Towards the Total Synthesis of Ajudazol B

Liam David Adair MSci

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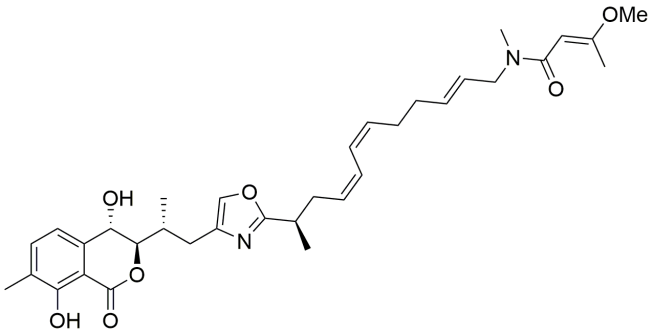
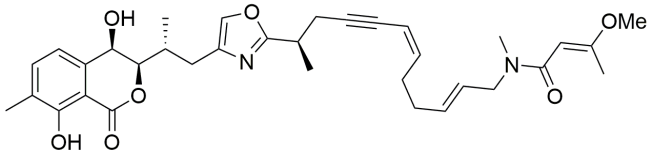
School of Chemistry
College of Science and Engineering
University of Glasgow

ABSTRACT

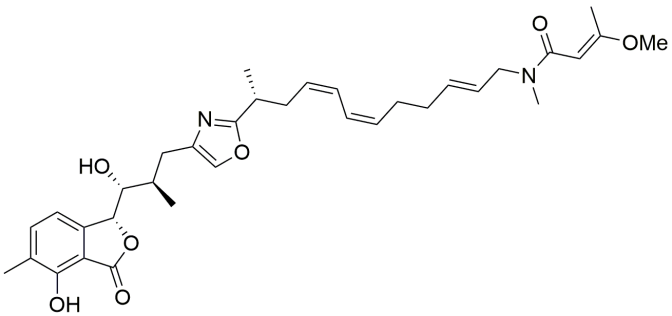
Ajudazol B is a polyketide secondary metabolite, isolated from *Chondromyces crocatus* in 2002, that exhibits anti-fungal activity through potent inhibition of the electron transport chain.



The main objective of the work described in this thesis was to use and expand the oxidative rearrangement of isobenzofurans to generate isochromanones, and apply this towards the total synthesis of ajudazol B. The rearrangement was used as a key step in the synthesis of the full ajudazol B framework. The synthesis was achieved in 20 steps and 11% overall yield.



The isomer of ajudazol B was synthesised in 21 steps and 8% overall yield. Its biological activity remains to be determined.



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I'd like to thank my family and friends, regardless of whether you had any idea what I've been doing for the last four years, without your love, support, and welcomed distractions, I wouldn't have managed to complete my research.

Finally, I'd like to thank Shona for her love, support, and patience.

In memory of Arthur Burgoyne

AUTHOR DECLARATION

This thesis represents the original work of Liam David Adair, unless explicitly stated otherwise in the text. The research upon which it is based was carried out in the Raphael laboratory, University of Glasgow, under the supervision of Dr Rodolfo Marquez and Dr Joëlle Prunet, during the period October 2013 to August 2017.

LIST OF ABBREVIATIONS

BAIB: [Bis(acetoxy)iodo]benzene

br: Broad

Bu: Butyl

BuLi: Butyllithium

CI: Chemical ionization

CSA: Camphor sulfonic acid

Conc.: Concentrated

d: Doublet

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC: *N*,*N*'-Dicyclohexylcarbodiimide

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEPBT: 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one

DIAD: Diisopropyl azodicarboxylate

DIBALH: Diisobutylaluminium hydride

DIPEA: *N*,*N*-Diisopropylethylamine

DMAD: Dimethyl acetylendicarboxylate

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

DMP: Dess-Martin periodinane

DMPS: Dimethylphenyl silyl

DMSO: Dimethyl sulfoxide

DPPA: Diphenylphosphoryl azide

DTBMP: 2,6-Di-*tert*-butyl-4-methylpyridine

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

ESI: Electrospray ionisation

h: Hour

HBPin: Pinacolborane

HBTU: *N*,*N*,*N*',*N*'-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate

HOBt: hydroxybenzotriazole

HPLC: High performance liquid chromatography

HRMS: high resolution mass spectrometry

IBX: 2-Iodoxybenzoic acid

Imid.: Imidazole

IR: Infrared

KHMDS: Potassium bis(trimethylsilyl)amide

LDA: Lithium diisopropylamide

m: Multiplet

*m*CPBA: *meta*-Chloroperoxybenzoic acid

min: Minutes

MsCl: Methanesulfonyl chloride

MW: Microwave

NADH: Nicotinamide adenine dinucleotide

NBS: *N*-Bromosuccinimide

NBSH: 2-Nitrobenzenesulfonylhydrazide

NIS: *N*-Iodosuccinimide

NMO: *N*-Methylmorpholine-*N*-oxide

NMR: Nuclear magnetic resonance

PCC: Pyridinium chlorochromate

PMB: *p*-Methoxybenzyl

PPTS: Pyridinium *p*-toluenesulfonate

PTSA: *p*-Toluenesulfonic acid

q: quartet

rt: Room temperature

s: singlet

SCX: Strong cation exchange

t: triplet

TASF: tris(Dimethylamino)sulfonium difluorotrimethylsilicate

TBAF: Tetra-*n*-butylammonium fluoride

TBDPS: *tert*-Butyldiphenyl silyl

TBS: *tert*-Butyldimethyl silyl

TEMPO: (2,2,6,6-Tetramethylpiperidin-1-yl)oxy

TES: Triethylsilyl

TESOTf: Triethylsilyl trifluoromethanesulfonate

TFA: Trifluoroacetic acid

TFE: Trifluoroethanol

THF: Tetrahydrofuran

THP: Tetrahydropyran

TIPS: Triisopropyl silyl

TLC: Thin layer chromatography

TMEDA: Tetramethylethylenediamine

TMS: Trimethylsilyl

TPAP: Tetra-*n*-propylammonium perruthenate

TsOH: *p*-Toluenesulfonic acid

µL: Microlitre

1 INTRODUCTION

1.1 MYXOBACTERIA

Myxobacteria are an order of Gram-negative bacteria that have been studied extensively.[1] They are ubiquitous, but are often found in areas possessing high levels of microbial life and organic matter: decomposing plant material, animal dung, soil, and in the bark of living or dead trees. They are particularly prevalent in warm and semi-arid climates, but have even been isolated from marine environments.[2]

They are discernible from other bacteria in two main ways: the cells move over the surface of, or within, the substrate they are grown in, by 'gliding' in swarms; and, secondly, under starvation conditions the cells aggregate and generate fruiting bodies consisting of 10^5 - 10^6 cells. Within these fruiting bodies, the cells are transformed into desiccation resistant myxospores and the fruiting body ensures that a new life cycle is initiated by a community of cells, as opposed to a singular individual.[1, 3]

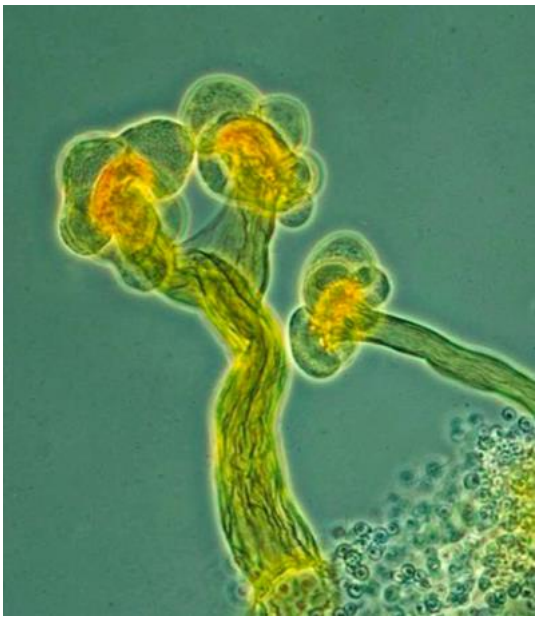
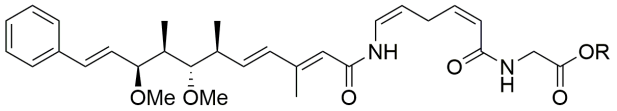


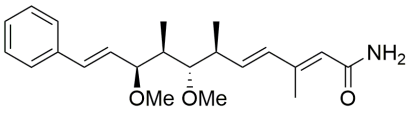
Figure 1.1: Chondromyces crocatus fruiting bodies.

Myxobacteria have long been studied as a rich source of novel secondary metabolites.[4] The microbes are attractive targets for drug discovery due to the wide assortment of metabolites they produce.[5] *C. crocatus* is particularly renowned for its anti-fungal and cytotoxic activities, which have been attributed to the large number of structurally diverse secondary metabolites it generates. Notable biologically active secondary metabolites isolated from

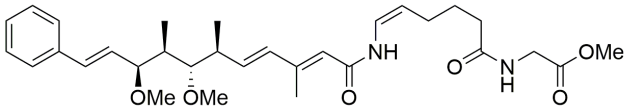
C.crocatus, as well as the ajudazols, include: the crocacins, unsual linear dipeptides possessing anti-fungal and cytotoxic antibiotic properties; the chondramides, cyclodepsipeptides that exhibit cytostatic activity against mammalian cell lines by interference with actin; chondrochlorens, anti-bacterial β-aminostyrenes; and the thuggacins, thiazole-containing macrolides possessing activity against *Mycobacterium tuberculosis*.[6-9]



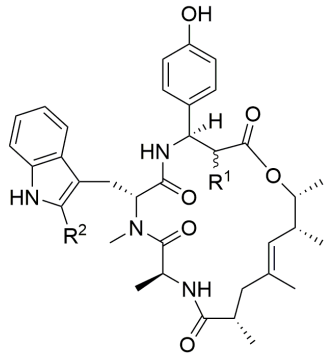
Crocacin A (**1**): R = Me
Crocacin B (**2**): R = H



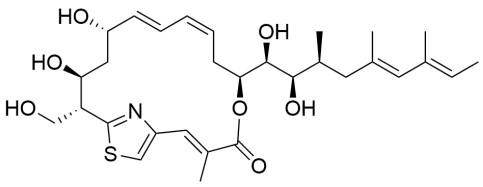
Crocacin C (**3**)



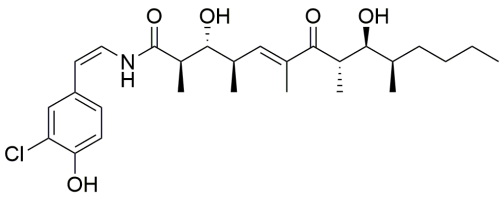
Crocacin D (**4**)



Chondramide A (**6**): R^1 = OMe, R^2 = H
Chondramide B (**7**): R^1 = OMe, R^2 = Cl
Chondramide C (**8**): R^1 = H, R^2 = H
Chondramide D (**9**): R^1 = H, R^2 = Cl



Thuggacin A (**5**)



Chondrochloren A (**10**): R = Me
Chondrochloren B (**11**): R = Et

Figure 1.2: Biologically active secondary metabolites isolated from Chondromyces crocatus.

The genome sequence of *C. crocatus* Cm c5 was reported in 2016, and represents one of the largest prokaryotic genomes. Containing an abundance of secondary metabolite biosynthetic gene clusters, including the known pathways of the ajudazol, crocacin, chondramide, chondrocloren, and thuggacin families, *C. crocatus* Cm c5 also contains many more

biosynthetic gene clusters bearing no significant sequence similarity to known bacterial genomes, so there is a high potential for discovery of more biologically active secondary metabolites.[10] This potential was exemplified by the discovery of the crocagins, biologically active novel polycyclic peptides containing a tetrahydropyrrolo[2,3-*b*] indoline core, unprecedented in bacterial natural products.[11]

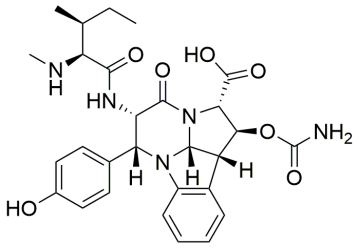


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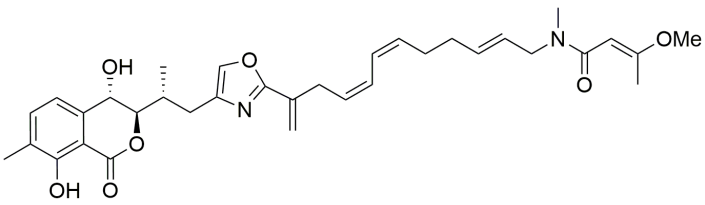
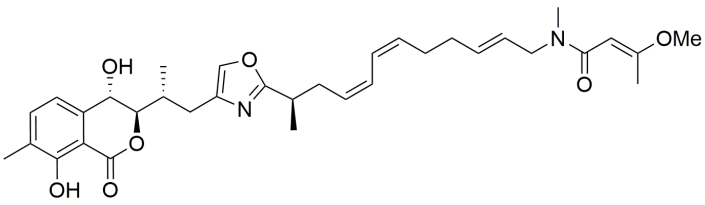
Figure 1.3: Crocagin A.

1.2 AJUDAZOL A AND B

Ajudazol A and B are structurally novel, biologically active, secondary metabolites, isolated in 2002, by Höfle and co-workers, from *Chondromyces crocatus*, a strain of myxobacteria.[12]



Ajudazol A (**13**)



Ajudazol B (**14**)

Figure 1.4: The ajudazols.

Structurally, the ajudazols represent a unique class of compounds. The isochroman-1-one core contains a hydroxy group at C8 and an extended side chain at C9. The side chain

possesses an oxazole, *Z,Z*-diene, *E*-olefin, and a (*E*)-3-methoxy-*N*-methylbut-2-enamide. The (*E*)-3-methoxy-*N*-methylbut-2-enamide moiety is an uncommon motif in natural products, and has only been reported in lyngbyapeptin A and the recently isolated biakamides C and D.[13, 14] The *anti,anti*-configured 8-hydroxyisochroman-1-one core is unique to the ajudazols.

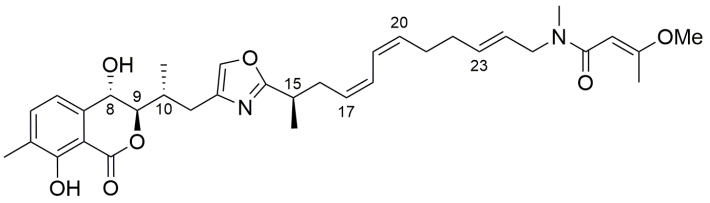


Figure 1.5: Ajudazol B.

1.3 BIOLOGICAL ACTIVITY

Ajudazol A **13**, the major metabolite, only showed weak activity against a few types of fungi and bacteria. As well as displaying activity against Gram-positive bacteria, ajudazol B possesses anti-fungal properties. Ajudazol B **14** was shown to inhibit the growth of several important fungi, that affect various agricultural and horticultural crops including *Botrytis cinera*, *Trichoderma koningii*, *Gibberella fujikori*, and *Ustilago maydis*.[15]

The ajudazols demonstrate potent inhibition of the mitochondrial respiratory chain, with an IC_{50} value of 13.0 ng/mL (22.0 nM) for ajudazol A and 10.9 ng/mL (18.4 nM) in the case of ajudazol B, in submitochondrial particles.[15] Ajudazol B selectively binds to NADH-dehydrogenase, complex I.

The aerobic production of energy *via* the mitochondrial respiratory chain is a key regulatory mechanism in an extensive assortment of cellular processes, and along with myxothiazol, stigmatellin, and crocacin D, the ajudazols are the fourth class of compounds isolated from myxobacteria to inhibit the electron transport chain.[6, 16, 17]

Most recently, Menche identified ajudazol B as being an effective inhibitor of 5-lipoxygenase.[18]

1.4 BIOSYNTHESIS OF THE AJUDAZOLS

The gene cluster involved in the biosynthesis of the ajudazols was identified by Müller and coworkers.[19, 20] It consists of a hybrid type I polyketide synthase (PKS) nonribosomal peptide synthetase (NRPS) multienzyme assembly line. These large, multimodular enzyme complexes synthesise natural products from acyl-coenzyme A thioester and amino acid components, in a stepwise fashion. Each module contains: a domain for selecting and loading the correct monomer; a carrier protein domain, which holds the monomer *via* a thioester link; and a catalytic domain that mediates chain extension by either C-C bond formation or C-N amide bond formation.[21] The vast structural diversity of polyketides is due to the wide range of organic acid substrates used by PKSs.[22]

During the biosynthesis of the ajudazols, the growing chain passes through 13 of these modules, with various domains that introduce the functionality present, until the chain reaches the termination stage. The ajudazols biosynthetic apparatus lacks a terminal cyclase, and instead contains a single, variant thioesterase (TE) domain. Upon reaching the end of the PKS-NRPS assembly line, the extended ajudazol chain *trans*-acylates onto the serine residue of AjuTE. Müller demonstrated that the isochromanone formation was mediated by this unusual thioesterase, AjuTE (figure 1.6).[20]

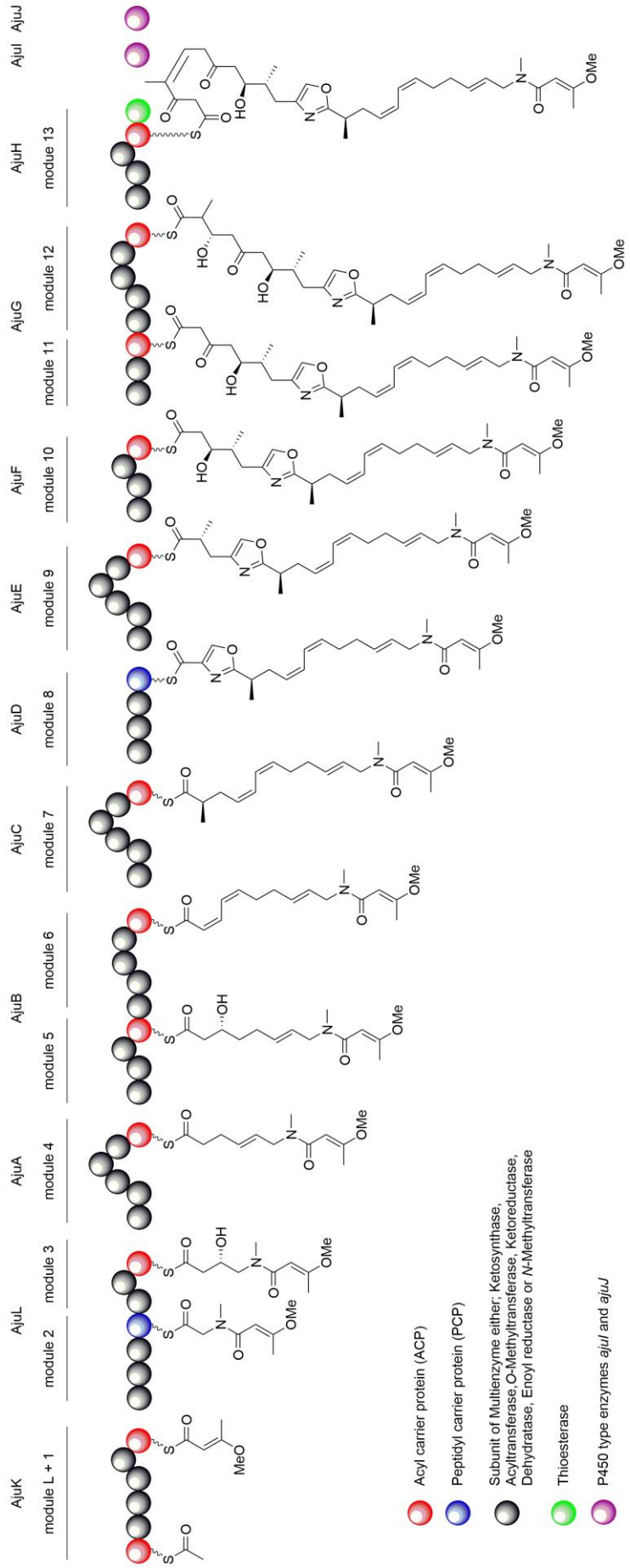
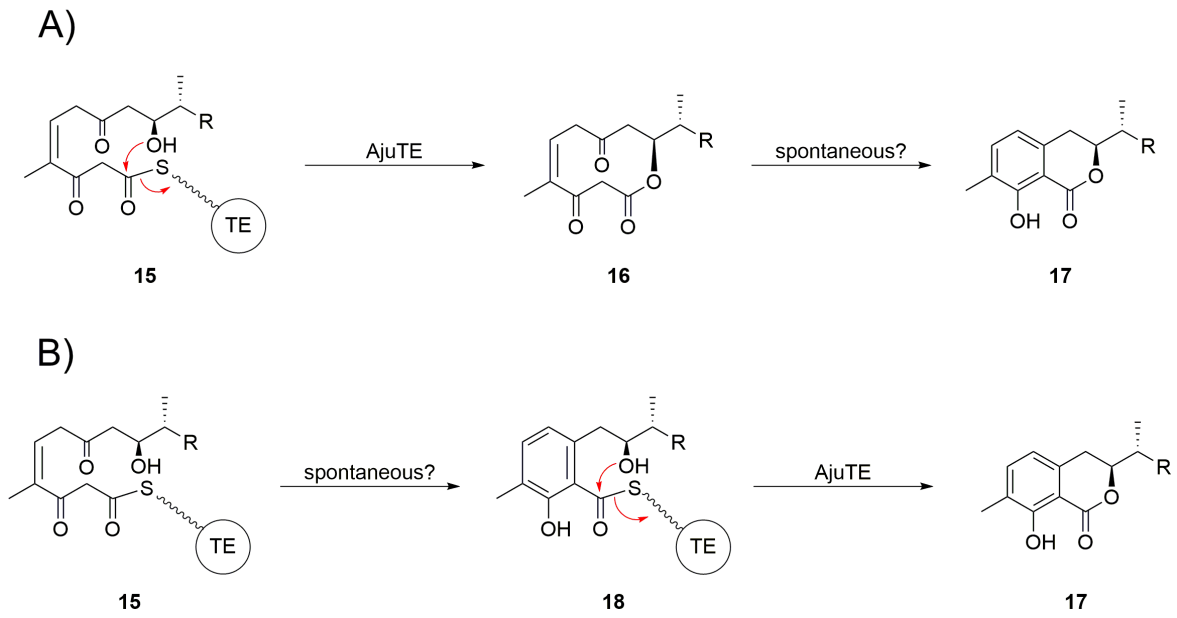


Figure 1.6: Biosynthesis on the ajudazol mixed PKS–NRPS synthetase.[20]

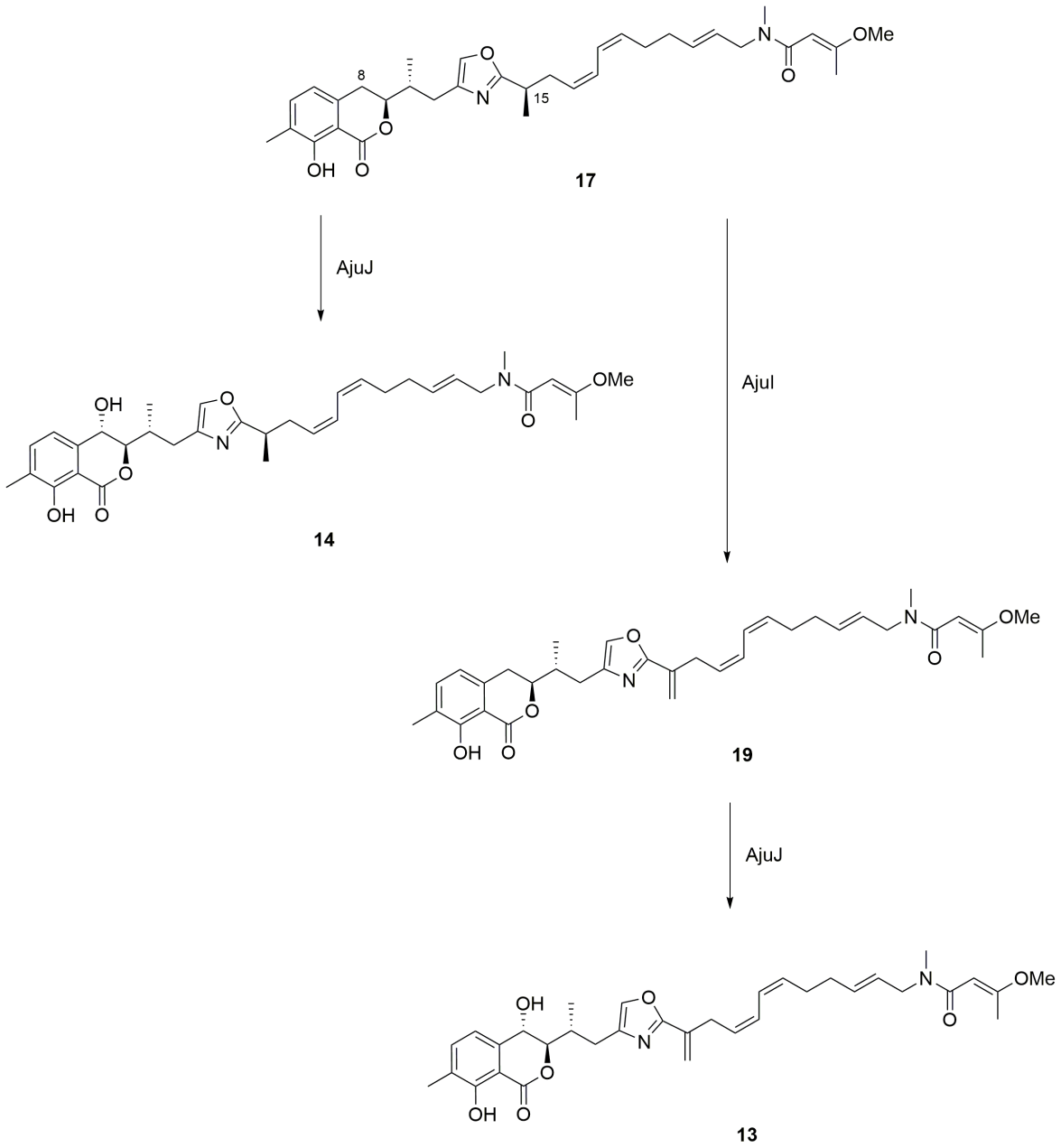
The mechanism for formation of the isochromanone moiety of the ajudazols could follow two potential pathways. AjuTE catalysed nucleophilic attack of the C9 hydroxy group, giving a ten-membered lactone intermediate **16**, and chain release, followed by intramolecular aldol condensation and aromatisation could give deshydroxyajudazol B **17**. Alternatively, intramolecular aldol condensation and aromatisation takes place whilst the chain is still bound to the enzyme giving intermediate **18**, followed by the TE catalysed nucleophilic attack and cleavage, generating the lactone of deshydroxajudazol B **17** (scheme 1.1).[19, 20]



Scheme 1.1: Proposed mechanisms of chain release and isochromanone formation in ajudazol biosynthesis.

Ajudazol A and ajudazol B, share the same PKS-NRPS assembly line, and the same AjuTE catalysed isochromanone formation and chain release, resulting in the generation of the shared putative intermediate deshydroxyajudazol B **17**. There are then post-PKS modifications, installing the C8 hydroxy group, and in the case of ajudazol A the *exo*-methylene at C15.

The enzymes responsible for these transformations are AjuI and AjuJ, and they bear significant homology to P_{450} enzymes. AjuI was discovered to carry out the dehydrogenation of the methyl group at C15, and AjuJ installed the hydroxy group. This results in two possible pathways: when AjuI acts first, followed by AjuJ the final metabolite formed is ajudazol A; when AjuJ acts first, this results in ajudazol B **14**, which is no longer a suitable substrate for AjuI, which therefore does not carry out the dehydrogenation. Ajudazol A **13** is the major metabolite isolated, which implies that AjuI is the more efficient enzyme (scheme 1.2).[19, 20]



Scheme 1.2: Post-PKS modifications in the biosynthesis of the ajudazols.

1.5 ABSOLUTE STEREOCHEMISTRY

Despite being isolated in 2002, due to the lack of comparable natural products, the lability of the compounds, and the inherent difficulty of assigning isolated methyl stereocentres, the absolute stereochemistry of the ajudazols was not determined until 2012, by Menche.[12, 23] Menche's determination was based on a bioinformatics approach, involving gene cluster analysis.

It was postulated that the stereochemistry at C9 is derived from a ketoreductase mediated process. McDaniel and Caffrey both proposed a model in which the presence or absence of an aspartate residue in the keto-reductase enzyme could be used to predict the configuration

of secondary alcohols.[24, 25] Analysis of the amino acid sequence of ajudazol keto-reductase enzyme KR10, coded in the AjuF gene cluster, showed the presence of the aspartate residue allowing Menche to assign the configuration of C9 as *R*.

The configuration of the methyl groups at C10 and C15 are determined by enoyl-reductase mediated reactions. Leadlay and coworkers discovered a correlation between the stereochemistry of a methyl group introduced by an enoyl-reductase enzyme and the presence of a tyrosine residue in the active site of the enzyme.[26] The amino acid sequence of the enoylreductases, AjuC ER7 and AjuE ER9, revealed that the tyrosine residue was absent in each case, allowing the two methyl bearing stereocentres at C10 and C15 to be assigned as *R*.

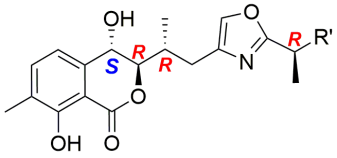


Figure 1.7: Ajudazol B absolute configuration.

1.6 EFFORTS TOWARDS THE SYNTHESIS OF THE AJUDAZOLS

The ajudazol's unusual structural features, combined with their potent biological activity, has made them desirable targets for synthetic chemists. Several research groups have published their approaches towards the Ajudazols, and to date only one group has completed the total synthesis of ajudazol B.[18, 23, 27-31]

1.6.1 Taylor's synthesis of the eastern section

In 2005, Taylor reported the synthesis of the C12-C29 fragment of ajudazol A. His approach hinged on a one pot double acetylene carbocupration to generate the *Z,Z*-diene, and a Stille-coupling to introduce the oxazole unit.[30]

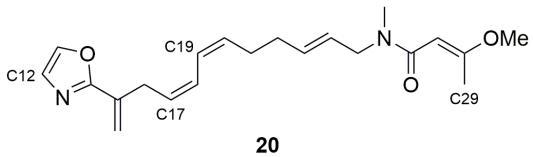


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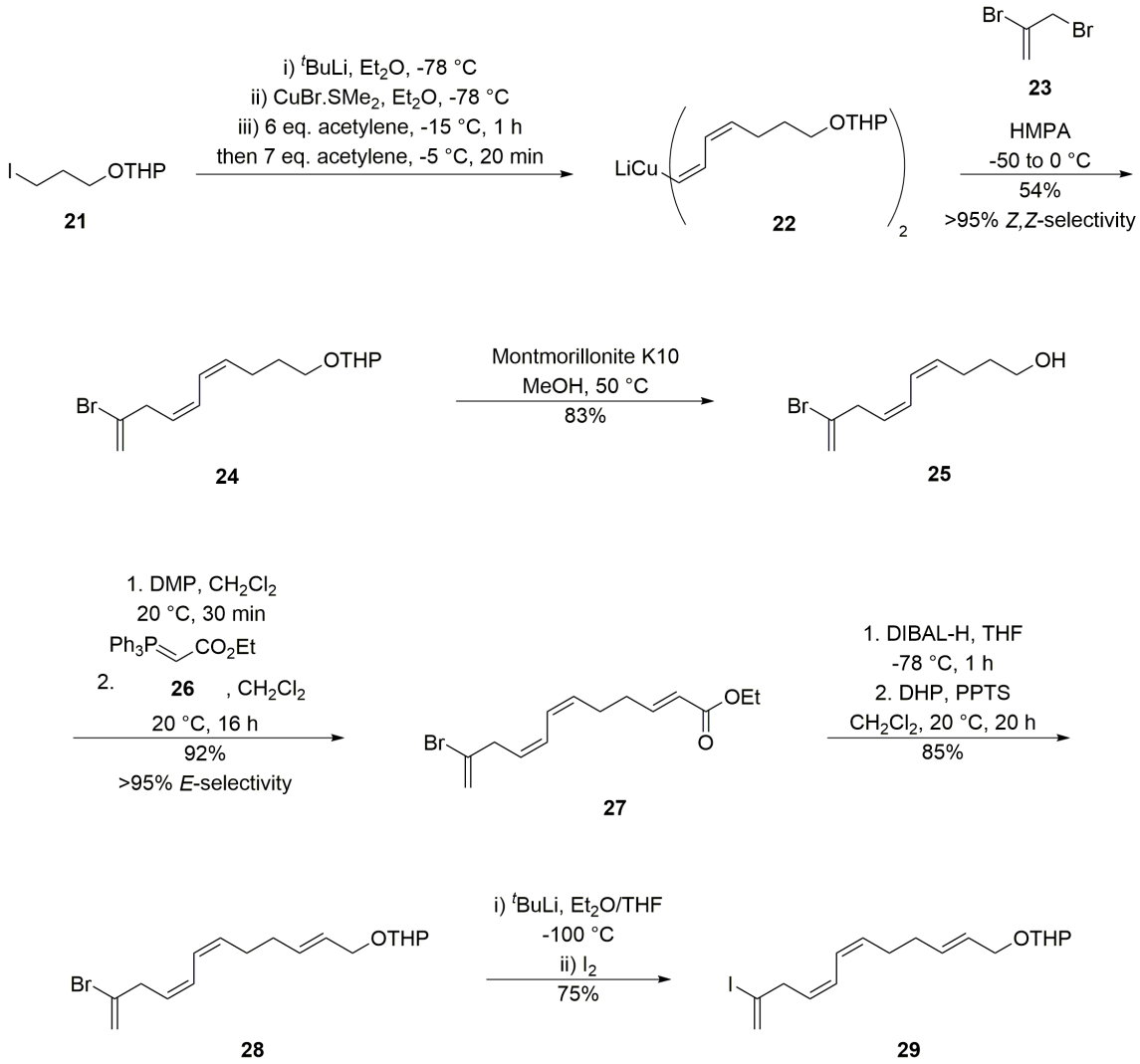
Figure 1.8: C12-C29 fragment of ajudazol A.

Taylor's synthesis began with the stereocontrolled double acetylene carbocupration of THP-protected 3-iodopropanol **21**, to generate dienyl cuprate **22**, which was treated with 2,3-dibromopropene **23**, to afford the *Z,Z*-diene **24** in 55% yield and excellent *Z,Z*-selectivity

(>95%). The THP protecting group was then removed to give the free alcohol **25**, which was then oxidized using Dess-Martin periodinane, to the corresponding aldehyde. Wittig olefination of the aldehyde intermediate then produced the *E*-configured α,β-unsaturated ester **27**, in excellent yield. Ester **27** was reduced to the primary alcohol using DIBAL-H, and the resulting alcohol protected as the THP ether **28**.

