19).[158,159]

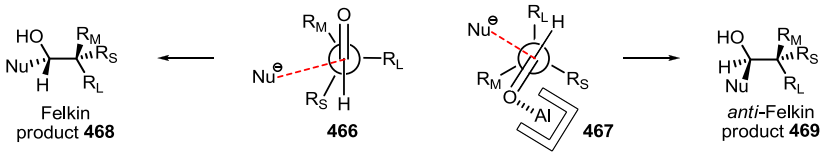
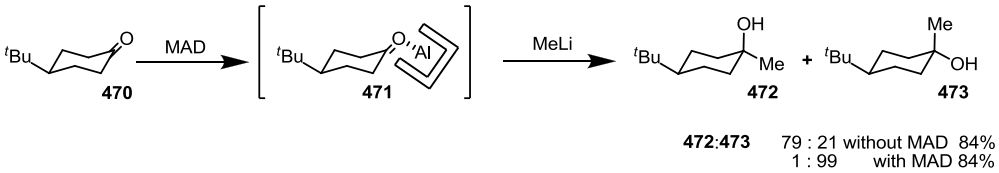


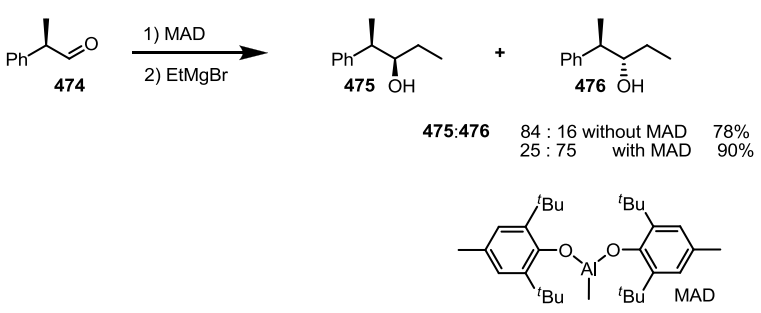
Figure 19 **Felkin and *Anti*-Felkin Newman Projections**

Yamamoto showed that complexation of a range of substituted cyclohexanones, for example **470**, with MAD, inverts the facial selectivity of attacking nucleophiles by shielding the favoured equatorial side. This results in the almost exclusive formation of the axial substituted alcohol **473** (99:1). In the absence of MAD, the equatorial substituted alcohol **472** (79:21) predominates (Scheme 159).[157]



Scheme 159 **Effect of MAD on Nucleophilic Addition to ^{t}Bu-Cyclohexanone**

Furthermore Yamamoto also demonstrated that complexation of the chiral α-aldehyde **474** with MAD reversed the selectivity of alkylation where no chelation control is possible. The MAD ligand coordinated to the least hindered face of the aldehyde followed by addition of the ethyl Grignard, which subsequently attacks the face opposite to the bulky MAD ligand, favouring the *anti*-Felkin product **476** in a ratio of 75:25. Meanwhile alkylation without preceeding complexation results in a 13:87 ratio in favour of the Felkin product **457** (Scheme 160).[157]



Scheme 160 **Effect of MAD on Nucleophilic Addition to Acyclic Aldehydes**

This selectivity is incredibly encouraging and the Yamamoto MAD protocol could possibly be implemented for use in the IBF alkylation step. In theory this could enhance the *anti*-Felkin selectivity and therefore increase the efficiency in the synthesis of the ajudazol western section **479** (Figure 20).

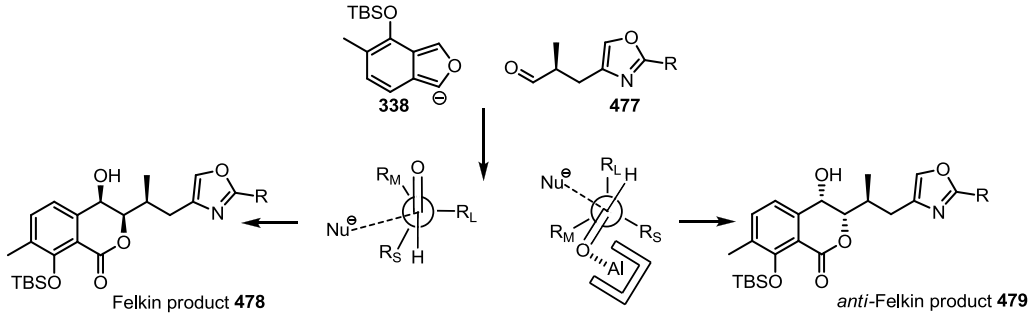


Figure 20 Using MAD to Enhance of Selectivity of IBF Anion Alkylation

11 Addendum

Since the submission of this thesis in September 2012, Menche and co-workers have fully assigned the absolute stereochemistry of the ajudazols A (**7b**) and B (**8c**), based exclusively on gene cluster analysis, and reported the first total synthesis of ajudazol B (**8c**) (Figure 21).[158]

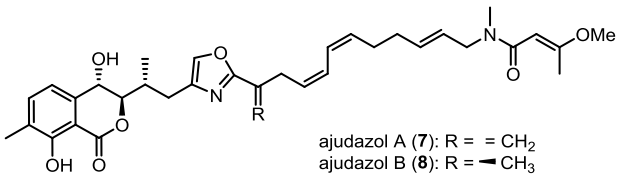


Figure 21 **Menche's Full Stereochemical determination of the Ajudazols**

12 Experimental

12.1 Apparatus

Solvents were evaporated under reduced pressure at 40 °C using a Buchi Rotavapor unless otherwise stated. IR spectra were recorded as thin films on NaCl plates using a JASCO FT/IR410 Fourier Transform spectrometer or using a Shimadzu FTIR-8400 spectrometer (thin-layer). Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by EI, CI and FAB mass spectrometry, operating at a resolution of 15000 full width at half height. Melting points were recorded with an Electrothermal IA 9100 apparatus.

Hydrogen magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were respectively recorded at 400 or 500 MHz and 100 or 125 MHz using a Bruker DPX Avance 400 or 500 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br. = broad), (3) and coupling constant (*J*) quoted in Hertz to the nearest 0.1. DEPT Q, 135, DEPT 90 and two-dimensional (COSY, HQC) NMR spectroscopy were used, where appropriate, to assist the assignment of signals in the 1H and 13C NMR spectra.

12.2 Chromatography

Flash chromatography was performed using silica gel (Fluorochem Silica Gel 60, 40-63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}) unless otherwise stated where aluminium oxide plates were used. The plates were visualised by the quenching of UV fluorescence (λ_{max}254nm) and/or by staining with either anisaldehyde, potassium permanganate, cerium ammonium molybdate or phosphomolybdic acid hydrate solution, followed by heating.

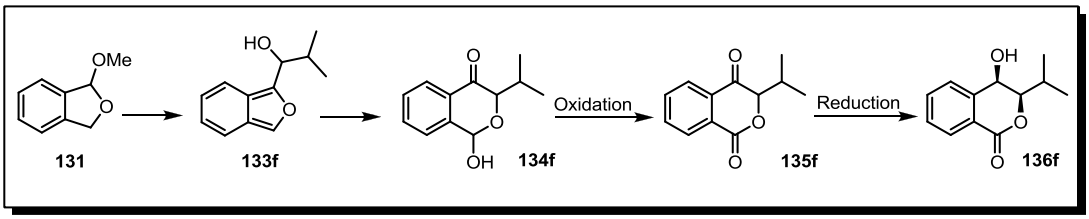
12.3 Solvents, Reagents and Reaction Conditions

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. THF, Et_2O, and DCM were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated.

12.4 Experimental Details

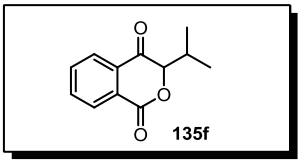
General Procedures 1-2: The Synthesis of Isochroman-1-ones from Phthalan Precursors

All of the IBF oxidative rearrangement sequences carried out here in this thesis were done so according to the following general procedures, unless explicitly stated otherwise. In the following general procedures the keto-lactone species **135f** has been purified and fully characterised; however, all intermediates were typically taken on crude through the entire sequence from phthalan precursor to isochromanone product. The general procedures have been exemplified for the synthesis of isochromanone **136f**



General Procedure 1: The Synthesis of Keto-Lactones from Phthalan Precursors

3-*Iso*propylisochroman-1,4-dione **135f**



A 0 ^{o}C solution of phthalan **131** (1.88 g, 12.6 mmol) in anhydrous THF (75 mL), was treated with $^{i}Pr_2NH$ (176 µL, 1.25 mmol) and stirred for 10 min. MeLi (1.6 M in Et_2O, 16.5 mL, 26.4 mmol) was then added slowly, and the solution was stirred for 30 min. The reaction mixture was cooled to –78 ^{o}C, and freshly distilled *iso*butyraldehyde (1.37 mL, 15.1 mmol) was added. The resulting solution was then stirred for a further 90 min at –78 ^{o}C (until TLC analysis on alumina plates showed reaction was complete) before being quenched with water at 0 ^{o}C. The mixture was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed with water (50 mL), brine (50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure at RT to afford the desired α-hydroxy-IBF intermediate **133f** which was used in the next step without further purification.

The crude α-hydroxy-IBF **133f** was dissolved in anhydrous DCM (50 mL) and cooled to 0 ^{o}C. The resulting solution was then treated with *m*CPBA, (77%, 3.09 g, 13.8 mmol) and the reaction was stirred at 0 ^{o}C for 2h (until completion by TLC analysis on alumina plates). The reaction was quenched with sat'd $NaHCO_3$ solution (60 mL), extracted with DCM (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4. The solvent was then removed under reduced pressure at RT to afford the crude keto-lactol **135f** (2.43 g, 11.80 mmol, 94% from phthalan **131**) as a yellow oil, which was taken on as crude immediately to the next step without further purification.

Oxidation Method 1A: Jones Reagent

Freshly prepared keto lactol **134f** (1.68 g, 8.2 mmol) was dissolved in acetone (40 mL) and treated with freshly made 2.5 M Jones reagent at RT. The resulting red / brown solution was then stirred for 45 min (until complete consumption of starting material indicated by TLC

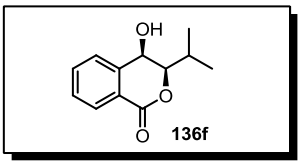
analysis on alumina plates). The reaction was quenched with water (100 mL), and the aqueous layer extracted with DCM (3 × 150 mL). The combined organic extracts were washed sequentially with water (3 × 30 mL), brine (50 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude residue was purified by flash column chromatography, elution with 100% DCM, to afford the desired keto-lactone **135f**, (1.60 g, 7.82 mmol, 96% from keto-lactol **135f**) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ**:** 0.89 (3H, d, *J* = 6.8, CH_3), 1.12 (3H, d, *J* = 7.0, CH_3), 2.43-2.51 (1H, m, $CH(CH_3)_2$), 4.91 (1H, d, *J* = 3.6, CH(^{i}Pr)), 7.78-7.86 (2H, m, ArH), 8.04 (1H, dd, *J* = 7.6, 1.2, ArH), 8.25 (1H, d, *J* = 7.3, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.3 (CH_3), 18.9 (CH_3), 33.4 ($CH(CH_3)_2$), 88.8 (CH(^{i}Pr)), 125.7 ($C^{Ar}H$), 128.1 ($C^{Ar}CO$), 130.6 ($C^{Ar}H$), 132.0 ($C^{Ar}CO_2$), 134.6($C^{Ar}H$), 135.6 ($C^{Ar}H$), 162.0 (CO_2), 192.5 (CO). *m/z* [FAB$^+$, NOBA] 205 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 205.0866, $C_{12}H_{13}O_3$ requires 205.0865. υ_{max} /cm^{-1} (film): 2969, 2935, 2877, 1731, 1698, 1599.

Oxidation Method 1B: TEMPO and BAIB

The freshly prepared keto-lactol **135f** (480 mg, 2.33 mmol) was dissolved in anhydrous DCM (12 mL) and sequentially treated with BAIB (2.40 g, 7.45 mmol) and TEMPO (73 mg, 0.47 mmol) under argon. The reaction mixture was stirred at RT for 45 min until reaction completion as indicated by TLC analysis. The reaction was then diluted with DCM (100 mL) and washed with sat'd aq. $Na_2S_2O_3$ solution (2 × 30 mL), water (2 × 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography, elution with 0-25% Et_2O:petroleum ether) to afford the desired keto-lactone **135f** (399 mg, 1.96 mmol, 84%) as a yellow oil.

General Procedure 2: The synthesis of Isochroman-1-ones from Keto-Lactones

4-Hydroxy-3-isopropylisochroman-1-one **136f**



Reduction Method 2A: Luche Conditions

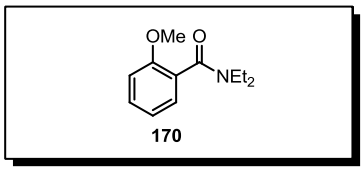
A –78 ^{o}C solution of the freshly prepared keto-lactone **135f** (300 mg, 1.47 mmol) in anhydrous DCM (7.4 mL) was treated with a 0.4 M solution of $CeCl_3$ in anhydrous MeOH (725 mg, (2.94 mmol) of $CeCl_3$ in 7.4 mL MeOH) and the resulting suspension was stirred for 10 min. $NaBH_4$ (84 mg, 2.21 mmol) was then added, and the reaction mixture was stirred at –78 ^{o}C for 30 min (until completion as indicated by TLC analysis on alumina plates). The reaction solution was quenched with water (10 mL) and 10% aq. citric acid solution (4 mL). The biphasic mixture was then stirred at RT for 20 min before being extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water (3 × 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography, elution with 0-40% Et_2O:petroleum ether, to yield the desired isochromanone **136f** (247 mg, 1.20 mmol, 82%) as a colourless crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.07 (3H, d, *J* = 6.8, CH_3), 1.15 (3H, d, *J* = 6.6, CH_3), 2.28-2.37 (1H, m, $CH(CH_3)_2$),

2.84 (1H, d, *J* = 7.6, OH), 3.95 (1H, dd, *J* = 9.8, 1.6, CH(O_2C)), 4.72 (1H, d, *J* = 6.6, CH(OH)), 7.43-7.48 (2H, m, ArH), 7.62 (1H, dt, *J* = 7.5, 1.2, ArH), 8.01 (1H, d, *J* = 8.0, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.2 (CH_3), 19.3 (CH_3), 28.6 ($CH(CH_3)_2$), 65.0 (CH(OH)), 86.7 ($CH(O_2C)$), 124.2 ($C^{Ar}CO_2$), 128.1 ($C^{Ar}H$), 129.8 ($C^{Ar}H$), 130.2 ($C^{Ar}H$), 134.3 ($C^{Ar}H$), 140.4 ($C^{Ar}CH(OH)$), 165.4 (CO_2). *m/z* [Cl^+, isobutane] 207 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 207.1022, $C_{12}H_{15}O_3$ requires 207.1021. υ_{max} /cm^{-1} (film): 3415, 2964, 2931, 2875, 1703, 1605. MP: 114-115 ^oC. The data observed is in accordance with literature values.[33]

Reduction Method 2B: $NaBH_4$

A –78 ^oC solution of the freshly obtained keto-lactone **135f** (181 mg, 0.89 mmol) in anhydrous MeOH (4 mL) was treated with $NaBH_4$ (41 mg, 1.09 mmol), and the resulting reaction mixture was stirred at –78 ^oC for 30 min (until completion as indicated by TLC analysis on alumina plates). The reaction mixture was then warmed to 0 ^oC and quenched with water (7 mL) and 10 % aq. citric acid solution (2 mL), and the biphasic solution was stirred at RT for 20 min before being extracted with DCM (3 × 70 mL). The combined organic extracts were washed with water (3 × 15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, elution with 0-50% Et_2O:petroleum ether, to give isochromanone **136f** (162 mg, 0.79 mmol, 89%) as a colourless crystalline solid.

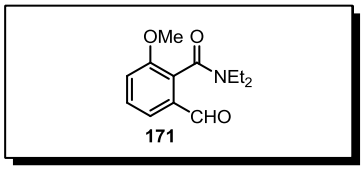
N,N-Diethyl-2-methoxybenzamide **170**



170

Neat $SOCl_2$ (86.8 ml, 1.19 mol) was added to *o*-anisic acid **169** (12.7 g, 83.2 mmol) and stirred under argon. DMF (213 µL, 2.75 mmol) was then added dropwise, after which vigorous effervescence occurred. The solution was stirred for 1h after which time no further effervescence was visible. The excess $SOCl_2$ was removed under reduced pressure by azeotroping with toluene (3 × 100 mL). The colourless oily residue obtained was dissolved in anhydrous THF (95 mL), cooled to 0 ^oC and treated by the slow addition of Me_2NH (31.8 ml, 308 mmol). The mixture was then stirred for 15 min before being concentrated under reduced pressure. The crude residue was dissolved in DCM (400 mL), and washed with water (3 × 70 mL) and brine (3 × 70 mL) before being concentrated under reduced pressure to afford a the desired benzamide **170** (17.1 g, 82.4 mmol, 99%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02 (3H, t, *J* = 7.4, CH_3CH_2N), 1.23 (3H, t, *J* = 7.4, CH_3CH_2N), 3.13 (2H, q, *J* = 6.6, NCH_2CH_3), 3.57 (2H, br s, NCH_2CH_3), 3.81 (3H, s, OCH_3), 6.89 (1H, d, *J* = 8.7, ArH), 6.95 (1H, t, *J* = 7.4, ArH), 7.18 (1H, d, *J* = 7.1, ArH), 7.31 (1H, t, *J* = 8.1, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.8 (CH_3CH_2N), 13.9(CH_3CH_2N), 38.8 (NCH_2CH_3), 42.7 (NCH_2CH_3), 55.4 (OCH_3), 110.9 ($C^{Ar}H$), 120.6 ($C^{Ar}H$), 126.9 ($C^{Ar}CON$, 127.3 ($C^{Ar}H$), 129.8, 155.1 ($C^{Ar}OCH_3$), 168.7 (CON). *m/z* [Cl^+, isobutane] 208 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 208.1340, $C_{12}H_{18}NO_2$ requires 208.1338. υ_{max} /cm^{-1} (film): 3063, 2973, 2935, 2875, 2838, 1634, 1601, 1584. The data observed is in accordance with literature values.[51]

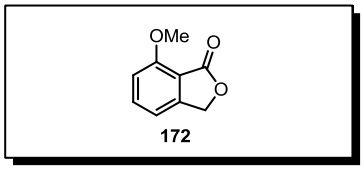
N,N-Diethyl-2-formyl-6-methoxybenzamide **171**



171

An oven dried flask was charged with THF (150 mL) and cooled to –78 ^{o}C under an atmosphere of argon. Freshly distilled TMEDA (16.0 mL, 107.1 mmol) and ^{s}BuLi (1.4 M in hexanes, 76.5 mL, 107 mmol) were added successively and the resulting solution was stirred for 5 min. benzamide **170** (17.1 g, 82.4 mmol) in anhydrous THF (150 ml) was then added dropwise and the reaction mixture was stirred for 1h. DMF (7.65 mL, 98.9 mmol) was then also added dropwise and the reaction was stirred at –78 ^{o}C for a further 5 min before being allowed to rise to RT over 16h. The reaction mixture was then concentrated under reduced pressure to give a crude oil which was cooled to 0 ^{o}C and acidified to pH 4-5 by the addition of aqueous 6 M HCl. The aqueous solution was extracted with EtOAc (5 × 100 mL) and the combined organic layers washed with water (3 × 40 mL) and brine (3 × 40 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired benzaldehyde **171** (17.3 g, 73.7 mmol, 89%) as a brown oil which was taken on without need for further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.01 (3H, t, *J* = 7.1, CH_3CH_2N), 1.29 (3H, t, *J* = 7.1, CH_3CH_2N), 3.10 (2H, q, *J* = 7.2, NCH_2CH_3), 3.49-3.58 (1H, m, NCH_2CH_3), 3.68-3.77 (1H, m, NCH_2CH_3), 3.86 (3H, s, OCH_3), 7.12 (1H, dd, *J* = 8.1, 1.9, ArH), 7.46 (1H, t, *J* = 7.8, ArH), 7.52 (1H, dd, *J* = 7.7, 1.0, ArH), 9.99 (1H, s, ArCHO). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.6 (CH_3CH_2N), 12.7 (CH_3CH_2N), 38.0 (NCH_2CH_3), 41.8 (NCH_2CH_3), 55.0 (OCH_3), 115.4 ($C^{Ar}H$), 120.2 ($C^{Ar}H$), 128.1 ($C^{Ar}CON$), 128.9 ($C^{Ar}H$), 132.7 ($C^{Ar}CO$), 154.7 ($C^{Ar}OCH_3$), 164.8 (CON), 189.6 (ArCHO). *m/z* [Cl^+, isobutane] 236$[M+H]^+$ (100%), HRMS found $[M+H]^+$ 236.1282, $C_{13}H_{18}NO_3$ requires 236.1287. υ_{max} /cm^{-1} (film): 2967, 2934, 2873, 2844, 2748, 1704, 1631, 1593, 1579. The data observed is in accordance with literature values.[51]

7-Methoxyphthalide **172**

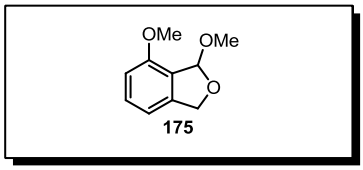


172

The crude benzaldehyde **171** (17.3 g, 73.7 mmol) was dissolved in anhydrous MeOH (400 mL) and the solution was cooled to 0 ^{o}C. $NaBH_4$ (4.43 g, 147 mmol) was then added slowly and the reaction mixture was stirred at RT for 3h under an argon atmosphere. The solution was then acidified to pH 4-5 by the addition of aqueous 6 M HCl at 0 ^{o}C. The reaction mixture was then heated at reflux for 16h after which, a white precipitate had formed. The solvent was removed under reduced pressure, and the resultant solid was dissolved in DCM (400 mL) and washed with water (3 × 50 mL) and brine (3 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue which was purified by recrystallization from EtOAc:hexane (1:1) to afford the desired phthalide **172** (8.87 g, 54.0 mmol, 74%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.99 (3H, s, CH_3CH_2N), 5.23 (2H, s, $ArCH_2O_2C$), 6.92 (1H, d, *J* = 8.2, ArH), 7.00 (1H, d, *J* = 7.5, ArH), 7.61 (1H, t, *J* = 8.0, ArH).^{13}C NMR ($CDCl_3$, 100 MHz) δ: 56.0 (OCH_3), 68.7 ($ArCH_2O$), 110.6 ($C^{Ar}H$), 113.3 ($C^{Ar}CO_2$), 113.7 ($C^{Ar}H$), 136.3 ($C^{Ar}H$), 149.4 ($C^{Ar}CH_2O_2C$), 158.8 ($C^{Ar}OCH_3$), 169.1 (CO_2), *m/z* [Cl^+, isobutane] 165 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 165.0555, $C_9H_9O_3$ requires 165.0552. υ_{max} /cm^{-1} (film): 2930,

2907, 2874, 1747, 1604. MP: 108-109 ^{o}C. The data observed is in accordance with literature values.[51]

1,7-Dimethoxy-1,3-dihydroisobenzofuran **175**



A –78 ^{o}C solution of phthalide **172** (5.05 g, 30.8 mmol) in anhydrous DCM (370 mL) was treated by the dropwise addition of DIBAL via syringe pump (1 M in hexanes, 30.0 mL, 30.0 mmol over 2h. The reaction mixture was then stirred until completion, indicated via TLC analysis, and was then diluted with Et_2O (300 mL). The reaction was quenched at –78 ^{o}C by the successive addition of water (1.50 mL), 15% aq. NaOH solution (1.50 mL) and water (3.75 mL). The resultant slurry was stirred for 30 min, before being treated with anhydrous Na_2SO_4. The newly formed suspension was stirred for a further 30 min and then the solids were removed by filtration. The clear solution was evaporated under reduced pressure to afford the crude lactol intermediate **173,** as colourless oil, and was used immediately without further purification.

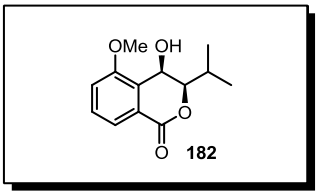
Method B: NaH and MeI

The crude lactol intermediate was dissolved in anhydrous THF (150 mL) and was cannulated to a solution of NaH (60% dispersion in oil, 1.54g, 38.49 mmol) in THF (150 mL) at –78^{o}C and stirred for 1Hr. MeI (filtered through basic alumina) was added (9.60 mL, 154 mmol) to the reaction mixture and the resulting solution was stirred for 12h. Once the reaction was complete according to TLC analysis, water (100 mL) was added and the mixture diluted with Et_2O (400 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (2 × 50 mL) and dried over anhydrous Na_2SO_4. Purification by flash column chromatography, elution with 0-13% Et_2O:petroleum ether, afforded the desired desired phthalan **175** (2.67 g, 14.81 mmol, 48%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.47 (3H, s, CH_3OCH), 3.86 (3H, s, CH_3OAr), 4.97 (1H, d, *J* = 12.7, CH_2), 5.20 (1H, d, *J* = 12.7, CH_2), 6.24 (1H, s, $CHOCH_3$) 6.78 (1H, d, *J* = 8.1, ArH), 6.83 (1H, d, *J* = 7.4, ArH), 7.32 (1H, t, *J* = 7.8, ArH). *m/z* [EI^{+}] 180 [M]$^{+}$ (100%), HRMS found [M]$^{+}$ 180.0790 $C_{10}H_{12}O_3$ requires 180.0786. υ_{max} /cm^{-1} (film): 2932, 2897, 2837, 1615, 1601. The data observed is in accordance with literature values.[159]

Methylation Method B: TsOH in MeOH

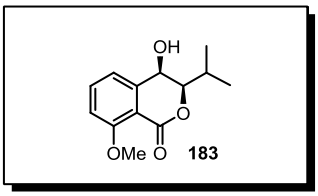
The crude lactol intermediate **173** was dissolved in anhydrous MeOH (50 mL) in the presence of 4 Å molecular sieves. TsOH.H_2O (293 mg, 1.54 mmol) was then added, and the resultant solution was stirred at RT for 30 min. The solution was neutralized to pH 7 by the addition of sat'd aqueous $NaHCO_3$ solution before the 4 Å molecular sieves were removed by filtration. The resultant solution was extacted with Et_2O (3 × 100 mL) and the combined organic extracts were washed with water (2 × 40 mL), aqueous aqueous $NaHCO_3$ solution (40 mL) and brine (50 mL) before being dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography, elution with 0-13% Et_2O:petroleum ether, to afford the desired phthalan **175** (3.79 g, 23.1 mmol, 75%) as a colourless oil.

(±)-(3*R*,4*R*)-4-Hydroxy-3-isopropyl-5-methoxyisochroman-1-one **182**



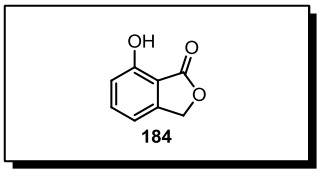
Using general procedure 1A, a solution phthalan **175** (897 mg, 4.98 mmol) in anhydrous THF (27 mL) was treated with $^{i}Pr_2NH$ (70 µL, 0.50 mmol), MeLi (1.6 M in Et_2O, 6.53 mL, 10.5 mmol) and *iso*butyraldehyde (542 µL, 5.97 mmol) to generate the α-hydroxyisobenzofuran intermediate. The oxidative rearrangement was performed using *m*CPBA (77%, 945 mg, 5.48 mmol) in anhydrous DCM (27 mL) to afford the keto-lactol intermediate. Oxidation was performed as a solution in acetone (27 mL) with 2.5 M Jones reagent to afford the keto-lactone unit which was taken on crude. Using general procedure 2B, reduction was performed at –78 ^{o}C in anhydrous MeOH (25 mL) with $NaBH_4$ (283 mg, 7.47 mmol). The crude products were purified by flash column chromatography, elution with 0-75% Et_2O:petroleum ether, to afford 5-methoxyisochromanone **182** (221 mg, 0.94 mmol, 18% from phthalan **175**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (3H, d, *J* = 6.6, CH_3), 1.20 (3H, d, *J* = 6.6, CH_3), 1.89 (1H, s, OH)), 2.3-2.42 (1H, m, $CH(CH_3)_2$), 3.92-3.94 (4H, m, CH_3OAr, $CH(O_2C)$), 5.13 (1H, s, CH(OH)), 7.15 (1H, d, *J* = 8.2, ArH), 7.45 (1H, t, *J* = 8.0, ArH), 7.73 (1H, d, *J* = 7.7, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.3 (CH_3), 19.4 (CH_3), 28.7 ($CH(CH_3)_2$), 55.9 (CH_3OAr), 59.1 (CH(OH)), 86.5 ($CH(O_2C)$), 115.5 ($C^{Ar}H$), 121.9 ($C^{Ar}H$), 125.5 ($C^{Ar}CO_2$), 128.8 ($C^{Ar}C(OH)$), 130.4 ($C^{Ar}H$), 155.9 ($C^{Ar}OCH_3$), 165.0 (CO_2). *m/z* [EI$^+$] 236 [M]$^+$ (100%), HRMS found [M]$^+$ 236.1052 $C_{13}H_{16}O_4$ requires 236.1049. υ_{max} /cm^{-1} (film): 3390, 2965, 2875, 2840, 1702, 1593. MP: 147-149 ^{o}C.

(±)-(3*R*,4*R*)-4-Hydroxy-3-isopropyl-5-methoxyisochroman-1-one **183**



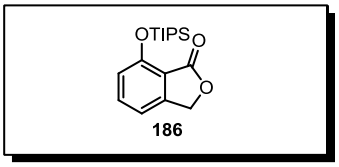
Further elution with 0-75% Et_2O:petroleum ether afforded 8-methoxyisochromanone **182** (425 mg, 1.80 mmol, 36% from phthalan **175**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (3H, d, *J* = 6.7, CH_3), 1.15 (3H, d, *J* = 6.5, CH_3), 2.26-2.32 (1H, m, $CH(CH_3)_2$), 2.36 (1H, d, *J* = 7.4, OH)), 3.87 (1H, d, *J* = 7.9, $CH(O_2C)$), 3.91 (3H, s, CH_3OAr), 4.69 (1H, d, *J* = 7.2, CH(OH)), 6.98-7.01 (2H, m, ArH), 7.52 (1H, t, *J* = 7.9, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.1 (CH_3), 19.4 (CH_3), 28.4 ($CH(CH_3)_2$), 56.2 (CH_3OAr), 66.0 (CH(OH)), 85.6 ($CH(O_2C)$), 112.6 ($C^{Ar}C(OH)$), 112.9 ($C^{Ar}H$), 119.7 ($C^{Ar}H$),135.2 ($C^{Ar}H$), 143.0 ($C^{Ar}CO_2$),161.0 ($C^{Ar}OCH_3$), 162.3 (CO_2). *m/z* [EI$^+$] 236 [M]$^+$ (100%), HRMS found [M]$^+$ 236.1046 $C_{13}H_{16}O_4$ requires 236.1049. υ_{max} /cm^{-1} (film): 3468, 2962, 2926, 2874, 1702, 1598. MP: 208-209 ^{o}C.

7-Hydroxyphthalide **184**



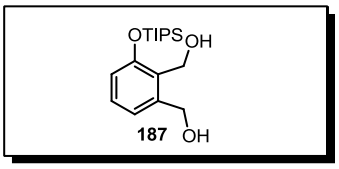
Iodocyclohexane (69.0 mL, 534 mmol) was added to a solution of phthalide **172** (8.80 g, 53.6 mmol) in anhydrous DMF (82 mL), and the resultant solution was heated at reflux for 5 days. The solution was diluted with water (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic extacts were then washed with sat'd aq. $Na_2S_2O_3$ solution (3 x 150 mL), brine (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography, elution with 0-20% EtOAc:petroleum ether) afforded the 7-hydroxyphthalide **184** (7.13 g, 47.5 mmol, 65%) as a white solid. Alternatively the pure product could be obtained by triturating a solution of the crude residue with DCM:petroleum ether, in comparable yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.33 (2H, s, CH_2), 6.94 (1H, dd, *J* = 8.3, 0.6, ArH), 6.97 (1H, dd, J =7.6, 0.5, ArH), 7.57 (1H, app. t, *J* = 7.8, ArH), 7.74 (1H, br. s, ArOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 70.7 ($ArCH_2O$), 110.9 ($C^{Ar}CO_2$), 113.4 ($C^{Ar}H$), 115.3 ($C^{Ar}H$), 137.0 ($C^{Ar}H$), 146.8 ($C^{Ar}CH_2O_2C$), 156.6 ($C^{Ar}OH$), 172.6 ($ArCO_2$). *m/z* [Cl^+, isobutene] 151 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 151.0398, $C_8H_7O_3$ requires 151.0395. υ_{max} /cm^{-1} (film): 3514, 3423, 2942, 2823, 17351638, 1606. MP: 134 - 135 ^{o}C. The data observed is in accordance with literature values.[160]

7-(Tri*iso*propylsilyloxy)phthalide **186**



To a solution of 7-hydroxyphthalide **184** (2.77 g, 18.5 mmol) in anhydrous DMF (28 ml), imidazole (2.51 g, 36.9 mmol) was added and the resultant solution was stirred for 5 min at 0 ^{o}C, to which TIPSCl (4.34 ml, 20.30 mmol) was added dropwise and the resultant solution was stirred for 60 min at 0^{o}C, before a further 12h at RT. Completion of the reaction was indicated by TLC analysis. The solution was taken up in water (50 ml) and extracted with EtOAc (3 × 150 ml). The resulting organic solution was the washed with brine (3 × 50ml) and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography, elution with 0-30% DCM:petroleum ether, followed by recrystallization from petroleum ether gave the desired product 7-hydroxyphthalide **186** (3.91 g, 12.8 mmol, 69%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.14 (18H, d, *J* = 7.6, CH_3), 1.33 - 1.41 (3H, m, CH), 5.19 (2H, s), 6.84 (1H, d, *J* = 8.3, ArH), 6.97 (1H, d, *J* = 7.6, ArH) 7.48 (1H, t, *J* = 8.0, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.9 (CH_2Si), 18.0 (CH_3), 68.3 ($ArCH_2O$) 114.0 ($C^{Ar}H$), 115.6 ($C^{Ar}CO_2$), 119.2 ($C^{Ar}H$), 135.7 ($C^{Ar}H$), 149.0 ($C^{Ar}CH_2$), 155.9 ($C^{Ar}OSi$), 168.6 ($ArCO_2$). m/z [FAB^+, NOBA] 307 $[M+H]^+$ (94%), HRMS found $[M+H]^+$ 307.1731, $C_{17}H_{27}O_3Si$ requires 307.1729. υ_{max} /cm^{-1} (film): 2946, 2892, 2866, 1764, 1604. MP: 69-70 ^{o}C

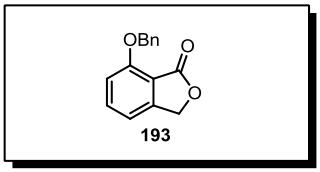
(3-(Tri*iso*propylsilyloxy)-1,2-phenylene)dimethanol **187**



187

7-TIPS-phthalide **186** (350 mg, 1.14 mmol) was dissolved in anhydrous DCM (30 mL) and cooled to –78 °C. DIBAL (1 M in hexanes, 1.12 mL, 1.12 mmol) was added dropwise via syringe pump over 2h. The reaction was stirred for a further 2h before the reaction was diluted with Et_2O (30 mL) and quenched by the successive addition of water (110 µL), 15% aq. NaOH solution (110 µL) and water (260 µL) at –40 to 0 °C. The resultant slurry was stirred for 30 min, anhydrous Na_2SO_4 was added and the resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution evaporated under reduced pressure. The crude residue was purified by flash column chromatography, elution with 0-20% EtOAc:petroleum ether, to afford the undesired diol **187** (60 mg, 0.19 mmol, 17%) as a white solid. Further elution afforded unreacted 7-TIPS-phthalide **186** (150 mg, 0.49 mmol, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.11 (18H, d, *J* = 7.6, CH_3), 1.27-1.38 (3H, m, CH), 3.38 (1H, br. s), 3.85 (1H, br. s), 4.61 (2H, s, CH_2) 4.80 (2H, s, CH_2) 6.81 (1H, d, *J* = 8.2, ArH), 6.90 (1H, d, *J* = 7.4, ArH) 7.48 (1H, t, *J* = 7.8, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.1 (CH_2Si), 18.1 (CH_3), 56.7 ($ArCH_2OH$), 64.1 ($ArCH_2OH$), 118.5 ($C^{Ar}H$), 122.3 ($C^{Ar}H$),128.8 ($C^{Ar}H$), 129.5 ($C^{Ar}CH_2OH$), 141.7 ($C^{Ar}CH_2OH$), 154.4 ($C^{Ar}OSi$). *m/z* [CI^+, isobutane] 293 $[M\text{-}OH]^+$ (94%), HRMS found $[M\text{-}OH]^+$ 293.1938, $C_{17}H_{29}O_2Si$ requires 293.1937. υ_{max} /cm^{-1} (film): 3333, 2944, 2866, 1584. MP: 83-85 °C.

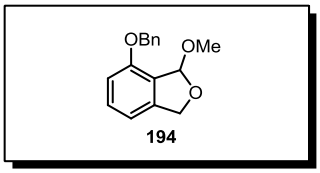
7-(Benzyloxy)phthalide **193**



193

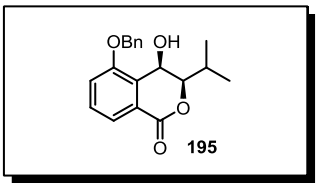
A solution of 7-benzloxyphthalide **184** (512 mg, 3.41 mmol) in anhydrous DMF (9.0 mL),under argon, was treated with anhydrous K_2CO_3 (1.41 g, 10.2 mmol) and the suspension was stirred for 5 min before the dropwise addition of BnBr (810 µL, 6.82 mmol). The heterogenous mixture was stirred at RT for 3h until reaction completion was indicated by TLC analysis. The reaction was quenched with water (40 mL) and extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with water (2 × 30 mL), brine (30 mL), dried over Na_2SO_4 and evaporated under vacuum, to yield the crude product as a white solid. Purification of the crude white solid by flash column chromatography, elution with 0-40% DCM:petroleum ether to afford phthalide **193** (731 mg, 3.04 mmol, 89%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.23 (2H, s, CH_2O_2C), 5.33 (2H, s, $CH_2Ph(Ar)$), 6.91 (1H, d, *J* = 8.2, ArH), 6.99 (1H, dd, *J* = 7.6, 0.5, ArH), 7.27-7.33 (1H, m, ArH) 7.34-7.40 (2H, m, ArH), 7.46-7.55 (3H, m, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 68.7 (CH_2O_2C), 70.5 ($CH_2Ph(OAr)$), 112.6 ($C^{Ar}H$), 114.0 ($C^{Ar}CO_2$), 114.0 ($C^{Ar}H$),126.8 ($C^{Ph}H$) 128.0 (*p*-$C^{Ph}H$), 128.7 ($C^{Ph}H$), 136.0 ($C^{Ar}H$), 136.2 ($C^{Ph}CH_2$), 149.4 ($C^{Ar}CH_2O$), 157.7 ($C^{Ar}OBn$) 168.8 (CO_2). *m/z* [EI^+] 240 $[M]^+$ (100%), HRMS found $[M]^+$ 240.0785, $C_{15}H_{12}O_3$ requires 240.0786. υ_{max} /cm^{-1} (film): 2933, 2870, 1746, 1614, 1602. MP: 110-111 °C. The data observed is in accordance with literature values.[160]

7-(Benzyloxy)-1-methoxy-1,3-dihydroisobenzofuran **194**



A –78 ^{o}C solution of phthalide **193** (1.72 g, 7.15 mmol) in anhydrous DCM (100 mL) was treated with the dropwise addition of DIBAL (1 M in hexanes, 7.08 mL, 7.08 mmol), via syringe pump over 2.5h. Upon completion, as indicated by TLC analysis (after 1 hr), the reaction was warmed up to -40 ^{o}C, diluted with Et_2O (80 mL) and quenched by the successive addition of water (0.3 mL), 15% aq. NaOH solution (0.3 mL) and water (0.7 mL). The resultant slurry was warmed up to RT and stirred for 30 min. Anhydrous Na_2SO_4 was then added, and the resulting suspension was stirred for a further 30 min. The solids were removed by filtration and the clear solution was evaporated under reduced pressure to afford the crude lactol intermediate, which was immediately dissolved in anhydrous MeOH (20 mL) in the presence of 4 Å molecular sieves. To the stirring solution, $TsOH.H_2O$ (68 mg, 0.36 mmol) was added and the reaction mixture was stirred at RT until completion by TLC analysis (30 min). The solution was neutralized to pH 7 by the addition of sat'd aqueous K_2CO_3 solution and then the 4 Å molecular sieves were removed by filtration through cotton wool. The solvent was evaporated under reduced pressure and the crude residue was taken up in Et_2O (150 mL), washed with water (2 × 50 mL), sat'd aqueous $NaHCO_3$ solution (40 mL) and brine (2 × 40 mL), before being dried over anhydrous Na_2SO_4. Solvent removal under reduced pressure afforded a crude oil which was purified by flash column chromatography, elution with 0-15% Et_2O:petroleum ether, yielded 7-benzyloxyphthalan **194** (964 mg, 3.76 mmol, 53%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.38 (3H, s, CH_3OCH), 4.89 (1H, d, *J* = 12.8, CH(H)OC(OCH_3)), 5.02-5.09 (3H, m, CH_2Ph & CH(H)OC(OCH_3)), 5.12 (1H, d, *J* = 13.4, CH(H)OC(OCH_3)), 5.20 (1H, d, *J* = 1.7, $CHOCH_3$), 6.71 (1H, d, *J* = 8.1, ArH), 6.74 (1H, d, *J* = 7.5, ArH), 7.13-7.24 (1H, m, ArH), 7.25-7.30 (1H, m, ArH), 7.31-7.36 (1H, m, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 54.7 (CH_3OCH), 70.0 ($CH_2OC(OCH_3)$), 72.5 ($CH_2Ph(OAr)$), 106.6 ($CH(OCH_3)$), 111.1 ($C^{Ar}H$), 113.5 ($C^{Ar}H$), 125.8 ($C^{Ar}CH(OCH_3)$), 127.0 ($C^{Ph}H$), 127.9 ($C^{Ar}Ph$), 128.6 ($C^{Ph}H$), 131.2 ($C^{Ar}H$), 137.0 ($C^{Ar}CH_2O$), 142.5 ($C^{Ar}CH_2O$) 154.5 ($C^{Ar}OBn$). *m/z* [EI$^+$] 256 [M]$^+$ (11%), HRMS found [M]$^+$ 256.1097, $C_{16}H_{16}O_3$ requires 256.1099. υ_{max} /cm^{-1} (film): 3063, 3033, 2925, 2827, 1616, 1600, 1545.

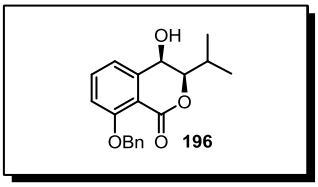
(±)-(3*R*,4*R*)-5-(Benzyloxy)-4-hydroxy-3-isopropylisochroman-1-one **195**



Using general procedure 1A a solution 7-benzyloxyphthalan **194** (1.06 g, 4.13 mmol) in anhydrous THF (23 mL) was treated with $^{i}Pr_2NH$ (58 µL, 0.41 mmol), MeLi (1.6 M in Et_2O, 5.43 µL, 8.68 mmol) and *iso*butyraldehyde (450 µL, 4.96 mmol) to generate the α-hydroxy-IBF intermediate. The oxidative rearrangement of the α-hydroxy isobenzofuran was carried out using *m*CPBA (77%, 784 mg, 4.54 mmol) in anhydrous DCM (23 mL). Oxidation was performed in acetone (23 mL) with 2.5 M Jones reagent to afford the keto lactone intermediate. Using general procedure 2B, reduction was performed at –78 ^{o}C in anhydrous DCM (21 mL), using a solution of cerium (III) chloride (2.04 g, 8.26 mmol) and $NaBH_4$ (283 mg, 7.47 mmol) in anhydrous MeOH (21 mL). The crude adducts were purified by flash column chromatography,

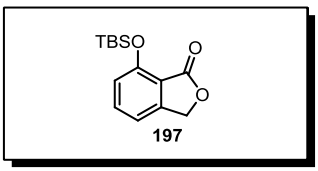
elution with 0-50% Et_2O in petroleum ether, to afford 5-benzyloxyisochromanone **182** (169 mg, 2.54 mmol, 13% from 7-benzyloxyphthalan **194**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (3H, d, *J* = 6.7, CH_3), 1.01 (3H, d, *J* = 6.6, CH_3), 1.39 (1H, br. s, OH), 2.14-2.23 (1H, m, $CH(CH_3)_2$), 3.75 (1H, d, *J* = 9.8, $CH(O_2C)$), 4.97-5.05 (3H, m, CH(OH), CH_2Ph), 7.02 (1H, d, *J* = 8.2, ArH), 7.07 (1H, s, ArH), 7.17-7.24 (5H, m, ArH), 7.57 (1H, d, *J* = 7.7, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.4 (CH_3), 19.4 (CH_3), 28.7 ($CH(CH_3)_2$), 59.2 (CH(OH)), 70.9 (CH_2Ph), 86.5 ($CH(O_2C)$), 117.5 ($C^{Ar}H$), 122.4 ($C^{Ar}H$), 125.7 ($C^{Ar}CO_2$) 127.3 ($C^{Ph}H$) 128.4 ($C^{Ar}H$), 128.9 ($C^{Ph}H$), 129.4 ($C^{Ph}CH_2$), 130.4 (*p*-$C^{Ph}H$), 136.1 ($C^{Ar}CH(OH)$), 155.0 ($C^{Ar}OBn$), 164.9 (CO_2). *m/z* [Cl^+, isobutane] 313 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 313.1442, $C_{19}H_{21}O_4$ requires 313.1440. υ_{max} /cm^{-1} (film): 3417, 2963, 2932, 2874, 1701, 1592. MP: 166-168 ^{o}C.

(±)-(3*R*,4*R*)-5-(Benzyloxy)-4-hydroxy-3-isopropylisochroman-1-one **196**



Further elution yielded 8-benzyloxyisochromanone **196** (677 mg, 2.17 mmol, 52% from 7-benzyloxyphthalan **194**) as white solids. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (3H, d, *J* = 6.7, CH_3), 1.17 (3H, d, *J* = 6.5, CH_3), 2.23 (1H, br s, OH), 2.27-2.35 (1H, m, $CH(CH_3)_2$), 3.90 (1H, d, *J* = 9.8, $CH(O_2C)$), 4.70 (1H, s, CH(OH)), 5.19 (1H, d, *J* = 12.4, CH_2Ph), 5.28 (1H, d, *J* = 12.3, CH_2Ph), 7.01-7.06 (2H, m, ArH), 7.27-7.31 (1H, t, *J* = 7.3, ArH), 7.35-7.39 (2H, t, *J* = 7.3, ArH), 7.48-7.55 (2H, m, *J* = 7.3, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.2 (CH_3), 19.3 (CH_3), 28.4 ($CH(CH_3)_2$), 66.0 (CH(OH)), 70.7 (CH_2Ph), 85.6 ($CH(O_2C)$), 113.3 ($C^{Ar}CO_2$), 114.8 ($C^{Ar}H$), 120.2 ($C^{Ar}H$), 126.7 ($C^{Ph}H$) 127.8 ($C^{Ar}H$), 128.6 ($C^{Ph}H$), 135.1 (*p*-$C^{Ph}H$), 136.3 ($C^{Ph}CH_2$), 143.0 ($C^{Ar}C(OH)$), 160.0 ($C^{Ar}OBn$), 162.1 (CO_2). *m/z* [Cl^+, isobutane] 313 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 313.1441, $C_{19}H_{21}O_4$ requires 313.1440. υ_{max} /cm^{-1} (film): 3430, 3065, 3033, 2963, 2874, 2637, 1709, 1599. MP: 47-49 ^{o}C.

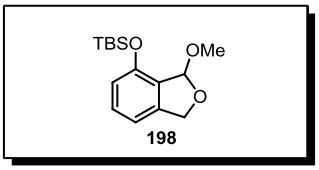
7-(*Tert*-butyldimethylsilyloxy)phthalide **197**



7-hydroxyphthalide **193** (1.47 g, 9.80 mmol) was dissolved in anhydrous DMF (30 mL) under argon and was sequentially treated with imidazole (1.33 g, 19.6 mmol) and TBSCl (1.78 g, 11.8 mmol). The reaction mixture was stirred at RT until completion as indicated by TLC analysis (3H). The reaction was diluted with water (80 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous $Na_2SO_4$and the solvent was evaporated under reduced pressure to yield the crude product as a crude white solid. Purification by flash column chromatography, elution with 0-33% DCM:petroleum ether) afforded 7-TBS-phthalide **197** (2.10 g, 7.91 mmol, 89%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.27 (6H, s, Me_2Si), 1.05 (9H, s, $(CH_3)_3CSi$), 5.20 (2H, s, CH_2O_2C), 6.85 (1H, d, *J* = 8.1, ArH), 7.01 (1H, d, *J* = 7.5, ArH) 7.51 (1H, t, *J* = 7.8, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -4.5 $(CH_3)_2Si$), 18.4 ($C(CH_3)_3Si$), 25.6 ($(CH_3)_3CSi$), 68.4 (CH_2O_2C), 114.4 ($C^{Ar}H$), 116.3 ($C^{Ar}CO_2$),120.2 ($C^{Ar}H$),135.6 ($C^{Ar}H$),148.9 ($C^{Ar}CH_2O$), 155.5 ($C^{Ar}OSi$), 168.7 ($ArCO_2$).

m/z [Cl^+, isobutane] 265 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 265.1259, $C_{14}H_{21}O_3Si$ requires 265.1260. υ_{max} /cm^{-1} (film): 2929, 2886, 2859, 1768, 1601. MP: 81-83 ^oC.

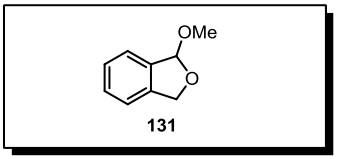
7-(*Tert*-butyldimethylsilyloxy)-1-methoxy-1,3-dihydroisobenzofuran **198**



198

A –78 ^oC solution of 7-TBS-phthalide **197**, 26 (2.59 g, 9.77 mmol) in anhydrous DCM (100 mL) was treated with the dropwise addition of DIBAL (1M in hexanes, 9.87 mL, 9.87 mmol), via syringe pump over 4h. The reaction was stirred at –78 ^oC for a furtherh, and was then diluted with Et_2O (75 mL) and quenched by the successive addition of water (0.5 mL), 15% aq. NaOH solution (0.5 mL) and water (1.3 mL). The resultant slurry was allowed to warm up to RT and stirred for 30 min. Anhydrous Na_2SO_4 was added, and the resulting suspension was stirred for a further 30 min. The solids were removed by filtration, and the clear solution concentrated under reduced pressure to afford the crude lactol intermediate, which was dissolved immediately in anhydrous MeOH (50 mL) in the presence of 4 Å molecular sieves and treated with $TsOH.H_2O$ (93 mg, 0.49 mmol). The resultant solution was stirred at RT until completion as indicated by TLC analysis (30 min). The reaction mixture was neutralized to pH 7 by the addition of sat'd aq. K_2CO_3 solution and the 4 Å molecular sieves were removed by filtration through cotton wool. The solvent was evaporated under reduced pressure and the crude residue was taken up in Et_2O (100 mL), washed with water (2 × 50 mL), sat'd aq. Na_2SO_4 (20 mL) and brine (2 × 20 mL) and was then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude oil which was purified by flash column chromatography, elution with 5% Et_2O:petroleum ether, to afford 7-TBS-phthalan **198** (1.32 g, 4.69 mmol, 48%) as a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.24 (6H, s, $(CH_3)_2Si$), 1.02 (9H, s, $(CH_3)_3CSi$), 3.45 (3H, s, CH_3OCH), 4.97 (1H, d, *J* = 12.7, $CH(H)OC(OCH_3)$), 5.19 (1H, d, *J* = 12.7, $CH(H)OC(OCH_3)$), 6.17 (1H, d, *J* = 1.6, $CHOCH_3$), 6.70 (1H, d, *J* = 8.0, ArH), 6.83 (1H, d, *J* = 7.4, ArH), 7.23 (1H, t, *J* = 7.7, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -4.4 (CH_3Si), -4.2 (CH_3Si), 18.1 ($C(CH_3)_3Si$), 25.6 ($(CH_3)_3CSi$), 54.7 (CH_3OCH), 72.4 ($CH_2OC(OCH_3)$, 106.6 ($CH(OCH_3)$), 113.6 ($C^{Ar}H$), 117.9 ($C^{Ar}H$),128.2 ($C^{Ar}CH(OCH_3)$,130.8 ($C^{Ar}H$),142.5 ($C^{Ar}CH_2O$), 151.5 ($C^{Ar}OSi$). *m/z* [Cl^+, isobutane] 281 $[M+H]^+$ (28%), HRMS found $[M+H]^+$ 281.1570, $C_{15}H_{25}O_3Si$ requires 281.1573. υ_{max} /cm^{-1} (film): 3069, 3041, 2954, 2929, 2896, 2859, 2826, 1600.

1-Methoxy-1,3-dihydroisobenzofuran **131**



131

Phthalide (5.00 g, 37.3 mmol) was dissolved in anhydrous DCM (150 mL) and cooled to –78 ^oC. DIBAL (1M in hexanes, 37.3 mL, 37.3 mmol) was added dropwise over 2H. The reaction was stirred until completion by TLC analysis. The reaction was diluted with Et_2O (150 mL) and quenched by the successive addition of water (1.5 mL), 15% aq. NaOH solution (1.5 mL) and water (3.8 mL) at –78 ^oC. The resultant slurry was stirred for 30 min, anhydrous Na_2SO_4 was added and the resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution evaporated under reduced pressure to afford the crude lactol intermediate as a pale yellow oil.

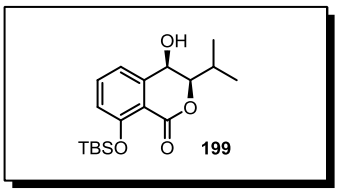
Methylation Method B: NaH and MeI

The crude lactol intermediate was dissolved in anhydrous THF (150 mL) and was transferred via cannulation to a solution of NaH (60% dispersion in mineral oil, 1.87 g, 47.0 mmol) in THF (150 mL) at –78 ^{o}C and stirred for 1Hr. MeI (filtered through basic alumina, 11.6 mL, 186 mmol) was added to the reaction mixture and the resulting solution was stirred for 12H. Once the reaction was complete according to TLC analysis, water (150 mL) was added and the mixture diluted with Et_2O (300 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (2 × 30 mL) and dried over anhydrous Na_2SO_4. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the desired phthalan **131** (3.45g, 23.0 mmol, 62%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.47 (3H, s, CH_3O), 5.08 (1H, d, *J* = 12.7, CH_2), 5.25 (1H, d, *J* = 12.7, CH_2), 6.22 (1H, d, *J* = 1.7, $CHOCH_3$), 7.25-7.44 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 54.2 (CH_3O), 72.3 (CH_2), 107.6 ($CHOCH_3$), 121.1 ($C^{Ar}H$), 123.0 ($C^{Ar}H$), 127.7 ($C^{Ar}H$), 129.2 ($C^{Ar}H$), 137.4 ($C^{Ar}CHOCH_3$), 140.0 ($C^{Ar}CH_2O$). *m/z* [Cl^+, isobutane] 180 $[M+H]^+$ (100%). HRMS found $[M]^+$ 151.0757. $C_9H_{11}O_2$ requires 151.0759. υ_{max} /cm^{-1} (film): 2927, 2871, 2828, 1693, 1614. The data observed is in accordance with literature values.[33]

Methylation Method B: TsOH in MeOH

Alternatively, the lactol intermediate was dissolved in anhydrous methanol (100 mL) in the presence of 4 Å molecular sieves. To the stirring solution, $TsOH.H_2O$ (70.0 mg, 0.37 mmol) was added and the resultant solution was stirred at room temperature for 2h. Completion of the reaction was indicated by TLC analysis. The solution was neutralized to pH 7 by the addition of sat'd aq. K_2CO_3 solution before the 4 Å molecular sieves were removed by filtration. The solvent was evaporated under reduced pressure and the resultant residue was taken up in EtO (100 mL), washed with water (2 × 30 mL), sat'd aq. $NaHCO_3$ solution (30 mL) and brine (2 × 50 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the desired phthalan **131** (4.51 g, 30.0 mmol, 81%) as a colourless oil.

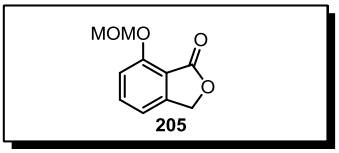
(±)-(3*R*,4*R*)-8-(*Tert*-butyldimethylsilyloxy)-4-hydroxy-3-isopropylisochroman-1-one **199**



Using general procedure 1B, a solution 7-TBS-phthalan **198** (833 mg, 2.97 mmol) in anhydrous THF (16 mL) was treated with $^{i}Pr_2NH$ (42 µL, 0.30 mmol), MeLi (1.6 M in Et_2O, 3.90 mL, 6.24 mmol) and *iso*butyraldehyde (323 µL, 3.57 mmol) to generate the α-hydroxy isobenzofuran intermediate. The oxidative rearrangement was performed using *m*CPBA, (77%, 732 mg, 3.27 mmol) in anhydrous DCM (16 mL) to afford the keto-lactol intermediate. Oxidation was performed in anhydrous DCM (15 mL) with TEMPO (93 mg, 0.60 mmol) and BAIB (3.06 g, 9.49 mmol) followed by filtration through a plug of silica, elution with 20% Et_2O:petroleum ether, to generate the keto-lactone intermediate. Using general procedure 2B, the reduction was performed in anhydrous MeOH (15 mL) with $NaBH_4$ (169 mg, 4.46 mmol). Purification via flash

column chromatography, elution with 0-30% Et_2O:petroleum ether, afforded 8-TBS-isochromanone **199** (600 mg, 1.78 mmol, 60% from 7-TBS-phthalan **198**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.23 (6H, d, *J* = 7.8, $(CH_3)_2Si$), 1.03 (9H, s, $(CH_3)_3CSi$), 1.06 (3H, d, *J* = 6.8, CH_3), 1.16 (3H, d, *J* = 6.6, CH_3),2.21 (1H, d, *J* = 7.6, OH), 2.25-2.34 (1H, m, $CH(CH_3)_2$), 3.88 (1H, d, *J* = 9.8, $CH(O_2C)$), 4.67 (1H, d, *J* = 7.4 CH(OH), 6.94 (1H, d, *J* = 8.2, ArH), 7.0 (1H, d, *J* = 7.3, ArH), 7.44 (1H, d, *J* = 7.9, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -4.3 ($(CH_3)_2Si$),18.2 (CH_3), 18.5 (CH_3), 19.3 ($C(CH_3)_3Si$), 25.8 ($(CH_3)_3CSi$), 28.5 ($CH(CH_3)_2$), 66.1 (CH(OH)), 85.4 ($CH(O_2C)$), 115.2 ($C^{Ar}CO_2$), 120.5 (ArH), 122.8 (ArH), 134.6 (ArH), 142.6 ($C^{Ar}CH(OH)$), 157.8 ($C^{Ar}OSi$), 162.0 (CO_2). *m/z* [CI^+, isobutane] 337 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 337.1834, $C_{18}H_{29}O_4Si$ requires 337.1835. υ_{max} /cm^{-1} (film): 3408, 2958, 2930, 2859, 1715, 1598, 1581. MP: 108-110 °C.

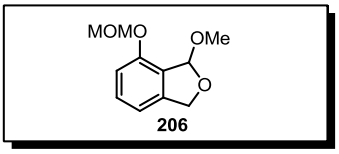
7-(Methoxymethoxy)phthalide **205**



205

7-hydroxyphthalide **184** (1.00 g, 6.66 mmol) was dissolved in anhydrous DCM (33 mL) to which DIPEA (2.82 mL, 20.0 mmol) was added. The reaction mixture was cooled to 0 °C and MOMBr (1.09 mL, 13.32 mmol) was added and stirred for 15 min before being warmed to room temperature and stirred for a further 16h. Water (40 mL) was added before extraction with DCM (3 × 100 mL). The combined organic extracts were washed with water (2 × 40 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated, to yield the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-50% DCM:petroleum ether, afforded the desired product, 7-MOM-phthalide **205** (1.07 g, 5.52 mmol, 83%) as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.53 (3H, s, CH_3O), 5.24 (2H, s, CH_2O_2C), 5.38 (1H, s, CH_2(OMe)OAr), 7.06 (1H, d, *J* = 7.5, ArH), 7.19 (1H, d, *J* = 8.3, ArH) 7.58 (1H, t, *J* = 7.9, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 56.6 (OCH_3), 68.7 ($ArCH_2O$), 94.8 (CH_2(OMe)OAr), 114.2 ($C^{Ar}CO_2$), 114.7 ($C^{Ar}H$),114.9 ($C^{Ar}H$), 136.1 ($C^{Ar}H$), 149.2 ($C^{Ar}CH_2O_2C$), 156.4 ($C^{Ar}OCH_2OCH_3$), 168.9 ($ArCO_2$). *m/z* [CI^+, isobutane] 195 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 195.0657, $C_{10}H_{11}O_4$ requires 195.0657. υ_{max} /cm^{-1} (film): 2939, 2908, 2852, 2829, 1765, 1614, 1603. MP: 104-107 °C. The data observed is in accordance with literature values.[161]

1-Methoxy-7-(methoxymethoxy)-1,3-dihydroisobenzofuran **206**

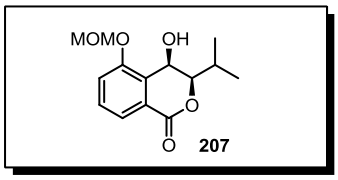


206

7-hydroxyphthalide **184** (929 g, 4.78 mmol) was dissolved in anhydrous DCM (48 mL) and cooled to –78 °C. DIBAL (1 M in hexanes, 4.78 mL, 4.78 mmol) was added dropwise over 3h. The reaction was diluted with DCM and quenched by the successive addition of water (0.2 mL), 15% aq. NaOH solution (0.2 mL) and water (0.5 mL) at –40 °C. The resultant slurry was warmed to room temperature and stirred for 30 min, anhydrous Na_2SO_4 was added and the resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution evaporated under reduced pressure. The crude lactol intermediate was dissolved in anhydrous MeOH (25 mL) in the presence of 4 Å molecular sieves. To the stirring solution, $TsOH.H_2O$ (46 mg, 0.24 mmol) was added and the resultant solution was stirred at room temperature for 30 min. Completion of the reaction was indicated by TLC analysis. The solution was neutralized to

pH 7 by the addition of sat'd aq. $NaHCO_3$ solution before the 4 Å molecular sieves were removed by filtration. The resultant solution was extacted with Et_2O (3 × 80 mL) and the resultant organics were washed with water (2 × 50 mL), sat'd aq. $NaHCO_3$ solution (20 mL) and brine (40 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product. Purification by flash column chromatography, elution with 0-15% Et_2O:petroleum ether, afforded the desired product, 7-MOM-phthalan **206** (642 mg, 3.06 mmol, 64%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.44 (3H, s, CH_3O), 3.48 (3H, s, CH_3O), 4.99 (1H, d, *J* = 12.8, CH_2O_2C), 5.19-5.27 (3H, m, CH_2O_2C (1H) & CH_2(OMe)OAr (2H)), 6.26 (1H, d, *J* = 1.7, CH(OMe)), 7.89 (1H, d, *J* = 7.4, ArH), 7.00 (1H, d, *J* = 8.1, ArH), 7.30 (1H, t, *J* = 7.8, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 54.3 (CH_3OCH), 56.1 (CH_3OCH_2O), 72.5 ($ArCH_2O$), 94.2 (CH_2(OMe)OAr), 106.2 (CH(OCH_3)), 113.2 ($C^{Ar}H$) 114.3 ($C^{Ar}H$), 126.0 ($C^{Ar}CH(OCH_3)$), 131.1 ($C^{Ar}H$),142.5 ($C^{Ar}CH_2O$), 152.8 ($C^{Ar}OCH_2OCH_3$). *m/z* [Cl^+, isobutane] 211 $[M+H]^+$(100%), HRMS found $[M+H]^+$ 211.0968, $C_{11}H_{15}O_4$ requires 211.0970. υ_{max} /cm^{-1} (film): 2929, 2905, 2870, 2827, 1618, 1600.