Using a vinyl bromide as a coupling partner in the final Stille cross-coupling had been shown in model systems to be non-viable, as the bromide was not sufficiently reactive. Therefore, vinyl bromide **28** was converted to the vinyl iodide **29**, through a lithium-halogen exchange (scheme 1.3).

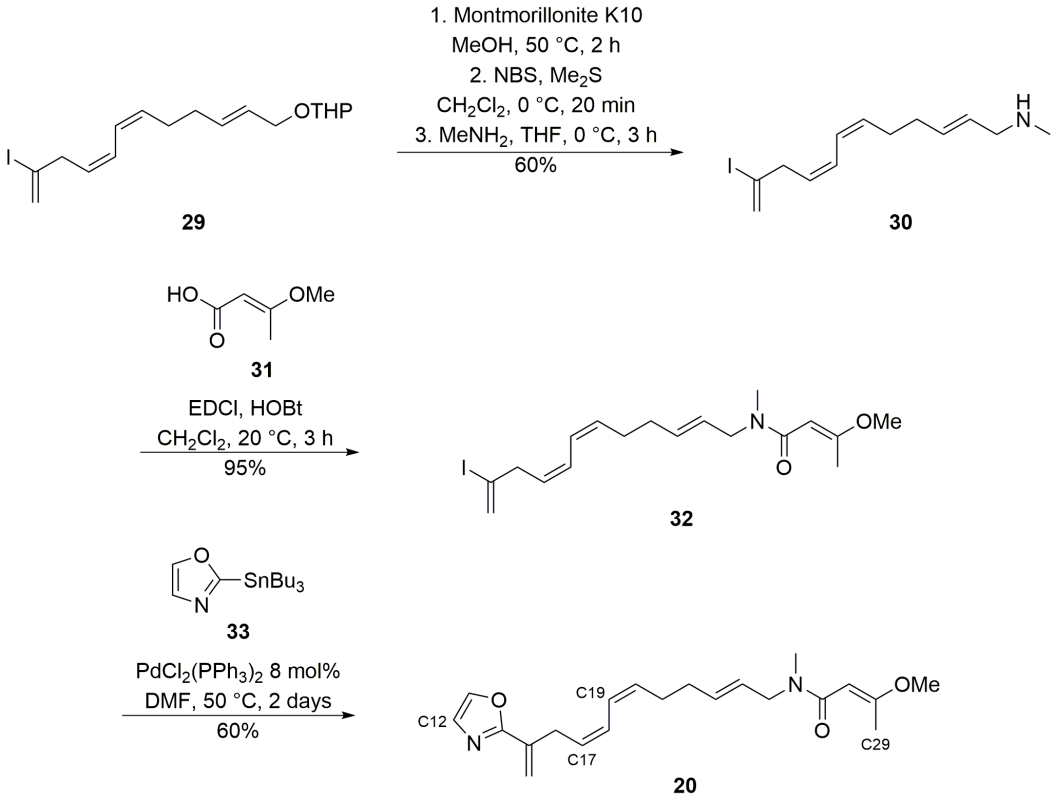


Scheme 1.3: Taylor's synthesis of polyene **29**.

The THP unit on vinyl iodide **29** was then removed and the resultant alcohol was converted to the corresponding bromide, which upon treatment with an excess of methylamine gave amine **30**. Peptide coupling between amine **30** and the known acid **31**, completed the synthesis of the eastern unit of ajudazol A.[32] Stille coupling of stannyl oxazole **33** with vinyl

iodide **32** was then successfully used to complete the synthesis of the C12-C29 fragment of ajudazol A **20** (scheme 1.4).

It is worth noting that optimal results were obtained for the Stille cross-coupling using a relatively low temperature of 50 °C, and a long reaction time of 2 days. However, these conditions were essential, as the diene was unstable at elevated temperatures.



Scheme 1.4: Taylor's completion of synthesis of C12-C29 fragment of ajudazol A **20**.

1.6.2 Rizzacasa's synthesis of the C9-C29 fragment of the ajudazols

Rizzacasa published a route to the C9-C29 fragments of both ajudazol A and B in 2007. The key steps of the synthesis comprise of a cyclodehydration step to form the oxazole unit, and a P2-Ni mediated partial alkyne reduction to install the *Z*-alkene at C17-C18. Rizzacasa's and Taylor's fragments differ only by the addition of an alkoxide tether, at the 4-position of the oxazole moiety (figure 1.9).[29]

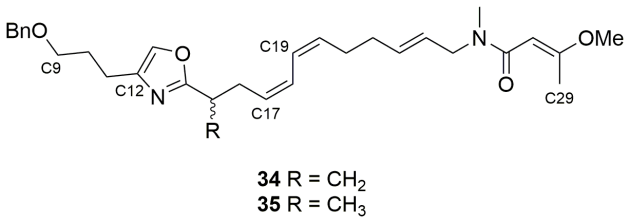
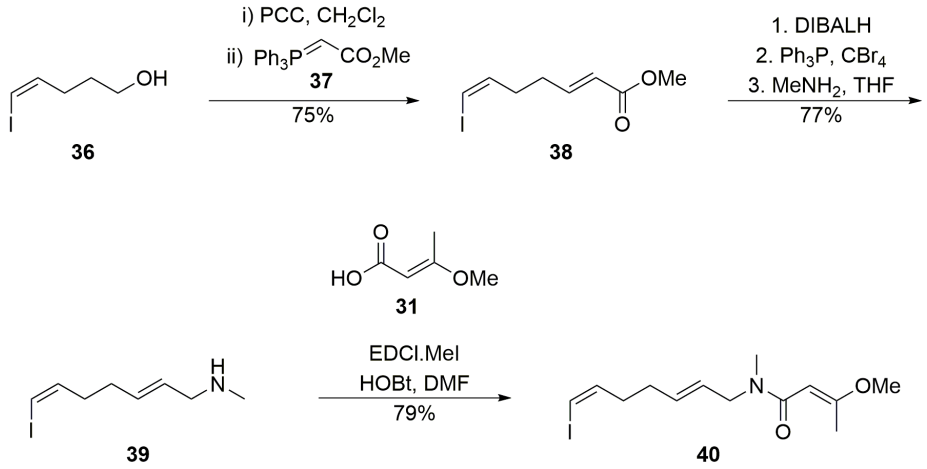


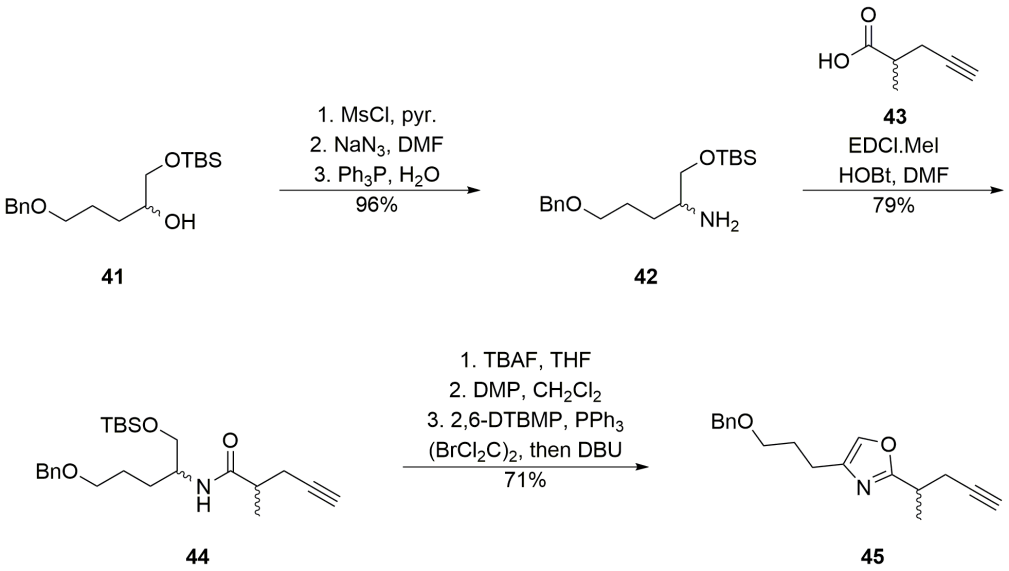
Figure 1.9: Rizzacasa's C9-C29 fragments of ajudazol A and B.

Rizzacasa's synthesis began with the known alcohol **36**, which was oxidized to the corresponding aldehyde, that was then subjected to an *E*-selective Wittig olefination to give *α,β*-unsaturated methyl ester **38**. Reduction of ester **38**, followed by conversion of the resultant alcohol to the bromide, and then displacement of the bromide with methylamine gave the desired amine **39** in good yield, over 3 steps. Acid **31** (prepared in the same manner as Taylor), was then coupled to the amine to afford vinyl iodide **40** (scheme 1.5).



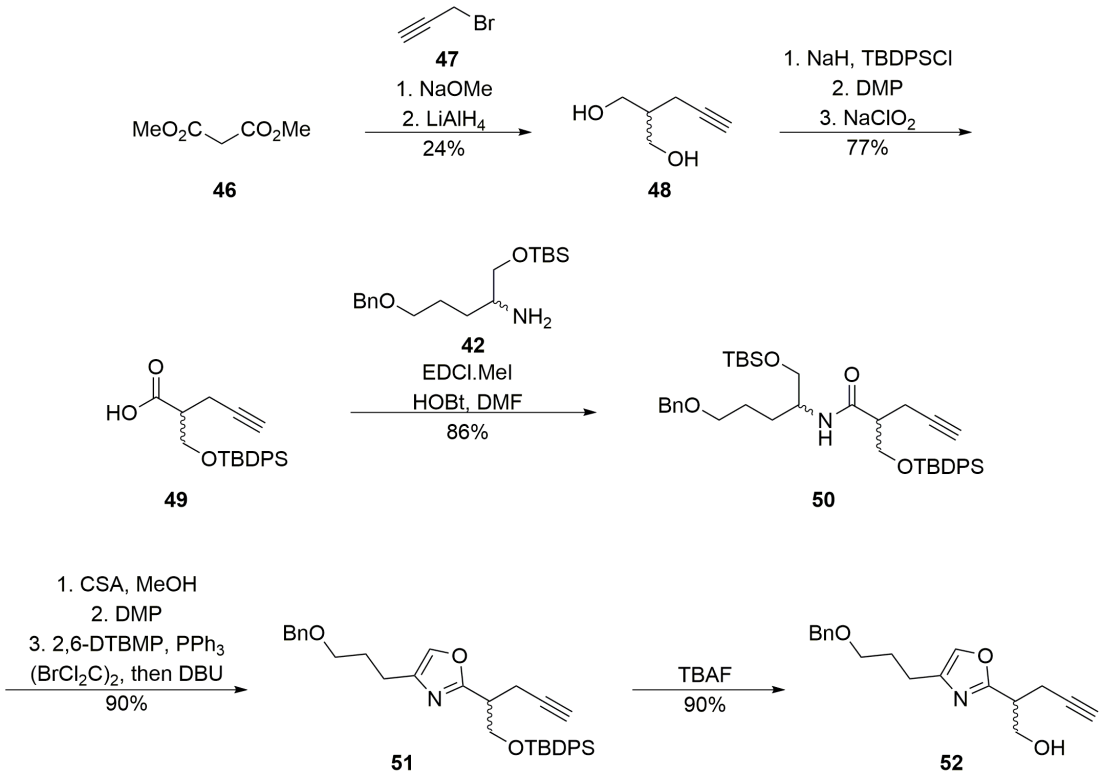
Scheme 1.5: Rizzacasa's synthesis of vinyl iodide **40**.

Synthesis of the racemic acetylene fragment **45**, to be used as a model for ajudazol B, began with the known racemic alcohol **41**.[33] Alcohol **41** was converted to the corresponding amine by conversion to the mesylate, which was then displaced using sodium azide, followed by a Staudinger reduction to give the desired adduct **42** in excellent yield. Amine **42** was then coupled to racemic acid **43** to give the amide product **44**, which was isolated as a mixture of diastereomers. Deprotection of silyl ether **44** using TBAF gave the *β*-hydroxy amide, which upon Dess-Martin oxidation, followed by cyclodehydration under Wipf's conditions yielded oxazole **45** (scheme 1.6).[34, 35]



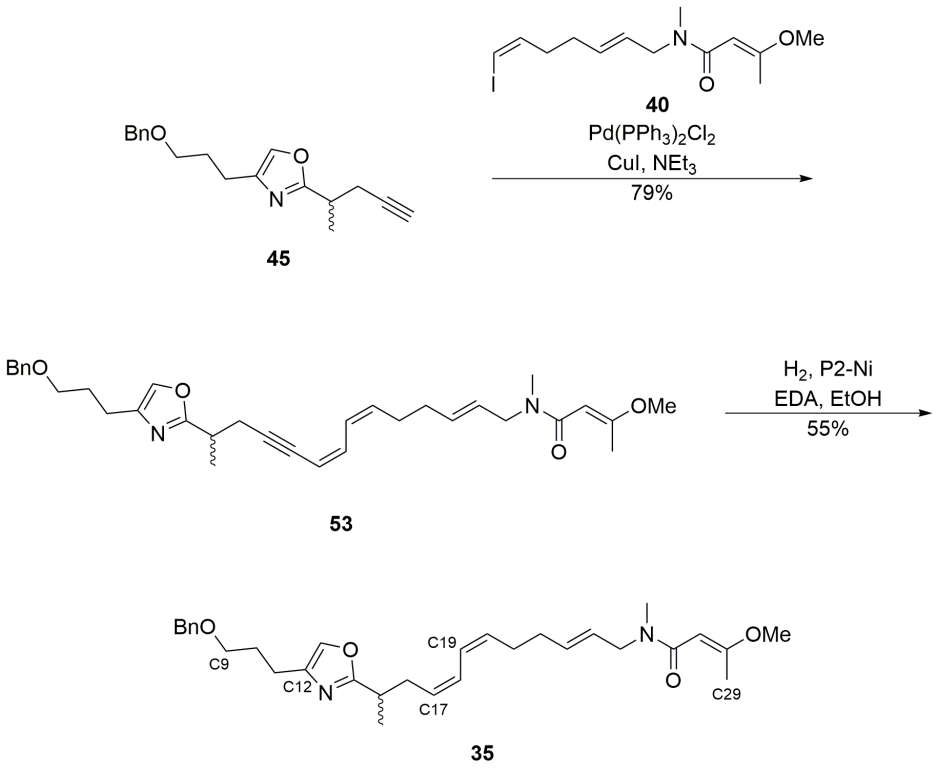
Scheme 1.6: Rizzacasa's synthesis of the ajudazol B model oxazole **45**.

Rizzacasa's synthesis of the oxazole model for ajudazol A, began with dimethyl malonate **46** which was alkylated and then reduced to diol **48**. Mono-protection of diol **48**, followed by two-step oxidation gave the corresponding acid **49**. Peptide coupling between carboxylic acid **49** and amine **42** afforded the key amide **50**. Removal of the TBS protecting group produced the desired alcohol, which was oxidised to the corresponding aldehyde. The aldehyde intermediate was then subjected to the previously employed cyclodehydration conditions to generate oxazole **51**. Finally, desilylation using TBAF completed the synthesis of acetylene **52** (scheme 1.7).



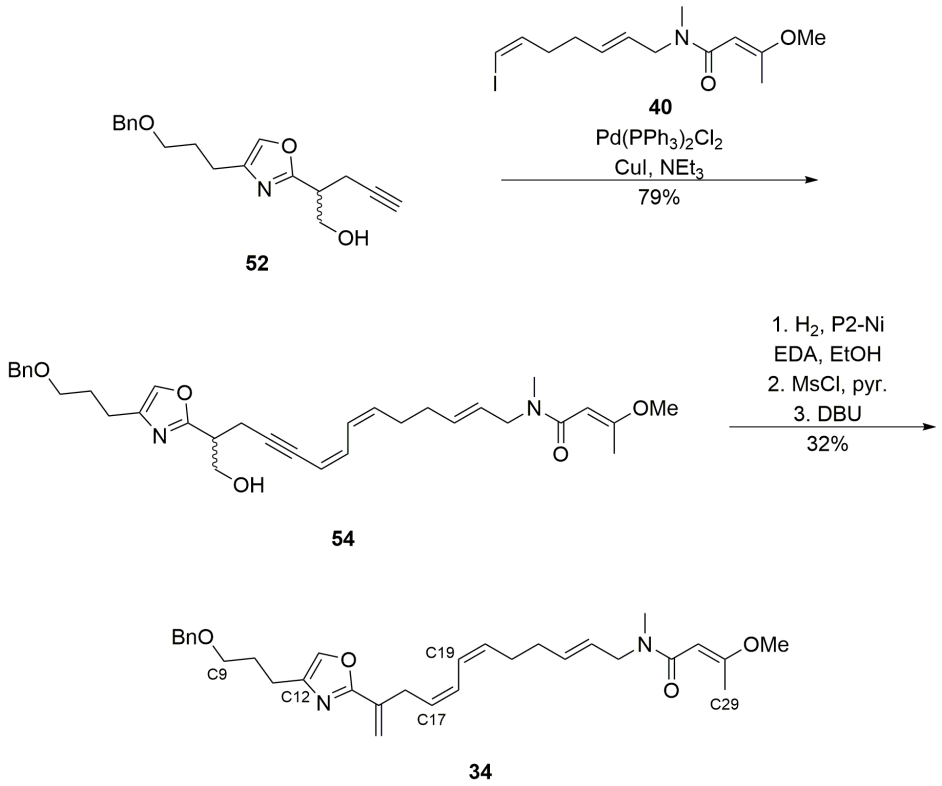
Scheme 1.7: Rizzacasa's synthesis of the ajudazol A model oxazole **52**.

With vinyl iodide **40** and acetylene **45** in hand, the crucial C18-C19 bond was successfully formed using a Sonogashira coupling to give enyne **53** in good yield. The partial reduction of the C17-C18 triple bond, on the other hand, proved to be challenging. Lindlar's catalyst in the presence of hydrogen gas gave no reaction, and prolonged reaction times gave over-reduction of the C17-C18 alkyne. Using Brown's P2-Ni catalyst, on the other hand, gave the desired *Z*,*Z*-diene **35** in 55% yield, completing the synthesis of the racemic C9-C29 fragment of ajudazol B.[36] Rizzacasa reported the synthesis of both enantiomers of oxazole **45** to demonstrate that the synthesis could be carried out enantioselectively (scheme 1.8).



Scheme 1.8: Rizzacasa's synthesis of C9-C29 fragment of ajudazol B **35**.

The synthesis of the ajudazol A model unit was completed following a similar approach to that for the ajudazol B fragment. Namely, alkyne **52** was coupled with vinyl iodide **40** using Sonogashira conditions, followed by partial reduction of the enyne unit **54** using P2-Ni. The disubstituted olefin was introduced *via* activation of the free alcohol as the mesylate, which was then eliminated, thus completing the synthesis of the C9-C29 ajudazol A fragment **34** (scheme 1.9).



Scheme 1.9: Rizzacasa's synthesis of C9-C29 fragment of ajudazol A **34**.

1.6.3 Rizzacasa's synthesis of of 8-deshydroxyajudazol B stereoisomer 55

In 2011, before the absolute configuration of the ajudazols had been determined, Rizzacasa published the synthesis of the proposed structure of 8-deshydroxyajudazol B (C15-epi-enantiomer). 8-Deshydroxyajudazol is a putative late-stage intermediate in the biosynthesis of ajudazol B, as proposed by Müller.[19]

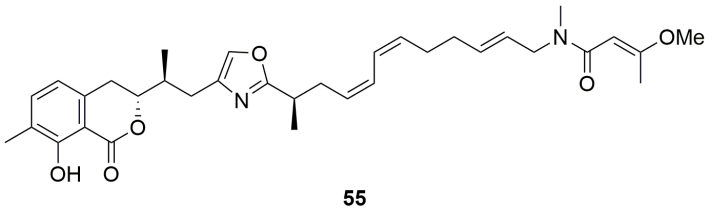
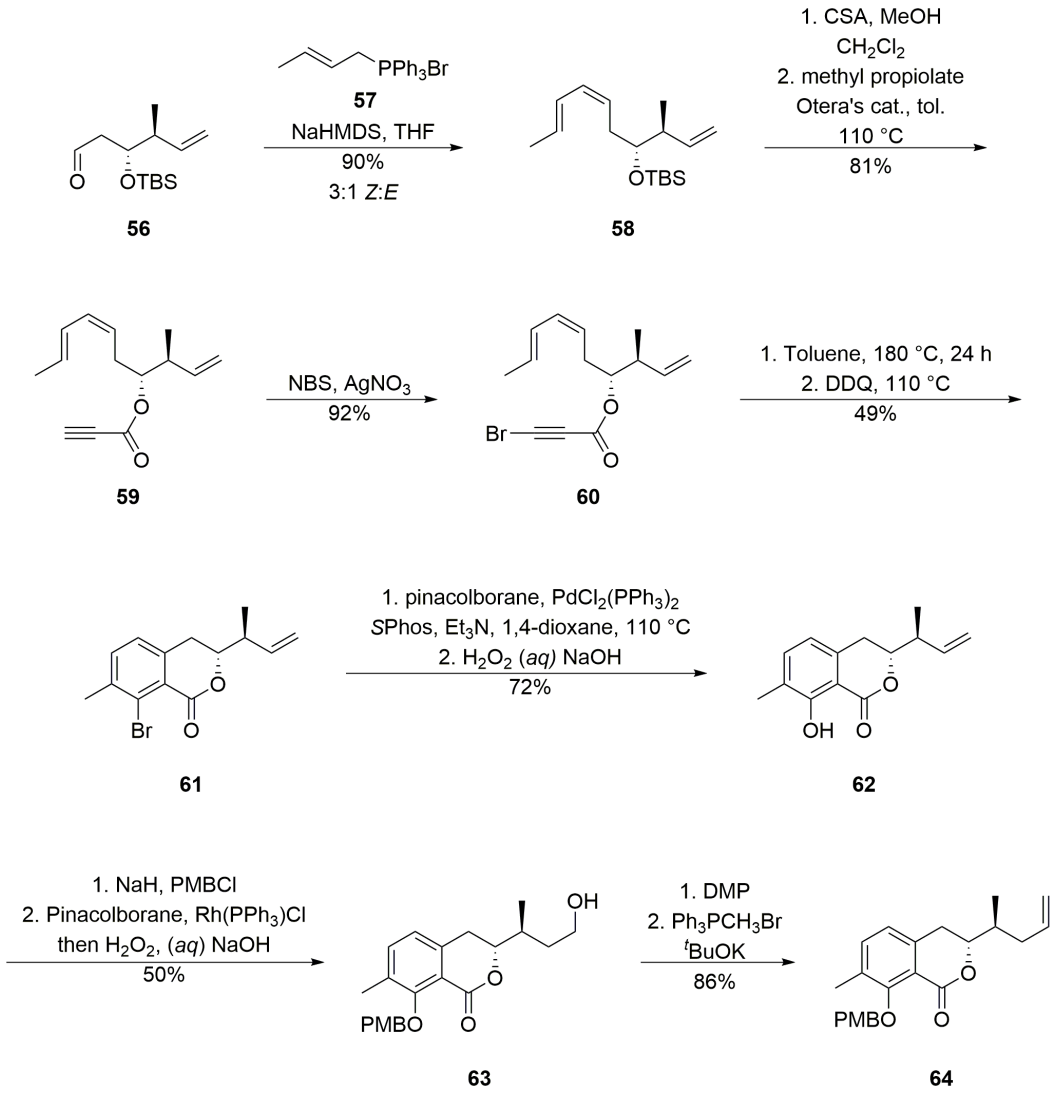


Figure 1.10: 8-Deshydroxyajudazol B stereoisomer **55**.

The synthesis began with the enantiopure, known aldehyde **56**, which upon Wittig olefination gave triene **58** as a 3:1 mixture favouring the *Z*,*E*-diene. Removal of the silyl protecting group, followed by transesterification with excess methyl propiolate facilitated by Otera's catalyst gave ester **59**. Bromination of the terminal alkyne moiety produced bromo-alkyne **60** which upon an intramolecular Diels-Alder, followed by aromatization,

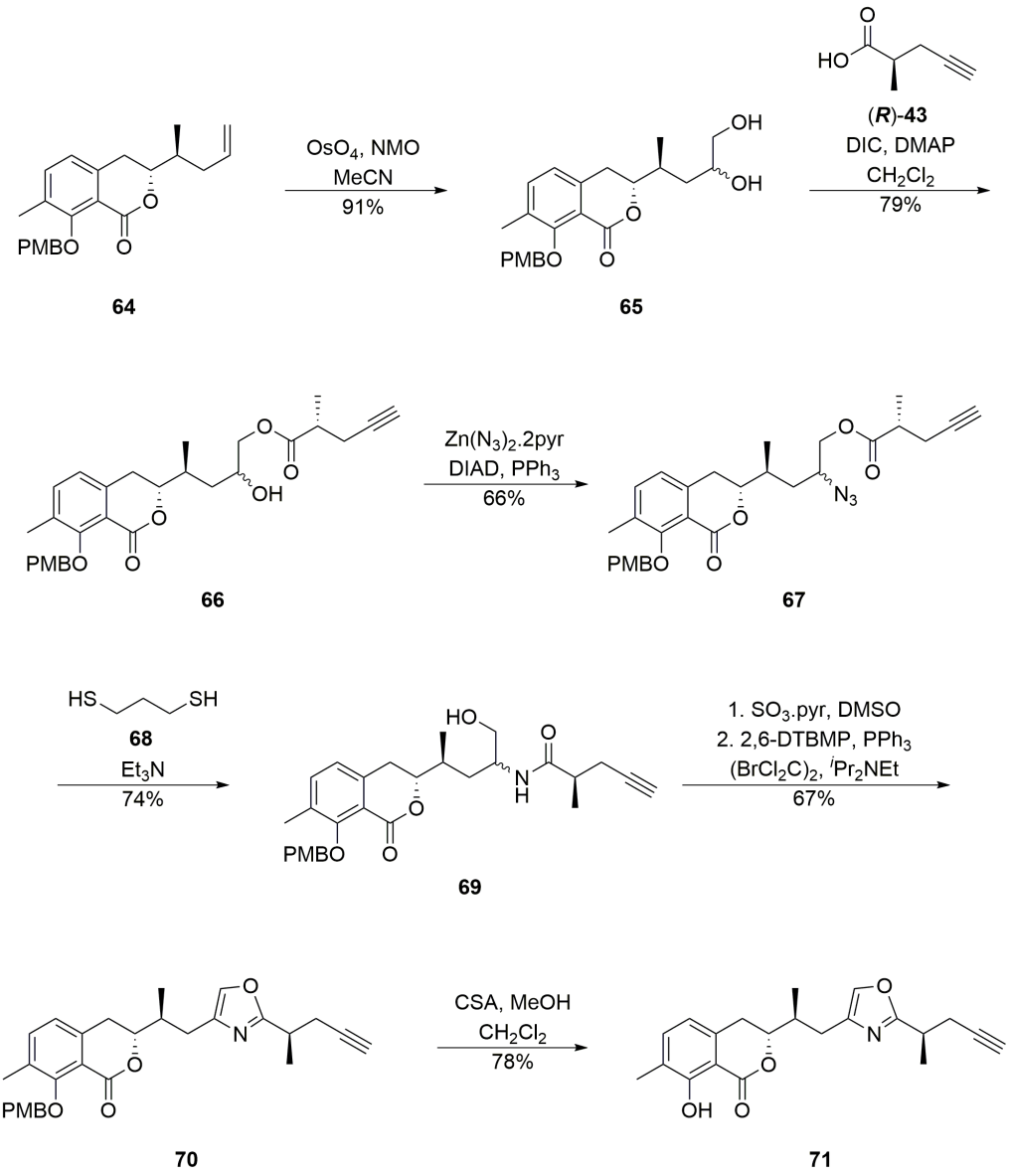
afforded the desired isochromanone **61**. The aromatic bromide was then exchanged for a hydroxyl group using palladium-catalyzed borylation conditions developed by Buchwald, to give the pinacol boronate ester.[37] Oxidation and subsequent hydrolysis afforded the phenol **62**. Protection of phenol **62** as the PMB ether, followed by hydroboration of the terminal alkyne under Rh-catalysed conditions gave primary alcohol **63**. Oxidation of alcohol **63** to the corresponding aldehyde, and subsequent Wittig methelynation gave the terminal olefin **64** (scheme 1.10).



Scheme 1.10: Rizzacasa's synthesis of terminal olefin **64**.

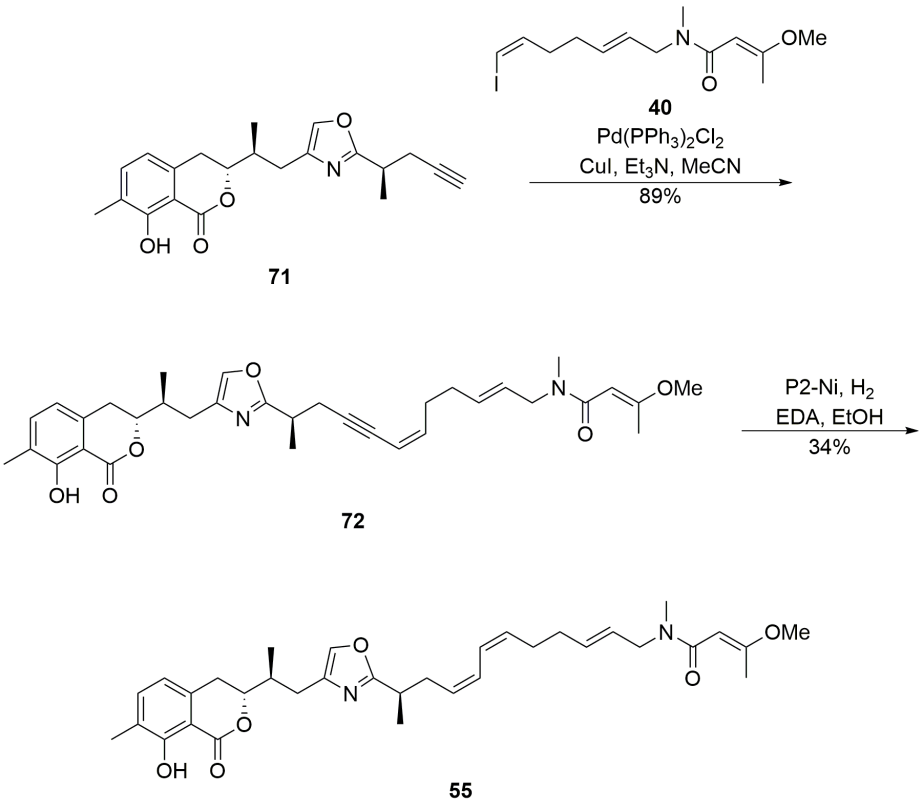
Upjohn dihydroxylation of olefin **64**, gave diol **65** as a mixture of diastereomers. The primary alcohol was chemoselectively coupled with enantiopure acid (***R***)-**43** to give the desired ester **66**, whilst the secondary alcohol was successfully converted to the corresponding azide **67**, using Mitsunobu conditions. A one-pot azide reduction, followed by *O*,*N*-acyl shift facilitated by triethylamine, gave the desired *β*-hydroxyamide **69**. Parikh-

Doering oxidation, and subsequent cyclodehydration gave the key oxazole core **70**. Finally, CSA removal of the PMB group yielded the desired acetylene **71** (scheme 1.11).



Scheme 1.11: Rizzacasa's synthesis of terminal acetylene **71**.

Sonogashira coupling between acetylene **71** and vinyl iodide **40** proceeded in excellent yield to give enyne **72**. The partial reduction of the enyne to the *Z,Z*-diene was achieved, employing the previously used P2-Ni conditions, in 34% yield to complete the synthesis of 8-deshydroxyajudazol B stereoisomer **55** (scheme 1.12).



Scheme 1.12: Rizzacasa's completion of the synthesis of 8-deshydroxyajudazol B stereoisomer **55**.

1.6.4 Rizzacasa's synthesis of 8-deshydroxyajudazol A stereoisomer 73

Rizzacasa published the synthesis of a proposed structure of 8-deshydroxyajudazol A **73**, shortly before the absolute stereochemistry of the ajudazols had been elucidated.[38] 8-Deshydroxyajudazol A is believed to be an intermediate in the biosynthesis of ajudazol A.

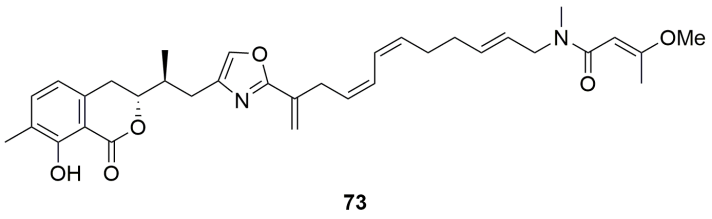
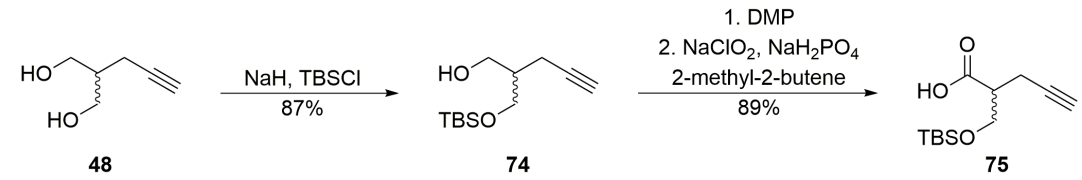


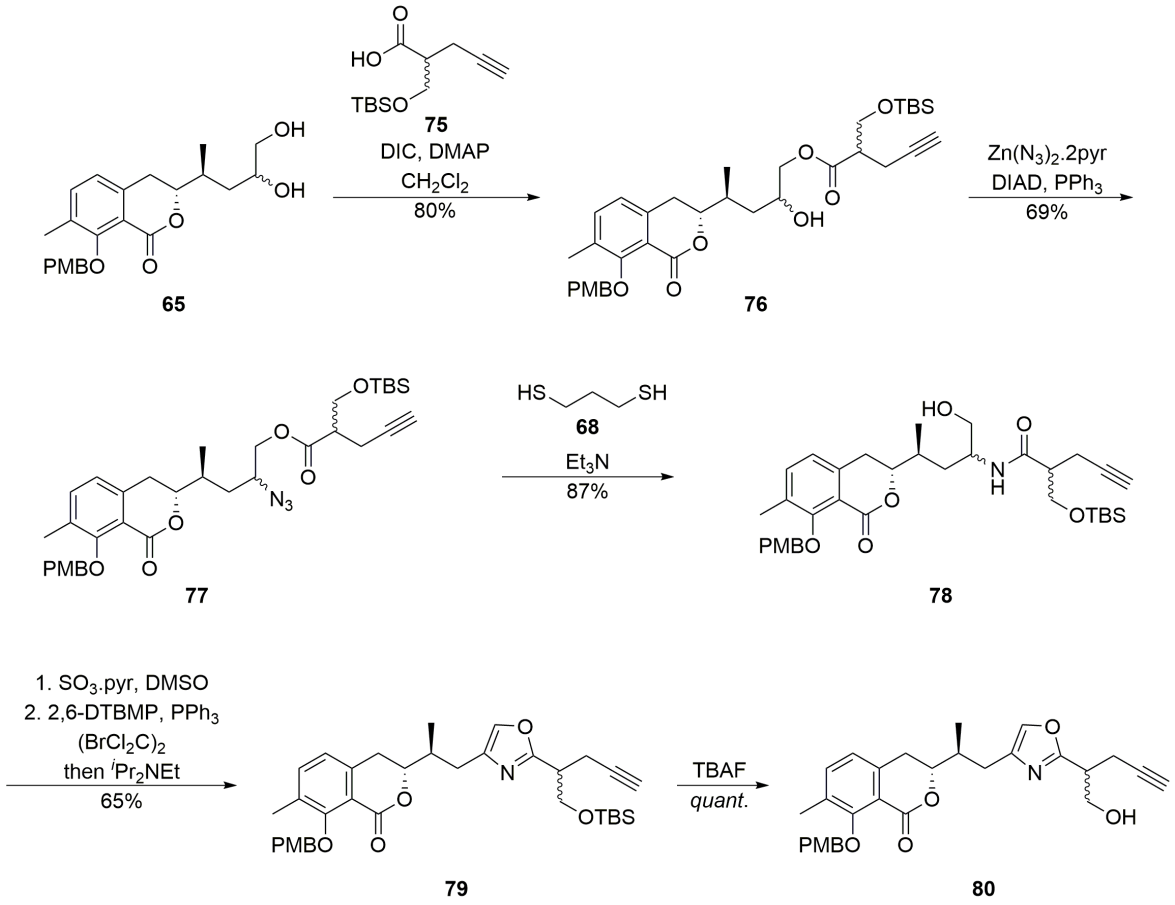
Figure 1.11: 8-Deshydroxyajudazol A stereoisomer **73**.