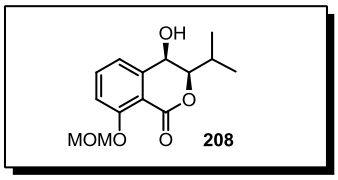
(3*R*,4*R*)-4-Hydroxy-3-isopropyl-5-(methoxymethoxy)isochroman-1-one **207**



207

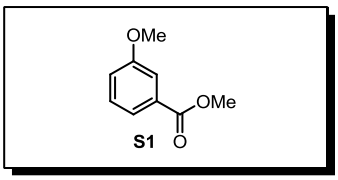
Using general procedure 1A, starting from a 7-MOM-phthalan **206** (538 mg, 2.56 mmol) in anhydrous THF (16 mL) with DIPEA (36 µL, 0.26 mmol), MeLi (1.6 M in Et_2O, 3.36 mL, 5.38 mmol) and isobutyraldehyde (279 µL, 3.07 mmol) to generate the α-hydroxyisobenzofuran intermediate. The oxidative rearrangement was performed using *m*CPBA, (77%, 632 mg, 2.82 mmol) in anhydrous DCM (16 mL) to afford the keto-lactol intermediate. Oxidation was performed in anhydrous DCM (13 mL) with TEMPO (80 mg, 0.51 mmol) and BAIB (2.60 g, 8.19 mmol) followed by filtration through a plug of silica, elution with 100% DCM to afford the keto-lactone intermediate. According to general procedure 2B, reduction was performed in anhydrous MeOH (9 mL) with $NaBH_4$ (104 mg, 2.74 mmol) at –78 °C. The crude products were purified by flash column chromatography, elution with 0-5% Et_2O: DCM, afforded 5-MOM-isochromanone **207** (112 mg, 0.42 mmol, 16% from 7-MOM-phthalan **206**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (3H, d, *J* = 6.8, CH_3), 1.21 (3H, d, *J* = 6.6, CH_3), 2.14 (1H, d, *J* = 6.1, OH), 2.34-2.43 (1H, m, $CH(CH_3)_2$), 3.53 (3H, s, CH_3O), 3.95 (1H, dd, *J* = 9.8, 1.8, $CH(O_2C)$), 5.12 (1H, d, *J* = 4.2, CH(OH), 5.24 (1H, d, *J* = 6.8, CH_2(OMe)OAr), 5.29 (1H, d, *J* = 6.8, CH_2(OMe)OAr), 7.387.46 (2H, m, ArH) 7.81 (1H, dd, *J* = 7.8, 2.8, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.3 (CH_3), 19.4 (CH_3), 28.7 ($CH(CH_3)_2$), 56.6 (CH_3O), 59.2 (CH(OH)), 86.5 ($CH(O_2C)$), 95.4 (CH_2(OMe)OAr), 120.4 ($C^{Ar}H$), 123.7 ($C^{Ar}H$), 125.5 ($C^{Ar}C$(OH)), 130.1 ($C^{Ar}CO_2$), 130.4 ($C^{Ar}H$), 153.9 ($C^{Ar}OCH_2OCH_3$), 164.9 (CO_2). *m/z* [Cl^+, isobbutane] 267 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 267.1238, $C_{14}H_{19}O_5$ requires 267.1232. υ_{max} /cm^{-1} (film): 3438, 2963, 2876, 2829, 1713, 1593. MP: 122-124 °C.

(3*R*,4*R*)-4-Hydroxy-3-isopropyl-8-(methoxymethoxy)isochroman-1-one **208**



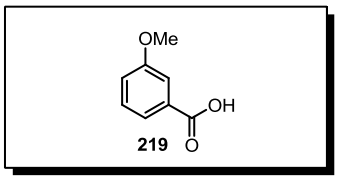
Further elution with 10% Et_2O:DCM afforded 8-MOM-isochromanone **208** (222 mg, 0.83 mmol, 32% from 7-MOM-phthalan **206**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.07 (3H, d, *J* = 6.8, CH_3), 1.17 (3H, d, *J* = 6.6, CH_3), 2.19 (1H, s, OH), 2.25-2.35 (1H, m, $CH(CH_3)_2$), 3.52 (3H, s, CH_3O), 3.91 (1H, dd, *J* = 9.8, 1.3, $CH(O_2C)$), 4.71 (1H, s, CH(OH), 5.27 (1H, d, *J* = 7.0, CH_2(OMe)OAr), 5.32 (1H, d, *J* = 7.0, CH_2(OMe)OAr), 7.07 (1H, dd, *J* = 7.4, 0.7, ArH), 7.26 (1H, dd, *J* = 8.5, 0.8, ArH), 7.50-7.52 (1H, m, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.2 (CH_3), 19.4 (CH_3), 28.4 ($CH(CH_3)_2$), 56.6 (CH_3O), 66.0 (CH(OH)), 85.6 ($CH(O_2C)$), 95.0 (CH_2(OMe)OAr), 113.8 ($C^{Ar}C$(OH)), 117.4 ($C^{Ar}H$), 121.1 ($C^{Ar}H$), 135.0 ($C^{Ar}H$), 142.8 ($C^{Ar}CO_2$),158.7 ($C^{Ar}OCH_2OCH_3$), 161.9 (CO_2). *m/z* [CI^+, isobutane] 267 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 267.1234, $C_{14}H_{19}O_5$ requires 267.1232. υ_{max} /cm^{-1} (film): 3443, 2963, 2933, 2875, 2829, 2249, 1709, 1600, 1587. MP: 122-124 ^oC.

Methyl 3-methoxybenzoate **S1**



3-Hydroxybenzoic acid (440 mg, 3.19 mmol) was dissolved in acetone (16 mL) to which K_2CO_3 (1.32 g, 9.56 mmol) and dimethyl sulphate (1.21 mL, 12.7 mmol) was added. The reaction mixture was stirred at reflux for 1h before being cooled to RT and filtered. From the filtrate the solvent was evaporated under reduced pressure and the resultant residue was taken up in Et_2O (150 mL) and washed with water (2 × 50 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-10% Et_2O:petroleum ether, afforded the desired product, methyl 3-methoxybenzoate (503 mg, 3.03 mmol, 95%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.85 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArCO_2CH_3$), 7.10 (1H. dd, *J* = 8.2, 1.8 ArH), 7.34 (1H, t, *J* = 7.9, ArH), 7.56 (1H, s, ArH), 7.63 (1H, d, *J* = 7.6, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.2 (H_3CO_2CAr), 55.4 ($ArOCH_3$), 113.9 ($C^{Ar}H$), 119.5 ($C^{Ar}H$), 122.0 ($C^{Ar}H$), 129.4 ($C^{Ar}H$), 131.5 ($C^{Ar}CO_2CH_3$), 159.6 ($C^{Ar}OCH_3$), 167.0 (CO). *m/z* [EI^+] 166 $[M]^+$ (58%), HRMS found $[M]^+$ 166.0629, $C_9H_{10}O_3$ requires 166.0630. υ_{max} /cm^{-1} (film): 3078, 3002, 2952, 2838, 2096, 1722, 1602, 1587. The data observed is in accordance with literature values.[162]

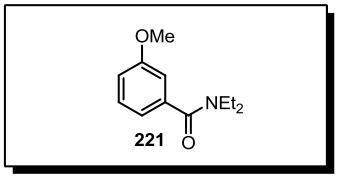
3-Methoxybenzoic acid **219**



Methyl-3-methoxybenzoate **S1** (503 mg, 3.03 mmol) was dissolved in MeOH (10 mL) to which 15% aq. NaOH solution (6 mL) was added and the resultant solution was stirred for 12h at RT. The solvent was evaporated under reduced pressure and the crude solid was taken up in water

(50 mL) and neutralized and adjusted to pH 5 by the addition of concentrated HCl, before being extracted with EtOAc (3 × 100 mL). The combined organics were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the desired benzoic acid **219** (404 mg, 2.66 mmol, 88%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ: 3.84 (3H, s, $ArOCH_3$), 7.14 (1H, ddd, *J* = 8.3, 2.7, 1.0 ArH), 7.37 (1H, t, *J* = 7.9, ArH), 7.54 (1H, dd, *J* = 2.6, 1.5, ArH), 7.60 (1H, dt, *J* = 5.2, 1.3, ArH). ^{13}C NMR (CD_3OD, 400 MHz) δ: 55.9 ($ArOCH_3$), 115.5 ($C^{Ar}H$), 120.0 ($C^{Ar}H$), 123.0 ($C^{Ar}H$), 130.5 ($C^{Ar}H$), 133.3 ($C^{Ar}CO_2H$), 161.2 (CH_3OAr), 169.8 ($ArCO_2H$). *m/z* [Cl^+, isobutane] 153 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 166.0555, $C_8H_9O_3$ requires 153.0552. υ_{max} /cm^{-1} (film): 3049, 2974, 2952, 2845, 1683, 1609, 1585. MP: 107-109 °C. The data observed is in accordance with literature values.[163]

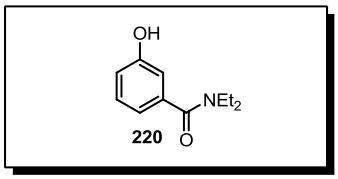
N,N-Diethyl-3-hydroxybenzamide **221**



221

$SOCl_2$ (1.70 mL, 23.28 mmol) was added to 3-methoxybenzoic acid **219** (253 mg, 1.66 mmol) and stirred under argon. DMF (10.3 µL, 0.10 mmol) was added dropwise after which vigorous effervescence occurred. The solution was stirred at reflux for 1h at which time no further effervescence was visible. The solution was cooled to RT and excess $SOCl_2$ was removed under reduced pressure and was azeotroped with toluene (3 × 15 mL). The colourless oil obtained was dissolved in DCM (3 mL), cooled to 0 °C and treated slowly with Et_2NH (0.64 mL, 6.15 mmol) and stirred for 1h before being concentrated under reduced pressure. The residue was dissolved in DCM (120 mL) and washed with water (3 × 25 mL) and brine (2 × 5 mL) before being dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude product as a brown oil. Purification by flash column chromatography, elution with 0-30% Et_2O:DCM, afforded the desired benzamide **221** (293 mg, 1.41 mmol, 85%), as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (3H, br. s, CH_3CH_2N), 1.23 (3H, br. s, CH_3CH_2N), 3.26 (2H, br. s, NCH_2CH_3), 3.53 (2H, br. s, NCH_2CH_3), 3.81 (3H, s, OCH_3), 6.89-6.93 (3H, m, ArH), 7.26-7.30 (1H, app. td, *J* = 7.8, 0.5, ArH), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.9 (CH_3CH_2N), 14.3 (CH_3CH_2N), 39.2 (NCH_2CH_3), 43.3 (NCH_2CH_3), 55.3 (OCH_3), 111.7 ($C^{Ar}H$), 115.0 ($C^{Ar}H$), 118.4 ($C^{Ar}H$), 129.5 ($C^{Ar}H$), 138.6 ($C^{Ar}CON$), 159.6 ($C^{Ar}OCH_3$), 171.0 (CON). *m/z* [EI^+] 207 $[M]^+$ (100%), HRMS found $[M]^+$ 207.1250, $C_{12}H_{17}NO_2$ requires 207.1259. υ_{max} /cm^{-1} (film): 2972, 2934, 2854, 1636. The data observed is in accordance with literature values.[164]

N,N-diethyl-3-hydroxybenzamide **220**

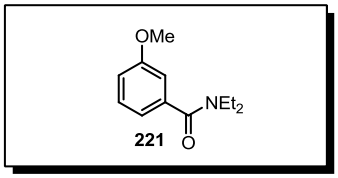


220

$SOCl_2$ (8.35 mL, 115 mmol) was added to 3-hydroxybenzoic acid (1.13 g, 8.18 mmol) and the mixture was stirred under argon. DMF (21.0 µL, 0.27 mmol) was then added dropwise which caused a vigorous effervescence to take place. The solution was then stirred at reflux for 1h after which time no further effervescence was visible. The solution was cooled down to RT, and the excess $SOCl_2$ was removed under reduced pressure, with tolune azeotroping (3 × 70 mL). The crude colourless oil obtained was dissolved in anhydrous DCM (10 mL), cooled to 0 °C

and treated slowly with Et_2NH (3.13 mL, 30.3 mmol). The resulting solution was then stirred for 60 min before being concentrated under reduced pressure. The crude residue was dissolved in DCM (300 mL) and washed with water (3 × 50 mL), brine (2 × 30 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum yielded a brown oil which was purified by flash column chromatography, elution with 0-50% Et_2O:DCM, to yield benzamide **220** (1.50 g, 7.77 mmol, 95%), as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.05 (3H, br. t, *J* = 6.2, CH_3), 1.21 (3H, br. t, *J* = 6.3, CH_3), 3.22 (2H, br. d, *J* = 6.6, CH_2), 3.51 (2H, br. d, *J* = 6.6, CH_2), 6.74 (2H, d, *J* = 7.9, ArH), 6.81 (1H, s, ArH), 7.11 (1H, t, *J* = 7.8, ArH), 8.85 (1H, s, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.8, 14.1, 39.6, 43.6, 114.1, 117.0, 117.1, 129.5, 137.1, 157.1, 172.2. *m/z* [Cl^+, isobutane] 194 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 194.1182, $C_{11}H_{16}NO_2$ requires 194.1181. υ_{max} /cm^{-1} (film): 3247, 2976, 2937, 2874, 2806, 1609, 1510. The data observed is in accordance with literature values.[165]

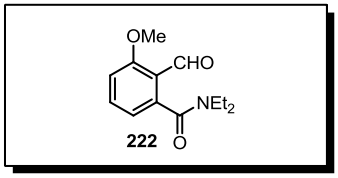
N,N-Diethyl-3-hydroxybenzamide **221**



221

Benzamide **220** (1.41 g, 7.27 mmol) was dissolved in anhydrous acetone (18 mL) and treated sequentially with K_2CO_3 (1.51 g, 10.9 mmol) and dimethyl sulphate (1.17 mL, 12.4 mmol). The reaction mixture was stirred at reflux for 18h before being cooled down to RT and filtered. The filtrate was evaporated under reduced pressure, and the resultant residue was taken up in DCM (300 mL) and washed with water (2 × 50 mL), brine (50 mL), dried over Na_2SO_4 and the solvent was evaporated to yield a crude colourless oil. Purification of the crude residue by flash column chromatography, elution with 0-15% Et_2O:DCM, afforded benzamide **221** (1.40 g, 6.76 mmol, 93%), as a colourless oil. The spectral and physical data obtained for **221** matched that obtained when **221** was obtained from 3-methoxybenzoic acid **219**.

N,N-Diethyl-2-formyl-3-methoxybenzamide **222**

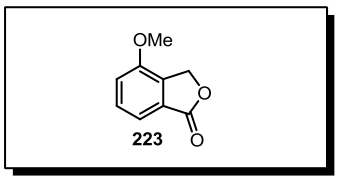


222

An oven dried flask was charged with anhydrous Et_2O (40 mL) and cooled to –78 ^{o}C under an argon atmosphere. Freshly distilled TMEDA (4.72 mL, 31.6 mmol) and ^{s}BuLi (1.4 M in ^{c}hex, 22.6 mL, 31.6 mmol) were added in quick succession, and the resulting mixture was and stirred for 15 min. A –78 ^{o}C solution of benzamide **221** (5.47 g, 26.37 mmol) in anhydrous Et_2O (40 mL), was transferred via cannular into the ^{s}BuLi/TMEDA solution and the resulting mixture was stirred at –78 ^{o}C for 1h. DMF (2.55 mL, 33.0 mmol) was then added dropwise with stirring at –78 ^{o}C and the reaction was stirred for a further 5 min before allowing the reaction to warm up to RT. The reaction was stirred at RT for 45 min, and then cooled down to 0 ^{o}C after which the reaction was quenched with water (60 mL). The pH of the solution was then adjusted to pH 5-6 through the careful addition of 6 M aq. HCl solution The phases were then separated and the organic layer was washed with water (2 × 25 mL) and brine (40 mL) before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude oil. The crude residue was purified by flash chromatography, elution with 0-40% EtOAc:petroleum ether, to

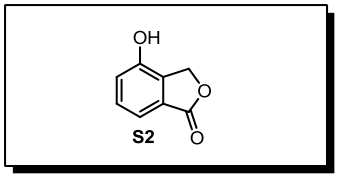
yield benzaldehyde **222** (2.98 g, 12.7 mmol, 48%), as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (3H, t, *J* = 7.2, CH_3CH_2N), 1.31 (3H, t, *J* = 7.1, CH_3CH_2N), 3.05 (2H, q, *J* = 7.1, NCH_2CH_3), 3.57 (2H, q, *J* = 7.1, NCH_2CH_3), 3.93 (3H, s, OCH_3), 6.83 (1H, d, *J* = 7.5, ArH), 6.99 (1H, d, *J* = 8.5, ArH), 7.53 (1H, dd, *J* = 8.4, 7.6, ArH), 10.47 (1H, d, *J* = 0.3, ArCHO). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.1 (CH_3CH_2N), 13.5 (CH_3CH_2N), 38.6 (NCH_2CH_3), 42.4 (NCH_2CH_3), 56.0 (OCH_3), 111.7 ($C^{Ar}H$), 119.1 ($C^{Ar}H$), 121.2 ($C^{Ar}CHO$), 135.6 ($C^{Ar}H$), 139.4 ($C^{Ar}CON$), 162.1 ($C^{Ar}OCH_3$), 169.7 (CON), 189.3 (ArCHO). *m/z* [FAB (+ve), NOBA] 236 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 236.1288, $C_{13}H_{18}NO_3$ requires 236.1287. υ_{max} /cm^{-1} (film): 3360, 2974, 2936, 2873, 1693, 1637, 1579. The data observed is in accordance with literature values.[51]

4-Methoxyphthalide **223**



Benzaldehyde **222** (1.68 g, 7.17 mmol) was dissolved in anhydrous MeOH (36 mL) and the resulting solution was cooled down to 0 °C. $NaBH_4$ (531 mg, 14.3 mmol) was slowly added to the solution, and the resulting mixture was warmed to RT and stirred until completion by TLC analysis (45 min). The solution was then cooled back down to 0 °C and its pH was adjusted to pH 4-5 by the addition of 6 M aq. HCl solution. The mixture was then heated at reflux for 16h, during which a white precipitate formed. The solvent was removed under reduced pressure, and the resultant solid was dissolved in DCM (150 mL), washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Trituration from petroleum ether afforded 4-methoxyphthalide **223** (938 mg, 5.71 mmol, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.90 (3H, s, OCH_3), 5.23 (2H, s, $ArCH_2O_2C$), 7.07-7.11 (1H, m, ArH), 7.44-7.47 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 55.6 (OCH_3), 68.2 ($ArCH_2O$), 114.8 ($C^{Ar}H$), 117.2 ($C^{Ar}H$), 127.3 ($C^{Ar}CO_2$), 130.8 ($C^{Ar}H$), 134.9 ($C^{Ar}CH_2O_2C$), 154.2 ($C^{Ar}OCH_3$), 171.2 ($ArCO_2$). *m/z* [EI^+] 164 $[M^+]$ (100%), HRMS found $[M^+]$ 164.0474, $C_9H_8O_3$ requires 164.0473. υ_{max} /cm^{-1} (film): 3110, 3085, 2980, 2948, 2927, 2872, 2848, 1771, 1609. MP: 117-120 °C. The data observed is in accordance with literature values.[51]

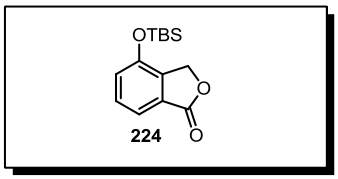
4-Hydroxyphthalide **223**



A solution of 4-methoxyphthalide **223** (2.78 g, 16.9 mmol) in anhydrous DMF (26 mL) and was treated with iodocyclohexane (11.0 mL, 84.7 mmol) and the resultant solution was heated at reflux until reaction completion, indicated by TLC analysis (78h). The solution was cooled down to RT, taken up in water (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with sat'd aq. $Na_2S_2O_3$ solution (3 × 150 mL), brine (3 × 50mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography, elution with 0-6% MeOH:DCM, afforded the desired 4-hydroxyphthalide **S2** (2.02 g, 13.5 mmol, 79%) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 5.29 (2H, s, CH_2), 7.11 (1H, d, *J* = 7.8, ArH), 7.27 (1H, d, J =7.4, ArH), 7.40 (1H, t, *J* = 7.6, ArH), 10.44 (1H, br. s, ArOH). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 68.2 ($ArCH_2O$), 115.3 ($C^{Ar}H$),

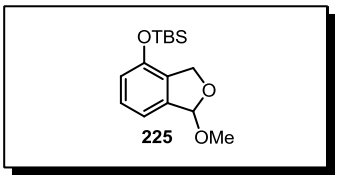
120.1 ($C^{Ar}H$), 126.7 ($C^{Ar}CO_2$), 130.6 ($C^{Ar}H$), 133.3 ($C^{Ar}CH_2O_2C$), 152.3 ($C^{Ar}OH$), 170.9 ($ArCO_2$). *m/z* [Cl^+ isobutene] 151 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 151.0394, $C_8H_7O_3$ requires 151.0395. υ_{max} /cm^{-1} (film): 3199, 2966, 2861, 2831, 1728, 1612. MP: 261-263 ^oC. The data observed is in accordance with literature values.[64]

4-(*Tert*-butyldimethylsilyloxy)phthalide **224**



A solution of 4-hydroxyphthalide **S2** (1.00 g, 6.66 mmol) in anhydrous DMF (20 mL) was treated sequentially with imidazole (906 g, 13.3 mmol) and TBSCl (1.21 g, 7.99 mmol). The resultant solution was stirred at RT under argon until completion as indicated by TLC analysis (16h). The reaction was quenched with water (80 mL), and the solution was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (50 mL), dried over $NaSO_4$ and concentrated under reduced pressure to yield a crude white solid. Purification of the crude residue by flash column chromatography, elution with 0-5% EtOAc:hexane, yielded 4-TBS-phthalide **224** (1.35 g, 5.09 mmol, 76%) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.25 (6H, s, Me_2Si), 0.99 (9H, s, $(CH_3)_3CSi$), 5.22 (2H, s, CH_2O_2C), 7.04 (1H, dd, *J* = 7.9, 0.6, ArH), 7.39 (1H, t, *J* = 7.4, ArH) 7.50 (1H, d, *J* = 7.5, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -4.3 $(CH_3)_2Si$), 18.1 ($C(CH_3)_3Si$), 25.5 ($(CH_3)_3CSi$), 68.1 (CH_2O_2C), 118.3 ($C^{Ar}H$), 123.5 ($C^{Ar}H$), 127.7 ($C^{Ar}CO_2$),130.6 ($C^{Ar}H$), 137.3 ($C^{Ar}CH_2O$), 150.5 ($C^{Ar}OSi$), 171.2 ($ArCO_2$). *m/z* [Cl^+, isobutane] 265 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 265.1261, $C_{14}H_{21}O_3Si$ requires 265.1260. υ_{max} /cm^{-1} (film): 2954, 2931, 2885, 2859, 1774, 1607. MP: 38-40 ^oC.

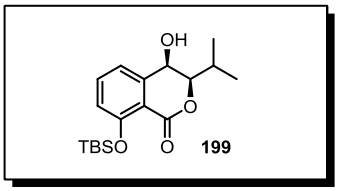
4-(*Tert*-butyldimethylsilyloxy)-1-methoxy-1,3-dihydroisobenzofuran **225**



A –78 ^oC solution of 4-TBS-phthalide **224** (1.25 g, 4.73 mmol) in anhydrous DCM (47 mL) was treated with the dropwise addition of DIBAL (1 M in hexanes, 5.00 mL, 5.00 mmol) via syringe pump, over 1h. Once the addition was complete, the reaction mixture was then stirred at –78 ^oC until completion as indicated by TLC analysis (1h). The reaction was then diluted with DCM (150 mL), and quenched by the successive addition of water (0.2 mL), 15% aq. NaOH solution (0.2 mL) and water (0.5 mL) at –40 ^oC. The resultant slurry was warmed up to RT and stirred for 30 min, anhydrous Na_2SO_4 was added, and the resulting suspension was stirred for a further 30 min. The solids were removed by filtration and the filtrate was concentrated under reduced pressure to afford the crude lactol intermediate, which was dissolved in anhydrous MeOH (23 mL) in the presence of 4 Å molecular sieves, treated with, $TsOH.H_2O$ (45 mg, 0.24 mmol), and the resulting solution was stirred at RT until completion as indicated by TLC analysis (60 min). The solution was neutralized to pH 7 by the addition of sat'd aq. $NaHCO_3$ solution before the 4 Å molecular sieves were removed by filtration. The filtrate was extracted with Et_2O (3 × 100 mL) and the combined organics phases were washed with water (2 × 25 mL), sat'd aq. $NaHCO_3$ solution (20 mL) and brine (20 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude oil that was then purified by flash

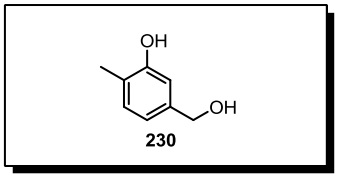
column chromatography, elution with 0-5% Et_2O:petroleum ether to yield 4-TBS-phthalan **225** (868 mg, 3.10 mmol, 65%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.21 (3H, s, CH_3Si), 0.22 (3H, s, CH_3Si), 0.98 (9H, s, $(CH_3)_3CSi$), 3.42 (3H, s, CH_3OCH), 5.02 (1H, d, *J* = 12.8, CH(H)), 5.16 (1H, dd, *J* = 12.8, 1.8, CH(H)), 6.18 (1H, d, *J* = 2.0, $CH(OCH_3)$), 6.77 (1H, d, *J* = 7.9, ArH), 6.99 (1H, d, *J* = 7.4, ArH), 7.22 (1H, t, *J* = 7.7, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -4.2 $(CH_3)_2Si$), -4.1 $(CH_3)_2Si$), 18.2 ($C(CH_3)_3Si$), 25.7 ($(CH_3)_3CSi$), 54.2 (CH_3OAr), 71.0 (CH_2), 108.1 ($CHOCH_3$), 115.8 ($C^{Ar}H$), 119.3 ($C^{Ar}H$), 129.5 ($C^{Ar}H$), 130.9 ($C^{Ar}CH(OCH_3)O$), 139.9 ($C^{Ar}CH_2O$), 150.1 ($C^{Ar}OCH_3$). *m/z* [CI^+, isobutane] 281 $[M+H]^+$ (37%), HRMS found $[M+H]^+$ 281.1574 $C_{15}H_{25}O_3Si$ requires 281.1573. υ_{max} /cm^{-1} (film): 2957, 2929, 2885, 2860, 2826, 1602.

(±)-(3*R*,4*R*)-8-(*Tert*-butyldimethylsilyloxy)-4-hydroxy-3-isopropylisochroman-1-one **199**



Using general procedure 1B a solution of 4-TBS-phthalan **225** (833 mg, 2.97 mmol) in anhydrous THF (16 mL) was treated with ^{i}Pr_2NH (42 µL, 0.30 mmol), MeLi (1.6 M in Et_2O, 3.90 mL, 6.24 mmol) and *iso*butyraldehyde (323 µL, 3.57 mmol) to generate the α-hydroxy-IBF intermediate. The oxidative rearrangement was performed using *m*CPBA (77%, 732 mg, 3.27 mmol) in anhydrous DCM (16 mL) to afford the keto-lactol intermediate. Oxidation of the lactol was performed in anhydrous DCM (15 mL) with TEMPO (93 mg, 3.06 mmol) and BAIB followed by filtration through a plug of silica gel eluting with 20% Et_2O:petroleum ether, to afford the keto-lactone intermediate. Using general procedure 2B, reduction was performed in anhydrous MeOH (15 mL) with $NaBH_4$ (169 mg, 4.46 mmol). Purification of the crude residue by flash column chromatography, elution with 0-30% Et_2O:petroleum ether, afforded the desired 8-TBS-isochromanone **199** (450 mg, 1.34 mmol, 45%) as a white solid. The spectral and physical data obtained for **199** matched that obtained when **199** was obtained from the regioisomeric 7-TBS-phthalan **198**.

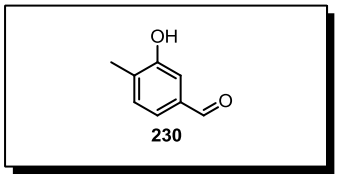
5-(Hydroxymethyl)-2-methylphenol **230**



4-Methylsalicyclic acid **229** (1.50 g, 9.86 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 °C under an atmosphere of argon. BH_3 (1 M in THF, 16.8 mL, 16.8 mmol) was added dropwise over 60 min via a syringe pump. The reaction was stirred for 12h at RT. The reaction was then quenched with 15% aq. NaOH solution (20 mL) at 0 °C and stirred for 20 min before being neutralized to pH 7 with dilute aq. HCl solution. The solution was then extracted with EtOAc (3 × 60 mL) and the resultant organic layer washed with water (15 mL), and brine (15 mL) before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography, elution with 0-25% diethyl ether:petroleum ether, afforded the desired product phenol (885 mg, 6.41 mmol, 65%) as a white crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.29 (3H, s, CH_3), 4.81 (2H, s, CH_2OH),

6.67 (1H, d, *J* = 7.6, ArH), 6.71 (1H, s, ArH), 6.91 (1H, d, *J* = 7.6, ArH), 7.21 (1H, s, ArOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.2 (CH_3), 64.4 (CH_2OH), 117.2 (ArH), 120.8 (ArH), 121.8 ($C^{Ar}Me$), 127.8 (ArH), 139.8 ($C^{Ar}CH_2OH$), 155.9 ($C^{Ar}OH$). *m/z* [EI$^+$] 138 [M]$^+$ (63 %), HRMS found [M]$^+$ 138.0683, $C_8H_{10}O_2$ requires 138.0681. υ_{max} /cm^{-1} (film): 3456, 3169, 3025, 2968, 2950, 2905, 1590. MP: 100-101 ^{o}C. The data observed is in accordance with literature values.[66]

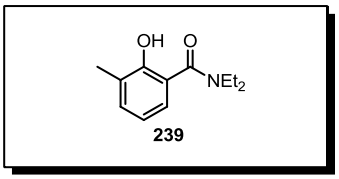
3-hydroxy-4-methylbenzaldehyde **230**



230

NEt_3 (1.70 mL, 12.2 mmol) and $SnCl_4$ (0.53 mL, 4.56 mmol) were added dropwise to a stirring solution of phenol **223** (420 mg, 3.04 mmol) in anhydrous MeCN and was stirred under an atmosphere of argon for 20 min. Paraformaldehyde (640 mg, 21.3 mmol) was added and the mixture was stirred at reflux for 17h after which the mixture was cooled, filtered and then extracted with Et_2O (3 × 100 mL). The resultant organic layer washed with water (50 mL), and brine (50 mL) before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a brown oil. Purification by flash column chromatography, elution with 0-20 % Et_2O: petroleum ether, afforded the undesired product, benzaldehyde **224** (33 mg, 0.20 mmol, 6%) as a white crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.36 (3H, s, CH_3), 6.78 (1H, s, ArH), 6.81 (1H, d, *J* = 8.0, ArH), 7.41 (1H, d, *J* = 7.8, ArH), 9.81 (1H, s, ArCHO), 11.03 (1H, s, ArOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.2 (CH_3), 116.7 (C^{Ar}), 117.6 ($C^{Ar}CH_3$), 120.1 (C^{Ar}), 132.6 (C^{Ar}), 147.9 ($C^{Ar}CHO$), 160.7 ($C^{Ar}OH$), 194.8 (CHO). *m/z* [EI$^+$] 136 [M]$^+$ (50 %), HRMS found [M]$^+$ 136.0524, $C_8H_8O_2$ requires 136.0525. υ_{max} /cm^{-1} (film): 3171, 2961, 2930, 2930, 2861, 1670, 1585, 1517. MP: 73-75 ^{o}C. The data observed is in accordance with literature values.[166]

N,N-Diethyl-2-hydroxy-3-methylbenzamide **239**

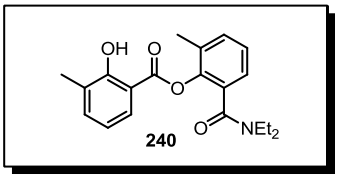


239

$SOCl_2$ (134 mL, 1840 mmol) was added to 3-methylsalicyclic acid **237** (20.0 g, 131 mmol) and stirred under argon at RT. DMF (340 µL, 4.34 mmol) was added dropwise, after which vigorous effervescence occurred. The solution was stirred for 1h at which time no further effervescence was visible. Excess $SOCl_2$ was removed under reduced pressure and was azeotroped with toluene (3 × 100 mL). The colourless oil obtained was dissolved in anhydrous DCM (164 mL), cooled to 0 ^{o}C and treated slowly with Me_2NH (50 mL, 486 mmol) and stirred for 60 min before being concentrated under reduced pressure. The residue was dissolved in DCM (400 ml) and washed with water (3 × 90 mL), sat'd aq. $NaHCO_3$ solution (100 mL) and saturated brine (2 × 70 ml) and concentrated under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography, elution with 0-10% Et_2O: petroleum ether gave the desired benzamide **239** (5.60 g, 27.0 mmol, 21%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (6H, t, *J* = 7.1, $(CH_3CH_2)_2N$), 2.24 (3H, s, CH_3Ar), 3.50 (4H, q, *J* = 7.1, $N(CH_2CH_3)_2$), 6.73 (1H, t, *J* = 6.7, ArH), 7.09 (1H, t, *J* = 7.1, ArH), 7.15 (1H, d, *J* = 7.2, ArH), 9.89 (1H, s, ArOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.4 (CH_3CH_2N), 16.0 ($ArCH_3$), 42.1 (NCH_2CH_3), 117.4 ($C^{Ar}CON$), 117.9 ($C^{Ar}H$), 124.8 ($C^{Ar}H$), 127.0 ($C^{Ar}CH_3$), 133.2 ($C^{Ar}H$), 156.9 ($C^{Ar}OH$), 171.9 (ArCON). *m/z* [EI$^+$] 207

$[M]^+$ (100%). HRMS found $[M+H]^+$ 207.1261, $C_{12}H_{17}NO_2$ requires 207.1259. υ_{max} /cm^{-1} (film): 3218, 3064, 2975, 2936, 2876, 1602, 1580. The data observed is in accordance with literature values.[167]

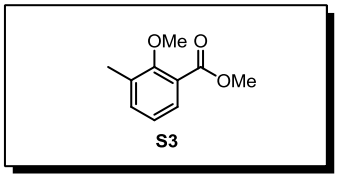
2-(Diethylcarbamoyl)-6-methylphenyl-2-hydroxy-3-methylbenzoate **240**



240

Further elution with 10-25% Et_2O:petroleum ether afforded ester **240** (6.88 g, 20.2 mmol, 31%) as a yellow crystalline solid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (3H, t, *J* = 7.1, (CH_3CH_2N), 1.10 (3H, t, *J* = 7.1, (CH_3CH_2N), 2.27 (3H, s, $ArOCH_3$), 2.30 (3H, s, $ArOCH_3$) 3.22-3.23 (2H, app. q, *J* = 7.0, $N(CH_2CH_3)$, 3.52-3.57 (2H, app. q, *J* = 7.0, $N(CH_2CH_3)$, 6.87 (1H, t, *J* = 7.7, ArH), 7.21 (1H, d, *J* = 7.0, ArH), 7.27 (1H, t, *J* = 7.6, ArH), 7.34 (1H, d, *J* = 7.3, ArH), 7.41 (1H, d, *J* = 7.1, ArH), 7.93 (1H, d, *J* = 7.9, ArH), 10.65 (1H, s, ArOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.3 (CH_3CH_2N), 14.0 (CH_3CH_2N), 15.7 ($ArCH_3$), 16.4 ($ArCH_3$), 38.5 (NCH_2CH_3), 42.8 (NCH_2CH_3), 110.5 ($C^{Ar}CO_2Ar$), 119.0 ($C^{Ar}H$), 124.6 ($C^{Ar}H$), 126.5 ($C^{Ar}H$), 126.8 ($C^{Ar}CON$), 128.1 ($C^{Ar}H$), 131.1 ($C^{Ar}CH_3$), 131.6 ($C^{Ar}H$), 131.9 ($C^{Ar}CH_3$), 137.4 ($C^{Ar}H$), 145.0 ($C^{Ar}O_2C$), 160.6 ($C^{Ar}OH$), 167.1 (ArCON), 168.6 ($ArCO_2$). *m/z* $[EI^+]$ 341 $[M]^+$ (100%). HRMS found $[M]^+$ 341.1625, $C_{20}H_{23}NO_4$ requires 341.1627. υ_{max} /cm^{-1} (film): 3218, 2974, 2933, 2873, 1736, 1685, 1638, 1615. MP: 93-95 ^oC.

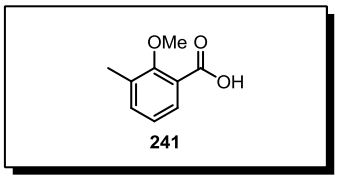
Methyl-2-methoxy-3-methylbenzoate **S3**



S3

A solution of benzoic acid **237** (20.0 g, 131.5 mmol) in anhydrous acetone (250 mL) was treated with anhydrous K_2CO_3 (52.7 g, 381.2 mmol) and dimethylsulfate (36.1 mL, 381.2 mmol). The resulting reaction mixture was stirred at reflux until completion by TLC analysis (16h). The reaction was cooled down to RT and the solid residue was removed by filtration. The solvent was removed under reduced pressure and the crude residue was taken up in water (1L), and stirred for 15 min before being extracted with EtOAc (3 × 500 mL).The combined organics were washed with water (800 mL) and brine (2 × 100 mL) before being dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to yield the crude product as a colourless oil. Purification by flash column chromatography, elution gradient 0-1% Et_2O:hexane, afforded benzoate **S3** (22.2 g, 124 mmol, 94%), as a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (3H, s, CH_3Ar), 3.83 (3H, s, CH_3OAr), 3.91 (3H, s, CH_3O_2CAr), 7.05 (1H, t, *J* = 7.7, ArH), 7.34 (1H, dd, *J* = 7.5, 0.9, ArH), 7.63 (1H, dd, *J* = 7.8, 1.9, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.2 (CH_3Ar), 52.3 (CH_3O_2CAr), 61.6 (CH_3OAr), 123.7 ($C^{Ar}H$), 124.7 ($C^{Ar}CO_2CH_3$), 129.3 ($C^{Ar}H$), 132.9 ($C^{Ar}CH_3$), 135.3($C^{Ar}H$), 158.5 ($C^{Ar}OCH_3$), 167.1(CO_2CH_3). *m/z* $[EI^+]$ 180 $[M]^+$ (68%), HRMS found $[M]^+$ 180.0785, $C_{10}H_{12}O_3$ requires 180.0786. υ_{max} /cm^{-1} (film): 2994, 2947, 1728, 1589, 1466, 1435. The data observed is in accordance with literature values.[168]

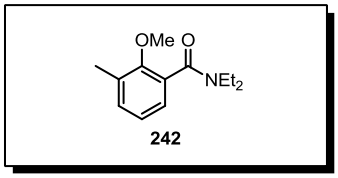
2-Methoxy-3-methylbenzoic acid **241**



241

Benzoate **S3** (22.2 g, 124 mmol) was dissolved in MeOH (250 mL) and treated with 15% aq. NaOH solution (100 mL). The resulting solution was stirred at RT (2h) and was then concentrated under reduced pressure. The crude residue was taken up in water (300 mL) and neutralized to pH 7 by the addition of 6 M aq. HCl solution, before being extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Trituration of the crude residue from petroleum ether, followed by filtration of the solid impurities gave a clear solution, which upon evaporation under reduced pressure yielded benzoic acid **241** (19.9 g, 120 mmol, 97%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.38 (3H, s, CH_3Ar), 3.93 (3H, s, CH_3OAr), 7.18 (1H, t, *J* = 7.7, ArH), 7.43 (1H, br. d, *J* = 7.4, ArH), 7.96 (1H, dd, *J* = 7.8, 1.8, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ pp: 16.1 (CH_3Ar), 62.3 (CH_3OAr), 122.1 ($C^{Ar}CO_2H$), 125.2 ($C^{Ar}H$), 130.9 ($C^{Ar}H$) 131.7 ($C^{Ar}CH_3$), 137.1 ($C^{Ar}H$), 157.9 ($C^{Ar}OCH_3$), 166.4 (CO_2H). *m/z* [EI^+] 166 $[M]^+$ (100%), HRMS found $[M]^+$ 180.0632, $C_9H_{10}O_3$ requires 166.0630. υ_{max} /cm^{-1} (film): 2955, 2928, 1697, 1593. MP: 82-84 °C. The data observed is in accordance with literature values.[169]

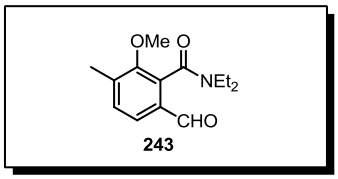
N,N-Diethyl-2-methoxy-3-methylbenzamide **242**



242

$SOCl_2$ (125 ml, 1.71 mol) was added to benzoic acid **241** (19.9 g, 120 mmol) and stirred under argon. DMF (306 µl, 3.96 mmol) was added dropwise, after which vigorous effervescence occurred. The solution was stirred for 1h at which time no further effervescence was visible. Excess $SOCl_2$ was removed under reduced pressure and was azeotroped with toluene (3 × 50 mL). The colourless oil obtained was dissolved in THF (100 mL), cooled to 0 °C and treated slowly with Et_2NH (45.8 ml, 443 mmol) and stirred for 15 min before being concentrated under reduced pressure. The residue was dissolved in DCM (400 ml) and washed with water (3 × 100 mL) and brine (3 × 77 mL) and concentrated under reduced pressure to give a brown oil. Purification by flash column chromatography, elution with 0-15% Et_2O:petroleum ether, afforded the desired product, benzamide **242** (1.92 g, 8.78 mmol, 91%), as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.01 (3H, t, *J* = 7.1, CH_3CH_2N), 1.25 (3H, t, *J* = 7.1, CH_3CH_2N), 2.28 (3H, s, $ArCH_3$), 3.12-3.17 (2H, app. dq, 12.2, 6.7, NCH_2CH_3), 3.34 (1H, m, NCH_2CH_3), 3.78 (4H, br. s, $ArOCH_3$, NCH_2CH_3), 6.99-7.06 (2H, m, ArH), 7.17 (1H, d, *J* = 7.0, ArH). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 12.8 (CH_3CH_2N), 13.9 (CH_3CH_2N), 16.0 ($ArCH_3$), 38.9 (NCH_2CH_3), 42.9 (NCH_2CH_3), 61.4 (OCH_3) 124.1 ($C^{Ar}H$), 125.2 ($C^{Ar}H$), 131.4 ($C^{Ar}CH_3$), 131.5 ($C^{Ar}CON$), 131.7 ($C^{Ar}H$), 154.1 ($C^{Ar}OCH_3$), 169.1 (CON). *m/z* [Cl^+, isobutane] 222 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 194.1495, $C_{13}H_{20}NO_2$ requires 222.1494. υ_{max} /cm^{-1} (film): 2973, 2935, 2873, 1634, 1596. The data observed is in accordance with literature values.[170]

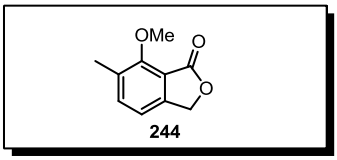
N,N-Diethyl-6-formyl-2-methoxy-3-methylbenzamide **243**



243

To an oven dried flask, anhydrous Et_2O (8 mL) was added and cooled to –78 ^{o}C under an atmosphere of argon. TMEDA (0.85 mL, 5.72 mmol) and ^{s}BuLi (4.08 mL, 1.4M, 5.72 mmol) were added and stirred for 15 min. A solution of benzamide **242** (1.05 g, 4.76 mmol) in anhydrous Et_2O (8 mL), cooled to –78 ^{o}C, was added dropwise to the ^{s}BuLi/TMEDA solution and stirred for 1h. DMF (0.46 mL, 5.95 mmol) was added dropwise with stirring at –78 ^{o}C for 5 min, before being allowed to rise to RT and stirred for a further 45 min. The resultant solution was cooled to 0 ^{o}C and quenched with water, before the solution was made mildly acidic (pH 5-6) via the careful addition of 6M aq. HCl solution. The organic layer was collected and was washed with water (2 × 20 mL) and brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product could be further purified by flash chromatography, elution with 1:1:1 Et_2O:petroleum ether:DCM to afford the benzaldehyde **243** (994 mg, 3.99 mmol, 84%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (3H, t, *J* = 7.2, CH_3CH_2N), 1.28 (3H, t, *J* = 7.1, CH_3CH_2N), 2.35 (3H, s, CH_3Ar), 3.06 (2H, qd, *J* = 7.2, 2.8, NCH_2CH_3), 3.53 (1H, dq, *J* = 13.6, 7.1, NCH_2CH_3), 3.69 (1H, dq, *J* = 13.6, 7.1, NCH_2CH_3), 3.79 (3H, s, OCH_3), 7.31 (1H, d, *J* = 7.9, ArH), 7.58 (1H, d, *J* = 7.8, ArH), 9.90 (1H, s, ArCHO). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.6 (CH_3CH_2N), 13.7 (CH_3CH_2N), 16.6 (CH_3Ar), 39.1 (NCH_2CH_3), 43.0 (NCH_2CH_3), 61.7 (OCH_3), 125.3 ($C^{Ar}H$), 131.7 ($C^{Ar}H$), 132.0 ($C^{Ar}CH_3$), 133.8 ($C^{Ar}CHO$), 139.3 ($C^{Ar}CON$), 154.5 ($C^{Ar}OCH_3$), 166.2 (CON), 190.1 (ArCHO). *m/z* [Cl^+, isobutane] 250 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 250.1444, $C_{14}H_{20}NO_3$ requires 250.1443. υ_{max} /cm^{-1} (film): 2978, 2936, 2871, 2833, 2747, 1701, 1634, 1592, 1572.

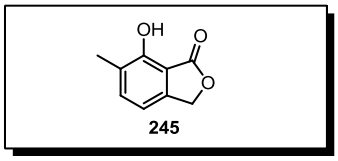
7-Methoxy-6-methylisobenzofuran-1(3*H*)-one **244**



244

Benzaldehyde **243** (994 mg, 7.17 mmol) was dissolved in MeOH (20 mL) and the resulting solution cooled down to 0 ^{o}C. $NaBH_4$ (295 mg, 3.99 mmol) was added slowly, and the reaction mixture was warmed up to RT and stirred for 45 min. The reaction was then acidified to pH 4-5 at 0 ^{o}C by the addition of aqueous 6 M aq. HCl solution, and the mixture was then heated at reflux for 16h during which a white precipitate formed. The solvent was removed under reduced pressure, and the resultant solid was dissolved in DCM (150 mL), washed with water (2 × 50 mL), brine (50 mL) and then dried over anhydrous Na_2SO_4. Solvent removal under reduced pressure gave a crude yellow solid, which was triturated from petroleum ether, to afford the phthalide **244** (583 mg, 3.27 mmol, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (3H, s, $ArCH_3$), 4.07 (3H, s, OCH_3), 5.22 (2H, s, $ArCH_2O_2C$), 7.04 (1H, d, *J* = 7.6, ArH), 7.47 (1H, d, *J* = 7.6, ArH).^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.6 ($ArCH_3$), 62.2 (OCH_3), 68.8 ($ArCH_2O$), 116.4 ($C^{Ar}H$), 116.9 ($C^{Ar}CO_2$), 131.6 ($C^{Ar}CH_2O_2C$), 137.5 ($C^{Ar}H$), 146.7 ($C^{Ar}CH_3$), 157.6 ($C^{Ar}OCH_3$), 168.9 ($ArCO_2$). *m/z* [El^+] 178 $[M^+]$ (71%), HRMS found $[M^+]$ 178.0627, $C_{10}H_{10}O_3$ requires 178.0630. υ_{max} /cm^{-1} (film): 2954, 2903, 2848, 1759, 1613, 1596. MP: 121-124 ^{o}C

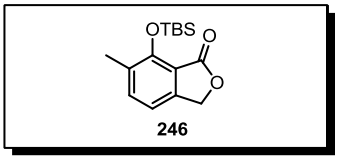
7-Hydroxy-6-methylphthalide **245**



245

A solution of phthalide **244** (0.46 g, 2.59 mmol) in anhydrous DMF (4 mL) was treated with iodocyclohexane (2.35 mL, 18.2 mmol), and the resultant solution was heated at reflux for 78h. The solution was then taken up in water (30 mL) and extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with sat'd aq. $Na_2S_2O_3$ solution (3 × 30 mL), brine (3 × 15ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Trituration of the crude residue from petroleum ether afforded hydroxyphthalide **245** (337 mg, 2.06 mmol, 79%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.29 (3H, s, CH_3), 5.28 (1H, s, CH_2), 6.86 (1H, d, *J* =7.5, ArH), 7.40 (1H, d, *J* = 7.5, ArH), 7.86 (1H, s, ArOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6 (CH_3), 70.5 ($ArCH_2O$), 110.5 ($C^{Ar}CO_2$), 112.8 ($C^{Ar}H$), 124.9 ($C^{Ar}CH_3$), 138.2 ($C^{Ar}H$), 144.1 ($C^{Ar}CH_2O_2C$), 154.6 ($C^{Ar}OH$), 173.1 ($ArCO_2$). *m/z* [EI^+] 164 $[M]^+$ (67%). HRMS found $[M]^+$ 164.0473, $C_9H_8O_3$ requires 164.0473. υ_{max} /cm^{-1} (film): 3438, 2958, 2924, 2871, 1743, 1630, 1609 1507. MP: 120-123 °C. The data observed is in accordance with literature values.[66]

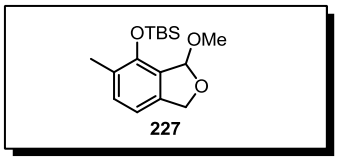
7-(*Tert*-butyldimethylsilyloxy)-6-methylphthalide **246**



246

A solution of hydroxyphthalide **245** (240 mg, 1.46 mmol) in anhydrous DMF (4.5 mL) was treated with imidazole (199 mg, 2.92 mmol) and TBSCl (264 mg, 1.75 mmol). The resultant homogeneous solution was stirred at RT under argon until completion as indicated by TLC analysis (16h). The reaction was diluted with water (25 mL), and was then extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (2 × 15 mL), brine (15 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the crude white residue by flash column chromatography, elution with 0-5% EtOAc:hexane yielded phthalide **246** (341 mg, 1.23 mmol, 84%) as a white solid. Phthalide **246** could also be purified via trituration of the crude residue from petroleum ether. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.26 (6H, s, Me_2Si), 1.05 (9H, s, $(CH_3)_3CSi$), 2.29 (3H, s, CH_3Ar), 5.15 (2H, s, CH_2O_2C), 6.91 (1H, d, *J* = 7.6, ArH), 7.41 (1H, d, *J* = 7.6, ArH). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: -3.5 ($(CH_3)_2Si$), 16.8 (CH_3Ar), 18.8 ($C(CH_3)_3Si$), 26.0 ($(CH_3)_3CSi$), 68.1 (CH_2O_2C), 114.4 ($C^{Ar}H$), 115.9 ($C^{Ar}CO_2$),130.2 ($C^{Ar}CH_3$),137.6 ($C^{Ar}H$),146.3 ($C^{Ar}CH_2O_2C$), 153.0 ($C^{Ar}OSi$), 169.1 ($ArCO_2$). *m/z* [CI^+, isobutane] 279 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 279.1412, $C_{15}H_{23}O_3Si$ requires 279.1416. υ_{max} /cm^{-1} (film): 2953, 2930, 2860, 1765, 1607. MP: 115-117 °C.

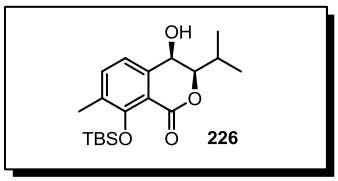
7-(*Tert*-butyldimethylsilyloxy)-1-methoxy-6-methyl-1,3-dihydroisobenzofuran **247**



227

A –78 ^{o}C solution of phthalide **246** (1.04 g, 3.74 mmol) in anhydrous DCM (37 mL) was treated with the dropwise addition of DIBAL (1 M in hexanes, 3.65 mL, 3.65 mmol) over 1Hr. The reaction was then stirred for an additional 1h and was then warmed up to -40 ^{o}C, diluted with DCM (150 mL) and quenched by the successive addition of water (0.2 mL), 15% aq. NaOH solution (0.2 mL) and water (0.4 mL). The resultant slurry was warmed to RT and stirred for 30 min, followed by the addition of anhydrous Na_2SO_4, and the resulting suspension was stirred for a further 30 min. The solids were removed by filtration, and the solution evaporated under reduced pressure to afford the crude lactol intermediate, which was dissolved in anhydrous MeOH (18 mL), in the presence of 4 Å molecular sieves and treated with $TsOH.H_2O$ (35 mg, 0.19 mmol). The reaction was stirred at RT until completion as indicated by TLC analysis (60 min). The solution was then neutralized to pH 7 by the addition of sat'd aq. $NaHCO_3$ solution and the 4 Å molecular sieves were removed by filtration. The clear solution was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with water (2 × 25 mL), sat'd aq. $NaHCO_3$ solution (20 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield a crude oil, which was purified by flash column chromatography, elution with 0-5% Et_2O:petroleum ether to afford phthalan **227** (836 mg, 2.84 mmol, 76%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.21 (3H, s, CH_3Si), 0.22 (3H, s, CH_3Si), 1.04 (9H, s, $(CH_3)_3CSi$), 2.23 (3H, s, CH_3Ar), 3.41 (3H, s, CH_3OCH), 4.95 (1H, dt, *J* = 12.4, 0.7, CH(H)), 5.15 (1H, dt, *J* = 12.4, 1.0, CH(H)), 6.17 (1H, d, *J* = 2.0, $CH(OCH_3)$), 6.77 (1H, d, *J* = 7.5, ArH), 7.14 (1H, d, *J* = 7.5, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -3.3 ($(CH_3)_2Si$), -3.3 ($(CH_3)_2Si$), 17.3 ($C(CH_3)_3Si$), 18.8 (CH_3Ar), 26.0 ($(CH_3)_3CSi$), 54.3 (CH_3O), 72.2 (CH_2), 106.5 ($CH(OCH_3)$), 114.0 ($C^{Ar}H$), 128.4 ($C^{Ar}CH_3$), 128.4 ($C^{Ar}CH(OCH_3)O$), 133.0 ($C^{Ar}H$), 140.1 ($C^{Ar}CH_2O$), 149.3 ($C^{Ar}OCH_3$). *m/z* [FAB$^+$, NOBA] 317 $[M+Na]^+$ (61%), HRMS found $[M+Na]^+$ 317.1561, $C_{16}H_{26}NaO_3Si$ requires 317.1549. υ_{max} /cm^{-1} (film): 2954, 2929, 2859, 2825, 2594.

(±)-(3*R*,4*R*)-8-(*Tert*-butyldimethylsilyloxy)-4-hydroxy-3-isopropyl-7-methylisochroman-1-one **226**

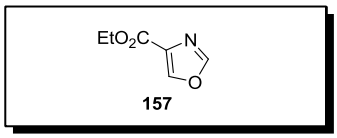


226

Using general procedure 1B, a solution phthalan **227** (380 mg, 1.29 mmol) in anhydrous THF (7 mL) was treated with $^{i}Pr_2NH$ (18 µL, 0.13 mmol), MeLi (1.6 M in Et_2O, 1.69 mL, 2.71 mmol) and *iso*butyraldehyde (141 µL, 1.55 mmol) to generate the α-hydroxy-IBF intermediate. Oxidative rearrangement of α-hydroxy-IBF was performed using *m*CPBA (77%, 318 mg, 1.42 mmol) in anhydrous DCM (7 mL) to afford the keto-lactol intermediate. Oxidation of the keto-lactol was performed in anhydrous DCM (15 mL) with TEMPO (40 mg, 0.26 mmol) and BAIB (1.33 g, 4.13 mmol), followed by filtration through a plug of silica gel, elution with 0-50% DCM:petroleum ether, to afford the keto-lactone intermediate. According to general procedure 2B, reduction was performed MeOH (7 mL) with $NaBH_4$ (50 mg, 1.33 mmol) at –78 ^{o}C. Purification of the

crude residue via flash column chromatography, elution with 0-30% Et_2O:petroleum ether), yielded 8-TBS-isochromanone **226** (232 mg, 0.66 mmol, 51%) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.11 (3H, s, CH_3Si), 0.19 (3H, s, CH_3Si), 1.03 (9H, s, $(CH_3)_3CSi$), 1.07 (3H, d, *J* = 6.6, $(CH_3)H$), 1.17 (3H, d, *J* = 6.6, $(CH_3)H$), 1.84 (1H, d, *J* = 7.6, OH), 2.27 (3H, s, CH_3Ar), 2.28-2.30 (1H, m, $CH(CH_3)_2$) 3.88 (1H, dd, *J* = 9.9, 1.5, $CH(O_2C)$), 4.67 (1H, dd, *J* = 7.3, 1.5, CH(OH),), 6.95 (1H, d, *J* = 7.3, ArH), 7.37 (1H, d, *J* = 7.6, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -3.5 $(CH_3)_2Si$), -3.5 $(CH_3)_2Si$), 17.6 (CH_3Ar), 18.3 ($CH_3(CH)$), 18.8 ($C(CH_3)_3Si$), 19.4 ($CH_3(CH)$), 26.1 (($(CH_3)_3CSi$), 28.6 ($CH(CH_3)_2$), 66.3 (CH(OH)), 85.9 ($CH(O_2C)$), 115.9 (($C^{Ar}CO_2$), 120.6 ($C^{Ar}H$), 132.8 ($C^{Ar}CH_3$), 136.4 ($C^{Ar}H$), 139.9 ($C^{Ar}CH(OH)$), 155.5 (($C^{Ar}OSi$), 163.3 (CO_2). *m/z* [Cl^+, isobutane] 351 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 351.1990, $C_{19}H_{31}O_4Si$ requires 351.1992. υ_{max} /cm^{-1} (film): 3395, 2955, 2932, 2862, 1705, 1589, 1474, 1420. MP: 105-108 °C.