Rizzacasa's approach began with the mono-protection of the previously synthesised diol **48,** to give silyl ether **74**. Oxidation of alcohol **74** through sequential Dess-Martin and Pinnick oxidations gave racemic acid **75**, in good yield (scheme 1.13).



Scheme 1.13: Rizzacasa's synthesis of acid **75**.

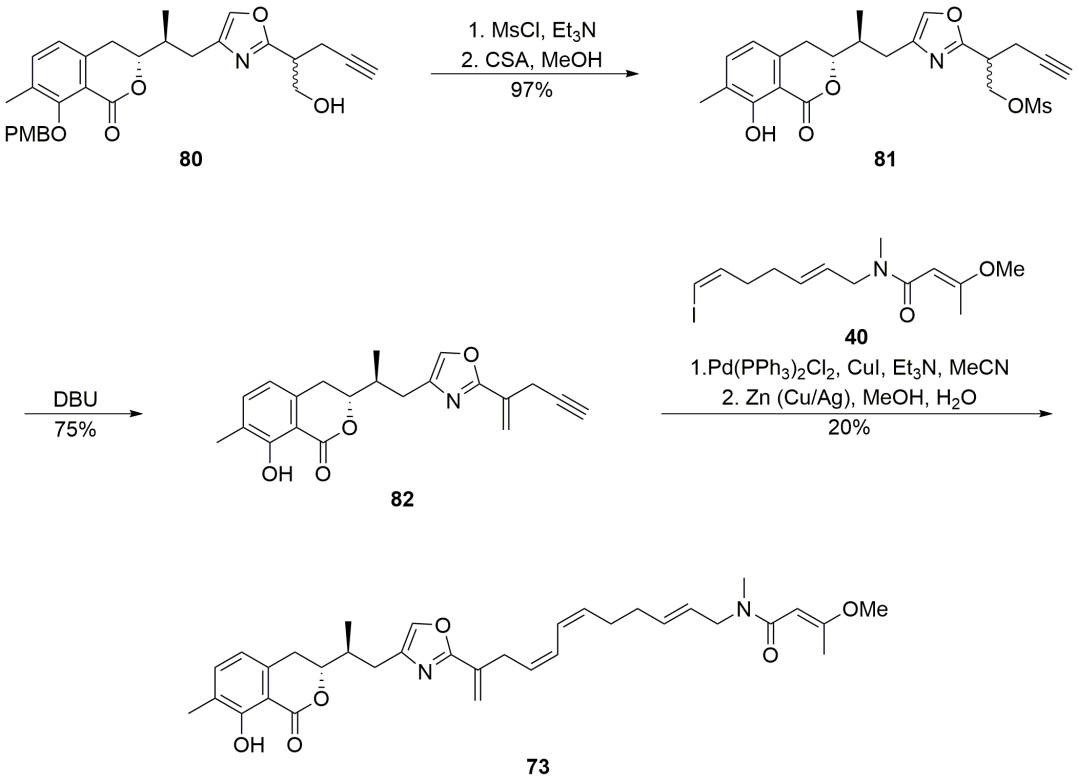
Acid **75** was then coupled selectively to the primary alcohol in diol **65**, which was an intermediate in Rizzacasa's synthesis of 8-deshydroxyajudazol B stereoisomer **55**, to generate ester **76** (schemes 1.10 and 1.11). A Mitsunobu reaction then converted alcohol **76** into azide **77**, which upon reduction and *O,N*-acyl shift gave the *β*-hydroxyamide **78**. Parikh-Doering oxidation to the aldehyde followed by cyclodehydration gave oxazole **79**, that was then treated with TBAF to give acetylene **80** (scheme 1.14).



Scheme 1.14: Rizzacasa's synthesis of acetylene **80**.

Rizzacasa then decided to install the 1,1-disubstituted alkene before the Sonogashira coupling, trying to achieve a more convergent approach. Thus, alcohol **80** was converted to the mesylate and the PMB-ether was removed in excellent yield to give **81**. DBU mediated elimination of the mesylate then gave the terminal olefin **82**, ready for the Sonogashira

coupling with known vinyl iodide **40**. The desired product was successfully formed, but proved to be inseparable from excess alkyne **82**, therefore the partial hydrogenation was carried out on the product mixture. Cu/Ag activated Zn was employed to achieve the partial reduction of the enyne, which proved superior to the previously established conditions comprising of P2-Ni/H_2/EDA, as over-reduction was completely suppressed. The two steps gave a poor yield of 20%, but 8-deshydroxyajudazol A stereoisomer **73** was successfully synthesized. Unfortunately, it was later discovered that Rizzacasa had completed the synthesis of *ent*-8-deshydroxyajudazol A **73** (scheme 1.15).



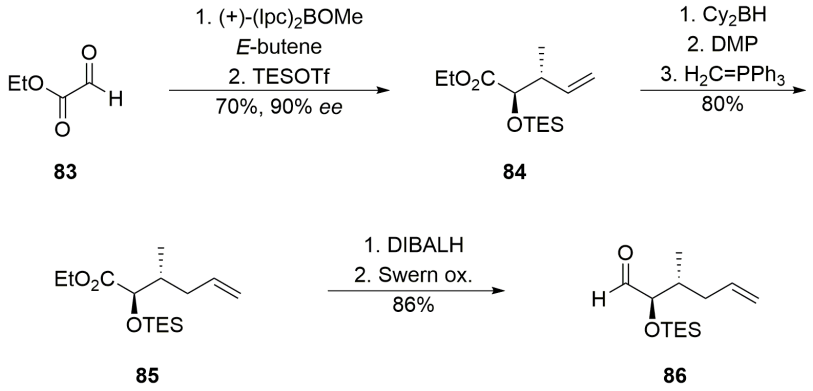
Scheme 1.15: Rizzacasa's completion of total synthesis of 8-deshydroxyajudazol A stereoisomer **73**.

1.6.5 Menche's total synthesis of ajudazol B

In 2012, Menche and coworkers reported the full stereochemical determination of ajudazol A and B using a bioinformatic approach (Section 1.5 Absolute stereochemistry), and completed the first total synthesis of ajudazol B.[23]

Menche's synthesis began with a Brown crotylation of ethyl glyoxylate **83**, with TES protection of the resultant alcohol to give silyl ether **84**, in 70% yield and 90% *ee*. Homologation via hydroboration, oxidation to the aldehyde, and then Wittig olefination gave

ester **85**, which was reduced to the corresponding alcohol and oxidized to give aldehyde **86** (scheme 1.16).

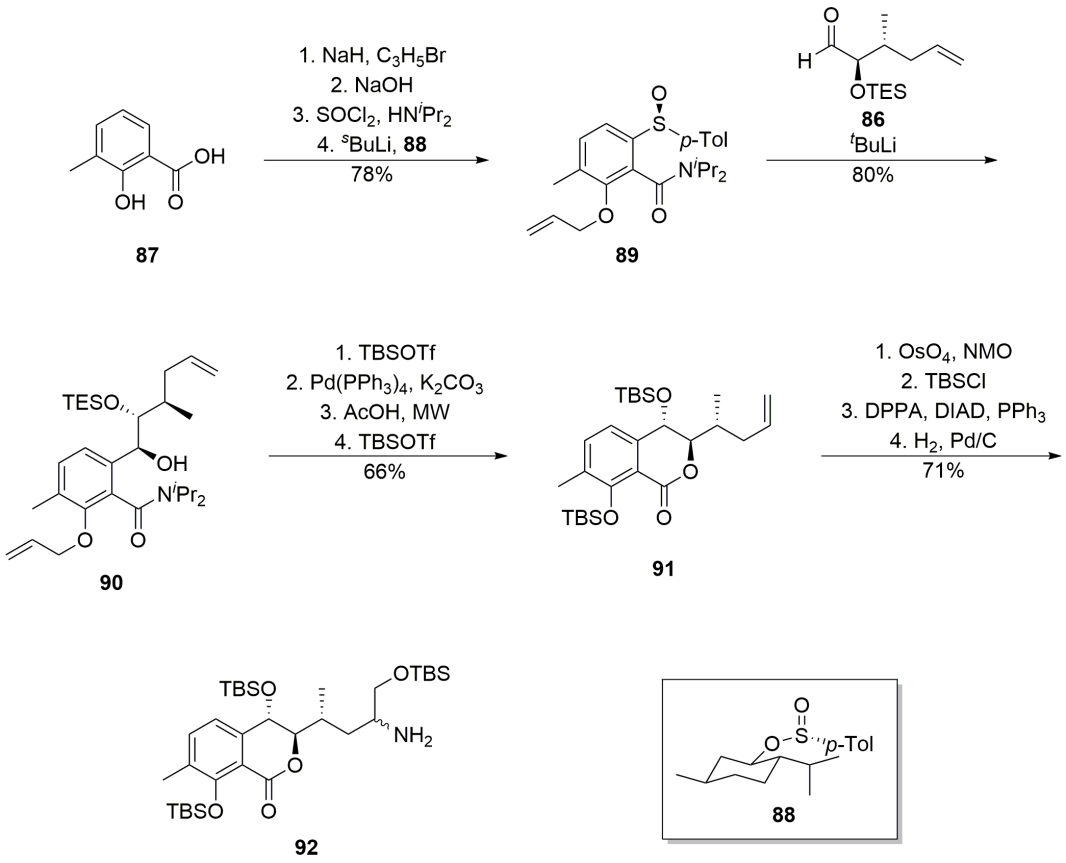


Scheme 1.16: Menche's synthesis of olefin **86**.

Synthesis of the aromatic section of the isochromanone unit began with 3-methylsalicylic acid **87** which was allylated, followed by conversion of the carboxylic acid to the diisopropyl amide. The amide axis was then fixed *via* ortho-lithiation and subsequent capture with Andersen's reagent **88**, to give sulfoxide **89**. Asymmetric lithiation of sulfoxide **89** and treatment with aldehyde **86**, gave the *anti*,*anti*-product **90**, with a d.r. of >95:5.

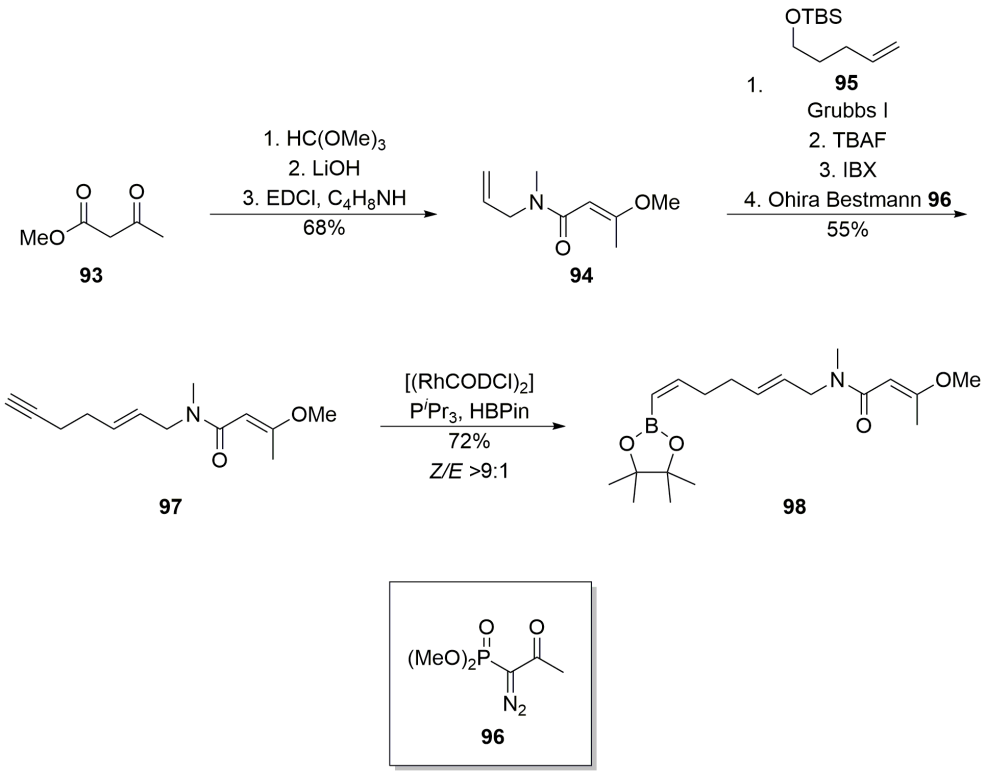
The benzylic alcohol was TBS protected, before removal of the allyl group, using $Pd(PPh_3)_4$, followed by microwave assisted amide hydrolysis and simultaneous TES cleavage gave the *anti*,*anti*-isochromanone core. Consequent TBS protection of the phenol group, gave isochromanone **91**, in 66% over 4 steps.

Dihydroxylation of alkane **91** with subsequent protection of the primary alcohol gave the TBS ether. Azide substitution of the secondary alcohol, using Mitsunobu conditions followed by hydrogenation to the primary amine completed the synthesis of western fragment **92** (scheme 1.17).



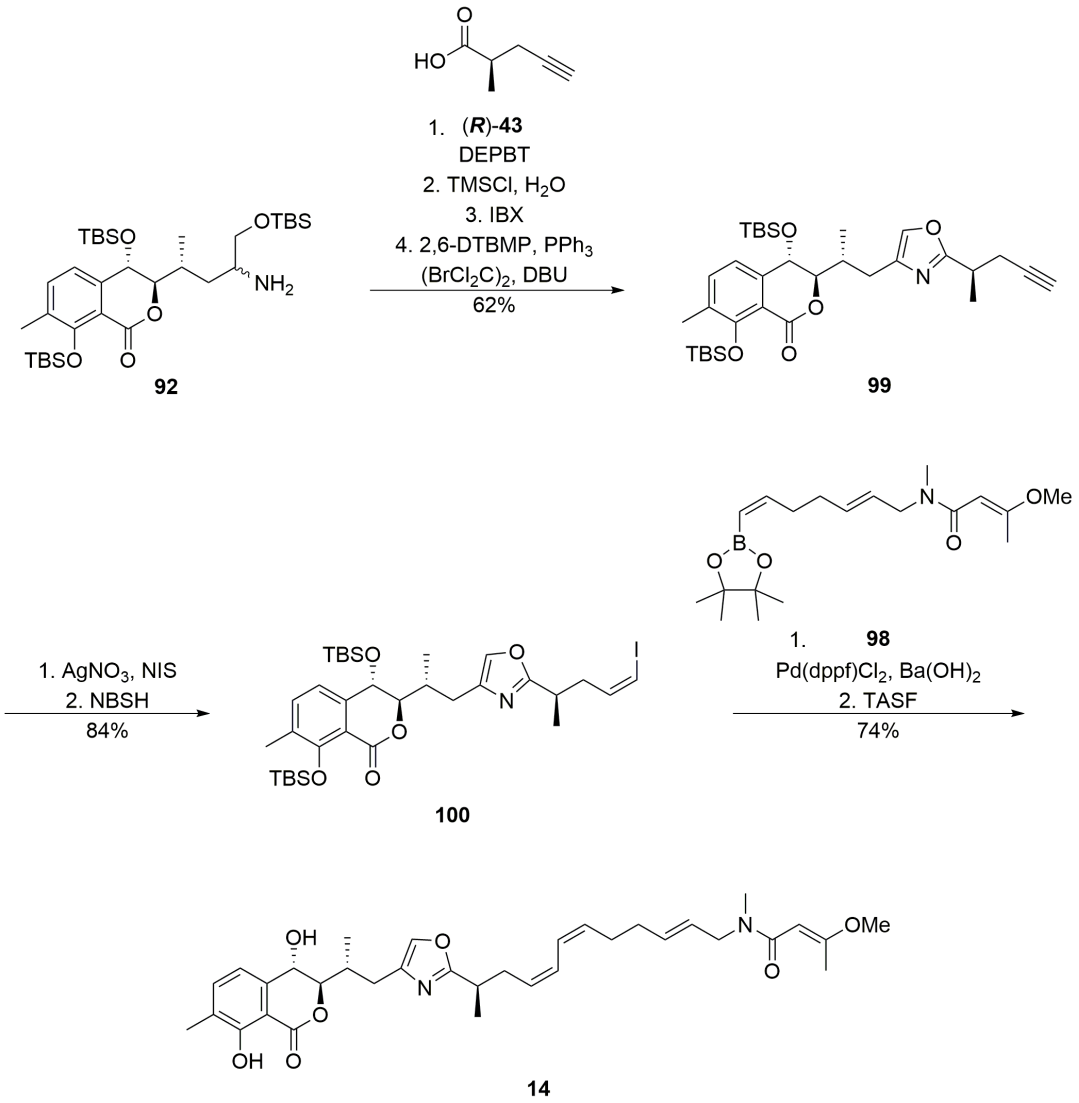
Scheme 1.17: Menche's synthesis of western fragment **92**.

Methyl acetoacetate **93** was treated following Taylor's and Rizzacasa's conditions to generate 3-methoxybutenoic acid **31**.[32] Acid **31** was then coupled to allyl amine, to give amide **94** in 68% over 3 steps. Allylic amide **94** then underwent a cross-metathesis with olefin **95**, promoted by Grubbs 1st Generation catalyst. Desilylation of the silyl ether intermediate followed by oxidation of the resultant alcohol to the aldehyde, and then Seyferth-Gilbert homologation gave the terminal acetylene **97**. Finally, a Rh-catalysed *trans*-selective hydroboration gave the *Z*-alkenyl boronate ester **98** with good selectivity (scheme 1.18).



Scheme 1.18: Menche's synthesis of Eastern fragment **98**.

Menche then coupled the western fragment **92** to known acid (***R***)-**43**, followed by the selective removal of the primary TBS group. The resultant *β*-hydroxyamide was oxidized to the corresponding aldehyde which was then treated with a modified Wipf cyclodehydration protocol, to give the oxazole **99**.[35] Iodination of the terminal alkyne, followed by a selective *syn*-reduction afforded the *Z*-vinyl iodide **100**. Suzuki cross-coupling of vinyl iodide **100** with eastern fragment **98**, followed by subsequent removal of the silyl groups completed the first reported total synthesis of ajudazol B **14** (scheme 1.19).



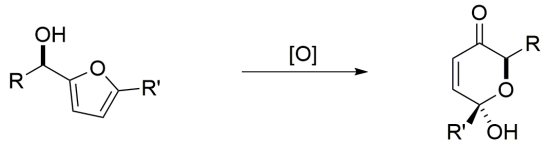
Scheme 1.19: Menche's completion of the total synthesis of ajudazol B **14**.

1.7 EFFORTS TOWARDS THE AJUDAZOLS WITHIN THE MARQUEZ GROUP

Research efforts within the Marquez group were initially focused on the synthesis of the isochromanone core of the ajudazols. This functionality was proven to be accessible *via* methodology developed within the Marquez group, comprising of an adaptation of the Achmatowicz rearrangement, employing highly reactive isobenzofurans as synthetic intermediates.

1.7.1 Achmatowicz rearrangement

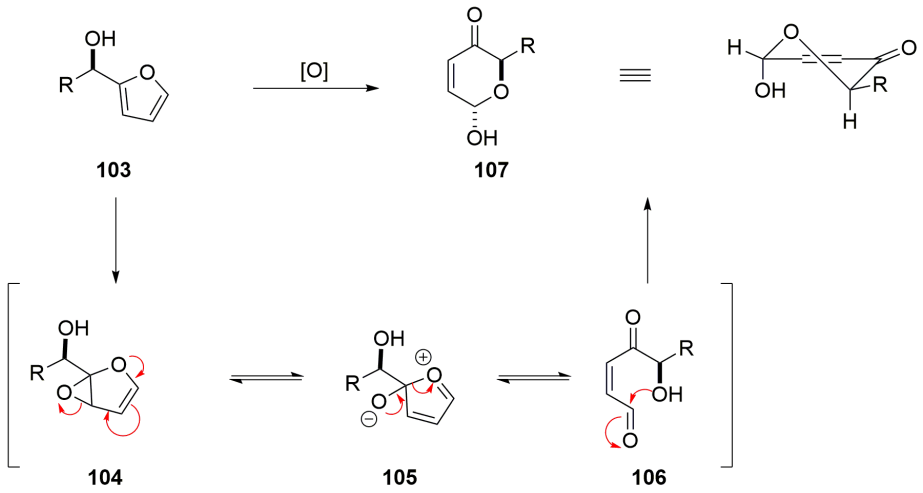
First reported in 1971, the Achmatowicz rearrangement generates α,β-unsaturated pyranones from the oxidative treatment of α-hydroxyfurans.[39] The original conditions employ bromine in MeOH, followed by H_2SO_4 to form the hydroxypyranone. However, several other one-pot oxidative conditions have been employed including, but not limited to: NBS in H_2O/THF; *m*CPBA, CH_2Cl_2; *t*BuOOH, $VO(acac)_2$; KBr, oxone; and photo-redox conditions using visible light.[39-44]



101 **102**

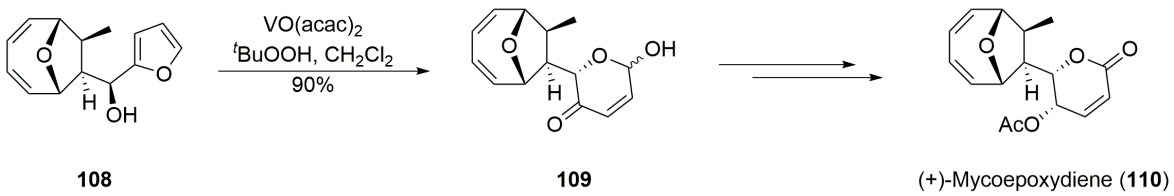
Scheme 1.20: Achmatowicz rearrangement.

Mechanistically, the Achmatowicz rearrangement proceeds through a hydroxy-directed epoxidation at the allylic position, to generate epoxide **104**. Ring opening of the epoxide, *via* formation of zwitterionic intermediate **105**, generates 1,4-dicarbonyl **106**. This is followed by intramolecular nucleophilic attack of the free hydroxy group onto the carbonyl, to generate α,β-unsaturated pyranone **107**, where the α-anomer is the major product (scheme 1.21).



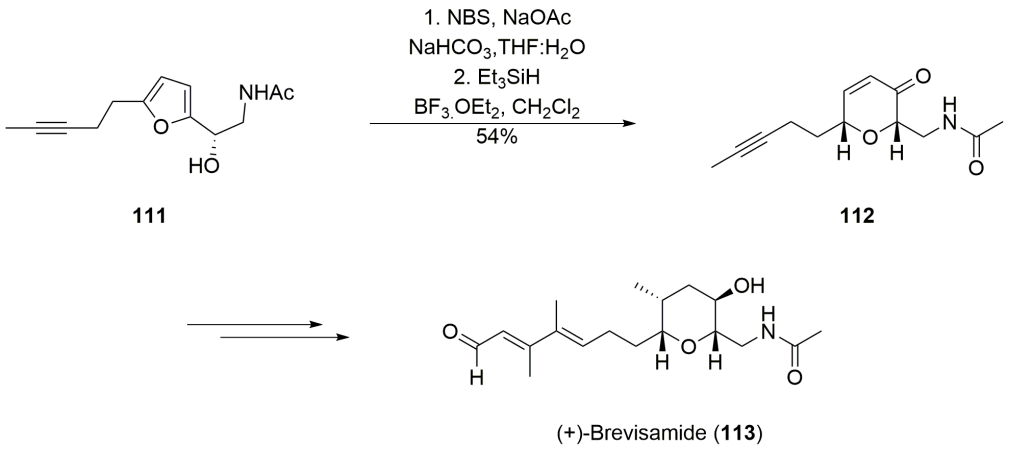
Scheme 1.21: Mechanism of the Achmatowicz Rearrangement.

Used widely in organic synthesis, the Achmatowicz rearrangement has been employed in the synthesis of carbohydrates, and in natural product synthesis due to its ability to tolerate a wide range of substrates and functionalities. The pyranone acetals formed are often used to generate substituted tetrahydropyrans, spiroketals, and oxa-bridged bicycles.[45] For example, an Achmatowicz rearrangement was used as the key step in Tadano's synthesis of (+)-mycoepoxydiene **110**. The furfuryl alcohol **108** was subjected to a $VO(acac)_2/^tBuOOH$ promoted Achmatowicz rearrangement to generate the pyranone ring in **109**, in excellent yield (scheme 1.22).[46]



Scheme 1.22: Achmatowicz rearrangement in Tadano's synthesis of (+)-mycoepoxydiene **110**.

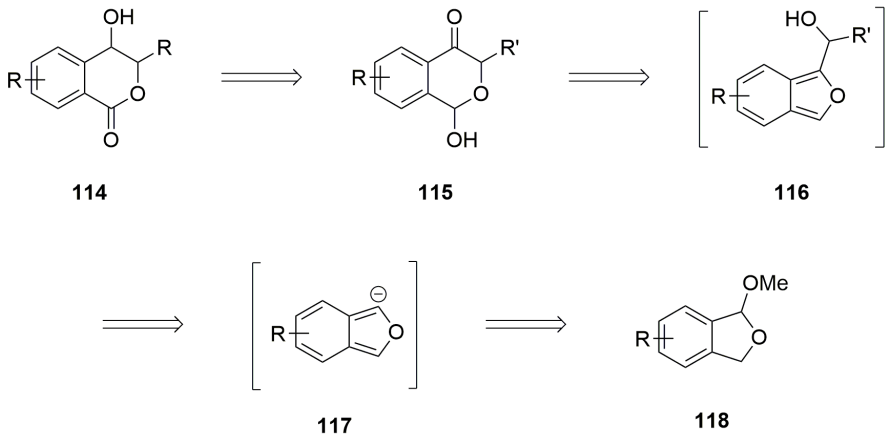
The pyranone intermediate in Zakarian's synthesis of (+)-brevisamide **113** was also generated using an Achmatowicz rearrangement.[47] The α-hydroxyfuran **111** underwent an NBS promoted Achmatowicz rearrangement, and the resulting hemi-ketal was reduced with triethylsilane to give pyranone **112**, in 54% yield (scheme 1.23).



Scheme 1.23: Achmatowicz rearrangement in Zakarian's synthesis of (+)-brevisamide **113**.

1.7.2 The oxidative rearrangement of isobenzofurans

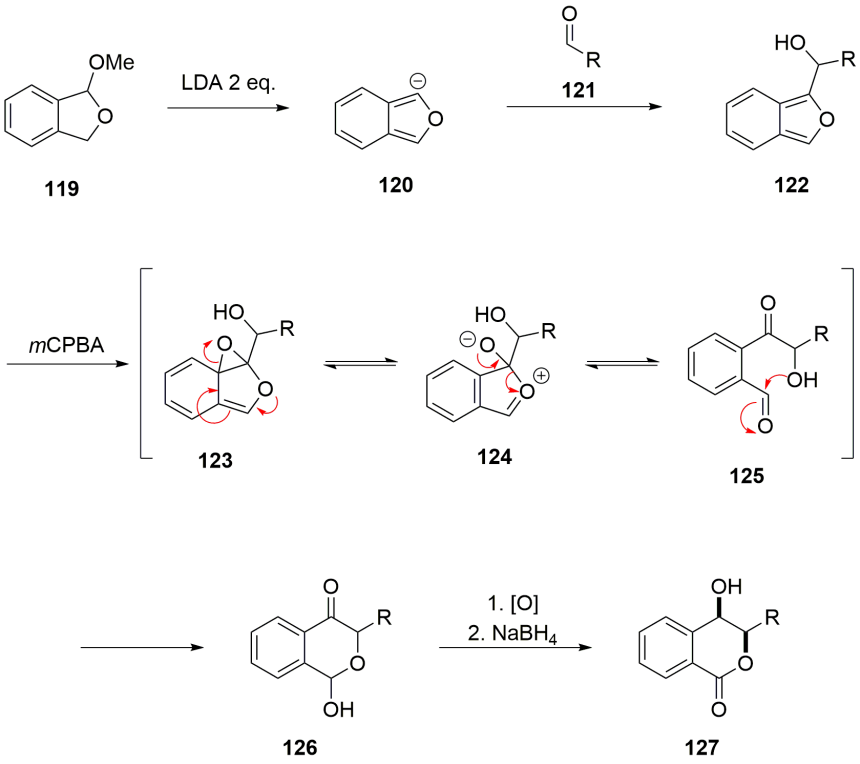
In 2008, the Marquez group reported the oxidative rearrangement of α-hydroxyisobenzofurans for the generation of isochromanones.[27] It was envisaged that substituted isochromanones **114** could be accessed through the oxidation and selective reduction of keto-lactol **115**. Lactol **115** in turn, would be generated from the Achmatowicz-type oxidative rearrangement of α-hydroxyisobenzofuran **116**, which was envisioned to be accessible from the alkylation of the isobenzofuran anion **117**, itself formed from phthalan **118** (scheme 1.24).



Scheme 1.24: Retrosynthetic analysis of isochromanone **114**.

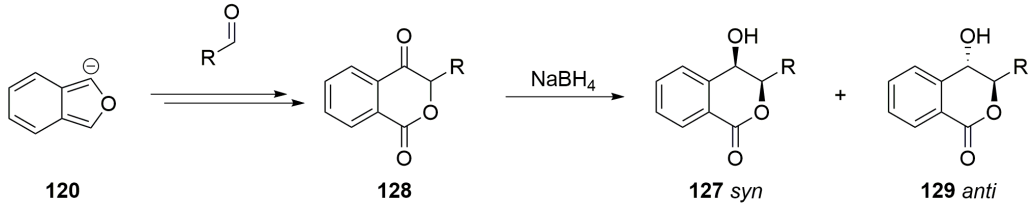
Using this approach isochroman-1-one cores were first synthesized starting from commercially available phthalide, which was reduced to the corresponding lactol, and then methylated to give phthalan **119**. Treatment of the phthalan intermediate with LDA then formed the key isobenzofuran anion intermediate **120**. Mechanisitically, the LDA promotes

the elimination of the methoxy group and generates the aromatic isobenzofuran unit, which is then deprotonated by a second equivalent of LDA to generate the anion. This highly reactive anion is then trapped with an aldehyde **121** to form the corresponding α-hydroxyisobenzofuran intermediate **122**. This highly unstable intermediate is then treated with *m*CPBA, to induce an Achmatowicz type rearrangement, to give the keto-lactol **126**. Oxidation to the keto-lactone, followed by reduction produces the desired isochroman-1-one unit **127** (scheme 1.25).



Scheme 1.25: Generation of isobenzofuran, alkylation, and oxidative rearrangement sequence.

This procedure was successfully applied using a wide range of aldehydes to give the desired isochroman-1-ones, in good yield. It is worth noting that the selectivity of the reduction step was highly dependent on the nature of the side-chain. Sterically bulky side-chains, particularly those with branched substituents α to the aldehyde unit gave solely the *syn*-product (table 1-1).



Scheme 1.26: Synthesis of ioschromanones.

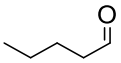
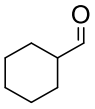
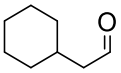
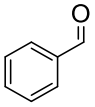
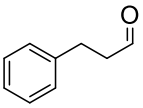
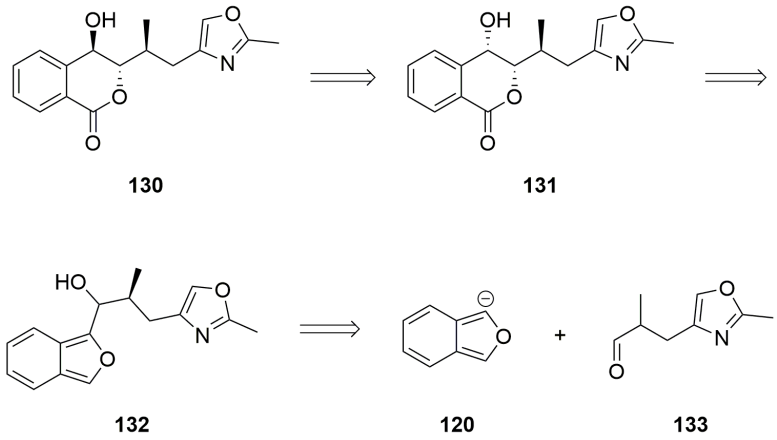
Entry	Aldehyde	Keto-lactone % (yield over 4 steps)	Reduction % (*syn*:*anti*)
1		85	96 (100:0)
2		94	90 (50:50)
3		84	71 (60:40)
4		82	56 (90:10)
5		72	80 (75:25)
6		83	77 (100:0)
7		57	82 (100:0)
8		67	58 (50:50)
9		64	48 (100:0)
10		93	90 (50:50)
11		95	76 (100:0)

Table 1-1: Oxidative rearrangement and reduction.

With this 5-step protocol allowing for the fast and efficient synthesis of isochroman-1-ones from simple aldehydes, it was decided to investigate the scope of the methodology, and the

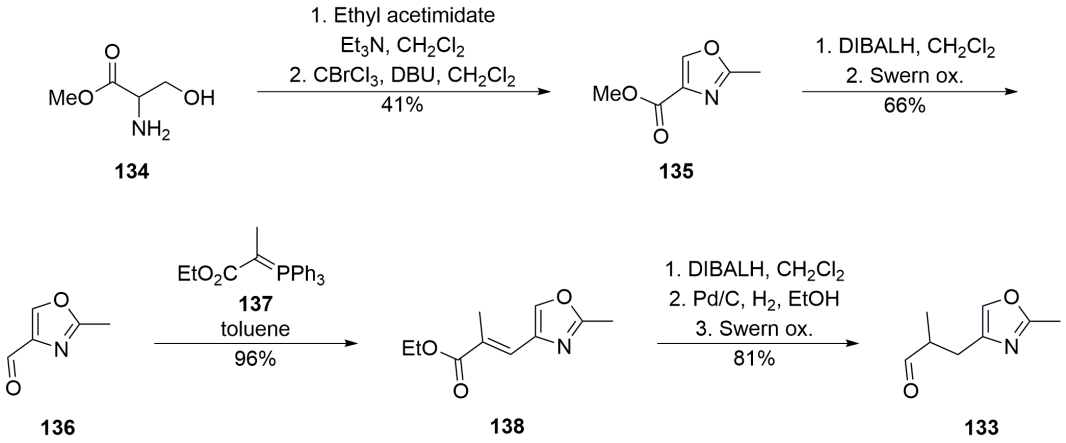
usefulness of α-hydroxyisobenzofurans as synthetic intermediates in complex natural product synthesis. Thus, the synthesis of a model system of ajudazol A was undertaken.

The ajudazol A model system **130**, was envisioned as being accessed through the inversion of the hydroxy group at C8 of the *syn-anti* isochromanone **131**, which in turn would be accessed from oxidative rearrangement of α-hydroxyisobenzofuran **132**. The key α-hydroxyisobenzofuran unit **132** could be synthesized from alkylation of the isobenzofuran anion **120** with the oxazole-containing aldehyde **133** (scheme 1.27).



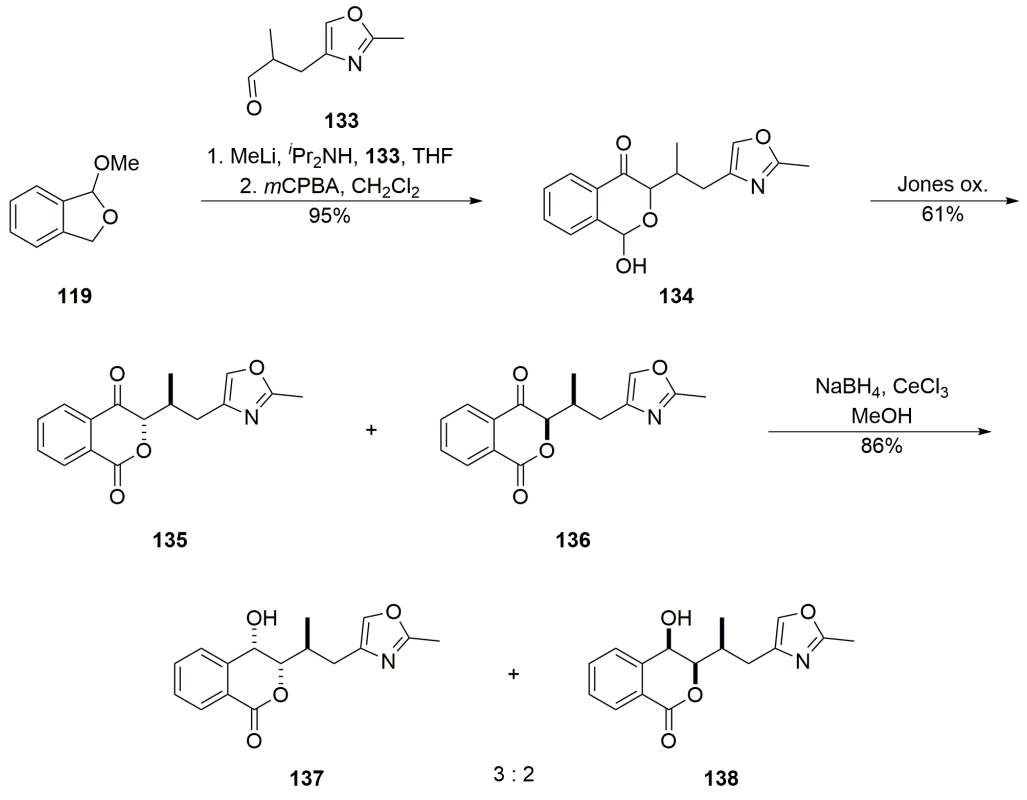
Scheme 1.27: Retrosynthetic analysis of ajudazol A model system **130**.

The forward synthesis of the oxazole containing aldehyde unit **133** began with D,L-serine methyl ester **134**, which was converted to the oxazole ester **135**. Reduction of the ester to the corresponding alcohol followed by Swern oxidation, gave the aldehyde coupling partner **136**, in reasonable yield over the two steps. Wittig olefination with stabilised ylide **137** then gave the *E*-olefin **138** in excellent yield, and as a single double bond isomer. Ester reduction followed by double bind hydrogenation and subsequent oxidation of the alcohol completed the synthesis of racemic oxazole-aldehyde **133** (scheme 1.28).



Scheme 1.28: Synthesis of oxazole-aldehyde **133**.

The isobenzofuran anion was generated using standard conditions, from phthalan **119**, and trapped with the newly generated oxazole-aldehyde **133** to afford the putative α-hydroxyisobenzofuran intermediate. Oxidative rearrangement of the α-hydroxyisobenzofuran with mCPBA then gave lactol **134** in excellent yield. Oxidation using Jones' reagent afforded the desired keto-lactones **135** and **136**, as a 3:2 mixture of diastereomers, which was then reduced using Luche reduction conditions to afford isochroman-1-ones **137** and **138** (scheme 1.29). The major diastereomer was separated via selective crystallisation, and the structure corroborated using X-ray crystallography (figure 1.12).



Scheme 1.29: Synthesis of isochromanones **137** & **138**.

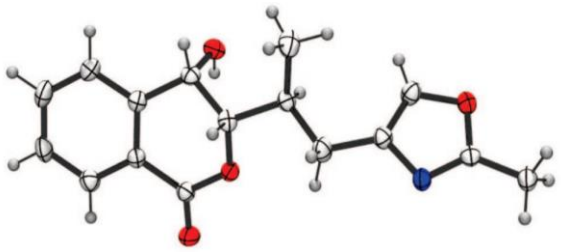
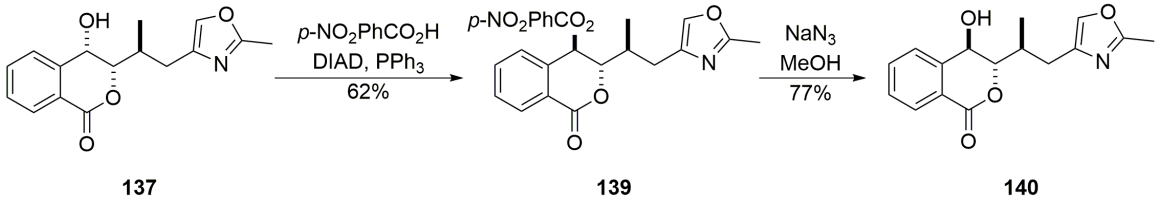


Figure 1.12: Crystal structure of isochromanone **137**.

Isochromanone **137** was then subjected to Mitsunobu conditions to give the desired *p*-nitrobenzoate ester **139**, which contains the key *anti-anti* stereochemical relationship present in the ajudazols. Mild hydrolysis of the *p*-nitrobenzoate ester gave the *anti,anti*-isochromanone **140**, completing the synthesis (scheme 1.30).



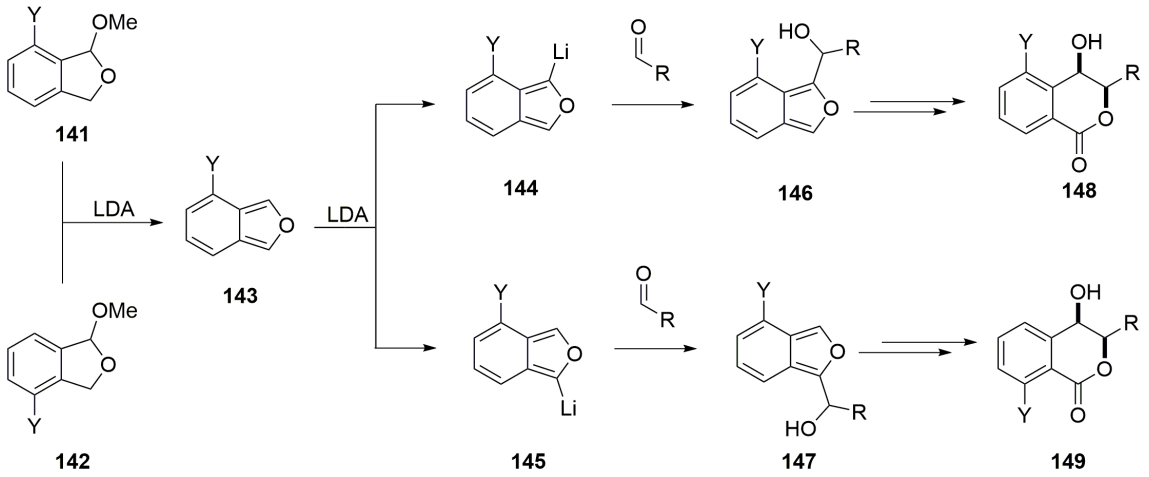
137 **139** **140**

Scheme 1.30: Synthesis of *anti,anti*-ajudazol model system **140**.

1.8 REGIOSELECTIVE OXIDATIVE REARRANGEMENT OF ISOBENZOFURANS

Initially, the methodology had only been used to successfully synthesize isochromanones using unsubsituted phthalan as a precursor. For the oxidative rearrangement methodology to be useful in the synthesis of the ajudazols, it would be required to handle the presence of substituents.

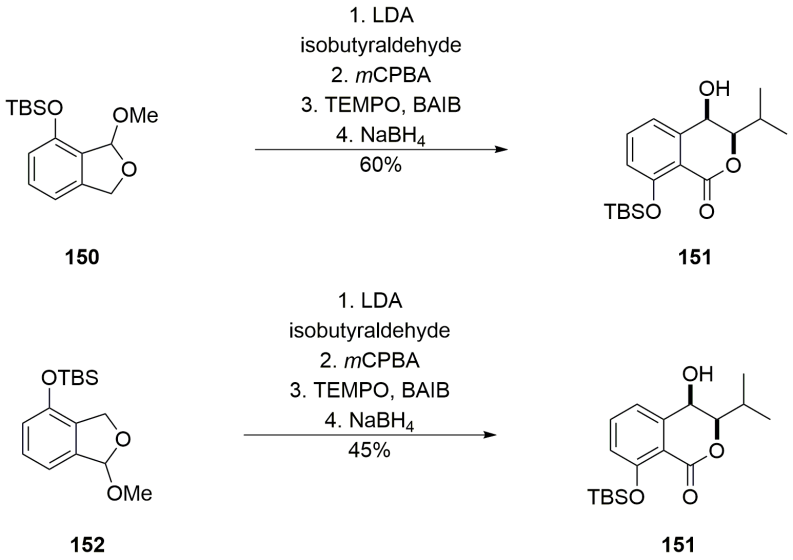
When unsubstituted phthalan was used as a precursor there were no regioselectivity issues, as the isobenzofuran intermediate is symmetrical. When substitution is present on the phthalan, the second deprotonation can take place on either the same side, or opposite side of the substituents, leading to a regioisomeric anions. However, it was hypothesized that by altering the group (Y) at C4 it would be possible to influence the site of deprotonation, and therefore the regiochemical outcome of the reaction (scheme 1.31).[48]



Scheme 1.31: Regioselective approach to isochromanones.

Indeed, it was demonstrated that substituents at the C4 position were able to sterically divert the second deprotonation step Additionally, the fact that the reaction goes through an isobenzofuran intermediate means that either C4 or C7 substituted phthalans would converge into the same intermediate.

Effectively, alkylation of the isobenzofuran generated from either C4 or C7 substituted phthalans **150** or **152**, and subsequent rearrangement led to the formation of C8 substituted isochromanone **151** as a single regioisomer in both cases (scheme 1.32).

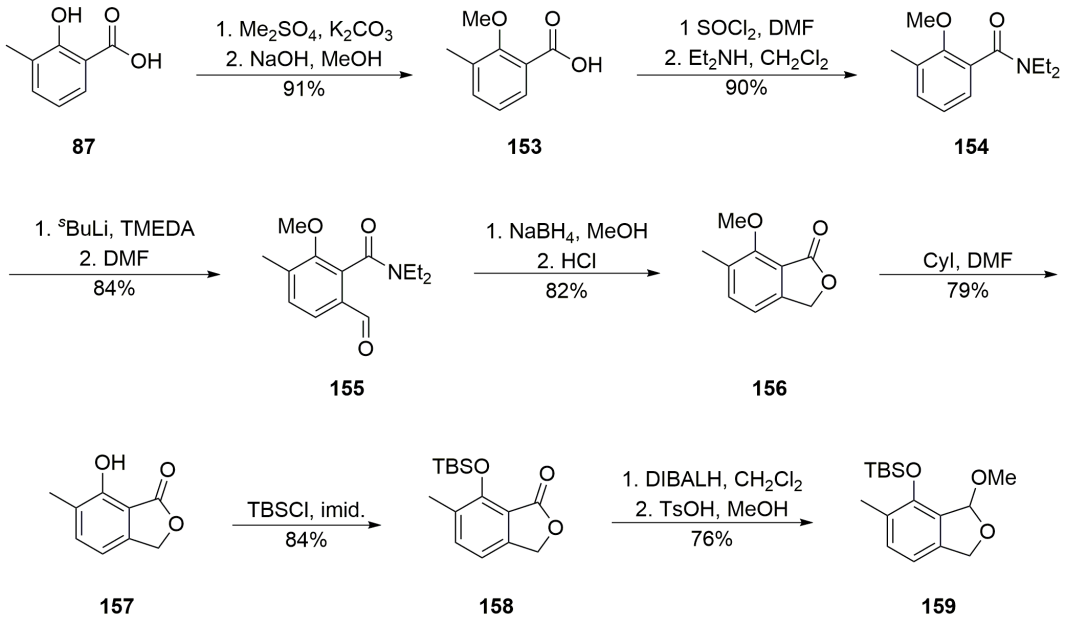


Scheme 1.32: Regioselectivity of rearrangement.

With complete control of the regiochemistry of alkylation demonstrated, work began on a phthalan unit containing the full functionality present in the ajudazol isochromanone core.

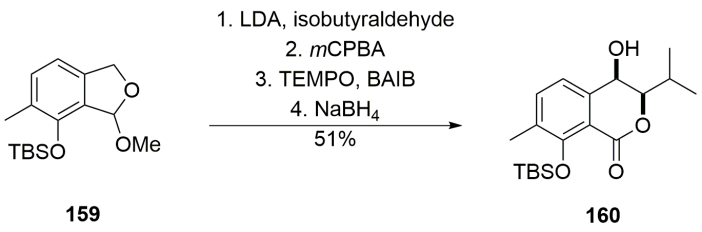
The synthesis of fully functionalised phthalan **159** began with 3-methylsalicylic acid **87**, which was converted to the diethyl amide **154** in four steps, and good overall yield. A

directed *ortho*-formylation, followed by reduction of the resultant aldehyde, and treatment with acid, gave the key phthalide **156**. Deprotection of the methyl group using iodocyclohexane, then re-protection of the phenol group using TBSCl gave phthalide **158**. DIBALH reduction to the corresponding lactol, and then treatment with methanol in the presence of tosic acid gave the phthalan **159**, ready for use in the rearrangement process (scheme 1.33).



Scheme 1.33: Synthesis of phthalan **159**.

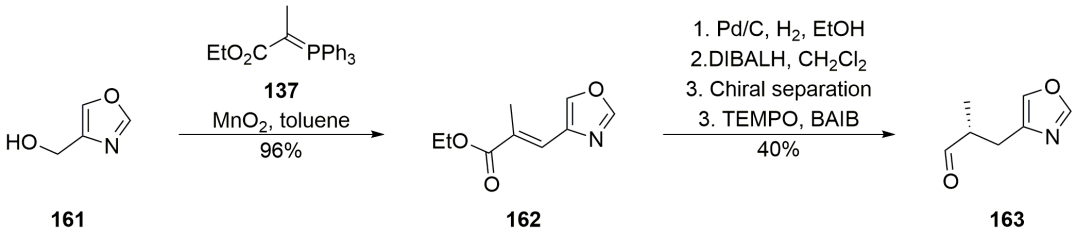
Following the standard isobenzofuran alkylation-rearrangement protocol, and trapping with isobutyraldehyde, the desired 4,8-dihydroxy-7-methylisochroman-1-one was formed, as a single regioisomer. Although the yield was lower than when unsubstituted phthalans were used, the product could be obtained in one day without difficulties.



Scheme 1.34: Synthesis of 4,8-dihydroxy-7-methylisochroman-1-one **160**.

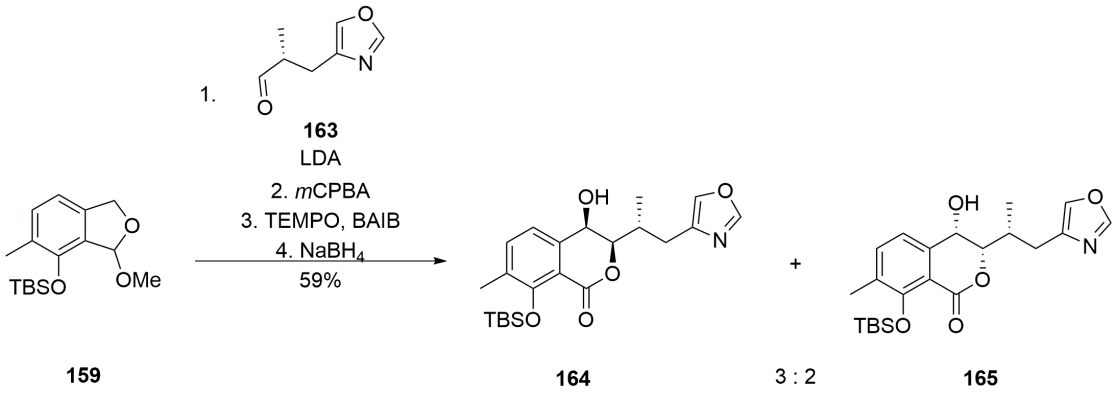
With phthalan **159** in hand, a more complex model aldehyde was synthesised which more closely resembled the ajudazol core structure. Thus, the known oxazole **161** was converted to α,β-unsaturated ester **162** in a one pot process using activated MnO_2, in the presence of

stabilised ylide **137**. Hydrogenation of the olefin, followed by reduction of the ester gave the corresponding racemic which was separated *via* chiral HPLC. Oxidation of the enantiomerically pure alcohol gave the enantiomerically pure (*R*)-aldehyde **163** (scheme 1.35).



Scheme 1.35: Synthesis of enantiomerically pure aldehyde **163**.

With aldehyde **163** in hand, the oxidative rearrangement protocol was implemented using the fully functionalised phthalan **159**. Gratifyingly, this afforded the desired isochromanone products **164** and **165** in 59% yield, thus demonstrating the applicability of the methodology towards the synthesis of the ajudazols (scheme 1.36).

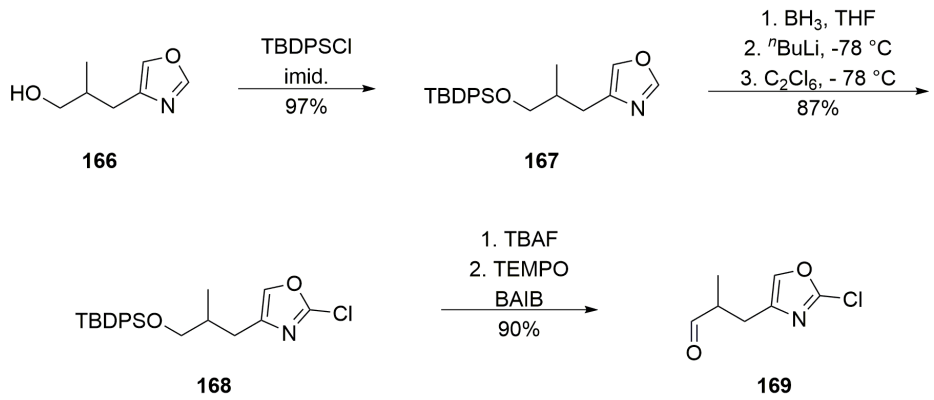


Scheme 1.36: Synthesis of isochromanones **164** and **165**.

With the knowledge that the methodology was compatible with functionalised phthalans, it was decided to investigate conditions to couple the isochromanone fragment to the full eastern section of ajudazol A. Disappointingly, C-H activation, following Taylor's approach, proved to be incompatible with the isochromanone moiety, and resulted in degradation.[28, 30] Chlorination of the oxazole unit was also unsuccessful so it was opted to introduce the chlorine atom earlier in the synthesis.

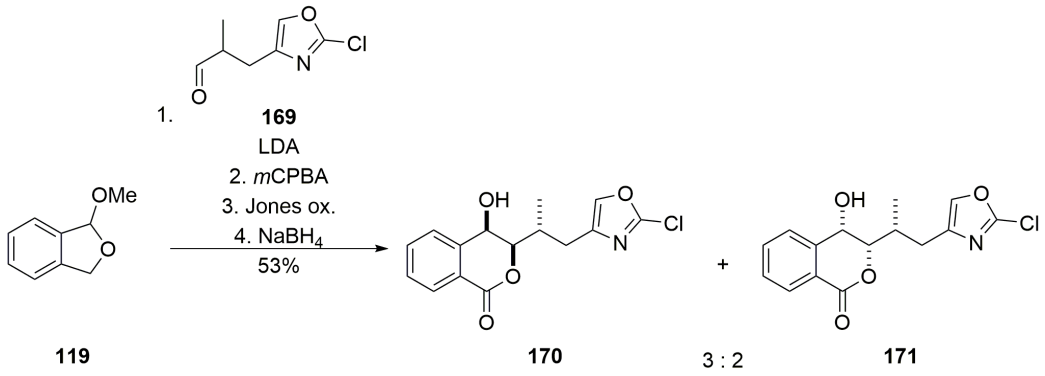
The modified synthetic approach began with oxazole **166**, which was TBDPS protected in excellent yield. Chlorination using conditions developed by Vedejs, employing borane as a

Lewis acid to complex with the nitrogen lone-pair, thus inhibiting ring-opening during the lithiation step, gave chloro-oxazole **168** in good yield.[49] Deprotection using TBAF and oxidation of the resulting alcohol gave the desired racemic aldehyde **169** (scheme 1.37).



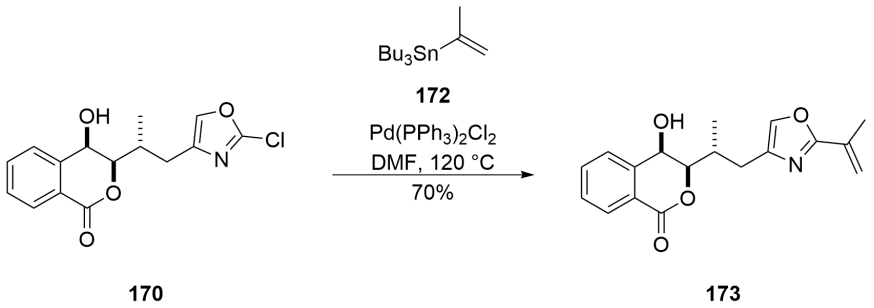
Scheme 1.37: Synthesis of chloro-aldehyde **169**.

Aldehyde **169** was then used in the oxidative rearrangement, to assess the suitability of chloro-oxazoles under the rearrangement conditions. Encouragingly, the reaction sequence gave the desired *syn,anti*-chloro-isochromanone **170** as well as the *syn,syn*-chloro-isochromanone **171** in good yield, proving the methodology was compatible with sensitive aldehydes. Also, interestingly, no de-halogenated products were detected (scheme 1.38).



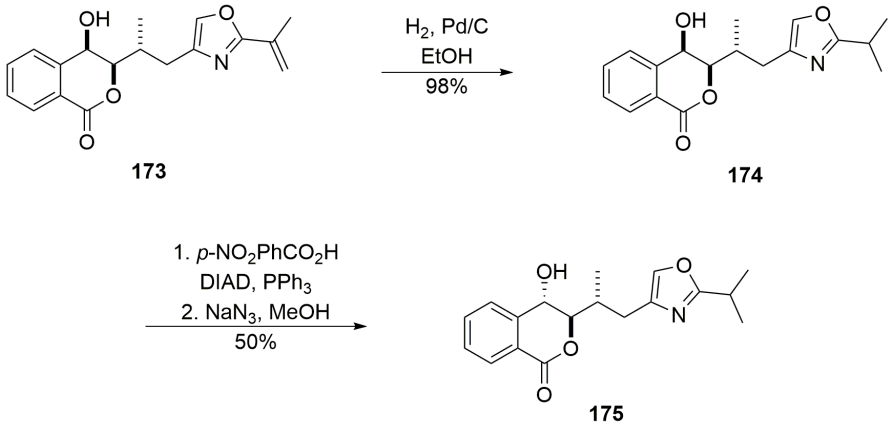
Scheme 1.38: Synthesis of chlorinated isochromanones **170** and **171**.

Finally, a Stille coupling between vinyl-stannane **172** and chloro-isochromanone **170**, completed the synthesis of the C1-C16 model system of ajudazol A **173**. The isochromanone core proved to be stable at the elevated temperature conditions (scheme 1.39).



Scheme 1.39: Synthesis of C1-C16 ajudazol A model system **173**.

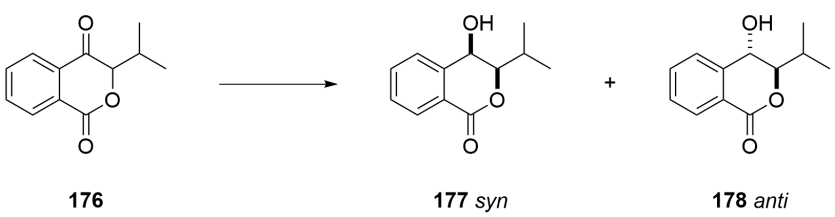
Standard hydrogenation conditions then reduced the methylene group in excellent yield. Mitsunobu inversion, followed by cleavage of the *p*-nitrobenzoate ester, gave the desired *anti,anti*-isochromanone and completed the synthesis of the C1-C16 model system of ajudazol B **175** (scheme 1.40).[28, 50]



Scheme 1.40: Synthesis of C1-C16 ajudazol B model system **175**.

One of the major limitations of the methodology towards the synthesis of the ajudazols, is that the *syn-iso*chromanone is the favoured diastereomer. Although inversion of the stereocentre to access the desired *anti-iso*chromanone could be achieved using Mitsunobu conditions, adapting the methodology to allow for direct access of the *anti-iso*chromanone would provide for a much more efficient synthesis.

With this goal in mind, several different reducing conditions were employed. Disappointingly all conditions gave the *syn-iso*chromanone as the major product (table 1-2).



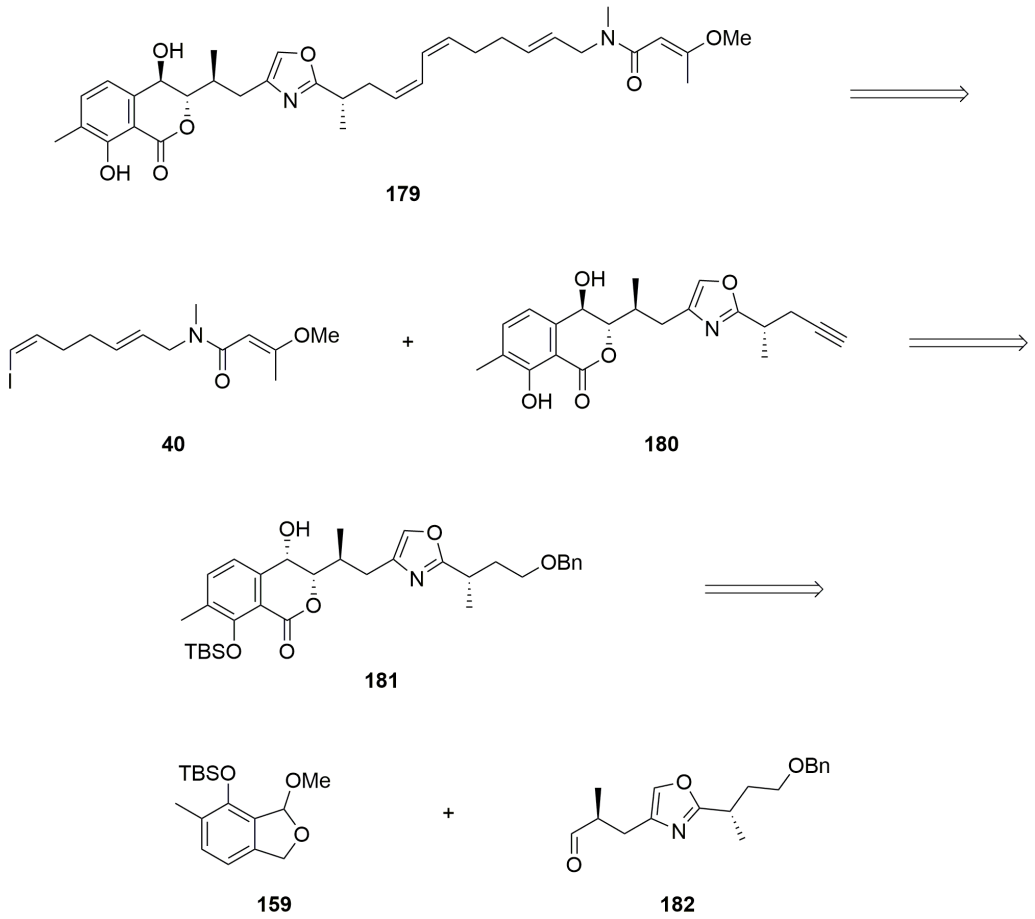
Scheme 1.41: Reduction of keto-lactone **176**.

Entry	Conditions	*Syn*:*Anti*	Yield (%)
1	$NaBH_4.CeCl_3$	100:0	82
2	$NaBH_4$	100:0	89
3	$Na(CN)BH_3$	100:0	52
4	*L*-selectride	-	-
5	Me_2AlCl	100:0	71
6	$Sm(O^iPr)_3$	100:0	64
7	BH_3	12:1	40
8	9-BBN	-	-
9	Alpine borane	-	-
10	(*R*)-CBS, BH_3	12:1	45
11	(*S*)-CBS, BH_3	12:1	45

Table 1-2: Reduction conditions

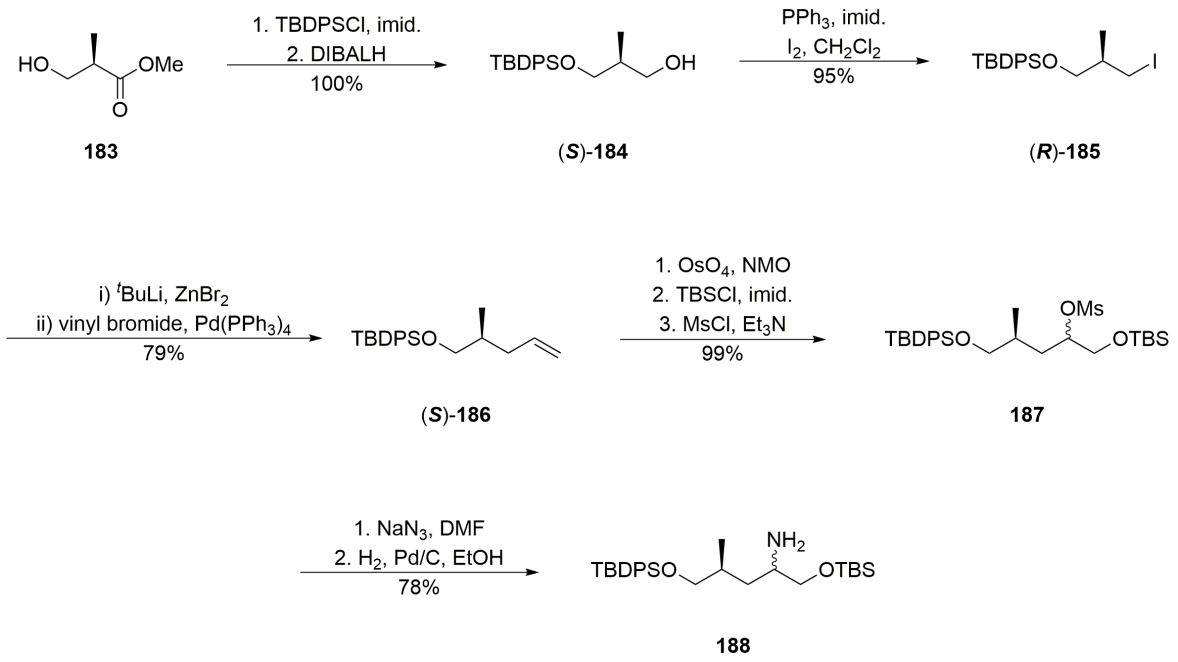
1.9 PREVIOUS EFFORTS TOWARDS THE TOTAL SYNTHESIS OF AJUDAZOL B

Studies towards the total synthesis of ajudazol B began in the group before the absolute stereochemistry had been determined, meaning initial efforts were directed towards what was later determined to be the enantiomer. (-)-Ajudazol B **179** was envisioned as being synthesised from Sonogashira coupling of vinyl iodide **40** and acetylene **180**, followed by partial reduction of the alkyne to the *Z*-diene. Alkyne **180** would be generated from isochromanone **181** *via* Mitsunobu inversion of the C8-hydroxy group, deprotection of the benzyl ether, oxidation of the resultant alcohol to the aldehyde and homologation to give the alkyne with concomitant deprotection of the TBS ether. Isochromanone **181** in turn would be synthesised from the oxidative rearrangement of fully functionalised phthalan **159** and oxazole-aldehyde **182** (scheme 1.42).



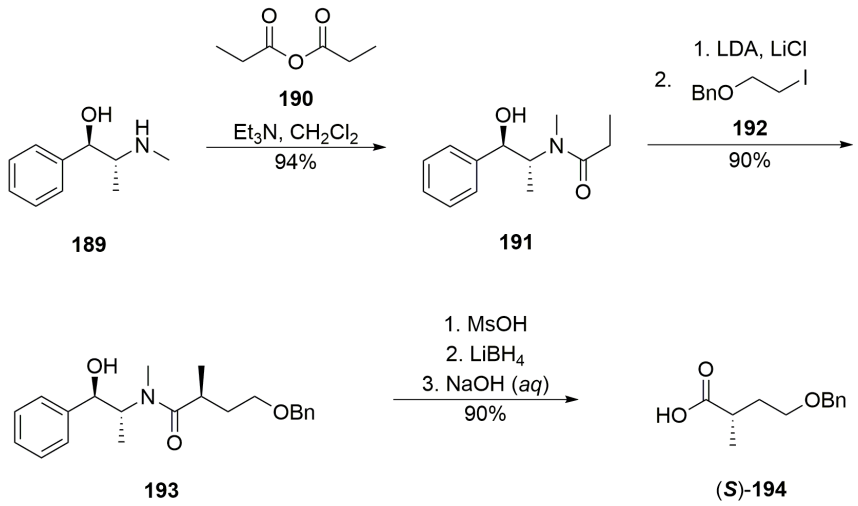
Scheme 1.42: Initial proposed route to (-)-ajudazol B **179**.