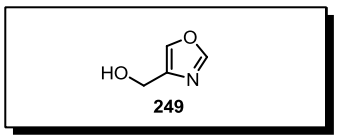
Ethyl oxazole-4-carboxylate **157**



157

To a solution of formic acid (1.58 mL, 42.0 mmol) in anhydrous THF (40 mL), CDI (6.81 g, 42.0 mmol) was added portionwise and the resultant solution was stirred for 30 min, before a solution of ethyl isocyanoacetate (4.83 g, 44.2 mmol) in NEt_3 (11.7 mL, 84.0 mmol) was added to the reaction mixture The mixture was stirred at RT for 1h and then under reflux for 16h. Completion of the reaction was indicated by TLC analysis. The solution was taken up in water (150 mL) and extracted with EtOAc (3 × 200 mL). The resulting organic solution was the washed with water (3 × 50 mL), brine (3 × 50 mL) and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography, elution with 0-35% Et_2O:petroleum ether, afforded the desired oxazole **157** (4.27 g, 30.2 mmol, 72%) as a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.36 (3H, t, *J* = 7.1, CH_3), 4.37 (2H, q, *J* = 7.1, CH_2), 7.92 (1H, d, *J* = 1.0, ArH), 8.25 (1H, d, *J* = 1.0, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2 (CH_3), 61.4 (CH_2), 133.4 ($C^{Ar}CO_2Et$), 144.2 ($C^{Ar}H$), 151.4 ($C^{Ar}H$), 161.2 (CO_2). *m/z* [Cl^+, isobutane] 142 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 142.0506, $C_6H_8NO_3$ requires 142.0504. υ_{max} /cm^{-1} (film): 3132, 2985, 2940, 2907, 1741, 1577, 1518. The data observed is in accordance with literature values.[171]

Oxazol-4-ylmethanol **249**

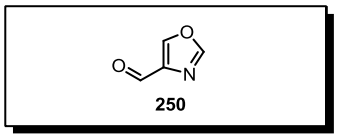


249

Oxazole **157** (7.30 g, 51.7 mmol) was dissolved in anhydrous THF (225 mL) and cooled to –78 °C. DIBAL (1.25 M in hexanes, 89.0 mL, 111 mmol) was added dropwise via syringe pump over 60 min and stirred at –78 °C for 60 min, before being allowed to warm to RT, and stirred for a further 12h. The reaction mixture was cooled to 0 °C and diluted with Et_2O (250 mL) before being quenched by the successive addition of water (4.5 mL), 15% aq. NaOH solution (4.5 mL) and water (11.2 mL) at –78 °C, with 30 min stirring time between each addition. The resultant slurry was warmed to RT and stirred for 60 min, before anhydrous Na_2SO_4 was added and the resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 100% Et_2O, afforded the desired

alcohol **249** (4.87 g, 49.1 mmol, 95%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.21 (1H, t, *J* = 6.1, OH), 4.63 (2H, d, *J* = 5.9, CH_2OH), 7.63 (1H, d, *J* = 0.9, ArH), 7.89 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 56.7 (CH_2), 135.6 (ArH), 140.1 ($C^{Ar}CH_2$), 151.6 (ArH). *m/z* [CI^+, isobutane] 100 $[M+H]^+$ (90%), HRMS found $[M+H]^+$ 100.0394, $C_4H_6NO_2$ requires 100.0399. υ_{max} /cm^{-1} (film): 3314, 3136, 2916, 2851, 1512. The data observed is in accordance with literature values.[172]

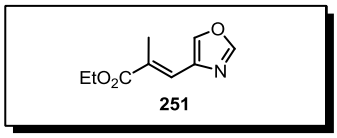
Oxazole-4-carbaldehyde **250**



250

A solution of oxalyl chloride (1.50 mL, 17.78 mmol) in anhydrous DCM (30 mL) was cooled to –78 °C to which DMSO (2.53 mL, 35.6 mmol) was added dropwise and stirred for 5 min. A solution of oxazole **249** (881 mg, 8.89 mmol) in DCM (30 mL) was then slowly transferred via cannulation into the reaction mixture and the reaction stirred for 90 min at –78 °C. NEt_3 (9.90 mL, 71.1 mmol) was then added to the reaction and stirring was continued at RT for a further 2h. The reaction was diluted with DCM (50 mL) and quenched by the addition of 10% aq. HCl solution (7 mL). The resulting biphasic mixture was extracted with DCM (3 × 50 mL) and the combined organic phases were washed with sat'd aq. $NaHCO_3$ (50 mL), water (2 × 30 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product. Purification by flash column chromatography, elution with 0-5% Et_2O:DCM, afforded the desired aldehyde **250** (300 mg, 3.09 mmol, 35%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98 (1H, s, ArH), 8.31 (1H, d, *J* = 1.0, ArH), 9.99 (1H, s, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 140.5 ($C^{Ar}CHO$), 144.0 ($C^{Ar}H$), 151.9 ($C^{Ar}H$), 184.3 (CHO). *m/z* [CI^+, isobutane] 98 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 98.0238, $C_4H_4NO_2$ requires 98.0242. υ_{max} /cm^{-1} (film): 3133, 3082, 2843, 1713, 1562, 1520. The data observed is in accordance with literature values.[173]

(*E*)-Ethyl 2-methyl-3-(oxazol-4-yl)acrylate **251**



251

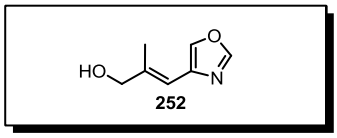
Method A: Wittig Olefination from Aldehyde **250**

To a solution of aldehyde **250** (320 mg, 3.30 mmol) in anhydrous toluene (14 mL) was added (carbethoxyethylidene)triphenylphosphorane (3.60 mg, 9.89 mmol) and the solution was heated at reflux (130 °C) for 16h under an atmosphere of argon. The reaction mixture was cooled to RT before the solvent was evaporated under reduced pressure. The crude residue was then loaded directly onto silica and purified by flash column chromatography, elution with 0-7.5% EtOAc:petroleum ether, to afforded the desired acrylate **251** (325 mg, 1.79 mmol, 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (3H, t, *J* = 7.2, CH_3CH_2), 2.24 (3H, d, *J* = 1.2, $(CH)(CO_2Et)$), 4.26 (2H, q, *J* = 7.2, CH_2CH_3), 7.48-7.49 (1H, m, $CH(CCH_3)(Ar)$)), 7.83 (1H, s, ArH), 7.92 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.4 (CH_3CH_2), 14.6 ($CH_3C(CH)(CO_2Et)$), 61.1 (CH_2CH_3), 126.9 (CH), 129.8 ($C(CH_3)(CH)(CO_2Et)$), 137.4 ($C^{Ar}CH$), 139.3 ($C^{Ar}H$), 151.0 ($C^{Ar}H$), 168.2 (CO). *m/z* [EI^+] 181 $[M]^+$ (81%), HRMS found $[M+H]^+$ 181.0740, $C_9H_{11}NO_3$ requires 181.0739. υ_{max} /cm^{-1} (film): 3090, 2943, 2928, 2870, 1751, 1643, 1451. MP: 35-37 °C.

Method B: Tandem Oxidation Wittig-Olefination from Alcohol **249**

To a solution of alcohol **249** (4.50 g, 45.4 mmol) in anhydrous toluene (225 mL) was added (carbethoxyethylidene)triphenylphosphorane (33.1 g, 90.8 mmol) and activated MnO_2 (19.7 g, 227 mmol) and the resulting mixture was heated at reflux (130 ^oC) for 16h under an atmosphere of argon. The reaction mixture was cooled to RT and filtered through Celite, before the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography, elution with 0-10% Et_2O:DCM, to afford acrylate **251** (7.20 g, 42.6 mmol, 94%) as a white solid.

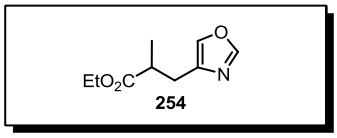
(*E*)-2-Methyl-3-(oxazol-4-yl)prop-2-en-1-ol **252**



252

Acrylate **251** (7.20 g, 42.6 mmol) was dissolved in anhydrous THF (215 mL) and cooled to –78 ^oC. DIBAL (1 M in hexanes, 93.6 mL, 93.6 mmol) was added dropwise via syringe pump over 1h and stirred at –78^oC for a further 1h, before being allowed to warm to RT, and stirred for a further 12h. The reaction mixture was cooled to 0 ^oC and diluted with Et_2O (250 mL) before being quenched by the successive addition of water (3.7 mL), 15% aq. NaOH solution (3.7 mL) and water (9.4 mL) at –78 ^oC, with 30 min stirring time between each addition. The resultant slurry was warmed to RT and stirred for a 60 min, anhydrous Na_2SO_4 was added and the resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-50% Et_2O: DCM afforded the desired allylic alcohol **252** (5.57 g, 40.05 mmol, 94%) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.97 (3H, s, CH_3), 2.10-2.14 (1H, m, OH), 4.18 (2H, d, *J* = 5.3, CH_2), 6.36 (1H, s, CHC(C^{Ar})), 7.62 (1H, s, ArH), 7.85 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.2 (CH_3), 68.3 (CH_2OH), 113.9 (CHC(C^{Ar})), 135.8 ($C^{Ar}H$), 137.8 ($C^{Ar}CH$), 140.3 ($CCH_2OH(CH_3)(CH)$), 150.5 ($C^{Ar}H$). *m/z* [CI^+, isobutane] 140 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 140.0712, $C_7H_{10}NO_2$ requires 140.0711. υ_{max} /cm^{-1} (film): 3345, 2917, 2859, 1726, 1660, 1516, 1447.

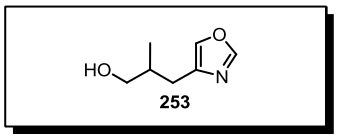
(±)-Ethyl 2-methyl-3-(oxazol-4-yl)propanoate **254**



254

A solution of acrylate **251** (4.00 g, 22.1 mmol) in EtOH (50 mL) was charged with 10% activated Pd/C (800 mg). The suspension was stirred under an atmosphere of hydrogen at RT for 2h. The suspension was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford the desired ester **254** (3.96 g, 21.6 mmol, 98%) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.18-1.25 (6H, m, $CH_3(CH)$, CH_3CH_2), 2.63 (1H, dd, *J* = 14.5, 6.6, CH(H)Ar), 2.85 (1H, dd, *J* = 13.9, 6.9, CH), 2.95 (1H, dd, *J* = 14.2, 7.5, CH(H)Ar), 4.12 (2H, q, *J* = 7.1, OCH_2CH_3), 7.43 (1H, app. q, *J* = 0.9, ArH), 7.80 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3CH_2), 17.1 ($CH_3(CH)$), 30.0 (CH_2Ar), 39.0 (CH), 60.5 (OCH_2CH_3), 135.3 ($C^{Ar}H$), 138.1 ($C^{Ar}CH_2$), 151.0 ($C^{Ar}H$), 175.9 (CO). *m/z* [EI^+] 183 $[M]^+$ (100%), HRMS found $[M]^+$ 183.0896, $C_9H_{13}NO_3$ requires 183.0895. υ_{max} /cm^{-1} (film): 2984, 2953, 1717.

(±)-2-Methyl-3-(oxazol-4-yl)propan-1-ol **253**



253

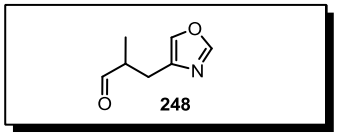
Method A: Hydrogenation of Allylic Alcohol **252**

A solution of allylic alcohol **252** (5.29 g, 38.0 mmol) in EtOH (100 mL) was charged with 10% activated Pd/C (400 mg). The suspension was stirred under an atmosphere of hydrogen at room temperature for 2h. The suspension was filtered through Celite and the filtrate was concentrated under reduced pressure to afford the crude product. Purification via flash column chromatography, elution with 0-40% EtOAc:hexane, afforded the desired alcohol **253** (5.36 g, 38.0 mmol, 100%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (3H, d, *J* = 6.9, CH_3), 1.99-2.04 (1H, m, $CHCH_3(CH_2OH)(CH_2Ar)$), 2.51 (1H, dd, *J* = 14.6, 6.6, $CH_2Ar(CHCH_3(CH_2OH))$), 2.61 (1H, dd, *J* = 14.6, 6.3, $CH_2Ar(CHCH_3(CH_2OH))$), 3.09 (1H, br. s, OH), 3.44 (1H, dd, *J* = 11.0, 6.5, CH_2OH), 3.53 (1H, dd, *J* = 11.0, 5.2, CH_2OH), 7.42 (1H, br. d, *J* = 1.0, ArH), 7.82 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.8 (CH_3), 29.7 ($CH_2Ar(CHCH_3(CH_2OH))$), 35.3 ($CHCH_3(CH_2OH)(CH_2Ar)$), 67.3 (CH_2OH), 135.3 ($C^{Ar}H$), 138.4 ($C^{Ar}CH_2$), 151.0 ($C^{Ar}H$). *m/z* [EI^+] 140 $[M]^+$ (100%), HRMS found $[M]^+$ 140.0790, $C_7H_{11}NO_2$ requires 140.0790. υ_{max} /cm^{-1} (film): 3364, 3137, 2959, 2913, 2874, 1593, 1516, 1462.

Method B: Reduction of Ester **254**

Ester **254** (3.14 g, 17.2 mmol) was dissolved in anhydrous THF (86 mL) and cooled to 0 ^{o}C. DIBAL (1 M in hexanes, 37.7 mL, 37.7 mmol) was added dropwise via syringe pump over 30 min and stirred at 0 ^{o}C for a further 30 min before being allowed to warm to RT, and stirred for a further 60 min. The reaction mixture was cooled to 0 ^{o}C and diluted with Et_2O (100 mL) before being quenched by the successive addition of water (1.5 mL), 15% aq. NaOH solution (1.5 mL) and water (3.9 mL) with 30 min stirring time between each addition. The resultant slurry was warmed to RT and stirred for 60 min, before anhydrous Na_2SO_4 was added and the resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-100% Et_2O:petroleum ether, afforded alcohol **253** (2.40 g, 17.2 mmol, 99%) as a colourless oil. The spectral and physical data obtained for **253**, via Method B, matched that obtained via Method A.

(±)-2-Methyl-3-(oxazol-4-yl)propanal **248**

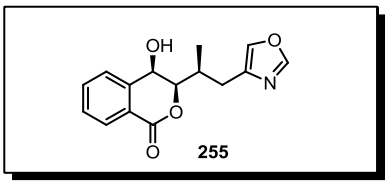


248

Alcohol **253** (2.33 mg, 16.5 mmol) was dissolved in anhydrous DCM (80 mL), and treated with BAIB (7.45 g, 23.1 mmol) and TEMPO (258 mg, 1.65 mmol). The reaction mixture was then stirred under argon at RT until completion as indicated by TLC analysis (16h). The reaction mixture was diluted with DCM (150 mL), washed with sat'd aq. $Na_2S_2O_3$ (2 × 60 mL), water (2 × 30 mL) and brine (30 mL). The phases were separated and the organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to afford the crude product as an orange oil. Purification of the crude residue by flash column chromatography, elution

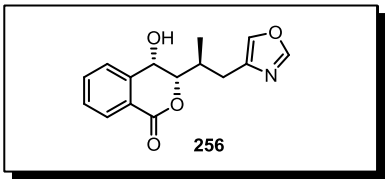
with 0-20% EtOAc:hexane, to afford aldehyde **248** (1.93 g, 13.9 mmol, 84%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (1H, d, *J* = 6.8, CH_3), 2.61 (1H, dd, *J* = 14.8, 6.9, CH_2), 2.76-2.86 (1H, m. $CH(CH_3)$), 2.97 (1H, ddd, *J* = 14.8, 6.5, 0.5, CH_2), 7.45 (1H, br. d, *J* = 1.0, ArH), 7.82 (1H, s, ArH), 9.73 (1H, d, *J* = 1.3, CHO). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.4 (CH_3), 26.9 (CH_2), 45.5 (CH), 135.5 ($C^{Ar}H$), 137.5 (C^{Ar}), 151.2 ($C^{Ar}H$), 204.1 (CHO). *m/z* [Cl^+, isobutane] 140 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 140.0711, $C_7H_{10}NO_2$ requires 140.0712. υ_{max} /cm^{-1} (film): 3137, 2974, 2936, 1724, 1516.

(±)- (3*R*,4*R*)-4-Hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one **255**



Using general procedure 1B, starting from a solution phthalan **131** (1.47 mg, 9.79 mmol) in anhydrous THF (50 mL) with $^{i}Pr_2NH$ (137 µL, 0.98 mmol), MeLi (1.6 M in Et_2O, 12.9 mL, 20.6 mmol) and aldehyde **248** (1.50 g, 10.8 mmol) to generate the α-hydroxy-IBF intermediate. The oxidative rearrangement was performed using *m*CPBA (77%, 2.41 g, 10.8 mmol) in anhydrous DCM (50 mL) to afford the keto-lactol intermediate. Oxidation was performed in anhydrous DCM (60 mL) with TEMPO (305 mg, 1.96 mmol) and BAIB (8.82 g, 27.4 mmol). Purification via flash chromatography, elution with 0-10% Et_2O:DCM afforded the keto-lactone intermediate. According to general procedure 2B, reduction was performed in anhydrous MeOH (50 mL) with $NaBH_4$ (518 mg, 13.7 mmol) at –78 °C. The crude products were purified by flash column chromatography, elution with 0-1.5% MeOH:DCM, to afford *syn,syn*-isochromanone **255** (749 mg, 2.74 mmol, 28%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (3H, d, *J* = 6.7, CH_3), 2.56-2.64 (1H, m, $CH(CH_3)$), 2.69 (1H, dd, *J* = 15.2, 5.5, CH(H)Ar), 2.78 (1H, ddd, *J* = 15.2, 5.4, 0.9, CH(H)Ar), 4.23 (1H, dd, *J* = 9.2, 1.7, $CH(O_2C)$), 5.02 (1H, s, CH(OH)), 7.49-7.55 (3H, m, ArH), 7.65 (1H, td, *J* = 7.5, 1.4, ArH), 7.85 (1H, br. s, ArH), 8.12-8.16 (1H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.9 (CH_3), 28.5 (CH_2Ar), 33.1 ($CH(CH_3)$), 65.0 (CH(OH)), 84.8 ($CH(O_2C)$), 124.6 ($C^{Ar}CH_2$), 128.2 ($C^{Ar}H$), 129.8 ($C^{Ar}H$), 130.4 ($C^{Ar}H$), 134.4 ($C^{Ar}H$), 135.7 ($C^{Ar}H$), 137.7 ($C^{Ar}CO_2$), 140.5 ($C^{Ar}CH(OH)$), 151.4 ($C^{Ar}H$), 165.2 (CO). *m/z* [Cl^+, isobutene] 274 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 274.1075, $C_{15}H_{16}NO_4$ requires 274.1079. υ_{max} /cm^{-1} (film): 3377, 2932, 1713. MP: 160-162 °C.

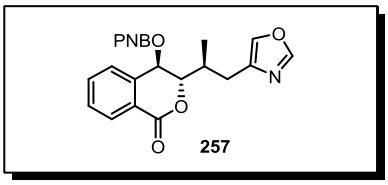
(±)-(3*S*,4*S*)-4-Hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one **256**



Further elution afforded the *syn,anti*-isochromanone **256** (1.12 g, 4.11 mmol, 42%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.11 (3H, d, *J* = 6.5, CH_3), 2.5-2.68 (2H, m, CH(H)Ar & $CH(CH_3)$), 3.04 (1H, br d, *J* = 5.6, OH), 3.14 (1H, d, *J* = 14.0, CH(H)Ar), 4.23 (1H, dd, *J* = 8.7, 1.3, $CH(O_2C)$), 4.78 (1H, d, *J* = 6.3, CH(OH)), 7.45-7.50 (2H, m, $C^{Ar}H$), 7.53 (1H, td, *J* = 7.7, 1.3, $C^{Ar}H$), 7.65 (1H, td, *J* = 7.3, 1.0, $C^{Ar}H$), 7.72 (1H, s, $C^{Ar}H$), 8.13 (1H, d, *J* = 7.7, $C^{Ar}H$). ^{13}C NMR ($CDCl_3$, 125

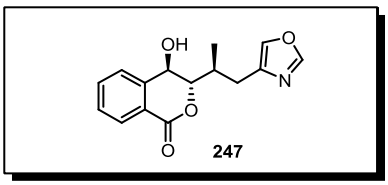
MHz) δ: 15.5 (CH_3), 28.2 (CH_2Ar), 33.6 ($CH(CH_3)$), 65.6 (CH(OH)), 84.0 ($CH(O_2C)$), 124.5 ($C^{Ar}CH_2$), 128.2 ($C^{Ar}H$), 130.1 ($C^{Ar}H$), 130.6 ($C^{Ar}H$), 134.5 ($C^{Ar}H$), 135.8 ($C^{Ar}H$), 138.2 ($C^{Ar}CO_2$), 140.4 ($C^{Ar}CH(OH)$), 150.9 ($C^{Ar}H$), 164.8 (CO_2). *m/z* [Cl^+ (+ve), isobutene] 274 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 274.1082, $C_{15}H_{16}NO_4$ requires 274.1079. υ_{max} /cm^{-1} (film): 3187, 2984, 2971, 1707. MP: 196-98 °C.

(±)-(3*S*,4*R*)-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)-1-oxoisochroman-4-yl 4-nitrobenzoate **257**



A solution of isochromanone **256** (413 mg, 1.51 mmol) was dissolved in anhydrous toluene (21 mL) was treated with PPh_3 (991 mg, 3.78 mmol) and 4-nitrobenzoic acid (480 mg, 3.78 mmol) and stirred for 3 min at RT. The resulting solution was treated dropwise with DIAD (744 µL, 3.78 mmol), before being heated at reflux for 16h under an atmosphere of argon. The reaction mixture was cooled to RT before the solvent was evaporated under reduced pressure and the crude residue purified by flash column chromatography, elution with 0-15% EtOAc:hexane, to afford the nitrobenzoate ester **257** (415 mg, 0.982 mmol, 65%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.04 (3H, d, *J* = 6.9, CH_3), 2.08-2.12 (1H, m, $CH(CH_3)$), 2.63 (1H, dd, *J* = 14.7, 8.2, CH(H)Ar), 2.94 (1H, dd, *J* = 14.6, 4.1, CH(H)Ar), 4.71 (1H, dd, *J* = 8.9, 2.9, $CH(O_2C)$), 6.35 (1H, d, *J* = 2.9, CH(OPNB)), 7.49 (1H, s, ArH), 7.56-7.57 (1H, m, ArH), 7.60 (1H, td, *J* = 7.6, 1.4, ArH), 7.67 (1H, td, *J* = 7.5, 1.4, ArH), 7.79 (1H, s, ArH), 8.17-8.21 (3H, m, ArH), 8.25-8.28 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.2 (CH_3), 28.5 (CH_2), 35.0 ($CH(CH_3)$), 68.7 (CH(OH)), 84.3 ($CH(O_2C)$), 123.8 ($C^{Ar}H$), 128.7 ($C^{Ar}H$), 128.8 ($C^{Ar}CH_2$), 128.9 ($C^{Ar}H$), 130.6 ($C^{Ar}H$), 130.9 ($C^{Ar}H$), 131.2 ($C^{Ar}H$), 132.2 ($C^{Ar}H$), 132.3 ($C^{Ar}CH(OH)$), 134.2 ($C^{Ar}CO_2$), 134.6 ($C^{Ar}H$), 136.0 ($C^{Ar}H$), 137.3 ($C^{Ar}CO_2$), 151.0 ($C^{Ar}NO_2$), 151.2 ($C^{Ar}H$), 163.1 (CO), 164.0 (CO). *m/z* [EI^+] 422 $[M]^+$ (100%), HRMS found $[M]^+$ 422.1119, $C_{22}H_{18}N_2O_7$ requires 422.1114. υ_{max} /cm^{-1} (film): 3115, 2970, 2936, 1722, 1607, 1528.

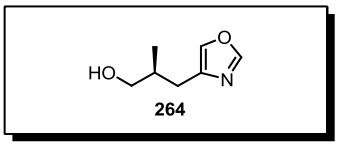
(±)-(3*S*,4*R*)-4-Hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one **247**



A solution of nitrobenzoate ester **257** (117 mg, 0.3 mmol) in anhydrous MeOH (2 mL) and was treated with NaN_3 (72 mg, 1.1 mmol) and stirred under argon at 40 °C for 24h. The reaction mixture was then cooled down to RT and quenched by the addition of water (5 mL), before being extracted with EtOAc (3 × 20 mL). The combined organics were washed with water (5 mL) and brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield a crude product which was purified by flash column chromatography, elution with 0-75% EtOAc:hexane, to afford the desired *anti,anti*-isochromanone **247** (58 mg, 77%) as a white crystalline solid. ^{1}H NMR (C_6D_6, 400 MHz) δ: 0.93 (3H, d, *J* = 7.1, CH_3), 2.06 (1H, dd, *J* = 15.6, 6.1, CH(H)Ar), 2.37-2.46 (1H, m, $CH(CH_3)$), 2.69 (1H,

ddd, *J* = 15.6, 5.8, 1.4, CH(H)Ar), 4.03 (1H, dd, *J* = 10.5, 2.2, CH(O_2C)), 4.68 (1H, dd, *J* = 10.4, 4.9, CH(OH)), 5.98 (1H, d, *J* = 5.9, OH), 6.62 (1H, s, ArH), 6.91 (1H, s, ArH), 7.00 (1H, tt, *J* = 7.6, 1.0, ArH), 7.21 (1H, td, *J* = 7.6, 1.3, ArH), 7.83 (1H, d, *J* = 7.7, ArH), 8.21 (1H, dd, *J* = 7.7, 1.1, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 18.2 (CH_3), 25.8 (CH_2Ar), 32.3 (CH(CH_3)), 65.1 (CH(OH)), 86.0 (CH(O_2C)), 123.6 ($C^{Ar}CH_2$), 124.6 ($C^{Ar}H$), 128.2 ($C^{Ar}H$), 130.1 ($C^{Ar}H$), 134.3 ($C^{Ar}H$), 135.3 ($C^{Ar}H$), 138.9 ($C^{Ar}CO_2$), 143.4 (C^{Ar}CH(OH)), 151.5 ($C^{Ar}H$), 165.3 (CO_2). *m/z* [EI^+ (+ve)] 273 $[M]^+$ (100%). HRMS found $[M]^+$ 273.1003, $C_{15}H_{15}O_4N$ requires 273.1001. υ_{max} /cm^{-1} (film): 3213, 2963, 2922, 2853, 1721, 1605, 1514, 1456. MP: 158-160 ^oC.

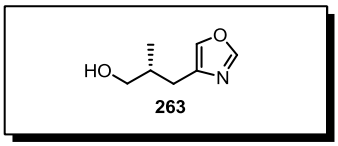
(*S*)-2-Methyl-3-(oxazol-4-yl)propan-1-ol **264**



264

The racemic alcohol **253** was subjected to chiral HPLC sepearation. The enantiomeric alcohols were separated using a Chiralpak AS-H column (250x20 mm i.d.) eluting with a 18 mL/min flow rate using a 9:1Heptane:^{i}PrOH mixture. The alcohols were detected using a UV detector operating at 220 and 254 nm. The (*S*)-alcohol **264** was eluted at 7.72 min and was obtained in 49% yield and >99% ee. [α]D -41.50 (c=1.75, CHCl3). Experimental data in agreement with racemic alcohol **253.**

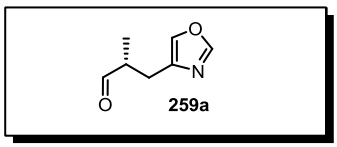
(*R*)-2-Methyl-3-(oxazol-4-yl)propan-1-ol **263**



263

The (*R*)-alcohol **263** was eluted at 7.75 min and was obtained in 49% yield and >99% ee. $[\alpha]_D$ +43.98 (c=1.91, $CHCl_3$). Experimental data in agreement with racemic alcohol **253.**

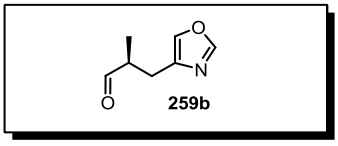
(*R*)-2-Methyl-3-(oxazol-4-yl)propanal **259a**



259a

(*R*)-alcohol **263** was oxidised to (*R*)-aldehyde **259a**, under identical conditions for the synthesis of aldehyde **248** in 84% yield**.** $[\alpha]_D$ +41.70 (c=0.93, $CHCl_3$). Experimental data in agreement with racemic aldehyde **248.**

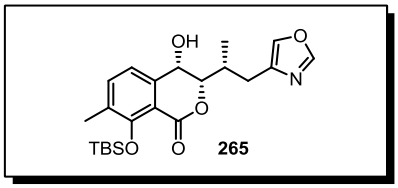
(*S*)-2-Methyl-3-(oxazol-4-yl)propanal **259b**



259b

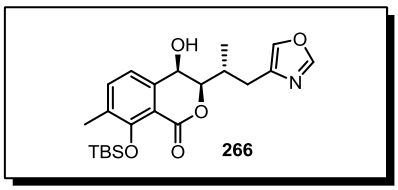
(*S*)-alcohol **264** was oxidised to (*S*)-aldehyde **259b**, under identical conditions for the synthesis of aldehyde **248** in 84% yield**.** $[\alpha]_D$ -40.02 (c=0.99, $CHCl_3$). Experimental data in agreement with racemic aldehyde **248.**

(*3S,4S*)-8-(*Tert*-Butyldimethylsilyloxy)-4-hydroxy-7-methyl-3-((*R*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one **265**



Using general procedure 1B, a solution phthalan **227** (758 mg, 2.57 mmol) in anhydrous THF (10 mL) was treated with $^{i}Pr_2NH$ (36 µL, 0.26 mmol), MeLi (1.6 M in Et_2O, 3.38 mL, 5.41 mmol) and (*R*)-aldehyde **259a** (376 mg, 2.70 mmol) in THF (5 mL) to generate the α-hydroxy-IBF. The oxidative rearrangement was performed using *m*CPBA (77%, 635 mg, 2.83 mmol) in anhydrous DCM (13 mL) to afford the keto-lactol intermediate. Oxidation was performed in anhydrous DCM (13 mL) with TEMPO (80 mg, 0.52 mmol) and BAIB (2.65 g, 8.24 mmol). Purification via flash chromatography, elution with 0-25% Et_2O:petroleum ether, afforded the keto-lactone intermediate. According to general procedure 2B, reduction was performed in anhydrous MeOH (50 mL) with $NaBH_4$ (122 mg, 3.21 mmol) at –78 ^{o}C. Purification via flash column chromatography, elution with 0-1% MeOH:DCM afforded the *syn,syn*-isochromanone **265** (258 mg, 0.62 mmol, 24%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.12 (3H, s, CH_3Si), 0.19 (3H, s, CH_3Si), 1.03 (9H, s, $(CH_3)_3C$), 1.21 (3H, d, *J* = 6.8, $CH_3(CH)$), 2.27 (3H, s, CH_3Ar), 2.50-2.57 (1H, m, $CH(CH_3)$), 2.66 (1H, dd, *J* = 14.9, 5.9, CH(H)Ar), 2.75-2.80 (1H, m, CH(H)Ar), 3.52 (1H, d, *J* = 6.1, OH), 4.12 (1H, dd, *J* = 8.8, 1.4, $CH(O_2C)$), 4.90 (1H, dd, *J* = 6.0, 1.0, CH(OH)), 6.98 (1H, d, *J* = 7.7, ArH), 7.38 (1H, dd, *J* = 7.5, 1.0, ArH), 7.48 (1H, br. d, *J* = 0.9, ArH), 7.84 (1H, br. d, *J* = 1.0, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -3.5 (CH_3Si), 16.8 ($CH_3(CH)$), 17.7 (CH_3Ar), 18.8 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3C$), 28.6 (CH_2), 33.2 ($CH(CH_3)$), 66.3 (CH(OH)), 83.7 ($CH(O_2C)$), 116.1 ($C^{Ar}CO_2$), 120.5 ($C^{Ar}H$), 132.6 ($C^{Ar}CH_2$), 135.6 ($C^{Ar}H$), 136.4 ($C^{Ar}H$), 138.0 ($C^{Ar}CH_3$), 139.9 ($C^{Ar}CH(OH)$), 151.3 ($C^{Ar}H$), 155.4 ($C^{Ar}OSi$), 163.1 (CO). *m/z* [Cl^+, isobutene] 418 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 418.2054, $C_{22}H_{32}NO_5Si$ requires 418.2050. υ_{max} /cm^{-1} (film): 3385, 2948, 2937, 2923, 2834, 1709, 1701, 1427. MP: 160-162 ^{o}C. $[\alpha]_D$ +80.77 (c=1.04, $CHCl_3$).

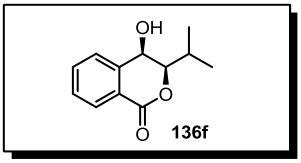
(*3R,4R*)-8-(*Tert*-Butyldimethylsilyloxy)-4-hydroxy-7-methyl-3-((*R*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one **266**



Further elution afforded the *syn,anti*-isochromanone **265** (376 mg, 0.90 mmol, 35%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.12 (3H, s, CH_3Si), 0.20 (3H, s, CH_3Si), 1.04 (9H, s, $(CH_3)_3C$), 1.13 (3H, d, *J* = 6.9, $CH_3(CH)$), 2.05 (1H, d, *J* = 7.2, OH), 2.27 (3H, s, CH_3Ar), 2.51-2.59 (1H, m, $CH(CH_3)$), 2.79 (1H, dd, *J* = 14.5, 7.6, CH(H)Ar), 3.03 (1H, dd, *J* = 14.6, 3.2, CH(H)Ar), 4.07 (1H, dd, *J* = 9.7, 1.3, $CH(O_2C)$), 4.67 (1H, dd, *J* = 7.2, 1.3, CH(OH)), 6.94 (1H, d, *J* = 7.5, ArH), 7.37 (1H, d, *J* = 7.9, ArH), 7.48 (1H, s, ArH), 7.79 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -3.5 (CH_3Si), -3.5 (CH_3Si), 15.3 ($CH_3(CH)$), 17.6 (CH_3Ar), 18.8 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3C$), 28.1 (CH_2), 33.1 ($CH(CH_3)$), 66.3 (CH(OH)), 82.9 ($CH(O_2C)$), 115.9 ($C^{Ar}CO_2$), 120.6 ($C^{Ar}H$), 133.0 ($C^{Ar}CH_2$), 135.9 ($C^{Ar}H$), 136.5 ($C^{Ar}H$), 138.0 ($C^{Ar}CH_3$), 139.7 ($C^{Ar}CH(OH)$), 150.8 ($C^{Ar}H$), 155.6 ($C^{Ar}OSi$), 163.0 (CO). *m/z* [Cl^+, isobutene] 418 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 418.2047, $C_{22}H_{32}NO_5Si$ requires

418.2050. υ_{max} /cm^{-1} (film): 3370, 2955, 2392, 2860, 1719, 1417. MP: 138-140 ^{o}C. $[\alpha]_D$ -226.42 (c=0.53, $CHCl_3$).

4-Hydroxy-3-isopropylisochroman-1-one **136f**



Reduction Method C: ZnI_2 and $NaBH_3CN$

To a solution of keto-lactone **135f** (140 mg, 0.69 mmol) in anhydrous DCE (4 mL), ZnI_2 (329 mg, 1.03 mmol) and $NaBH_3CN$ (323 mg, 5.15 mmol) were added and the resultant suspension was heated at reflux under an atmosphere of argon for 16h. The resultant orange solution was cooled to RT and diluted with DCM (30 mL) and filtered through a pad of Celite, before the solvent was evaporated under reduced pressure. The crude residue was taken up in EtOAc (100 mL) and washed with water (2 × 20 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-35% Et_2O:petroleum ether, afforded isochromanone **136f** (74 mg, 0.36 mmol, 52%) as a white solid.

Reduction Method D: Meerwein Ponndorf Verley Reduction

To a solution of keto-lactone **135f** (131 mg, 0.64 mmol) in anhydrous toluene (4 mL), Me_2AlCl (1M in hexane, 130 µL, 130 µmol) and ^{i}PrOH (196 µg, 2.57 mmol) were added and the resultant solution was stirred at RT for 8H before being heated at 50 ^{o}C under an atmosphere of argon for 24h in microdistillation apparatus. TLC analysis indicated incomplete reaction therefore further Me_2AlCl (1M in hexane, 130 µL, 130 µmol) and ^{i}PrOH (196 µg, 2.57 mmol) were added and the solution was heated at 50 ^{o}C for a further 48H. The reaction was quenched at RT by the addition of water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organics were washed with water (2 × 5 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded unreacted keto-lactone **135f** (21 mg, 103 µmol, 16%). Further elution with 50% Et_2O:petroleum ether afforded isochromanone **136f** (94 mg, 0.46 mmol, 71%, 85% brsm) as a white crystalline solid.

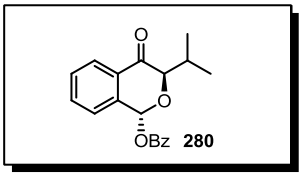
Reduction Method E: Samarium Mediated Meerwein Ponndorf Verley Reduction

To a flask containing Samarium (78 mg, 0.52 mmol) and I_2 (5 - 8 mg) was added anhydrous ^{i}PrOH (1 mL) and the resulting mixture was stirred at RT for 1Hr. The colour change from brown to deep purple indicated the formation of $Sm(^{i}PrO)_3$. To this a solution of keto-lactone **135f** (106 mg, 0.52 mmol) in anhydrous ^{i}PrOH (1 mL) was added and the reaction mixture was stirred at room temperature for 72h. TLC analysis indicated reaction completion. The reaction was quenched at room temperature by the addition of water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organics were washed with water (2 × 5 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced

pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-40% Et_2O:petroleum ether, afforded the isochromanone **136f**, (69 mg, 0.33 mmol, 64 %) as a white crystalline solid.

The spectral and physical data obtained for **136f** via reduction methods C to E matched that obtained when **136f** was synthesised via methods A and B.

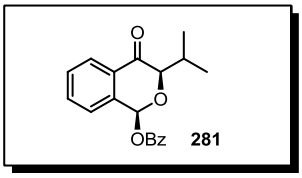
(±)-(1*R*,3*R*)-3-Isopropyl-4-oxoisochroman-1-yl benzoate **280**



280

Keto-lactol **134f** (231 mg, 1.12 mmol) was dissolved in anhydrous DCM (6.5 mL) and cooled to –78 ^oC, under an atmosphere of argon. NEt_3 (0.94 mL, 6.72 mmol) was added, together with DMAP (14 mg, 0.11 mmol), before the dropwise addition of BzCl (133 µL, 1.14 mmol). After stirring for 60 min, TLC analysis indicated reaction completion. The reaction was quenched by the addition of sat'd aq. $NaHCO_3$ solution and extracted with Et_2O (2 × 50 mL). The organics were collected and washed with water (10 mL) and brine (10 mL). Solvent evaporation afforded the crude product. Purification via flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded α-diastereoisomer **280** (137 mmol, 0.44 mmol) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.93 (3H, d, *J* = 6.9, (CH_3(CH)), 1.09 (3H, d, *J* = 7.1, CH_3(CH)), 2.56-2.65 (1H, m, CH(CH_3)$_2$), 4.67 (1H, d, *J* = 2.8, CH(CHMe_2)), 7.43 (1H, s, CH(OBz)), 7.41-7.44 (2H, m, ArH), 7.50 (1H, br. d, *J* = 7.6, ArH), 7.54-7.59 (2H, m, ArH), 7.65 (1H, td, *J* = 7.5, 1.4, ArH), 8.00-8.03 (2H, m, ArH), 8.07 (1H, dd, *J* = 7.8, 1.0, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.1 (CH_3(CH)), 19.3 (CH_3(CH)), 26.7 (CH(CH_3)$_2$), 80.0 CH(CHMe_2)), 91.1 (CH(OBz)), 126.2 (C^{Ar}H), 126.4 (C^{Ar}H), 128.5 (C^{Ar}H), 129.5 (C^{Ar}), 129.5 (C^{Ar}), 129.9 (C^{Ar}H), 130.0 (C^{Ar}H), 133.6 (C^{Ar}H), 134.5 (C^{Ar}H) 138.0 (C^{Ar}), 165.1 (CO), 195.2 (CO). *m/z* [CI^+, isobutane] 311 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 311.1280, $C_{19}H_{19}O_4$ requires 311.1283. υ_{max} /cm^{-1} (film): 2965, 2932, 2876, 1724, 1695, 1603, 1540.

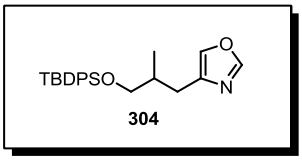
(±)-(1*S*,3*R*)-3-Isopropyl-4-oxoisochroman-1-yl benzoate **281**



281

Further elution afforded the β-diastereoisomer **281** (73 mg, 0.24 mmol) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (3H, d, *J* = 6.7, (CH_3(CH)), 1.07 (3H, d, *J* = 6.9, CH_3(CH)), 2.51-2.58 (1H, m, CH(CH_3)$_2$), 4.19 (1H, d, *J* = 6.0, CH(CHMe_2)), 7.32 (1H, s, CH(OBz)), 7.44-7.51 (3H, m, ArH), 7.55 (1H, td, *J* = 7.6, 0.7, ArH), 7.61-67 (2H, m, ArH), 8.08 (1H, dd, *J* = 7.8, 1.0, ArH), 8.13-8.15 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.9 (CH_3(CH)), 19.0 (CH_3(CH)), 30.3 (CH(CH_3)$_2$), 84.9 CH(CHMe_2)), 90.6 (CH(OBz)), 125.1 (C^{Ar}H), 126.4 (C^{Ar}H), 128.6 (C^{Ar}H), 129.3 (C^{Ar}), 129.6 (C^{Ar}H), 129.8 (C^{Ar}), 130.1 (C^{Ar}H), 133.6 (C^{Ar}H), 134.5 (C^{Ar}H) 139.1 (C^{Ar}), 165.3 (CO), 195.2 (CO). *m/z* [CI^+, isobutane] 311 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 311.1281, $C_{19}H_{19}O_4$ requires 311.1283. υ_{max} /cm^{-1} (film): 2966, 2930, 2876, 1725, 1690, 1603, 1542.

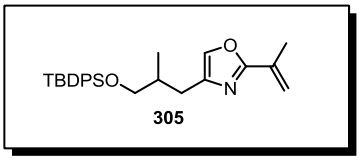
(±)-4-(3-(*Tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **304**



304

Alcohol **253** (959 mg, 6.79 mmol) was dissolved in anhydrous DMF (14 mL) together with finely ground imidazole (924 mg, 13.59 mmol) and TBDPSCl (2.12 mL, 8.15 mmol) and stirred under argon at RT for 4h. The reaction mixture was then diluted with Et_2O (300 mL) and washed sequentially with water (5 × 60 mL) and brine (50 mL), before being dried over anhydrous Na_2SO_4 and the solvent was evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-10% Et_2O:petroleum ether) afforded the silyl ether **304** (2.51 g, 6.60 mmol, 97%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (3H, d, *J* = 6.8, CH_3CH), 1.06 (6H, s, $(CH_3)_2C(CH_3)Si$) 1.07 (3H, s, $CH_3C(CH_3)_2Si$), 2.05-2.13 (1H, m, $CHCH_3$), 2.38 (1H, dd, *J* = 14.6, 8.0, $CH_2Ar(CH)$), 2.75 (1H, dd, *J* = 14.5, 5.9, $CH_2Ar(CH)$), 3.53 (2H, d, *J* = 5.6, $CH_2OTBDPS$), 7.30 (1H, s, ArH), 7.36-7.45 (6H, m, ArH), 7.66 (3H, d, *J* = 6.8, ArH), 7.71-7.73 (1H, m, ArH), 7.79 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.7 (CH_3CH), 19.5 ($C(CH_3)_3Si$), 26.7 ($CH_3C(CH_3)_2$), 27.0 ($(CH_3)_2C(CH_3)$), 29.7 (CH_2Ar), 35.3 ($CHCH_3$), 68.2 (CH_2OSi), 127.8(C^{Ar}), 127.9(C^{Ar}), 129.7(C^{Ar}), 129.8(C^{Ar}), 134.0(C^{Ar}), 134.0(C^{Ar}), 134.9(C^{Ar}), 135.0(C^{Ar}), 135.8(C^{Ar}), 135.8(C^{Ar}), 139.2(C^{Ar}), 150.8 (C^{Ar}). *m/z* [Cl^+, isobutane] 380 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 380.2050, $C_{23}H_{30}NO_2Si$ requires 380.2046. υ_{max} /cm^{-1} (film): 2959, 2932, 2859, 1427.

(±)-4-(3-(*Tert*-butyldiphenylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole **305**



305

Method A: Pd(0) Catalyzed C-H Activation

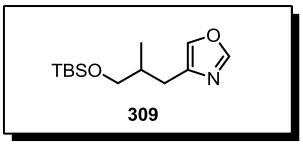
Oxazole **304** (80 mg, 0.21 mmol), $Pd(PPh_3)_4$ (13 mg, 11 µmol), LiO^tBu (34 mg, 0.42 mmol) and 2-bromopropene (38 µL, 0.42 mmol) in anhydrous 1,4-dioxane (0.6 mL) was stirred in a sealed tube at 110 ^{o}C for 24h under an atmosphere of argon. The reaction mixture was cooled to RT, before being quenched with water (5 mL) and extracted with EtOAc (3 × 20 mL). The resultant organics were washed with water (2 × 7 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4 and solvent evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-0.5% EtOAc:pentane, afforded the desired alkenyl oxazole **305** (51 mg, 0.12 mmol, 58%, 64% brsm) as a colourless oil. Further elution with 5% EtOAc:pentane afforded the recovered oxazole **304** (9 mg, 24 µmol, 11%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.00 (3H, d, *J* = 6.7, $CH_3CH(CH_2)(CH_2')$), 1.07 (9H, s, $(CH_3)_3CSi$), 2.05-2.12 (1H, m, CH), 2.14-2.16 (3H, m, $CH_3C(CH_2)(Ar)$), 2.39 (1H, ddd, *J* = 14.6, 7.8, 0.9, CH(H)Ar), 2.71 (1H, ddd, *J* = 14.6, 6.3, 0.9, CH(H)Ar), 3.54 (1H, dd, *J* = 9.9, 5.6, CH(H)OSi), 3.59 (1H, dd, *J* = 9.9, 5.3, CH(H)OSi), 5.32-5.33 (1H, m, $C_{alkene}H$), 5.89-5.91 (1H, m, $C_{alkene}H$), 7.20 (1H, br. s, ArH), 7.36-7.44 (6H, m, ArH), 7.65-7.68 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.9 ($CH_3(CH)$), 19.3 (CH_3), 19.5 ($SiC(CH_3)_3$), 27.0 ($(CH_3)_3C$), 30.0 (CH_2Ar), 35.2 (CH), 68.1 (CH_2OSi), 117.6 ($C_{alkene}H_2$), 127.7 ($C^{Ar}H$), 129.7 ($C^{Ar}H$), 132.0 ($C^{Ar}CH_2$), 134.0 ($C^{Ar}Si$), 134.0 ($C^{Ar}Si$), 134.5 ($C^{Ar}H$), 135.7 ($C^{Ar}H$), 140.6 ($C_{alkene}(CH_3)$), 162.3 (C^{Ar}(alkene)). *m/z* [FAB$^+$, NOBA] 420 $[M+H]^+$ (100%),

HRMS found $[M+H]^+$ 420.2354, $C_{26}H_{34}NO_2Si$ requires 420.2359. υ_{max} /cm^{-1} (film): 2959, 2930, 2857, 1589, 1532, 1462, 1427.

Method B: Pd(0)/Cu(I) Catalyzed C-H Activation

Oxazole **304** (80 mg, 0.21 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (6 mg, 42 µmol), CuI (4 mg, 21 µmol), LiO^tBu (34 mg, 0.42 mmol) and 2-bromopropene (38 µL, 0.42 mmol) in anhydrous 1,4-dioxane (0.6 mL) was stirred in a sealed tube at 110 ^oC for 24h under an atmosphere of argon. The reaction mixture was cooled to RT, before being quenched with water (5 mL) and extracted with EtOAc (3 × 20 mL). The resultant organics were washed with water (2 × 7 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4 and solvent evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-1% EtOAc:pentane, afforded the desired alkenyl oxazole **305** (55 mg, 0.13 mmol, 62%, 73% brsm) as a colourless oil. Further elution with 5% EtOAc:pentane afforded the recovered oxazole **304** (10 mg, 25 µmol, 12%) as a colourless oil.

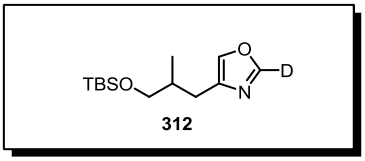
(±)-4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazole **309**



309

Alcohol **253** (1.31 g, 9.27 mmol) was dissolved in anhydrous DMF (15 mL) together with finely ground imidazole (1.26 g, 18.5 mmol) and TBSCl (1.66 g, 10.7 mmol) and stirred under argon at RT for 16h. The reaction mixture was then diluted with Et_2O (300 mL) and washed sequentially with water (5x60 mL) and brine (50 mL) before being dried over anhydrous Na_2SO_4 and the solvent was evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-10% Et_2O:petroleum ether, afforded the silyl ether **309** (2.09 g, 8.18 mmol, 88%) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.03 (6H, s, $(CH_3)_3Si$), 0.90 (12H, m, $(CH_3)_3C$, $CH_3(CH)$), 1.98-2.02 (1H, m, CH), 2.32 (1H, dd, *J* = 14.6, 8.2, CH(H)Ar), 2.68 (1H, ddd, *J* = 14.6, 5.8, 1.0, CH(H)Ar), 3.43-3.49 (2H, m, CH_2OSi), 7.40 (1H, m, ArH), 7.81 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ:-5.3 (CH_3Si), -5.2 (CH_3Si), 16.6 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 26.1 $(CH_3)_3C$), 29.6 (CH_2Ar), 35.3 (CH), 67.5 (CH_2OSi), 135.0 ($C^{Ar}H$), 139.3 ($C^{Ar}CH_2$), 150.8 ($C^{Ar}H$). *m/z* [Cl^+, isobutane] 256 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 256.1737, $C_{13}H_{26}NO_2Si$ requires 256.1733. υ_{max} /cm^{-1} (film): 2959, 2930, 2859.

(±)-4-(3-(*Tert*-butyldiphenylsilyloxy)-2-methylpropyl)-2-deuterooxazole **312**



312

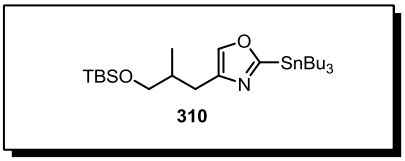
Oxazole **309** (40 mg, 105 µmol) was dissolved in anhydrous Et_2O (1 mL) to which ^{n}BuLi (2.5M in hexane, 46 µL, 116 µmol) was added and the solution was stirred at –78 ^oC for 30 min under an atmosphere of argon. The reaction mixture was then quenched by the dropwise addition D_2O (1 mL) before being warmed to RT. The mixture was diluted with Et_2O (20 mL) and the organics were sequentially washed with water (3 × 5 mL) and brine (8 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the

crude product. Purification by flash column chromatography, elution with 0-10% Et_2O:petroleum ether, afforded the deutero-oxazole **312** (34 mg, 89 µmol, 85%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.03 (6H, s, $(CH_3)_3Si$), 0.90 (12H, m, $(CH_3)_3C$, $CH_3(CH)$), 1.98-2.02 (1H, m, CH), 2.32 (1H, dd, *J* = 14.6, 8.2, CH(H)Ar), 2.68 (1H, ddd, *J* = 14.6, 5.8, 1.0, CH(H)Ar), 3.43-3.49 (2H, m, CH_2OSi), 7.40 (1H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.3 (CH_3Si), -5.2 (CH_3Si), 16.6 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 26.1 $(CH_3)_3C$), 29.6 (CH_2Ar), 35.3 (CH), 67.5 (CH_2OSi), 135.0 ($C^{Ar}H$), 139.3 ($C^{Ar}CH_2$). *m/z* [Cl^+, isobutane] 381 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 381.2104, $C_{23}H_{29}DNO_2Si_2$ requires 381.2124. υ_{max} /cm^{-1} (film): 2961, 2932, 2859, 1471, 1427.

General Procedure 3: C2 Functionalization of Oxazoles

The general procedure for the BH_3-mediated C2 functionalisation of oxazoles is exemplified in the synthesis of stannyl-oxazole **310**.

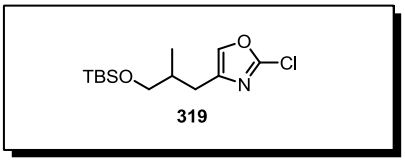
(±)-4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(tributylstannyl)oxazole **310**



310

Oxazole **309** (78 mg, 0.21 mmol) was dissolved in anhydrous THF (1 mL) to which BH_3 (1 M in THF, 216 µL, 0.22 mmol) was added and the solution was stirred at RT for 30 min under an atmosphere of argon. After cooling to –78 ^{o}C, ^{n}BuLi (2.5 M in hexane, 86 µL, 0.22 mmol) was added dropwise over 5 min and the solution was allowed to stir for a further 25 min before being quenched with the dropwise addition of Bu_3SnCl (59 µL, 0.21 mmol). The reaction mixture was stirred for 30 min at –78 ^{o}C before being warmed to 0 ^{o}C and quenched with water (4 mL). The mixture was diluted with Et_2O (25 mL) and the organics were sequentially washed with water (3 × 5 mL) and brine (8 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product. Purification by flash column chromatography, elution with 0-2% Et_2O:petroleum ether, afforded the stannyl-oxazole **310** (98 mg, 0.15 mmol, 71%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.89 (18H, m, $(CH_3)_3C$, $(CH_3(CH_2))_3$), 0.94 (3H, d, *J* = 6.7, $CH_3(CH)$), 1.26-1.35 (12H, m, $(CH_2CH_2)_3$), 1.55-1.61 (6H, m, $(SnCH_2)_3$), 2.07-2.12 (1H, m, CH), 2.49 (1H, ddd, *J* = 15.4, 8.0, 0.9, CH(H)Ar), 2.81 (1H, ddd, *J* = 15.4, 6.2, 1.0, CH(H)Ar), 3.46-3.51 (2H, m, CH_2OSi), 7.58 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.3 ($(CH_3)Si$), -5.3 ($(CH_3)Si$), 12.1 ($SnCH_2$), 13.8 ($CH_3(CH_2)$), 16.8 ($CH_3(CH)$), 18.5 (CH_2Ar), 26.1 ($(CH_3)_3C$), 27.0 ($C(CH_3)_3$), 27.2 ($CH_2(CH_3)$), 28.8 ($CH_2(CH_2Sn)(CH_2CH_3)$), 34.1 (CH), 67.4 (CH_2OSi), 137.4 ($C^{Ar}CH_2$), 139.9 ($C^{Ar}H$), 177.5 ($C^{Ar}Sn$). *m/z* [Cl^+] 546 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 546.2792, $C_{25}H_{52}NO_2Si^{118}Sn$ requires 546.2794. υ_{max} /cm^{-1} (film): 2957, 2928, 2854, 1462.

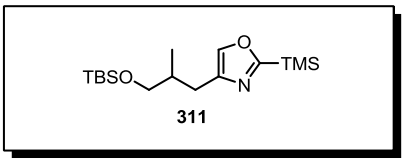
(±)-4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-chlorooxazole **319**



319

Using general procedure 3, oxazole **309** (2.16 g, 8.44 mmol) was dissolved in anhydrous THF (40 mL) was treated with BH_3 (1 M in THF, 8.86 mL, 8.86 mmol), ^{n}BuLi (1.6 M in hexane, 5.54 mL, 8.86 mmol) and quenched with C_2Cl_6 (3.99 g, 16.9 mmol). Purification of the crude material by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the chloro oxazole **319** (2.12 g, 7.31 mmol, 87%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.02 (6H, s, $(CH_3)_2Si$), 0.88, (9H, s, $(CH_3)C$), 0.89 (3H, d, *J* = 6.5), 1.97-1.99 (1H, m, CH), 2.25 (1H, ddd, *J* = 14.7, 8.2, 0.9, CH(H)Ar), 2.63 (1H, ddd, *J* = 14.7, 5.8, 1.1, CH(H)Ar), 3.42-3.47 (2H, m, CH_2OSi), 7.35 (1H, br. t, *J* = 1.1, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.3 ($(CH_3)_2Si$), 16.5 ($CH_3(CH)$), 18.4 ($SiC(CH_3)_3$), 26.0 ($(CH_3)_3C$), 29.9 (CH_2Ar), 35.0 (CH), 67.3 (CH_2OSi), 137.2 ($C^{Ar}H$), 142.2 ($C^{Ar}CH_2$), 146.4 ($C^{Ar}Cl$). *m/z* [Cl^+, isobutane] 290 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 290.1350, $C_{13}H_{25}{}^{35}ClNO_2Si$ requires 290.1343. υ_{max} /cm^{-1} (film): 2957, 2930, 2886, 2857, 1520, 1472, 1464.

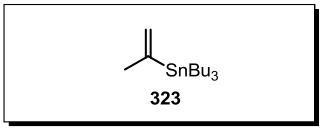
(±)-4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(trimethylsilyl)oxazole **311**



311

Using general procedure 3, oxazole **309** (237 mg, 0.93 mmol) was dissolved in anhydrous THF (5 mL) was treated with BH_3 (1 M in THF, 974 µL, 0.97 mmol), ^{n}BuLi (1.6M in hexane, 609 µL, 0.97 mmol) and quenched with TMSCl (135 µL, 1.07 mmol). Purification of the crude material by flash column chromatography, elution with 0-1.5% Et_2O:petroleum ether, afforded the silyl oxazole **311** (231 mg, 0.71 mmol, 76%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.04 (6H, s, $(CH_3)_2Si$), 0.50 (9H, s, $(CH_3)_3Si$), 0.89 (9H, s, $(CH_3)_3C$), 0.95 (3H, d, *J* = 6.7, $CH_3(CH)$), 2.06-2.13 (1H, m, CH), 2.51 (1H, ddd, *J* = 15.5, 8.0, 1.1, CH(H)Ar), 2.84 (1H, ddd, *J* = 15.5, 6.1, 1.2, CH(H)Ar), 3.50 (2H, d, *J* = 5.5, CH_2OSi), 7.55 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.3 ($(CH_3)_2Si$), -5.3 ($(CH_3)_2Si$), -1.9 ($(CH_3)_3Si$), 16.9 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3C$), 26.9 (CH_2Ar), 33.9 (CH), 67.4 (CH_2OSi), 138.6 ($C^{Ar}CH_2$), 138.7 ($C^{Ar}H$), 171.7 ($C^{Ar}Si$). *m/z* [Cl^+] 4328 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 328.2132, $C_{16}H_{34}NO_2Si_2$ requires 328.2128. υ_{max} /cm^{-1} (film): 2957, 2930, 2857, 1471, 1464.

Tributyl(prop-1-en-2-yl)stannane **323**

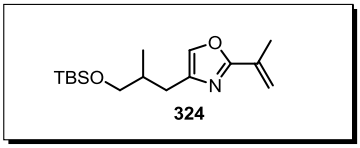


323

A round bottom flask charged with magnesium turnings (175 mg, 7.2 mmol), was treated with anhydrous THF (36 mL), followed by Bu_3SnCl (1.50 mL, 5.5 mmol). The heterogeneous mixture was then sonicated at RT under an argon atmosphere for 2 min before being treated with the dropwise addition of 2-bromopropene (639 µL, 7.2 mmol). The reaction mixture was sonicated

for a further 3h, by which time no magnesium turnings were longer visible. The reaction was quenched by the addition of water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were washed with water (15 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a colourless oil. Purification of the crude residue by flash column chromatography, elution with petroleum ether, stannane **323** (1.95 g, 96%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.89-0.92 (15H, m, $CH_3(CH_2)$, CH_2Sn), 1.30-1.35 (6H, m, $CH_2(CH_3)$), 1.47-1.54 (6H, m, $CH_2(CH_2Sn)(CH_2CH_3)$), 1.97 (3H, t, *J* = 1.6, $CH_3C(CH_2)$), 5.09 (1H, dq, *J* = 3.0, 1.4, $C_{alkene}H$), 5.69 (1H, dq, *J* = 3.1, 1.7, $C_{alkene}H$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 9.3 (CH_2Sn), 13.9 ($CH_3(CH_2)$), 27.5 ($CH_2(CH_3)$), 27.6 ($CH_2(CH_3)$), 29.3 ($CH_2(CH_2Sn)(CH_2CH_3)$), 125.7 ($C_{alkene}H_2$), 150.5 (C^Q_{alkene}). *m/z* [EI$^+$] 332 [M]$^+$ (100%), HRMS found [M]$^+$ 332.1534, $C_{15}H_{32}{}^{120}Sn$ requires 332.1529; υ_{max} / cm^{-1} (film): 2957, 2928, 2872, 2853, 1458. The data observed is in accordance with literature values.[175]

(±)-4-(3-(*Tert*-Butyldimethylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole **324**



324

Method A: Stille Cross-Coupling

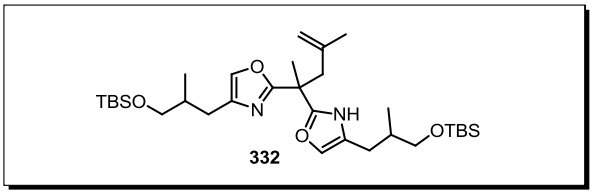
Chloro oxazole **319** (60 mg, 0.21 mmol), stannane **323** (83 mg, 2.28 mmol) and $Pd(PPh_3)_2Cl_2$ (12 mg, 17 µmol) were combined in an oven dried MW vial and degassed anhydrous DMF (2 mL) was added. The resulting heterogeneous solution was heated under an atmosphere of argon under MW irradiation at 130 ^{o}C for 12h. The reaction was cooled and the crude mixture was passed through a pad of Celite and eluted with Et_2O (10 mL). The organics were then washed with water (4 × 4 mL) and brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-2% Et_2O:petroleum ether, afforded alkenyl oxazole **324** (50 mg, 86%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.03 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3C$), 0.92 (3H, d, *J* = 6.7, $(CH_3)CH$), 1.96-2.04 (1H, m, CH), 2.15 (3H, dd, *J* = 1.5, 1.0, $CH_3(C_{alkene})$), 2.32 (1H, ddd, *J* = 14.6, 7.9, 0.9, CH(H)Ar), 2.64 (1H, ddd, *J* = 14.6, 6.1, 1.0, CH(H)Ar), 3.45 (1H, dd, *J* = 9.8, 5.9, CH(H)OSi), 3.50 (1H, dd, *J* = 9.9, 5.5, CH(H)OSi), 5.32 (1H, quint, *J* = 1.5, $C_{alkene}H$), 5.87-5.90 (1H, m, $C_{alkene}H$), 7.30 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.2 $(CH_3)_2Si$), 16.8 ($CH_3(CH)$), 18.5 ($SiC(CH_3)$), 19.3 ($CH_3(C_{alkene})$), 26.1 ($(CH_3)_3C$), 29.9 (CH_2Ar), 35.2 (CH), 67.5 (CH_2OSi), 117.6 ($C_{alkene}H_2$), 132.0 ($C^{Ar}CH_2$), 134.5 ($C^{Ar}H$), 140.7 ($C=CH_2$), 162.4 ($C^{Ar}C_{alkene}$). *m/z* [Cl$^+$, isobutane] 296 [M+H]$^+$ (100%), HRMS found [M+H]$^+$ 296.2049, $C_{16}H_{30}NO_2Si$ requires 296.2046; υ_{max} /cm^{-1} (film): 2959, 2930, 2858, 1671, 1541, 1548, 1465.

Method B: Nucleophilic Aromatic Substitution

To an oven dried flask containing magnesium turnings (10 mg, 0.41 mmol) in anhydrous THF (0.5 mL) was added 2-bromopropene (37 µL, 0.41 mmol) under an atmosphere of argon. The flask was submerged in a sonic water bath and subjected to sonication for 45 min by which time a white precipitation formed. The reaction mixture was cooled to 0 ^{o}C before being transferred via cannulation to a solution of chloro oxazole **319** (60 mg, 0.21 mmol) in

anhydrous THF (0.5 mL) at 0 °C. The resultant reaction mixture was warmed to RT and stirred for a further 6h before being quenched by the addition of water (5 mL) and extracted with Et_2O (3 × 20 mL). The combined organics were washed with water (2 × 5 mL) and brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-2% Et_2O:petroleum ether, afforded unreacted chloro oxazole **319** (30 mg, 103 µmol). Further elution afforded the desired alkenyl oxazole **324** (19 mg, 64 µmol, 31%, 62% brsm) as a colourless oil. The spectral and physical data obtained for **324**, via Method B, matched that obtained via Method A.