Synthesis of the oxazole fragment **182** began with TBDPS protection of (*R*)-Roche ester **183** to give alcohol (***S***)-**184**, in quantitative yield. The alcohol (***S***)-**184** was then converted to iodide (***R***)-**185**, using Appel conditions in high yield. Negishi coupling between iodide (***R***)-**185** and vinyl bromide then gave olefin (***S***)-**186**.[51] Upjohn dihydroxylation, followed by selective protection of the primary alcohol, and conversion of the secondary alcohol to the mesylate gave intermediate **187**, in excellent yield. Displacement of the mesylate with sodium azide, followed by reduction of the azide intermediate completed the synthesis of amine **188** (scheme 1.43).[50]



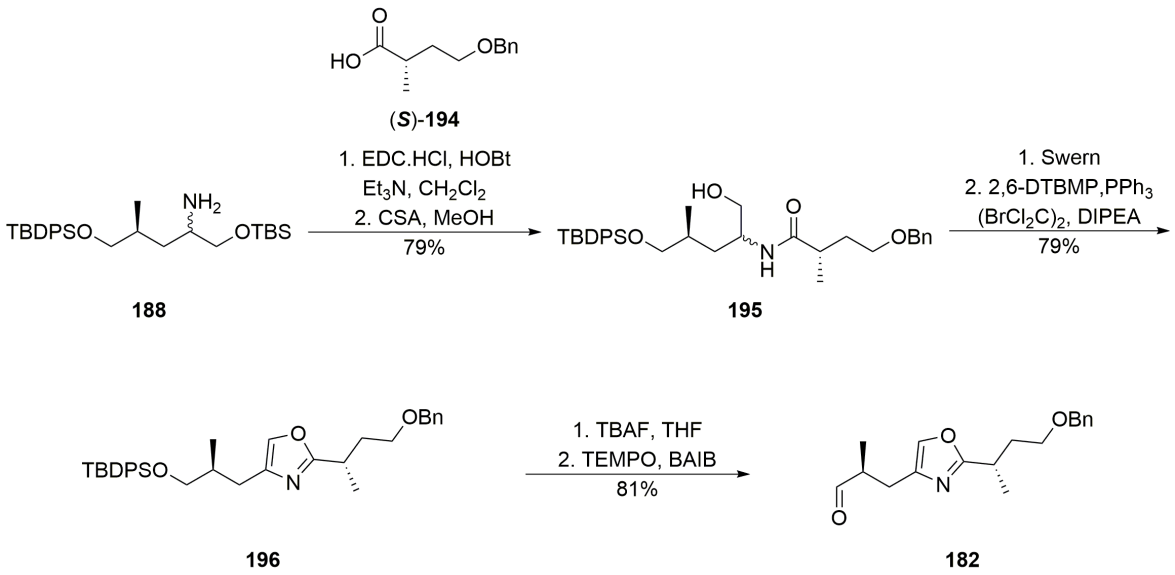
Scheme 1.43: Synthesis of amine **188**.

The synthesis of enantiopure acid (***S***)-**194**, began with (-)-pseudoephedrine **189** which was propionylated to generate amide **191**, in excellent yield. Amide **191** was then used in a diastereoselective Myer's alkylation with the known iodide **192**.[52] *N*,*O*-acyl transfer, borane complexation, and finally ester hydrolysis, gave the enantiopure acid (***S***)-**194** (scheme 1.44).



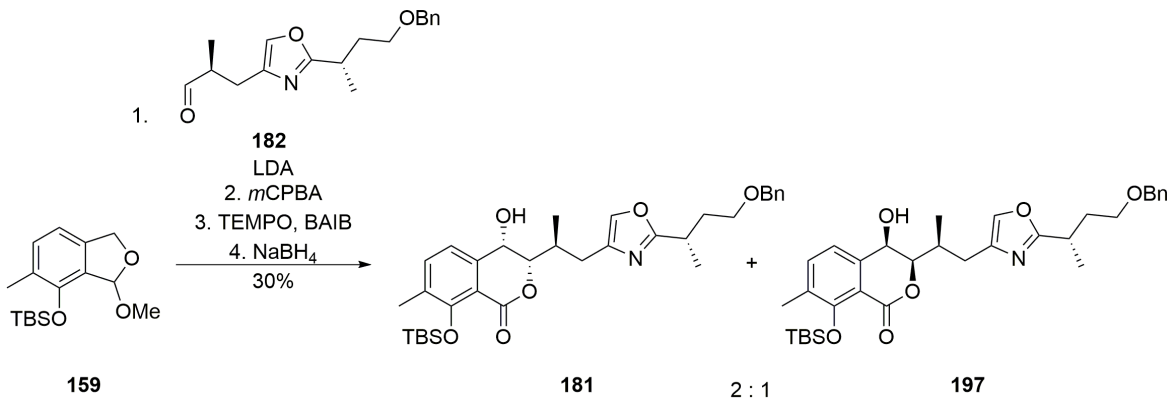
Scheme 1.44: Synthesis of enantiopure acid (**S**)-**194**.

Amide coupling between acid (***S***)-**194** and amine **188** followed by removal of the TBS group yielded *β*-hydroxyamide **195**. Swern oxidation followed by Wipf's cyclodehydration of the resulting *β*-formylamide then gave oxazole **196**.[34] Desilylation and oxidation of the primary alcohol completed the synthesis of oxazole-aldehyde **182** (scheme 1.45).



Scheme 1.45: Synthesis of aldehyde **182**.

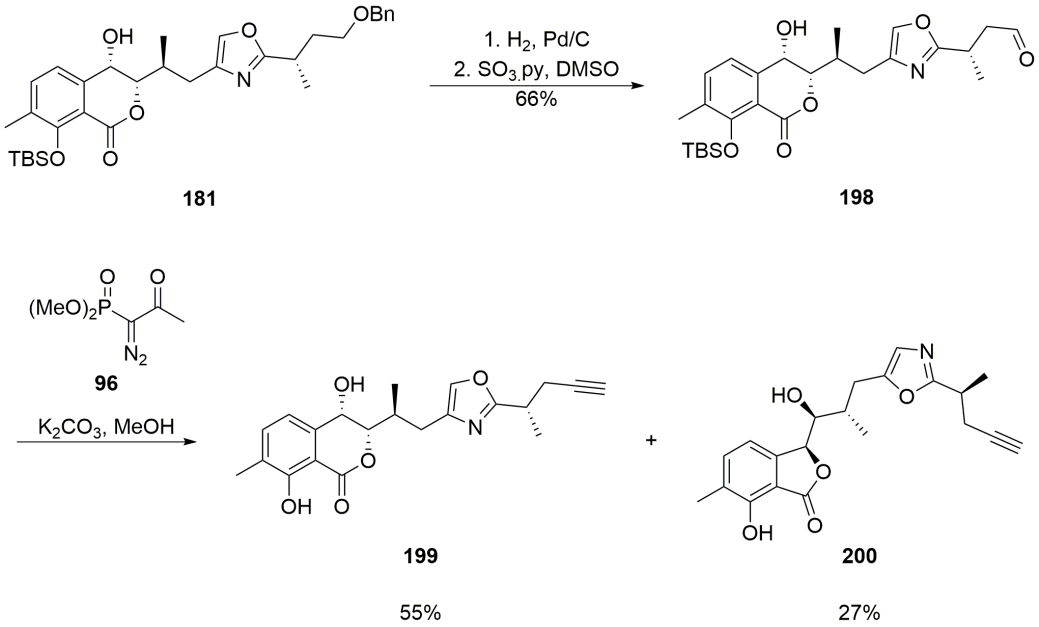
With the phthalan **159** and aldehyde **182** in hand, the decisive oxidative rearrangement sequence was carried out. After optimization, the *syn*,*anti*-diastereomer **181** and *syn*,*syn*-diastereomer **197** were successfully synthesized in a 2:1 mixture. The diastereomers were separable *via* HPLC (scheme 1.46).



Scheme 1.46: Synthesis of the C1-C17 fragment of ajudazol B.

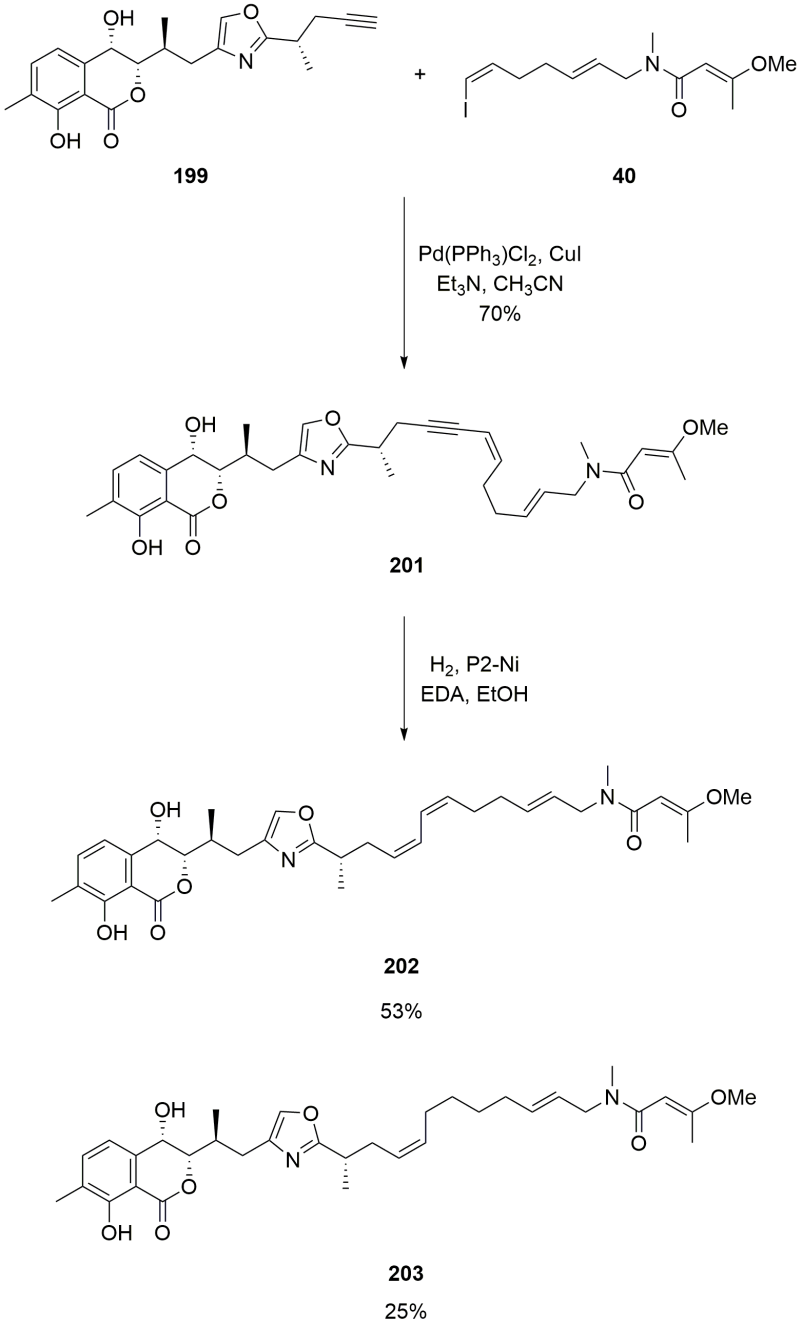
Hydrogenolysis of benzyl ether **181** followed by oxidation of the resulting alcohol yielded the key aldehyde **198**. It is worth noting that Parikh-Doering oxidation conditions demonstrated best selectivity, with negligible amounts of oxidative side products being detected. Seyferth-Gilbert homologation of aldehyde **198**, using Ohira-Bestmann reagent **96** proceeded to afford the desired alkyne unit **199**, with concomitant removal of the TBS group. Unfortunately, *trans*-lactonised 5-membered lactone **200** was the main product isolated.

However, after optimisation, the desired product **199** could be isolated as the major product in 55% isolated yield (scheme 1.47).



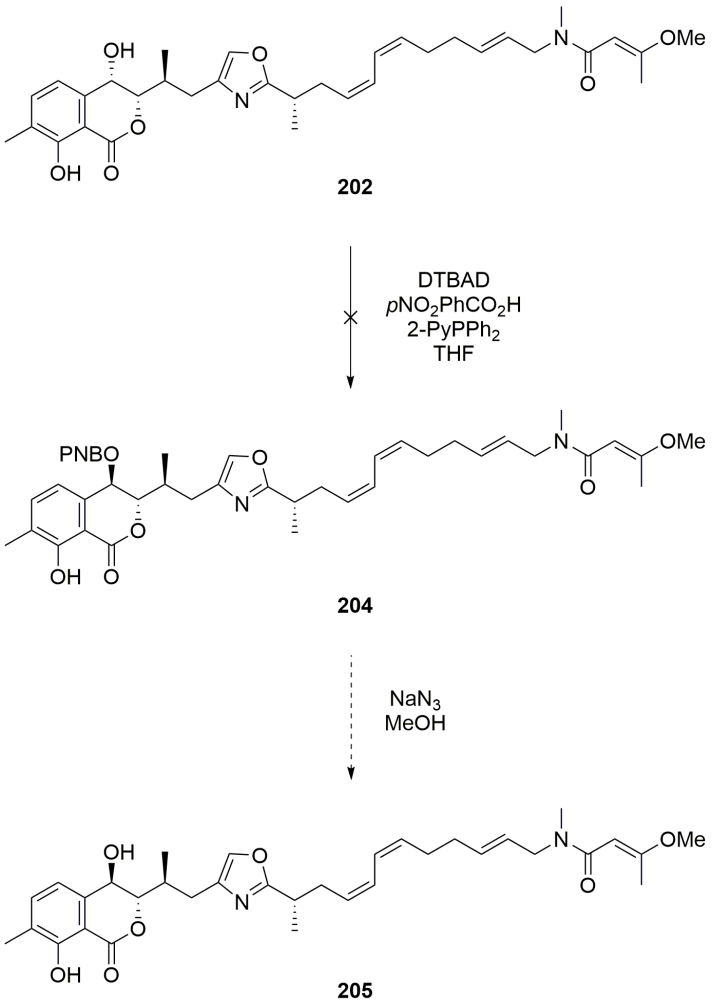
Scheme 1.47: Synthesis of acetylene **199**.

Acetylene **199** was then coupled to vinyl iodide **40**, using Sonogashira coupling conditions, to successfully yield enyne **201**. The enyne **201** was then partially reduced under P2-Ni conditions to give *ent*-8-*epi*-ajudazol B **202**, in a 2:1 mixture with the over-reduced compound **203**. The two compounds were separable *via* HPLC with *ent*-8-*epi*-ajudazol B **202** being isolated in 53%, and the over-reduced product **203**, in 25% yield (scheme 1.48).



Scheme 1.48: Synthesis of *ent*-C8-*epi*-ajudazol B **202**.

Next, the Mitsunobu conditions that were successfully employed to give the *anti*,*anti*-isochromanone **175** (scheme 1.40), were trialled. Unfortunately, in this more structurally complicated system they were unsuccessful affording only starting material. More forceful conditions involving the addition of excess reagents, or elevated temperatures only led to decomposition of the starting material (scheme 1.49).[50]



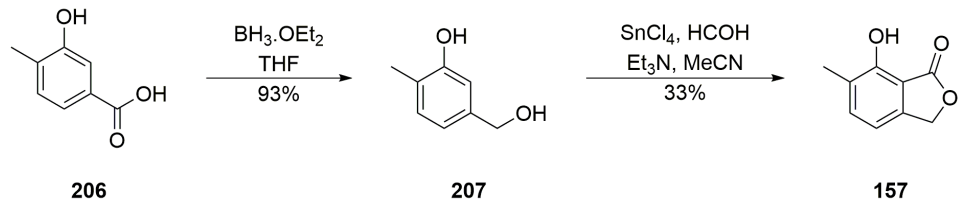
Scheme 1.49: Unsuccessful Mitsunobu inversion to yield *anti*,*anti*-isochromanone core.

2 SYNTHESIS OF PHTHALIDE FRAGMENT

The initial aim of the project was to develop a more efficient, shorter synthesis of phthalide precursor **158**, which would then be used as a key building block in the synthesis of the ajudazols. The synthesis of phthalide **158** previously established within the group was lengthy, consisting of 10 steps, and requiring multiple purifications (scheme 1.33).

2.1 PREVIOUS WORK

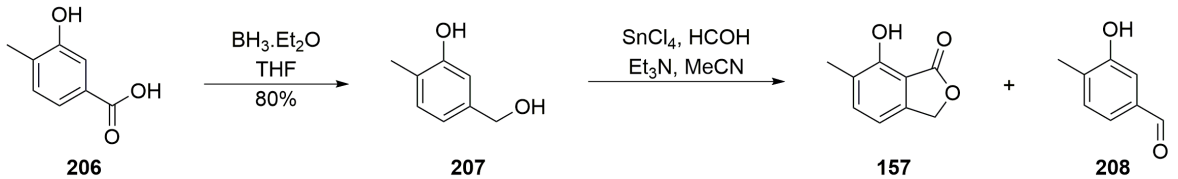
In 2006, Toney published the synthesis of 7-hydroxy-6-methyl phthalide **157**. In Toney's approach, 3-hydroxy-4-methylbenzoic acid **206** was reduced to generate 3-hydroxy-4-methylbenzyl alcohol **207**. Treatment of alcohol **207** with tin (IV) chloride, and formaldehyde, gave the desired phthalide **157**, with high regioselectivity, albeit in poor yield (scheme 2.1).[53]



206 **207** **157**

Scheme 2.1: Toney's synthesis of 7-hydroxy-6-methyl phthalide **157**.

Faced with such close precedent, Toney's approach was emulated within the group. Interestingly, although the borane reduction proceeded in good yield, the lactone formation step gave none of the desired phthalide product **157**. The only identifiable product was 3-hydroxy-4-methylbenzaldehyde **208**, in 6% yield (scheme 2.2).[50] Toney did report the formation of this compound as a side product, however no mention was made of the yield obtained.[53]

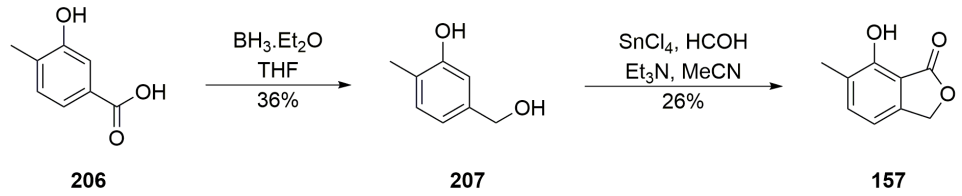


206 **207** **157** **208**

0% 6%

Scheme 2.2: Initial reproduction of Toney's synthesis of phthalide **157** within the Marquez group.

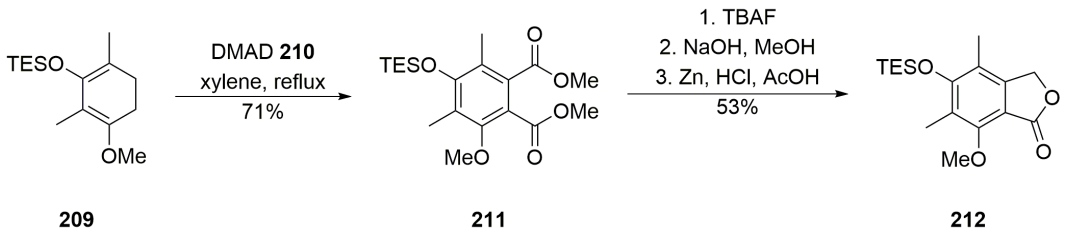
Due to the large discrepancy between the previous efforts within the group and the literature procedure, Toney's synthesis was attempted again. In this case, the borane reduction was successful, but low yielding. The subsequent lactone formation was successful resulting in the generation of the desired phthalide product in 26% yield (scheme 2.3). Although the product was obtained, the low yield, and the lack of reproducibility meant that a new route was investigated.



Scheme 2.3: Synthesis of 7-hydroxy-6-methyl phthalide **157**.

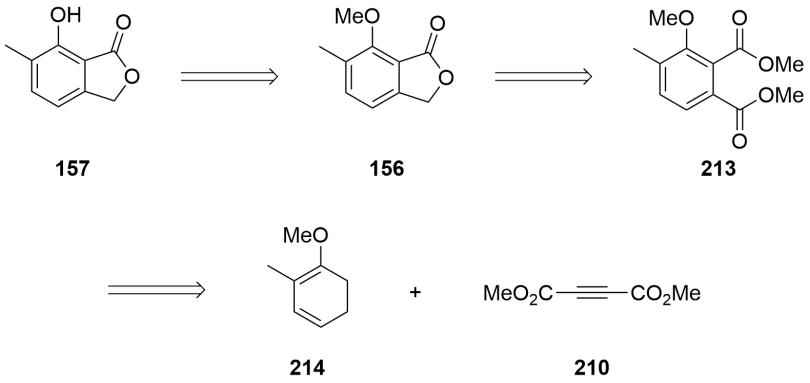
2.2 ALDER-RICKERT APPROACH

In 2008, Kuwahara published a synthesis of novel anti-fungal phthalides, using an Alder-Rickert reaction to generate the poly-substituted aromatic diester **211**. Hydrolysis of the diester intermediate **211** followed by reduction, completed the synthesis of the phthalide **212** (scheme 2.4).[54]



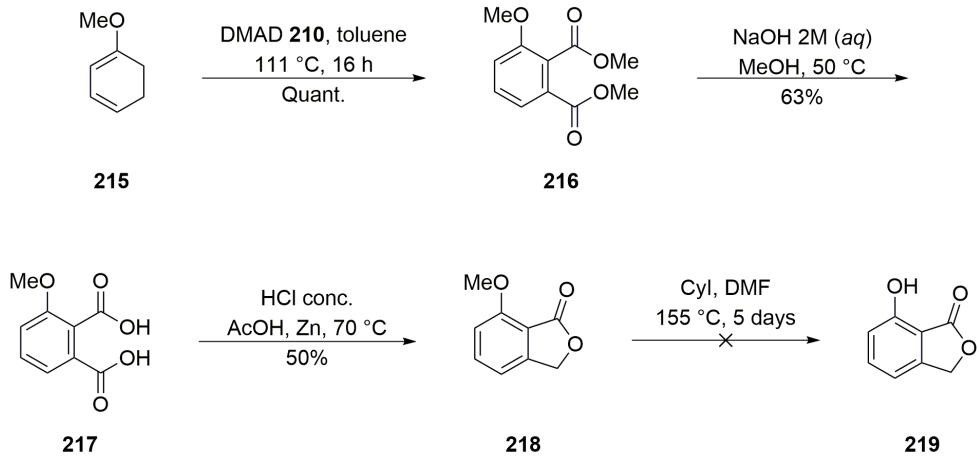
Scheme 2.4: Kuwahara's Alder-Rickert approach to phthalide **212**.

Inspired by this tactic, an alternative approach to 7-hydroxy-6-methyl phthalide **157** was envisaged. In this new scheme, the target phthalide was thought of as being accessed through the demethylation of methoxy phthalide **156**, which in turn would be generated from hydrolysis and reduction of diester **213**. The key diester could be synthesized through an Alder-Rickert reaction between cyclohexadiene **214** and dimethyl acetylenedicarboxylate (DMAD) **210** (scheme 2.5).



Scheme 2.5: Proposed Alder-Rickert approach to 7-hydroxy-6-methyl phthalide **157**.

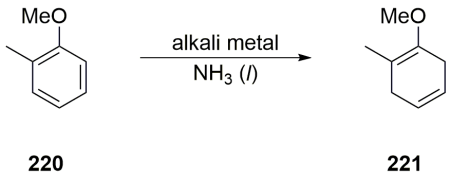
To test the reaction conditions, a model system was devised in which commercially available diene, 1,3-methoxycyclohexyl-1,3-diene **215**, was subjected to an Alder-Rickert reaction with DMAD. Gratifyingly, this reaction gave 3-methoxy phthalate **216** in quantitative yield. The diester **216** was then hydrolysed to give the diacid **217** in 63% yield. Kuwahara's conditions were then applied, and 7-methoxyphthalide **218**, was successfully synthesised in 50% yield, without the need for purification. Unfortunately, demethylation of the crude methyl ether **218** failed to yield any of the desired product.[55] However, despite the failure of the last step, the validity of this synthetic approach was demonstrated (scheme 2.6).



Scheme 2.6: Synthesis of 7-methoxyphthalide **218** using an Alder-Rickert approach.

With the success of the model system, synthesis of the fully functionalised diene **214** was explored. It was envisaged that diene **214** could be generated through the Birch reduction of 2-methylanisole **220**, followed by a double bond isomerisation. Alternatively, it was postulated that the 1,4-diene **221** might isomerise *in-situ* under the Alder-Rickert thermal conditions. Unfortunately, treatment of 2-methylanisole **220** with sodium under Birch conditions failed to produce the characteristic deep blue metallic colour, and only starting material was recovered, regardless of solvent or proton source. Switching the alkali metal to

lithium caused the reaction to afford a 5:1 ratio of starting material to product. Switching the solvent from THF to Et_2O, and removing the proton source, further increased product formation, and an optimised 57% yield of the desired 1,4-diene **221** was obtained (table 2-1).[56]



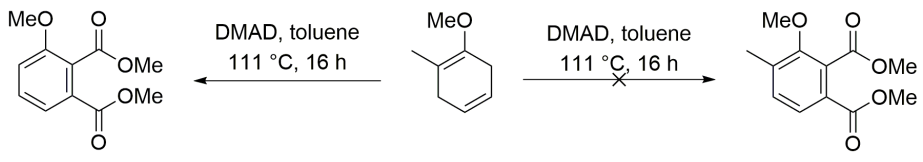
220 **221**

Scheme 2.7: Birch reduction of **220**.

Entry	Alkali metal	Solvent	Proton source	Yield	SM : Product
1	Na	THF	^{t}BuOH	-	1:0
2	Na	Et_2O	-	-	1:0
3	Na	THF	EtOH	-	1:0
4	Li	THF	^{t}BuOH	-	5:1
5	Li	Et_2O	-	57%	0:1

Table 2-1: Birch reduction of 2-methylanisole **220** conditions.

With the 1,4-diene **221** at hand, the isomerisation was then attempted. Disappointingly, all attempts to isomerise the disubstituted double bond to give 1,3-diene **214**, proved to be unfruitful, thus 1-methoxy-2-methyl-1,4-cyclohexadiene **221** was used in a thermal Alder-Rickert reaction with DMAD **210**. It was hoped that the double bond could isomerise *in-situ*, and then undergo the required Alder-Rickert reaction to generate the desired product **213**. Frustratingly, none of the desired compound was isolated, and only 3-methoxy phthalate **216** was obtained (scheme 2.8).



216 **221** **213**

Scheme 2.8: Alder-Rickert using 1-methoxy-2-methyl-1,4-cyclohexadiene **221** and DMAD **210**.

Formation of **216** could be rationalised by isomerisation of the tetra-substituted double bond to generate diene **222**, which upon an Alder-Rickert reaction with DMAD **210**, affords compound **216**, with the elimination of propene **224** as shown in figure 2.1.

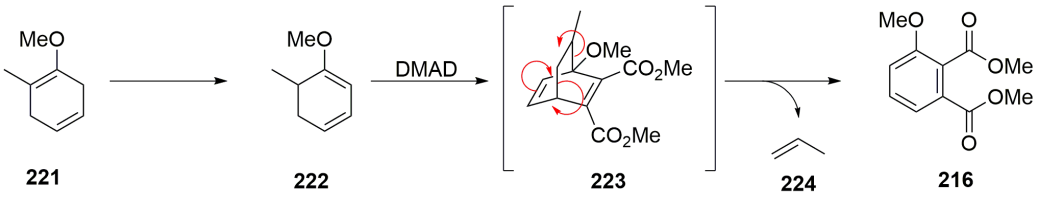
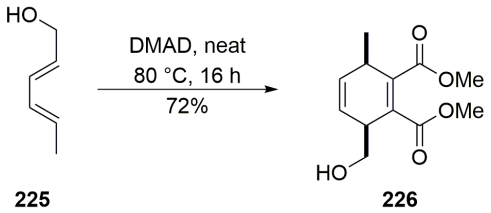


Figure 2.1: Mechanism of undesired elimination of propene.

Next, *trans*,*trans*-2,4-hexadien-1-ol **225** was investigated as the diene partner. It was hoped that upon cyclisation, the 5-membered lactone could be formed either simultaneously or upon basic treatment. Although the thermal cycloaddition did take place, spontaneous formation of the lactone did not take place as hoped. Using toluene as the solvent allowed isolation of the product in 45% yield after 16 h. Increasing the reaction time to 60 h improved the yield slightly to 51%, whilst performing the reaction without solvent gave the product **226** in 72% after 16 h (scheme 2.9).



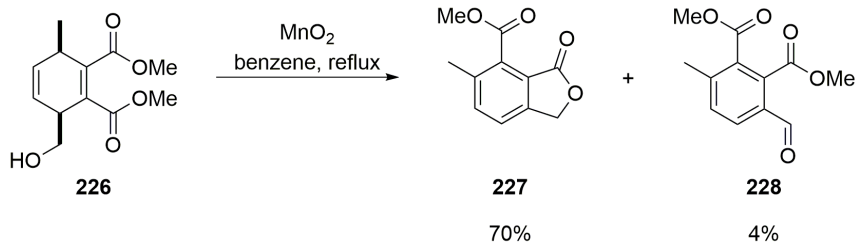
Scheme 2.9: Synthesis of diene **226**.

Next, conditions were trialled to facilitate the aromatisation and formation of the lactone. DDQ was initially used as an oxidant. At room temperature, the oxidation failed to proceed. Heating the reaction to either 50 °C or reflux resulted in only recovery of starting material.

Singaram had reported the synthesis of substituted benzenes *via* a Diels-Alder reaction, and subsequent oxidation using $KMnO_4$ under mild conditions.[57] Using Singaram's conditions failed to give any of the desired product, with only starting material being recovered, as well as undesired partial oxidation of the alcohol to the aldehyde. A different approach using palladium on carbon and cyclohexene, as a sacrificial hydrogen acceptor, gave no reaction. Methanolic K_2CO_3 also did not yield any of the desired products, and merely led to decomposition.

Keehn had published the use of activated MnO_2 to mediate oxidative dehydrogenations on very similar substrates.[58] Using refluxing benzene and a Dean-Stark apparatus, treatment of diene **226** with ten equivalents of activated MnO_2, resulted in formation of the phthalide

227 in 12% yield. Reducing the reaction time from 16 h to 4 h, increased the yield of phthalide **227** to 70%. A small amount of aldehyde **228** was isolated, where aromatisation had occurred and the benzylic alcohol was oxidised, as opposed to forming the lactone (scheme 2.10, table 2-2).



Scheme 2.10: Synthesis of phthalide **227**.

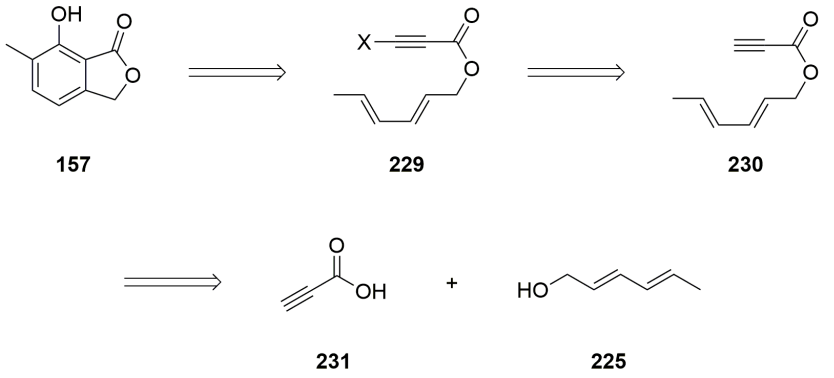
Entry	Reagents	Temp. (°C)	Yield 227 (%)	Yield 228 (%)
1	DDQ, toluene	rt	-	-
2	DDQ, toluene	50	-	-
3	DDQ, toluene	110	-	-
4	$KMnO_4/Al_2O_3$, acetone	0	-	-
5	Pd/C, Cyclohexene, MeOH	rt	-	-
7	K_2CO_3, MeOH	rt	-	-
8	MnO_2, benzene, 16 h	80	12	-
9	MnO_2, benzene, 4 h	80	70	4

Table 2-2: Oxidation of diene **226**.

2.3 [4+2] ESTER TETHERED CYCLOADDITION APPROACH

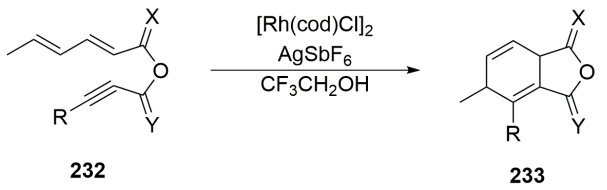
Encouraged by the promising results obtained in the Diels-Alder reaction, a new strategy was devised. In a new approach, 7-hydroxy-6-methyl phthalide **157**, would be accessed through the key [4+2] intramolecular cycloaddition of the ester tethered alkyne-diene **229**. Alkyne **229** would originate from the functionalisation of terminal acetylene **230**, which in

turn would be generated from the esterification of propiolic acid **231** and *trans,trans*-2,4-hexadien-1-ol **225** (scheme 2.11).



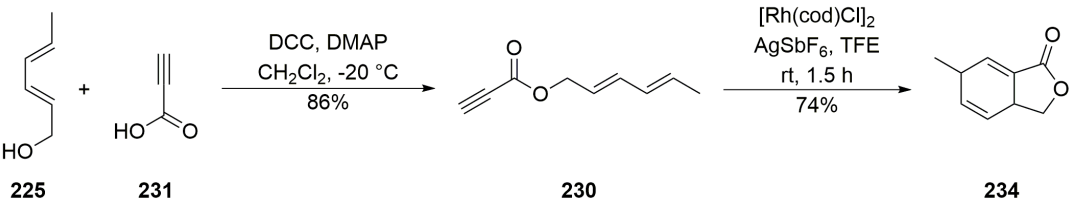
Scheme 2.11: Intramolecular approach to 7-hydroxy-6-methyl phthalide **157**.

Conditions for the intramolecular [4+2] cycloaddition were inspired by the work of Saito. Saito and coworkers reported the use of a cationic rhodium catalyst to mediate the [4+2] cycloaddition of ester-tethered 1,3-diene-8-yne derivatives. The resulting dienes were then oxidised to the corresponding bicyclic lactones (scheme 2.12).[59]



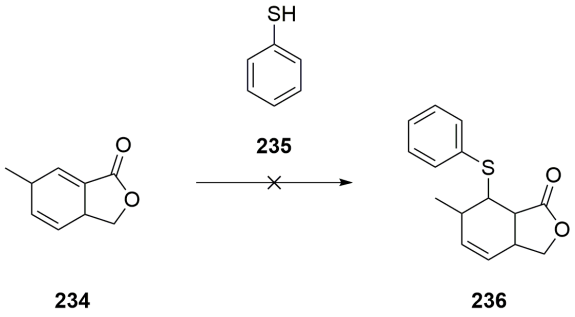
Scheme 2.12: Saito's Rh(I) catalyzed [4+2] cycloaddition of ester-tethered 1,3-diene-8-yne derivatives.

Our new approach began with a Steglich esterification between *trans-trans* -2,4-hexadien-1-ol **225** and propiolic acid **231** to generate diene-yne **230** in high yield.[59-61] Intramolecular [4+2] cycloaddition under Saito's conditions then proceeded to afford the desired lactone **234** in good overall yield (scheme 2.13).



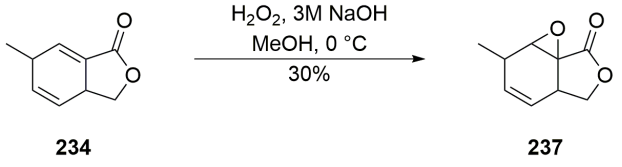
Scheme 2.13: Synthesis of lactone **234**.

With lactone **234** in hand, it was decided to investigate whether further functionalisation was possible. It was hoped a conjugate addition to **234** would allow for the installation of the hydroxyl group on the C7 carbon. Thiophenol was initially chosen as the nucleophile, as the thioether product could potentially then be oxidised to the corresponding hydroxy group. Several sets of conditions were attempted for the conjugate addition utilising thiophenol. Unfortunately, this approach proved to be unsuccessful and none of the desired product was synthesised (scheme 2.14).



Scheme 2.14: Unsuccessful conjugate addition to **234** using thiophenol.

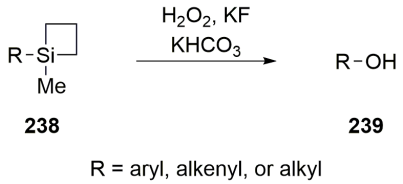
Faced with the lack of success in the nucleophilic addition using thiophenol, it was decided to investigate the nucleophilic epoxidation of **234**, to functionalise the aromatic ring. Treatment of lactone **234** with 3M NaOH (*aq*) and H_2O_2 afforded the desired epoxide **237**, albeit in low yield (scheme 2.15).



Scheme 2.15: Nucleophilic epoxidation of **234**.

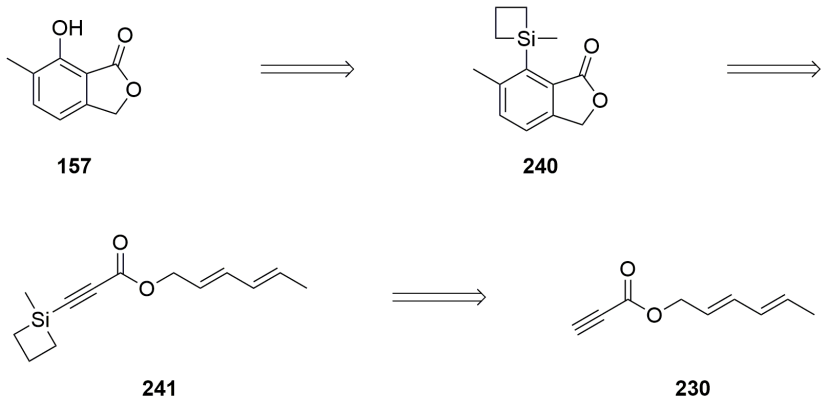
It must be noted that this process was unoptimised and carried out on a small scale. Although this reaction provided a potentially useful pathway, it was decided to focus our efforts on more step economic approaches.

Due to the efficiency of the ester-tethered [4+2] cycloaddition, but the limited success of the subsequent functionalisation, it was decided to investigate alternative ways of installing the oxygen at the C7 position. In 2003, Dudley and coworkers demonstrated the usefulness of strained siletanes as substrates for Tamao-type carbon-silicon oxidation to give alcohols. Dudley reported a range of substrates that were stable and readily oxidised to give the corresponding alcohols, in good yields (scheme 2.16).[62]



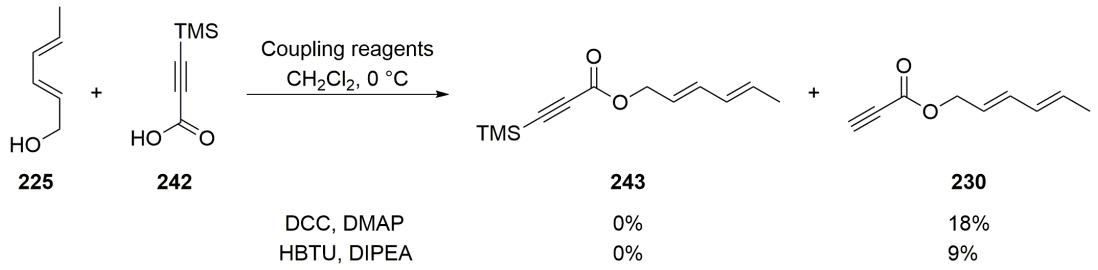
Scheme 2.16: Dudley's oxidation of strained siletanes.

Thus, a modified approach to the synthesis of phthalide **157** was envisaged in which the terminal acetylene **230** was functionalised with a strained siletane ring, before being subjected to Saito's [4+2] cycloaddition conditions.[59] If successful, mild oxidation of the resulting siletane **240** should afford the desired phthalide unit **157** (scheme 2.17).



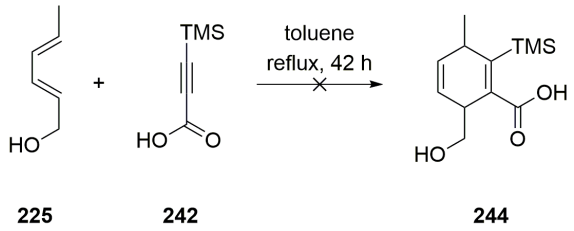
Scheme 2.17: Proposed synthesis of **157** using a strained siletane.

As 1-chloro-1-methylsilacyclobutane was not readily available, TMSCl was used to test the compatibility of a silyl group with the cycloaddition conditions. Thus, the coupling of *trans-trans*-2,4-hexadien-1-ol **225** and 3-(trimethylsilyl)prop-2-ynoic acid **242** was attempted initially using both DCC and HBTU. However, in each case only the desilylated product **230** was isolated (scheme 2.18).



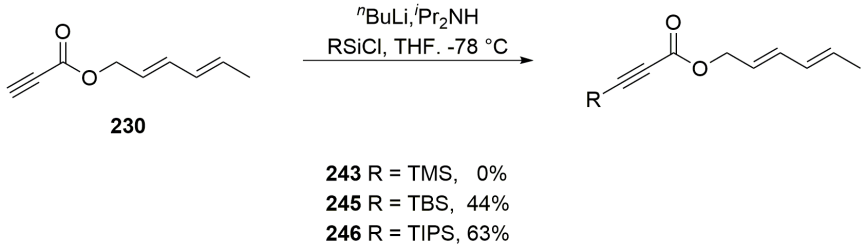
Scheme 2.18: Failed synthesis of TMS-alkyne **243**.

Due to the lack of success with the coupling, it was decided to attempt the cycloaddition before the esterification step. Unfortunately, the reaction of diene **225** with alkyne **242** under thermal conditions at different concentrations (0.15 M and 0.7 M) failed to give any of the desired diene **244** (scheme 2.19).



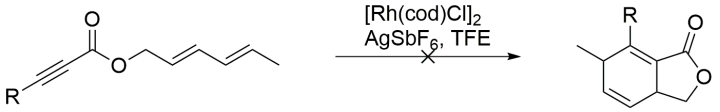
Scheme 2.19: Unsuccessful cycloaddition of **225** and **242**.

Faced with the latest setback, a different approach was attempted in which the esterification was carried out before the incorporation of the silyl group. Thus, treatment of acetylene **230** with LDA followed by capturing the resulting alkyne anion with different chlorosilanes was attempted (scheme 2.20).



Scheme 2.20: Silylation of **225**.

The newly synthesised silyl acetylenes **245** and **246**, were then subjected to Saito's conditions.[59] Disappointingly, this led to decomposition of the starting materials, with none of the cyclised products being observed (scheme 2.21).

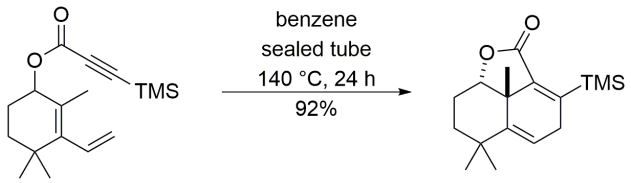


245 R = TBS **247**
246 R = TIPS **248**

Scheme 2.21: Unsuccessful cycloaddition of **245** and **246** employing Saito's conditions.

The instability of either the silyl acetylenes or the silylated products under Saito's conditions prompted us to consider alternative reaction conditions. We were particularly interested in moving away from the use of $AgSbF_6$ to minimise the possible loss of the silyl groups.

Nicolaou had reported the use of an ester-tethered silyl substituted alkyne-diene substrate, in an intramolecular [4+2] cycloaddition to access tricyclic intermediate **250** as part of his synthesis of forskolin (scheme 2.22).[63]



249 **250**

Scheme 2.22: Nicolaou's ester tethered silyl substituted alkyne-diene **249** [4+2] cycloaddition.

Thus, it was hoped that a thermal [4+2] cycloaddition would therefore allow the cyclisation of substrates **245** and **246**. In each case however, the substrate was refluxed in toluene for 24 h with no desired products being observed, and only starting material detected. Attempts to push the reaction forward by increasing the temperature, changing the solvent, and using the microwave initiator proved unsuccessful (table 2-3).

245 R = TBS **247**
246 R = TIPS **248**

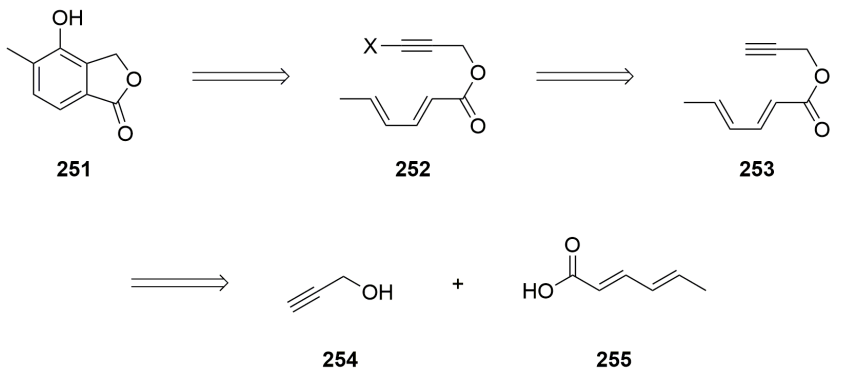
Scheme 2.23: Unsuccessful cycloaddition of **245** and **246**.

Entry	Solvent	Temperature (°C)	Time (h)	247 yield (%)	248 yield (%)
1	toluene	111	24	SM	SM
2	toluene	160 (sealed vial)	24	SM	SM
3	DMF	200 (MW)	3	decomposition	decomposition

Table 2-3: Unsuccessful cycloaddition of **245** and **246**.

Previous work in the group had demonstrated that the oxidative rearrangement followed a convergent/divergent approach in which both the C3 and C7 OTBS substituted phthalides converged into a common isobenzofuran intermediate which then would react regioselectively due to the presence of the TBS group (scheme 1.32).[48]

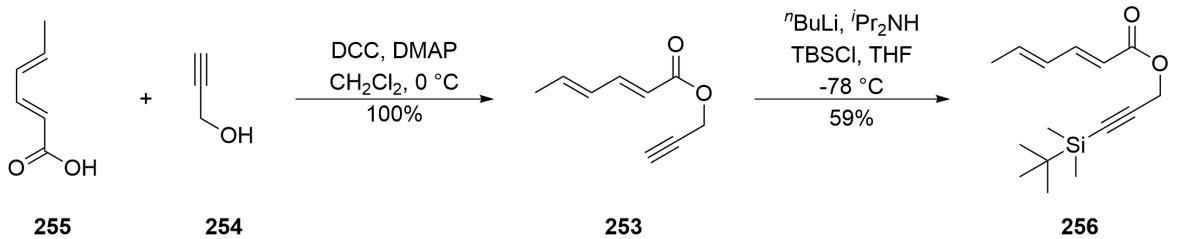
Thus, the alternative 4-hydroxy-5-methyl phthalide **251** was envisaged as originating from the esterification of 2,4-hexadienoic acid **255** with propargyl alcohol **254**, to give ester-tethered alkyne-diene **253**. Alkyne **253** would then be functionalised and a [4+2] cycloaddition should yield the desired phthalide **251** (scheme 2.24).



251 **252** **253** **254** **255**

Scheme 2.24: Proposed synthesis of 4-hydroxy-5-methyl phthalide **251**.

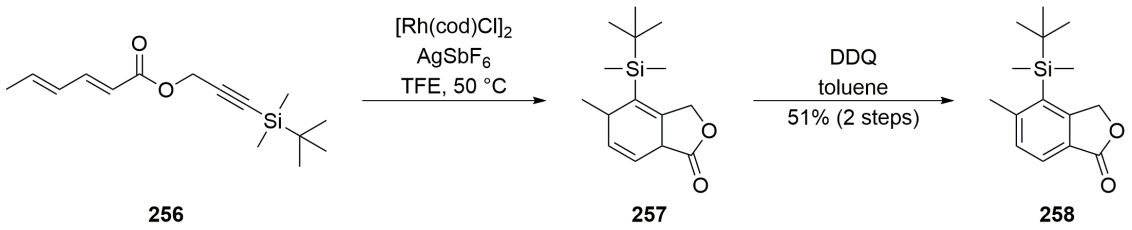
Steglich esterification of 2,4-hexadienoic acid **255** and propargyl alcohol **254** gave the desired ester **253**, in quantitative yield.[61] Next, the terminal alkyne was deprotonated with LDA and the resulting anion was trapped with TBSCl, to yield the silylated product **256** (scheme 2.25).



255 **254** **253** **256**

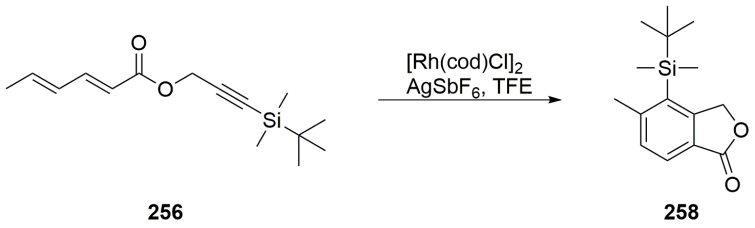
Scheme 2.25: Synthesis of alkyne **256**.

Saito reported that the cycloaddition of diene-yne **256** took place at 50 °C, and the product was oxidised using DDQ to give the aromatic phthalide product **258** (scheme 2.26).



Scheme 2.26: Saito's synthesis of phthalide **258**.

In our hands, the cyclisation could not be repeated, with no reaction taking place under the reported conditions. However, heating the reaction mixture to reflux for 72 h yielded the fully aromatic product in low yield (19%), negating the need for the additional oxidation step. Encouragingly, when the reaction was undertaken in the microwave, the yield was improved to 32% (61% based on recovery of starting material) (scheme 2.27, table 2-4).



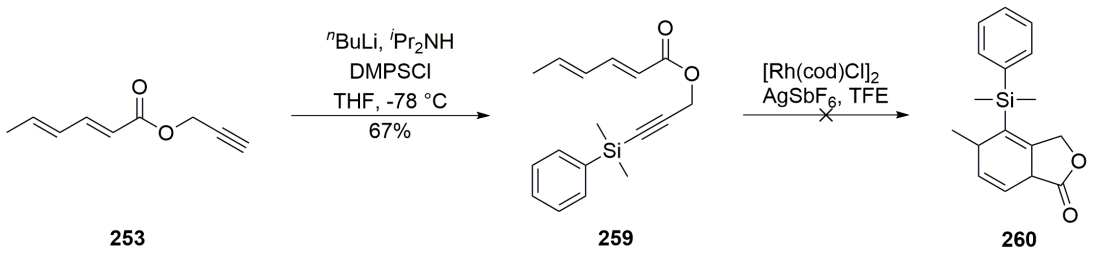
Scheme 2.27. Synthesis of phthalide **258**.

Entry	Temperature (°C)	Time (h)	Yield 258 (%)
1	50	48	-
2	78	72	19
3	100 (MW)	2	32 (61 brsm)

Table 2-4: Cycloaddition conditions.

Despite this partial success, there was no precedent for the oxidation of an aromatic bound TBS-group to the corresponding phenol. Thus, the TBS group was replaced with a DMPS group. It was hoped that the DMPS group would allow the Fleming-Tamao oxidation to take place and generate the desired phenol functionality.

Synthetically, ester-tethered alkyne-diene **253**, was treated with LDA and then DMPSCl to give the desired silane **259**. Frustratingly, when silane **259** was used a substrate under Saito's conditions no reaction took place under all attempted reaction conditions (scheme 2.28).



Scheme 2.28: Synthesis of diene-yne **259** and failed cyclisation.

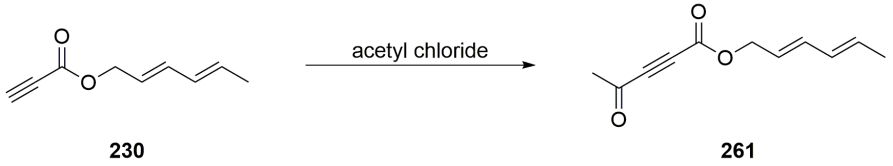
The disappointing results obtained by substitution of the alkyne with silicon groups meant that alternative functionalities were required.

Substitution with an acetyl group was trialled next as an alternative, as this would make the alkyne electron deficient, which should facilitate the cycloaddition reaction. Once the cyclisation was complete a Baeyer-Villiger type oxidation, followed by hydrolysis, could be employed to install the hydroxy group.

Initial attempts using either KHMDS or *n*BuLi to deprotonate the alkyne, followed by dropwise addition of acetyl chloride proved to be unfruitful, and no formation of the desired product was observed.

Cox and coworkers reported the palladium catalysed coupling of acyl chlorides with terminal alkynes, to generate alkynones in good yield.[64] Unfortunately, Cox's conditions failed to generate any of the desired product when applied to the coupling of alkyne **230** with acetyl chloride. A test reaction using 4-nitrobenzoyl chloride, to investigate whether acetyl chloride was unsuitable as a reagent under the reaction conditions, also failed to yield any of the desired product, with only decomposition taking place.

In 1956, Scheiber demonstrated the preparation of acetylenic ketones using silver acetylides as intermediates.[65] This methodology negated the need for a strong base for the deprotonation of the alkyne unit. In our hands, treatment of alkyne **230** with silver nitrate allowed the formation of the putative silver acetylide intermediate as a white precipitate. Disappointingly, none of the desired product was obtained using acetyl chloride under refluxing conditions (table 2-5).



230 261

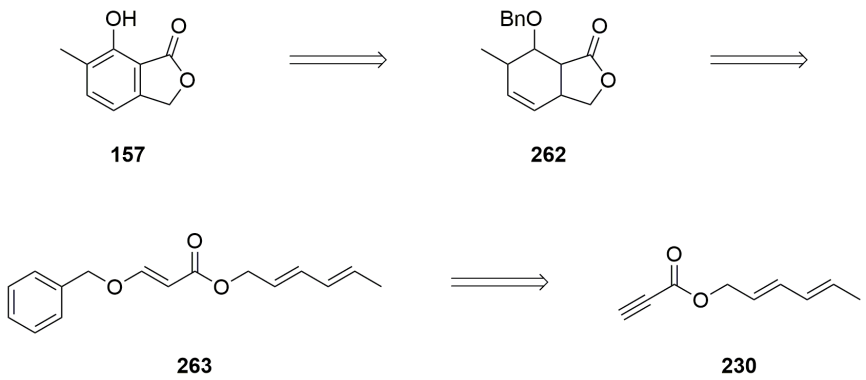
Scheme 2.29: Attempted synthesis of ester **261**.

Entry	Conditions	Yield 261 (%)
1	KHMDS, THF, -78 °C	-
2	^{n}BuLi, THF, -78 °C	-
3	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, rt	decomposition
4	(i) $AgNO_3$, H_2O, MeOH, NH_4OH (ii) CCl_4, 77 °C	-

Table 2-5:Acylation of acetylene **230**.

At this point, it was unclear as to whether the product was too unstable, or was not being formed under any of the sets of conditions investigated. Nevertheless, an alternative approach was required.

It was theorised that a conjugate addition to the alkyne unit using benzyl alcohol would give enol ether **263**. Enol ether **263** would then be able to undergo a cycloaddition, followed by subsequent oxidation/aromatisation with concomitant removal of the benzyl group to yield phthalide **157** (scheme 2.30).

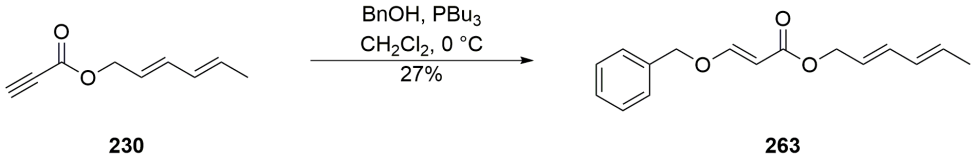


157 262 263 230

Scheme 2.30: Enol ether Diels Alder approach to phthalide **157**.

The conjugate addition was attempted using conditions employed by Procter, who had demonstrated the phosphine-catalysed conjugate addition of several alcohols, including benzyl alcohol, to methyl propiolate in excellent yield.[66] Using tributylphosphine as the catalyst, and benzyl alcohol as the nucleophile the desired product **263** was isolated,

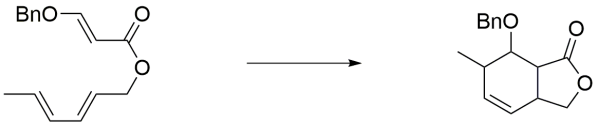
exclusively as the *E*-isomer, in poor yield of 27%, however enough material was isolated to investigate the following steps (scheme 2.31).



230 **263**

Scheme 2.31: Phosphine-catalysed conjugate addition.

It was hoped that enol ether **263** would undergo a thermal [4+2] cycloaddition to give lactone **262**. However, under reflux in toluene for 24 h, no formation of the desired products took place and only starting material was observed. Frustratingly, all attempts to push the reaction forward by increasing the temperature, reaction time, running the reaction neat, and in the microwave initiator proved to be unsuccessful (table 2-6).



262 **263**

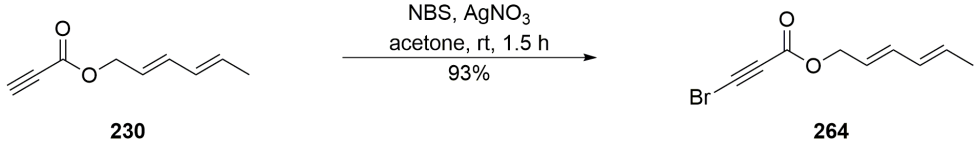
Scheme 2.32: Unsuccessful cyclisation of enol ether **262**.

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	toluene	111	24	-
2	toluene	120 (sealed tube)	72	-
3	toluene	160 (sealed tube)	72	-
4	neat	160 (sealed tube)	72	-
5	DMF	170 (MW)	2	-

Table 2-6: Attempted cyclisation conditions of enol ether **262**.

Failure of the benzyl ether, made us consider a different handle which would be stable to the cyclisation conditions, and could then be converted into the required phenol group.

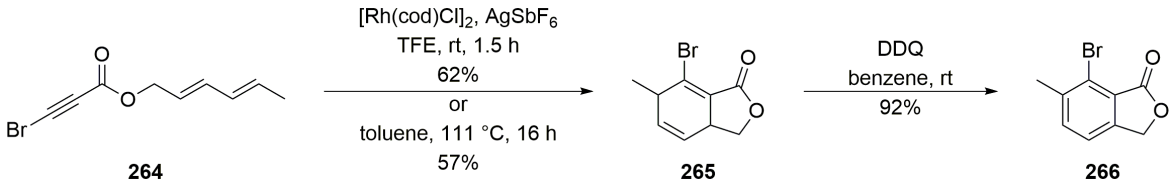
In 1992, Leroy adapted conditions originally developed by Hofmeister and coworkers for bromination of 17-ethynyl steroids to prepare 3-bromopropiolic esters.[67, 68] Employing Leroy's conditions, using *N*-bromosuccinimide and silver nitrate in acetone, the brominated alkyne **264** was generated in excellent yield, without the need for purification (scheme 2.33).



230 **264**

Scheme 2.33: Bromination of terminal acetylene **264**.

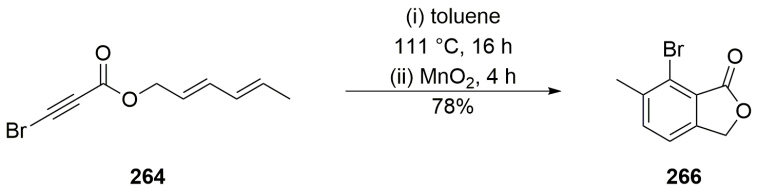
With **264** in hand, the Rh-catalysed [4+2] cycloaddition utilising Saito's conditions furnished the desired cyclic product **265** in good yield. Following this success, it was decided to attempt the thermal cyclisation in refluxing toluene to investigate whether the use of a catalyst was necessary. Pleasingly, the same cyclised product **265** was isolated *via* this method, in similar yield. The corresponding phthalide **266** was then obtained upon aromatisation, using DDQ in benzene (scheme 2.34)



264 **265** **266**

Scheme 2.34: Synthesis of bromo-phthalide **266**.

Following the successful synthesis of bromo-phthalide **266**, it was hoped that the cyclisation and aromatisation steps could be optimised, or preferably, combined. The bromo-alkyne **264**, was left to reflux in toluene overnight, before adding activated MnO_2. Excitingly. this combination successfully yielded the desired bromo-phthalide **266** in 78% yield, in a one pot process without the need for purification (scheme 2.35).

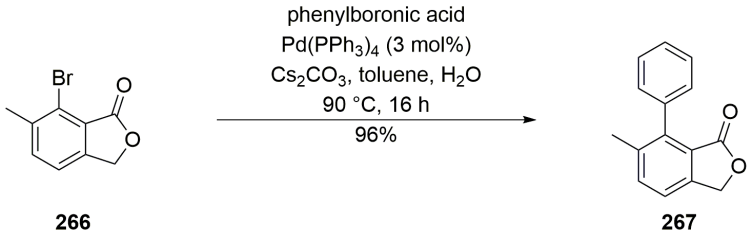


264 **266**

Scheme 2.35: One-pot cyclisation-oxidation of bromo-alkyne **266**.

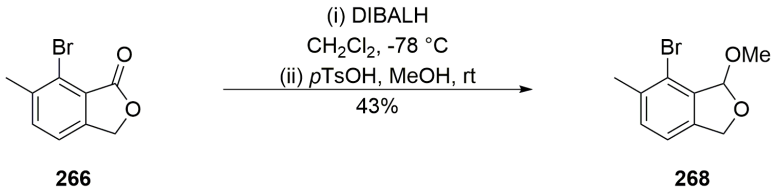
It was envisaged that not only could **266** be used as not only an intermediate in the synthesis of the phthalan **159**, but also as an intermediate in the synthesis of a number of potential analogues of ajudazol B. To test the use of the bromide as a synthetic handle, a Suzuki

coupling with phenylboronic acid was attempted. Satisfyingly, the coupling proceeded in excellent yield to give the desired product **267** (scheme 2.36).



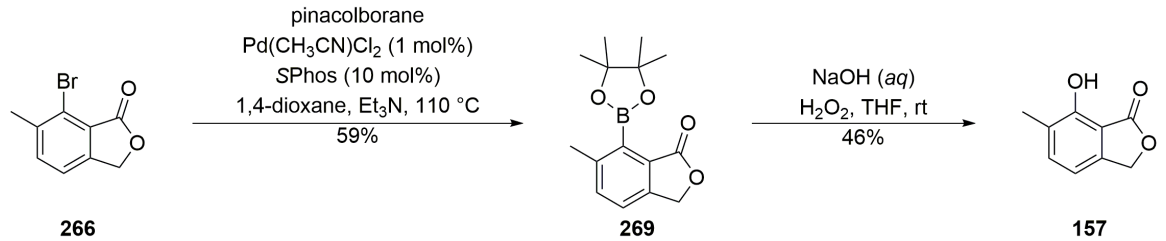
Scheme 2.36: Synthesis of **267** via Suzuki coupling.

Next, the conditions required to form the necessary phthalan units were tested. Encouragingly, the reduction, followed by methylation, gave the desired phthalan product **268** in reasonable yield (scheme 2.37).



Scheme 2.37: Synthesis of bromo-phthalan **266**.

With bromide **266** in hand, and its synthetic utility demonstrated, conditions to convert the bromide to the phenol whilst conserving the lactone functionality were explored. Buchwald, in 2008, reported conditions for the palladium catalysed borylation of aryl halides with pinacol borane.[37] These conditions successfully yielded pinacol borane **269**, which was then oxidised to the free phenol using hydrogen peroxide and sodium hydroxide to give **157** (scheme 2.38). These reactions were not optimised.

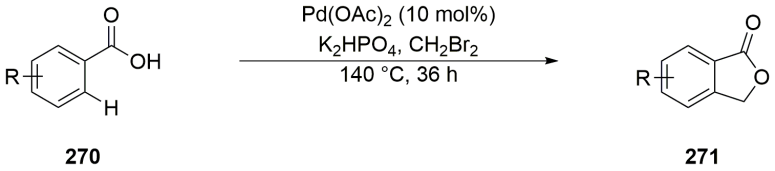


Scheme 2.38: Synthesis of 7-hydroxy-6-methyl phthalide **157** from bromo-phthalide **266**.

This approach, although resulting in the successful synthesis of 7-hydroxy-6-methyl phthalide **157**, was not developed further due to time constraints, and the simultaneous development of an alternative, more step economic approach.

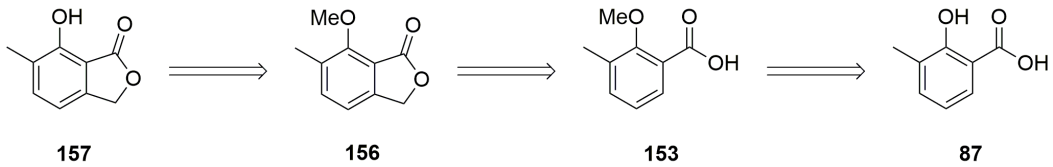
2.4 C-H ACTIVATION APPROACH

In 2009, Yu reported the palladium (II)-catalysed *ortho*-alkylation of benzoic acids with alkyl dihalides.[69] Mechanistically, the aryl C-H bond *ortho* to the benzoic acid is activated and an alkylation takes place, followed by an intramolecular S_N2 reaction to form the lactone product. Yu described the use of dichloroethane as solvent, and electrophile, to give the 6-membered lactone, whilst dibromomethane yielded the 5-membered lactone (scheme 2.39).



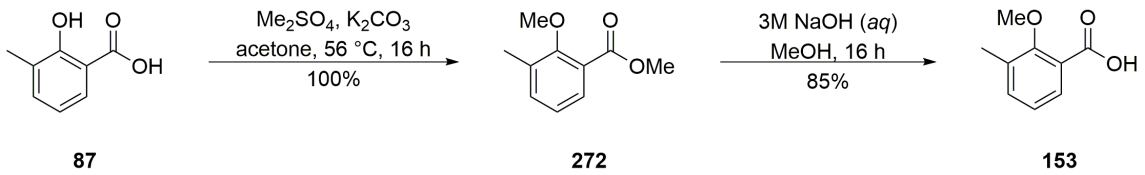
Scheme 2.39: Yu's Pd(II)-catalysed ortho-alkylation of benzoic acids.

This opened the possibility of a potentially more efficient approach to the required phthalan **159**. In the new approach, it was thought that 7-hydroxy-6-methyl phthalide **157** could be synthesised from 7-methoxy-6-methyl phthalide **156** *via* deprotection of the methyl ether. The phthalide core would in turn be accessed *via* Yu's C-H activation protocol from 2-methoxy-3-methyl benzoic acid **153**.[55, 59] Acid **153** is commercially available, but very expensive so it would be synthesised from 3-methylsalicylic acid **87** by methylation of the phenol group (scheme 2.40).



Scheme 2.40: Proposed synthesis of phthalide **157** via Yu's ortho-alkylation of benzoic acids protocol.

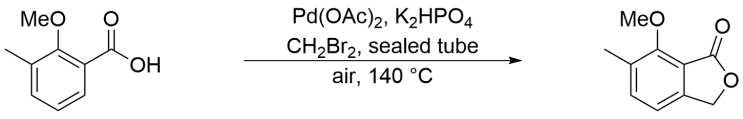
Synthetically, 3-methylsalicylic acid **87** was treated with dimethyl sulfate and potassium carbonate in refluxing acetone, to produce ester **272** in quantitative yield. Ester **272** was then saponified to give the desired 2-methoxy-3-methylbenzoic acid **153**, in excellent overall yield (scheme 2.41).[48]



87 **272** **153**

Scheme 2.41: Synthesis of 2-methoxy-3-methyl benzoic acid **153**.

With 2-methoxy-3-methyl benzoic acid **153** in hand, the Pd (II)- catalysed *ortho*-alkylation was investigated (scheme 2.42). Each reaction was carried out in a sealed reaction tube, and the reagents were added before the reaction vessel was lowered into a pre-heated oil bath. Using Yu's reported conditions, 10 mol% $Pd(OAc)_2$ and 36 h reaction time, lactone **156** was obtained in a very poor 22% yield. However, when the catalyst loading was increased to 20 mol% the yield rose significantly to 72%. Doubling the reaction time, to 72 h, increased the yield further to 84%. When the reaction time was increased further to 88 h, a 10 mol% loading of $Pd(OAc)_2$ gave the product in 88% yield. Further increase in catalyst loading to 20 mol% resulted in negligible increases in yield. Each of these results were obtained on a multi-gram scale (table 2-7).



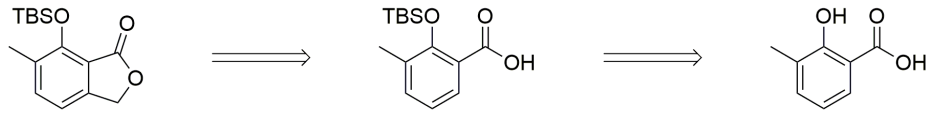
153 **156**

Scheme 2.42: C-H activation synthesis of 7-methoxy-6-methyl phthalide **156**.

Entry	Catalyst loading (mol%)	Time (h)	Yield (%)
1	10	36	22
2	20	36	72
3	20	72	84
4	10	88	88
5	20	88	89

Table 2-7: C-H activation synthesis of 7-methoxy-6-methyl phthalide **156**.