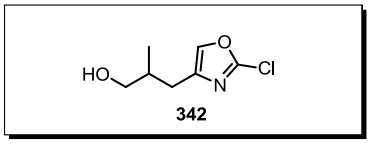
2,2'-(4-Methylpent-4-ene-2,2-diyl)bis(4-(3-(tert-butyldimethylsilyloxy)-2-methylpropyl)oxazole) **332**



332

To an oven dried flask containing magnesium turnings (60 mg, 2.47 mmol) in anhydrous THF (2 mL) was added 2-bromopropene (219 µL, 2.47 mmol) under an atmosphere of argon. The flask was submerged in a sonic water bath and subjected to sonication for 2h by which time a white precipitation formed. The reaction mixture was cooled to 0 °C before being transferred, via cannulation, to a solution of chloro oxazole **319** (120 mg, 0.41 mmol) in anhydrous THF (1 mL) at 0 °C. The resultant reaction mixture was warmed to RT and stirred for a further 6H before being quenched by the addition of water (20 mL) and extracted with Et_2O (3 × 40 mL). The combined organics were washed with water (2 × 10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the bis-oxazole **332** (103 mg, 179 µmol, 44%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: -0.01 (12H, s, $(CH_3)_2Si$), 0.85 (18H, s, $(CH_3)_3C$), 0.86-0.89 (6H, m, $CH_3(CH)$), 1.31 (3H, s, $CH_3(CAr(Ar'))$), 1.74 (3H, s, $CH_3(C_{alkene})$), 1.91-1.99 (2H, m, CH), 2.28 (2H, ddt, *J* = 14.7, 7.7, 0.9, CH(H)Ar), 2.57 (2H, dd, *J* = 14.7, 6.0, CH(H)Ar), 3.00 (2H, s, $CH_2(C_{alkene})$), 3.38 (2H, ddd, *J* = 9.8, 6.0, 3.8, CH(H)OSi), 3.45 (2H, dd, *J* = 9.8, 5.3, CH(H)OSi), 4.60 (1H, s, $C_{alkene}H(H)$), 4.77-4.81 (1H, m, $C_{alkene}H(H)$), 7.26 (2H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.3 (CH_3Si), 16.7 ($CH_3(CH)$), 16.8 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 21.9 ($CH_3(C_{alkene})$, 22.9 ($CH_3(CArAr')$), 26.1 $(CH_3)_3CSi$), 29.8 (CH_2Ar), 29.8 (CH_2Ar), 35.1 ($CH(CH_3)$), 35.2 ($CH(CH_3)$), 42.3 ($C(CH_3)(Ar)(Ar')(CH_2R)$), 46.3 ($CH_2(C_{alkene})$), 67.4 (CH_2OSi), 67.5 (CH_2OSi), 116.1 ($C_{alkene}H_2$), 134.9 ($C^{Ar}H$), 134.9 ($C^{Ar}H$), 139.7 ($C^{Ar}CH_2$), 139.7 ($C^{Ar}CH_2$), 140.7 (C^{Q}_{alkene}), 164.9 ($C^{Ar}C(CH_3)$). *m/z* [CI^+, isobutane] 591 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 591.4019, $C_{32}H_{59}N_2O_4Si_2$ requires 591.4013. υ_{max} /cm^{-1} (film): 2954, 2929, 2896, 2857, 1558, 1471, 1463.

(±)-3-(2-Chlorooxazol-4-yl)-2-methylpropan-1-ol **342**

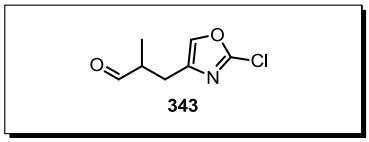


342

A 0 °C solution of chloro oxazole **319** (2.00 g, 6.90 mmol) in anhydrous THF (28 mL) was treated with the dropwise addition of TBAF (1 M in THF, 10.4 mL, 10.4 mmol). After 30 min,

the reaction mixture was warmed up to RT and stirred for 16H before being quenched with water (20 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were washed sequentially with water (3 × 10 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude product that was purified by flash column chromatography, elution with 0-50% Et_2O:petroleum ether to yield alcohol **342** (1.15 g, 6.57 mmol, 95%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.92 (3H, d, *J* = 6.7, CH_3), 1.97-2.06 (1H, m, CH), 2.29 (1H, br. s, OH), 2.43 (1H, ddd, *J* = 14.7, 7.0, 0.8, CH(H)Ar), 2.58 (1H, ddd, *J* = 14.7, 6.2, 1.1, CH(H)Ar), 3.47 (1H, dd, *J* = 11.0, 6.4, CH(H)OH), 3.54 (1H, dd, *J* = 10.9, 5.4, CH(H)OH), 7.40 (1H, br. t, *J* = 0.9, 0.9, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.6 (CH_3), 29.8 (CH_2Ar), 35.0 (CH), 67.0 (CH_2OH), 137.4 (C^{Ar}H), 141.5 ($C^{Ar}CH_2$), 146.6 (C^{Ar}Cl). *m/z* [EI$^+$] 175 [M]$^+$ (100%), HRMS found [M]$^+$ 175.0404, $C_7H_{10}NO_2Cl$ requires 175.0400. υ_{max} /cm^{-1} (film): 3390, 2963, 2930, 2875, 1520.

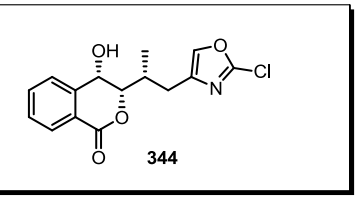
(±)-3-(2-Chlorooxazol-4-yl)-2-methylpropanal **343**



343

A solution of alcohol **342** (1.15 mg, 6.57 mmol) in anhydrous DCM (30 mL) was treated sequentially with BAIB (2.54 g, 7.88 mmol) and TEMPO (103 mg, 0.66 mmol). The resulting mixture was stirred at RT under an atmosphere of argon for 16h before being diluted with DCM (250 mL) and washed with sat'd aq. $Na_2S_2O_3$ solution (2 × 60 mL), water (2 × 30 mL) and brine (30 mL). The organic fraction was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude orange oil. Purification of the crude residue by flash column chromatography, elution with 0-10% Et_2O:petroleum ether, afforded aldehyde **343** (1.09 g, 6.24 mmol 95%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.15 (3H, d, *J* = 7.2), 2.53 (1H, ddd, *J* = 14.9, 7.1, 0.9, CH(H)Ar), 2.76-2.84 (1H, m, CH), 2.93 (1H, ddd, *J* = 14.9, 6.6, 1.1, CH(H)Ar), 7.42 (1H, t, *J* = 1.0, ArH), 9.71 (1H, d, *J* = 1.1, CHO). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.5 (CH_3), 27.1 (CH_2Ar), 45.2 (CH), 137.7 (C^{Ar}H), 140.4 ($C^{Ar}CH_2$), 146.9 (C^{Ar}), 203.5 (CHO). m z [Cl$^+$, isobutane] 174 [M+H]$^+$ (100%), HRMS found [M+H]$^+$ 174.0321, $C_7H_9NO_2Cl$ requires 174.0322. υ_{max} /cm^{-1} (film): 2967, 2930, 2884, 2856, 1724.

(±)-(3*S*,4*S*)-3-((*R*)-1-(2-chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one **344**

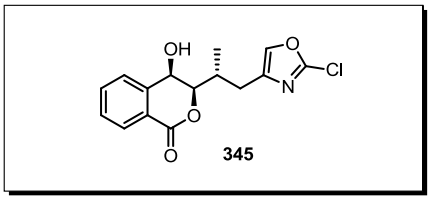


344

Using general procedure 1A, a solution of phthalan **131** (1.36 mg, 9.08 mmol) in anhydrous THF (45 mL) was treated with ^{i}Pr$_2$NH (2.67 mL, 19.1 mmol), *n*BuLi (1.6 M in hexanes, 11.9 mL, 19.1 mmol) and aldehyde **343** (1.67 g, 9.63 mmol) to generate the α-hydroxy-IBF intermediate. Oxidative rearrangement of the crude intermediate was performed using *m*CPBA, (77%, 2.24 g, 9.99 mmol) in anhydrous DCM (45 mL) to afford the crude keto-lactols. Oxidation of the lactol unit was performed in acetone (45 mL) using 2.5 M Jones reagent (6 mL). Purification of the crude residue using flash chromatography, elution with 0-20% Et_2O:petroleum ether, afforded the keto-lactone intermediates (1.60 g, 5.21 mmol 58%) as a 2:3 ratio of *syn*:*anti*

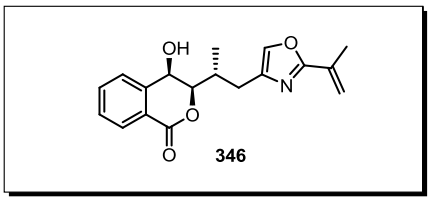
diastereoisomers, as a yellow oil. According to general procedure 2A, reduction was performed in anhydrous DCM (20 mL) with anhydrous $CeCl_3$ (2.19 g, 8.90 mmol), MeOH (16 mL) and $NaBH_4$ (243 mg, 6.68 mmol) at –78 °C. The crude products were purified by flash column chromatography, elution with 0-1% MeOH:DCM, to afford the *syn,syn*-isochromanone **344** (581 mg, 1.89 mmol, 21%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.20 (3H, d, *J* = 6.7, CH_3), 2.56-2.65 (2H, m, $CH(CH_3)$ & CH(H)Ar), 2.77-2.81 (1H, m, CH(H)Ar), 3.05 (1H, br. d, *J* = 6.1, OH), 4.25 (1H, dd, *J* = 8.5, 1.7, $CH(O_2C)$), 4.98 (1H, d, *J* = 3.6, CH(OH)), 7.47 (1H, s, ArH), 7.50 (1H, br. d, *J* = 7.6, ArH), 7.53 (1H, td, *J* = 7.7, 1.2, ArH), 7.66 (1H, td, *J* = 7.5, 1.3, ArH), 8.13 (1H, dd, *J* = 7.8, 1.3, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) 16.2 (CH_3), 28.9 (CH_2Ar), 33.1 ($CH(CH_3)$), 65.3 (CH(OH)), 84.0 ($CH(O_2C)$), 124.3 (C^{Ar}), 128.0 ($C^{Ar}H$), 129.8 ($C^{Ar}H$), 130.4 ($C^{Ar}H$), 134.4 ($C^{Ar}H$), 137.7 ($C^{Ar}H$), 140.2 (C^{Ar}), 140.5 (C^{Ar}), 146.9 (C^{Ar}), 164.8 (CO_2). *m/z* [EI$^+$] 307 [M]$^+$ (100%). HRMS found [M]$^+$ 307.0613, $C_{15}H_{14}NO_4Cl$ requires 307.0611. υ_{max} /cm^{-1} (film): 3399, 3134, 2976, 2934, 1715, 1518, 1462.

(±)-(3*R*,4*R*)-3-((*R*)-1-(2-chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one **345**



Further elution afforded afford the *syn,anti*-isochromanone **345** (889 mg, 2.89 mmol, 32%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (3H, d, *J* = 6.7, CH_3), 2.27-2.28 (1H, m, OH), 2.56-2.65 (2H, m, $CH(CH_3)$ & CH(H)Ar), 3.08 (1H, dd, *J* = 11.2, 1.0, CH(H)Ar), 4.21 (1H, dd, *J* = 9.1, 1.6, $CH(O_2C)$), 4.76 (1H, d, *J* = 3.8, CH(OH)), 7.46-7.47 (2H, m, ArH), 7.54 (1H, td, *J* = 7.6, 1.2, ArH), 7.66 (1H, td, *J* = 7.5, 1.3, ArH), 8.13 (1H, dd, *J* = 7.8, 1.3, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) 15.1 (CH_3), 28.5 (CH_2Ar), 33.1 ($CH(CH_3)$), 65.2 (CH(OH)), 83.7 ($CH(O_2C)$), 124.2 (C^{Ar}), 128.1 ($C^{Ar}H$), 130.0 ($C^{Ar}H$), 130.5 ($C^{Ar}H$), 134.5 ($C^{Ar}H$), 137.9 ($C^{Ar}H$), 140.1 (C^{Ar}), 140.9 (C^{Ar}), 146.4 (C^{Ar}), 164.6 (CO_2). *m/z* [EI$^+$] 307 [M]$^+$ (100%), HRMS found [M]$^+$ 307.0616, $C_{15}H_{14}NO_4Cl$ requires 307.0611. υ_{max} /cm^{-1} (film): 3399, 3129, 2974, 2934, 1717, 1518.

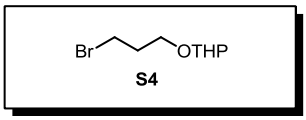
(±)-(3*R*,4*R*)-4-hydroxy-3-((*R*)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one **346**



Syn,anti-isochromanone **345** (197 mg, 0.64 mmol), stannane **323** (251 mg, 0.69 mmol) and $Pd(PPh_3)_2Cl_2$ (36 mg, 51 µmol) were combined together in an oven dried MW vial with degassed, anhydrous DMF (3.2 mL), and heated at 120 °C under MW for 12h under an atmosphere of argon. The crude mixture was passed through a pad of Celite and eluted with Et_2O (50 mL). The organics were then washed with water (2 × 10) and brine (10 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-10% Et_2O:DCM, afforded the alkenyl oxazole **346** (140 mg, 0.45 mmol, 70%), as a pale

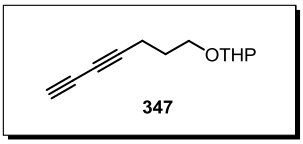
yellow oil ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.16 (3H, d, *J* = 6.7, CH_3(CH)), 2.12 (3H, br. s, CH_3(alkene)), 2.53-2.63 (2H, m, CH_2Ar, CH), 2.93 (1H, d, *J* = 6.8, OH), 3.13-3.16 (1H, m, CH_2Ar), 4.23 (1H, dd, *J* = 8.5, 1.6, CH(O_2C)), 4.79 (1H, d, *J* = 5.4, CH(OH)), 5.32 (1H, br. t, *J* = 1.5, C_{alkene}H), 5.89 (1H, s, C_{alkene}H), 7.39 (1H, s, $C^{Ar}_{oxazole}$H), 7.46 (1H, d, *J* = 7.7, ArH), 7.52 (1H, td, *J* = 7.6, 1.2, ArH), 7,64 (1H, td, *J* = 7.5, 1.4, ArH), 8.14 (1H, dd, *J* = 7.7, 1.2, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.9 (CH_3(CH)), 19.2 (CH_3(C_{alkene})), 28.4 (CH_2Ar), 33.9 (CH(CH_3)), 65.7 (CH(OH)), 84.1 (CH(O_2C)), 117.9 ($C_{alkene}H_2$), 124.5 ($C^{Ar}CH_2$), 128.1 (C^{Ar}H), 130.0 (C^{Ar}H), 130.6 (C^{Ar}H),131.8 ($C^{Ar}CO_2$), 134.5 (C^{Ar}H), 135.1 (C^{Ar}H), 139.7 (C^{Ar}CH(OH)), 140.5 (C^{Q}_{alkene}(CH_2)), 162.5 (C^{Ar}(alkene)), 164.9 (CO_2). *m/z* [Cl^+, isobutane] 314 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 314.1390, $C_{18}H_{20}NO_4$ requires 314.1392. υ_{max} /cm^{-1} (film): 3372, 2961, 2928, 2880, 1713, 1666, 1605, 1556, 1463.

2-(3-Bromopropoxy)tetrahydro-2H-pyran **S4**



3-bromopropanol (3.00 mL, 34.32 mmol), DHP (7.78 mL, 85.79 mmol) and TsOH.H_2O (326 mg, 1.72 mmol) were added to an oven dried flask together with anhydrous DCM (150 mL) and the resultant solution was stirred at RT for 16h under an atmosphere of argon. The reaction mixture was diluted with DCM (150 mL) before being quenched by the addition of sat'd aqueous $NaHCO_3$ solution (60 mL). The organics were collected and further washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a brown oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the desired alkyl bromide **S4** (7.32 g, 33.6 mmol, 98%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.50-1.60 (4H, m, *1H:* CH_2(CH_2)(CH_2CH_2O), *1H:* CH_2(CH_2O)(CH_2CH_2), *2H:* CH_2(CH)), 1.68-1.75 (1H, m, CH_2(CH)), 1.77-1.84 (1H, m, CH_2(CH_2)(CH_2CH_2O)), 2.10-2.16 (2H, m, CH_2(CH_2Br)(CH_2OTHP)), 3.48-3.55 (4H, m, *1H:* CH_2OTHP, *1H:* CH_2O($CH_2CH_2CH_2$), *2H:* CH_2Br), 3.83-3.89 (2H, m, 1H: CH_2OTHP, *1H:* CH_2O($CH_2CH_2CH_2$)), 4.60 (1H, t, *J* = 2.8, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.6 (CH_2(CH_2)(CH_2CH_2O)), 25.6 (CH_2(CH_2O)(CH_2CH_2)), 30.7 (CH_2Br), 30.8 (CH_2(CH)), 33.0 (CH_2(CH_2Br)(CH_2OTHP)), 62.4 (CH_2O), 65.0 (CH_2OTHP), 99.0 (CH). *m/z* [Cl^+, isobutane] 223 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 223.0335, $C_8H_{16}O_2Br$ requires 223.0334. υ_{max} /cm^{-1} (film): 2941, 2870, 1441. The data observed is in accordance with literature values.[175]

2-(hepta-4,6-diynyloxy)tetrahydro-2H-pyran **347**



To a flame dried flask was added diyne **341** (300 mg, 1.54 mmol) and anhydrous THF (3 mL) and cooled to –78 ^{o}C under an atmosphere of argon. MeLi.LiBr (1.5 M in Et_2O, 1.06 mL, 1.59 mmol) was added dropwise and after 5 min the reaction mixture was warmed to RT and stirred for a further 2h. TLC analysis indicated all of starting material had been consumed. An anhydrous solution of bromide **S4** (387 mg, 1.77 mmol) in DMPU (3 mL) was added dropwise at –78 ^{o}C and stirred for a further 30 min before being warmed to RT and stirred for a further 30 min. The reaction was quenched by the addition of water (20 mL) before being extracted with Et_2O (3 × 50 mL). The combined organics were collected and washed with water (20 mL)

and brine (20 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude intermediate, as a brown oil, which was dissolved in anhydrous THF (5 mL) and TBAF (1 M in THF, 1.70 mL, 1.70 mmol) was added and the reaction mixture was stirred at RT for 4h before being quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organics were washed with water (10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a brown oil. Purification by flash column chromatography, elution with 0-7% Et_2O:petroleum ether, afforded the diyne **347** (200 mg, 1.04 mmol, 67%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.50-1.59 (4H, m, *1H:* $CH_2(CH_2)(CH_2CH_2O)$, *1H:* $CH_2(CH_2O)(CH_2CH_2)$, *2H:* $CH_2(CH)$), 1.67-1.74 (1H, m, $CH_2(CH)$), 1.77-1.80 (1H, m, $CH_2(CH_2)(CH_2CH_2O)$), 1.82 (2H, quint, *J* = 6.5, $CH_2(CH_2OTHP)(CH_2')$), 1.95 (1H, *J* = 1.2, $C_{alkyne}H$), 2.39 (2H, t, *J* = 7.0, $CH_2(alkyne)(CH_2')$), 3.43-3.53 (2H, m, *1H:* CH_2OTHP, *1H:* $CH_2O(CH_2CH_2CH_2)$), 3.78-3.88 (2H, m, *1H:* CH_2OTHP, *1H:* $CH_2O(CH_2CH_2CH_2)$), 4.58 (1H, t, *J* = 7.0, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.2 ($CH_2(alkyne)(CH_2')$), 19.6 ($CH_2(CH_2)(CH_2CH_2O)$), 25.6 ($CH_2(CH_2O)(CH_2CH_2)$), 28.4 ($CH_2(CH_2OTHP)(CH_2')$, 30.7 ($CH_2(CH)$), 62.3 (CH_2O), 64.7 ($C_{alkyne}H$), 65.0 (C^Q_{alkyne}), 65.8 (CH_2OTHP), 68.5 (C^Q_{alkyne}), 77.9 (C^Q_{alkyne}), 99.0 (CH). *m/z* [CI^+, isobutane] 193 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 193.1228, $C_{12}H_{17}O_2$ requires 193.1229. υ_{max} /cm^{-1} (film): 3295, 2940, 2870, 2295, 2222, 1443, 1350. The data observed is in accordance with literature values.[108]

(Bromoethynyl)tri*iso*propylsilane **353**

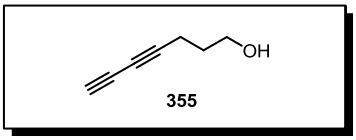
Ethynyltri*iso*propylsilane (0.50 mL, 2.25 mmol), $AgNO_3$ (38 mg, 0.23 mmol) and freshly recrystalized NBS (441 mg, 2.48 mmol) were dissolved in acetone (12 mL) and the resultant solution was stirred at RT for 50 min by which time a white precipitate had formed. The suspension was then filtered (washed with petroleum ether) and the supernatant was collected and the solvent evaporated to afford the crude product as a white gum. The crude gum was then triturated with petroleum ether and the supernatant was collected and solvent evaporated to afford the bromo acetylene **353** (582 mg, 2.23 mmol, 99%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.07 (21H, app. s, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.4 (CH), 18.6 (CH_3), 61.8 ($C_{alkyne}Br$), 83.6 ($C_{alkyne}TIPS$).*m/z* [EI^+] 262 $[M]^+$ (100%), HRMS found $[M]^+$ 260.0602, $C_{11}H_{21}BrSi$ requires 260.0596. υ_{max} /cm^{-1} (film): 2959, 2943, 2892, 2866, 2121, 1463. The data observed is in accordance with literature values.[176]

7-(triisopropylsilyl)hepta-4,6-diyn-1-ol **354**

CuCl (64 mg, 0.65 mmol) was added to a fla*sk* containing ^{n}BuNH$_2$ (30% w/w in H_2O, 10 mL) resulting in a blue solution. $NH_2OH.HCl$ crystals were added until the blue colour dissipated, followed by the addition of 4-pentyn-1-ol (1.01 mL, 10.9 mmol). Within 2 min a bright orange salt has formed and the reaction mixture was immediately cooled to 0 ^{o}C before the dropwise addition of bromo acetylene **353** (2.82 g, 10.9 mmol). Immediately the reaction mixture turned to a burnt orange colour. After stirring for a further 5 min the reaction was diluted with water

(50 mL) before being extracted with Et_2O (3 × 100 mL). The combined organics were washed with water (2 × 25 mL) and brine (25 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as an oil. Purification by flash column chromatography, elution with 0-50% DCM:petroleum ether, afforded the desired product, diyne **354** (2.80 g, 10.6 mmol, 97%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.06 (21H, app. s, TIPS), 1.77 (2H, quint, *J* = 6.6, $CH_2(CH_2OH)(CH_2C_{alkyne})$), 1.88 (1H, br. s, OH), 2.40 (2H, t, *J* = 7.0, $CH_2(C_{alkyne})$), 3.73 (2H, t, *J* = 6.1, CH_2OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 11.4 ($SiCH(CH_3)_2$), 15.9 ($CH_2(C_{alkyne})$), 18.6 ($(CH_3)_2CH$), 30.9 ($CH_2(CH_2OSi)(CH_2C_{alkyne})$), 61.4 ($CH_2OH$), 66.4 ($C_{alkyne}(C_{alkyne}CH_2)$), 78.0 ($C_{alkyne}$TIPS), 80.5 ($C_{alkyne}(CH_2)$), 90.0 ($C_{alkyne}(C_{alkyne}$TIPS)). *m/z* [$Cl^+$, isobutane] 265 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 265.1990, $C_{16}H_{29}OSi$ requires 265.1988. υ_{max} /cm^{-1} (film): 3325, 2940, 2862, 2222, 2106, 1466.

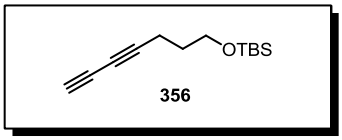
Hepta-4,6-diyn-1-ol **355**



355

Diyne **354** (219 mg, 0.83 mmol) was dissolved in anhydrous THF (4 mL) before the dropwise addition of TBAF (1 M in THF, 1.00 mL, 1.00 mmol) under an atmosphere of argon at RT. The reaction mixture was stirred for a further 2h before being quenched with water (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organics were washed with water (2 × 5 mL) and brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-100% DCM:petroleum ether, afforded diyne **355** (83 mg, 0.77 mmol, 93%) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.38 (1H, t, *J* = 5.1, OH), 1.79 (2H, quint, *J* = 6.5, $CH_2(CH_2OH)(CH_2C_{alkyne})$), 1.97 (1H, s, $C_{alkyne}H$), 2.40 (2H, t, *J* = 7.0, $CH_2(C_{alkyne})$), 3.75 (2H, q, *J* = 5.7, CH_2OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.7 ($CH_2(C_{alkyne})$), 30.8 ($CH_2(CH_2OSi)(CH_2C_{alkyne})$), 61.4 ($CH_2OH$), 64.9 ($C_{alkyne}H$), 65.2 ($C_{alkyne}(C_{alkyne}H)$), 68.4 ($C_{alkyne}(C_{alkyne}CH_2)$, 77.7 ($C_{alkyne}(CH_2)$). *m/z* [$Cl^+$, isobutane] 109 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 109.0666, C_7H_9O requires 109.0653. υ_{max} /cm^{-1} (film): 3356, 3302, 2947, 2886, 2230, 1427. The data observed is in accordance with literature values.[177]

Tert-butyl(hepta-4,6-diynyloxy)dimethylsilane **356**

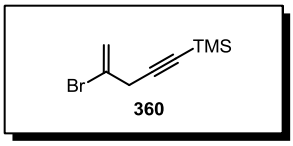


356

Diyne **355** (41 mg, 0.38 mmol) was dissolved in anhydrous DMF (1 mL) together with finely ground imidazole (52 mg, 0.76 mmol) and TBSCl (69 mg, 0.46 mmol) and stirred under argon at RT for 2h. The reaction mixture was quenched with water (10 mL) and extracted with DCM (3 × 30 mL) and the combined organics were washed sequentially with water (5 × 20 mL) and brine (30 mL) before being dried over anhydrous Na_2SO_4 and the solvent evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-2.5% Et_2O:petroleum ether, afforded silyl ether **356** (79 mg, 0.36 mmol, 94%) as colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.06 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.70-1.77 (2H, m, $CH_2(CH_2OH)(CH_2C_{alkyne})$), 1.95 (1H, t, *J* = 1.1, $C_{alkyne}H$), 2.36 (2H, td, *J* = 7.1, 1.1, $CH_2(C_{alkyne})$), 3.68 (2H, t, *J* = 5.9, CH_2OSi). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.2 ($(CH_3)_2Si$), 15.7 ($CH_2(C_{alkyne})$), 18.4

($SiC(CH_3)_3$), 26.0 ($(CH_3)_3CSi$), 31.2 ($CH_2(CH_2OSi)(CH_2C_{alkyne})$), 61.4 ($CH_2OSi$), 64.6 ($C_{alkyne}H$), 64.9 ($C_{alkyne}(C_{alkyne}H)$), 68.6 ($C_{alkyne}(C_{alkyne}CH_2)$), 78.3 ($C_{alkyne}(CH_2)$). *m/z* [$CI^+$, isobutane] 223 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 223.1523, $C_{13}H_{23}OSi$ requires 223.1518. υ_{max} /cm^{-1} (film): 3310, 2955, 2932, 2862, 2308, 2222, 1466.

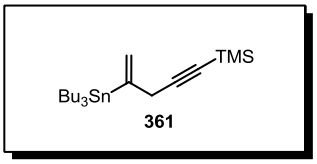
4-Bromopent-4-en-1-ynyl)trimethylsilane **360**



360

To a flame dried flask was added anhydrous THF (17 mL) and ethynyltrimethylsilane (0.50 mL, 3.54 mmol) and the solution was cooled to 0 ^oC under an atmosphere of argon. EtMgBr (1 M in THF, 3.54 mL, 3.54 mmol) was added dropwise and the resultant solution was warmed to RT and then heated at 50 ^oC for 30 min before being cooled back down to RT. $CuBr.Me_2S$ was added to the reaction mixture and was heated to 40 ^oC for 30 min before 2,3-dibromopropene was added and the resultant mixture heated to 55 ^oC for 2h, under a atmosphere of argon. Upon cooling to 0 ^oC the reaction was quenched by the addition of sat'd aq. NH_4Cl solution (40 mL) and extracted with Et_2O (3 × 75 mL). The combined organics were washed with water (2 × 40 mL) and brine (40 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a pale yellow oil. Purification by flash column chromatography, elution with petroleum ether, afforded vinyl bromide **360** (606 mg, 2.79 mmol, 79%) as a colourless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.18 (9H, s, $Si(CH_3)_3$), 3.37 (2H, t, *J* = 1.6, CH_2), 5.56 (1H, q, *J* = 1.6, $C_{alkene}H_2$), 6.02 (1H, q, *J* = 1.6, $C_{alkene}H_2$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.0 ($Si(CH_3)_3$), 32.8 (CH_2), 89.0 ($C_{alkyne}(CH_2)$), 101.1 ($C_{alkyne}TMS$), 118.1 ($C_{alkene}H_2$), 126.8 ($C_{alkene}(CH_2)(CH_2)Br$). *m/z* [EI^+] 217 $[M]^+$ (100%). HRMS found $[M]^+$ 217.0022, $C_8H_{14}BrSi$ requires 217.0048. υ_{max} /cm^{-1} (film): 2963, 2901, 2183, 1636, 1412.

Trimethyl(4-(tributylstannyl)pent-4-en-1-ynyl)silane **361**

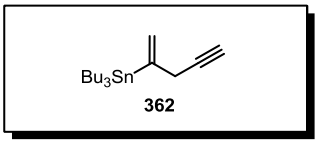


361

To a flask containing magnesium turnings (282 mg, 11.6 mmol), anhydrous THF (30 mL) was added followed by Bu_3SnCl (2.64 mL, 9.74 mmol). The mixture was sonicated under an atmosphere of argon at RT for 2 min before vinyl bromide **360** (2.01 g, 9.27 mmol) in anhydrous THF (10 mL) was added dropwise. The reaction mixture was subjected to sonication for 60 min. The reaction was quenched by the addition of water (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organics were washed with water (40 mL), sat'd aq. KF solution (2 × 50 mL) and brine (50 mL), before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with petroleum ether, afforded the stannane **361** (3.32 g, 7.77 mmol, 84%) as a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.16 (9H, s, $(CH_3)_3Si$), 0.88-0.97 (15H, m, $CH_3(CH_2)$, CH_2Sn), 1.27-1.36 (6H, m, $(CH_2(CH_3))$), 1.47-1.55 (6H, m, $CH_2(CH_2Sn)(CH_2CH_3)$), 3.17 (2H, t, *J* = 1.7, CH_2(alkene)(alkyne)), 5.22-5.23 (1H, m, CH_{alkene}), 5.90-5.91 (1H, m, CH_{alkene}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 0.3 ($(CH_3)_3Si$), 10.0 (CH_2Sn), 13.9 ($CH_3(CH_2)$), 27.6 ($CH_2(CH_3)$), 29.3 ($CH_2(CH_2Sn)(CH_2CH_3)$), 31.5 (CH_2(alkene)(alkyne)), 87.4

($C_{alkyne}(CH_2)$), 104.9 ($C_{alkyne}(TMS)$), 126.3 ($C_{alkene}H_2$), 148.7 (C_{alkene}). υ_{max} /cm^{-1} (film): 2955, 2924, 1466.

Tributyl(pent-1-en-4-yn-2-yl)stannane **362**



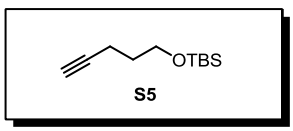
Method A: K_2CO_3

Stannane **361** (191 mg, 0.45 mmol) was dissolved in MeOH (2.5 mL), together with K_2CO_3 (65 mg, 0.47 mmol), and the resultant mixture was stirred at RT for 24h before being quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organics were washed with water (2 × 20 mL), and brine (20 mL) before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with petroleum ether, afforded the desired acetylene **362** (135 mg, 0.38 mmol, 84%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88-0.94 (15H, m, $CH_3(CH_2)$, CH_2Sn), 1.26-1.33 (6H, m, ($CH_2(CH_3)$), 1.44-1.52 (6H, m, $CH_2(CH_2Sn)(CH_2CH_3)$), 2.12 (1H, *J* = 2.6, $C_{alkyne}H$), 3.09-3.10 (2H, m, CH_2(alkene)(alkyne)), 5.22-5.23 (1H, m, CH_{alkene}), 5.92-5.93 (1H, m, CH_{alkene}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.8 (CH_2Sn), 13.8 ($CH_3(CH_2)$), 27.5 ($CH_2(CH_3)$), 29.2 ($CH_2(CH_2Sn)(CH_2CH_3)$), 29.7 (CH_2(alkene)(alkyne)), 71.2 ($C_{alkyne}H$), 82.2 ($C_{alkyne}(CH_2)$), 126.4 ($C_{alkene}H_2$), 148.3 (C_{alkene}). υ_{max} /cm^{-1} (film): 3310, 2955, 2947, 2855, 2122, 1458, 1422.

Method B: TBAF

Stannane **361** (114 mg, 0.27 mmol) was dissolved in anhydrous THF (1.3 mL) and cooled to 0 ^{o}C under an atmosphere of argon, before the dropwise addition of TBAF (1 M in THF, 0.29 mL, 0.29 mmol) and the resultant mixture was stirred for 30 min, before being warmed to RT and stirred for an additional 2h. The reaction was quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organics were washed with water (2 × 10 mL), and brine (15 mL) before being dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with petroleum ether, afforded the desired acetylene **362** (71 mg, 0.20 mmol, 75%) as a colourless oil. The spectral and physical data obtained for **362**, via Method B, matched that obtained via Method A.

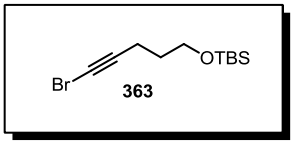
Tert-butyldimethyl(pent-4-ynyloxy)silane **S5**



4-pentyn-1-ol (940 µL, 10.34 mmol) was dissolved in anhydrous DMF (10 mL) together with finely ground imidazole (1.41 g, 20.7 mmol) and TBSCl (1.64 g, 10.86 mmol) and stirred under argon at RT for 2h. The reaction mixture was diluted with Et_2O (50 mL) before being washed sequentially with water (5 × 80 mL) and brine (50 mL) before being dried over anhydrous Na_2SO_4, and the solvent evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-1.5% Et_2O:petroleum ether, afforded the desired silyl ether **S5**

(1.99 g, 10.0 mmol, 97%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.06 (6H, s, $(CH_3)_2Si$)), 0.89 (9H, s, $(CH_3)_3CSi$), 1.69-1.76 (2H, m, $CH_2(CH_2OSi)(CH_2C_{alkyne})$, 1.92 (1H, t, *J* = 2.7, $C_{alkyne}H$), 2.27 (2H, td, *J* = 7.1, 2.7, $CH_2(C_{alkyne})$), 3.70 (2H, t, *J* = 6.1, CH_2OSi). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -5.2 ($(CH_3)_2Si$), 15.0 (CH_2Br), 18.4 ($SiC(CH_3)_3$), 26.0 ($(CH_3)_3CSi$), 31.7 ($CH_2(CH_2OSi)(CH_2C_{alkyne})$), 61.6 ($CH_2OSi$), 68.3 ($C_{alkyne}H$), 84.4 ($C_{alkyne}(CH_2)$). *m/z* [$Cl^+$, isobutane] 199 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 199.1517, $C_{11}H_{23}OSi$ requires 199.1518. υ_{max} /cm^{-1} (film): 3310, 2955, 2932, 2862, 2235, 1466. The data observed is in accordance with literature values.[178]

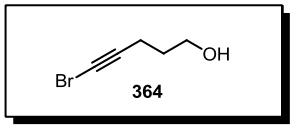
(5-bromopent-4-ynyloxy)(*tert*-butyl)dimethylsilane **363**



363

Acetylene **S5** (1.62 mg, 8.16 mmol), $AgNO_3$ (139 mg, 0.82 mmol) and freshly recrystallised NBS (1.53 g, 8.57 mmol) were dissolved in anhydrous acetone (40 mL), and the resultant solution was stirred at RT under an atmosphere of argon. The reaction mixture was stirred for 50 min by which time a white precipitate had formed. Reaction completion was indicated by TLC analysis. The suspension was filtered (elution with petroleum ether) and the supernatant was collected and the solvent evaporated to afford the crude product as a white gum. The crude gum was then triturated with petroleum ether and the supernatant was collected and solvent evaporated to afford bromo acetylene **363** (2.23 g, 8.04 mmol, 99%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.06 (6H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 1.72 (2H, m, $CH_2(CH_2OTBS)(CH_2C_{alkyne})$), 2.30 (2H, t, *J* = 7.1, $CH_2(C_{alkyne})$), 3.68 (2H, t, *J* = 5.9, CH_2OTBS). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -5.2 ($(CH_3)_2Si$), 16.3 ($CH_2(C_{alkyne})$), 18.5 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3CSi$), 31.4 ($CH_2(CH_2OSi)(CH_2C_{alkyne})$), 61.5 ($CH_2OTBS$), 77.4 ($C_{alkyne}$), 80.1 ($C_{alkyne}$). *m/z* [$Cl^+$, isobutane] 277 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 277.0626, $C_{11}H_{22}OBrSi$ requires 277.0623. υ_{max} /cm^{-1} (film): 2955, 2932, 2863, 1466. The data observed is in accordance with literature values.[177]

5-Bromopent-4-yn-1-ol **364**



364

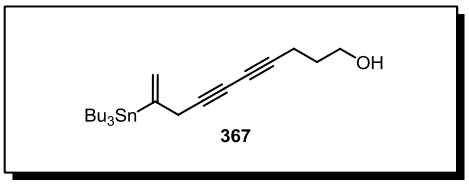
Method A: Desilylation of Silyl Ether **363**

Silyl ether **363** (849 mg, 3.06 mmol) was dissolved in anhydrous THF (12 mL), before the dropwise addition of TBAF (1 M in THF, 3.52 mL, 3.52 mmol) under an atmosphere of argon at RT. The reaction mixture was stirred for a further 60 min before being quenched with water (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organics were washed with water (2 × 5 mL) and brine (5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded alcohol **364** (493 mg, 3.02 mmol, 99%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (1H, s, OH), 1.76 (2H, app. quint, *J* = 6.6, $CH_2(CH_2OH)(CH_2')$), 2.34 (2H, t, *J* = 7.0, CH_2(alkyne)), 3.74 (2H, t, *J* = 6.1, CH_2OH). ^{1}13 NMR ($CDCl_3$, 100 MHz) δ: 16.3 (CH_2(alkyne)), 31.0 ($CH_2(CH_2OH)(CH_2')$), 38.4 (C_{alkyne}) 61.5 (CH_2OH), 79.7 (C_{alkyne}). The data observed is in accordance with literature values.[115]

Method B: Bromination of Acetylene **364**

In the absence of light, KOH (4.94 g, 88.1 mmol) was dissolved in distilled water (85 mL), cooled to 0 ^{o}C, before Br_2 (1.18 mL, 23.1 mmol) was added, followed by the addition of pent-4-yn-1-ol (2.00 mL, 22.0 mmol). The resultant reaction mixture was stirred at 0 ^{o}C for 3h. The aqueous reaction mixture was extracted with Et_2O (3 × 100 mL) and the combined organics were washed with water (20 mL) and brine (20 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded alcohol **364** (2.33 g, 14.3 mmol, 65%) as a pale yellow oil. The spectral and physical data obtained for **2364**, via Method B, matched that obtained via Method A.

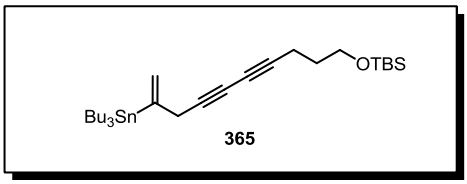
9-(Tributylstannyl)deca-9-en-4,6-diyn-1-ol **367**



367

CuCl (14 mg, 0.14 mmol) was added to a fla*sk* containing $^{n}BuNH_2$ (30% w/w in H_2O, 2 mL) resulting in a blue solution. $NH_2OH.HCl$ crystals were added until the blue colour dissipated, followed by the addition of acetylene **362** (815 mg, 2.30 mmol) Within 2 min a bright orange salt has formed and the reaction mixture was immediately cooled to 0 ^{o}C before the dropwise addition of bromo acetylene **364** (450 mg, 2.76 mmol). Immediately the reaction mixture turned to a burnt orange colour. After stirring for a further 5 min, the reaction was diluted with water (10 mL) before being extracted with Et_2O (3 × 50 mL). The combined organics were washed with water (2 × 15 mL) and brine (25 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as an oil. Purification by flash column chromatography, elution with 0-75% DCM:petroleum ether, afforded the desired diyne **367** (802 mg, 1.83 mmol, 80%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88-0.97 (15H, m, $CH_3(CH_2)$, CH_2Sn), 1.27-1.36 (6H, m, $(CH_2(CH_3))$), 1.46-1.55 (6H, m, $CH_2(CH_2Sn)(CH_2CH_3)$), 1.78 (2H, quint, *J* = 6.4, $CH_2(CH_2OH)(CH_2')$), 2.40 (2H, t, *J* = 6.9, CH_2(alkyne)(CH_2')), 3.18 (2H, br. s, CH_2(alkene)(alkyne), 3.75 (2H, q, *J* = 5.9, CH_2OH), 5.24-5.24 (1H, m, $C_{alkene}H$), 5.91-5.92 (1H, m, $C_{alkene}H$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.8 (CH_2Sn), 13.8 ($CH_3(CH_2)$), 15.9 (CH_2(alkyne)(CH_2')), 27.5 ($CH_2(CH_3)$), 29.2 ($CH_2(CH_2Sn)(CH_2CH_3)$), 30.5 (CH_2(alkene)(alkyne)), 31.2 ($CH_2(CH_2OH)(CH_2')$), 61.5 (CH_2OH), 65.9 (C_{alkyne}), 68.1 (C_{alkyne}), 75.2 (C_{alkyne}), 77.5 (C_{alkyne}), 126.9 ($C_{alkene}H_2$), 147.9 (C_{alkene}). *m/z* [CI^+, isobutane] 437 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 437.1871, $C_{22}H_{37}O^{120}Sn$ requires 437.1871. υ_{max} /cm^{-1} (film): 3315, 2955, 2927, 2871, 2854, 1458.

Tert-butyldimethyl(9-(tributylstannyl)deca-9-en-4,6-diynyloxy)silane **365**



365

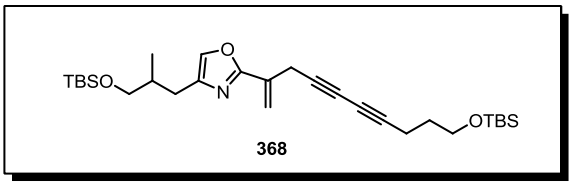
Method A: Cadiot-Chodkiewicz Coupling from Acetylene **362**

CuCl (9 mg, 89 μmol) was added to a flask containing $^{n}BuNH_2$ (30% w/w in H_2O, 1.5 mL) resulting in a blue solution. $NH_2OH.HCl$ crystals were added until the blue colour dissipated, followed by the addition of acetylene **362** (525 mg, 1.48 mmol) was added. Within 2 min a bright orange salt has formed and the reaction mixture was immediately cooled to 0 ^{o}C before the dropwise addition of bromo acetylene **363** (373 mg, 1.35 mmol). Immediately the reaction mixture turned to a burnt orange colour. After stirring for a further 5 min the reaction was diluted with water (10 mL) before being extracted with Et_2O (3 × 50 mL). The combined organics were washed with water (2 × 15 mL) and brine (25 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as an oil. Purification by flash column chromatography, elution with 0-1% Et_2O:petroleum ether, afforded diyne **365** (511 mg, 0.93 mmol, 69%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.05 (6H, s, $(CH_3)_2Si$), 0.88-0.96 (15H, m, $CH_3(CH_2)$, CH_2Sn), 0.89 (9H, s, $(CH_3)_3CSi$), 1.28-1.35 (6H, m, $(CH_2(CH_3))$), 1.47-1.55 (6H, m, $CH_2(CH_2Sn)(CH_2CH_3)$), 1.72 (2H, quint, *J* = 6.5, $CH_2(CH_2OTBS)(CH_2')$), 2.35 (2H, t, *J* = 7.0, $CH_2(alkyne)(CH_2')$), 3.18 (2H, s, $CH_2(alkene)(alkyne)$, 3.68 (2H, t, *J* = 6.0, CH_2OTBS), 5.24 (1H, br. d, *J* = 1.7, $C_{alkene}H$), 5.91 (1H, br. d, *J* = 1.7, $C_{alkene}H$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.2 ($(CH_3)_2Si$), 9.8 (CH_2Sn), 13.8 (CH_3CH_2), 15.8 ($CH_2(alkyne)(CH_2')$), 18.4 ($SiC(CH_3)_3$), 26.0 ($(CH_3)_3CSi$), 27.5 ($CH_2(CH_3)$), 29.2 ($CH_2(CH_2Sn)(CH_2CH_3)$), 30.6 ($CH_2(alkene)(alkyne)$), 31.5 ($CH_2(CH_2OTBS)(CH_2')$), 61.5 (CH_2OTBS), 65.5 (C_{alkyne}), 68.3 (C_{alkyne}), 74.8 (C_{alkyne}), 78.1 (C_{alkyne}), 126.8 ($C_{alkene}H_2$), 148.0 (C_{alkene}). *m/z* [CI^+, isobutane] 553 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 553.2890, $C_{28}H_{53}OSi^{120}Sn$ requires 553.2893. υ_{max} /cm^{-1} (film): 2954, 2928, 2856, 1472, 1464.

Method B: Silylation of Alcohol **367**

Alcohol **367** (1.88 g, 4.30 mmol) was dissolved in anhydrous DMF (7 mL), to which imidazole (585 mg, 8.60 mmol) and TBSCl (745 mg, 4.94 mmol) were added. The resultant suspension was stirred at RT under an atmosphere of argon. After 3h, TLC analysis indicated reaction completion. Water (30 mL) was added before extraction with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (2 × 30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product as a pale yellow oil. Purification by flash column chromatography, elution with 0-2% Et_2O:petroleum ether, yielded diyne **365** (2.24 g, 4.06 mmol, 94%) as a colourless oil. The spectral and physical data obtained for **365**, via Method B, matched that obtained via Method A.

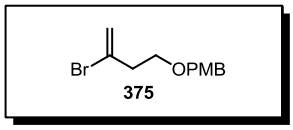
4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(10-(*tert*-butyldimethylsilyloxy)deca-1-en-4,6-diyn-2-yl)oxazole **368**



368

Chloro oxazole **319** (131 mg, 0.45 mmol), stannane **365** (270 mg, 0.49 mmol) and $Pd(PPh_3)_4$ (32 mg, 45 µmol) were combined together in an oven dried MW vial with degassed anhydrous DMF (2 mL), and heated under MW irradiation at 120 ^oC for 12h, under an atmosphere of argon. The crude mixture was passed through a pad of Celite and eluted with Et_2O (30 mL). The organics were then washed with water (4x10 mL) and brine (10 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a brown oil. Purification by flash column chromatography, elution with 0-2% Et_2O:petroleum ether, afforded alkenyl oxazole **368** (164 mg, 0.32 mmol, 70%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (6H, s, $(CH_3)_2Si$), 0.06 (6H, s, $(CH_3)_2Si$), 0.89 (18H, br. s, $(CH_3)_3Si$ *x2*), 0.90 (3H, d, *J* = 6.9, $CH_3(CH)$), 1.73 (2H, quint, *J* = 6.5, $CH_2(CH_2OTBS)(CH_2')$), 1.94-2.02 (1H, m, $CH(CH_3)$), 2.30 (1H, dd, *J* = 14.9, 7.5, CH(H)Ar), 2.37 (2H, t, *J* = 7.0, $CH_2(alkyne)(CH_2')$), 2.62 (1H, dd, *J* = 14.0, 6.9, CH(H)Ar), 3.43-3.51 (2H, m, $CH_2OTBS(CH)$), 3.51 (2H, br. s, $CH_2(alkene)(alkyne)$, 3.69 (2H, t, *J* = 5.9, CH_2OTBS), 5.78 (1H, br. s, $C_{alkene}H$), 6.09 (1H, br. s, $C_{alkene}H$), 7.31 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -5.3 ($(CH_3)_2Si$), -5.2 ($(CH_3)_2Si$), 15.8 ($CH_2(alkyne)(CH_2')$), 16.7 ($CH_3(CH)$), 18.4 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$, 23.0 ($CH_2(alkene)(alkyne)$, 26.1 ($(CH_3)_3CSi$), 26.1 ($(CH_3)_3CSi$), 29.8 (CH_2Ar), 31.4 ($CH_2(CH_2OTBS)(CH_2')$), 35.2 ($CH(CH_3)$), 61.5 (CH_2OTBS), 65.2 (C_{alkyne}), 67.5 ($CH_2OTBS(CH)$), 68.9 (C_{alkyne}), 72.6 (C_{alkyne}), 78.6 (C_{alkyne}), 118.2 ($C_{alkene}H_2$), 130.6 ($C^{Ar}(CH_2)$), 134.9 ($C^{Ar}H$), 140.8 ($C_{alkene}(C^{Ar})$), 160.6 (C^{Ar}(alkene)). *m/z* [FAB$^+$, NOBA] 516 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 516.3329, $C_{29}H_{50}O_3Si_2$ requires 516.3329. υ_{max} /cm^{-1} (film): 2954, 2928, 2857, 1590, 1531.

1-((3-Bromobut-3-enyloxy)methyl)-4-methoxybenzene **375**

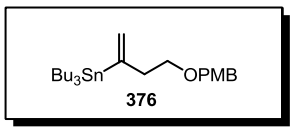


375

3-bromobut-3-en-1-ol (1.22 g, 8.13 mmol) was dissolved in anhydrous DCM (40 mL) and cooled to 0 ^oC before the dropwise addition of freshly prepared 4-methoxybenzyl-2,2,2-trichloroacetimidate (2.76 g, 9.76 mmol). CSA (94 mg, 0.41 mmol) was added to the reaction mixture and the resultant solution was stirred at 0 ^oC under argon before being warmed to RT and stirred for a further 16h. The reaction mixture was filtered through a pad of Celite, and the resultant organics were washed sequentially with sat'd aq. $NaHCO_3$ solution (10 mL), water (2 × 10 mL) and brine (10 mL), before being dried over anhydrous Na_2SO_4, and the solvent evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-2.5% Et_2O:petroleum ether, afforded PMB-ether **375** (1.87 g, 6.91 mmol, 85%) as colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.71 (2H, td, *J* = 6.4, 0.6, $CH_2(alkene)(CH_2OPMB)$), 3.63 (2H, t, *J* = 6.4, CH_2OPMB), 5.48 (1H, br. d, *J* = 1.6, $C_{alkene}H$), 5.66 (1H, br. d, $C_{alkene}H$), 6.88 (2H, d, *J* = 8.6, $C^{Ar}H$), 7.26 (2H, d, *J* = 8.6, $C^{Ar}H$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 41.9 ($CH_2(alkene)(CH_2OPMB)$), 55.4 (CH_3O), 67.6 (CH_2OPMB), 72.9 (OCH_2Ar) 113.9 (ArH), 118.5 ($C_{alkene}H_2$), 129.4 ($C^{Ar}H$), 159.4 (C^{Q}_{alkene}). *m/z* [EI$^+$] 270 $[M]^+$ (100%), HRMS found $[M]^+$ 270.0258,

$C_{12}H_{15}O_2Br$ requires 270.0255. υ_{max} /cm^{-1} (film): 2936, 2909, 2859, 2835, 1632, 1613 1586, 1512, 1462.

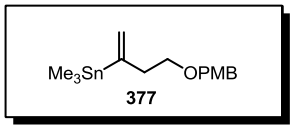
Tributyl(4-(4-methoxybenzyloxy)but-1-en-2-yl)stannane **376**



376

Vinyl bromide **375** (1.22 g, 4.52 mmol) was dissolved in anhydrous THF (15 mL) and cooled to –78 °C under an atmosphere of argon. ^{t}BuLi (1.9 M in pentane, 4.75 mL, 9.03 mmol) was added quickly over 1 min, and the resultant solution was stirred for 10 min, before Bu_3SnCl (1.26 mL, 4.65 mmol) was added. After stirring to 10 min at –78 °C, the reaction was quenched by the addition of water (20 mL), and allowed to warm to RT, before being extracted with Et_2O (3 × 50 mL). The resultant organics were washed sequentially with water (20 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4, and the solvent evaporated, to afford the crude product. Purification by flash column chromatography, elution with 0-1.25% Et_2O:petroleum ether, afforded vinyl stannane **376** (1.86 g, 3.86 mmol, 86%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.84-0.90 (15H, m, $CH_3(CH_2)$, CH_2Sn), 1.25-1.34 (6H, m, $CH_2(CH_3)$), 1.42-1.50 (6H, m, $CH_2(CH_2Sn)(CH_2CH_3)$), 2.55 (2H, t, *J* = 7.1, CH_2(alkene)(CH_2OPMB)), 3.45 (2H, t, *J* = 7.1, CH_2OPMB), 3.80 (3H, s, OCH_3), 4.44 (2H, s, CH_2Ph(*p*-OMe)), 5.18-5.18 (1H, m, $C_{alkene}H$), 5.73-5.75 (1H, m, $C_{alkene}H$), 6.87 (2H, d, *J* = 8.6, ArH), 7.26 (2H, d, *J* = 8.6, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 9.8 (CH_2Sn), 13.8 ($CH_3(CH_2)$), 27.6 ($CH_2(CH_3)$), 29.2 ($CH_2(CH_2Sn)(CH_2CH_3)$), 41.5 (CH_2(alkene)(CH_2OPMB)), 55.4 (OCH_3), 70.1 (CH_2OPMB), 72.8 (CH_2Ph(*p*-OMe)), 113.9 ($C^{Ar}H$), 127.0 ($C_{alkene}H_2$), 129.5 ($C^{Ar}H$), 130.7 ($C^{Ar}(CH_2O)$), 151.7 (C^{Q}_{alkene}), 159.3 ($C^{Ar}(OCH_3)$). *m/z* [CI^+, isobutane] 483 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 483.2313, $C_{24}H_{43}O_2{}^{120}Sn$ requires 483.2290. υ_{max} /cm^{-1} (film): 2955, 2924, 2851, 1613, 1512, 1462.

(4-(4-methoxybenzyloxy)but-1-en-2-yl)trimethylstannane **377**

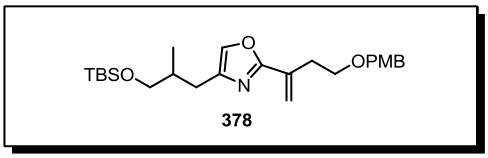


377

Vinyl bromide **375** (2.29 g, 8.46 mmol) was dissolved in anhydrous THF (56 mL) and cooled to –78 °C under an atmosphere of argon. ^{t}BuLi (1.9 M in pentane, 9.34 mL, 17.7 mmol) was added over 5 min, and the resultant solution was stirred for 10 min before being treated Me_3SnCl (1 M in THF, 11.0 mL, 11.0 mmol). The resultant solution was stirred at –78 °C for 20 min before being quenched by the addition of water (20 mL) and was allowed to warm to RT before being extracted with Et_2O (3 × 50 mL). The resultant organics were washed sequentially with water (20 mL) and brine (20 mL), before being dried over anhydrous Na_2SO_4 and the solvent was evaporated to afford the crude product. Purification by flash column chromatography, elution with 0-1.5% Et_2O:petroleum ether, afforded the desired stanane **377** (2.65 g, 7.45 mmol, 88%) as colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.10 (9H, s, $(CH_3)_3Sn$), 2.57 (2H, tt, *J* = 6.8, 1,2, CH_2(alkene)), 3.47 (2H, t, *J* = 6.8, CH_2OPMB), 3.80 (3H, s, OCH_3), 4.43 (2H, s, CH_2Ar), 5.22 (1H, dt, *J* = 2.7, 1.1, $C_{alkene}H$), 5.72 (1H, dt, *J* = 2.7, 1.5, $C_{alkene}H$), 6.87 (2H, d, *J* = 8.7, ArH), 7.25 (2H, d, *J* = 8.8, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -9.2 ($(CH_3)_3Sn$), 40.9 (CH_2(alkene)), 55.3 (OCH_3), 69.9 (CH_2OPMB), 72.7 (CH_2Ar), 113.8 ($C^{Ar}H$), 126.5 ($C_{alkene}H_2$), 129.4 ($C^{Ar}H$), 130.5 ($C^{Ar}(CH_2O)$), 152.4 (C^{Q}_{alkene}), 159.1 ($C^{Ar}(OCH_3)$). *m/z* [CI^+, isobutane] 357 $[(M+H]^+$ (28%), HRMS found $[M+H]^+$

357.0875, $C_{15}H_{25}O^{120}Sn$ requires 357.0877. υ_{max} /cm^{-1} (film): 2934, 2907, 2853, 2839, 1613, 1513, 1464.

4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(4-(4-methoxybenzyloxy)but-1-en-2-yl)oxazole **378**



378

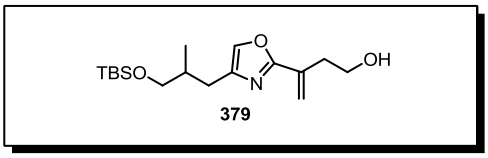
Method A: Stille Coupling with Tributylstannane **377**

Chloro oxazole **319** (57 mg, 197 µmol), stannane **377** (2.09 g, 210 µmol) and $Pd(PPh_3)_4$ (18 mg, 16 µmol) were combined together in an oven dried MW with degassed anhydrous DMF (1 mL) and heated at 120 ^{o}C under MW irradiation for 12h under an atmosphere of argon. The crude mixture was passed through a pad of Celite and silica, and eluted with Et_2O (30 mL). The organics were then washed with water (2 × 5 mL) and brine (5 mL) before being dried anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-10% Et_2O:petroleum ether, afforded alkenyl oxazole **378** (65 mg, 0.15 mmol, 74%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.04 (6H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3C$), 0.91 (3H, d, *J* = 7.2, ($CH_3(CH)$), 1.94-2.02 (1H, m, $CH(CH_3)(CH_2Ar)(CH_2OTBS)$), 2.28 (1H, ddd, *J* = 15.2, 7.2, 0.8, CH_2Ar), 2.62 (1H, ddd, *J* = 14.7, 8.4, 0.6, CH_2Ar), 2.83 (2H, td, *J* = 6.4, 0.8, $CH_2(alkene)(CH_2OPMB)$), 3.44 (1H, dd, *J* = 9.2, 5.6, CH_2OTBS), 3.49 (1H, dd, *J* = 9.7, 5.6, CH_2OTBS), 3.70 (2H, t, *J* = 6.8, CH_2OPMB), 3.80 (3H, s, OCH_3), 4.46 (2H, s, $OCH_2Ph(p\text{-}OCH_3)$), 5.41 (1H, br. d, *J* = 1.2, $C_{alkene}H$), 5.99 (1H, br. s, $C_{alkene}H$), 6.86 (2H, d, *J* = 8.4, ArH), 7.24 (2H, d, *J* = 8.8, ArH), 7.29 (1H, s, $C_{oxazole}H$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.2 ($(CH_3)_2Si$), 16.7 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3CSi$), 29.9 (CH_2Ar), 33.2 ($CH_2(alkene)(CH_2OPMB)$), 35.3 ($CH(CH_3)$), 55.4 (OCH_3), 67.6 (CH_2OTBS), 68.6 (CH_2OPMB), 72.6 ($CH_2Ph(p\text{-}OCH_3)$), 113.9 ($C^{Ar}H$), 118.5 ($C_{alkene}H_2$), 129.4 ($C^{Ar}H$), 130.7 ($C_{oxazole}(CH_2)$), 133.3 ($C^{Ar}(CH_2O)$), 134.5 ($C_{oxazole}H$),, 140.7 (C^{Q}_{alkene}), 159.3 ($C^{Ar}(OCH_3)$), 161.7 ($C^{Ar}(C_{alkene})$). *m/z* [CI^+, isobutane] 446 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 446.2729, $C_{25}H_{40}NO_4Si$ requires 446.2727. υ_{max} /cm^{-1} (film): 2955, 2928, 2855, 1613, 1589, 1512, 1462.

Method B: Stille Coupling with Trimethylstannane **377**

Under analogous conditions to Method A above, starting from chloro oxazole **319** (1.18 g, 4.08 mmol), stannane **376 (**4.35 mmol), $Pd(PPh_3)_4$ (377 mg, 0.33 mmol), and DMF (16 mL), the desired alkenyl oxazole **378** 1.53 mg, 3.43 mmol, 84%) was accessed as a colourless oil. The spectral and physical data obtained for **378**, via Method B, matched that obtained via Method A.

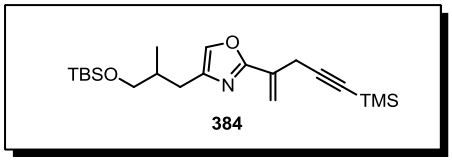
3-(4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazol-2-yl)but-3-en-1-ol **379**



379

PMB ether **378** (1.08 g, 2.52 mmol) was dissolved in DCM (12 mL) and water (0.6 mL) and cooled to 0 ^{o}C. DDQ was added and the resultant solution was stirred for 10 min before being warmed to RT and stirred for a further 25 min. The crude mixture was passed through a pad of Celite and eluted with DCM (30 mL). The organics were then washed with sat'd aq. $NaHCO_3$ solution (2 × 5 mL) and brine (2 × 5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a brown oil. Purification by flash column chromatography, elution with 0-30 % Et_2O:petroleum ether, afforded alcohol **379** (696 mg, 2.14 mmol, 88%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.03 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3C$), 0.90 (3H, d, *J* = 6.8, $(CH_3(CH))$, 1.95-2.01 (1H, m, $CH(CH_3)(CH_2Ar)(CH_2OTBS)$), 2.29 (1H, ddd, *J* = 14.6, 8.1, 0.8, CH_2Ar), 2.64 (1H, ddd, *J* = 14.6, 5.9, 0.9, CH_2Ar), 2.76-2.78 (2H, m, $CH_2(alkene)(CH_2OH)$), 3.44 (2H, d, *J* = 5.7, CH_2OTBS), 3.82 (2H, dd, *J* = 11.0, 5.6, CH_2OH), 4.06 (1H, t, *J* = 5.8, OH), 5.41 (1H, br. d, *J* = 1.0, $C_{alkene}H$), 5.97 (1H, br. d, *J* = 1.0, $C_{alkene}H$), 7.32 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.3 ($(CH_3)_2Si$), -5.2 ($(CH_3)_2Si$), 16.6 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3CSi$), 29.6 (CH_2Ar), 35.2 ($CH(CH_3)$), 37.5 ($CH_2(alkene)(CH_2OH)$), 62.3 (CH_2OH), 67.5 (CH_2OTBS), 119.5 ($C_{alkene}H_2$), 134.6 ($C_{oxazole}(CH_2)$), 134.9 ($C_{oxazole}H$), 140.4 (C^{Q}_{alkene}), 162.3 ($C^{Ar}(C_{alkene})$). *m/z* [CI$^+$, isobutane] 326 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 326.2153, $C_{17}H_{32}NO_3Si$ requires 326.2151. υ_{max} /cm^{-1} (film): 3356, 2955, 2928, 2886, 2859, 1593, 1528, 1462.