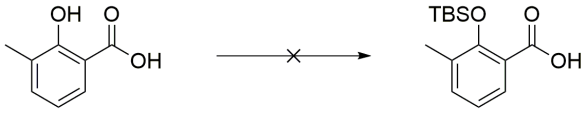
To shorten the synthesis even further, it was investigated to determine whether this methodology would allow access to TBS-protected phthalide **158**, directly from the TBS protected phenol-carboxylic acid **273**. The TBS protected intermediate could potentially be accessed from 3-methylsalicylic acid **87**, further reducing the synthesis to two steps (scheme 2.43).



158 273 87

Scheme 2.43: Proposed synthesis of phthalide **158** using Yu's C-H activation methodology.

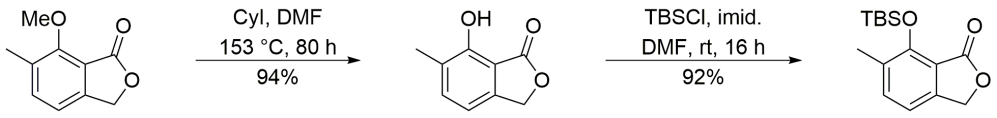
Unfortunately, no literature procedure for synthesis of the acid intermediate **273** exists, and all attempts to synthesise it were unsuccessful. This was thought to be due to migration of the silyl group, from the phenol to the acid group. This lead to inseparable mixtures of products (scheme 2.44).



87 273

Scheme 2.44: Unsuccessful synthesis of acid **273**.

Thus, our approach reverted to the use of 7-methoxy-6-methyl phthalide **156** intermediate which was demethylated in excellent yield.[55] The resulting free phenol was then TBS-protected to complete the synthesis of phthalide **158** (scheme 2.45).



156 157 158

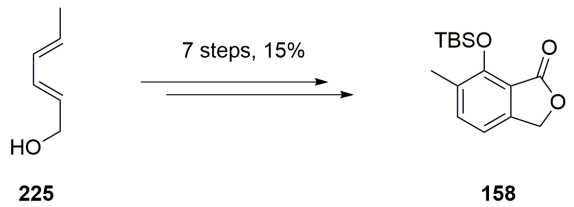
Scheme 2.45: Synthesis of TBS-phthalide **158**.

2.5 SUMMARY

Two new routes for the synthesis of phthalide **158** have been established: *via* an ester-tethered [4+2] cycloaddition or *via* a Pd (II)-catalysed C-H activation.

The cycloaddition route successfully furnished 7-hydroxy-6-methyl phthalide **156** in 5 synthetic steps from 2,4-hexadien-1-ol **225**, in 17% overall yield, and TBS-protected phthalide **158** in 15% overall yield. This was previously achieved in 10 synthetic steps.

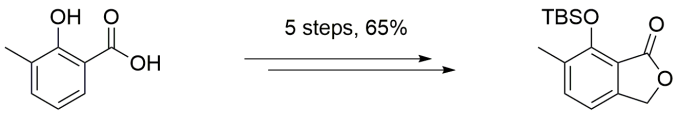
Additonally, the bromide intermediate **266**, allows for potential diversification through its use as a synthetic handle in the synthesis of analogues.



225 **158**

Scheme 2.46: Ester-tethered [4+2] cycloaddition route to **158**.

The second approach culminated in the synthesis of 7-methoxy-6-methyl phthalide **156** in 3 synthetic steps from 3-methylsalicylic acid **87**, in 76% overall yield, or 65% to the TBS-protected phthalide **158** in 5 synthetic steps, in a multi-gram scale. This is a marked increase in efficiency from the 10 synthetic steps and 37% overall yield reported previously.



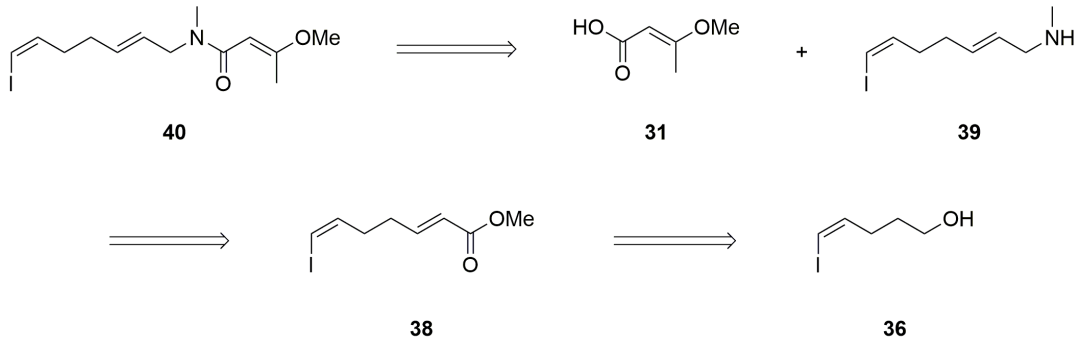
87 **158**

Scheme 2.47: C-H activation route to **158**.

3 SYNTHESIS OF EASTERN FRAGMENT

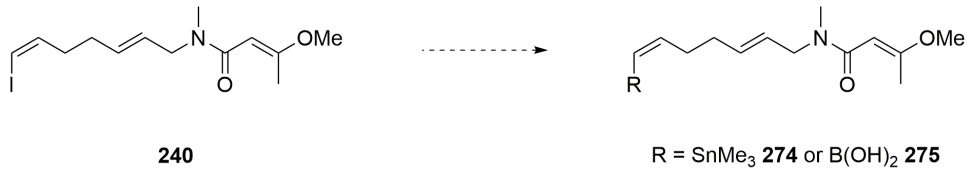
As in previous work completed within the group, it was decided to use vinyl iodide **40** as the eastern fragment of the ajudazols, inspired by Rizzacasa's initial work.[29, 50]

Retrosynthetically it was envisaged that the vinyl iodide eastern fragment **40** could be obtained *via* an amide coupling between (*E*)-3-methoxybutenoic acid **31** and amine **39**. The amine intermediate **39** in turn, would be synthesised from reduction of ester **38**, followed by conversion of the corresponding alcohol to the bromide, and amination using methylamine. Ester **38** could be generated from oxidation and Wittig olefination of vinyl iodide **36** (scheme 3.1).



Scheme 3.1: Proposed synthesis of eastern fragment **40**.

Additionally, it was expected that vinyl iodide **40** could be converted the corresponding vinyl stannane **274** or vinyl boronic acid **275** to provide the route with more flexibility if needed (scheme 3.2).

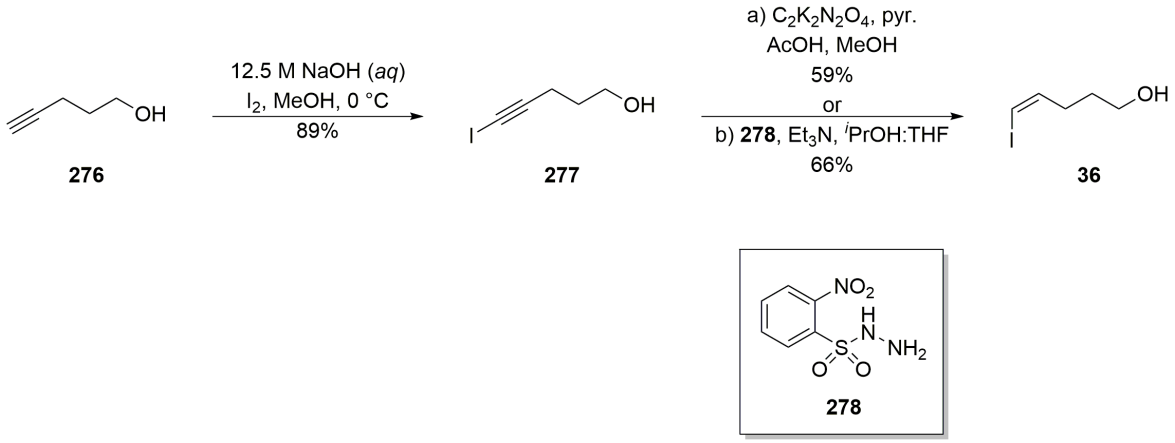


Scheme 3.2: Possible conversion of eastern fragment **40** to alternatives **274** and **275**.

3.1 SYNTHESIS

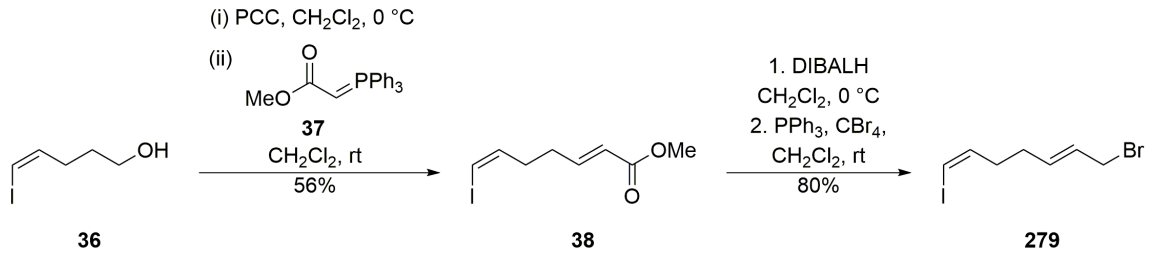
The synthesis began as before, with pent-4-yn-1-ol **276** being converted into iodo-alkyne **277** in very good yield, as reported by Yang.[70] Reduction to the *Z*-vinyl iodide had previously been achieved in the group using dipotassium azodicarboxylate as a source of diimide. However, on repetition of this methodology, this reaction proved to be low yielding

and required a lengthy work up procedure. Therefore *o*-nitrobenzenesulfonylhydrazide (NBSH) **278** was investigated as an alternative *in-situ* source of diimide for the reduction. NBSH **278** was synthesised according to Myers' procedure, and used immediately for the reduction step.[71] Pleasingly, this reagent was easier to handle and the procedure more user-friendly. Furthermore, the yield was also improved, giving the desired *Z*-vinyl iodide **36** with complete selectivity in 66% yield (scheme 3.3).



Scheme 3.3: Synthesis of vinyl iodide **36**.

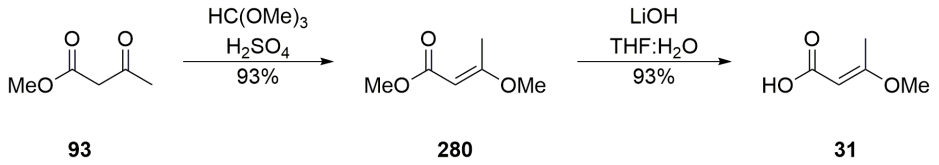
Oxidation of alcohol **36** using PCC followed by immediate treatment of the resultant aldehyde with methyl (triphenylphosphoranylidene)acetate **37**, gave the desired *E*-conjugated ester product **38**, as a single double bond isomer. DIBALH reduction of the ester to the corresponding alcohol then proceeded in excellent yield. Finally, conversion of the alcohol to the bromide, using Appel conditions, gave the key bromide intermediate **279** in very high yield for the entire sequence (scheme 3.4).



Scheme 3.4: Synthesis of bromide **279**.

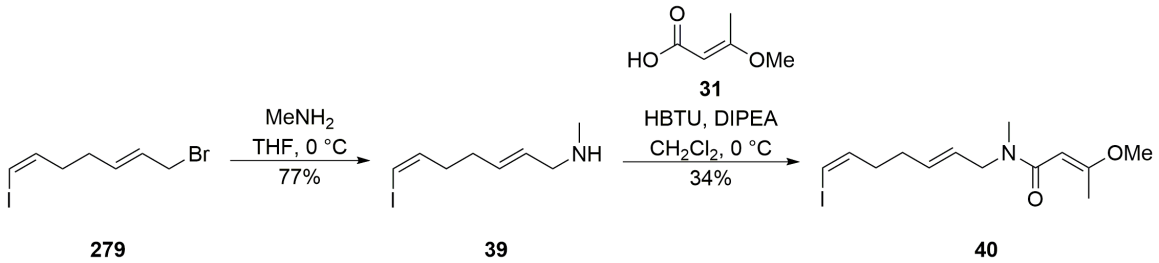
The synthesis of (*E*)-3-methoxybutenoic acid **31** began with treatment of neat trimethyl orthoformate with neat methyl acetoacetate, under acidic conditions to generate ester **280**.

Ester **280** was then hydrolysed using LiOH to give acid **31**, exclusively as the (*E*)-isomer (scheme 3.5).[30, 32]



Scheme 3.5: Synthesis of (E)-3-methoxybutenoic acid **31**.[a]

The synthesis of the amine coupling partner began with allylic bromide **279** which was treated with methyl amine to yield the desired secondary amine **39**. Coupling of amine **39** with (*E*)-3-methoxybutenoic acid **31**, using HBTU completed the efficient synthesis of the eastern fragment **40** (scheme 3.6).



Scheme 3.6: Completion of eastern fragment synthesis.

3.2 SUMMARY

The eastern fragment, vinyl iodide **40**, was successfully synthesised starting from 4-pentyn-1-ol, in 8 steps and 7% overall yield. The procedure allows for scale-up during the synthesis.

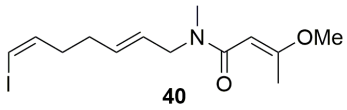


Figure 3.1: Eastern fragment **40**.

Additionally, should vinyl iodide **40** prove to be an unsuitable coupling partner, Egan had demonstrated previously that it could be converted to stannane **274**.[28, 50]

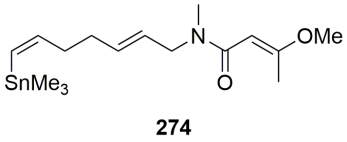


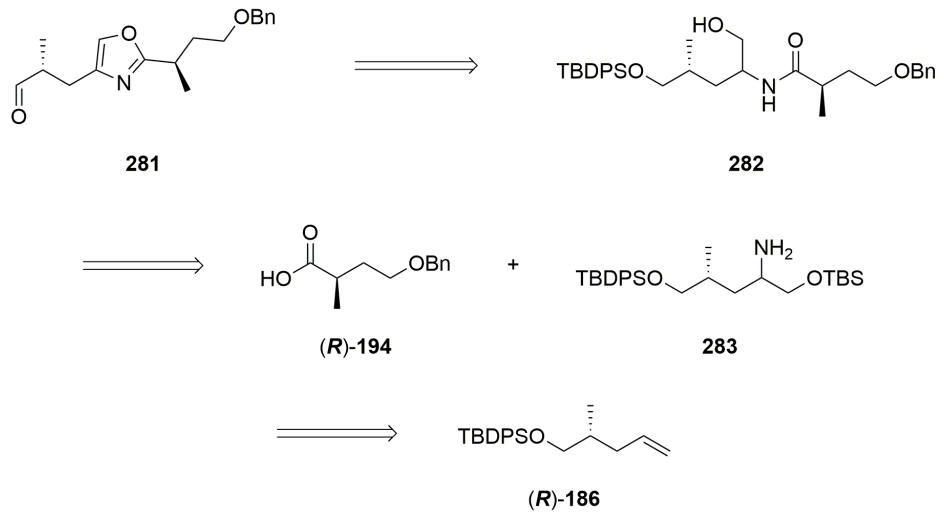
Figure 3.2: Alternative eastern fragment **274**.

[a] (*E*)-3-Methoxybutenoic acid synthesised by Dr. B. Egan

4 SYNTHESIS OF OXAZOLE ALDEHYDE FRAGMENT

The initial goals of the project required the synthesis of enantiomerically pure oxazole **281**. Oxazole **281** being the enantiomer of the oxazole unit previously synthesised in the group (**182** scheme 1.45). Thus, it was decided to mirror the approach initially developed.

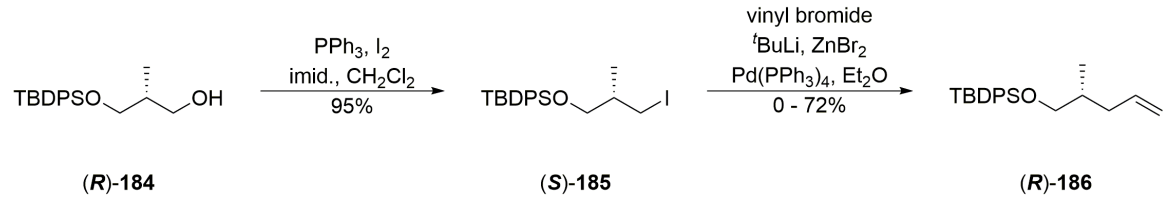
Oxazole **281** was envisioned as being generated from the oxidation and cyclodehydration of *β*-hydroxyamide **282**, followed by removal of the silyl group and oxidation. Amide **282** could be generated from the coupling of acid (***R***)-**194** and amine **283**, then selective removal of the TBS group. Amine **283** could be obtained from olefin (***R***)-**186**, *via* dihydroxylation, and functional group manipulation (scheme 4.1).



Scheme 4.1: Proposed synthesis of oxazole-aldehyde **281**.

4.1 SYNTHESIS OF OLEFIN FRAGMENT (*R*)-186

The synthesis of oxazole-aldehyde **281** began with known alcohol (***R***)-**184**, which was derived from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate ((*S*)-Roche ester), which was converted to the iodide (***S***)-**185** in excellent yield. Negishi coupling of iodide (***S***)-**185** with vinyl bromide then gave the desired terminal olefin (***R***)-**186**, albeit in variable yields (scheme 4.2).[51]

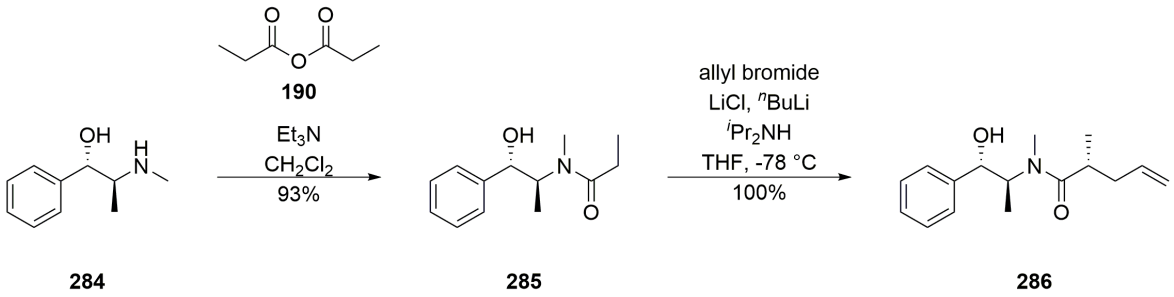


(***R***)-**184** (***S***)-**185** (***R***)-**186**

Scheme 4.2: Synthesis of olefin (***R***)-**186** via Negishi coupling.

The Negishi approach delivered alkene (***R***)-**186** in good yield on a small scale, however when attempted on a multi-gram scale, the yield depreciated significantly and was inconsistent. Due to this lack of reproducibility, an alternative approach to the synthesis of alkene (***R***)-**186** was investigated.

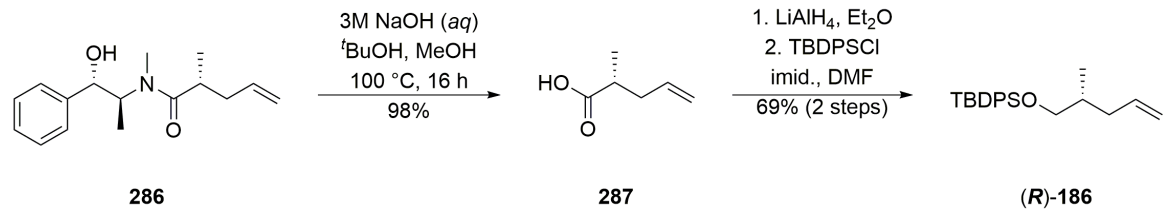
In an alternative approach, (1*S*,2*S*)-(+)-pseudoephedrine **284** was propionylated to give amide **285**. Amide **285** was then used as the chiral auxiliary for a Myers' diastereoselective alkylation, using allyl bromide.[72, 73] Gratifyingly, the desired olefin **286** was isolated in quantitative yield as a single diastereomer (scheme 4.3).



284 **285** **286**

Scheme 4.3: Myers' approach to the synthesis of olefin **286**.

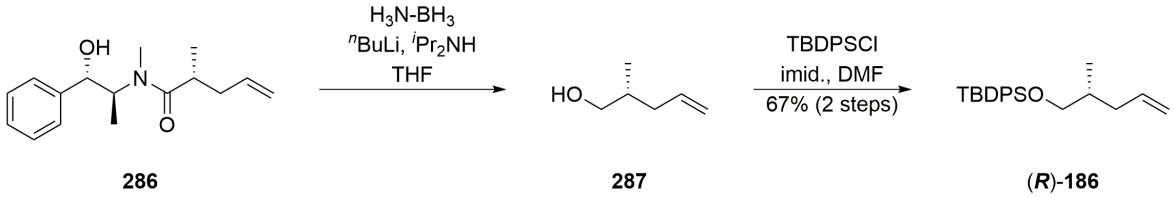
With diasteromerically pure amide **286** in hand, the next step was to generate the corresponding alcohol, which would then be TBDPS-protected to give the desired unit (***R***)-**186**. The alkylated pseudoephedrine amide **286** was treated with a mixture of 3M NaOH (*aq*), methanol, and *tert*-butanol to give the desired acid **287**, which was then reduced to the primary alcohol using lithium aluminium hydride.[73, 74] Subsequent TBDPS-protection gave the desired silyl ether (***R***)-**186** (scheme 4.4).



286 **287** (***R***)-**186**

Scheme 4.4: Basic hydrolysis of amide **286** in synthesis of (***R***)-**186**.

As an alternative approach, the reduction of amide **286** directly using lithium ammonia-borane was carried out to yield alcohol **287**.[73] The crude volatile alcohol **287** was then immediately TBDPS-protected, to give the silyl ether **(*R*)-186** in 67% yield over 2 steps (scheme 4.5).



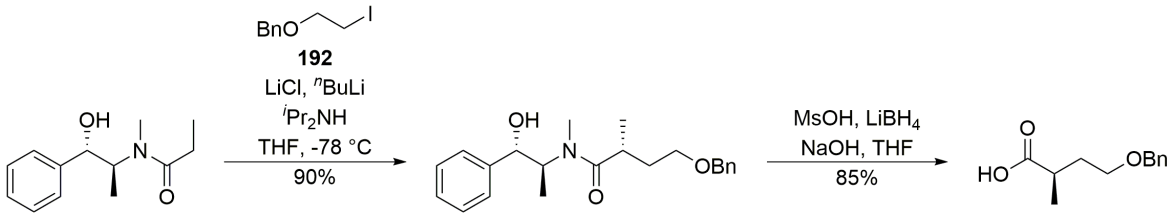
286 **287** (***R***)-**186**

Scheme 4.5: LAB reduction of amide **286** in synthesis of (***R***)-**186**.

Although the difference in yield between the two approaches to olefin (***R***)-**186** is negligible, the ease of handling and cheaper reagents meant that the hydrolysis-reduction approach was the preferred method.

4.2 SYNTHESIS OF ACID FRAGMENT (*R*)-194

The synthesis of (*R*)-4-(benzyloxy)-2-methylbutanoic acid (***R***)-**194** also began with propionylated (1*S*,2*S*)-(+)-pseudoephedrine **285** which was alkylated according to Myers' procedure using the known iodide **192**.[52, 73] After alkylation, amide **289** underwent mild hydrolysis, using MsOH to facilitate *N*,*O*-acyl transfer followed by saponification to give the desired enantiomerically pure acid (***R***)-**194** (scheme 4.6).[b]



285 **289** (***R***)-**194**

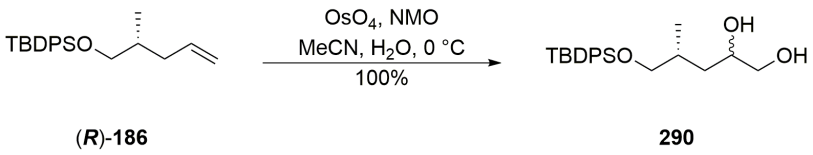
Scheme 4.6: Synthesis of (R)-4-(benzyloxy)-2-methylbutanoic acid.

[b] Synthesis of (*R*)-4-(benzyloxy)-2-methylbutanoic acid carried out by Dr. Colin Pearson

4.3 COMPLETION OF OXAZOLE FRAGMENT 281

With both olefin (***R***)-**186** and acid (***R***)-**194** fragments in hand, completion of the oxazole fragment was attempted. The sequence began with an Upjohn dihydroxylation of olefin (***R***)-**186** which gave the desired diol **290**, in quantitative yield.[75] The product was isolated as a 3:2 mixture of diastereomers, that co-eluted during flash chromatography. This was inconsequential as the cyclodehydration step to form the oxazole would lead to the formation of an sp^2 centre, so the newly introduced stereocentre would be lost at that point. However, the NMR spectra for the mixture of diastereomers was very complex, and more so once the amide bond was introduced and rotamers were formed.

Asymmetric dihydroxylation procedures were investigated to see if the NMR spectra could be simplified. Sharpless asymmetric dihydroxylation was performed using both commercially available AD-mix-β, as well as using the individual reagents.[76, 77] Disappointingly, the selectivity in either case was poor (*d.r.* approximately 2.7:1 in both cases), and the yield for the transformation dropped slightly, to 86% and 93% respectively, compared to the racemic procedure. The poor selectivity obtained meant that the NMR spectra were no easier to interpret, and as the introduction of chirality was unnecessary, the Upjohn dihydroxylation remained the preferred method (scheme 4.7).

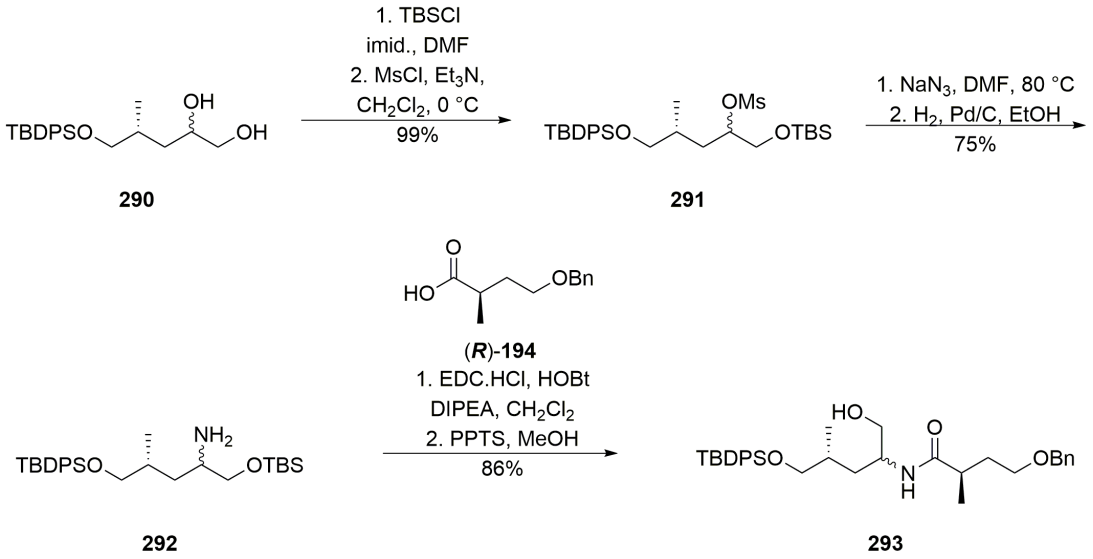


(***R***)-**186** **290**

Scheme 4.7: Dihydroxylation in synthesis of diol **290**.

Regioselective silylation of the primary alcohol using TBSCl, followed by mesylation of the free secondary alcohol gave mesylate **291** in near quantitative yield. Displacement of the mesylate using sodium azide, followed by reduction of the azide intermediate using palladium on charcoal gave amine **292** in good yield. Staudinger conditions were also explored for the azide reduction, however the yield of amine **292** produced decreased significantly.[78] The newly generated amine **292** was then coupled with the enantiomerically pure acid (***R***)-**194** to generate amide **293**, as a mixture of diastereomers.

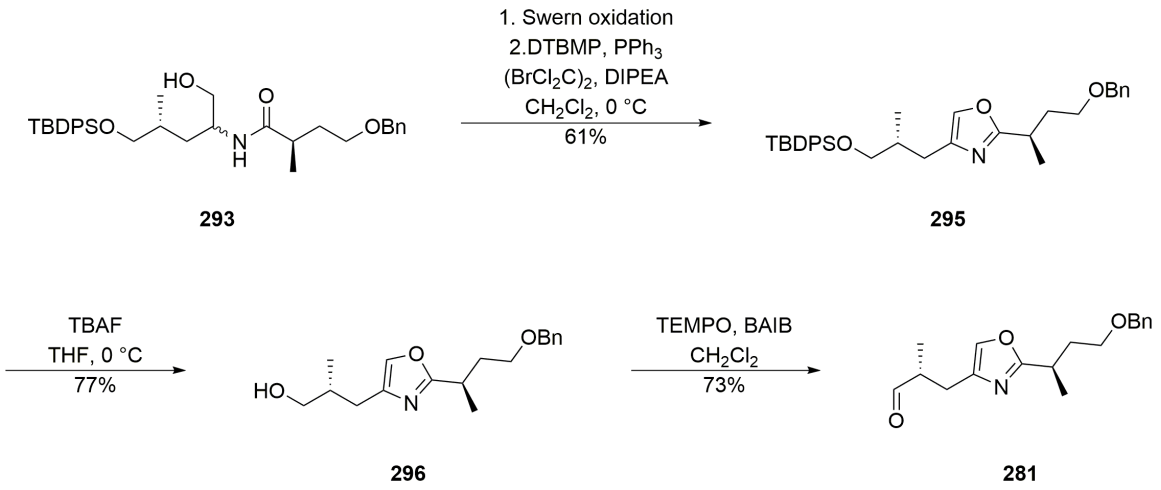
Selective deprotection of the primary TBS group, whilst leaving the primary TBDPS group in place, was successfully realised using PPTS in 88% yield.[79] However, the reaction was sluggish and took four days to reach completion. Switching to the stronger CSA decreased the reaction time to four hours, however the yield decreased to 62% (scheme 4.8).[80]



Scheme 4.8: Synthesis of β-hydroxyamide **293**.

With *β*-hydroxyamide **293** in hand, we focused on the generation of the required oxazole unit. Unfortunately, the initial oxidation of *β*-hydroxyamide **293** to the corresponding *β*-formylamide proved to be troublesome. Use of a Swern oxidation proved unreliable with 63% as the best isolated yield, however, there was no need for chromatographic purification. Switching to Dess-Martin oxidation conditions resulted in a slight improvement in yield (69%) but column purification of the product was necessary.[81] The best result over the two steps was obtained by oxidation of alcohol **293** under Swern conditions, and then immediately subjecting the resulting crude aldehyde to the Forsyth modification of the Wipf cyclodehydration protocol.[34, 35, 82] Using this combination, oxazole **295** was generated in consistent and reliable yields.

Removal of the TBDPS group using TBAF gave a reasonable, but lower than expected yield of alcohol **296** (77%). The use of alternative sources of fluoride failed to increase the efficiency of the deprotection, with TASF giving a disappointing 66% yield of the free alcohol.[83] Mild oxidation using TEMPO and BAIB gave the desired aldehyde, and completed the synthesis of oxazole-aldehyde **281** (scheme 4.9).



Scheme 4.9: Synthesis of oxazole-aldehyde **281**.

4.4 SUMMARY

The desired oxazole fragment was successfully synthesised starting from (2*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (***R*)-184**. The synthetic sequence is 16 steps long and can reliably generate oxazole-aldehyde **281** in 15% overall yield.

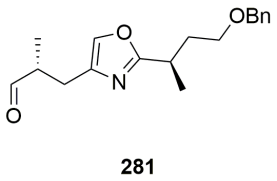
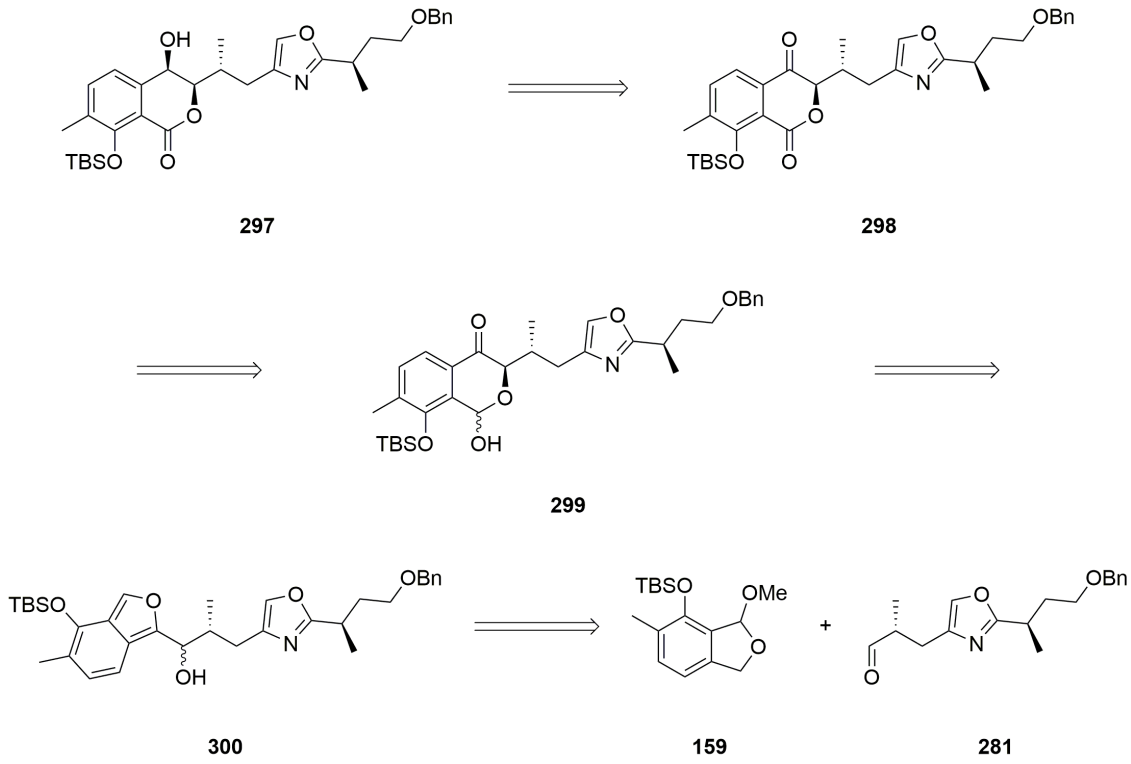


Figure 4.1: Oxazole-aldehyde **281**.

With the completion of the synthesis of oxazole-aldehyde **281**, efforts were then focused on the synthesis of the isochromanone core of ajudazol B, using the isobenzofuran oxidative rearrangement approach.

5 OXIDATIVE REARRANGEMENT INITIAL WORK

The next step in the proposed synthesis towards ajudazol B, was the synthesis of the isochromanone core. It was envisioned that the isochromanone core **297** could be generated through the reduction of the keto-lactone intermediate **298**. Keto-lactone **298** being formed through the oxidation of lactol **299**, which in turn could be obtained through the oxidative rearrangement of α-hydroxyisobenzofuran intermediate **300**, produced using phthalan **159** and aldehyde **281** (scheme 5.1).