4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(5-(trimethylsilyl)pent-1-en-4-yn-2-yl)oxazole **384**

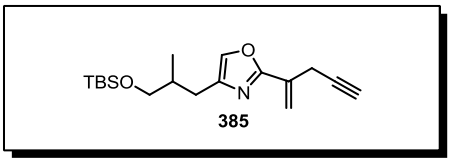


384

Chloro oxazole **319** (84 mg, 0.29 mmol), stannane **361** (136 mg, 0.32 mmol) and $Pd(PPh_3)_2Cl_2$ (16 mg, 23 µmol) were combined together in an oven dried MW vial with degassed anhydrous DMF (2 mL) and heated 120 ^{o}C under MW for 12h under an atmosphere of argon. The crude mixture was passed through a pad of Celite and eluted with Et_2O (30 mL). The organics were then washed with water (2 × 5) and brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-2% Et_2O:petroleum ether, afforded alkenyl oxazole **384** (94 mg, 0.24 mmol, 83%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (6H, s, $(CH_3)_2Si$), 0.19 (9H, s, $(CH_3)_3Si$), 0.90 (9H, s, $(CH_3)_3C$), 0.91 (3H, d, *J* = 6.7, $(CH_3)CH$), 1.95-2.03 (1H, m, $CH(CH_3)(CH_2Ar)(CH_2OTBS)$), 2.30 (1H, ddd, *J* = 14.4, 7.8, 0.8, CH(H)Ar), 2.63 (1H, ddd, *J* = 14.6, 6.2, 0.9, CH(H)Ar), 3.43-3.50 (4H, m, CH_2OTBS, $CH_2(C_{alkyne})$), 5.81 (1H, br. d, *J* = 0.8, $C_{alkene}H$), 6.09 (1H, br. d, *J* = 0.9, $C_{alkene}H$), 7.31 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -5.2 ($(CH_3)_2Si$), 0.2 ($(CH_3)_3Si$), 16.7 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 23.5 ($CH_2(C_{alkyne})(C_{alkene})$, 26.1 ($(CH_3)_3CSi$), 29.8 ($CH_2Ar$), 35.2 ($CH(CH_3)$), 67.5 ($CH_2OTBS$), 88.8 ($C_{alkyne}(CH_2)$), 102.5 ($C_{alkyne}$ (TMS)), 118.0 ($C_{alkene}H_2$), 131.1 ($C^{Ar}(CH_2)$), 134.8 ($C^{Ar}H$), 140.8 ($C_{alkene}(C^{Ar})$), 160.9 ($C^{Ar}(C_{alkene})$). *m/z* [FAB$^+$, NOBA] 392 $[M+H]^+$ (100%), HRMS found $[M+H]^+$

392.2438, $C_{21}H_{38}NO_2Si_2$ requires 392.2441. υ_{max} /cm^{-1} (film): 2955, 2932, 2901, 2855, 2183, 1589, 1525, 1466.

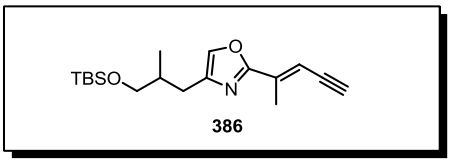
4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(pent-1-en-4-yn-2-yl)oxazole **385**



385

TMS-acetylene **384** (70 mg, 0.18 mmol) was dissolved in MeOH (1 mL), together with K_2CO_3 (26 mg, 0.19 mmol), and the resultant mixture was stirred at RT for 24h, before being quenched by the addition of water (5 mL), and extracted with Et_2O (3 × 15 mL). The combined organics were washed with water (2 × 5 mL) and brine (5 mL), before being dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the desired acetylene **385** (51 mg, 0.16 mmol, 89%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (6H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3C$), 0.91 (3H, d, *J* = 6.7, $(CH_3)CH$), 1.95-2.03 (1H, m, $CH(CH_3)(CH_2Ar)(CH_2OTBS)$), 2.21 (1H, t, *J* = 2.6, $C_{alkyne}H$), 2.31 (1H, dd, *J* = 14.4, 7.9, CH(H)Ar), 2.63 (1H, ddd, *J* = 14.6, 6.1, 0.5, CH(H)Ar), 3.43-3.51 (4H, m, CH_2OTBS, $CH_2(C_{alkyne})$), 5.82 (1H, br. s, $C_{alkene}H$), 6.10 (1H, br s, $C_{alkene}H$), 7.31 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -5.2 ($(CH_3)_2Si$), 16.7 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 22.2 ($CH_2(C_{alkyne})(C_{alkene})$, 26.1 ($(CH_3)_3CSi$), 29.9 ($CH_2Ar$), 35.3 ($CH(CH_3)$), 67.5 ($CH_2OTBS$), 72.0 ($C_{alkyne}H$), 80.2 ($C_{alkyne}(CH_2)$), 118.0 ($C_{alkene}H_2$), 130.9 ($C^{Ar}(CH_2)$), 134.8 ($C^{Ar}H$), 140.9 ($C_{alkene}(C^{Ar})$), 160.8 ($C^{Ar}(C_{alkene})$).

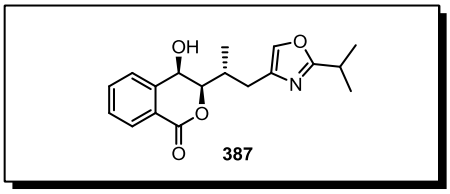
(*E*)-4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(pent-2-en-4-yn-2-yl)oxazole **386**



386

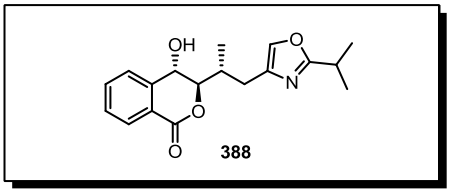
Under analogous conditions and scale to the procedure described above for the synthesis of acetylene **385**, except with a reaction temperature of 35 °C, enyne **386** (30 mg, 94 µmol, 52%) was generated, as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3C$), 0.91 (3H, d, *J* = 6.8, $(CH_3)CH$), 1.96-2.04 (1H, m, $CH(CH_3)(CH_2Ar)(CH_2OTBS)$), 2.30 (3H, br. d, *J* = 0.8, $CH_3(C_{alkene})$), 2.32 (1H, ddd, *J* = 14.5, 7.8, 0.6, CH_2Ar), 2.64 (1H, ddd, *J* = 14.6, 6.1, 0.8, CH_2Ar), 3.43-3.50 (3H, m, CH_2OTBS, $C_{alkyne}H$), 6.39-6.40 (1H, m, $C_{alkene}H$), 7.32 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: -5.2 ($(CH_3)_2Si$), 16.0 ($CH_3(C_{alkene})$) 16.7 ($CH_3(CH)$), 18.5 ($SiC(CH_3)_3$), 26.1 ($(CH_3)_3CSi$), 29.9 (CH_2Ar), 35.2 ($CH(CH_3)$), 67.5 (CH_2OTBS), 80.9 (C^Q_{alkyne}), 86.7 ($C_{alkyne}H$), 110.1 ($C_{alkene}H$), 135.1 ($C^{Ar}H$), 137.3 ($C^{Ar}(CH_2)$), 141.6 ($C_{alkene}(C^{Ar})$), 161.7 ($C^{Ar}(C_{alkene})$). *m/z* [Cl^+, isobutane] 320 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 320.2045, $C_{18}H_{30}NO_2Si$ requires 320.2046. υ_{max} /cm^{-1} (film): 3310, 2955, 2938, 2857, 1587, 1534, 1472, 1462.

(±)-(3*R*,4*R*)-4-Hydroxy-3-((*R*)-1-(2-isopropyloxazol-4-yl)propan-2-yl)isochroman-1-one **387**



A solution of alkenyl oxazole **346** (72 mg, 230 µmol) in EtOH (3 mL) was charged with 10% activated Pd/C (11 mg). The suspension was stirred under an atmosphere of hydrogen at RT for 4h. TLC analysis indicated reaction completion. The suspension was filtered through a plug of Celite and silica, and the filtrate was concentrated under reduced pressure to afford the isopropyl oxazole **287** (71 mg, 225 µmol, 98%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.15 (3H, d, *J* = 6.7, $CH_3(CH)$), 1.30 (6H, d, *J* = 6.9, $(CH_3)_2CH$), 2.50-2.57 (2H, m, CH_2Ar, $CH(CH_2)(CH_2')$), 3.02 (1H, sept, *J* = 7.0, $CH(CH_3)_2$), 3.11-3.16 (1H, m, CH_2Ar), 3.19 (1H, d, *J* = 6.7, OH), 4.23 (1H, dd, *J* = 7.9, 1.7, $CH(O_2C)$), 4.79 (1H, d, *J* = 5.0, CH(OH)), 7.34 (1H, s, $C^{Ar}_{oxazole}H$), 7.47 (1H, d, *J* = 7.5, ArH), 7.52 (1H, td, *J* = 7.5, 1.2, ArH), 7,64 (1H, td, *J* = 7.5, 1.3, ArH), 8.14 (1H, dd, *J* = 7.8, 1.1, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2 ($CH_3(CH)$), 20.5 ($CH_3(CH(CH_3)))$, 20.6 ($CH_3(CH(CH_3)))$ 28.2 (CH_2Ar), 28.6 ($CH(CH_3)_2$) 34.1 ($CH(CH_3)(CH_2)(CH_2')$), 65.9 (CH(OH)), 84.2 ($CH(O_2C)$), 124.5 ($C^{Ar}CH_2$), 128.1 ($C^{Ar}H$), 129.9 ($C^{Ar}H$), 130.6 ($C^{Ar}H$), 134.4 ($C^{Ar}H$), 134.6 ($C^{Ar}H$), 138.3 ($C^{Ar}CO_2$), 140.6 ($C^{Ar}CH(OH)$), 165.0 (CO_2), 168.9 ($C^{Ar}CH(CH_3)_2$). *m/z* [Cl^+, isobutane] 316 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 316.1551 $C_{18}H_{22}NO_4$ requires 316.1549. υ_{max} /cm^{-1} (film): 3374, 2972, 2936, 2878, 1717, 1605, 1566.

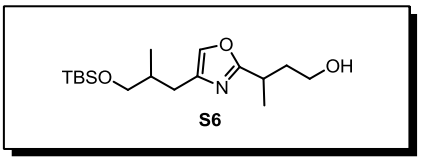
(±)-(3*R*,4*S*)-4-Hydroxy-3-((*R*)-1-(2-isopropyloxazol-4-yl)propan-2-yl)isochroman-1-one **388**



A solution of *syn,anti*-isochromanone **387** (58 mg, 184 µmol) in anhydrous toluene (1.8 mL) was treated with PPh_3 (121 mg, 460 µmol) and 4-nitrobenzoic acid (58 mg, 460 µmol) and cooled to 0 °C. The resulting solution was treated dropwise with DIAD (91 µL, 460 µmol) and stirred for 10 min, before being heated at 80 °C for 16h, under an atmosphere of argon. The reaction mixture was cooled to RT before the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography, elution with 0-100% DCM:petroleum ether, to afford the *p*-nitrobenzoate intermediate (43 mg, 92 µmol, 50%) as a pale yellow oil. The intermediate was then dissolved in MeOH (1.5 mL) and treated with NaN_3 (53 mg, 0.82 mmol) and stirred at 30 °C for 16h. The solvent was evaporated and the crude residue was purified by flash column chromatography, elution with 0-35% Et_2O:petroleum ether, to afford *anti,anti*-isochromanone **388** (23 mg, 72 µmol, 39%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.27 (3H, d, *J* = 7.2, $CH_3(CHCH_2Ar)$), 1.34 (3H, d, *J* = 7.0, $(CH_3)_2CH$), 1.35 (3H, d, *J* = 7.0, $(CH_3)_2CH$), 2.42 (2H, ddd, *J* = 16.3, 3.5, 0.6, CH_2Ar) 2.60-2.65 (1H, m, $CH(CH_3)_2$), 3.03 (1H, ddd, *J* = 16.3, 7.2, 1.7, CH_2Ar), 3.03-3.12 (1H, m, $CH(CH_2Ar)$), 4.25 (1H, dd, *J* = 10.8, 2.2, $CH(O_2C)$), 4.92 (1H, br. d, *J* = 10.8, CH(OH)), 7.34-7.35 (1H, m, ArH), 7.39-7.44 (1H, m, ArH), 7.64 (1H, td, *J* = 7.6, 1.3, ArH), 7.77-7.79 (1H, m, ArH), 8.03 (1H, dd, *J* = 7.8, 1.0, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.6 ($CH_3(CHCH_2Ar)$), 20.2 (($CH_3)_2CH$), 20.2 (($CH_3)_2CH$), 25.6

(CH_2Ar), 28.4 ($CH(CH_2Ar)$), 32.0 ($CH(CH_3)_2$), 64.9 (CH(OH)), 86.0 ($CH(O_2C)$), 123.4 ($C^{Ar}CH_2$), 124.1 ($C^{Ar}H$), 127.8 ($C^{Ar}H$), 129.9 ($C^{Ar}H$), 133.9 ($C^{Ar}H$), 134.1 ($C^{Ar}H$), 138.7 ($C^{Ar}CO_2$), 143.9 ($C^{Ar}CH(OH)$), 165.5 (CO_2), 169.7 ($C^{Ar}CH(CH_3)_2$). *m/z* [Cl^+, isobutane] 316 $[M+H]^+$ (43%). HRMS found $[M+H]^+$ 316.1552, $C_{18}H_{22}NO_4$ requires 316.1549. υ_{max} /cm^{-1} (film): 3310, 2972, 2878, 1728, 1607, 1566, 1460.

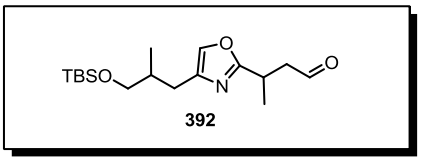
(±)-3-(4-(3-(tert-butyldimethylsilyloxy)-2-methylpropyl)oxazol-2-yl)butan-1-ol **S6**



S6

A solution of alkenyl oxazole **379** (67 mg, 206 µmol) in EtOH (1 mL) was charged with 10% activated Pd/C (10 mg). The suspension was stirred under an atmosphere of hydrogen at RT for 50 min. TLC analysis indicated reaction completion. The suspension was filtered through a plug of Celite and silica, and the filtrate was concentrated under reduced pressure to afford the alcohol **S6** (67 mg, 204 µmol, 99%), as a colourless oil. ^{1}H NMR (C_6D_6, 500 MHz) δ: 0.05 (6H, s, $(CH_3)_2Si$), 0.94 (3H, d, *J* = 6.8, $CH_3(CH(CH_2(oxazole)))$, 0.98 (9H, s, $(CH_3)_3C$), 1.15 (3H, d, *J* = 7.1, $CH_3(CH(oxazole)))$, 1.59-1.66 (1H, m, $CH_2(CH_2OH)$, 1.85-1.91 (1H, m, $CH_2(CH_2OH)$ 2.08-2.15 (1H, m, $CH(CH_3)(CH_2Ar)(CH_2OTBS)$), 2.26 (1H, dd, *J* = 14.4, 7.9, CH_2Ar), 2.41 (1H, br. s, OH), 2.63 (1H, ddd, *J* = 14.4, 5.9, 1.0, CH_2Ar), 2.98 (1H, sext, *J* = 6.9, $CH(CH_3)(oxazole)(CH_2)$), 3.41 (1H, dd, *J* = 9.8, 5.7, CH_2OTBS), 3.45 (1H, dd, *J* = 9.8, 5.5, CH_2OTBS), 3.49-3.52 (1H, m, CH_2OH), 6.93 (1H, s, ArH). ^{13}C NMR (C_6D_6, 125 MHz) δ: -5.2 ($(CH_3)_2Si$), 16.8 $CH_3(CH(CH_2(oxazole))$ *diastereoisomer A*), 16.8 $CH_3(CH(CH_2(oxazole))$ *diastereoisomer B*) 18.6 ($CH_3(CH(oxazole)))$, 18.7 ($SiC(CH_3)_3$), 26.2 ($(CH_3)_3CSi$), 29.9 (CH_2Ar), 31.6 ($CH(CH_3)(oxazole)(CH_2)$), 35.6 ($CH(CH_3)(CH_2Ar)(CH_2OTBS)$ *diastereoisomer A*), 35.6 ($CH(CH_3)(CH_2Ar)(CH_2OTBS)$ *diastereoisomer B*), 38.1 ($CH_2(CH)(CH_2OH)$ *diastereoisomer A*), 38.1 ($CH_2(CH)(CH_2OH)$ *diastereoisomer B*), 60.4 (CH_2OH), 67.8 (CH_2OTBS *diastereoisomer A*), 67.8 (CH_2OTBS *diastereoisomer A*), 134.3 ($C_{oxazole}(CH_2)$), 139.6 ($C_{oxazole}H$), 168.2 ($C^{Ar}(CH)$). *m/z* [Cl^+, isobutane] 328 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 328.2310, $C_{17}H_{34}NO_3Si$ requires 328.2308. υ_{max} /cm^{-1} (film): 3352, 2955, 2932, 2886, 2859, 1566, 1462.

(±)-3-(4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazol-2-yl)butanal **392**

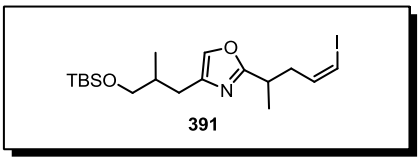


392

Alcohol **S6** (58 mg, 177 µmol) was dissolved in anhydrous DCM (1.8 mL) and treated with BAIB (68 g, 212 µmol) and TEMPO (3 mg, 18 µmol). The reaction mixture was stirred under argon at RT for 4h. The reaction mixture was diluted with DCM (20 mL) and washed with sat'd aq. $Na_2S_2O_3$ solution (2 × 8 mL), water (2 × 5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product as an orange oil. Purification by flash column chromatography, elution with 0-20% Et_2O:petroleum ether, afforded the desired product aldehyde **392** ((55 mg, 169 µmol, 95%) as a colourless oil. ^{1}H NMR (C_6D_6, 500 MHz) δ: 0.05 (6H, s, $(CH_3)_2Si$), 0.94 (3H, d, *J* = 6.7, $CH_3(CH(CH_2(oxazole)))$, 0.98 (9H, s, $(CH_3)_3C$), 1.07 (3H, d, *J* = 7.1, $CH_3(CH(oxazole)))$, 2.01 (1H,

dd, *J* = 17.6, 6.5, CH_2(CHO)), 2.08-2.15 (1H, m, CH(CH_3)(CH_2Ar)(CH_2OTBS)), 2.25 (1H, dd, *J* = 14.4, 7.9, CH_2Ar), 2.58 (1H, dd, *J* = 17.6, 7.2, CH_2(CHO)), 2.62 (1H, dd, *J* = 14.4, 5.9, CH_2Ar), 3.19 (1H, sext, *J* = 7.0, CH(CH_3)(oxazole)(CH_2)), 3.41 (1H, dd, *J* = 10.0, 5.9, CH_2OTBS), 3.46 (1H, ddd, *J* = 9.7, 5.6, 2.4, CH_2OTBS), 6.91 (1H, s, ArH), 9.31 (1H, s, CHO). ^{13}C NMR (C_6D_6, 125 MHz) δ: -5.2 ((CH_3)$_2$Si), 16.8 CH_3(CH(CH_2(oxazole))), 18.5 (CH_3(CH(oxazole))), 18.6 (SiC(CH_3)$_3$), 26.2 ((CH_3)$_3$CSi), 28.3 (CH(CH_3)(oxazole)(CH_2)), 30.0 (CH_2Ar), 35.6 (CH(CH_3)(CH_2Ar)(CH_2OTBS) *diastereoisomer A*), 35.6 (CH(CH_3)(CH_2Ar)(CH_2OTBS) *diastereoisomer B*), 48.0 (CH_2(CHO)), 67.8 (CH_2OTBS), 134.5 ($C_{oxazole}$(CH_2)), 139.9 ($C_{oxazole}$H), 166.6 (C^{Ar}(CH)), 198.7 (CHO). *m/z* [CI^+, isobutane] 326 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 326.2148, $C_{17}H_{32}NO_3Si$ requires 326.2151. υ_{max} /cm^{-1} (film): 2955, 2932, 2889, 2859, 1728, 1570, 1462.

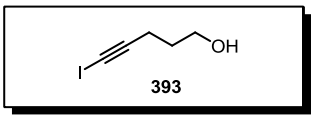
(*Z*)-4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(5-iodopent-4-en-2-yl)oxazole **391**



391

In the absence of light, a solution of NaHMDS (1 M in THF, 0.93 mL, 0.93 mmol) in anhydrous THF (4 mL) was prepared at 10 °C. To this, a suspension of (iodomethyl)triphenylphosphonium iodide (493 mg, 0.93 mmol) in HMPA (2.80 mL, 16.1 mmol) was added via cannular. After stirring for 1 min, the resultant mixture was cooled to –78 °C. A solution of aldehyde **392** (202 mg, 0.62 mmol) in anhydrous THF (1.5 mL) was added dropwise to the reagent mixture and was stirred for 30 min at –78 °C. TLC analysis indicated reaction completion. The reaction was quenched by the addition of sat'd aq. $Na_2S_2O_3$ (10 mL). After warming to RT, the solution was extracted with Et_2O (3 × 15 mL). The combined organics were washed with water (2 × 5 mL) and brine (15 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-7% Et_2O:petroleum ether, afforded the vinyl iodide **391** (212 mg, 0.47 mmol, 76%), as a colourless oil. ^{1}H NMR (C_6D_6, 500 MHz) δ: 0.05 (3H, s, (CH_3)$_2$Si), 0.05 (3H, s, (CH_3)$_2$Si), 0.96 (3H, dd, *J* = 6.8, 0.9, CH_3(CH(CH_2(oxazole))), 0.98 (9H, s, (CH_3)$_3$C), 1.17 (3H, d, *J* = 7.0, CH_3(CH(oxazole))), 2.12-2.19 (1H, m, CH(CH_3)(CH_2Ar)(CH_2OTBS)), 2.29 (1H, dd, *J* = 14.4, 7.8, CH_2Ar), 2.36-2.41 (1H, m, CH_2(CH)(alkene)), 2.51-2.58 (1H, m, CH_2(CH)(alkene)), 2.66 (1H, dd, *J* = 14.4, 7.8, CH_2Ar), 2.84 (1H, sext, *J* = 7.0, CH(CH_3)(oxazole)(CH_2)), 3.43 (1H, dd, *J* = 9.7, 5.9, CH_2OTBS), 3.48 (1H, ddd, *J* = 9.7, 5.6, 0.9, CH_2OTBS), 5.84 (1H, q, *J* = 7.0, C_{alkene}(CH_2)(CHI)), 5.91 (1H, dt, *J* = 7.4, 1.1, C_{alkene}HI), 6.95 (1H, s, ArH).

5-Iodopent-4-yn-1-ol **393**

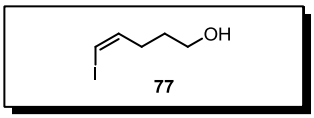


393

Pent-4-yn-1-ol (2.54 g, 30.9 mmol) was dissolved in MeOH (30 mL) and cooled to 0 °C before the addition of 12.5 M aq. NaOH solution (6.2 mL, 77.5 mmol). After stirring for 10 min, I_2 crystals (8.62 g, 34.0 mmol) were added in a single portion and the resultant solution was warmed to RT and stirred for a further 3h. Dilution with water (30 mL) was followed by extraction with Et_2O (3 × 50 mL). The combined organics were washed with sat'd aq. $Na_2S_2O_3$ (3 × 80 mL) and brine (2 × 25 mL), before being dried over anhydrous Na_2SO_4. The solvent was

evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-100% DCM:petroleum ether, afforded iodo alkyne **393** (5.51 g, 26.3 mmol, 85%), as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (1H, br. s, OH), 1.72-1.78 (2H, m, $CH_2(CH_2OH)(CH_2')$), 2.48 (2H, t, *J* = 7.0, CH_2(alkyne)), 3.72 (2H, t, *J* = 6.1, CH_2OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: -6.4 ($C_{alkyne}I$), 17.4 (CH_2(alkyne)), 31.2 ($CH_2(CH_2OH)(CH_2')$), 61.5 (CH_2OH), 93.9 ($C_{alkyne}(CH_2)$). *m/z* [EI$^+$] 210 [M]$^+$ (43%), HRMS found [M]$^+$ 209.9534, C_5H_7OI requires 209.9542. υ_{max} /cm^{-1} (film): 3329, 2947, 2877, 2184, 1431. The data observed is in accordance with literature values.[179]

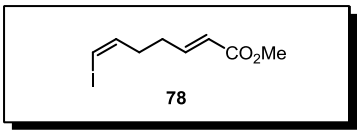
(*Z*)-5-Iodopent-4-en-1-ol **77**



77

Iodo alkyne **393** (10.5 g, 50.2 mmol) was dissolved in MeOH (90 mL) together with pyridine (24 mL) and potassium azodicarboxylate (29.2 g, 151 mmol) at RT, under an atmosphere of argon. Acetic acid (100% w/w, 18 mL) was added to the reaction mixture dropwise via syringe pump over 3h. The reaction mixture was then allowed to stir for a further 16h. 1 M aq. HCl solution (100 mL) was added and the resultant solution stirred for 5 min before extraction with Et_2O (3 × 200 mL). The combined organics were washed with 1 M aq. HCl solution (50 mL), sat'd aq. $NaHCO_3$ solution (100 mL), sat'd aq. $CuSO_4$ solution (5x100 mL) and brine (2 × 50 mL). The solvent was evaporated under reduced pressure to afford a yellow oil, which was dissolved in Et_2O (50 mL) and water (15 mL), before $^{n}BuNH_2$ (13 mL) was added and the resultant mixture stirred at RT for 30 min. The organics were washed with 1 M aq. HCl solution (2 × 30 mL) and brine (2 × 25 mL), before being dried over anhydrous Na_2SO_4. Solvent evaporation afforded the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-15% Et_2O:petroleum ether, afforded viny iodide **77** (6.63 g, 31.3 mmol, 62%), as a colourless oil. ^{1}H NMR (C_6D_6, 400 MHz) δ: 0.65 (1H, br. s, OH), 1.25-1.35 (2H, m, $CH_2(CH_2OH)(CH_2')$), 1.99-2.05 (2H, m, CH_2(alkene)), 3.21 (2H, t, *J* = 6.1, CH_2OH), 5.68 (1H, q, *J* = 7.0, $C_{alkene}(CH_2)$), 5.85 (1H, dt, *J* = 7.3, 2.0, $C_{alkene}HI$). ^{13}C NMR (C_6D_6, 125 MHz) δ: 31.1 ($CH_2(CH_2OH)(CH_2')$), 31.5 (CH_2(alkene)), 61.8 (CH_2OH), 82.7 ($C_{alkene}HI$), 141.0 ($C_{alkene}(CH_2)$). *m/z* [EI$^+$] 212 [M]$^+$ (100 %), HRMS found [M]$^+$ 211.9700, C_5H_9OI requires 211.9698. υ_{max} /cm^{-1} (film): 3310, 2936, 2866, 1609, 1435. The data observed is in accordance with literature values.[27]

(2*E*,6*Z*)-Methyl 7-iodohepta-2,6-dienoate **78**

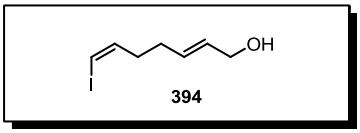


78

Alcohol **77** was disolved in anhydrous DCM (100 mL) at 0 ^{o}C and treated with PCC (9.94 g, 46.1 mmol) and the resultant mixture was stirred for 2h, before being warmed to RT and stirred for a further 3h. The reaction mixture was filtered through a pad of Florisil and eluted with DCM. The solvent was carefully evaporated until approx 100 mL remained. The resultant crude aldehyde intermediate, dissolved in DCM, was treated with methyl (triphenylphosphoranylidene)acetate (13.1 g, 14.4 mmol) and stirred at RT for 1h, under an atmosphere of argon. The crude mixture was pre-absorbed onto silica and purified by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, to afford acrylate **78** (5.60 g, 21.1 mmol, 91%), as a colourless oil. 1H NMR (C_6D_6, 500 MHz) δ: 1.79-1.83 (2H, m, CH_2(alkene(*E*)), 1.96-2.01 (2H, m, CH_2(alkene(*Z*)), 3.51 (3H, s, CH_3O_2C), 5.61 (1H, q, *J* = 7.0,

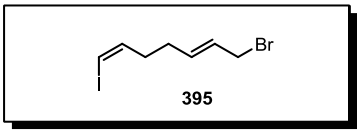
$C_{alkene(I)}H(CH_2)(CHI)$), 5.85 (1H, dt, *J* = 15.6, 1.6, $C_{alkene(E)}H(CO_2Me)$), 5.93 (1H, dt, *J* = 7.4, 1.3, $C_{alkene(Z)}HI$), 6.95 (1H, dt, *J* = 15.6, 6.9, $C_{alkene(E)}(CH_2)$). ^{13}C NMR (C_6D_6, 125 MHz) δ: 30.3 (CH_2(alkene(*E*)), 33.3 (CH_2(alkene(*Z*)), 51.0 (CH_3O), 83.6 ($C_{alkene}HI$), 122.2 ($C_{alkene(E)}H(CO_2Me)$, 139.6 ($C_{alkene(Z)}H(CH_2)(CHI)$), 147.4 ($C_{alkene(E)}(CH_2)$), 166.3 ($CO_2Me$). *m/z* [$CI^+$, isobutane] 267 $[M+H]^+$ (100 %). HRMS found $[M+H]^+$ 266.9883, $C_8H_{12}O_2I$ requires 266.9882. υ_{max} /cm^{-1} (film): 3067, 2990, 2947, 2847, 1721, 1659, 1609, 1435. The data observed is in accordance with literature values.[27]

(2*E*,6*Z*)-7-Iodohepta-2,6-dien-1-ol **394**



Ester **78** (5.10 g, 19.2 mmol) was disolved in anhydrous DCM (130 mL) at 0 °C, and treated with DIBAL (1 M in hexanes, 42.2 mL, 42.2 mmol) and the resultant mixture was warmed to RT stirred for 16h. After re-cooling to 0 °C, the reaction mixture was diluted with DCM (100 mL) and quenched by the successive addition of water (1.1 mL), 15% aq. NaOH solution (1.65 mL) and water (4.1 mL), at 30 min intervals. The resultant slurry was warmed to RT and stirred for 30 min, anhydrous Na_2SO_4 was added, and the resulting slurry was stirred for a further 30 min. The solids were removed by filtration and the solvent was evaporated under reduced pressure. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded the allylic alcohol **394** (4.34 g, 18.2 mmol, 95%) as a colourless oil. 1H NMR (C_6D_6, 500 MHz) δ: 0.71 (1H, br. s, OH), 1.93-1.97 (2H, m, CH_2(alkene(*E*)), 2.11-2.16 (2H, m, CH_2(alkene(*Z*)), 3.88 (2H, br. d, *J* = 3.9, CH_2OH), 5.43-5.52 (2H, m, $C_{alkene(E)}H(CH_2OH)$ & $C_{alkene(E)}(CH_2)$), 5.81 (1H, q, *J* = 6.9, $C_{alkene(Z)}H(CH_2)(CHI)$), 5.98 (1H, dt, *J* = 7.3, 1.4, $C_{alkene(Z)}HI$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 30.5 (CH_2(alkene(*E*)), 34.2 (CH_2(alkene(*Z*)), 63.3 (CH_2OH), 83.0 ($C_{alkene(Z)}HI$), 130.0 ($C_{alkene(E)}H$), 131.5 ($C_{alkene(E)}$), 140.3 ($C_{alkene(Z)}H(CH_2)(CHI)$). *m/z* [$CI^+$, isobutane] 221 $[M-OH]^+$ (100%), HRMS found $[M-OH]^+$ 220.9825, $C_8H_{12}O_2I$ requires 220.9827. υ_{max} /cm^{-1} (film): 3321, 2920, 2851, 1670, 1435. The data observed is in accordance with literature values.[27]

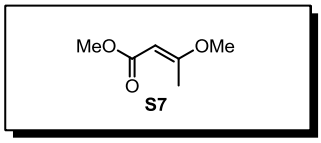
(1*Z*,5*E*)-7-Bromo-1-iodohepta-1,5-diene **395**



NBS (5.83 g, 32.8 mmol) was added to an oven-dried flask, together with anhydrous DCM (100 mL), under an atmosphere of argon. After cooling to 0 °C, DMS (3.61 mL, 49.1 mmol) was added, and the resultant suspension was cooled to –10 °C. A solution of alcohol **394** (3.90 g, 16.4 mmol), in anhydrous DCM (50 mL), was added via cannular, to the reaction vessel. After the addition, the reaction mixture was warmed to RT and stirred for 90 min, before being filtered through a pad of Celite, followed by solvent evaporation under reduced pressure to afford the crude product. Purification by flash column chromatography, elution with petroleum ether, afforded the allylic bromide **395** (3.37 g, 11.2 mmol, 68%) as a colourless oil. 1H NMR ($CDCl_3$, 500 MHz) δ: 2.20-2.26 (4H, m, CH_2(alkene(*Z*), CH_2(alkene(*E*)), 3.95 (2H, d, *J* = 6.6, CH_2Br), 5.70-5.82 (2H, m, $CH_2(C_{alkene(Z)}H(CH_2))$ & $CH_2(C_{alkene(E)}H(CH_2))$), 6.17 (1H, q, *J* = 6.6, $C_{alkene(Z)}H(CH_2)(CHI)$), 6.25 (1H, dt, *J* = 7.4, 1.3, $C_{alkene(Z)}HI$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 30.5 (CH_2(alkene), 33.2 (CH_2Br), 34.0 (CH_2(alkene), 83.4 ($C_{alkene(Z)}HI$), 127.5 ($C_{alkene(E)}(CH_2CH_2)$), 131.5 ($C_{alkene(E)}(CH_2Br)$), 140.1 ($C_{alkene(Z)}H(CH_2)(CHI)$). *m/z* [$EI^+$] 300 $[M(Br^{79})]^+$ and 302 $[M(^{81}Br)]$ 100%.

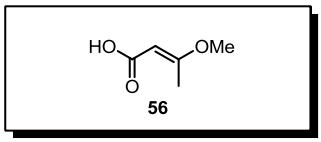
HRMS found $[M(^{79}Br)]^+$ 299.9021, $C_7H_{10}{}^{79}BrI$ requires 299.9011. υ_{max} /cm^{-1} (film): 2959, 2928, 2847, 1690, 1659, 1609, 1435. The data observed is in accordance with literature values.[27]

(*E*)-Methyl 3-methoxybut-2-enoate **S7**



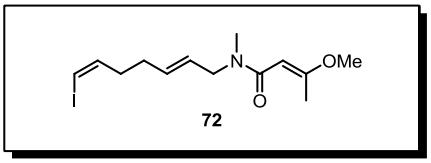
Trimethyl orthoformate (14.0 g, 132 mmol) was added to neat methyl acetoacetate (15.0 g, 129 mmol) and to this stirring solution was added 5 drops of conc. H_2SO_4. The resulting mixture was stirred at RT for 24h. 10 drops of quinoline were added to neutralise the acid, before vacuum distillation (98 ^oC, 30 mbar) afforded ester **S7** (15.6 g, 120 mmol, 93%) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.29 (3H, br. d, *J* = 1.2, CH_3(alkene)), 3.62 (3H, br. d, *J* = 1.1, CH_3O(alkene)), 3.67 (3H, br. d, *J* = 1.4, CH_3O_2C), 5.02 (1H, s, $C_{alkene}H$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.0 (CH_3(alkene)), 50.9 (CH_3O_2C), 55.5 (CH_3O(alkene)), 90.6 ($C_{alkene}H$), 168.5 (CO_2Me), 173.4 ($C_{alkene}(CH_3)(OCH_3)$). *m/z* [EI^+] 130 $[M]^+$ (100 %). HRMS found $[M]^+$ 130.0626, $C_6H_{10}O_3$ requires 130.0630. υ_{max} /cm^{-1} (film): 2952, 2843, 1709, 1620, 1435. The data observed is in accordance with literature values.[29]

(*E*)-3-Methoxybut-2-enoic acid **56**



Ester **S7** (15.6 g, 120 mmol) was dissolved in a mixture of THF (380 mL) and water (150 mL) and cooled to 0 ^oC. KOH (20.2 g, 360 mmol) was added and the resultant solution was warmed to RT, before being stirred at 70 ^oC for 24h. After cooling to 0 ^oC, the reaction mixture was acidified to approx. pH 3, by the careful addition of 6 M aq. HCl solution. The acidified solution was extracted with Et_2O (3 × 300 mL) and the combined organics were washed with water (75 mL) and brine (75 mL), before being dried over anhydrous Na_2SO_4. Solvent evaporation afforded the crude product. Trituration from petroleum ether, followed by drying under vacuum, afforded acid **56** (13.0 g, 112 mmol, 93%) as a colourless crystalline solid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.30 (3H, s, CH_3(alkene)), 3.66 (3H, s, CH_3O(alkene)), 5.04 (1H, s, $C_{alkene}H$), 11.94 (1H, br. s, CO_2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.4 (CH_3(alkene)), 55.8 (CH_3O(alkene)), 90.6 ($C_{alkene}H$), 173.6 ($C_{alkene}(CH_3)(OCH_3)$), 175.4 (CO_2H). *m/z* [CI^+, isobutane] 117 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 117.0551, $C_5H_9O_3$ requires 117.0552. υ_{max} /cm^{-1} (film): 2966, 2872, 2840, 1690, 1667, 1597. MP: 125-127 ^oC. The data observed is in accordance with literature values.[29]

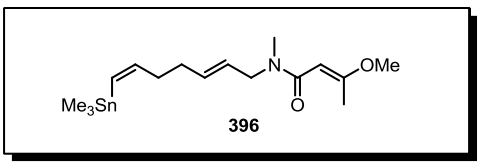
(*E*)-N-((2*E*,6*Z*)-7-Iodohepta-2,6-dienyl)-3-methoxy-*N*-methylbut-2-enamide **72**



72

Bromide **395** (2.20 g, 7.31 mmol) was dissolved in anhydrous THF (17 mL) and cooled to 0 ^{o}C under an atmosphere of argon. $MeNH_2$ (2 M in THF, 18.3 mL, 36.5 mmol) was added and the resultant reaction mixture was stirred at 0 ^{o}C for 1h, before being warmed to RT and stirred for a further 1h until reaction completion, as indicated by TLC analysis. The solvent and excess $MeNH_2$ was evaporation to afforded the crude product. Purification by SCX ion-exchange chromatography, elution with MeOH and then 7 M NH_3/MeOH, afforded the amine intermediate (1.71 g, 6.80 mmol, 93%) as a pale orange oil which was used immediately in the next step. The amine intermediate was combined with acid **56** (908 mg, 7.82 mmol) in anhydrous DCM (50 mL) and the resultant solution was cooled to 0 ^{o}C under an atmosphere of argon. HBTU (3.10 g, 8.16 mmol) was added before the dropwise addition of DIPEA (2.37 mL, 13.6 mmol). The reaction mixture was stirred at 0 ^{o}C for 20 min before being warmed to RT and stirred for a further 2h. The solvent was evaporated and the resultant slurry was partitioned between Et_2O (100 mL) and water (50 mL). The organics were collected and further washed with sat'd aq. $NaHCO_3$ solution (20 mL), 10% aq. citric acid solution (20 mL) and brine (2 × 25 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as an orange oil. Purification by flash column chromatography, elution with 0-67% Et_2O:petroleum ether, afforded the desired amide **72** (1.84 g, 5.28 mmol, 72%), as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: 2.21-2.34 (7H, m, CH_3(alkene), CH_2CH_2), 2.94 (3H, s, CH_3N), 3.59 (3H, br. s, CH_3O), 3.61 (3H, br. s, CH_3O*), 3.88 (2H, br. s, CH_2N), 3.97 (2H, br. s, CH_2N*), 5.16 (1H, br. s, CH_{alkene}(CON)), 5.18 (1H, br. s, CH_{alkene}(CON)*), 5.45 (1H, dtt, *J* = 15.4, 5.7, 1.3, $CH_{alkene}(CH_2CH_2)$), 5.58 (1H, dtt, *J* = 15.3, 6.5, 1.3, $CH_{alkene}(CH_2N)$), 6.15 (1H, q, *J* = 6.8, CH_{alkene}(CHI)), 6.22 (1H, d, *J* = 7.3, CH_{alkene}I). ^{13}C NMR ($CDCl_3$, 125 MHz, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: 18.8 (CH_3(alkene)), 30.5 (CH_2(alkene)), 33.4 (CH_3N*), 34.3 (CH_2(alkene)), 35.1 (CH_3N), 49.0 (CH_2N*), 52.1 (CH_2N), 54.9 (CH_3O), 82.8 (C_{alkene}HI*), 83.1 (C_{alkene}HI), 91.2 (C_{alkene}(CON)), 125.7 ($C_{alkene}H(CH_2CH_2)$), 126.3 ($C_{alkene}H(CH_2CH_2)$*), 131.5 ($C_{alkene}H(CH_2N)$), 132.0 ($C_{alkene}H(CH_2N)$*), 140.2 (C_{alkene}H(CHI)), 140.5 (C_{alkene}H(CHI)*), 167.8 (C^{Q}_{alkene}), 168.4 (CO). *m/z* [CI^{+}, isobutane] 350 $[M+H]^{+}$ (100%). HRMS found $[M+H]^{+}$ 350.0616, $C_{13}H_{21}NO_2I$ requires 350.0617. υ_{max} /cm^{-1} (film): 3292, 2955, 2924, 2851, 1643, 1601, 1477, 1439. The data observed is in accordance with literature values.[27]

(*E*)-3-methoxy-*N*-methyl-*N*-((2*E*,6*Z*)-7-(trimethylstannyl)hepta-2,6-dienyl)but-2-enamide **396**

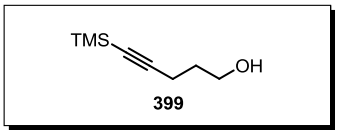


396

Vinyl iodide **72** (204 mg, 584 µmol) was dissolved in degassed, anhydrous NMP (3 mL) before $Pd_2(dba)_3$ (27 mg, 29 µmol) was added under an atmosphere of argon. After stirring for 2 min, $(Me_3Sn)_2$ (145 µL, 701 µmol) was added and the reaction mixture was stirred in the dark for 4

days. Additional $Pd_2(dba)_3$ (27 mg, 29 µmol) and $(Me_3Sn)_2$ (145 µL, 701 µmol) were added and the reaction was stirred for a further 3 days, before being filtered through a pad of Celite and Florisil, eluting with Et_2O (50 mL) The organics were then washed with water (2 × 5 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded vinyl stannane **396** (65 mg, 169 µmol, 29%, 45% brsm), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: 0.15 (9H, s, $(CH_3)_3Sn$), 2.12-2.19 (4H, m, CH_2CH_2), 2.21 (3H, s, CH_3(alkene)), 2.93 (3H, s, CH_3N), 3.57 (3H, br. s, CH_3O), 3.61 (3H, br. s, CH_3O*), 3.87 (2H, br. s, CH_2N), 3.97 (2H, br. s, CH_2N*), 5.15 (1H, br. s, CH_{alkene}(CON)), 5.17 (1H, br. s, CH_{alkene}(CON)*), 5.42 (1H, dt, *J* = 15.3, 5.8, $CH_{alkene}(CH_2CH_2)$), 5.53-5.60 (1H, m,, $CH_{alkene}(CH_2N)$), 5.83 (1H, d, *J* = 12.4, $CH_{alkene}Sn$), 6.41-6.46 (1H, m, CH_{alkene}(CHn)). ^{13}C NMR ($CDCl_3$, 125 MHz, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: -8.6 ($(CH_3)_3Sn$), 18.8 (CH_3(alkene)), 32.5 (CH_2(alkene)), 33.3 (CH_3N), 35.0 (CH_3N*), 35.9 (CH_2(alkene)), 49.0 (CH_2N*), 52.2 (CH_2N), 54.8 (CH_3O), 91.3 ($C_{alkene}H$(CON)), 125.2 ($C_{alkene(E)}H(CH_2CH_2)$), 125.8 ($C_{alkene(E)}(CH_2CH_2)$*), 129.8 ($C_{alkene(E)}(CH_2N)$*), 130.1 ($C_{alkene(E)}(CH_2N)$), 132.3 ($C_{alkene(Z)}$Hn*), 133.0 ($C_{alkene(Z)}$Hn), 147.8 ($C_{alkene(Z)}$(CHn)), 148.1 ($C_{alkene(Z)}$(CHn)*), 167.9 (C^Q_{alkene}), 168.4 (CO). *m/z* [CI^+, isobutane] 388 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 388.1308, $C_{16}H_{30}NO_2{}^{120}Sn$ requires 388.1299 . υ_{max} /cm^{-1} (film): 2963, 2918, 2847, 1651, 1603, 1479, 1441.

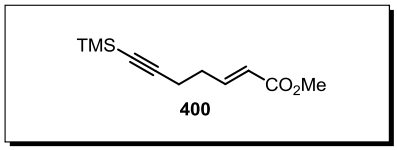
5-(Trimethylsilyl)pent-4-yn-1-ol **399**



399

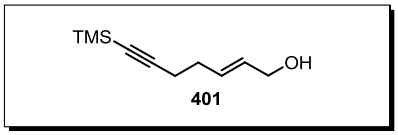
Pent-4-yn-1-ol (4.80 g, 58.5 mmol) was dissolved in anhydrous THF (200 mL) and cooled to 0 ^oC under an atmosphere of argon. EtMgBr (3 M in diethyl ether, 58.5 mL, 175 mmol) was added and the resultant solution was warmed to RT and stirred for 1h before being recooled to 0 ^oC. TMSCl (22.3 mL, 175 mmol) was added and the resultant solution was warmed to RT and stirred for 16h. The reaction was quenched by the addition of 10% aq. HCl solution (50 mL) and stirred for 10 min before being before extraction with Et_2O (3 × 100 mL). The combined organics were washed with sat'd aq. $NaHCO_3$ solution (50 mL), water (50 mL) and brine (2 × 50 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-4% Et_2O:DCM, afforded TMS-acetylene **399** (9.09 g, 56.9 mmol, 97%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.15 (9H, s, $(CH_3)_3Si$), 1.59 (1H, t, *J* = 5.5, OH), 1.77 (2H, quint, *J* = 6.5, $CH_2(CH_2OH)(CH_2')$), 2.34 (2H, t, *J* = 6.5, CH_2(alkyne)), 3.76 (2H, q, *J* = 6.0, CH_2OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.0 ($(CH_3)_3Si$), 16.5 ($CH_2(CH_2OH)(CH_2')$), 31.1 (CH_2(alkyne)), 61.9 (CH_2OH), 85.2 ($C^Q_{alkyne}Si$),106.6 ($C^Q_{alkyne}(CH_2)$). *m/z* [CI^+, isobutane] 157 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 157.1046, $C_8H_{17}OSi$ requires 157.1049. υ_{max} /cm^{-1} (film): 3331, 2957, 2899, 2176. The data observed is in accordance with literature values.[180]

(*E*)-Methyl 7-(trimethylsilyl)hept-2-en-6-ynoate **400**



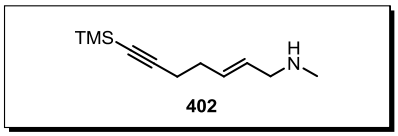
TMS-acetylene **399** (5.45 g, 34.9 mmol) was dissolved in anhydrous DCM (175 mL) and cooled to 0 ^{o}C under an atmosphere of argon. PCC (15.6 g, 69.7 mmol) was added portionwise over 45 min, and the resultant reaction mixture was stirred for 5h at 0 ^{o}C until reaction completion, indicated by TLC analysis. The resultant mixture was filtered through Florisil, with DCM elution. The solvent was concentrated *in vacuo* until approximately 175 mL remained. Methyl (triphenylphosphoranylidene)acetate (170g, 52.3 mmol) was added to the solution of crude aldehyde and the resultant reaction mixture was stirred for 16h at RT, under an atmosphere of argon. The solvent was evaporated before the resultant slurry was filtered, elution with petroleum ether. Solvent evaporation afforded the crude product. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the acrylate **400** (5.92 g, 28.1 mmol, 81%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.14 (9H, s, $(CH_3)_3Si$), 2.35-2.45 (4H, m, CH_2CH_2), 3.73 (3H, s, OMe), 5.88 (1H, dt, *J* = 15.6, 1.6, $CH(CO_2Me)$), 6.97 (1H, dt, *J* = 15.6, 6.4, $CH(CH_2)$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.0 ($(CH_3)_3Si$), 18.8 (CH_2(alkyne)), 31.2 (CH_2(alkene)), 51.5 (CH_3O), 85.9 ($C^{Q}_{alkyne}Si$), 105.3 ($C^{Q}_{alkyne}(CH_2)$), 122.0 ($C_{alkene}H(CO_2Me)$), 146.8 ($C_{alkene}H(CH_2)$), 166.8 (CO_2). *m/z* [Cl^+, isobutane] 211 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 211.1157, $C_{11}H_{19}O_2Si$ requires 211.1154. υ_{max} /cm^{-1} (film): 2957, 2903, 2178, 1726, 1661.

(*E*)-7-(trimethylsilyl)hept-2-en-6-yn-1-ol **401**



Ester **400** (2.02 g, 9.60 mmol) was dissolved in anhydrous Et_2O (50 mL) and cooled to 0 ^{o}C. DIBAL (1 M in hexanes, 21.1 mL, 21.1 mmol) was added and the reaction was stirred at 0 ^{o}C for 30 min before being allowed to warm to RT over 16h. The reaction mixture was cooled to 0 ^{o}C and diluted with Et_2O (100 mL), before being quenched by the successive addition of water (0.5 mL), 15% aq. NaOH solution (0.5 mL) and water (2.1 mL) with 30 min stirring time between each addition. The resultant slurry was warmed to RT and stirred for 90 min before anhydrous Na_2SO_4 was added. The resulting slurry stirred for a further 30 min. The solids were removed by filtration and the solution was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-40% Et_2O: petroleum ether, afforded the desired alcohol **401** (1.49 g, 8.17 mmol, 85%) as a colourless oil. ^{1}H NMR (C_6D_6, 400 MHz) δ: 0.21 (9H, s, $(CH_3)_3Si$), 2.03-2.08 (4H, m, CH_2CH_2), 3.77 (2H, br. t, *J* = 4.8, CH_2OH), 5.38-5.50 (2H, m, $CH_{alkene}CH_{alkene}$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.1 ($(CH_3)_3Si$), 19.8 (CH_2(alkyne)), 31.2 (CH_2(alkene)), 63.5 (CH_2OH), 84.9 ($C^{Q}_{alkyne}Si$), 106.4 ($C^{Q}_{alkyne}(CH_2)$), 130.2 ($C_{alkene}H$), 130.7 ($C_{alkene}H$). *m/z* [Cl^+, isobutane] 183 $[M+H]^+$ (43%), HRMS found $[M+H]^+$ 183.1207, $C_{10}H_{19}OSi$ requires 183.1205. υ_{max} /cm^{-1} (film): 3333, 2957, 2903, 2861, 2176.

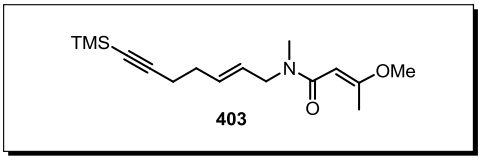
(*E*)-*N*-Methyl-7-(trimethylsilyl)hept-2-en-6-yn-1-amine **402**



402

A solution of freshly recrystallised NBS (2.87 g, 16.1 mmol) in anhydrous DCM (40 mL) was cooled to 0 ^{o}C under an atmosphere of argon. DMS (1.78 mL, 16.1 mmol) was added and the resultant solution was cooled to -10 ^{o}C, to which a solution of alcohol **401** (1.47 g, 8.06 mmol) in anhydrous DCM (10 mL) was added dropwise. The reaction mixture was warmed to RT over 45 min and stirred for a further 2h, before being filtered through a pad of Celite, followed by elution with petroleum ether. Solvent evaporation afforded the crude allyl bromide intermediate which was rapidly purified via passing it through a pad of silica, elution with 0-1% Et_2O:petroleum ether, to afforded the allyl bromide intermediate (1.41 g, 6.16 mmol, 76%), as a colourless oil. The allyl bromide intermediate was immediately dissolved in anhydrous THF (17 mL) and cooled to 0 ^{o}C under an atmosphere of argon. Methylamine (2 M in THF, 23.0 mL, 46.2 mmol) was added and the resultant reaction mixture was stirred at 0 ^{o}C for 1h before being warmed to RT and stirred for a further 3h until reaction completion, as indicated by TLC analysis. Solvent evaporation afforded the crude product. Purification by flash column chromatography, elution with 0.2:1:1 methanol:DCM:petroleum ether, afforded the allylic amine **402** (1.13 g, 5.80 mmol, 72%), as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.13 (9H, s, $(CH_3)_3Si$), 2.32-2.34 (CH_2CH_2), 2.63 (3H, s, $(CH_3)NH$), 3.59 (2H, d, *J* = 7.2, CH_2N), 5.74 (1H, dt, *J* = 15.4, 7.2, $C_{alkene}H(CH_2CH_2)$), 5.97 (1H, dt, *J* = 15.4, 6.7, $C_{alkene}H(CH_2N)$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.0 ($(CH_3)_3Si$), 19.4 (CH_2(alkyne)), 30.9 (CH_3N), 31.2 (CH_2(alkene)), 50.1 (CH_2N), 85.5 ($C^{Q}_{alkyne}Si$), 105.5 ($C^{Q}_{alkyne}(CH_2)$), 119.7 ($C_{alkene}H(CH_2CH_2)$), 140.0 ($C_{alkene}H(CH_2N)$). *m/z* [CI^+, isobutane] 196 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 196.1523, $C_{11}H_{22}NSi$ requires 196.1522. υ_{max} /cm^{-1} (film): 3013, 2957, 2901, 2783, 2729, 2172, 1672, 1580, 1458.

(*E*)-3-Methoxy-*N*-methyl-*N*-((*E*)-7-(trimethylsilyl)hept-2-en-6-ynyl)but-2-enamide **403**

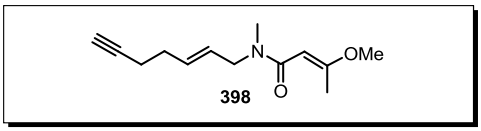


403

Amine **402** (475 mg, 2.43 mmol) and acid **56** (257 mg, 2.21 mmol) were dissolved in anhydrous DCM (12 mL) and the resultant solution was cooled to 0 ^{o}C under an atmosphere of argon. HBTU (965 mg, 2.55 mmol) was added before the dropwise addition of DIPEA (0.77 mL, 4.42 mmol). The reaction mixture was stirred at 0 ^{o}C for 15 min, before being warmed to RT and stirred for a further 2h. The solvent was evaporated and the resultant slurry was partitioned between Et_2O (50 mL) and water (30 mL). The organics were collected and further washed with sat'd aq. $NaHCO_3$ solution (10 mL), 10% aq. HCl solution (10 mL) and brine (2 × 10 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-50% Et_2O:petroleum ether, afforded amide **403** (512 mg, 1.74 mmol, 79%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 55 ^{o}C) δ: 0.14 (9H, s, $(CH_3)_3Si$), 2.21 (3H, s, CH_3(alkene)), 2.23-2.31 (4H, m, CH_2CH_2), 2.95 (3H, s, CH_3N), 3.60 (3H, s, CH_3O), 3.94 (2H, br. s, CH_2N), 5.18 (1H, s, CH_{alkene}(CON)), 5.49 (1H, dtt, *J* = 15.4, 5.8, 1.4, $CH_{alkene}(CH_2CH_2)$, 5.63 (1H, dtt, *J* = 15.4, 6.4, 1.3, $CH_{alkene}(CH_2N)$. ^{13}C NMR ($CDCl_3$, 125 MHz, 55 ^{o}C) δ: 0.0 ($(CH_3)_3Si$), 18.5

(CH_3(alkene)), 19.9 (CH_2(alkyne)), 31.2 (CH_2(alkene)), 33.2 (CH_3N* only observed at 25 °C), 34.9 (CH_3N only observed at 25 °C), 48.7 (CH_2N* only observed at 25 °C), 52.0 (CH_2N only observed at 25 °C), 54.6 (CH_3O), 89.2 ($C^Q_{alkyne}Si$), 91.3 (C_{alkene}(CON)), 106.3 ($C^Q_{alkyne}Si(CH_2)$), 126.4 ($CH_{alkene}(CH_2CH_2)$), 131.2 ($C_{alkene}H(CH_2N)$), 168.3 (C^Q_{alkene}), 168.4 (CO). *m/z* [CI^+, isobutane] 294 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 294.1887, $C_{16}H_{28}NO_2Si$ requires 294.1889. υ_{max} /cm^{-1} (film): 2958, 2922, 2783, 2174, 1722, 1709, 1646, 1603, 1430.

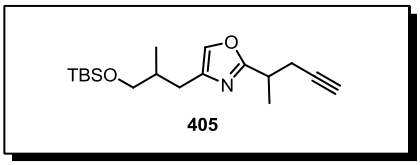
(*E*)-*N*-((*E*)-hept-2-en-6-ynyl)-3-methoxy-*N*-methylbut-2-enamide



398

TMS-acetylene **403** (249 mg, 0.85 mmol) was dissolved in MeOH (4 mL) and the resultant solution was treated with K_2CO_3 (123 mg, 0.89 mmol) and stirred at 30 °C for 16h, after which TLC analysis indicated reaction completion. The solvent was evaporated and the resultant residue was partitioned between Et_2O (30 mL) and water (15 mL). The organics were collected and further washed with brine (2 × 5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-50% Et_2O:petroleum ether, afforded acetylene **398** (180 mg, 0.81 mmol, 96%), as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz, 55 °C) δ: 1.93 (1H, br. t, CH_{alkyne}), 2.21 (3H, br. d, CH_3(alkene)), 2.26-2.28 (4H, m, CH_2CH_2), 2.95 (3H, s, CH_3N), 3.60 (3H, s, CH_3O), 3.94 (2H, br. s, CH_2N), 5.18 (1H, s, CH_{alkene}(CON)), 5.50 (1H, dtt, *J* = 15.4, 5.8, 1.3, $CH_{alkene}(CH_2CH_2)$), 5.64 (1H, dtt, *J* = 15.4, 6.5, 1.5, $CH_{alkene}(CH_2N)$). ^{13}C NMR ($CDCl_3$, 125 MHz, 55 °C) δ: 18.6 (CH_3(alkene)), 18.6 (CH_2(alkyne)), 31.1 (CH_2(alkene)), 33.4 (CH_3N* only observed at 25 °C), 35.1 (CH_3N only observed at 25 °C) 48.4 (CH_2N* only observed at 25 °C), 52.1 (CH_2N only observed at 25 °C), 54.7 (CH_3O), 68.7 ($C_{alkyne}H$), 83.5 (C^Q_{alkyne}), 91.3 (C_{alkene}(CON)), 126.6 ($C_{alkene}H(CH_2CH_2)$), 131.0 ($C_{alkene}H(CH_2N)$), 168.1 (C^Q_{alkene}), 168.5 (CO). *m/z* [CI^+, isobutane] 222 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 222.1496, $C_{13}H_{20}NO_2$ requires 222.1494.

4-(3-(tert-butyldimethylsilyloxy)-2-methylpropyl)-2-(pent-4-yn-2-yl)oxazole **405**

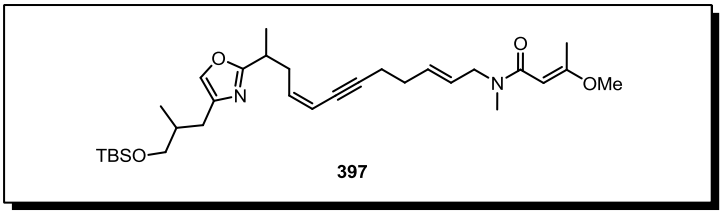


405

NaN_3 (23 mg, 0.36 mmol), MsCl (28 µL, 0.36 mmol) and anhydrous MeCN (1 mL) were added to an oven dried flask and stirred at RT for 16h, under an atmosphere of argon. The resultant cloudy solution was cooled to 0 °C before dimethyl 2-oxopropylphosphonate (29 µL, 0.31 mmol) was added. After 2 min, Cs_sCO_3 (111 mg, 0.34 mmol) was added and the solution was stirred at 0 °C for a further 30 min, before being warmed to RT and stirred for a further 3h. The solution was recooled to 0 °C and diluted with MeOH (0.5 mL) and stirred for 1hr. Aldehyde **392** (50 mg, 0.15 mmol) in MeOH (0.5 mL) was added, followed by Cs_sCO_3 (90 mg, 0.28 mmol). The reaction mixture was allowed to warm to RT and stirred for 16h. The reaction was quenched with water (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organics were washed with water (2 × 5 mL) and brine (10 mL), before being dried over sodium Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow

oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded acetylene **405** (33 mg, 0.10 mmol, 67%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.02 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3CSi$), 0.91 (3H, d, *J* = 6.7, $CH_3(CHCH_2Ar)$), 1.43 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 1.93-2.02 (1H, m, $CH(CH_3)(CH_2Ar)$), 1.98 (1H, t, *J* = 2.7, $C_{alkyne}H$), 2.28 (1H, ddd, *J* = 13.7, 7.9, 0.9, CH_2Ar), 2.51 (1H, ddd, *J* = 16.7, 8.1, 2.7, CH_2(alkyne)), 2.59 (1H, ddd, *J* = 14.6, 8.4, 1.0, CH_2Ar), 2.69 (1H, ddd, *J* = 16.7, 5.7, 2.7, CH_2(alkyne)), 3.11-3.18 (1H, $CH(CH_3)$(Ar)), 3.43 (1H, dd, *J* = 9.8, 5.9, CH_2OSi), 3.49 (1H, dd, *J* = 9.8, 5.4, CH_2OSi), 7.28 (1H, t, *J* = 1.0, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.4 ($(CH_3)_2Si$), 16.6 ($C(CH_3)_3$), 17.6 ($CH_3(CHCH_2Ar)$), 17.6 ($CH_3(CHAr)$), 23.8 (CH_2(alkyne)), 24.3 ($(CH_3)_3CSi$), 29.7 (CH_2Ar), 33.2 ($CH(CH_3)$(Ar)), 35.1 ($CH(CH_3)(CH_2Ar)$), 67.4 (CH_2OSi), 70.0 ($C_{alkyne}H$), 81.5 (C^Q_{alkyne}), 134.3 ($C^{Ar}H$), 139.3 (C^{Ar}), 166.0 (C^{Ar}). *m/z* [CI^+, isobutane] 322 $[M+H]^+$ (70%), HRMS found $[M+H]^+$ 322.2205, $C_{18}H_{32}NO_2Si$ requires 322.2202. υ_{max} /cm^{-1} (film): 3314, 2955, 2930, 2886, 1570, 1471, 1462.

(*Z*)-*N*-((2*E*,8*Z*)-11-(4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazol-2-yl)dodeca-2,8-dien-6-ynyl)-3-methoxy-*N*-methylbut-2-enamide **397**

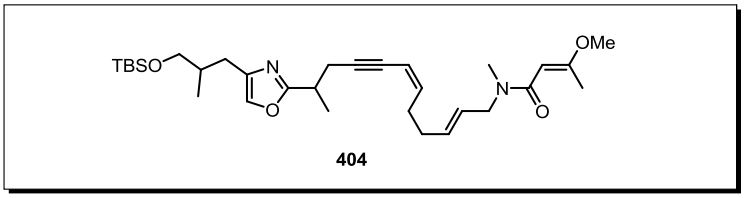


397

Vinyl iodide **391** (134 mg, 0.30 mmol) and acetylene **398** (106 mg, 0.48 mmol) were dissolved in anhydrous MeCN (3 mL) and degrassed by passing a stream of argon through the solution, before being cooled to 0 ^oC. The reaction was carried out in the absence of light. $Pd(PPh_3)_4Cl_2$ (15 mg, 21 μmol) and CuI (11 mg, 60 μmol) were added to the reaction mixture before the addition of NEt_3 (190 μmol, 1.34 mmol) and the resultant solution was stirred at 0 ^oC for 15 min and then warmed to RT and stirred for a further 90 min, after which TLC analysis indicated reaction completion. The solvent was evaporated and the resultant residue was purified by flash column chromatography, elution with 0-30% Et_2O:petroleum ether, to afford the enyne **397** (132 mg, 0.24 mmol, 82%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 55 ^oC) δ: 0.04 (6H, br. s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 0.92 (3H, d, *J* = 6.7, $CH_3(CHCH_2Ar)$), 1.33 (3H, dd, *J* = 7.0, 0.8, $CH_3(CHAr)$), 1.95-2.02 (1H, m, $CH(CH_2Ar)$), 2.21 (3H, s, CH_3(alkene)), 2.27-2.31 (3H, m, $CH_2(CH_{alkene(E)})(CH_2)$, CH_2Ar), 2.42 (2H, td, *J* = 6.9, 1.8, CH_2(alkyne)), 2.59 (1H, dd, *J* = 14.6, 6.1, CH_2Ar), 2.62-2.73 (2H, m, $CH_2(CH_{alkene(Z)})(CH)$), 2.94 (3H, s, CH_3N), 3.02-3.09 (1H, m, $CH(CH_3)$(Ar)), 3.45 (1H, dd, *J* = 9.8, 6.0, CH_2OSi), 3.51 (1H, ddd, *J* = 9.8, 5.5, 0.7, CH_2OSi), 3.59 (3H, br. s, CH_3O), 3.94 (2H, br. s, CH_2N), 5.18 (1H, br. s, $CH_{alkene}(CON)$), 5.48-5.53 (2H, m, $CH_{alkene(Z)}$(alkyne)), $CH_{alkene(E)}(CH_2N)$), 5.66 (1H, dt, *J* = 15.4, 6.6, $CH_{alkene(E)}(CH_2CH_2)$), 5.78 (1H, dt, *J* = 10.7, 7.3, $CH_{alkene(Z)}(CH_2)$), 7.25 (1H, br. q, *J* = 0.9, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz, 55 ^oC, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: -5.5 $(CH_3)_2Si$, 16.5 ($CH_3(CHCH_2Ar)$), 17.8 ($CH_3(CHAr)$), 18.3 ($SiC(CH_3)_3$)), 18.6 (CH_3(alkene)), 19.7 (CH_2(alkyne)), 25.9 ($(CH_3)_3CSi$), 29.8 (CH_2Ar), 31.5 ($CH_2(C_{alkene(E)}H)(CH_2)$),33.5 ($CH(CH_3)$(Ar)), 33.5 ($CH_3N$* only observed at 25 ^oC), 35.2 ($CH(CH_2Ar)$), 35.2 (CH_3N only observed at 25 ^oC), 35.3 $CH_2(C_{alkene(Z)}H)(CH)$), 48.9 (CH_2N* only observed at 25 ^oC), 52.1 (CH_2N only observed at 25 ^oC), 54.7 (CH_3O), 67.6 (CH_2OSi), 77.7 ($C_{alkyne}(C_{alkene(Z)}H)$), 82.8 ($C_{alkyne}(CH_2)$ only observed at 25 ^oC), 91.3 ($C_{alkene}(CON)$), 111.4 ($C_{alkene(Z)}H$(alkyne)), 126.5 (($C_{alkene(E)}H(CH_2N)$), 131.5 ($C_{alkene(E)}H(CH_2CH_2)$), 133.9 ($C^{Ar}H$), 138.8 ($C_{alkene(Z)}H(CH_2)$), 139.3 (C^{Ar}), 167.0 (C^{Ar}), 168.5 (CO).b*m/z* [CI^+, isobutane] 543.6 $[M+H]^+$

(100%), HRMS found $[M+H]^+$ 543.3621, $C_{31}H_{51}N_2O_4Si$ requires 543.3618. υ_{max} /cm^{-1} (film): 2955, 2928, 2857, 1647, 1603, 1568, 1456, 1439.

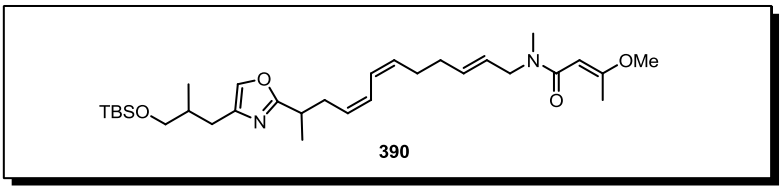
(*E*)-*N*-((2*E*,6*Z*)-11-(4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazol-2-yl)dodeca-2,6-dien-8-ynyl)-3-methoxy-*N*-methylbut-2-enamide **404**



404

Acetylene **405** (145 mg, 450 µmol) and vinyl iodide **72** (98 mg, 281 µmol) were dissolved in anhydrous MeCN (3 mL) and degassed by passing a stream of argon through the solution, before being cooled to 0 °C. The reaction was carried out in the absence of light. $Pd(PPh_3)_4Cl_2$ (14 mg, 20 µmol) and CuI (11 mg, 60 µmol) were added to the reaction mixture before the addition of NEt_3 (181 µmol, 1.30 mmol) and the resultant solution was stirred at 0 °C for 15 min, before being warmed to RT and stirred for 16h, after which TLC analysis indicated reaction completion. The solvent was evaporated and the resultant residue was purified by flash column chromatography, elution with 0-100% Et_2O:petroleum ether, to afford the reverse enyne **404** (128 mg, 235 µmol, 84%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: 0.02 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3CSi$), 0.90 (3H, d, *J* = 6.8, $CH_3(CHCH_2Ar)$), 1.43 (3H, d, *J* = 6.7, $CH_3(CHAr)$), 1.94-2.00 (1H, m, $CH(CH_2Ar)$), 2.13-2.17 (2H, m, $CH_2(CH_{alkene(E)})(CH_2)$), 2.21 (3H, br. s, CH_3(alkene)), 2.26 (1H, dd, *J* = 14.6, 8.0, CH_2Ar), 2.32 (2H, q, *J* = 7.1, $CH_2(CH_{alkene(Z)})(CH_2)$), 2.59 (1H, dd, *J* = 14.6, 6.0, CH_2Ar), 2.65 (1H, ddd, *J* = 16.8, 8.4, 2.0, CH_2(alkyne)), 2.83 (1H, ddd, *J* = 16.9, 5.6, 2.0, CH_2(alkyne)), 2.93 (3H, s, CH_3N), 3.11-3.19 (1H, m, $CH(CH_3)(Ar)$), 3.43 (1H, dd, *J* = 9.8, 5.9, CH_2OSi), 3.48 (1H, dd, *J* = 9.8, 5.5, CH_2OSi), 3.57 (3H, br. s, CH_3O), 3.61 (3H, br. s, CH_3O*), 3.87 (2H, br. s, CH_2N), 3.97 (2H, br. s, CH_2N*), 5.15 (1H, br. s, $CH_{alkene}(CON)$), 5.18 (1H, br. s, $CH_{alkene}(CON)$*), 5.39-5.44 (2H, m, $CH_{alkene(Z)}$(alkyne)), $CH_{alkene(E)}(CH_2N)$), 5.56 (1H, dt, *J* = 15.3, 6.8, $CH_{alkene(E)}(CH_2CH_2)$), 5.75-5.79 (1H, m, $CH_{alkene(Z)}(CH_2CH_2)$), 7.27 (1H, s, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz, 55 °C, *3:2 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: -5.5 $(CH_3)_2Si$, 16.5 ($CH_3(CHCH_2Ar)$), 17.6 ($CH_3(CHAr)$), 18.3 ($SiC(CH_3)_3$)), 18.6 (CH_3(alkene)), 25.5 CH_2(alkyne), 25.9 ($(CH_3)_3CSi$), 29.5 ($CH_2(CH_{alkene(E)})$), 29.8 (CH_2Ar), 31.4 ($CH_2(C_{alkene(Z)}H)$), 33.6 (CH_3N* only observed at 25 °C), 33.6 ($CH(CH_3)(Ar)$), 35.1 (CH_3N only observed at 25 °C), 35.1 ($CH(CH_2Ar)$), 49.0 (CH_2N* only observed at 25 °C), 52.2 (CH_2N only observed at 25 °C), 54.8 (CH_3O), 67.5 (CH_2OSi), 78.9 ($C_{alkyne}(C_{alkene(Z)}H)$), 91.4 ($C_{alkene}(CON)$), 91.7 ($C_{alkyne}(CH_2)$), 109.0 ($C_{alkene(Z)}H$ (alkyne)), 125.2 ($C_{alkene(E)}H(CH_2N)$), 132.7 $C_{alkene(E)}H(CH_2CH_2)$), 134.1 ($C^{Ar}H$), 139.5 (C^{Ar}), 141.6 $C_{alkene(Z)}H(CH_2CH_2)$), 166.2 (C^{Ar}), 168.4 (CO). *N.B: (C^{Q}_{alkene}) not observed. m/z* [CI^+, isobutane] 543 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 543.3621, $C_{31}H_{51}N_2O_4Si$ requires 543.3618.

N-((2*E*,6*Z*,8*Z*)-11-(4-(3-(*Tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazol-2-yl)dodeca-2,6,8-trienyl)-3-methoxy-*N*-methylbut-2-enamide **390**



390

Method A: Stille Coupling

Vinyl iodide **391** (13.0 mg, 28.9 µmol) and vinyl stannane **396** (13.4 mg, 34.7 µmol) were dissolved in degassed anhydrous DMF (0.5 mL) before $Pd(PPh_3)_4$ (2.7 mg, 2.3 µmol) was added, under an atmosphere of argon. The reaction mixture was stirred for 12h at 60 ^oC under MW irradiation. The crude mixture was passed through a pad of Celite and eluted with Et_2O (20 mL). The organics were then washed with water (2 × 5 mL) and brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by HPLC, using a Waters Aquidity UPLC BEH C18 column (50 nm x 2.1 mm i.d. 1.7 µm) at 40 ^oC, eluting with 0.1% v/v HCO_2H/H_2O-0.1% v/v HCO_2H/MeCN, to afford *Z,Z*-diene **390** (8.7 mg, 16.0 µmol, 55%), as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz, 55 ^oC) δ: 0.04 (6H, br. s, $(CH_3)_2Si$), 0.91 (9H, s, $(CH_3)_3CSi$), 0.92 (3H, d, *J* = 6.8, $CH_3(CHCH_2Ar)$), 1.32 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 1.95-2.02 (1H, m, $CH(CH_2Ar)$, 2.12-2.17 (2H, m, $CH_2(CH_{alkene(E)})(CH_2)$), 2.21 (3H, s, CH_3(alkene)), 2.23-2.32 (3H, m, $CH_2(CH_{alkene(Z)})(CH_2)$, CH_2Ar), 2.46-2.53 (1H, m, $CH_2(CH_{alkene(Z)})(CHCH_3)$), 2.54 (1H, ddd, *J* = 14.6, 6.1, 1.0, CH_2Ar), 2.60-2.67 (1H, m, $(CH_{alkene(Z)})(CHCH_3)$), 2.93 (3H, s, CH_3N), 2.97-3.04 (1H, m, $CH(CH_3)(Ar)$), 3.45 (1H, ddd, *J* = 9.7, 6.0, 1.0, CH_2OSi), 3.51 (1H, ddd, *J* = 9.8, 5.4, 1.2, CH_2OSi), 3.59 (3H, br. s, CH_3O), 3.91 (2H, br. s, CH_2N), 5.17 (1H, br. s, $CH_{alkene}(CON)$), 5.39-5.46 (3H, m, $CH_{alkene(E)}(CH_2N)$, $CH_{alkene(Z)}(CH_2CH_2)$, $CH_{alkene(Z)}(CH_2CHCH_3)$), 5.58 (1H, dtt, *J* = 15.4, 6.6, 1.4, $CH_{alkene(E)}(CH_2CH_2)$), 6.21-6.31 (2H, m, $CH_{alkene(Z)}(CH_{alkene(Z)}(CH_2CH_2))$, $CH_{alkene(Z)}(CH_{alkene(Z)}(CH_2CHCH_3))$), 7.24 (1H, t, *J* = 1.1, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz, 55 ^oC) δ: -5.5 $(CH_3)_2Si$, 16.5 $(CH_3(CHCH_2Ar))$, 18.0 $(CH_3(CHAr))$, 18.3 $(SiC(CH_3)_3)$), 18.6 $(CH_3$(alkene)), 25.9 $((CH_3)_3CSi)$, 27.2 $(CH_2(CH_{alkene(Z)})(CH_2))$, 29.8 ($CH_2Ar$), 32.0 $(CH_2(C_{alkene(E)}H)(CH_2))$, 32.9 $(CH_2(C_{alkene(Z)}H)(CHCH_3))$, 34.0 $(CH(CH_3)(Ar))$, 35.1 $(CH(CH_2Ar))$, 35.1 (CH_3N), 52.5 (CH_2N), 54.6 (CH_3O), 67.6 (CH_2OSi), 91.4 ($C_{alkene}(CON)$), 124.0 ($C_{alkene(Z)}H$(Z-alkene(CH_2CH_2))), 125.4 ($C_{alkene(E)}H(CH_2N)$), 125.4 ($C_{alkene(Z)}H(CH_{alkene(Z)}(CH_2CHCH_3))$), 128.4 $C_{alkene(Z)}H(CHCH_3)$), 131.7 ($C_{alkene(Z)}H(CH_2CH_2)$), 132.9 ($C_{alkene(E)}H(CH_2CH_2)$), 133.9 ($C^{Ar}H$), 139.3 (C^{Ar}), 167.2 (C^{Ar}), 167.2 (CO). *N.B: (C^Q_{alkene}) not observed. m/z* [CI^+ (+ve), isobutane] 545 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 545.3771, $C_{31}H_{53}N_2O_4Si$ requires 545.3775 υ_{max} /cm^{-1} (film): 2951, 2928, 2857, 1726, 1645, 1601, 1454.

Method B: P-2 Ni Reduction from Enyne **397**

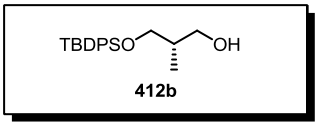
In the absence of light, $Ni(OAc)_2.4H_2O$ (62 mg, 248 µmol) was dissolved in degassed EtOH (2 mL), before $NaBH_4$ (9 mg, 239 µmol) was added. The resultant black solution was stirred under an atmosphere of argon for 2 min before being placed under a hydrogen atmosphere. EDA (59 µL, 884 µmol) was added before a solution of enyne **397** (48 mg, 88 µmol) in degassed EtOH (1.5 mL). The reaction mixture was stirred at RT under an atmosphere of hydrogen for 3h, before being passed through Celite, and eluted with EtOH, followed by solvent evaporation, to afford the crude product. Purification by HPLC, using a Waters Aquidity UPLC BEH C18 column (50 nm x 2.1 mm i.d. 1.7 µm) at 40 ^oC, eluting with 0.1% v/v HCO_2H/H_2O-0.1% v/v

HCO_2H/MeCN, to afford Z,Z-diene **390** (26 mg, 49 µmol, 55%), as a colourless oil. The spectral and physical data obtained for **390**, via Method B, matched that obtained via Method A.

Method C: P-2 Ni Reduction from Reverse-Enyne **404**

Under analogous conditions and scale to that described in Method B above, reverse enyne **404** (48 mg, 88 µmol) was reduced to afford Z,Z-diene **390** (25 mg, 47 µmol, 53%), as a colourless oil. The spectral and physical data obtained for **390**, via Method C, matched that obtained via Methods A and B.

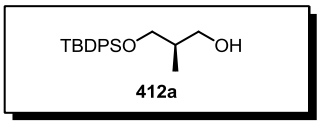
(S)-3-(*Tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **412b**



412b

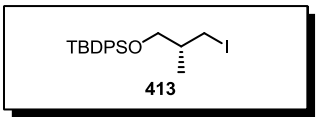
(*R*)-methyl 3-hydroxy-2-methylpropanoate (9.82 g, 83.1 mmol) was dissolved in anhydrous DMF (30 mL) and cooled to 0 ^oC under an atmosphere of argon. TBDSCl (23.4 g, 85.2 mmol) and imidazole (11.3 g, 166 mmol) were added, and the resultant solution was stirred for 30 min until TLC analysis of the reaction indicated completion. The reaction was quenched with water (250 mL) and was extraction with Et_2O (3 × 300 mL). The combined organic extracts were washed with water (2 × 100 mL) and brine (3 × 100 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude ester intermediate, (*R*)-methyl 3-(tert-butyldiphenylsilyloxy)-2-methylpropanoate (29.8 g, 83.6 mmolm 100%), as a colourless oil. The intermediate was dissolved in Et_2O (275 mL) and cooled to –78 ^oC under an atmosphere of argon before DIBAL (1 M in THF, 183 mL, 183 mmol) was added. The resultant solution was stirred at –78 ^oC for 2h before being warmed to 0 ^oC and was slowly added to a rapidly stirring solution of Rochelle's salt (150 g) in water (500 mL) at 0 ^oC. The slurry was warmed to RT and stirred for a further 2h until the organic and aqueous layers became transparent. The organic layer was collected and the aqueous layer was extraction with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (75 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-15% Et_2O:petroleum ether, afforded the desired *S*-alcohol **412b** (27.3 g, 83.6 mmol, 100%), as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.83 (3H, d, *J* = 7.0, CH_3), 1.06 (9H, s, $(CH_3)_3CSi$), 1.96-2.04 (1H, m, $CH(CH_3)$), 2.49 (1H, t, *J* = 5.7, OH), 3.59 (1H, dd, *J* = 10.0, 7.7, CH_2OH), 3.67 (2H, t, *J* = 5.8, CH_2OH, CH_2OSi), 3.72 (1H, dd, *J* = 10.0, 4.5, CH_2OSi), 7.38-7.44 (6H, m, ArH), 7.66-7.69 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.3 ($SiC(CH_3)_3$), 19.3 ($CH_3(CH)$), 27.0 ($(CH_3)_3CSi$), 37.5 ($CH(CH_3)$), 67.9 (CH_2OSi), 68.9 (CH_2OH), 127.9($C^{Ar}H$), 129.9($C^{Ar}H$), 133.3 (C_Q^{Ar}), 135.7 ($C^{Ar}H$). *m/z* [Cl^+, isobutane] 329 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 329.1942, $C_{20}H_{29}O_2Si$ requires 329.1937. υ_{max} /cm^{-1} (film): 3385, 2957, 2930, 2859, 1471. $[\alpha]_D^{22.0}$ -11.77 (c=1.70, $CHCl_3$). The data observed is in accordance with literature values.[128]

(R)-3-(*Tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **412a**



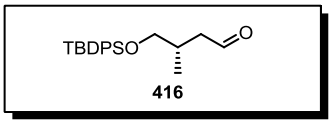
R-alcohol **412a** was obtained in the same quantity, yield and purity as *S*-alcohol **412b**, under analagous experimental conditions, starting from (*S*)-methyl 3-hydroxy-2-methylpropanoate. $[\alpha]_D^{21.8}$ 10.04 (c=1.50, $CHCl_3$). The data observed is in accordance with literature values.[128]

(R)-Tert-butyl(3-iodo-2-methylpropoxy)diphenylsilane **413**



S-alcohol **412b** was dissolved in anhydrous DCM (350 mL) and cooled to 0 ^oC under an atmosphere of argon. Imidazole (6.18 g, 90.8 mmol), PPh_3 (21.1 g, 80.4 mmol) and I_2 (20.4 g, 80.4 mmol) were added sequentially and the resultant solution was stirred at 0 ^oC for 10 min, before being warmed to RT and and stirred for a further 70 min, until TLC analysis of the reaction indicated completion. The reaction was quenched with sat'd aq. $Na_2S_2O_3$ solution (250 mL) and extraction with DCM (3 × 300 mL). The combined organic extracts were washed with sat'd aq. $Na_2S_2O_3$ solution (2 × 75 mL) and brine (2 × 75 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude product. Purification by flash column chromatography, elution with petroleum ether, afforded the iodide **413** (30.2 g, 66.3 mmol, 95%), as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.96 (3H, d, *J* = 6.7, CH_3), 1.06 (9H, s, $(CH_3)_3CSi$), 1.69-1.76 (1H, m, $CH(CH_3)$), 2.49 (1H, t, *J* = 5.7, OH), 3.34 (1H, dd, *J* = 9.5, 5.8, CH_2OSi), 3.40 (1H, dd, *J* = 9.5, 5.8, CH_2OSi), 3.46 (1H, dd, *J* = 10.1, 6.9, CH_2I), 3.58 (1H, dd, *J* = 10.1, 4.9, CH_2I), 7.38-7.44 (6H, m, ArH), 7.66-7.69 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.8 (CH_2I), 17.5 ($CH_3(CH)$), 19.4 ($SiC(CH_3)_3$), 26.9 ($(CH_3)_3CSi$), 37.7 ($CH(CH_3)$), 67.4 (CH_2OSi), 127.8($C^{Ar}H$), 129.8 ($C^{Ar}H$), 133.7 (C_Q^{Ar}), 135.8 ($C^{Ar}H$). *m/z* [CI^+, isobutane] 439 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 439.0953, $C_{20}H_{28}IOSi$ requires 439.0954. υ_{max} /cm^{-1} (film): 2959, 2930, 2857, 1471. $[\alpha]_D^{21.6}$ -9.72 (c=1.44, $CHCl_3$).

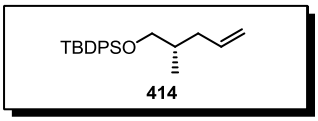
(S)-4-(tert-butyldiphenylsilyloxy)-3-methylbutanal **416**



Anhydrous DCM (400 mL) was added to a flame-dried flask and cooled to –78 ^oC, before the addition of oxalyl chloride (11.6 mL, 137 mmol). A solution of DMSO (16.2 mL, 229 mmol) in anhydrous DCM (35 mL) was added dropwise over 30 min via syringe pump, ensuring that the internal temperature did not exceed –70 ^oC. The mixture was stirred for a further 20 min. A solution of *S*-alcohol **412b** (27.3 g, 83.1 mmol) in anhydrous DCM (30 mL) was added dropwise, via syringe pump, over a period of 20 min, ensuring that the internal temperature did not exceed –70 ^oC. After stirring for a further 45 min at –78 ^oC, NEt_3 (69.0 mL, 499 mmol) was added dropwise, via syringe pump, over a period of 40 min, ensuring that the internal temperature did not exceed –70 ^oC. The resultant mixture was then stirred for a further 10 min at –78 ^oC before being warmed to 0 ^oC over 45 min. TLC analysis of the reaction indicated completion. The reaction was quenched with water (250 mL) and the organic layer was collected. The aqueous layer was extraction with DCM (3 × 150 mL). The combined organic

extracts were washed with water (2 × 75 mL) and brine (2 × 75 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude aldehyde intermediate, **415** (27.1 g, 83.1 mmol 100%), as a colourless oil. (Methoxymethyl)triphenylphosphonium chloride (62.5 g, 182 mmol) was dissolved in anhydrous THF (375 mL) and cooled to –78 ^{o}C under an atmosphere of argon, before NaHMDS (1 M in THF, 164 mL, 164 mmol) was added. After stirring at –78 ^{o}C for 1h, a solution of the *R*-aldehyde intermediate **415** (27.1 g, 83.1 mmol) in anhydrous THF (50 mL) was added dropwise over 10 min. The reaction was stirred at –78 ^{o}C for 30 min before being warmed to RT stirred for a further 90 min. TLC analysis of the reaction indicated completion. The reaction was quenched by the addition of sat's aq. $NaHCO_3$ solution (150 mL) and was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (75 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated, to yield the crude enol ether intermediate as a colourless oil. The intermediate was dissolved in THF and cooled to 0 ^{o}C. 6 M aq. HCl solution (156 mL, 936 mmol) was slowly added and the solution was warmed to RT and stirred for 90 min, after which TLC analysis indicated completion. The reaction was extracted with Et_2O (3 × 200 mL) and the combined organic extracts were washed with water (2 × 75 mL) and brine (75 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product as a pale yellow oil. Purification by flash column chromatography, elution with 0-3.5% Et_2O:petroleum ether, afforded the desired homologated aldehyde **416** (22.6 g, 66.5 mmol, 80%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (3H, d, *J* = 6.5, CH_3), 1.07 (9H, s, $(CH_3)_3CSi$), 2.27-2.40 (2H, m, $CH(CH_3)$, $CH_2(CHO)$), 2.63 (1H, ddd, *J* = 15.6, 5.6, 2.0, $CH_2(CHO)$), 3.46 (1H, dd, *J* = 10.0, 6.8, CH_2OSi), 3.61 (1H, dd, *J* = 10.0, 4.5, CH_2OSi), 3.72 (1H, dd, *J* = 10.0, 4.5, CH_2OSi), 7.39-7.49 (6H, m, ArH), 7.66-7.69 (4H, m, ArH), 9.82 (1H, s, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.8 ($SiC(CH_3)_3$), 19.3 ($CH_3(CH)$), 26.9 ($(CH_3)_3CSi$), 31.3 ($CH(CH_3)$),48.2 ($CH_2(CHO)$), 68.4 (CH_2OSi), 127.7 ($C^{Ar}H$), 129.8 ($C^{Ar}H$), 133.5 (C_Q^{Ar}), 135.7 ($C^{Ar}H$), 202.5 (CHO). *m/z* [Cl^+, isobutane] 341 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 341.1939, $C_{21}H_{29}O_2Si$ requires 341.1937 . υ_{max} /cm^{-1} (film): 2930, 2858, 1720, 1471. $[\alpha]_D^{21.6}$ -2.50 (c=1.00, $CHCl_3$). The data observed is in accordance with literature values.[133]

(S)-Tert-butyl(2-methylpent-4-enyloxy)diphenylsilane **414**



Method A: Negishi Coupling with Vinyl Iodide **413**

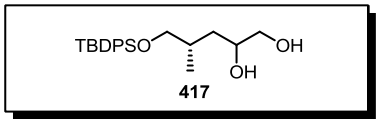
Vinyl iodide **413** (14.9 g, 33.9 mmol) was dissolved in anhydrous Et_2O (50 mL) and cooled to –78 ^{o}C under an atmosphere of argon. ^{t}BuLi (1.9 M in hexanes, 37.4 mL, 71.1 mmol) was added and the resultant solution stirred for 30 min. In a separate flask, $ZnBr_2$ (4.96 g, 22.0 mmol) was flame dried and dissolved in anhydrous THF and cooled to 0 ^{o}C, before being added dropwise, via cannulation, to the solution of lithiate in Et_2O. The resultant suspension was stirred at –78 ^{o}C for 45 min, before being warmed to 0 ^{o}C and stirred for a further 20 min. In a separate flask, $Pd(PPh_3)_4$ (1.17 g, 1.02 mmol) and vinyl bromide (1 M in THF, 102 mL, 102 mmol) were combined and the resultant suspension was added dropwise, via cannular, to the zincate. The reaction mixture was stirred at 0 ^{o}C for 1h before being warmed to RT and stirred for 72h. The reaction was quenched with water (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with water (100 mL) and brine (2 x 75mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product. Purification by flash column chromatography, elution with petroleum ether, afforded the desired olefin **414**

(9.11 g, 26.9 mmol, 79%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (3H, d, *J* = 6.8, CH_3), 1.06 (9H, s, $(CH_3)_3CSi$), 1.72-1.79 (1H, m, $CH(CH_3)$), 1.87-1.93 (1H, m, CH_2(alkene)), 2.23-2.29 (1H, m, CH_2(alkene)), 3.34 (1H, dd, *J* = 9.5, 5.8, CH_2OSi), 3.49 (2H, dd, *J* = 6.0, 3.7, CH_2OSi), 4.95-5.02 (2H, m, $C_{alkene}H_2$), 5.72-5.80 (1H, m, $C_{alkene}H(CH_2)(CH_2')$), 7.36-7.42 (6H, m, ArH), 7.66-7.68 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.4 ($CH_3(CH)$), 19.3 ($SiC(CH_3)_3$), 26.9 ($(CH_3)_3CSi$), 35.7 ($CH(CH_3)$), 37.6 (CH_2(alkene)), 68.4 (CH_2OSi), 115.7 ($C_{alkene}H_2$), 127.6 ($C^{Ar}H$), 129.5 ($C^{Ar}H$), 134.0 ($C_Q{}^{Ar}$), 135.6 ($C^{Ar}H$), 137.3 ($C_{alkene}H(CH_2)(CH_2')$). *m/z* [Cl^+, isobutane] 339 $[M+H]^+$ (100%),HRMS found $[M+H]^+$ 339.2147, $C_{22}H_{31}OSi$ requires 339.2144 . υ_{max} /cm^{-1} (film): 2959, 2932, 2859, 1641, 1589, 1471. $[\alpha]_D{}^{21.7}$ -11.5 (c=1.56, $CHCl_3$). The data observed is in accordance with literature values.[128]

Method B: Wittig Olefination with Aldehyde **416**

Methyltriphenylphosphonium bromide (31.7 g, 88.8 mmol) was dissolved in anhydrous THF (300 mL) and cooled to 0 °C under an atmosphere of argon. ^{t}BuLi (1.9 M in hexanes, 40.1 mL, 76.1 mmol) was added and the resultant mixture was stirred for 30 min, before a solution of aldehyde **416** (17.3 g, 50.7 mmol), in anhydrous THF (50 mL), was added dropwise over 10 min. The reaction was stirred at 0 °C for 1h before being warmed to RT stirred for a further 10h. TLC analysis of the reaction indicated completion. The reaction mixture was diluted with petroleum ether and filtered. The supernatant was collected and solvent evaporated. The crude material was taken up in petroleum ether and filtered for a second time to remove the majority of excess methyltriphenylphosphonium bromide and PPh_3O solids. Solvent evaporation afforded the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-1% Et_2O:petroleum ether, afforded the desired olefin **414** (15.0 g, 44.2 mmol, 87%), as a colourless oil. The spectral and physical data obtained for **414**, via Method B, matched that obtained via Method A.[128]

(*4S*)-5-(*Tert*-butyldiphenylsilyloxy)-4-methylpentane-1,2-diol

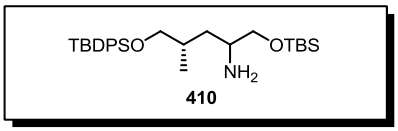


417

Olefin **414** (10.4 g, 30.8 mmol) was dissolved in anhydrous MeCN (30 mL) and cooled to 0 °C under an atmosphere of argon. Water (10 mL), NMO (7.93 g, 67.7 mmol) and then OsO_4 (4% w/w in H_2O, 2.0 mL, 0.32 mmol) was added, and the resultant solution was warmed to RT and stirred for 3h, after which TLC analysis indicated reaction completion. The reaction was quenched with a solution of sat'd aq. Na_2SO_3 (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (50 mL) and brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product. Purification by flash column chromatography, elution with 0-100% Et_2O:petroleum ether, afforded diol **417** (11.5 g, 30.8 mmol, 100%), as a colourless oil and a 1.3:1 mixture of diastereoisomers. ^{1}H NMR ($CDCl_3$, 500 MHz, *1.3:1 mixture of diastereoisomers, A & B*) δ: 0.86 (3H, d, *J* = 6.9, $CH_3(CH)$, A), 0.92 (3H, d, *J* = 6.9, $CH_3(CH)$, *B*), 1.06 (9H, s, $(CH_3)_3CSi$), 1.37 (1H, ddd, *J* = 14.3, 6.4, 2.9, $CH_2(CHCH_3)(CHOH)$, *A*), 1.47-1.53 (1H, m, $CH_2(CHCH_3)(CHOH)$), 1.52-1.55 (1H, m, $CH_2(CHCH_3)(CHOH)$, *B*), 1.85-1.94 (1H, m, $CH(CH_3)$), 1.97 (1H, dd, *J* = 7.3, 4.7, OH(CH), *B*), 2.02 (1H, dd, *J* = 7.1, 4.9, OH(CH), *A*), 2.86 (1H, d, *J* = 4.1, OH, *B*), 3.67 (1H, d, *J* = 3.5, OH, *A*), 3.41-3.64 (4H, m, CH_2OSi, CH_2OH), 3.80-3.87 (1H, m, CH(OH)), 7.38-7.45 (6H, m, ArH), 7.65-

7.68 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.3 (CH_3(CH), *B*), 15.3 (CH_3(CH), *A*), 19.2 ($SiC(CH_3)_3$, *B*), 19.2 ($SiC(CH_3)_3$, *A*), 26.8 ($(CH_3)_3CSi$, *A*), 26.9 ($(CH_3)_3CSi$, *B*), 32.2 ($CH(CH_3)$, *B*), 33.6 ($CH(CH_3)$, *A*), 37.8 ($CH_2(CHCH_3)(CHOH)$, *B*), 38.8 ($CH_2(CHCH_3)(CHOH)$, *A*), 67.1 (CH_2OH, *B*), 67.4 (CH_2OH, *A*), 68.9(CH_2OSi,B), 69.8 (CH(OH), B), 70.0 (CH_2OSi, A), 70.7 (CH(OH), A) 127.7 ($C^{Ar}H$), 129.8 ($C^{Ar}H$), 133.3 (C^{Ar}, A), 133.3 (C^{Ar}, *A*), 133.3 (C^{Ar}, *B*), (C^{Ar}, *B*), 135.6 ($C^{Ar}H$, *B*), 135.6 ($C^{Ar}H$, *A*), 135.7 ($C^{Ar}H$, *B*). *m/z* [Cl^+, isobutane] 373 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 373.2202, $C_{22}H_{33}O_3Si$ requires 373.2199. υ_{max} /cm^{-1} (film): 3372, 2957, 2930, 2857, 1471.

(4*S*)-1-[*Tert*-butyl(dimethyl)silyl]oxy-5-[*tert*-butyl(diphenyl)silyl]oxy-4-methyl-pentan-2-amine **410**

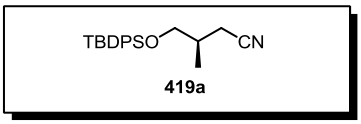


410

Diol **417** (15.0 g, 44.2 mmol) was dissolved in anhydrous DMF (44 mL) and cooled to 0 °C under an atmosphere of argon. TBSCl (6.92 g, 45.9 mmol) and imidazole (6.01 g, 88.3 mmol) were added and the resultant solution was stirred for 90 min, until TLC analysis of the reaction indicated completion. The reaction was quenched with water (100 mL) and was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (4 × 75 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude alcohol intermediate (21.3 g, 43.8 mmol, 99%), as a colourless oil. The crude alcohol intermediate was dissolved in anhydrous DCM (150 mL) and cooled to 0 °C under an atmosphere of argon. MsCl (3.73 mL, 48.1 mmol) was added, followed by NEt_3 (12.2 mL, 87.5 mmol) and the resultant solution was stirred for 15 min. TLC analysis indicated reaction completion. The reaction was quenched with water (100 mL) and was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water (3 × 75 mL) and brine (75 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude mesylate intermediate **418** (25.0 g, 44.3 mmol, 99% from diol **417**), as a colourless oil. The mesylate intermediate was dissolved in anhydrous DMF (110 mL), before NaN_3 (8.53 g, 131 mmol) was added and the resultant solution was heated to 80 °C for 4h. TLC analysis indicated reaction completion. The reaction was quenched with water (100 mL) and was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude material was passed through a plug of silica, elution with 0-2% Et_2O:petroleum ether, to afforded the azide intermediate (19.6 g, 38.4 mmol, 88% from diol **417**), as a pale yellow oil. The azide intermediate was dissolved in anhydrous EtOH (120 mL) and charged with 10% activated Pd/C (1.2 g). The suspension was stirred under an atmosphere of hydrogen at RT for 4h. TLC analysis indicated reaction completion. The suspension was filtered through Celite and the filtrate was concentrated under reduced pressure to afford the crude product. Purification via flash column chromatography, elution with 0-7% MeOH:DCM, afforded the amine **410** (14.6 g, 30.0 mmol, 78%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, *1.3:1 mixture of diastereoisomers, A & B*) δ: 0.05 (6H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 0.90 (9H, s, $(CH_3)_3CSi$), 0.94 (3H, d, *J* = 6.7, CH_3(CH), *B*), 0.96 (3H, d, *J* = 6.8, CH_3(CH), *A*), 1.05 (9H, s, $(CH_3)_3CSi$), 1.05 (9H, s, $(CH_3)_3CSi$), 1.04-1.11 (1H, m, $CH_2(CHNH_2)$, *A*), 1.13-1.18 (1H, m, $CH_2(CHNH_2)$, *B*), 1.27-1.38 (1H, m, $CH_2(CHNH_2)$, *A*), 1.43-1.48 (1H, m, $CH_2(CHNH_2)$, *B*), 1.72-1.81 ($CH(CH_3)$, *A*) 1.82-1.91 ($CH(CH_3)$, *B*), 2.85-2.90 (1H, m, $CH(NH_2)$), 3.25 (1H, dd, *J* = 9.8, 7.6, CH_2OSi, *A*), 3.30 (1H, dd, *J* = 9.7, 7.6, CH_2OSi, *B*), 3.41-3.56 (3H, dd, *J* = 9.7, 7.6, CH_2OSi), 7.35-7.44 (6H, m, *A*rH), 7.65-7.67 (4H, m, *A*rH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.4 ($(CH_3)_2Si$, *A*), -5.3 ($(CH_3)_2Si$, *B*), 16.6 (CH_3(CH), *B*), 17.9 (CH_3(CH), *A*),

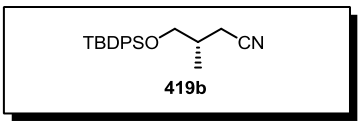
18.3 ($SiC(CH_3)_3$, *A*), 19.3 ($SiC(CH_3)_3$, *B*), 25.9 ($(CH_3)_3CSi$, *B*), 26.9 ($(CH_3)_3CSi$, *A*), 32.6 ($CH(CH_3)$, *B*), 32.7 ($CH(CH_3)$, *A*), 37.5 ($CH_2(CHNH_2)$, *B*), 38.3 ($CH_2(CHNH_2)$, *A*), 50.5 ($CH(NH_2)$, *A*), 50.8 ($CH(NH_2)$, *B*), 68.6 (CH_2OSi, *A*), 68.7 (CH_2OSi, *A*), 69.2 (CH_2OSi, *B*), 69.8 (CH_2OSi, *B*), 127.9 ($C^{Ar}H$, *A*), 127.6 ($C^{Ar}H$, *B*), 129.5 ($C^{Ar}H$, *A*), 129.5 ($C^{Ar}H$, *B*), 133.9 (C^{Ar}, *A*), 139.9 (C^{Ar}, *B*), 134.0 (C^{Ar}, *B*), 134.0 (C^{Ar}, *A*). *m/z* [Cl^+, isobutane] 486 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 486.3222, $C_{28}H_{48}O_2NSi$ requires 486.3224. υ_{max}/cm^{-1} (film): 3033, 2959, 2929, 2857, 1471.

(R)-4-(*Tert*-butyldiphenylsilyloxy)-3-methylbutanenitrile **419a**



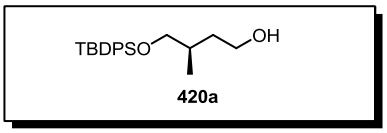
R-alcohol **412a** (7.30 g, 21.3 mmol) was dissolved in anhydrous DCM (100 mL) and cooled to 0 ^oC under an atmosphere of argon. MsCl (2.00 mL, 25.6 mmol) was added, followed by NEt_3 (5.92 mL, 42.6 mmol) and the resultant solution was stirred for 5 min. TLC analysis indicated reaction completion. The reaction was quenched with water (100 mL) and was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water (3 × 75 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude mesylate intermediate as a colourless oil. The mesylate intermediate was dissolved in anhydrous DMF (60 mL), before KCN (5.55 g, 85.2 mmol) was added and the resultant solution was heated to 65 ^oC for 16h, under an atmosphere of argon. TLC analysis indicated reaction completion. The reaction was quenched with water (100 mL) and was extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product as a yellow oil. Purification via flash column chromatography, elution with 0-20% Et_2O:petroleum ether, afforded nitrile **419a** (6.47 g, 18.3 mmol, 86%) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.97 (3H, d, *J* = 7.0, CH_3), 1.06 (9H, s, $(CH_3)_3CSi$), 2.00-2.08 (1H, m, $CH(CH_3)$), 2.38 (1H, dd, *J* = 16.5, 7.0, CH_2CN), 2.55 (1H, dd, *J* = 17.0, 5.5, CH_2CN), 3.46 (1H, dd, *J* = 10.5, 7.5, CH_2OSi), 3.63 (1H, dd, *J* = 10.0, 4.5, CH_2OSi), 7.38-7.44 (6H, m, ArH), 7.63-7.65 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.9 ($CH_3(CH)$), 19.3 ($SiC(CH_3)_3$), 21.1 (CH_2CN), 26.8 ($(CH_3)_3CSi$), 33.3 ($CH(CH_3)$), 66.9 (CH_2OSi), 68.9 (CH_2OH), 119.9 (CN), 127.8 ($C^{Ar}H$), 129.8 ($C^{Ar}H$), 133.2 (C_Q^{Ar}), 135.5 ($C^{Ar}H$). *m/z* [Cl^+, isobutane] 338 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 338.1943, $C_{21}H_{28}ONSi$ requires 338.1940. υ_{max} /cm^{-1} (film): 2961, 2930, 2859, 1471, 1427. $[\alpha]_D^{21.4}$ 5.96 (c=1.41, $CHCl_3$).

(S)-4-(*Tert*-butyldiphenylsilyloxy)-3-methylbutanenitrile **419b**



S-Nitrile **419b** was obtained in the same quantity, yield and purity as *R*-nitrile **412a**, under analagous experimental conditions, starting from *S*-alcohol **412b**. $[\alpha]_D^{21.4}$ -6.41 (c=1.53, $CHCl_3$).

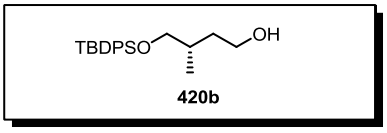
(R)-4-(*Tert*-butyldiphenylsilyloxy)-3-methylbutan-1-ol **420a**



420a

Nitrile **419a** (4.68 g, 13.2 mmol) was dissolved in anhydrous DCM (130 mL) and cooled to –78 ^{o}C under an atmosphere of argon. DIBAL (1M in THF, 14.6 mL, 14.6 mmol) was added dropwise, via syringe pump, over 1h and the reaction mixture was then stirred for a further 2h at –78 ^{o}C. TLC analysis indicated reaction completion. The reaction mixture was slowly added to a rapidly stirring solution of Rochelle's salt (15 g) in water (150 mL) at 0 ^{o}C. The slurry was warmed to RT and stirred for a further 2h until the organic and aqueous layers became transparent. The organic layer was collected and the aqueous layer was extraction with DCM (3 × 100 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude aldehyde intermediate as a colourless oil. The intermediate was immediately dissolved in anhydrous MeOH (65 mL) and DCM (30 mL) and cooled to –78 ^{o}C. $NaBH_4$ (900 mg, 23.8 mmol) was added portionwise over 5 min and the resulting reaction mixture was stirred at –78 ^{o}C for 2h. TLC analysis indicated reaction completion The reaction mixture was warmed to 0 ^{o}C and quenched with water (50 mL) and 10% aq. citric acid solution (40 mL) and stirred at RT for 10 min before being extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water (3 × 20 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude product as a colourless oil. Purification via flash column chromatography, elution with 0-40% Et_2O:petroleum ether, afforded *R*-alcohol **420a** (3.15 g, 9.24 mmol, 70%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.89 (3H, d, *J* = 8.5, CH_3), 1.06 (9H, s, $(CH_3)_3CSi$), 1.50-1.55 (1H, m, $CH_2(CH)(CH_2OH)$), 1.66-1.71 (1H, m, $CH_2(CH)(CH_2OH)$), 1.82-1.90 (1H, m, $CH(CH_3)$), 2.10 (1H, br. s, OH), 3.47-3.53 (2H, m, CH_2OSi), 3.68-3.76 (2H, m, CH_2OH), 7.37-7.43 (6H, m, ArH), 7.65-7.68 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.2 ($CH_3(CH)$), 19.3 ($SiC(CH_3)_3$), 26.9 ($(CH_3)_3CSi$), 33.3 ($CH(CH_3)$), 37.4 ($CH_2(CH)(CH_2OH)$), 61.2 (CH_2OSi), 69.3 (CH_2OH), 127.6 ($C^{Ar}H$), 129.7 ($C^{Ar}H$), 133.5 (C_Q^{Ar}), 135.6 ($C^{Ar}H$). *m/z* [CI^+, isobutane] 343 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 343.2091, $C_{21}H_{31}O_2Si$ requires 343.2093. υ_{max} / cm^{-1} (film): 3352, 2957, 2930, 2857, 1472. $[\alpha]_D^{22.6}$ 1.69 (c = 1.40, $CHCl_3$).

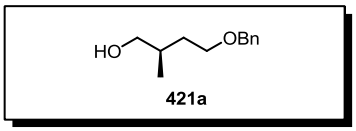
(*S*)-4-(*Tert*-butyldiphenylsilyloxy)-3-methylbutan-1-ol **420b**



420b

S-Alcohol **420b** was obtained in the same quantity, yield and purity as *R*-alcohol **420a**, under analagous experimental conditions, starting from *S*-nitrile **419b**. $[\alpha]_D^{22.4}$ -2.88 (c=1.02, $CHCl_3$).

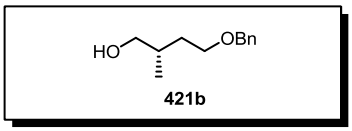
(*R*)-4-(Benzyloxy)-2-methylbutan-1-ol **421a**



421a

NaH (60% w/w in mineral oil, 489 g, 12.3 mmol) was washed with petroleum ether (× 3) under an atmosphere of argon, before anhydrous THF (50 mL) was added and the suspension was cooled to 0 ^{o}C, under an atmosphere of argon. A solution of alcohol **420a** (3.23 g, 9.42 mmol) in THF (15 mL) was added and the resultant mixture was stirred at 0 ^{o}C for 30 min and then at RT for 30 min. BnBr (1.57 mL, 13.2 mL) was added and the reaction was stirred for 1h before being heated at 45 ^{o}C for 72h. After cooling to RT, the reaction was quenched with water (75 mL) and extracted with Et_2O (3 × 75 mL).The combined organic extracts were washed with water (2 × 40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude intermediate as a yellow oil. This was passed through a plug of silica, elution with 0-3% Et_2O:petroleum ether, to afforded the benzylated intermediate as a colourless oil. The intermediate was dissolved in anhydrous THF (30 mL) and cooled to 0 ^{o}C under an atmosphere of argon. TBAF (1 M in THF, 28.0 mL, 28.0 mmol) was added, and after stirring for 30 min at 0 ^{o}C, the reaction mixture was warmed to RT and stirred for a further 16h, before being quenched with water (20 mL), and extracted with Et_2O (3 × 50 mL). The combined organics were washed sequentially with water (2 × 10 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification via flash column chromatography, elution with 0-100% Et_2O:petroleum ether, afforded *R*-alcohol **421a** (1,28 g, 6.57 mmol, 69%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.91 (3H, d, *J* = 6.8, CH_3), 1.53-1.61 (1H, m, $CH_2(CH_2OBn)$), 1.65-1.74 (1H, m, $CH_2(CH_2OBn)$), 1.79-85 (1H, m, $CH(CH_3)$), 2.82 (1H, br. s, OH), 3.42 (1H, dd, *J* = 10.9, 6.6, CH_2OBn), 3.47-3.55 (2H, m, CH_2OBn, CH_2OH), (1H, m, CH_2OH), 4.52 (2H, s, OCH_2Ph), 7.28-38 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.3 (CH_3), 34.1 ($CH_2(CH_2OBn)$, 34.2 ($CH(CH_3)$), 68.2 (CH_2OH), 68.8 (CH_2OBn), 73.3 (OCH_2Ph), 127.8 ($C^{Ar}H$), 127.9 ($C^{Ar}H$), 128.6 ($C^{Ar}H$), 138.2 (C^{Ar}). *m/z* [Cl^+, isobutane] 195 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 195.1384, $C_{12}H_{19}O_2$ requires 195.1385. υ_{max} /cm^{-1} (film): 3393, 2955, 2928, 2868, 1454. $[\alpha]_D^{21.8}$ -3.87 (c = 0.93, $CHCl_3$).

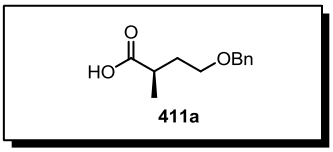
(S)-4-(Benzyloxy)-2-methylbutan-1-ol **421b**



421b

S-Alcohol **421b** was obtained in the same quantity, yield and purity as *R*-alcohol **421a**, under analagous experimental conditions, starting from *S*-alcohol **420b**. $[\alpha]_D^{21.8}$ 5.11 (c=1.00, $CHCl_3$).

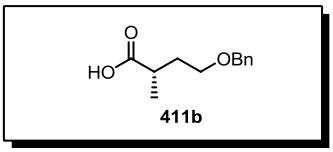
(*R*)-4-(Benzyloxy)-2-methylbutanoic acid **411a**



Method A: Oxidation of Alcohol **421a**

To a stirring solution of DCM (90 mL) at 0 ^{o}C, $NaHCO_3$ (3.60 g, 42.9 mmol), ^{t}BuOH (5 mL) and DMP (4.52 g, 10.7 mmol) were added sequentially. A solution of *R*-alcohol **421a** (1.80 g, 9.27 mmol) in DCM (15 mL) was added dropwise to the reaction mixture and the resultant suspension was stirred for 1h at 0 ^{o}C, until TLC analysis indicated reaction completion. Half of the solvent was removed under reduced pressure and the crude material was passed through a plug of silica, elution with 0-50% Et_2O:petroleum ether, to afford the aldehyde intermediate as a colourless oil, which was immediately dissolved in THF (20 mL) and ^{t}BuOH (10 mL). The resultant solution was cooled to 0 ^{o}C and solution of $NaH_2PO_4.2H_2O$ (6.51g, 41.7 mmol) and 2-methyl-2-butene (11.3 mL, 107 mmol) in water (20 mL) was added dropwise to the reaction mixture and was stirred for 1h at 0 ^{o}C and then for 16h at RT, after which TLC analysis indicated reaction completion. The reaction was diluted with water (30 mL) and was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product as a pale yellow. Purification via flash column chromatography, elution with 0-20% Et_2O:petroleum ether, afforded *R*-acid **411a** (1.50 g, 7.21 mmol, 78%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.26 (3H, d, *J* = 7.0, CH_3), 1.74-1.81 (1H, m, $CH_2(CH_2OBn)$), 2.06-2.13 (1H, m, $CH_2(CH_2OBn)$), 2.70-2.77 (1H, m, $CH(CH_3)$), 3.59 (2H, t, *J* = 6.0, CH_2OBn), 4.55 (2H, s, OCH_2Ph), 7.31-40 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.1 (CH_3), 33.3 ($CH_2(CH_2OBn)$, 36.6 ($CH(CH_3)$), 67.9 (CH_2OBn), 73.1 (OCH_2Ph), 127.7 ($C^{Ar}H$), 127.8 ($C^{Ar}H$), 128.4 ($C^{Ar}H$), 138.4 (C^{Ar}), 182.3 (CO). *m/z* [EI$^+$] 208 [M]$^+$ (100%), HRMS found [M]$^+$ 208.1105, $C_{12}H_{16}O_3$ requires 208.1099. υ_{max} /cm^{-1} (film): 3090, 2934, 2857, 1705, 1456. $[\alpha]_D^{24.0}$ -1.78 (c = 1.00, $CHCl_3$).

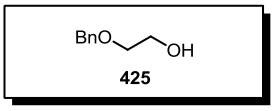
(*S*)-4-(Benzyloxy)-2-methylbutanoic acid **411b**



Method A: Oxidation of Alcohol **421b**

S-Acid **411b** was obtained in the same quantity, yield and purity as *R*-Acid **411a**, under analagous experimental conditions, starting from *S*-alcohol **421b**. $[\alpha]_D^{24.1}$ 2.91 (c=1.45, $CHCl_3$).

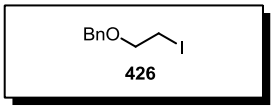
2-(Benzyloxy)ethanol **425**



NaH (60% w/w in mineral oil, 8.80 g, 220 mmol) was washed with petroleum ether (× 3) under an atmosphere of argon, before anhydrous THF (175 mL) was added. To this suspension, a solution of ethylene glycol (60.0 mL, 1.00 mol) in THF (175 mL) was added via cannular. After

stirring for 1h at RT, the reaction mixture became homogeneous. NaI (3.00g, 20.0 mmol) and benzyl chloride (25.4 g, 200 mmol) were added and the resultant solution was heated at reflux for 12h under an atmosphere of argon. After cooling to RT, the reaction was quenched with water (200 mL) and extracted with Et_2O (3 × 200 mL).The combined organic extracts were washed with water (2 × 75 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-100% Et_2O:petroleum ether, afforded the desired product, alcohol **425** (27.0 g, 177 mmol, 89%), as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.14 (1H, t, *J* = 6.0, OH), 3.63 (2H, t, *J* = 4.5, CH_2OH), 3.78-3.90 (2H, m, CH_2OBn), 4.60 (2H, s, CH_2Ph), 7.31-7.40 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 61.9 (CH_2OH), 71.4 (CH_2OBn), 73.6 (CH_2Ar), 128.1 ($C^{Ar}H$), 128.1 ($C^{Ar}H$), 128.8 ($C^{Ar}H$), 138.0 (C^{Ar}). *m/z* [CI^+, isobutane] 153 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 153.0914, $C_9H_{13}O_2$ requires 153.0916. υ_{max} /cm^{-1} (film): 3390, 2959, 2927, 2855, 1456. The data observed is in accordance with literature values.[181]

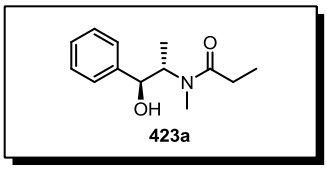
1-Benzyloxy-2-iodoethane **426**



426

Alcohol **425** (25.2 g, 165 mol) was dissolved in anhydrous THF (400 mL) and cooled to 0 °C under an atmosphere of argon. Imidazole (13.5 g, 199 mmol), PPh_3 (46.8 g, 179 mmol) and I_2 (45.3 g, 179 mmol) were added sequentially and the resultant suspension was stirred at 0 °C for 30 min, before being warmed to RT, and was stirred for a further 2h. TLC analysis indicated reaction completion. The reaction was quenched by the addition of sat'd aq. $Na_2S_2O_3$ solution (300 mL) and extracted with Et_2O (3 × 300 mL).The combined organic extracts were washed with sat'd aq. $Na_2S_2O_3$ solution (2 × 75 mL) and brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield a cloudy oil. This was taken up in petroleum ether at 0 °C, filtered, and the supernatant was collected and evaporated to yield the crude product as a colourless oil Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded iodide **425** (42.5 g, 162 mmol, 98%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.29 (2H, t, *J* = 7.0, CH_2I), 3.75 (2H, t, *J* = 6.5 CH_2OBn), 4.59 (2H, s, CH_2Ph), 7.29-7.37 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 2.9 (CH_2I), 70.8 (CH_2OBn), 72.9 (CH_2Ar), 127.8 ($C^{Ar}H$), 127.9 ($C^{Ar}H$), 128.5 ($C^{Ar}H$), 137.8 (C^{Ar}). *m/z* [CI^+, isobutane] 263 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 263.9930, $C_9H_{12}IO_2$ requires 263.9933. υ_{max} /cm^{-1} (film): 3028, 2859, 1495, 1452. The data observed is in accordance with literature values.[182]

N-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide **423a**

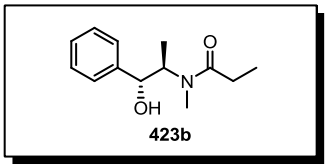


423a

(+)-Pseudoephedrine (**422a**) (8.84 g, 53.5 mmol) was dissolved in anhydrous DCM (100 mL) at RT, under an atmosphere of argon. NEt_3 (8.93 mL, 64.2 mL) was added followed by the dropwise addition of propionic anhydride, over 10 min. The resultant solution was stirred for 30 min, after which TLC analysis indicated reaction completion. The reaction was quenched by the addition of water (200 mL) and extracted with DCM (3 × 200 mL). The combined organic extracts were washed with sat'd aq. $NaHCO_3$ solution (2 × 50 mL), 1 M aq. HCl solution (2 × 50 mL) and brine (2 × 50 mL), before being dried over anhydrous Na_2SO_4. The solvent was

concentrated *in vacuo* to afford a colourless oil. The crude product was triturated from petroleum ether at 0 °C and dried under reduced pressure to yield amide **423a** (12.4 g, 56.0 mmol, 94%), as a white solid. ^{1}H NMR (C_6D_6, 500 MHz, *2:1 rotamer ratio, asterisk denotes minor rotamer peaks*) δ: 0.58 (3H, d, *J* = 7.0, CH_3(CH)*), 0.94 (3H, d, *J* = 7.0, CH_3(CH)), 1.01 (3H, t, *J* = 7.5, CH_3CH_2), 1.20 (3H, t, *J* = 7.5, CH_3CH_2*), 1.69-1.83 (2H, m, CH_2CH_3), 2.08-2.13 (1H, m, CH_2CH_3*), 2.13 (3H, s, CH_3N), 2.46-2.51 (1H, m, CH_2CH_3*), 2.84 (3H, s, CH_3N*), 3.71-3.74 (1H, $CH(CH_3)$*), 3.79 (1H, br. s, OH*), 4.26 (1H, d, *J* = 8.8, CH(OH)*), 4.32 (1H, br. s, $CH(CH_3)$), 4.53 (1H, br. t, *J* = 5.7, CH(OH)), 4.95 (1H, br. s, OH), 7.06-7.34 (5H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 9.3 (CH_3CH_2), 9.8 (CH_3CH_2*), 14.2 (CH_3(CH)), 15.1 (CH_3(CH)*), 26.6 (CH_3N*), 26.8 (CH_2CH_3*), 27.4 (CH_2CH_3), 32.3 (CH_3N), 58.4 ($CH(CH_3)$*), 58.8 ($CH(CH_3)$), 75.2 (CH_2OH*), 76.3 (CH_2OH), 126.8 ($C^{Ar}H$), 127.3 ($C^{Ar}H$*), 127.3 ($C^{Ar}H$), 128.2 ($C^{Ar}H$*), 128.2 ($C^{Ar}H$), 128.4 ($C^{Ar}H$*), 142.8 (C^{Ar}*), 143.7 (C^{Ar}), 174.3 (CO*), 175.1 (CO). *m/z* [CI^+, isobutane] 222 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 222.1497, $C_{13}H_{20}O_2N$ requires 222.1494. υ_{max} /cm^{-1} (film): 3364, 2978, 2937, 1614, 1452. MP: 114-115 °C. $[\alpha]_D^{21.6}$ 77.60 (c=1.92, $CHCl_3$). The data observed is in accordance with literature values.[143]

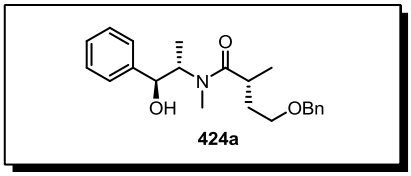
N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide **423b**



423b

Amide **423b** was obtained in the same quantity, yield and purity as amide **423a**, under analagous experimental conditions, starting from (-)-pseudoephedrine (**422a**). MP: 113-115 °C. $[\alpha]_D^{21.6}$ -73.00 (c=1.50, $CHCl_3$). The data observed is in accordance with literature values.[143]

(*R*)-4-(Benzyloxy)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylbutanamide **424a**

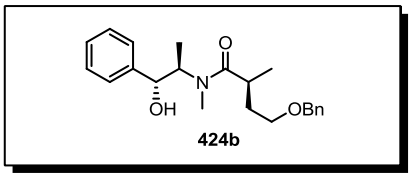


424a

LiCl (13.2 g, 312 mmol) was flame dried under vacuum and allowed to cool to RT, before being placed under an atmosphere of argon. Anhydrous THF (100 mL) was added to the flask before cooling to –78 °C. $^{i}Pr_2NH$ (13.1 mL, 100 mmol) was added, followed by ^{n}BuLi (2.5 M in hexanes, 37.4 mL, 37.4 mmol) and the resultant suspension was stirred for 20 min at –78 °C, 5 min at 0 °C, followed by 5 min at RT, before recooling back to –78 °C. A solution of pseudoephedrine amide **423a** (9.85 g, 44.5 mmol) in anhydrous THF (100 mL) was added dropwise via cannulation. The reaction mixture was at was stirred for 45 min at –78 °C, 20 min at 0 °C, followed by 5 min at RT, before recooling to 0 °C. Iodide **426** (14.0 g, 53.4 mmol) was added dropwise over 10 min, and the resultant mixture was warmed to RT over 14h. TLC analysis indicated reaction completion. The reaction was quenched by the addition of water (200 mL) and extracted with Et_2O (3 × 300 mL). The combined organic extracts were washed with water (2 × 100 mL) and brine (2 × 75 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-85% Et_2O:petroleum ether, afforded the desired pseudoephedrin amide **424a** (14.2 g, 40.0 mmol, 90%), as a colourless oil. The data observed is

in accordance with literature values.[144] Amide **424a** was taken onto the hydrolysis step and characterised as *R*-acid **411a** *(vide infra).*

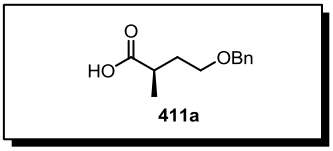
(*S*)-4-(Benzyloxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylbutanamide **424a**



424b

Amide **424b** was obtained in the same quantity, yield and purity as amide **424a**, under analagous experimental conditions, starting from amide **423b**. The data observed is in accordance with literature values.[144] Amide **424b** was taken onto the hydrolysis step and characterised as *S*-acid **411b** *(vide infra).*

(*R*)-4-(Benzyloxy)-2-methylbutanoic acid **411a**

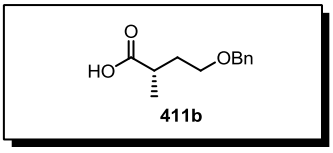


411a

Method B: Hydrolysis of Pseudoephedrine Amide **424a**

Pseudoephedrin amide **424a** (15.3 g, 43.0 mmol) was dissolved in anhydrous THF (120 mL) under an atmosphere of argon. MsOH (4.00 mL, 62.0 mmol) was added and the reaction mixture was heated at 70 ^{o}C for 1h. The solution was then cooled to 0 ^{o}C and $LiBH_4$ (2 M in THF, 32.3 mL, 64.4 mL) was added dropwise over 10 min and stirred for a further 10 min at 0 ^{o}C, and then warmed to RT and stirred for 10 min, before being recooled back to 0 ^{o}C. 1.5 M aq. NaOH solution (143 mL, 215 mmol) was then cautiously added, and the resulting mixture was stirred for 18h at RT. The aqueous layer was separated extracted with DCM (3 × 250 mL) and cooled to 0 ^{o}C before being acidified to pH ≤ 2, by the slow addition of 3 M aq. HCl solution. Extraction with DCM (5 × 200 mL) followed by drying over anhydrous Na_2SO_4 and solvent evaporation, yielded the *R*-acid **411a** (8.04 g, 38.6 mmol, 90%), as a colourless oil. $[\alpha]_D^{23.9}$ -2.00 (c=0.98, $CHCl_3$).

(*S*)-4-(Benzyloxy)-2-methylbutanoic acid **411b**

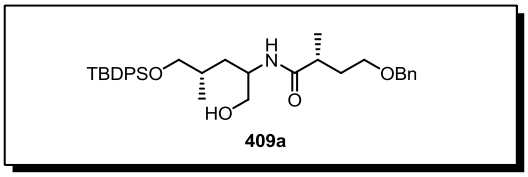


411b

Method B: Hydrolysis of Pseudoephedrine Amide **424b**

$[\alpha]_D^{23.9}$ 2.59 (c=1.20, $CHCl_3$). The spectral and physical data obtained for **411b**, via Method B, matched that obtained via Method A.

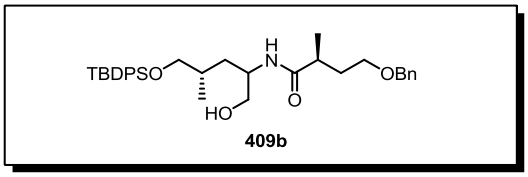
(2*R*) *R* -4-(Benzyloxy)-*N*-((4*S*)-5-(*tert*-butyldiphenylsilyloxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide **409a**



409a

Amine **410** (10.81 g, 22.3 mmol) and *R*-acid **411a** (4.86 g, 23.4 mmol) were dissolved in anhydrous DCM (100 mL) and the resultant solution was cooled to 0 ^{o}C under an atmosphere of argon. EDC.HCl (5.12 g, 26.7 mmol) and HOBt (3.60, 26.7 mmol) were added was added before the dropwise addition of DIPEA (7.75 mL, 44.5 mmol). The reaction mixture was stirred at 0 ^{o}C for 2h and then at RT for 16h. TLC analysis indicated reaction completion. The solvent was evaporated and the resultant slurry was partitioned between Et_2O (200 mL) and water (100 mL). The organics were collected and further washed with sat'd aq. $NaHCO_3$ (50 mL), 10% aq. HCl solution (40 mL) and brine (2 × 50 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude amide product as a colourless oil. The crude intermediate was dissolved in MeOH (100 mL), CSA (516 mg, 2.23 mmol) was added and the resultant solution was stirred at RT for 4h, until TLC analysis indicated reaction completion. NEt_3 (0.44 mL, 3,34 mL) was added to the reaction mixture prior to solvent evaporation. Purification by flash column chromatography, elution with 0-80% Et_2O:petroleum ether, afforded β-hydroxy amide **409a** (9.88 g, 17.6 mmol, 79%), as a colourless oil. *m/z* [CI^+, isobutane] 562 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 562.3350, $C_{34}H_{48}NO_4Si$ requires 562.3353. υ_{max} /cm^{-1} (film): 3283, 2959, 2930, 2857, 1645, 1541, 1518, 1471. β-Hydroxy amide **409a** was taken on to the oxidation and cyclodehydration steps, and subsequently fully characterised as oxazole **427a**.

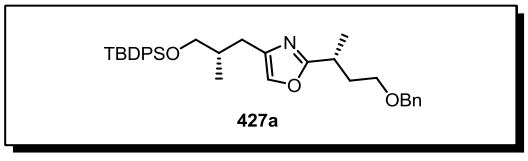
(2*S*) *S* -4-(Benzyloxy)-*N*-((4*R*)-5-(*tert*-butyldiphenylsilyloxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide **409b**



409b

β-Hydroxy amide **409b** was obtained in the same quantity, yield and purity as β-hydroxy amide **409a**, under analagous experimental conditions, starting from amine **410** and *S*-acid **411b**. β-Hydroxy amide **409b** was taken on to the oxidation and cyclodehydration steps, and subsequently fully characterised as oxazole **427b**.

2-((*R*)-4-(Benzyloxy)butan-2-yl)-4-((*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **427a**

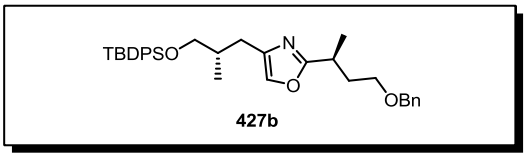


427a

Anhydrous DCM (30 mL) was added to a flame-dried flask and cooled to –78 ^{o}C, before the addition of oxalyl chloride (1.09 mL, 12.9 mmol). A solution of DMSO (1.52 mL, 21.5 mmol) in

anhydrous DCM (4 mL) was added dropwise over 20 min via syringe pump, ensuring that the internal temperature did not exceed –70 °C. The mixture was stirred for a further 20 min. A solution of β-hydroxy amide **409a** (4.16 g, 7.80 mmol) in anhydrous DCM (8 mL) was added dropwise, via syringe pump, over a period of 20 min, ensuring that the internal temperature did not exceed –70 °C. After stirring for a further 30 min at –78 °C, NEt_3 (6.72 mL, 48.4 mmol) was added dropwise, via syringe pump, over a period of 40 min, ensuring that the internal temperature did not exceed –70 °C. The resultant mixture was then stirred for a further 10 min at –78 °C before being warmed to 0 °C over 45 min. TLC analysis of the reaction indicated completion. The reaction was quenched with water (50 mL) and the organic layer was collected. The aqueous layer was extraction with DCM (3 × 75 mL). The combined organic extracts were washed with water (2 × 30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield the crude aldehyde intermediate as a pale yellow oil. The aldehyde intermediate was immediately dissolved in anhydrous DCM (50 mL) and cooled to 0 °C under an atmosphere of argon. PPh_3 (5.73 g, 21.8 mmol), DTBMP (5.60 g, 27.3 mmol) and $(BrCCl_2)_2$ (7.62 g, 23.4 mmol) were added sequentially to the reaction vessel. After stirring at 0 °C for 10 min, the reaction was warmed to RT and stirred for a further 45 min. DIPEA (6.80 mL, 39.0 mmol) was added and the reaction was stirred for a further 45 min. The solvent was removed under reduces pressure and the crude residue was purified by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, to afford the oxazole **427a** (3.17 g, 6.18 mmol, 79%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.95 (3H, d, *J* = 6.7, $CH_3(CHCH_2Ar)$), 1.05 (9H, s, $(CH_3)_3CSi$), 1.30 (3H, d, *J* = 7.1, $CH_3(CHAr)$), 1.84-1.90 (1H, m, $CH_2(CH_2OBn)$), 2.02-2.14 (2H, m, $CH(CH_2Ar)$, $CH_2(CH_2OBn)$), 2.32 (1H, ddd, *J* = 14.7, 8.0, 0.6, CH_2Ar), 2.66 (1H, ddd, *J* = 14.6, 6.1, 0.8, CH_2Ar), 3.12-3.19 (1H, m, $CH(CH_3)(Ar)$), 3.40-3.51 (3H, m, CH_2OBn, CH_2OSi), 3.55 (1H, dd, *J* = 9.9, 5.1, CH_2OSi), 4.44 (2H, d, *J* = 2.3, OCH_2Ph), 7.15 (1H, br. s, ArH), 7.24-7.43 (10H, m, ArH), 7.64-7.67 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.7 ($CH_3(CHCH_2Ar)$, 18.7 ($CH_3(CHAr)$), 19.4 ($SiC(CH_3)_3$), 26.9 ($(CH_3)_3CSi$), 29.8 (CH_2Ar), 30.8 ($CH(CH_3)(Ar)$), 35.0 ($CH_2(CH_2OBn)$), 35.1 ($CH(CH_2Ar)$), 67.9 (CH_2OBn), 68.1 (CH_2OSi), 72.9 (OCH_2Ph), 127.5 ($C^{Ar}H$), 127.6 ($C^{Ar}H$), 128.3 ($C^{Ar}H$), 129.5 ($C^{Ar}H$), 133.9 ($C^{Ar}H$), 134.0 (C^{Ar}), 135.6 ($C^{Ar}H$), 135.6 ($C^{Ar}H$), 138.5 (C^{Ar}), 139.0 (C^{Ar}), 167.5 (C^{Ar}). *m/z* [CI^+, isobutane] 542 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 542.3087, $C_{34}H_{44}O_3NSi$ requires 542.3090. υ_{max} /cm^{-1} (film): 2959, 2930, 2857, 1719, 1568, 1471. $[\alpha]_D^{22.0}$ -25.85 (c=0.82, $CHCl_3$).

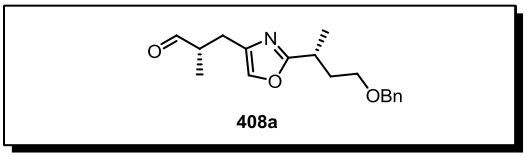
2-((*S*)-4-(Benzyloxy)butan-2-yl)-4-((*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **427b**



427b

Oxazole **427b** was obtained in the same quantity, yield and purity as oxazole **427a**, under analagous experimental conditions, starting from β-Hydroxy amide **409b**. $[\alpha]_D^{22.0}$ 15.00 (c=0.70, $CHCl_3$).

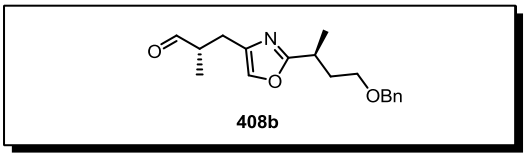
(*S*)-3-(2-((*R*)-4-(benzyloxy)butan-2-yl)oxazol-4-yl)-2-methylpropanal **408a**



408a

Oxazole **427a** (2.70 g, 5.26 mmol) was dissolved in anhydrous THF (25 mL) and cooled to 0 ^{o}C under an atmosphere of argon. TBAF (1 M in THF, 21.0 mL, 21.0 mmol) was added and, after stirring for 30 min at 0 ^{o}C, the reaction mixture was warmed to RT and stirred for a further 16h, before being quenched with water (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were washed sequentially with water (2 × 10 mL) and brine (20 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude intermediate as a colourless oil. This was passed through a plug of silica gel, elution with 0-60% Et_2O:petroleum ether, to afforded the alcohol intermediate **428a**, as a colourless oil. To a stirring solution of DCM (12 mL) at 0 ^{o}C, $NaHCO_3$ (1.85 g, 22.01 mmol), ^{t}BuOH (3 mL) and DMP (2.28 g, 5.38 mmol) were added sequentially. A solution of the alcohol intermediate **428a** in DCM (5 mL) was added dropwise to the reaction mixture and the resultant suspension was stirred for 45 min at 0 ^{o}C, until TLC analysis indicated reaction completion. Half of the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography, elution with 0-40% Et_2O:petroleum ether, to afford the desired aldehyde **408a** (1.28 g, 4.25 mmol, 81% over 2 steps) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.08 (3H, d, *J* = 7.1, $CH_3(CHCH_2Ar)$), 1.31 (3H, d, *J* = 7.1, $CH_3(CHAr)$), 1.84-1.91 (1H, m, $CH_2(CH_2OBn)$), 2.07-2.14 (2.28 ($CH_2(CH_2OBn)$), 2.54 (1H, ddd, *J* = 14.8, 7.1, 0.8, CH_2Ar), 2.77-2.80 (1H, m, $CH(CH_2Ar)$), 2.90 (1H, ddd, *J* = 14.8, 6.6, 0.9, CH_2Ar), 3.13-3.20 (1H, m, $CH(CH_3)(Ar)$), 3.42-3.46 (1H, m, CH_2OBn), 3.48-3.52 (1H, m, CH_2OBn), 4.46 (2H, s, OCH_2Ph), 7.25-7.34 (6H, m, ArH), 9.71 (1H, d, *J* = 1.3, CHO). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.3 ($CH_3(CHCH_2Ar)$, 18.6 ($CH_3(CHAr)$), 27.2 (CH_2Ar), 30.7 ($CH(CH_3)(Ar)$), 35.0 ($CH_2(CH_2OBn)$), 45.4 ($CH(CH_2Ar)$), 67.8 (CH_2OBn), 72.9 (OCH_2Ph), 127.5 ($C^{Ar}H$), 127.6 ($C^{Ar}H$), 128.3 ($C^{Ar}H$), 134.3 ($C^{Ar}H$), 137.3 (C^{Ar}), 138.4 (C^{Ar}), 168.1 (C^{Ar}), 204.1 (CHO). *m/z* [Cl^+, isobutane] 302 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 302.1752, $C_{18}H_{24}O_3NSi$ requires 302.1756. υ_{max} /cm^{-1} (film): 2972, 2932, 2874, 2861, 1722, 1568, 1454. $[\alpha]_D^{21.5}$ -40.00 (c=0.66, $CHCl_3$).

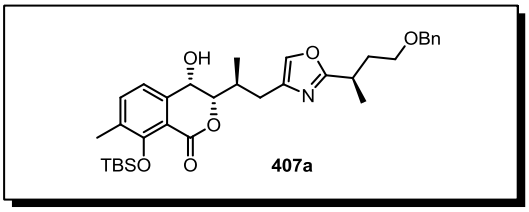
(*R*)-3-(2-((*S*)-4-(benzyloxy)butan-2-yl)oxazol-4-yl)-2-methylpropanal **408b**



408b

Aldehyde **408b** was obtained in the same quantity, yield and purity as aldehyde **408a**, under analagous experimental conditions, starting from oxazole **427b**. $[\alpha]_D^{21.6}$ 21.72 (c=1.16, $CHCl_3$).

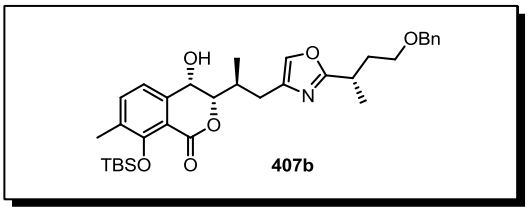
(3*S*,4*S*)-3-((*S*)-1-(2-((R)-4-(benzyloxy)butan-2-yl)oxazol-4-yl)propan-2-yl)-8-(*tert*-butyldimethylsilyloxy)-4-hydroxy-7-methylisochroman-1-one **407a**



407a

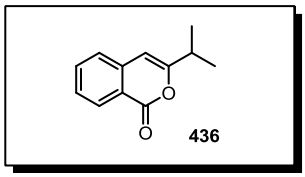
Using general procedure 1B, starting from a solution phthalan **227** (3.42 g, 11.6 mmol) in anhydrous THF (50 mL) with $^{i}Pr_2NH$ (2.80 mL, 21.4 mmol), MeLi (1.6 M in Et_2O, 15.1 mL, 24.1 mmol) and aldehyde **408a** (1.75 g, 5.81 mmol) to generate the α-hydroxy-IBF intermediate. The oxidative rearrangement was performed using *m*CPBA (77%, 1.30 g, 5.81 mmol) in anhydrous DCM (50 mL) to afford the crude keto-lactols. Oxidation was performed in anhydrous DCM (20 mL) with TEMPO (63 mg, 0.40 mmol) and BAIB (3.87 g, 12.1 mmol). Purification via flash chromatography, elution with 0-13% EtOAc:petroleum ether, afforded the keto-lactone intermediates (1.54 g, 2.67 mmol, 46%) as a yellow oil. According to general procedure 2A, reduction was performed in anhydrous DCM (10 mL) with $CeCl_3.7H_2O$ (3.05 g, 8.19 mmol), MeOH (10 mL) and $NaBH_4$ (137 mg, 3.60 mmol) at –78 ^{o}C. The crude products were purified by flash column chromatography, elution with 0-60% Et_2O:petroleum ether, to afford the isochromanone products **430a** and **407a** (1.01 g, 1.74 mmol, 30% overall yield from aldehyde **408a**, as a colourless oil, in a 1:2 mixture of diastereoisomers. HPLC separation, conducted on a Sunfire C18 column (150mm x 30mm i.d. 5μm) at RT, allowed for the isolation of *syn,anti*-isochromanone **407a** (662 mg, 1.14 mmol, 20% overall yield from aldehyde **408a**) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.11 (3H, s, CH_3Si), 0.19 (3H, s, CH_3Si), 1.04 (9H, s, $(CH_3)_3CSi$), 1.10 (3H, d, *J* = 6.9, $CH_3(CHCH_2Ar)$), 1.29 (3H, d, *J* = 7.1, $CH_3(CHAr)$), 1.83-1.89 (1H, m, $CH_2(CH_2OBn)$), 2.05-2.14 (1H, m, $CH_2(CH_2OBn)$), 2.27 (3H, s, CH_3Ar), 2.44-2.50 (1H, m, $CH(CH_2Ar)$), 2.63 (1H, dd, *J* = 14.7, 7.6, CH_2Ar), 3.01 (1H, dd, *J* = 14.6, 2.5, CH_2Ar), 3.11-3.18 (1H, m, $CH(CH_3)(Ar)$), 3.40-3.50 (2H, m, CH_2OBn), 4.06 (1H, dd, *J* = 9.3, 1.2, $CH(O_2C)$), 4.43 (2H, s, OCH_2Ph), 4.66 (1H, br. d, *J* = 0.8, CH(OH)), 6.94 (1H, d, *J* = 7.6, ArH), 7.23-7.33 (6H, m, ArH), 7.37 (1H, dd, *J* = 7.5, 0.6, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -3.7 (CH_3Si), -3.6 (CH_3Si), 15.4 ($CH_3(CHCH_2Ar)$, 17.5 (CH_3Ar), 18.6 ($CH_3(CHAr)$), 18.6 ($SiC(CH_3)_3$), 25.9 ($(CH_3)_3CSi$), 28.1 (CH_2Ar), 30.3 ($CH(CH_3)(Ar)$), 33.2 ($CH(CH_2Ar)$), 35.0 ($CH_2(CH_2OBn)$), 66.6 (CH(OH)), 67.8 (CH_2OBn), 73.0 (OCH_2Ph), 83.0 ($CH(O_2C)$), 115.8 (C^{Ar}), 120.4 ($C^{Ar}H$), 127.5 ($C^{Ar}H$), 127.6 ($C^{Ar}H$), 128.3 ($C^{Ar}H$), 132.7 (C^{Ar}), 134.6 ($C^{Ar}H$), 136.3 ($C^{Ar}H$), 138.0 (C^{Ar}), 138.4 (C^{Ar}), 139.7 (C^{Ar}), 155.4 (C^{Ar}), 162.9 (C^{Ar}), 167.6 (CO). *m/z* [Cl^+, isobutane] 581 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 580.8071, $C_{33}H_{46}NO_6Si$ requires 580.8069. υ_{max} /cm^{-1} (film): 3383, 2951, 2930, 2859, 1729, 1597, 1584, 1472, 1455. $[\alpha]_D^{24.5}$ 20.21 (c = 0.40, $CHCl_3$).

(3*R*,4*R*)-3-((*S*)-1-(2-((S)-4-(benzyloxy)butan-2-yl)oxazol-4-yl)propan-2-yl)-8-(*tert*-butyldimethylsilyloxy)-4-hydroxy-7-methylisochroman-1-one **407b**



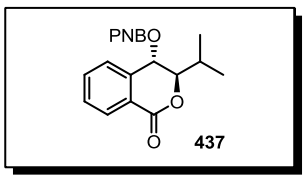
Syn,anti-isochromanone **407b** was obtained in the same quantity, yield and purity as *syn,anti*-isochromanone **407a**, under analagous experimental conditions, starting from aldehyde **408b**. $[\alpha]_D^{24.5}$ 68.42 (c=0.38, $CHCl_3$).

3-Isopropyl-*1H*-isochromen-1-one **436**



Anti-isochromanone **136f** (31 mg, 150 µmol) was dissolved in anhydrous THF (1.5 mL) and sequentially treated with 4-nitrobenzoic acid (28.7 mg, 226 µmol) and 2-$PyPPh_2$ (51.4 mg, 195 µmol) before the portionwise addition of DTBAD (45.0 mg, 195 µmol). The resultant reaction mixture was stirred at RT for 10h, under an atmosphere of argon. TLC analysis indicated reaction completion. The reaction was quenched with 3 M aq. HCl solution (5 mL) and the resultant solution was stirred for 20 min, before being extracted with Et_2O (3 × 15 mL). The combined organics were washed with 3 M aq. HCl solution (5 mL), sat'd aq. $NaHCO_3$ solution (5 mL) and brine (7 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the side-product, **436** (7.1 mg, 37.7 µmol, 25%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.29 (6H, d, *J* = 6.8, CH_3), 2.74-2.84 (1H, m, $CH(CH_3)_2$), 6.26 (1H, s, CH_{alkene}), 7.37 (1H, d, *J* = 7.8, ArH), 7,45 (1H, td, *J* = 7.6, 1.1, ArH), 7.67 (1H, td, *J* = 7.6, 1.4, ArH), 8.25 (1H, d, *J* = 7.8, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.2 (CH_3), 29.7 ($CH(CH_3)_2$), 100.6 ($C_{alkene}H$), 120.3 (C^{Ar}), 125.2 ($C^{Ar}H$), 127.6 ($C^{Ar}H$), 129.5 ($C^{Ar}H$), 134.7 ($C^{Ar}H$), 137.7 (C^{Ar}), 163.0 (CO), 163.1 (C^{Q}_{alkene}). *m/z* [EI^+] 188 $[M]^+$ (100%), HRMS found $[M]^+$ 188.0836, $C_{12}H_{12}O_2$ requires 188.0837. υ_{max} /cm^{-1} (film): 2969, 2928, 2874, 1724, 1653, 1605, 1570, 1483. The data observed is in accordance with literature values.[183]

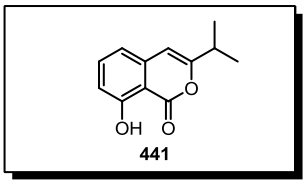
(±)-(3*R*,4*S*)-3-isopropyl-1-oxoisochroman-4-yl 4-nitrobenzoate **437**



Further elution with 5-10% Et_2O:petroleum ether, afforded the nitrobenzoate ester **437** (27.0 mg, 76.2 µmol, 51%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.06 (3H, d, *J* = 6.3, CH_3), 1.10 (3H, d, *J* = 6.8, CH_3), 1.77-1.84 (1H, m, $CH(CH_3)_2$), 4.54 (1H, dd, *J* = 8.1, 3.3 $CH(O_2C)$), 6.34 (1H, d, *J* = 3.3, CH(OPNB)), 7.55 (1H, d, *J* = 7.6, ArH), 7,59 (1H, td, *J* = 7.6, 1.3, ArH), 7.67 (1H, td, *J* = 7.5, 1.4, ArH), 8.18-8.21 (3H, m, ArH), 8.26-8.29 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ:

18.4 (CH_3), 19.1 (CH_3), 30.6 ($CH(CH_3)$), 68.7 (CH(OPNB)), 85.7 ($CH(O_2C)$), 123.7 ($C^{Ar}H$), 125.3 (C^{Ar}), 128.5 ($C^{Ar}H$), 130.4 ($C^{Ar}H$), 130.5 ($C^{Ar}H$), 131.1 ($C^{Ar}H$), 134.4 ($C^{Ar}H$), 134.5 (C^{Ar}), 134.6 (C^{Ar}), 150.9 (C^{Ar}), 163.2 (CO), 163.0 (CO). *m/z* [CI^+, isobutane] 356 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 356.1132, $C_{19}H_{18}NO_6$ requires 356.1134. υ_{max} /cm^{-1} (film): 2969, 2928, 2870, 1729, 1680, 1527, 1463.

8-Hydroxy-3-isopropyl-*1H*-isochromen-1-one **436**



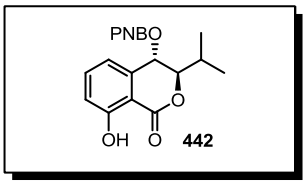
441

Method A: From Protected Phenol **199**

Isochromanone **136f** (146 mg, 434 µmol) was dissolved in anhydrous THF (4.5 mL) and sequentially treated with 4-nitrobenzoic acid (110 mg, 868 µmol) and 2-$PyPPh_2$ (228 mg, 868 µmol) before the portionwise addition of DTBAD (200 mg, 868 µmol). The resultant reaction mixture was stirred at RT for 16h, under an atmosphere of argon. TLC analysis indicated reaction completion. The reaction mixture was cooled to 0 ^oC and diluted with THF (5 mL) and pyridine (1 mL), before the dropwise addition of HF.Py (0.5 mL). The resultant mixture was stirred at 0 ^oC for 2h before being carefully quenched by the dropwise addition of sat'd aq. $NaHCO_3$ solution (20 mL). The solution was extraction with Et_2O (3 × 30 mL). The combined organics were washed with 3 M aq. HCl solution (2 × 15 mL), sat'd aq. $NaHCO_3$ solution (15 mL) and brine (15 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude products as a yellow oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the side-product **441** (33 mg, 161 µmol, 37%), as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.29 (6H, d, *J* = 6.9, CH_3), 2.74-2.82 (1H, m, $CH(CH_3)_2$), 6.26 (1H, s, CH_{alkene}), 6.83 (1H, dd, *J* = 7.7, 0.7, ArH), 6.92 (1H, dd, *J* = 8.3, 0.9, ArH), 7.56 (1H, t, *J* = 8.0, ArH), 11.02 (1H, s, OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.1 (CH_3), 31.1 ($CH(CH_3)_2$), 100.8 ($C_{alkene}H$), 113.6 ($C^{Ar}H$), 114.5 ($C^{Ar}H$), 136.2 ($C^{Ar}H$), 137.1 (C^{Ar}), 158.2 (C^{Ar}), 160.6 (C^{Q}_{alkene}), 161.3 (C^{Ar}) 165.9 (CO). *m/z* [CI^+, isobutane] 205 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 205.0862, $C_{12}H_{12}O_3$ requires 205.0865. υ_{max} /cm^{-1} (film): 3115, 2976, 2938, 2874, 1771, 1685, 1643, 1458.

Method A (cont): From Protected Phenol **199**

(±)-(3*R*,4*S*)-8-Hydroxy-3-isopropyl-1-oxoisochroman-4-yl 4-nitrobenzoate **442**

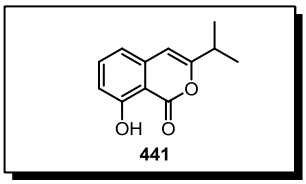


442

Further elution with 5-10% Et_2O:petroleum ether, afforded the desired nitrobenzoate **442** (71 mg, 191 µmol, 44%), as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.08 (3H, d, *J* = 6.8, CH_3), 1.11 (3H, d, *J* = 6.7, CH_3), 1.84-1.91 (1H, m, $CH(CH_3)_2$), 4.56 (1H, dd, *J* = 8.4, 3.0 $CH(O_2C)$), 6.30 (1H, d, *J* = 3.0, CH(OPNB)), 7.01 (1H, d, *J* = 7.4, ArH), 7.59 (1H, dd, *J* = 8.5, 1.0, ArH), 7.54 (1H,

dd, *J* = 8.4, 7.5, ArH), 8.18-8.20 (2H, m, ArH), 8.27-8.30 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.5 (CH_3), 19.0 (CH_3), 30.5 ($CH(CH_3)$), 68.4 (CH(OPNB)), 86.7 ($CH(O_2C)$), 107.9 (C^{Ar}), 119.5 ($C^{Ar}H$), 119.6 ($C^{Ar}H$), 123.7 ($C^{Ar}H$), 131.1 ($C^{Ar}H$), 134.5 (C^{Ar}), 134.5 (C^{Ar}), 136.8 ($C^{Ar}H$), 150.9 (C^{Ar}), 162.2 (C^{Ar}), 163.8 (CO), 167.6 (CO). *m/z* [EI^+] 371 $[M]^+$ (100%). HRMS found $[M]^+$ 371.1006, $C_{19}H_{17}NO_7$ requires 371.1005. υ_{max} /cm^{-1} (film): 3111, 2970, 2928, 2874, 1728, 1682, 1611, 1609, 1527, 1464.

8-Hydroxy-3-isopropyl-*1H*-isochromen-1-one **436**

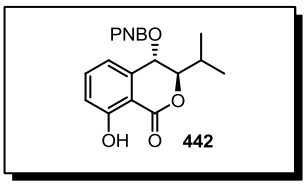


441

Method B: From Phenol **200**

Isochromanone **136f** (101 mg, 434 µmol) was dissolved in anhydrous THF (4.5 mL) and sequentially treated with 4-nitrobenzoic acid (110 mg, 868 µmol) and 2-$PyPPh_2$ (228 mg, 868 µmol) before the portionwise addition of DTBAD (200 mg, 868 µmol). The resultant reaction mixture was stirred at RT for 16h, under an atmosphere of argon. TLC analysis indicated reaction completion. The reaction mixture was extracted with Et_2O (3 × 30 mL). The combined organics were washed with 3 M aq. HCl solution (2 × 15 mL), sat'd aq. $NaHCO_3$ solution (15 mL) and brine (15 mL), before being dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-5% Et_2O:petroleum ether, afforded the by-product **442** (27 mg, 130 µmol, 37%), as a colourless oil. The spectral and physical data obtained for **441**, via Method B, matched that obtained via Method A.

(±)-(3*R*,4*S*)-8-Hydroxy-3-isopropyl-1-oxoisochroman-4-yl 4-nitrobenzoate **442**

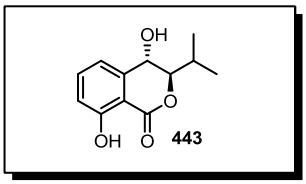


442

Method B (cont.): From Phenol **200**

Further elution with 5-10% Et_2O:petroleum ether, afforded the nitrobenzoate ester **442** (50 mg, 135 µmol, 44%), as a colourless oil. The spectral and physical data obtained for **442**, via Method B, matched that obtained via Method A.

(±)-(*3R,4S*)-4,8-Dihydroxy-3-isopropylisochroman-1-one **443**



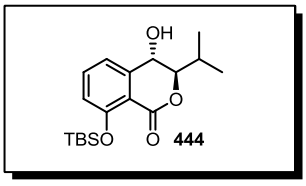
Method A: NaN_3/MeOH

Nitrobenzoate ester **442** (22 mg, 59 µmol) was dissolved in MeOH (1.5 mL) and treated with NaN_3 (64 mg, 0.99 mmol) and stirred at RT for 36h. The reaction was quenched with water (10 mL) and extracted with with Et_2O (3 × 10 mL). The combined organics were washed with brine (2 × 5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded the *anti,anti*-isochromanone **443** (11 mg, 47 µmol, 79%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.08 (3H, d, *J* = 6.7, CH_3), 1.09 (3H, d, *J* = 6.7, CH_3), 2.09-2.15 (1H, m, $CH(CH_3)_2$), 2.19 (1H, d, *J* = 7.2, OH), 4.28 (1H, dd, *J* = 7.3, 4.9 $CH(O_2C)$), 4.83 (1H, t, *J* = 7.2, CH(OH)), 6.98 (1H, br. d, *J* = 8.4, ArH), 7.02 (1H, dt, *J* = 7.5, 0.9, ArH), 7.53 (1H, dd, *J* = 8.3, 7.6, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.5 (CH_3), 19.2 (CH_3), 28.9 ($CH(CH_3)_2$), 65.7 (CH(OH)), 87.9 ($CH(O_2C)$), 106.8 (C^{Ar}), 116.1 ($C^{Ar}H$), 117.7 ($C^{Ar}H$), 136.8 ($C^{Ar}H$), 141.6 (C^{Ar}), 161.9 (C^{Ar}), 168.7 (CO). *m/z* [Cl^+, isobutane] 223 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 223.0973, $C_{12}H_{15}O_4$ requires 223.0970.

Method B: TBAF

Nitrobenzoate ester **442** (22 mg, 59 µmol) was dissolved in THF (1.5 mL) and treated with TBAF (1 M in THF, 1.00 mL, 1.00 mmol) and the resultant solution was stirred at RT for 24h. The reaction was quenched with water (10 mL) and extracted with with Et_2O (3 × 10 mL). The combined organics were washed with brine (2 × 5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-25% Et_2O:petroleum ether, afforded the *anti,anti*-isochromanone **443** (9.0 mg, 41 µmol, 69%), as a colourless oil. The spectral and physical data obtained for **443**, via Method B, matched that obtained via Method A.

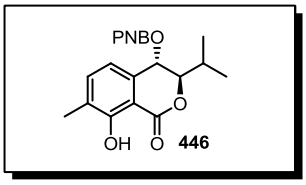
(±)-(*3R,4S*)-8-(*Tert*-butyldimethylsilyloxy)-3-isopropyl-1-oxoisochroman-4-yl 4-nitrobenzoate **444**



Isochromanone **443** (18.0 mg, 48.5 µmol) was dissolved in anhydrous DCM (1 mL) and cooled to –10 °C under an atmosphere of argon. TBSOTf (13.2 µL, 72.8 µmol) was added, followed by 2,6-lutidine (11.3 µL, 97.0 µmol). The reaction mixture was stirred for 5 min, after which TLC analysis indicated reaction completion. The reaction was quenched with water (5 mL) and extracted with with Et_2O (3 × 10 mL). The combined organics were washed with sat'd aq. $CuSO_4$ solution (2 × 5 mL) and brine (2 × 5 mL), before being dried over anhydrous Na_2SO_4. The

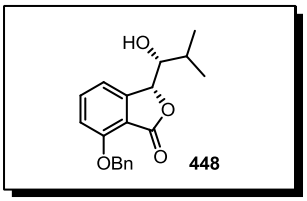
solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-10% Et_2O:petroleum ether, afforded the silyl phenol **444** (21.0 mg, 43.2 µmol, 89%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.25 (3H, s, CH_3Si), 0.26 (3H, s, CH_3Si), 1.04 (3H, d, *J* = 6.8, CH_3), 1.04 (9H, s, $(CH_3)_3CSi$)), 1.09 (3H, d, *J* = 6.7, CH_3), 1.72-1.79 (1H, m, $CH(CH_3)_2$), 4.39 (1H, dd, *J* = 8.4, 3.5, $CH(O_2C)$), 6.25 (1H, d, *J* = 3.5, CH(OPNB)), 7.01 (1H, br. d, *J* = 7.4, ArH), 7.08 (1H, dd, *J* = 8.4, 1.0, ArH), 7.46 (1H, dd, *J* = 8.3, 7.6), 8.18-8.21 (2H, m, ArH), 8.25-8.28 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 4.4 (CH_3Si), 18.4 (CH_3), 19.0 (CH_3), 30.3 ($CH(CH_3)_2$), 69.6 (CH(OPNB)), 84.6 ($CH(O_2C)$), 116.2 (C^{Ar}), 121.0 ($C^{Ar}H$), 123.6 ($C^{Ar}H$), 123.9 ($C^{Ar}H$), 131.1 ($C^{Ar}H$), 134.6 ($C^{Ar}H$), 134.7 (C^{Ar}), 136.4 (C^{Ar}), 150.9 (C^{Ar}), 157.6 (C^{Ar}), 160.2 (CO), 163.9 (CO). *m/z* [Cl^+, isobutane] 486 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 486.1945, $C_{25}H_{32}NO_7Si$ requires 486.1948. υ_{max} /cm^{-1} (film): 2961, 2930, 2859, 1726, 1599, 1582, 1530.

(±)-(*3R,4S*)-8-Hydroxy-3-isopropyl-7-methyl-1-oxoisochroman-4-yl 4-nitrobenzoate **446**



Isochromanone **226** (18.9 mg, 53.9 µmol) was dissolved in anhydrous THF (1 mL) and sequentially treated with 4-nitrobenzoic acid (9.2 mg, 72.8 µmol) and 2-$PyPPh_2$ (17.7 mg, 67.4 µmol) before the portionwise addition of DTBAD (15.5 mg, 67.4 µmol). The resultant reaction mixture was stirred at RT for 16h, under an atmosphere of argon. TLC analysis indicated reaction completion. The reaction mixture was cooled to 0 ^oC and diluted with THF (2 mL) and pyridine (0.5 mL), before the dropwise addition of HF.Py (100 µL). The resultant mixture was stirred at 0 ^oC for 2h before being carefully quenched by the dropwise addition of sat'd aq. $NaHCO_3$ solution (5 mL). The solution was extraction with Et_2O (3 × 10 mL). The combined organics were washed with 3 M aq. HCl solution (2 × 5 mL), sat'd aq. $NaHCO_3$ solution (5 mL) and brine (5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 5-10% Et_2O:petroleum ether, afforded the nitrobenzoate **446** (8.8 mg, 22.8 µmol, 42%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.07 (3H, d, *J* = 6.8, CH_3), 1.10 (3H, d, *J* = 6.7, CH_3), 1.82-1.89 (1H, m, $CH(CH_3)_2$), 2.29 (3H, s, CH_3Ar), 4.56 (1H, dd, *J* = 8.7, 2.6 $CH(O_2C)$), 6.26 (1H, d, *J* = 2.6, CH(OPNB)), 6.93 (1H, d, *J* = 7.5, ArH), 7.39 (1H, d, *J* = 7.5, ArH), 8.16-8.19 (2H, m, ArH), 8.25-8.28 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.8 (CH_3Ar), 18.7 (CH_3), 19.0 (CH_3), 30.6 ($CH(CH_3)_2$), 68.7 (CH(OPNB)), 87.0 ($CH(O_2C)$), 107.1 (C^{Ar}), 119.2 ($C^{Ar}H$), 123.6 ($C^{Ar}H$), 129.2 (C^{Ar}), 131.0 ($C^{Ar}H$), 131.5 (C^{Ar}), 134.7 (C^{Ar}), 137.3 ($C^{Ar}H$), 150.9 (C^{Ar}), 160.4 (C^{Ar}), 163.8 (CO), 168.1 (CO). *m/z* [Cl^+, isobutane] 386 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 386.1237, $C_{20}H_{20}NO_7$ requires 386.1240. υ_{max} /cm^{-1} (film): 3107, 2970, 2926, 2874, 1728, 1678, 1613, 1609, 1530, 1459.

(±)-(*R*)-7-(benzyloxy)-3-((*R*)-1-hydroxy-2-methylpropyl)isobenzofuran-1(*3H*)-one **448**



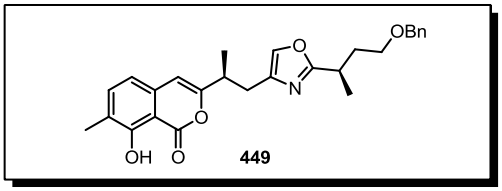
Method A: KH/THF

Isochromanone **196** (50 mg, 160 µmol) was dissolved in anhydrous THF (5 mL) and cooled to –20 ^{o}C under an atmosphere of argon, before KH (30% w/w in mineral oil, 85 mg, 640 µmol). TLC analysis after 20 min indicated reaction completion. The reaction was quenched by the addition of water (10 mL). The solution was extraction with Et_2O (3 × 10 mL). The combined organics were washed with brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 30% Et_2O:petroleum ether, afforded phthalide **448** (31 mg, 99.0 µmol, 62%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.12 (3H, d, *J* = 6.7, CH_3), 1.12 (3H, d, *J* = 6.7, CH_3), 2.07-2.13 (1H, m, $CH(CH_3)_2$), 3.58 (1H, td, *J* = 7.5, 2.8, CH(OH)), 5.33 (2H, s, OCH_2Ph), 5.48 (1H, d, *J* = 2.7, ($CH(O_2C)$), 6.93 (1H, d, *J* = 8.3, ArH), 6.98 (1H, d, *J* = 7.6, ArH), 7.31 (1H, t, *J* = 7.4, ArH), 7.38 (2H, t, *J* = 7.5, ArH), 7.49 (2H, d, *J* = 7.5, ArH), 7.55 (1H, t, *J* = 7.9, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.5 (CH_3), 19.4 (CH_3), 31.5 ($CH(CH_3)_2$), 70.5 (OCH_2Ph), 77.7 (CH(OH)), 80.3 ($CH(O_2C)$), 112.9 ($C^{Ar}H$), 113.8 ($C^{Ar}H$), 114.8 (C^{Ar}), 126.8 ($C^{Ar}H$), 128.0 ($C^{Ar}H$), 128.7 ($C^{Ar}H$), 136.2 ($C^{Ar}H$), 150.6 (C^{Ar}), 157.8 (C^{Ar}), 168.2 (CO). *m/z* [CI^+, isobutane] 313 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 313.1443, $C_{19}H_{21}O_3$ requires 313.1440. υ_{max} /cm^{-1} (film): 3482, 2961, 2914, 2872, 1759, 1605, 1485.

Method B: K_2CO_3/MeOH

Isochromanone **196** (50 mg, 160 µmol) was dissolved in MeOH (5 mL) and treated with K_2CO_3 (28 mg, 0.20 mmol) ansdstirred for 12h at RT. The reaction was quenched by the addition of water (10 mL). The solution was extraction with Et_2O (3 × 10 mL). The combined organics were washed with brine (5 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 30% Et_2O:petroleum ether, afforded phthalide **448** (35 mg, 112 µmol, 70%), as a colourless oil. The spectral and physical data obtained for **448**, via Method B, matched that obtained via Method A.

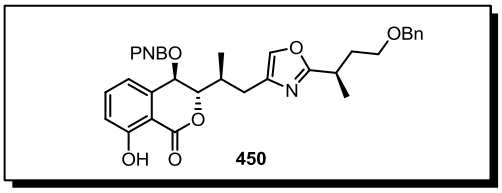
3-((*S*)-1-(2-((*R*)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)propan-2-yl)-8-hydroxy-7-methyl-*1H*-isochromen-1-one **449**



449

Syn,anti-isochromanone **407a** (110 mg, 190 µmol) was dissolved in anhydrous THF (5 mL) and sequentially treated with 4-nitrobenzoic acid (43.5 mg, 342 µmol) and 2-$PyPPh_2$ (90.0 mg, 342 µmol), before the portionwise addition of DTBAD (79 mg, 340 µmol). The resultant reaction mixture was stirred at RT for 16h, under an atmosphere of argon. TLC analysis indicated reaction completion. The reaction mixture was cooled to 0 ^{o}C and diluted with THF (5 mL) and pyridine (1 mL), before the dropwise addition of HF.Py (0.2 mL). The resultant mixture was stirred at 0 ^{o}C for 2h before being carefully quenched by the dropwise addition of sat'd aq. $NaHCO_3$ solution (10 mL). The solution was extraction with Et_2O (3 × 15 mL). The combined organics were washed with 3 M aq. HCl solution (2 × 4 mL), sat'd aq. $NaHCO_3$ solution (4 mL) and brine (5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-20% Et_2O:petroleum ether, afforded isochromen-1-one by-product **449** (33.6 mg, 70.3 µmol, 37%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.28 (6H, d, *J* = 7.0, CH_3(CHAr), CH_3($CHCH_2Ar$)), 1.83-1.89 (1H, m, CH_2(CH_2OBn)), 2.04-2.11 (1H, m, CH_2(CH_2OBn)), 2.28 (3H, s, CH_3Ar), 2.70 (1H, dd, *J* = 14.5, 7.2, CH_2Ar), 2.91 (1H, dd, *J* = 14.5, 7.5, CH_2Ar), 3.00-3.07 (1H, m, CH(CH_2Ar), 3.11-3.18 (1H, m, CH(CH_3)(Ar)), 3.36-3.41 (1H, m, CH_2OBn), 3.44-3.48 (1H, m, CH_2OBn), 4.42 (2H, s, OCH_2Ph), 6.16 (1H, s, CH_{alkene}), 6.69 (1H, d, *J* = 7.7, ArH), 7.23 (1H, s, ArH), 7.25-7.34 (5H, m, ArH), 7.40 (1H, d, *J* = 7.8, ArH), 11.24 (1H, s, OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3Ar), 18.0 (CH_3(CH)), 18.7 ((CH_3(CH)), 30.7 (CH(CH_3)(Ar)), 31.0 (CH_2Ar), 35.0 (CH_2(CH_2OBn)), 37.3 (CH(CH_2Ar)), 67.8 (CH_2OBn), 72.9 (OCH_2Ph), 103.8 ($C_{alkene}H$), 105.4 (C^{Q}_{alkene}), 114.8 ($C^{Ar}H$), 124.2 (C^{Ar}), 127.5 ($C^{Ar}H$), 127.6 ($C^{Ar}H$), 128.3 ($C^{Ar}H$), 134.3 ($C^{Ar}H$), 135.4 (C^{Ar}), 135.8 (C^{Ar}), 137.6 (C^{Ar}), 138.4 ($C^{Ar}H$), 158.9 (C^{Ar}), 159.5 (C^{Ar}), 167.2 (C^{Ar}), 168.0 (CO). *m/z* [EI^{+}] 447 $[M]^{+}$ (100%), HRMS found $[M]^{+}$ 447.2049, $C_{27}H_{29}NO_5$ requires 447.2046. υ_{max} /cm^{-1} (film): 3065, 2971, 2928, 2857, 1724, 1682, 1648, 1622, 1570, 1454. $[\alpha]_D^{25.3}$ 3.16 (c = 0.20, $CHCl_3$).

(*3S,4R*)-3-((*S*)-1-(2-((*R*)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)propan-2-yl)-8-hydroxy-7-methyl-1-oxoisochroman-4-yl 4-nitrobenzoate

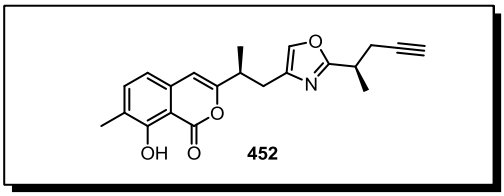


450

Further elution with 20-25% Et_2O:petroleum ether, afforded the nitrobenzoate ester **450** (12.4 mg, 20.2 µmol, 11%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.01 (3H, d, *J* = 6.8, CH_3($CHCH_2Ar$)), 1.28 (3H, d, *J* = 7.1, CH_3(CHAr)), 1.81-1.88 (1H, m, CH_2(CH_2OBn)), 2.04-2.11 (1H, m, CH_2(CH_2OBn)), 2.10-2.18 (1H, m, CH(CH_2Ar)), 2.29 (3H, s, CH_3Ar), 2.53 (1H, dd, *J* = 14.7, 8.0, CH_2Ar), 2.84 (1H, dd, *J* = 14.7, 4.6, CH_2Ar), 3.10-3.17 (1H, m, CH(CH_3)(Ar)), 3.40-3.49 (2H, m, CH_2OBn), 4.43 (2H, s, OCH_2Ph), 4.71 (1H, dd, *J* = 9.0, 2.0, CH(O_2C)), 6.27 (1H, d, *J* = 2.1,

CH(OPNB)), 6.95 (1H, d, *J* = 7.5, ArH), 7.23-7.34 (6H, m, ArH), 7.39 (1H, d, *J* = 7.5, ArH), 8.14-8.17 (2H, m, ArH), 8.23-8.26 (2H, m, ArH), 11.21 (1H, s, OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.7 (CH_3Ar), 16.0 ($CH_3(CHCH_2Ar$), 18.6 ($CH_3(CHAr)$), 28.9 (CH_2Ar), 30.8 ($CH(CH_3)(Ar)$), 34.8 ($CH(CH_2Ar)$), 34.9 ($CH_2(CH_2OBn)$), 66.6 (CH(OPNB)), 67.8 (CH_2OBn), 72.9 (OCH_2Ph), 85.9 ($CH(O_2C)$), 107.2 (C^{Ar}), 113.8 ($C^{Ar}H$), 118.6 (C^{Ar}), 118.9 ($C^{Ar}H$), 127.5 ($C^{Ar}H$), 127.6 ($C^{Ar}H$), 128.3 ($C^{Ar}H$), 128.4 (C^{Ar}),132.1 ($C^{Ar}H$), 132.8 (C^{Ar}), 134.7 ($C^{Ar}H$), 137.2 ($C^{Ar}H$), 137.4 (C^{Ar}), 138.4 (C^{Ar}), 151.4 (C^{Ar}), 160.2 (C^{Ar}), 165.5 (CO), 167.8 (CO), 168.3 (C^{Ar}). *m/z* [EI$^+$] 600 [M]$^+$ (100%). HRMS found [M]$^+$ 600.2107, $C_{18}H_{24}O_3NSi$ requires 600.2108. υ_{max} /cm^{-1} (film): 3270, 2950, 2930, 2859, 1729, 1682, 1597, 1584, 1472, 1456. $[\alpha]_D^{24.5}$ 20.21 (c = 0.40, $CHCl_3$).

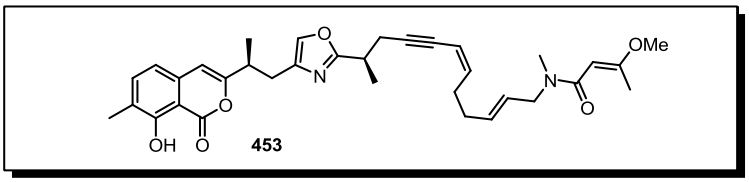
8-Hydroxy-7-methyl-3-((*S*)-1-(2-((*R*)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)-*1H*-isochromen-1-one



452

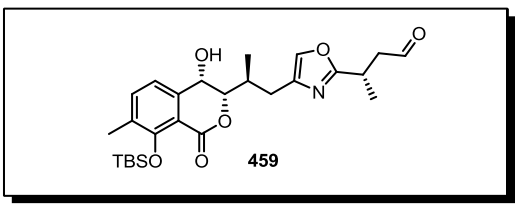
Benzyl ether **449** (20.0 mg, 44.7 µmol) was dissolved in anhydrous EtOH (120 mL) and charged with 10% activated Pd/C (1.2 mg). The suspension was stirred under an atmosphere of hydrogen at RT for 16h. TLC analysis indicated reaction completion. The suspension was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford the crude alcohol intermediate as a colourless oil, and was oxidised without further purification. The alcohol intermediate was dissolved in anhydrous DCM (2 mL) and treated with BAIB (57.6 mg, 178 µmol) and TEMPO (2.1 mg, 13.4 µmol). The reaction mixture was stirred under argon at RT for 16h until reaction completion, as indicated by TLC analysis. The crude reaction mixture was purified by flash column chromatography, elution with 0-100% Et_2O:petroleum ether, to afforded the aldehyde intermediate **451** (10.3 mg, 29.1 µmol, 65%) as a yellow oil. The aldehyde intermediate **451** (10.3, 29.1 µmol) was immediately dissolved in anhydrous MeOH (1.5 mL), before the sequential addition of dimethyl (1-diazo-2-oxopropyl)phosphonate (8.4 mg, 43.7 µmol) in MeOH (0.2 mL), and K_2CO_3 (12.1 mg, 87.3 µmol). The resultant mixture was stirred at RT for 3h until TLC analysis indicated reaction completion. The solvent was evaporated and the crude residue was purified by flash column chromatography, elution with 0-15% Et_2O:petroleum ether, to afford acetylene **452** (7.4 mg, 21.1 µmol, 73%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.30 (3H, d, *J* = 6.9, $CH_3(CHCH_2Ar)$), 1.40 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 1.94 (1H, t, *J* = 2.6, CH_{alkyne}), 2.29 (3H, s, CH_3Ar), 2.48 (1H, ddd, *J* = 16.7, 7.8, 2.6, CH_2(alkyne)), 2.64 (1H, ddd, *J* = 16.7, 6.0, 2.7, CH_2(alkyne)), 2.72 (1H, ddd, *J* = 14.5, 7.1, 0.9, CH_2Ar), 2.93 (1H, ddd, *J* = 14.4, 7.6, 0.8, CH_2Ar), 3.01-3.10 (1H, m, $CH(CH_2Ar)$), 3.10-3.17 (1H, m, $CH(CH_3)(Ar)$), 6.19 (1H, s, CH_{alkene}), 6.71 (1H, d, *J* = 7.7, ArH), 7.26 (1H, s, ArH), 7.42 (1H, d, *J* = 7.8, ArH), 11.24 (1H, d, *J* = 0.4, OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3Ar), 17.6 ($CH_3(CHAr)$), 18.0 ($CH_3(CHCH_2Ar)$), 24.3 (CH_2(alkyne)), 30.9 (CH_2Ar), 33.2 ($CH(CH_3)(Ar)$), 37.3 ($CH(CH_2Ar)$), 70.0 ($C_{alkyne}H$), 81.4 ($C_{alkyne}(CH_2)$), 103.9 ($C_{alkene}H$), 105.4 (C^Q_{alkene}), 114.8 ($C^{Ar}H$), 134.7 ($C^{Ar}H$), 135.5 (C^{Ar}), 137.8 (C^{Ar}), 138.4 ($C^{Ar}H$), 158.8 (C^{Ar}), 159.5 (C^{Ar}), 166.4 (C^{Ar}), 167.2 (CO). *m/z* [EI$^+$] 351 [M]$^+$ (100%), HRMS found [M]$^+$ 351.1473, $C_{21}H_{21}NO_4$ requires 351.1471. υ_{max} /cm^{-1} (film): 3304, 2957, 2926, 2854, 1724, 1684, 1647, 1622, 1456. $[\alpha]_D^{26.3}$ 51.35 (c=0.07, $CHCl_3$).

(*E*)-*N*-((*R,2E,6Z*)-11-(4-((*S*)-2-(8-hydroxy-7-methyl-1-oxo-*1H*-isochromen-3-yl)propyl)oxazol-2-yl)dodeca-2,6-dien-8-ynyl)-3-methoxy-*N*-methylbut-2-enamide **453**



8-hydroxy-7-methyl-3-((*S*)-1-(2-((*R*)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)-1*H*-isochromen-1-one **452** (6.0 mg, 17.1 µmol) and *(E)-N*-((2*E*,6*Z*)-7-iodohepta-2,6-dienyl)-3-methoxy-*N*-methylbut-2-enamide **72** (7.4 mg, 21.3 µmol) were dissolved in anhydrous MeCN (1.0 mL) and degassed by passing a stream of argon through the solution, before being cooled to 0 ^{o}C. The reaction was carried out in the absence of light. $Pd(PPh_3)_4Cl_2$ (1.2 mg, 1.8 µmol) and CuI (0.7 mg, 3.6 µmol) were added to the reaction mixture before the addition of NEt_3 (12.4 µmol, 89.0 mmol) and the resultant solution was stirred at 0 ^{o}C for 15 min and then warmed to room temperature and stirred for 24h, after which TLC analysis indicated reaction completion. The solvent was evaporated and the resultant residue was purified by flash column chromatography, elution with 0-70% Et_2O:petroleum ether, to afford the desired enyne **453** (6.6 mg, 11.5 µmol, 65%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.29 (3H, d, *J* = 6.9, $CH_3(CHCH_2Ar)$), 1.41 (3H, d, *J* = 7.1, $CH_3(CHAr)$), 2.13-2.17 (2H, m, $CH_2(CH_{alkene(E)})(CH_2)$), 2.21 (3H, br. s, CH_3(alkene)), 2.27-2.34 (2H, m, $CH_2(CH_{alkene(Z)})(CH_2)$), 2.29 (3H, s, CH_3Ar), 2.63 (1H, ddd, *J* = 16.8, 8.1, 2.2, CH_2(alkyne)), 2.70 (1H, dd, *J* = 14.5, 7.3, CH_2Ar), 2.80 (1H, ddd, *J* = 16.8, 5.7, 2.0, CH_2(alkyne)), 2.90-2.96 (1H, m, CH_2Ar), 2.93 (3H, s, CH_3N), 3.01-3.08 (1H, m, $CH(CH_2Ar)$), 3.10-3.17 (1H, m, $CH(CH_3)(Ar)$), 3.59 (3H, br. s, CH_3O), 3.92 (2H, br. s, CH_2N), 5.17 (1H, br. s, CH_{alkene}(CON)), 5.39-5.45 (2H, m, $CH_{alkene(Z)}$(alkyne)), $CH_{alkene(E)}(CH_2N)$), 5.56 (1H, dt, *J* = 15.4, 6.6, $CH_{alkene(E)}(CH_2CH_2)$), 5.74-5.82 (1H, m, $CH_{alkene(Z)}(CH_2CH_2)$), 6.19 (1H, s, $CH_{alkene}Ar$), 6.71 (1H, d, *J* = 7.8, ArH), 7.26 (1H, s, ArH), 7.42 (1H, d, *J* = 7.8, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz, 3:2 rotamer ratio, asterisk denotes minor rotamer peaks, 55 ^{o}C) δ: 15.5 (CH_3Ar), 17.6 ($CH_3(CHAr)$), 18.0 ($CH_3(CHCH_2Ar)$), 18.7 (CH_3(alkene)), 25.4 CH_2(alkyne), 29.6 ($CH_2(CH_{alkene(Z)})$), 31.0 (CH_2Ar), 31.4 ($CH_2(CH_{alkene(E)})(CH_2)$), 33.6 ($CH(CH_3)(Ar)$), 34.2 ($CH_3N$), 37.3 ($CH(CH_2Ar)$), 49.0 ($CH_2N$* only observed on DEPT135), 52.2 (CH_2N only observed on DEPT135), 54.8 (CH_3O), 77.2 (C_{alkyne}), 78.9 (C_{alkyne}), 91.2 ($C_{alkene}H$(CON)), 103.5 (C_{alkene}HAr), 105.6 (C^{Ar}), 109.9 ($CH_{alkene(Z)}$(alkyne)), 114.7 ($C^{Ar}H$), 124.2 (C^{Ar}), 125.3 ($C_{alkene(E)}H(CH_2N)$), 125.8 (C^{Ar}), 132.3 $C_{alkene(E)}H(CH_2CH_2)$), 134.4 ($C^{Ar}H$), 135.6 (C^{Ar}), 138.2 ($C^{Ar}H$), 141.4 ($C_{alkene(Z)}H(CH_2CH_2)$), 159.1 (C^{Q}), 159.7 (C^{Q}), 166.5 (C^{Q}), 166.9 (C^{Q}), 168.4 (C^{Q}). *m/z* [EI^{+}] 572 [M]$^{+}$ (27%), HRMS found [M]$^{+}$ 572.2882, $C_{34}H_{40}N_2O_6$ requires 572.2886. υ_{max} /cm^{-1} (film): 3296, 2958, 2925, 2851, 1730, 1685, 1647, 1606, 1455, 1431. $[\alpha]_D^{23.5}$ 42.50 (c=0.32, $CHCl_3$).

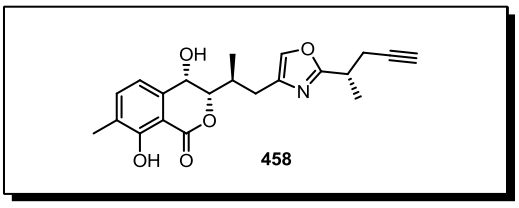
(*S*)-3-(4-((*S*)-2-((*3S,4S*)-8-(*Tert*-butyldimethylsilyloxy)-4-hydroxy-7-methyl-1-oxoisochroman-3-yl)propyl)oxazol-2-yl)butanal **459**



Benzyl ether **407b** (60.0 mg, 103 µmol) was dissolved in anhydrous EtOH (2 mL) and charged with 10% activated Pd/C (10 mg). The suspension was stirred under an atmosphere of

hydrogen at RT for 14h. TLC analysis indicated reaction completion. The suspension was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford the crude alcohol intermediate as a colourless oil that was taken on the next step without further purification. The alcohol intermediate was dissolved in anhydrous DCM (2 mL) and cooled to 0 ^{o}C under an atmosphere of argon. DMSO (500 µL) and NEt_3 (172 µL, 1.24 mmol) were added, before the portionwise addition of SO_3.Py (131 mg, 824 µmol). The reaction mixture was allowed to warm to RT and stirred for 14h until reaction completion, as indicated by TLC analysis. The crude reaction mixture was quenched with water (10 mL) and diluted with Et_2O (30 mL). The organics were collected and further washed with sat'd aq. $CuSO_4$ solution (3 × 5 mL) and brine (3 × 5 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a colourless oil. Purification by flash column chromatography, elution with 0-100% Et_2O: petroleum ether afforded aldehyde **459** (33.2 mg, 68.1 µmol, 66% over 2 steps) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.14 (3H, s, CH_3Si), 0.22 (3H, s, CH_3Si), 1.05 (9H, s, $(CH_3)_3CSi$), 1.11 (3H, d, *J* = 6.9, $CH_3(CHCH_2Ar)$), 1.36 (3H, d, *J* = 7.1, $CH_3(CHAr)$), 2.15 (1H, d, *J* = 6.8, OH), 2.28 (3H, s, CH_3Ar), 2.46-2.54 (1H, m, $CH(CH_2Ar)$), 2.63-2.69 (2H, m, CH_2Ar, $CH_2(CHO)$), 2.97-3.04 (2H, m, CH_2Ar, $CH_2(CHO)$), 3.44-3.51 (1H, m, $CH(CH_3)(Ar)$), 4.06 (1H, dd, *J* = 9.3, 1.1, $CH(O_2C)$), 4.66 (1H, br. d, *J* = 5.4, CH(OH)), 6.94 (1H, d, *J* = 7.6, ArH), 7.34 (1H, s, ArH), 7.37 (1H, d, *J* = 7.5, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -3.6 (CH_3Si), -3.5 (CH_3Si), 15.3 ($CH_3(CHCH_2Ar)$, 17.4 (CH_3Ar), 18.5 ($CH_3(CHAr)$), 18.7 ($SiC(CH_3)_3$), 25.9 ($(CH_3)_3CSi$), 28.2 (CH_2Ar), 28.2 ($CH(CH_3)(Ar)$), 33.1 ($CH(CH_2Ar)$), 48.0 ($CH_2(CHO)$), 66.4 (CH(OH)), 82.9 ($CH(O_2C)$), 115.8 (C^{Ar}), 120.2 ($C^{Ar}H$), 132.7 (C^{Ar}), 135.1 ($C^{Ar}H$), 136.2 ($C^{Ar}H$), 138.3 (C^{Ar}), 139.8 (C^{Ar}), 155.5 (C^{Ar}), 162.6 (C^{Ar}), 166.1 (CO_2), 199.9 (CHO). *m/z* [EI$^+$] 487 $[M+H]^+$ (100%), HRMS found $[M]^+$ 487.2394, $C_{26}H_{37}O_6NSi$ requires 487.2390. υ_{max} /cm^{-1} (film): 3385, 2957, 2930, 2854, 1728, 1588, 1584, 1464. $[\alpha]_D^{24.1}$ 64.00 (c=0.35, $CHCl_3$).

(*3S,4S*)-4,8-dihydroxy-7-methyl-3-((*S*)-1-(2-((*S*)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one **458**

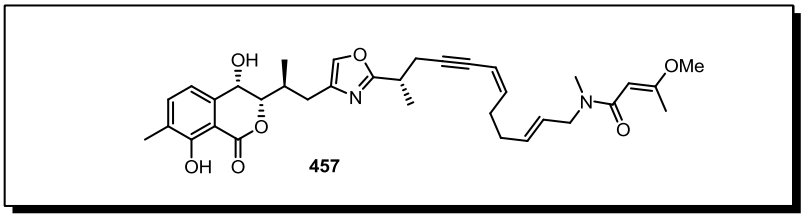


458

Aldehyde **459** (27.8 mg, 57.0 µmol) was dissolved in anhydrous MeOH (1.0 mL), before the sequential addition of dimethyl (1-diazo-2-oxopropyl)phosphonate (21.9 mg, 114 µmol) in MeOH (0.2 mL) and K_2CO_3 (23.6 mg, 171 µmol). The resultant mixture was stirred at RT for 6h under an atmosphere of argon, until TLC analysis indicated reaction completion. The solvent was evaporated and the crude residue was purified by flash column chromatography, elution with 0-35% Et_2O:petroleum ether, afforded acetylene **458** (11.6 mg, 31.5 µmol, 55%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (3H, d, *J* = 6.7, $CH_3(CHCH_2Ar)$), 1.42 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 1.95 (1H, br. s, CH_{alkyne}), 2.28 (3H, s, CH_3Ar), 2.42-2.62 (2H, m, $CH(CH_2Ar)$, CH_2Ar), 2.50 (1H, ddd, *J* = 16.8. 7.9, 2.6, CH_2(alkyne)), 2.67 (1H, ddd, *J* = 16.8. 5.9, 2.7, CH_2(alkyne)), 3.06-3.19 (2H, m, CH_2Ar, $CH(CH_3)(Ar)$), 4.24 (1H, dd, *J* = 8.5, 1.6, $CH(O_2C)$), 4.73 (1H, br. d, *J* = 4.4, CH(OH)), 6.82 (1H, d, *J* = 7.4, ArH), 7.37-7.39 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.6 ($CH_3(CHCH_2Ar)$, 15.7 (CH_3Ar), 17.5 ($CH_3(CHAr)$), 24.3 (CH_2(alkyne)), 28.2 (CH_2Ar), 33.1 ($CH(CH_3)(Ar)$), 33.6 ($CH(CH_2Ar)$), 65.4 (CH(OH)), 77.2 ($C_{alkyne}H$) 85.0 ($CH(O_2C)$), 106.4 (C^{Ar}), 117.8 ($C^{Ar}H$), 128.0 (C^{Ar}), 135.0 ($C^{Ar}H$), 137.3 ($C^{Ar}H$), 138.1 (C^{Ar}), 138.2 (C^{Ar}), 160.5 (C^{Ar}), 166.2 (C^{Ar}), 169.5 (CO). N.B: C^{Q}_{alkyne} not observed. *m/z* [EI$^+$] 369 $[M]^+$ (100%), HRMS

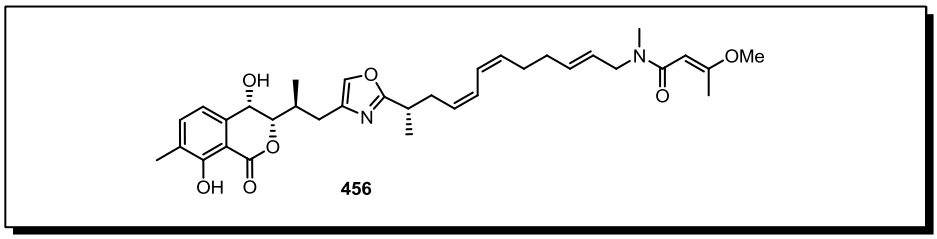
found $[M]^+$ 369.1581, $C_{21}H_{23}O_5N$ requires 369.1576. υ_{max} /cm^{-1} (film): 3304, 2959, 2924, 2854, 1734, 1672, 1618, 1568, 1560, 1458, 1427. $[\alpha]_D^{23.6}$ -24.00 (c=0.05, $CHCl_3$).

(*E*)-*N*-((*S,2E,6Z*)-11-(4-((*S*)-2-((*3S,4S*)-4,8-dihydroxy-7-methyl-1-oxoisochroman-3-yl)propyl)oxazol-2-yl)dodeca-2,6-dien-8-ynyl)-3-methoxy-N-methylbut-2-enamide **457**



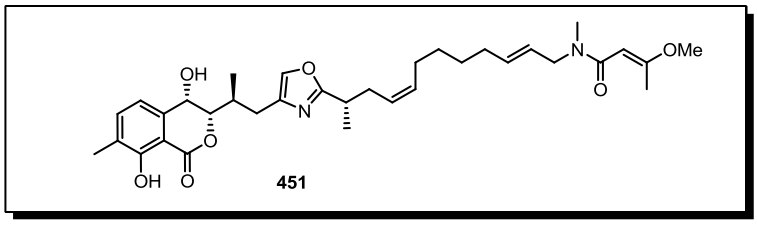
Acetylene **458** (10.0 mg, 27.0 µmol) and vinyl iodide **72** (11.3 mg, 32.4 µmol) were dissolved in anhydrous MeCN (1.0 mL) and degassed by passing a stream of argon through the solution, before being cooled to 0 °C. The reaction was carried out in the absence of light. $Pd(PPh_3)_4Cl_2$ (1.9 mg, 2.7 µmol) and CuI (1.0 mg, 5.4 µmol) were added to the reaction mixture before the addition of NEt_3 (23.0 µmol, 162 mmol) and the resultant solution was stirred at 0 °C for 15 min and then warmed to RT. After stirring for 14h, TLC analysis indicated reaction completion. The reaction mixture was partitioned between Et_2O (20 mL) and water (5 mL). The organics were collected and further washed with brine (2 × 3 mL), before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography, elution with 0-100% Et_2O:petroleum ether, afforded enyne **457** (8.5 mg, 14.4 µmol, 53%), as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (3H, d, *J* = 6.8, $CH_3(CHCH_2Ar)$), 1.43 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 2.12-2.16 (2H, m, $CH_2(CH_{alkene(E)})(CH_2)$), 2.15 (3H, br. s, CH_3(alkene)), 2.27-2.34 (2H, m, $CH_2(CH_{alkene(Z)})(CH_2)$), 2.28 (3H, s, CH_3Ar), 2.53-2.63 (2H, m, CH_2Ar, $CH(CH_2Ar)$), 2.67 (1H, dd, *J* = 16.6, 6.5, CH_2(alkyne)), 2.80 (1H, ddd, *J* = 17.0, 6.1, 2.0, CH_2(alkyne)), 2.93 (3H, s, CH_3N), 3.07-3.19 (1H, m, $CH(CH_3)(Ar)$, CH_2Ar), 3.59 (3H, br. s, CH_3O), 3.92 (2H, br. s, CH_2N), 4.22 (1H, dd, *J* = 8.7, 1.6, $CH(O_2C)$), 4.71 (1H, d, *J* = 4.4, CH(OH)), 5.16 (1H, br. s, CH_{alkene}(CON)), 5.39 (1H, br. d, *J* = 10.7, $CH_{alkene(Z)}$(alkyne)), 5.44 (1H, dt, *J* = 15.4, 5.8, $CH_{alkene(E)}(CH_2N)$), 5.57 (1H, dt, *J* = 15.4, 6.6, $CH_{alkene(E)}(CH_2CH_2)$), 5.76 (1H, dt, *J* = 10.7, 7.3, $CH_{alkene(Z)}(CH_2CH_2)$), 6.82 (1H, d, *J* = 7.4, ArH), 7.36 (1H, s, ArH), 7.37 (1H, d, *J* = 7.4, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.4 (CH_3Ar), 15.4 ($CH_3(CHCH_2Ar)$), 17.6 ($CH_3(CHAr)$), 18.6 (CH_3(alkene)), 25.5 CH_2(alkyne), 28.4 (CH_2Ar), 29.5 ($CH_2(CH_{alkene(Z)})$), 31.4 ($CH_2(CH_{alkene(E)})(CH_2)$), 33.5 ($CH(CH_2Ar)$), 33.6 ($CH(CH_3)(Ar)$), 34.2 ($CH_3N$), 54.7 ($CH_3O$), 65.3 (CH(OH)), 77.5 ($C_{alkyne}$), 78.9 ($C_{alkyne}$), 85.2 ($CH(O_2C)$), 91.3 ($C_{alkene}H(CON)$), 106.6 ($C^{Ar}$), 109.8 ($CH_{alkene(Z)}$(alkyne)), 117.7 ($C^{Ar}H$), 125.4 ($C_{alkene(E)}H(CH_2N)$), 127.7 ($C^{Ar}$), 132.4 $C_{alkene(E)}H(CH_2CH_2)$), 134.8 ($C^{Ar}H$), 137.1 ($C^{Ar}H$), 138.4 (C^{Ar}), 138.5 (C^{Ar}), 141.7 ($C_{alkene(Z)}H(CH_2CH_2)$), 160.5 (C^Q), 166.4 (C^Q), 168.4 (C^Q), 168.5 (C^Q), 168.5 (C^Q), 169.5 (C^Q). N.B; *CH_2N not observed. m/z* [CI^+, isobutane] 591 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 591.3065, $C_{34}H_{43}N_2O_7$ requires 591.3070. υ_{max} / cm^{-1} (film): 3100, 2958, 2925, 2851, 1730, 1685, 1647, 1606, 1455, 1431. $[\alpha]_D^{23.7}$ -11.33 (c=0.35, $CHCl_3$).

(*E*)-*N*-((*S,2E,6Z,8Z*)-11-(4-((*S*)-2-((*3S,4S*)-4,8-dihydroxy-7-methyl-1-oxoisochroman-3-yl)propyl)oxazol-2-yl)dodeca-2,6,8-trienyl)-3-methoxy-*N*-methylbut-2-enamide **456**



In the absence of light, $Ni(OAc)_2.4H_2O$ (26 mg, 105 µmol) was dissolved in degassed EtOH (2 mL) before $NaBH_4$ (3.4 mg, 90.3 µmol) was added. The resultant black solution was stirred under an atmosphere of argon for 2 min before being placed under a hydrogen atmosphere. EDA (70 µL, 1.05 mmol) was added, followed by a solution of enyne **457** (17.0 mg, 30.1 µmol) in degassed EtOH (0.5 mL). The reaction mixture was stirred at RT under an atmosphere of hydrogen for 90 min, before being passed through Celite, elution with EtOH, followed by solvent evaporation to afford the crude product. Purification by HPLC, using a Waters Aquidity UPLC BEH C18 column (50 nm x 2.1 mm i.d. 1.7 µm) at RT, eluting with 0.1% v/v HCO_2H/H_2O-0.1% v/v HCO_2H/MeCN, afforded *ent*-C8-*epi*-ajudazol B **456** (9.5 mg, 16.0 µmol, 53%), as a colourless oil. ^{1}H NMR ($(CD_3)_2CO$), 500 MHz) δ: 1.09 (3H, d, *J* = 6.8, $CH_3(CHCH_2Ar)$), 1.30 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 2.12-2.16 (2H, m, $CH_2(CH_{alkene(E)})(CH_2)$), 2.14 (3H, br. s, CH_3(alkene)), 2.23-2.28 (2H, m, $CH_2(CH_{alkene(Z)})(CH_2)$), 2.24 (3H, s, CH_3Ar), 2.46-2.52 (1H, m, $CH_2(CH_{alkene(Z)})(CHCH_3)$), 2.54 (1H, dd, *J* = 14.2, 8.8, CH_2Ar), 2.60-2.67 (2H, m, $CH_2(CH_{alkene(Z)})(CHCH_3)$), $CH(CH_2Ar)$), 2.91 (3H, br. s, CH_3N), 2.98-3.03 (1H, m, $CH(CH_3)(Ar)$), 3.04 (1H, ddd, *J* = 14.3, 3.4, 0.9, CH_2Ar), 3.62 (3H, br. s, CH_3O), 3.93 (2H, dd, *J* = 5.7, 0.9, CH_2N), 4.37 (1H, dd, *J* = 7.7, 1.7, $CH(O_2C)$), 4.56 (1H, d, *J* = 6.1, OH), 4.81 (1H, dd, *J* = 5.9, 1.5, CH(OH)), 5.33 (1H, br. s, $CH_{alkene}(CON)$), 5.40-5.51 (3H, m, $CH_{alkene(Z)}(CH_2CHCH_3)$, $CH_{alkene(Z)}(CH_2CH_2)$, $CH_{alkene(E)}(CH_2N)$), 5.62 (1H, dt, *J* = 15.4, 6.7, $CH_{alkene(E)}(CH_2CH_2)$), 6.25 (1H, ddt, *J* = 11.7, 10.7, 1.4, $CH_{(Z)}(CH_{(Z)}(CH_2CH_2))$), 6.29 (1H, ddt, *J* = 11.7, 10.7, 1.4, $CH_{(Z)}(CH_{(Z)}(CH_2CHCH_3))$), 6.91 (1H, d, *J* = 7.5, ArH), 7.44 (1H, dd, *J* = 7.5, 0.6, ArH), 7.58 (1H, s, ArH), 11.37 (1H, s, ArOH). ^{13}C NMR ($((CD_3)_2CO$), 125 MHz) δ: 15.0 ($CH_3(CHCH_2Ar)$), 15.4 (CH_3Ar), 18.3 ($CH_3(CHAr)$), 18.6 (CH_3(alkene)), 27.9 ($CH_2(CH_{alkene(Z)})(CH_2)$), 29.3 ($CH_2Ar$), 32.8 ($CH_2(CH_{alkene(E)})(CH_2)$), 33.6 ($CH_2(CH_{alkene(Z)})(CHCH_3)$), 33.9 ($CH(CH_2Ar)$), 34.7 ($CH(CH_3)(Ar)$), 55.2 ($CH_3O$), 65.1 (CH(OH)), 86.5 ($CH(O_2C)$), 92.3 ($C_{alkene}H(CON)$), 107.9 ($C^{Ar}$), 119.1 ($C^{Ar}H$), 124.7 ($C_{alkene(Z)}H(CH_{(Z)}CH_2CH_2)$), 126.2 ($C_{alkene(Z)}H(CH_{(Z)}CH_2CHCH_3$), 127.1 ($C_{alkene(E)}H(CH_2N)$), 127.2 ($C^{Ar}$), 129.2 ($C_{alkene(Z)}H(CH_2CHCH_3)$), 132.3 ($C_{alkene(Z)}H(CH_2CH_2)$), 133.0 ($C_{alkene(E)}H(CH_2CH_2)$), 135.8 ($C^{Ar}H$), 137.7 ($C^{Ar}H$), 139.4 ($C^{Ar}$), 140.7 ($C^{Ar}$), 160.7 ($C^{Ar}$), 167.9 ($C^{Q}$), 168.6 ($C^{Q}$), 170.5 ($C^{Q}$), 170.7 ($C^{Q}$). N.B. *$CH_3N$ and CH_2N not observed. m/z* [Cl^+, isobutane] 543 $[M+H]^+$ (100%), HRMS found $[M+H]^+$ 593.3206, $C_{34}H_{43}O_7N_2$ requires 593.3227. υ_{max} /cm^{-1} (film): 3306, 2967, 2924, 2855, 1670, 1642, 1456, 1427. $[\alpha]_D^{23.8}$ -18.57 (c=0.84, $CHCl_3$).

(*E*)-*N*-((*S,2E,8Z*)-11-(4-((*S*)-2-((*3S,4S*)-4,8-Dihydroxy-7-methyl-1-oxoisochroman-3-yl)propyl)oxazol-2-yl)dodeca-2,8-dienyl)-3-methoxy-*N*-methylbut-2-enamide **451**



Further elution afforded the over-reduced product **451** (4.5 mg, 7.6 µmol, 25%) as a colourless oil. ^{1}H NMR ($(CD_3)_2CO$), 500 MHz) δ: 1.09 (3H, d, *J* = 6.8, $CH_3(CHCH_2Ar)$), 1.29 (3H, d, *J* = 7.0, $CH_3(CHAr)$), 1.30-1.46 (4H, m, $CH_2(CH_2CH_{alkene(E)})$, $CH_2(CH_2CH_{alkene(Z)})$), 1.97-2.08 (4H, m, $CH_2(CH_{alkene(Z)})(CH_2CH_2CH_2)$, $CH_2(CH_{alkene(E)})(CH_2CH_2CH_2)$), 2.13 (3H, br. s, CH_3(alkene)), 2.24 (3H, s, CH_3Ar), 2.33-2.39 (1H, m, $CH_2(CH_{alkene(Z)})(CHCH_3)$), 2.47-2.56 (2H, m, $CH_2(CH_{alkene(Z)})(CHCH_3)$, CH_2Ar), 2.61-2.68 (1H, m, $CH(CH_2Ar)$), 2.91 (3H, br. s, CH_3N), 2.93-3.00 (1H, m, $CH(CH_3)(Ar)$), 3.05 (1H, ddd, *J* = 14.6, 3.4, 0.9, CH_2Ar), 3.61 (3H, br. s, CH_3O), 3.93 (2H, dd, *J* = 5.8, 1.0, CH_2N), 4.37 (1H, dd, *J* = 9.7, 1.6, $CH(O_2C)$), 4.57 (1H, d, *J* = 6.0, OH), 4.81 (1H, dd, *J* = 6.0, 1.5, CH(OH)), 5.30-5.47 (3H, m, $CH_{alkene(Z)}(CH_2CHCH_3)$, $CH_{alkene(Z)}(CH_2CH_2CH_2)$, $CH_{alkene(E)}(CH_2N)$), 5.34 (1H, br. s, CH_{alkene}(CON)), 5.61 (1H, dtt, *J* = 15.4, 6.7, 1.3, $CH_{alkene(E)}(CH_2CH_2CH_2)$), 6.90 (1H, d, *J* = 7.5, ArH), 7.44 (1H, dd, *J* = 7.5, ArH), 7.58 (1H, s, ArH), 11.37 (1H, s, ArOH). ^{13}C NMR ($((CD_3)_2CO$), 125 MHz) δ: 15.0 ($CH_3(CHCH_2Ar)$), 15.4 (CH_3Ar), 18.2 ($CH_3(CHAr)$), 18.6 (CH_3(alkene)), 27.6 ($CH_2(CH_{alkene(Z)})(CH_2CH_2\ CH_2)$), 29.3 ($CH_2Ar$), 32.6 ($CH_2(CH_{alkene(E)})(CH_2CH_2CH_2)$), 33.4 ($CH_2(CH_{alkene(Z)})(CHCH_3)$), 33.9 ($CH(CH_2Ar)$), 34.7 ($CH(CH_3)(Ar)$), 55.2 ($CH_3O$), 65.1 (CH(OH)), 86.5 ($CH(O_2C)$), 92.3 ($C_{alkene}H$(CON)), 107.9 ($C^{Ar}$), 119.0 ($C^{Ar}H$), 127.2 ($C^{Ar}$), 127.4 ($C_{alkene(Z)}H(CH_2CHCH_3)$), 130.0 ($C_{alkene(E)}H(CH_2N)$), ($C_{alkene(Z)}H(CH_2CHCH_3)$), 132.3 ($C_{alkene(Z)}H(CH_2CH_2CH_2)$), 133.7 ($C_{alkene(E)}H(CH_2CH_2CH_2)$), 135.8 ($C^{Ar}H$), 137.7 ($C^{Ar}H$), 139.4 ($C^{Ar}$), 140.7 ($C^{Ar}$), 160.7 ($C^{Ar}$), 168.0 ($C^{Q}$), 168.1 ($C^{Q}$), 170.7 ($C^{Q}$), 170.7 ($C^{Q}$). N.B: *$CH_3N$ and CH_2N not observed. m/z* [EI^+] 594 $[M]^+$ (100%), HRMS found $[M]^+$ 594.3309, $C_{34}H_{46}O_7N_2$ requires 594.3305. υ_{max} /cm^{-1} (film): 3296, 2967, 2924, 2855, 1670, 1645, 1593, 1456, 1427. $[\alpha]_D^{23.5}$ -24.00 (c = 0.45, $CHCl_3$).

13 X-Ray Crystallographic Data

X-ray diffraction data for crystals of **23a**, **23b**, **29b** and **20** were collected at 100 K on a Rigaku R-Axis RAPID Image Plate diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device and using graphite monochromated Mo Kα radiation (λ = 0.71069 Å) radiation Data reduction was carried out using CrystalClear software version 1.4.0 [CRYSTALCLEAR 1.4.0. Rigaku, 9009 New Trails Dr., The Woodlands, Texas 77381, USA, 1998]. X-ray data for **48b** were collected at 150 K on a Nonius KappaCCD diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device and using graphite monochromated Mo Kα radiation (λ = 0.71069 Å) radiation. Data reduction and empirical absorption corrections were carried out with DENZO [Otwinowski, Z.; Minor, W. *Methods in Enzymology,* **1997**, *276*, 307-326.]. No absorption correction was applied to either dataset due to the light atom contents. The structures were both solved by direct methods using the program SHELXS [SHELXS86. Sheldrick, G.M. (1986)]. Program for the solution of crystal structures. Univ. of Göttingen, Germany] and refined using full-matrix least-squares refinement on F ($I > 2\sigma_I$) using CRYSTALS [Betteridge, P.W.; Carruthers, J.R.; Cooper, R.I.; Prout, K.; Watkin, D.J. *J. Appl. Cryst.*, **2003**, *36*, 1487]. All non-hydrogen atoms were refined anisotropically. H atoms were placed in geometrically calculated positions and refined as riding groups, except for the atoms involved in hydrogen bonding, which were located on a difference map in each case, and their positions allowed to refine.

Crystal data for **182**: $C_{13}H_{16}O_4$, M_r=236.26, orthorhombic, Pbcn, a=13.500(3), b=15.178(3), c=11.351(12) Å, β=90 °, T=100 K, Z=8, R=0.0386 for 2086 data with $F_0>2\sigma(F)$, $wR2$=0.1519 for 2670 unique data, GOF=0.518. CCDC809799 contains the supplementary crystallographic data for this structure. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

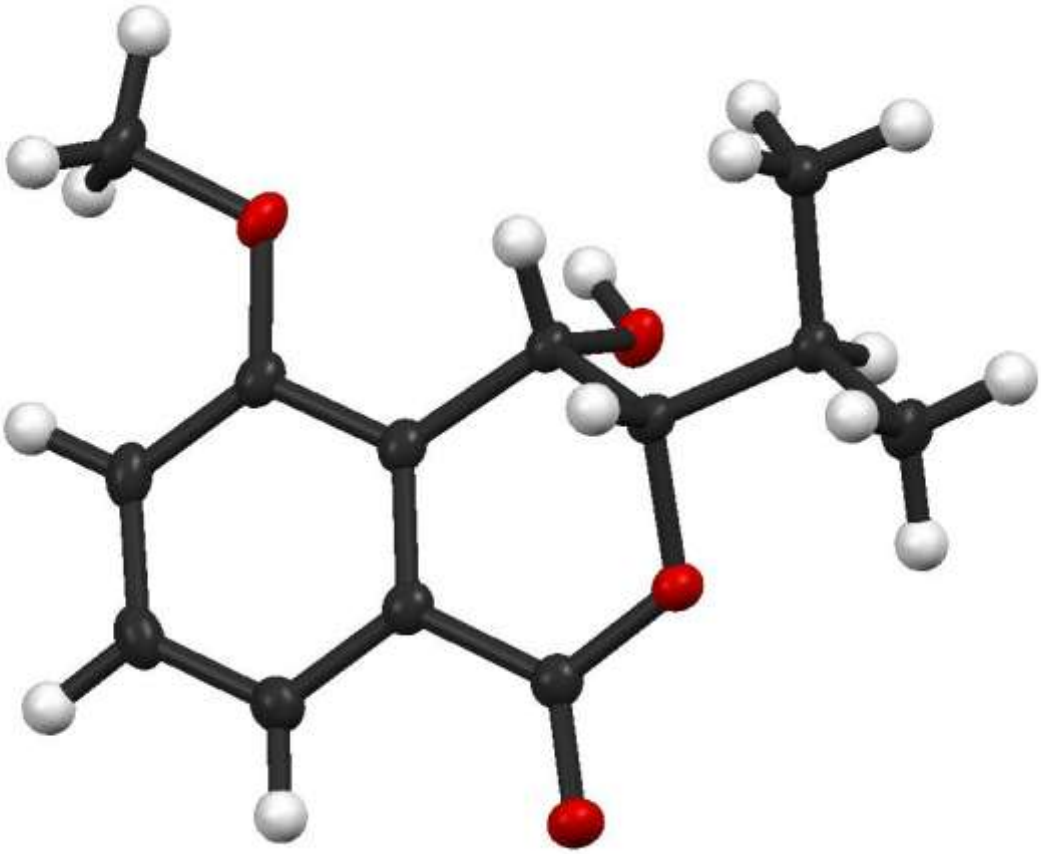


Figure 22 X-Ray Structure of 182

Crystal data for **183**: $C_{13}H_{16}O_4$, M_r=236.26, orthorhombic, $P2_12_12_1$, a=8.8027(2), b=9.9264(2), c=13.7092(3) Å, β=90 °, T=100 K, Z=4, R=0.0251 for 2630 data with $F_0>2\sigma(F)$, $wR2$=0.0750 for 2723 unique data, GOF=0.418. CCDC809800 contains the supplementary crystallographic data for this structure. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

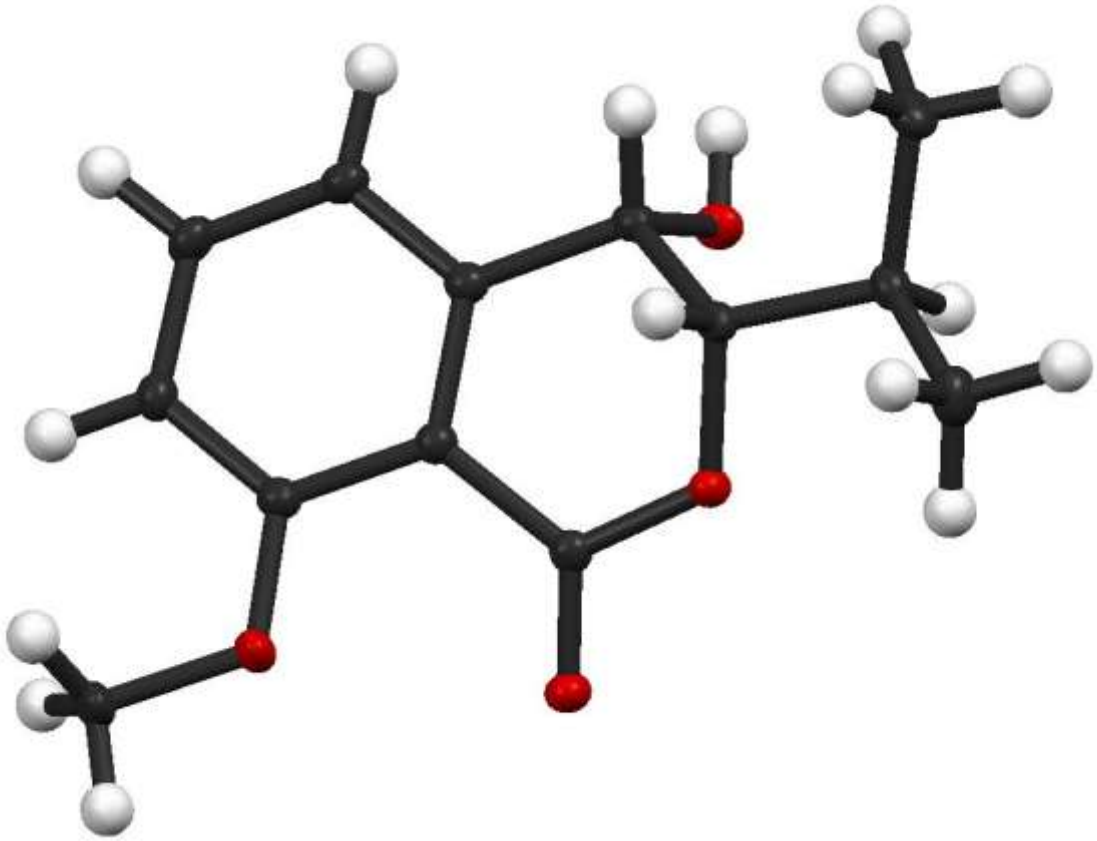


Figure 23 X-Ray Structure of 183

Crystal data for **196**: $C_{19}H_{20}O_4$, M_r=312.35, monoclinic, P2(1)/c, a=8.0746(1), b=10.5381(1), c=19.0147(3) Å, β=98.000(1)°, T=100 K, Z=4, R=0.0461 for 2638 data with $F_0>2\sigma(F)$, $wR2$=0.1261 for 3687 unique data, GOF=0.923. CCDC809801 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

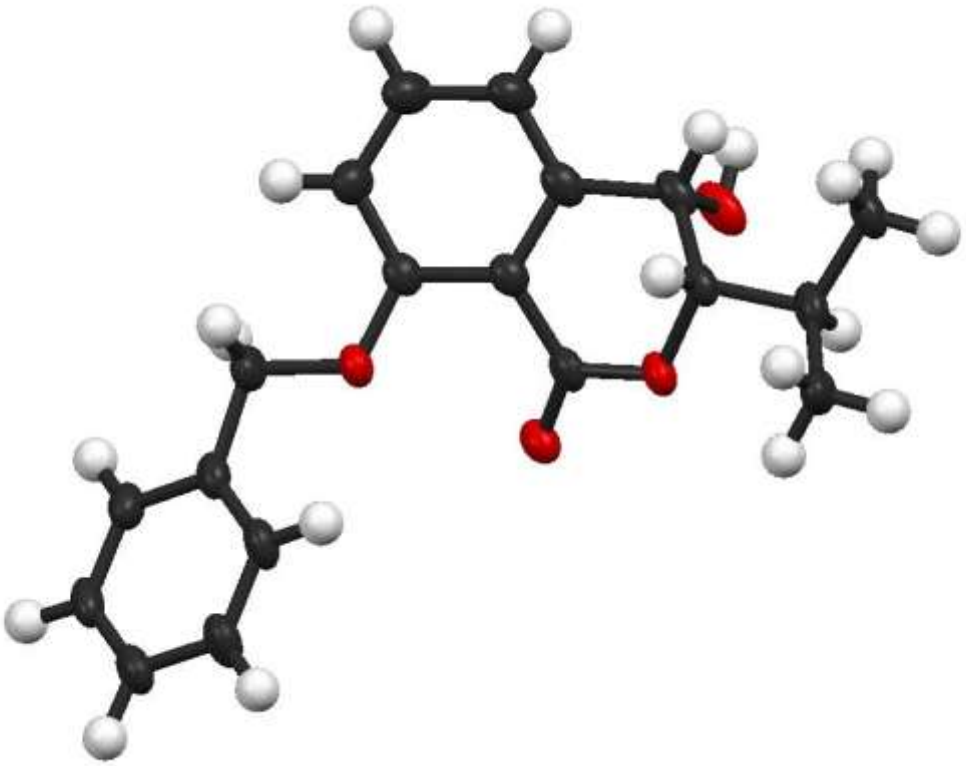


Figure 24 X-Ray Structure of 196

Crystal data for **208**: $C_{14}H_{18}O_5$, M_r=266.28, monoclinic, P2(1)/c, a=5.4288(3), b=26.7497(16), c=12.1509(8) Å, β=99.520(4)°, T=100 K, Z=4, R=0.0503 for 1855 data with $F_0>2\sigma$(F), $wR2$=0.1400 for 2230 unique data, GOF=1.103.

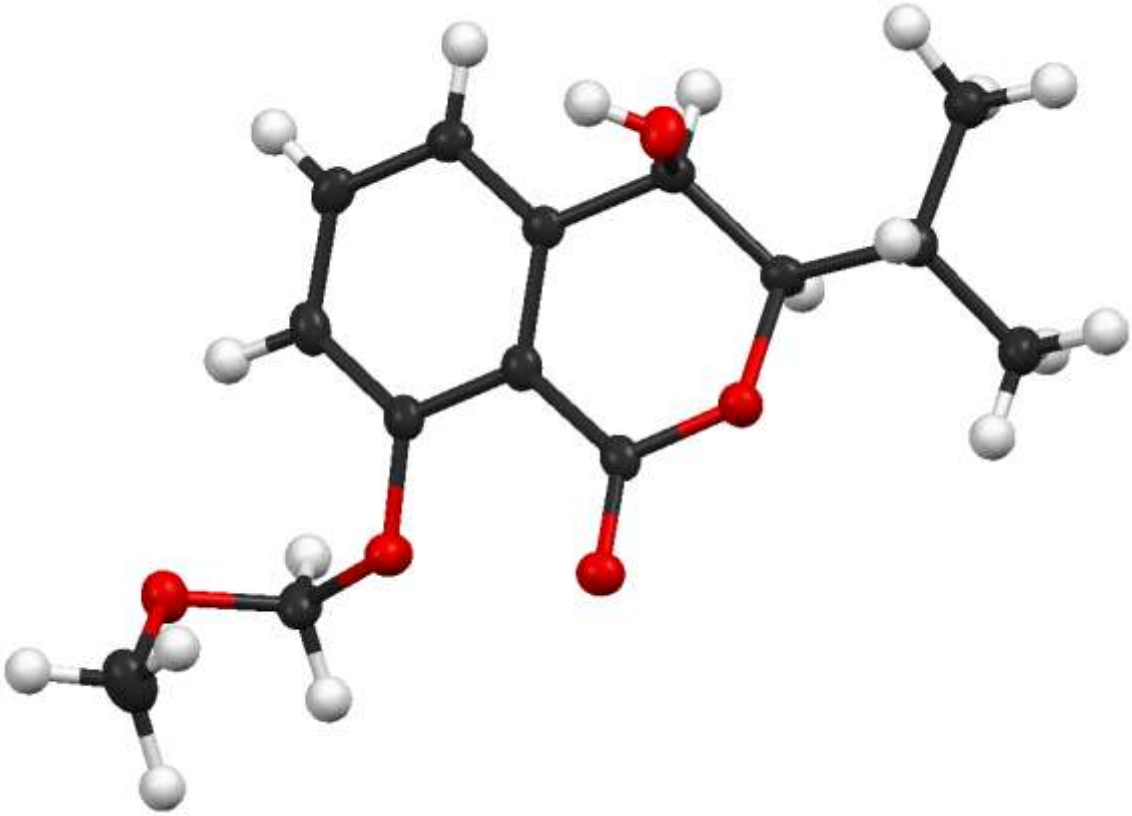


Figure 25 X-Ray Structure of 208

Crystal data for **255**: $C_{15}H_{15}NO_4$, M_r=273.28, monoclinic, P2(1)/c, a=12.7652(10), b=10.9486(9), c=10.4039(8) Å, β=111.548(4)°, T=100 K, Z=4, R=0.0343 for 2020 data with $F_0>2\sigma(F)$, $wR2$=0.0898 for 2488 unique data, GOF=1.049.

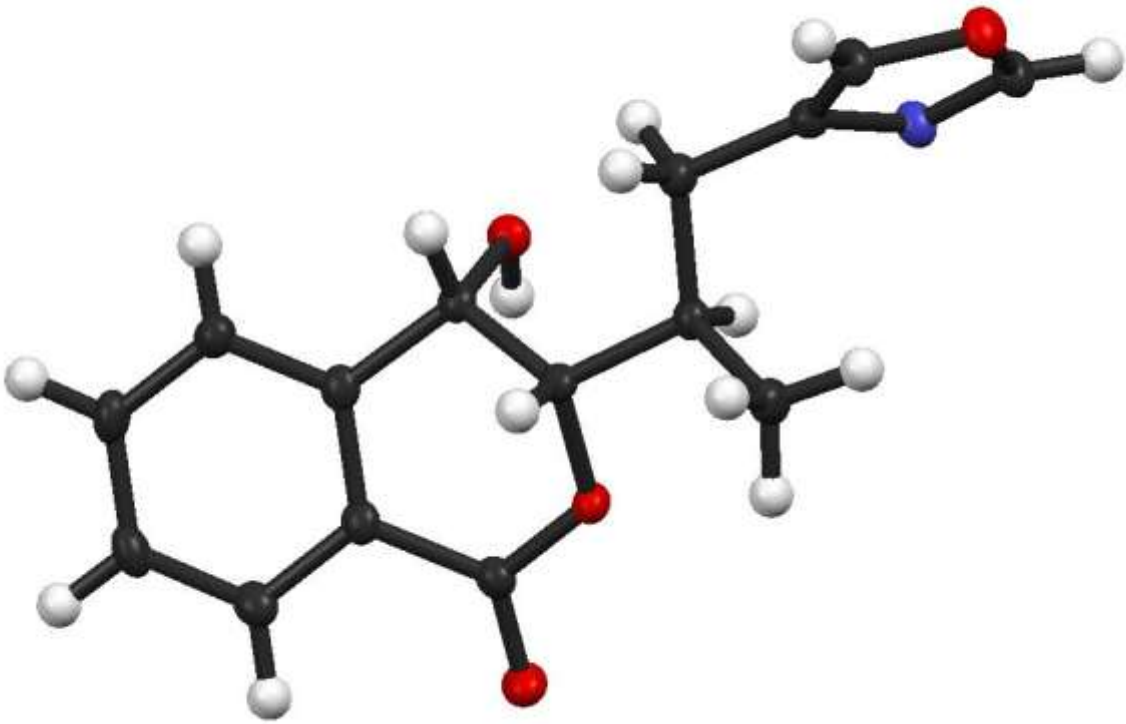


Figure 26 X-Ray Structure of 255

Crystal data for **256**: $C_{15}H_{15}NO_4$, M_r=273.28, monoclinic, P2(1)/c, a=12.7055(10), b=9.9875(9), c=11.4011(9) Å, β=111.377(4)°, T=100 K, Z=4, R=0.0373 for 1729 data with $F_0>2\sigma(F)$, $wR2$=0.0954 for 2446 unique data, GOF=1.028.

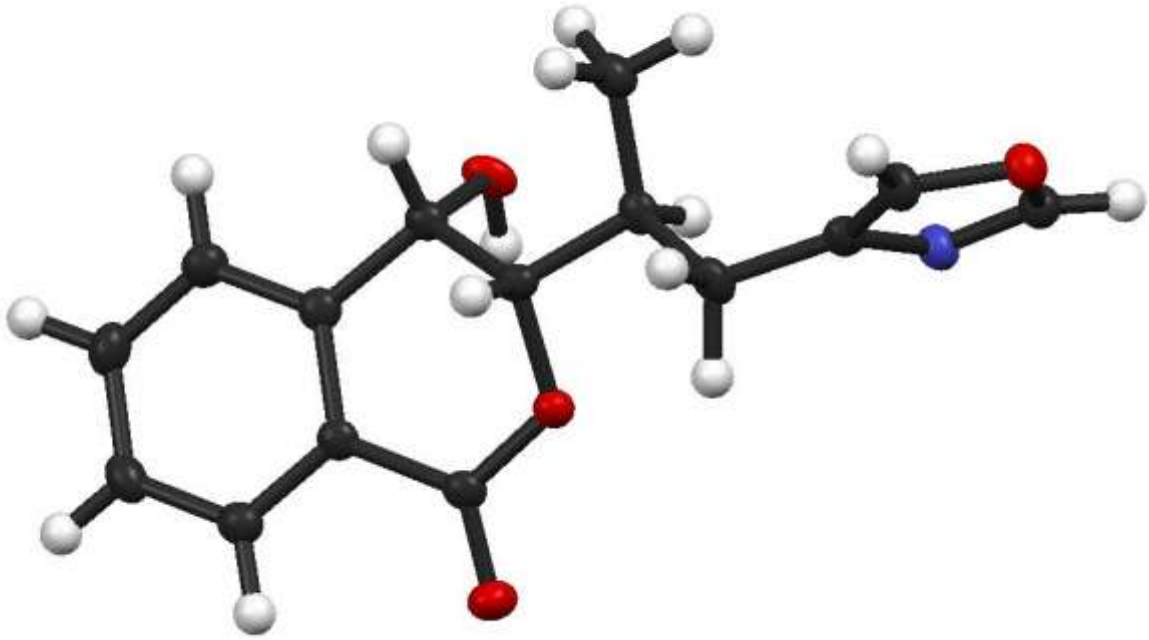


Figure 27 X-Ray Structure of 256

Crystal data for **247**: $C_{15}H_{15}NO_4$, M_r=273.28, monoclinic, C2/c, a=13.5059(9), b=9.3899(6), c=21.6502(17) Å, β=105.593 °, T=100 K, Z=8, R=0.0783 for 1726 data with $F_0>2\sigma$(F), $wR2$=0.2634 for 3031 unique data, GOF=1.132.

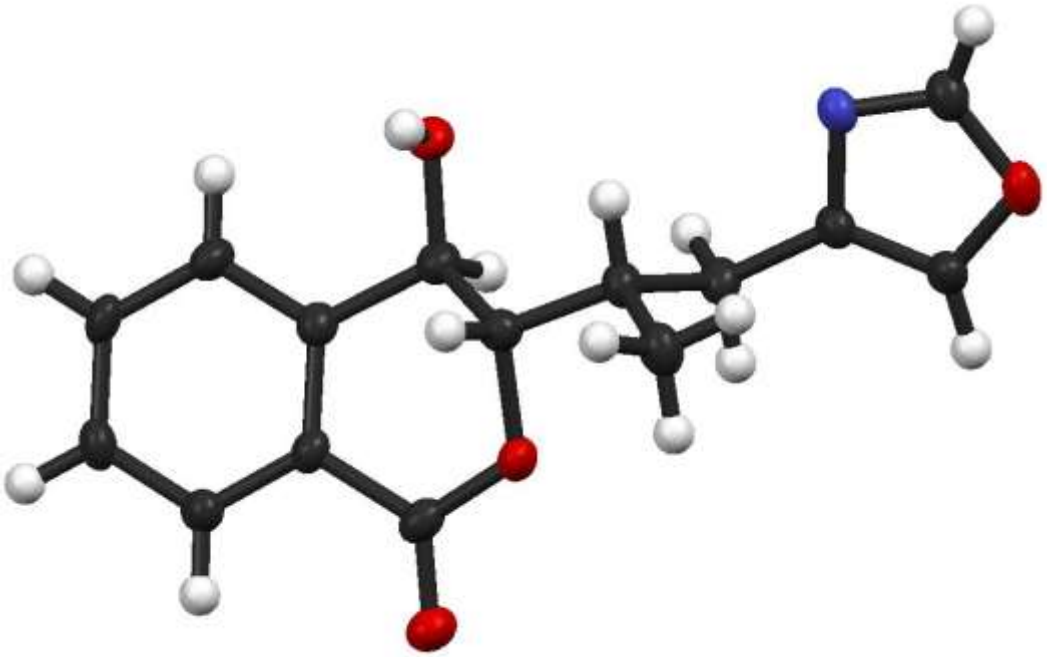


Figure 29 X-Ray Structure of 247

Crystal data for **258**: $C_{22}H_{31}NO_5Si$, M_r=417.57, orthorhombic, $P2_12_12_1$, a=10.7398(3), b=8.2057(2), c=25.4880(9) Å, β=90 °, T=150 K, Z=4, R=0.0391 for 2907 data with $F_0>2\sigma(F)$, $wR2$=0.0919 for 3524 unique data, GOF=1.060. CCDC813670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

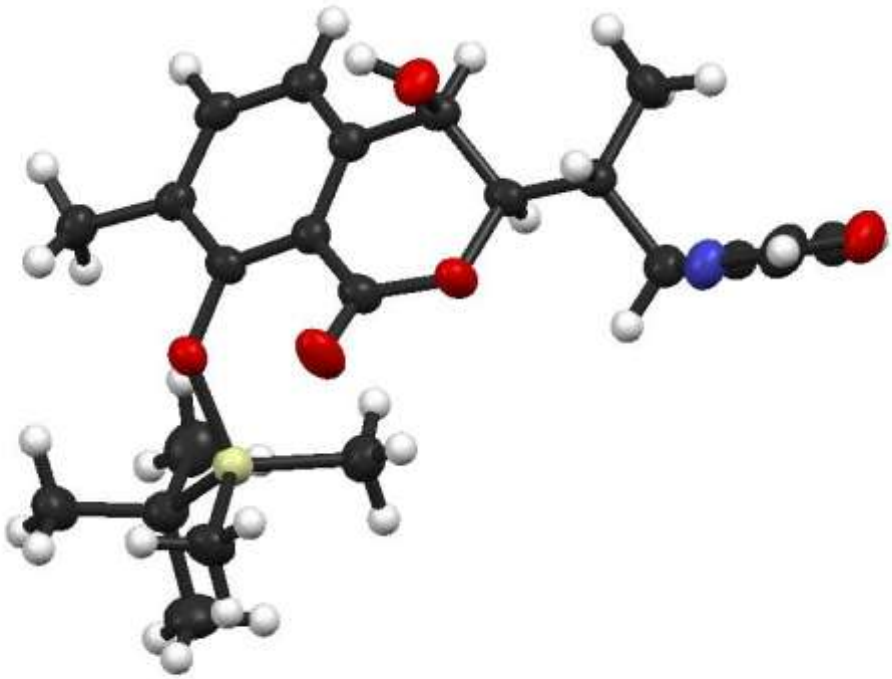


Figure 28 X-Ray Structure of 258

14 References

1. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000,** *39*, 44.
2. Nicolaou, K. C.; Snyder, S. A. *PNAS,* **2004,** *101*, 11929.
3. Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957,** *79*, 1962.
4. Nicolaou, K. C.; Yang, Z.; Shi, G.; Gunzner, J. L.; Agrios, K. A.; Gartner, P. *Nature,* **1998,** *392*, 264.
5. Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994,** *116*, 1597.
6. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature,* **1994,** *367*, 630.
7. Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999,** *5*, 121.
8. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.***1996,** *118*, 2843.
9. Ma, C.; Schiltz, S.; Le Goff, X. F.; Prunet, J. *Chem. Eur. J.* **2008,** *14*, 7314.
10. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010,** *75*, 4657-4673.
11. Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2002**, 917.
12. Reichenbach, H. *J. Ind. Microbiol. Biotechnol.* **2001,** *27*, 149.
13. Kunze, B.; Rolf, J. A.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **2004,** *57*, 151.
14. Wenzel, S. C.; Müller, R. *Mol. BioSyst.* **2009,** *5*, 567.
15. Zepnik, H.; Pahler, A.; Schauer, U.; Dekant, W. *Toxicol. Sci.* **2001,** *59*, 59.
16. Appendino, G.; Ozen, H. C.; Jakupovic, J. *Phytochem.* **1994,** *36*, 531.
17. Dethoup, T.; Manoch, L.; Kijjoa, A.; Pinto, M.; Gales, L.; Damas, A. M.; Silva, A. M. S.; Eaton, G.; Herz, W. *J. Nat. Prod.* **2007,** *70*, 1200.
18. Takahashi, H.; Kosada, M.; Watanabe, Y.; Nakade, K.; Fukuyawa, Y. *Bioorg. Med. Chem.* **2003,** *11*, 1781.
19. Arai, K. O., M; Koizumi, F; Koda, S; Iwasaki, Y; Kanemoto, Y. *US Patent Int. 5530146,* **1996**.
20. Hentemann, M. F.; Allen, J. G.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2000,** *39*, 1937.
21. Chen, J.; Zhou, L.; Tan, C. K.; Yeung, Y. *J. Org. Chem.* **2012,** *77*, 999.
22. Fujita, M.; Mori, K.; Shimogaki, M.; Sugimura, T. *Org. Lett.* **2012,** *14*, 1294.
23. Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem. Int. Ed.* **2010,** *122*, 7222.
24. Kwan, D. H.; Schulz, F. *Molecules,* **2011,** *16*, 6092.
25. Buntin, K. *Angew. Chem. Int. Ed.* **2008,** *47*, 4595.
26. Buntin, K.; Weissman, K. J.; Müller, R. *ChemBioChem,* **2010,** *11*, 1137.
27. Ganame, D.; Quach, T.; Poole, C.; Rizzacasa, M. A. *Tetrahedron Lett.* **2007,** *48*, 5841.
28. Birkett, S.; Ganame, D.; Hawkins, B. C.; Meiries, S. b.; Quach, T.; Rizzacasa, M. A. *Org. Lett.* **2011**, *13*, 1964.

29. Krebs, O.; Taylor, R. J. K. *Org. Lett.* **2005,** *7*, 1063.
30. Normant, J. F.; Bourgain, M. *Tetrahedron Lett.***1971,** *12*, 2583.
31. Furber, M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1.* **1986**, 1809.
32. Smissman, E. E.; Voldeng, A. N. *J. Org. Chem.* **1964,** *29*, 3161.
33. Hobson, S. J.; Parkin, A.; Marquez, R. *Org. Lett.* **2008,** *10*, 2813.
35. Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron,* **1971,** *27*, 1973.
36. Abrams, J. N.; Babu, R. S.; Guo, H.; Le, D.; Le, J.; Osbourn, J. M.; O'Doherty, G. A. *J. Org. Chem.* **2008,** *73*, 1935.
37. Guo, H.; O'Doherty, G. A. *Tetrahedron,* **2008,** *64*, 304.
38. Coombs, T. C.; Lee; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008,** *73*, 882.
39. Constantinou-Kokotou, V.; Couladouros, E. A.; Georgiadis, M. P.; Kokotos, G.; Georgiadis, T. M. *Carbohyd. Res.* **1991,** *222*, 163.
40. Lefebvre, Y. *Tetrahedron Lett.***1972,** *13*, 133.
41. Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989,** *111*, 5902.
42. Haukaas, M. H.; O'Doherty, G. A. *Org. lett.***2002,** *4*, 1771.
43. Takao, K.; Yasui, H.; Yamamoto, S.; Sasaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K. *J. Org. Chem.* **2004,** *69*, 8789.
44. Rodrigo, R. *Tetrahedron,* **1988,** *44*, 2093.
45. Junic, A. S., A; Trinajstic, N;. *J. Heterocycl. Chem.* **1984,** *21*, 273.
46. Chacko, E.; Bornstein, J.; Sardella, D. J. *J. Am. Chem. Soc.* **1977,** *99*, 8248.
47. Dewar, J. S.; Harget, A. J.; Trinajstic, N.; Worley, S. D. *Tetrahedron*, **1970,** *26*, 4505.
48. Warrener, R. N. *J. Am. Chem. Soc.* **1971,** *93*, 2346.
49. Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980,** *26*, 135.
50. Crump, S. L.; Rickborn, B. *J. Org. Chem.* **1984,** *49*, 304.
51. de Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron,* **1992,** *48*, 4863.
52. Thibault, M. E.; Pacarynuk, L. A.; Closson, T. L. L.; Dibble, P. W. *Tetrahedron Lett.* **2001,** *42*, 789.
53. Brown, E. A. *US Patent Int. 3855207,* **1974**.
54. Vivekananda Bhatt, M.; Ramesh Babu, J. *Tetrahedron Lett.* **1984,** *25*, 3497.
55. Zuo, L.; Yao, S.; Wang, W.; Duan, W. *Tetrahedron Lett.* **2008,** *49*, 4054.
56. Katz, C. E.; Ribelin, T.; Withrow, D.; Basseri, Y.; Manukyan, A. K.; Bermudez, A.; Nuera, C. G.; Day, V. W.; Powell, D. R.; Poutsma, J. L.; Aube, J. *J. Org. Chem.* **2008,** *73*, 3318.
57. Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *J. Chem. Ber.* **1956,** *89*, 2060.
58. Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982,** *47*, 5391.
59. Couché, E.; Fkyerat, A.; Tabacchi, R. *Helv. Chim. Acta.* **2003**
    86, 210.
60. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991,** *113*, 7277.
61. Moorthy, J. N.; Singhal, N.; Mal, P. *Tetrahedron Lett.* **2004,** *45*, 309.

62. Pedersen, D. S.; Robinson, T. V.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2009,** *74*, 4400.
63. Buckley, S. L. J.; Harwood, S. L.; Macías-Sánchez, A. J. *ARKIVOC,* **2002,** *8*, 46.
64. Buehler, C. A.; Powers, T. A.; Michels, J. G. *J. Am. Chem. Soc.* **1944,** *66*, 417.
65. Black, M.; Cadogan, J. I. G.; McNab, H. *J. Chem. Soc. Perkin Trans. 1.* **1994**, 155.
66. Duan, M.; Toney, M. D. *Synth. Comm.* **2005,** *35*, 2869.
67. Palmer, D. C.; Venkatraman, S.; . *The Chemistry of Heterocyclic Compounds Volume 60, Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A*, Wiley; New Jersey 2004.
68. Reeves, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007,** *9*, 1875.
69. Lang, S.; Taylor, R. J. K. *Tetrahedron Lett.* **2006,** *47*, 5489.
70. Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998,** *110*, 3047.
71. Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.
72. Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1971**, 383.
73. Anh, N. T.; Eisenstein, O.; Lefour, J.; Tran Huu Dau, M. *J Am. Chem. Soc.* **1973,** *95*, 6146.
74. Klein, J. *Tetrahedron Lett.* **1973**, 4307.
75. Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001,** *3*, 2391.
76. Fukuzawa, S. i.; Nakano, N.; Saitoh, T. *Eur. J. Org. Chem.* **2004,** *2004*, 2863.
77. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998,** *37*, 1986.
78. Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohyd. Res.* **2000,** *328*, 17.
79. Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999,** *64*, 2982.
80. Harris, J. M.; O'Doherty, G. A. *Org. Lett.* **2000,** *2*, 2983.
81. Jackson, K. L.; Henderson, J. A.; Morris, J. C.; Motoyoshi, H.; Phillips, A. J. *Tetrahedron Lett.* **2008,** *49*, 2939.
82. Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron. Lett.* **1978,** *5*, 419.
83. Anastasia, L.; Negishi, E. *In Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002.
84. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry- A Guide to the Synthetic Chemist*; Pergamon Press, 2000.
85. Alberico, D.; Scott, M. E.; Lauten, M. *Chem. Rev.* **2007,** *107*, 174.
86. Liegault, B. T.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009,** *74*, 1826.
87. Verrier, C.; Lassalas, P.; Theveau, L.; Queguiner, G.; Trecourt, F.; Marsais, F.; Hoarau, C. *Bellstein J. Org. Chem* **2011,** *7*, 1584.
88. Hoarau, C.; Kerdaniel, A. D. F.; Bracq, N.; Grandclaucon, P.; Couture, A.; Marsais, F. *Tetrahedron Lett.* **2005,** *46*, 8573.
89. Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998,** *71*, 467.
90. Do, H.; Daugulis, O. *J. Am. Chem. Soc.* **2007,** *129*, 12404.

91. Bellina, F.; Cauteruccio, S.; Rossi, R. *Curr. Org. Chem.* **2008,** *12*, 774.
92. Sánchez, R. S. Z., F. A. *J. Am. Chem. Soc.* **2007,** *129*, 5824.
93. Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009,** *7*, 647.
94. Besselievre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008,** *10*, 4029.
95. Besselièvre, F.; Lebrequier, S.; Mahuteau-Betzer, F.; Piguel, S. *Synthesis,* **2009,** *2009*, 3511.
96. Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991,** *56*, 3058.
97. Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991,** *56*, 449.
98. Crowe, E.; Hossner, F.; Hughes, M. J. *Tetrahedron,* **1995,** *51*, 8889.
99. Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996,** *61*, 5192.
100. Atkins, J. M.; Vedejs, E. *Org. Lett.* **2005,** *7*, 3351.
101. de Lemos, E.; Porée, F.; Bourin, A.; Barbion, J.; Agouridas, E.; Lannou, M.; Commerçon, A.; Betzer, J.; Pancrazi, A.; Ardisson, J. *Chem. Eur. J.* **2008,** *14*, 11092.
102. Peng, L. Z.; Mei, T. S.; Zhang, T.; Li, Y. L. *Chin. Chem. Lett.* **2003,** *14*, 341.
103. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002,** *124*, 6343.
104. Yamanaka, H.; Ohba, S.; Sakamoto, T. *Heterocycles,* **1990,** *31*, 1115.
105. Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009,** *131*, 10386.
106. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987,** *52*, 3413.
107. Iguchi, K.; Kitade, M.; Kashiwagi, T.; Yamada, Y. *J. Org. Chem.* **1993,** *58*, 5680.
108. Hennies, P. T.; Santana, M. H. C.; Correia, C. R. D. *J. Braz. Chem. Soc.* **2001,** *12*, 64.
109. Maleczka Jr, R. E.; Terrell, L. R.; Geng, F.; Ward III, J. S. *Org. Lett.* **2002,** *4*, 2841.
110. Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002,** *67*, 6841.
111. Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2001,** *42*, 3387.
112. Furstner, A.; Larionov, O.; Flugge, S. *Angew. Chem. Int. Ed.* **2007,** *46*, 5545.
113. Tuyet, J. *Tetrahedron Lett.* **1989,** *30*, 2225.
114. Lopez, S.; Fernaįndez-Trillo, F.; Midon, P.; Castedo, L.; Saa, C. *J. Org. Chem.* **2006,** *71*, 2802.
115. Montierth, J. M.; DeMario, D. R.; Kurth, M. J.; Schore, N. E. *Tetrahedron,* **1998,** *54*, 11741.
116. Khrimian, A. *Tetrahedron,* **2005,** *61*, 3651.
117. Meisters, A.; Wailes, P. C. *Aust. J. Chem.* **1960,** *13*, 347.
118. Tani, K.; Ono, N.; Okamoto, S.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1993**, 386.
119. Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990,** *31*, 2397.
120. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987,** *109*, 813.
121. Congreve, M. S.; Holmes, A. B.; Hughes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993,** *115*, 5815.
122. Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429.
123. Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Am. Chem. Soc.* **2009,** *131*, 11678.
124. Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1998,** *120*, 3935.
125. Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001,** *101*, 997.

126. Nicolaou, K. C.; Schlawe, D.; Kim, D. W.; Longbottom, D. A.; Noronha, R. G. d.; Lizos, D. E.; Manam, R. R.; Faulkner, D. J. *Chem. Eur. J.* **2005,** *11*, 6197.
127. Canova, S.; Bellosta, V. r.; Bigot, A.; Mailliet, P.; Mignani, S.; Cossy, J. *Org. Lett.* **2006,** *9*, 145.
128. Tan, Z.; Negishi, E. *Angew. Chem. Int. Ed.* **2004,** *43*, 2911.
129. Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987,** *109*, 1186.
130. McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004,** *45*, 2551.
131. Arda, A.; G. Soengas, R.; Nieto, M. I.; Jimenez, C.; Rodriguez, J. *Org. Lett.* **2008,** *10*, 2175.
132. Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.; Miura, D.; Chokki, M.; Ishizuka, S.; Yamaguchi, K.; Kan, Y.; Kurihara, M.; Miyata, N.; Smith, C.; DeLuca, H. F.; Takayama, H. *J. Med. Chem.***2000,** *43*, 4247.
133. Canova, S.; Bellosta, V.; Bigot, A.; Mailliet, P.; Mignani, S.; Cossy, *J. Org. Lett.* **2007,** *9*, 145.
134. Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Finlay, M. R. V.; Boddy, C. N. C. *Angew. Chem. Int. Ed.* **1998,** *37*, 81.
135. Aoyagi, Y.; Saitoh, Y.; Ueno, T.; Horiguchi, M.; Takeya, K.; Williams, R. M. *J. Org. Chem.* **2003,** *68*, 6899.
136. Jacobsen, E. N.; Markd, I.; Mungall, W. S.; Schrcider, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988,** *110*, 1968.
137. Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem.* **2005,** *70*, 9447.
138. Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron,* **1988,** *44*, 2149.
139. Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011***, 13*, 4164.
140. Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Synth.* **2005,** *81*, 195.
141. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997,** *119*, 6496.
142. Borbas, K. E.; Chandrashaker, V.; Muthiah, C.; Kee, H. L.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2008,** *73*, 3145.
143. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997,** *119*, 6496.
144. White, J. D.; Xu, Q.; Lee, C.; Valeriote, F. A. *Org. Biomol. Chem.* **2004,** *2*, 2092.
145. Crouch, R. D. *Tetrahedron,* **2004,** *60*, 5833.
146. Wang, B.; Forsyth, C. J. *Org. Lett.* **2006,** *8*, 5223.
147. Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994,** *59*, 234.
148. Gomez-Vidal, J. A.; Forrester, M. T.; Silverman, R. B. *Org. Lett.* **2001,** *3*, 2477.
149. Figlus, M.; Tarruella, A. C.; Messer, A.; Sollis, S. L.; Hartley, R. C. *Chem. Comm***.** *46*, 4405.
150. Lipshutz;, B. H.; Chung;, D. W.; Rich;, B.; Corral, R. *Org. Lett.* **2006,** *8*, 5069.
151. Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999,** *40*, 4497.
152. Ley, S. V. *PNAS,* **2004,** *101*, 12073.
153. Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998,** *120*, 8661.
154. Nicolaou, K. C.; Peng, X.-S.; Sun, Y.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009,** *131*, 10587.

155. Egan, B. A.; Paradowski, M.; Thomas, L. H.; Marquez, R. *Org. Lett.* **2011,** *13*, 2086.
156. Egan, B. A.; Paradowski, M.; Thomas, L. H.; Marquez, R. *Tetrahedron,* **2011,** *67*, 9700.
157. Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985,** *107*, 4573.
158. Essig, S.; Bretzke, S.; Muller, R.; Menche, D. *J. Am. Chem. Soc.* **2011**, *134*, 19362.
159. Wulff, G.; Wolf, G. *Chem. Ber.* **1986,** *119*, 1876.
160. Couché, E.; Fkyerat, R.; Tabacchi, R. *Helv. Chim. Acta.* **2003,** *89* 210.
161. Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H. N. *Tetrahedron,* **2003,** *59*, 3201.
162. Cleaver, L.; Nimgirawath, S.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1976,** *29*, 2003.
163. Bourne, D. J.; Barrow, K. D.; Milborrow, B. V. *Phytochem.***1991,** *30*, 4041.
164. Maresh, J.; Zhang, J.; Tzeng, Y.-L.; Goodman, N. A.; Lynn, D. G. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 3281.
165. Billedau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983,** *24*, 4515.
166. Guth, V.; Leitich, J.; Specht, W.; Wessely, F. *Monatsh. Chem.* **1963,** *94*, 1262.
167. Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983,** *48*, 1935.
168. Cannon, J. G.; Koble, D. L.; Long, J. P.; Verimer, T. *J. Med. Chem.* **1980,** *23*, 750.
169. Nguyen, T.; Chau, N. T. T.; Castanet, A.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007,** *72*, 3419.
170. Hoffmann, B.; Lackner, H. *Liebigs. Ann.* **1995,** *1995*, 87.
171. Henneke, K.-W.; Schöllkopf, U.; Neudecker, T. *Liebigs Ann.* **1979,** *1979*, 1370.
172. Chittari, P.; Hamada, Y.; Shioiri, T. *Synlett,* **1998,** 1022.
173. Reeves, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007,** *9*, 1875.
174. Ratier, M.; Khatmi, D.; Duboudin, J. G.; Minh, D. T. *Synth. Comm.* **1989,** *19*, 285.
175. Gupta, A.; Beazley, G.; Lee, J.; Berube, G. *Synth. Comm.* **2007,** *37*, 2031.
176. Doak, B. C.; Scanlon, M. J.; Simpson, J. S. *Org. Lett.* **2011,** *13*, 537.
177. Sabitha, G.; Reddy, C. S.; Srihari, P.; Yadav, J. S. *Synthesis,* **2003,** 2699.
178. Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005,** *7*, 3921.
179. Denmark, S. E.; Yang, S. *J. Am. Chem. Soc.* **2002,** *124*, 2102.
180. Plug, C.; Friedrichsen, W. *J. Prakt. Chem.* **1997**, 205.
181. Borbas, K. E.; Chandrashaker, V.; Muthiah, C.; Kee, H. L.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2008,** *73*, 3145.
182. Berlage, U.; Schmidt, Jr.; Peters, U.; Welzel, P. *Tetrahedron Lett.* **1987,** *28*, 3091.
183. Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977,** *42*, 1329.