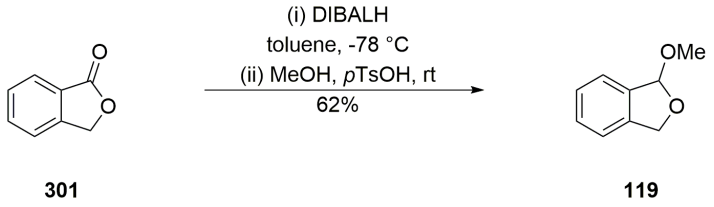
Scheme 5.1: Retrosynthesis of isochromanone **297**.

5.1 COMPLETION OF PHTHALAN FRAGMENT

The primary task, before the oxidative rearrangement process could be carried out, was the completion of the synthesis of the phthalan fragment **159**. TBS-phthalide **158** was to be reduced, and the resultant lactol intermediate methylated to give the key phthalan unit **159**.

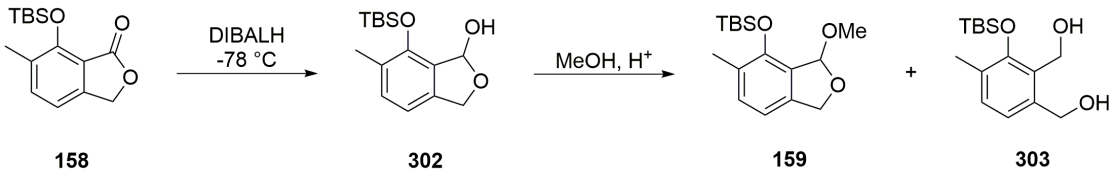
The reduction-methylation approach was initially tested on phthalide **301**. Using CH_2Cl_2 as the solvent, as reported in previous work, proved to be extremely problematic. Switching to toluene, and running the reaction at a 0.06 M concentration, led to an increase in reproducibility. It was eventually found that omitting the work up after the DIBALH

reduction step, and by adding the methanol and acid in a one-pot process increased the yield of phthalan **119** (scheme 5.2).



Scheme 5.2: Synthesis of phthalan **119**.

This optimised approach was then attempted for the synthesis of phthalan **159**, from phthalide **158**. The two-step, and one-pot process, proved to be extremely temperamental. In some instances, none of the desired product was isolated, and the sole product obtained was diol **303**. When the acid was switched from *p*TsOH to CSA, the yield was low. Reverting to CH_2Cl_2 as the solvent gave an even lower yield of 48%. Changing the proton source to PPTS proved to be high yielding and reproducible (scheme 5.3, table 5-1).

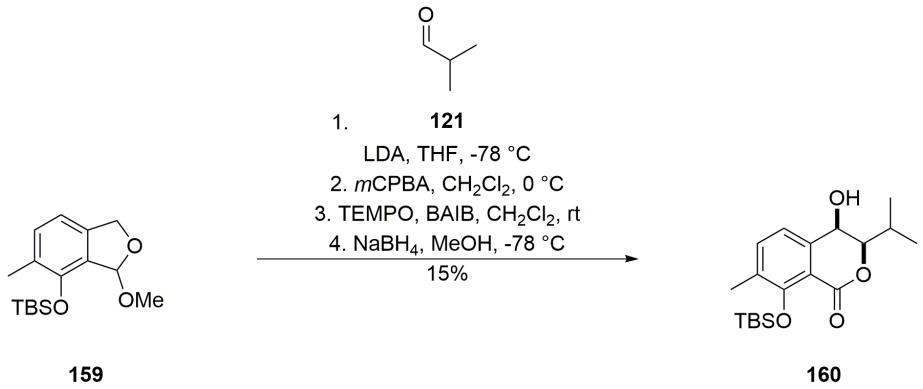


Scheme 5.3: Synthesis of phthalan **159**.

Entry	Conditions	Diol	Yield 159 (%)
1	1. DIBALH, toluene, -78 °C 2. *p*TsOH, MeOH	Y	0 – 68
2	DIBALH, toluene, -78 °C, then *p*TsOH, MeOH	Y	0 – 54
3	1. DIBALH, toluene, -78 °C 2. CSA, MeOH	Y	49
4	1. DIBALH, CH_2Cl_2, -78 °C 2. *p*TsOH, MeOH	Y	48
5	1. DIBALH, toluene, -78 °C 2. PPTS, MeOH	N	88

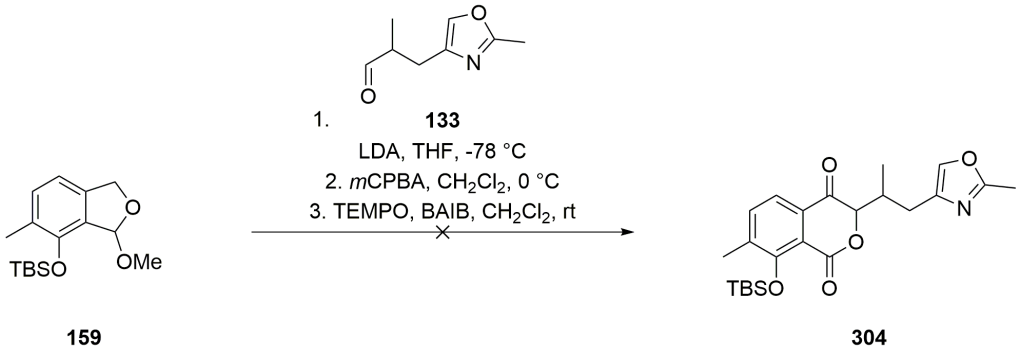
Table 5-1: Conditions attempted in synthesis of **159**.

With phthalan **159** in hand, the oxidative rearrangement procedure was executed, using isobutyraldehyde **121** as a model aldehyde. The initial attempt successfully furnished isochromanone **160**, but in a very poor 15% yield over the four steps, compared with 51% yield, reported by Egan (scheme 5.4).[48, 50]



Scheme 5.4: Synthesis of isochromanone **160**.

Based on the low yield obtained, it was decided to attempt a second model substrate, rather than using the precious aldehyde **281**. Surprisingly, reaction of phthalan **159** with oxazole-aldehyde **133** under the oxidative rearrangement conditions failed to generate any of the desired product **304** (scheme 5.5).



Scheme 5.5: Unsuccessful synthesis of **304**.

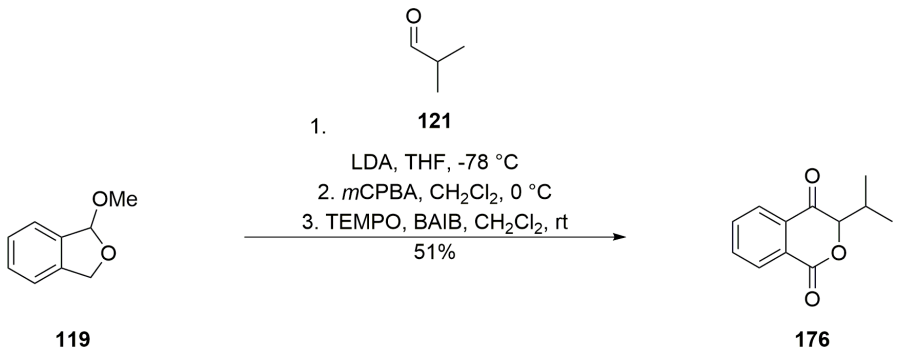
Due to the vastly reduced yield in repeating the synthesis of isochromanone **160**, and the failure to synthesise keto-lactone **304**, the oxidative rearrangement procedure was scrutinised, and the reasons for the discrepancies in yield identified.

5.2 INVESTIGATION OF REARRANGEMENT

As part of the optimisation work, the unsubstituted phthalan **119** and isobutyraldehyde **121** were used as model units. The intial attempt using previously reported conditions, gave the keto-lactone **176** in 34% yield, compared to the reported yield in previous work of 79%.

In the general procedure for the oxidative rearrangement, the putative deprotonation takes place at 0 °C. As part of our preliminary investigations, this was lowered to -78 °C to ensure the isobenzofuran anion was not decomposing before addition of the aldehyde. This change however, failed to affect the yield of the reaction.

Two sources of anhydrous THF were used: the in-house solvent purification system (SPS), and anhydrous THF was purchased from Acros Organics®. The yield increased using the solvent from the external supplier, but not appreciably enough to explain the decrease in yield from previous work (table 5-2). From this point onwards, anhydrous THF used in the rearrangement procedure was thoroughly degassed, using the freeze-pump-thaw method.



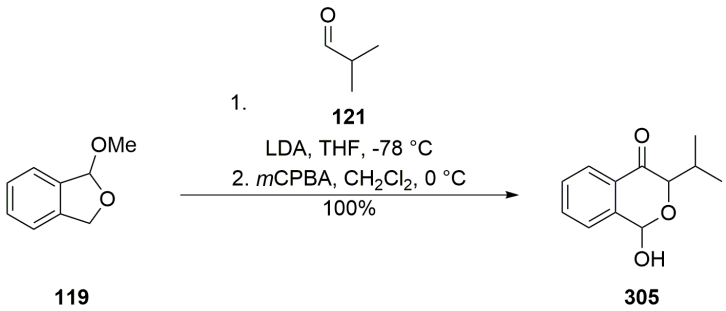
Scheme 5.6: Synthesis of keto-lactone **176**.

Entry	THF source	MeLi addition	Yield (%)
1	SPS	0 °C	34
2	SPS	-78 °C	33
3	Acros	0 °C	51

Table 5-2: Conditions used in the synthesis of keto-lactone **176**.

There were several reasons besides the source of the solvent which could be responsible for the low yield obtained for the synthesis of the keto-lactone product **176**. There was concern that the keto-lactol or keto-lactone intermediates would be unstable either during the reaction or purification conditions. Thus, the decision was made to test the stability of the keto-lactol intermediates.

If the keto-lactol was stable, the oxidation step would not have to be undertaken immediately and different oxidants could be investigated, without having to carry out the entire sequence on every occasion. Synthesis of the model keto-lactol **305** was achieved, using the unsubstituted phthalan **119** and isobutyraldehyde **121**, in quantitative crude yield (scheme 5.7).



Scheme 5.7: Synthesis of keto-lactol **305**.

To check the stability of the lactol product **305**, a crude NMR sample was prepared, and measurements taken at 0, 7, 15, and 120 h. Encouragingly, there were no visible signs of degradation even after 120 h, so it was deemed that the lactol **305** was stable enough to be stored in the freezer, thus allowing the examination of different oxidation conditions (figure 5.1).

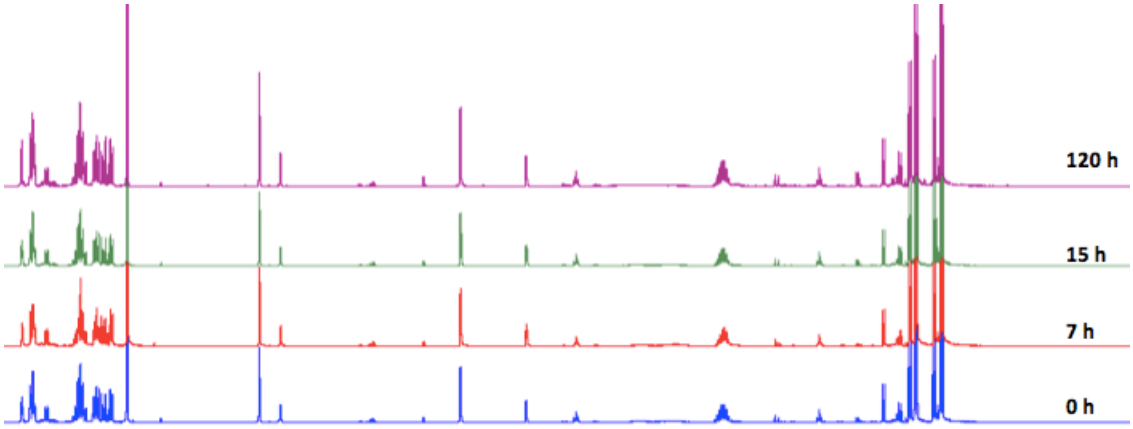
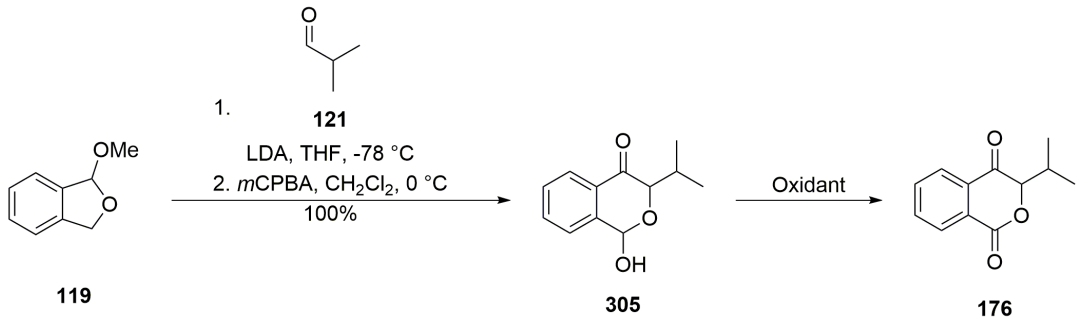


Figure 5.1: NMR spectra of lactol **305** over time.

Preliminary studies using TEMPO/BAIB oxidation gave the desired keto-lactone **176** in 60% yield. When the aqueous work up was omitted, and the crude product dry-loaded onto silica before flash chromatography, the yield was increased to 80%, equal to that as demonstrated by Egan in previous work.[50]

TPAP, has been used for the oxidation of lactols to lactones in several natural product syntheses. Disappointingly, use of TPAP resulted in decomposition of the lactol **305**, with no product formation being observed.[84, 85]

PCC and MnO_2 were also trialled, as they would require a simple filtration as opposed to flash chromatography for purification. However, despite the synthetic ease of the procedures, the yields were inferior, giving a 45% and 13% yield of **305** respectively (scheme 5.8, table 5-3).

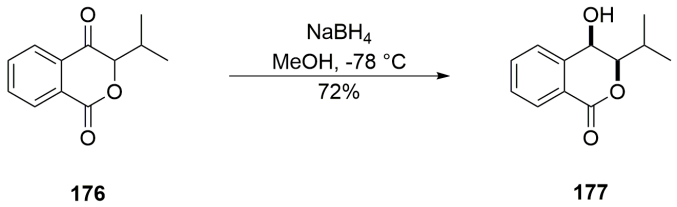


Scheme 5.8: Synthesis of keto-lactone **176**.

Entry	Oxidant	Yield 176 (%)
1	TEMPO, BAIB	60
2	TEMPO, BAIB (no *aq* work up)	80
3	TPAP, NMO	decomposition
4	PCC	45
5	MnO_2	13

Table 5-3: Oxidation conditions used in synthesis of keto-lactone **176**.

It was decided that TEMPO/BAIB conditions followed by a non-aqueous work-up were the best oxidation conditions. Finally, reduction of the keto-lactone **176** using sodium borohydride, gave solely the *syn*-isochromanone **177**, in good yield after purification (scheme 5.9).



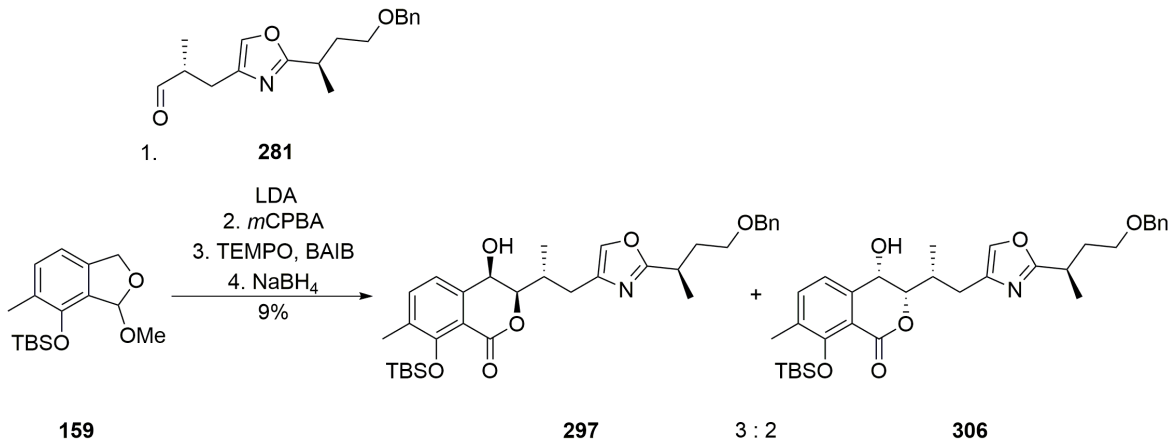
Scheme 5.9: Synthesis of isochromanone **177**.

With the new results and optimised conditions, the methodology was applied towards the total synthesis of ajudazol B.

5.3 OXIDATIVE REARRANGEMENT USING OXAZOLE-ALDEHYDE 281

Using the optimised procedure, phthalan **159** was deprotonated and the resulting isobenzofuran anion was treated with oxazole-aldehyde **281** to generate the keto-lactol intermediate, as observed in the crude NMR spectrum. Unfortunately, oxidation of the crude lactol using TEMPO/BAIB was sluggish and did not go to completion, requiring extensive purification to yield the keto-lactone intermediate. Luche reduction, as used in previous

studies, gave the desired isochromanone products as a 3:2 mixture of *syn*,*anti*- and *syn*,*syn*-diastereomers, **297** and **306**, inseparable by flash chromatography, in a very disappointing 9% yield (scheme 5.10).



Scheme 5.10: Synthesis of isochromanones **297** and **306**.

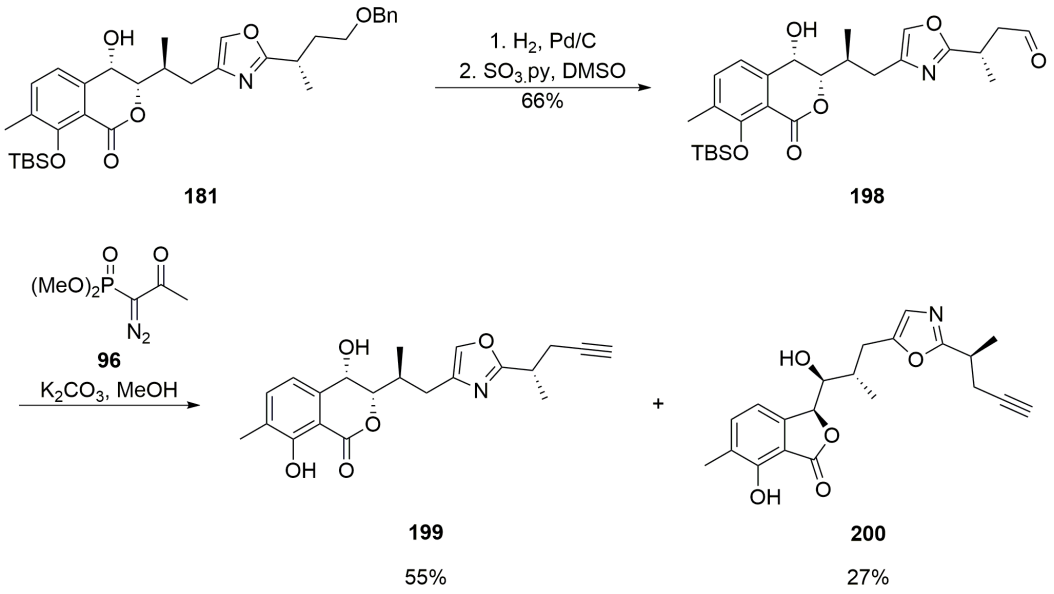
5.4 SUMMARY

As expected the level of water contained in the solvent was crucial to the successful outcome of the isobenzofuran rearrangement, however, this could be easily addressed by changing the source of the THF.

More significantly, the stability of the keto-lactol intermediates was also explored. Interestingly, the keto-lactols were determined to be more stable than previously thought, which opened the possibility of exploring different oxidation conditions for the generation of the keto-lactones and gives the rearrangement more flexibility and scope.

The oxidative conditions for the formation of the keto-lactone units were also explored. Crucially, the keto-lactones are unstable and extensive purification is detrimental to the yield obtained.

Unfortunately, in the route towards *ent*-8-*epi*-ajudazol B, with the isochromanone core in place the three steps required to install the alkyne functionality gave a relatively poor overall yield of 36%. Additionally, the Ohira-Bestmann homologation step also led to a significant amount of ring-contracted lactone product **200** (scheme 5.11).

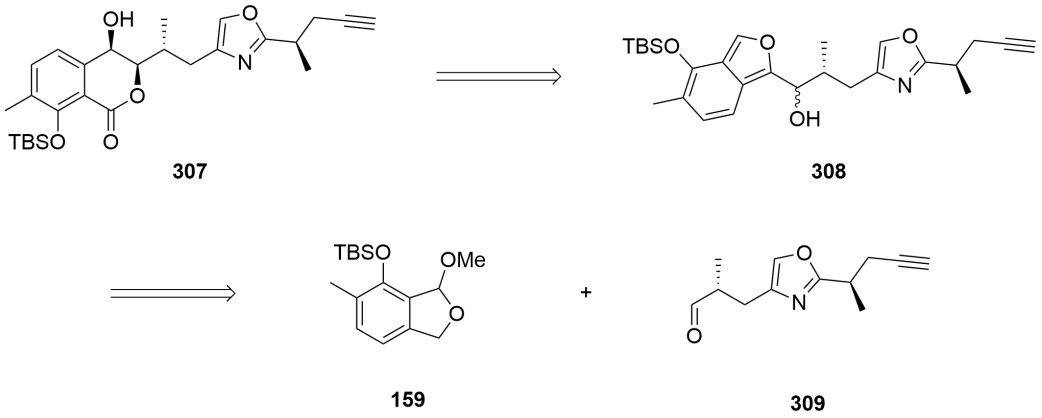


Scheme 5.11: Egan's synthesis of acetylene **199**.

The slow oxidation of the keto-lactol intermediate, combined with the poor yield in previous work for the transformation of the benzyl ether **181** into the desired alkyne **199**, meant that a fresh, alternative approach was necessary.

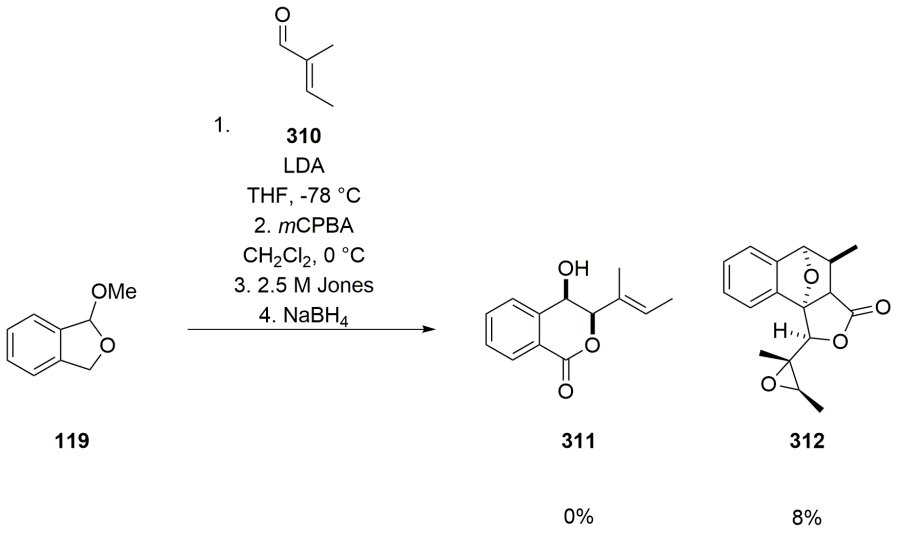
6 EXPANSION OF SCOPE OF REARRANGEMENT

A more convergent, and step-economic synthesis was envisioned which, would incorporate the desired alkyne functionality into the aldehyde coupling partner used in the rearrangement step (scheme 6.1).



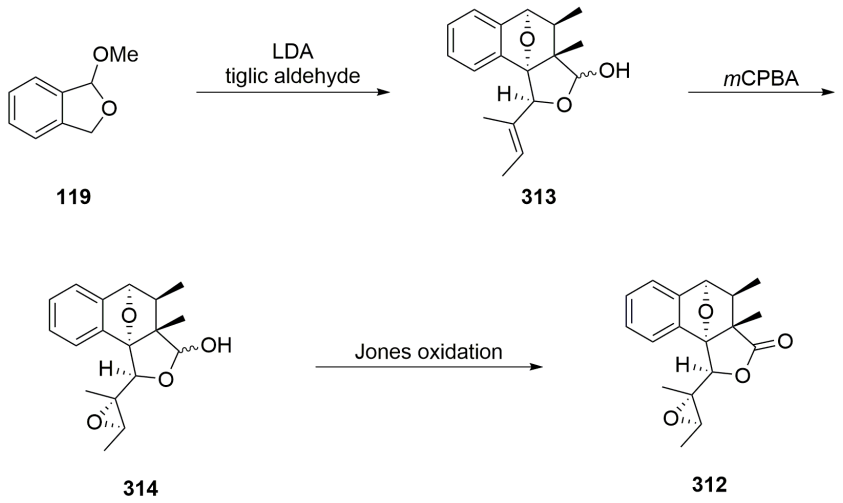
Scheme 6.1: Proposed route to acetylene **307**.

Although this approach would significantly shorten the synthesis, there were some concerns to be noted. Previously, during the development of the rearrangement methodology, the presence of alkene functionality within the aldehyde partner was found not to be tolerated. Tiglic aldehyde had been used as a substrate, and instead of forming the expected isochromanone product **311**, a highly unusual bridged-tetracycle **312** was isolated (scheme 6.2).[86]



Scheme 6.2: Hobson's formation of unexpected tetracycle **312**.

Mechanistically it is believed that the isobenzofuran anion first reacts as expected with tiglic aldehyde, then the α-hydroxy-isobenzofuran intermediate undergoes a [4+2] cycloaddition with the excess aldehyde present in the reaction, to give the *endo* product, which then cyclises to form the 5-membered lactol **313**. Epoxidation with *m*CPBA generates intermediate **314**, which upon oxidation with Jones reagent generates the observed lactone tetracyclic product **312** (scheme 6.3).



Scheme 6.3: Proposed mechanism for the generation of tetracycle **312**.

Therefore, there was the possibility that the α-hydroxyisobenzofuran intermediate **308** could undergo a [4+2] cycloaddition with the alkyne functional group either inter- or intramolecularly (figure 6.1). Hence, it was decided to investigate whether the rearrangement protocol would tolerate the presence of an alkyne in the system.

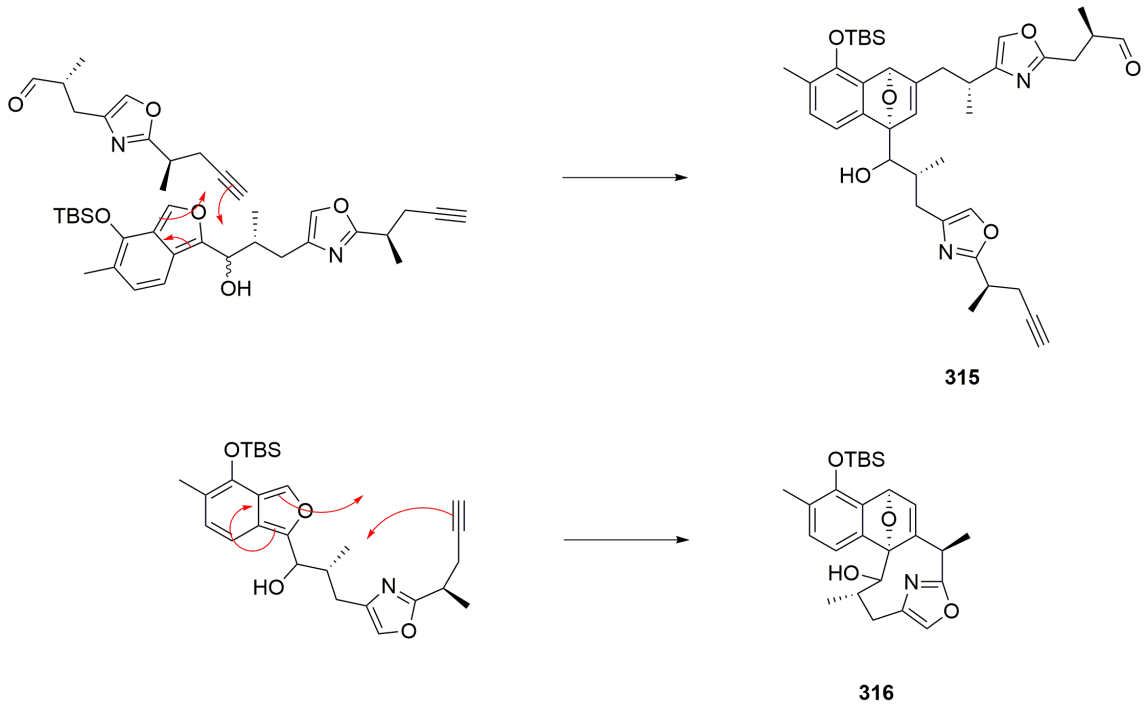
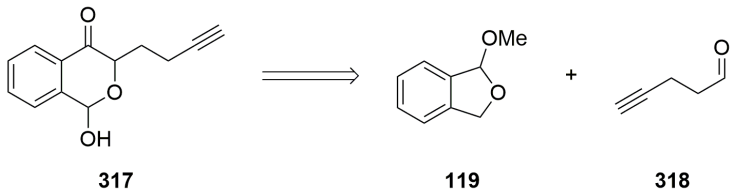


Figure 6.1: Possible undesired cycloaddition reactions of isobenzofuran intermediate **308**.

6.1 DESIGN OF AN ALKYNE BEARING MODEL SYSTEM

A simplistic model system was designed, employing 4-pentyn-1-al **318** as the aldehyde and unsubstituted phthalan **119**, to test whether the rearrangement would tolerate the presence of the alkyne functionality, and whether a simple alkyne-containing keto-lactol **317** could be synthesised (scheme 6.4).



Scheme 6.4: Proposed synthesis of keto-lactol **317**.

As in the more complex system, two unwanted scenarios could theoretically take place. In the first one, the isobenzofuran could add to the carbonyl and the resulting α-hydroxyisobenzofuran intermediate **319** could undergo a Diels-Alder reaction with a second molecule of alkyne **318**. Alternatively, the α-hydroxyisobenzofuran intermediate **319** could undergo an intramolecular Diels-Alder (figure 6.2).

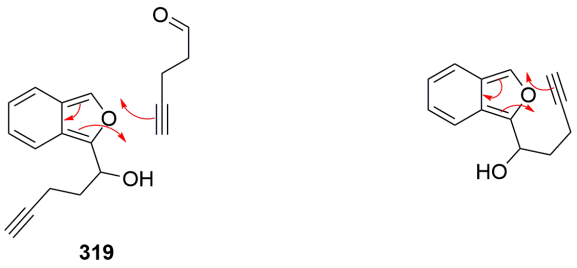
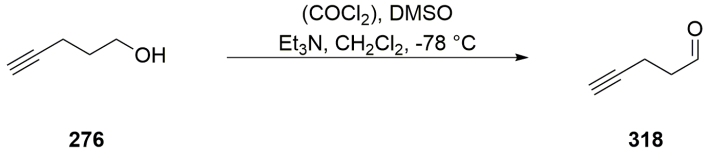


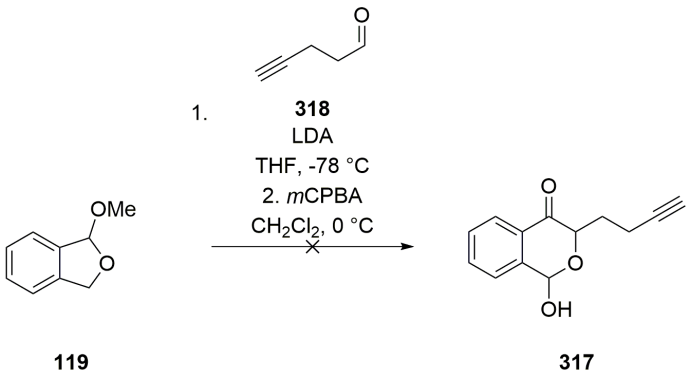
Figure 6.2: Possible undesired cycloaddition reactions of intermediate **319**.

4-Pentyn-1-al **318** was synthesised from 4-pentyn-1-ol **276** using a Swern oxidation. Due to volatility and the consequential difficulty in handling **318**, the solvent was evaporated carefully after the oxidation, and the aldehyde used crude immediately (scheme 6.5).



Scheme 6.5: Swern oxidation of 4-pentyn-1-ol **276** to 4-pentyn-1-al **318**.

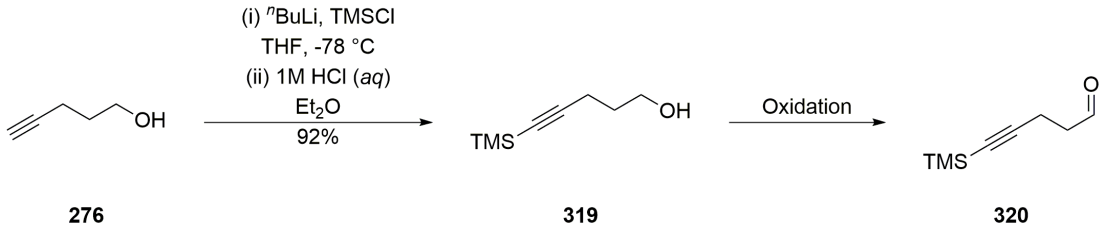
Frustratingly, the rearrangement using these starting materials did not yield any of the desired product **317**, and the crude NMR spectra showed only what was deemed to be decomposition products. It was thought that instead of nucleophilic addition of the isobenzofuran anion to the carbonyl taking place, that the terminal alkyne was deprotonated thus, quenching the reaction. Residual solvent from the Swern oxidation was likely to have also impacted on the outcome of the reaction (scheme 6.6).



Scheme 6.6: Unsuccessful synthesis of lactol **317**.

To eliminate the possibility of competing deprotonation of the acetylene, the model aldehyde was TMS-protected. Terminal alkyne **276** was deprotonated using *n*BuLi, then treated with TMSCl. The *bis*-silylated intermediate was then hydrolysed using 1M HCl to give 5-

trimethylsilanyl-pent-4-yn-1-ol **319** in 92% yield.[87] Oxidation using TEMPO/BAIB gave the corresponding aldehyde **320** in 43% yield. This low yield could be partially attributed to the lengthy purification required, therefore alternative oxidation conditions were used. PCC was then trialled, due to its ease of work up and likely lack of purification required. Gratifyingly, PCC oxidation afforded 5-(trimethylsilyl)pent-4-ynal **320** in a slightly improved 52% yield. The use of IBX further improved the yield to an acceptable 62% (table 6-1).[88]



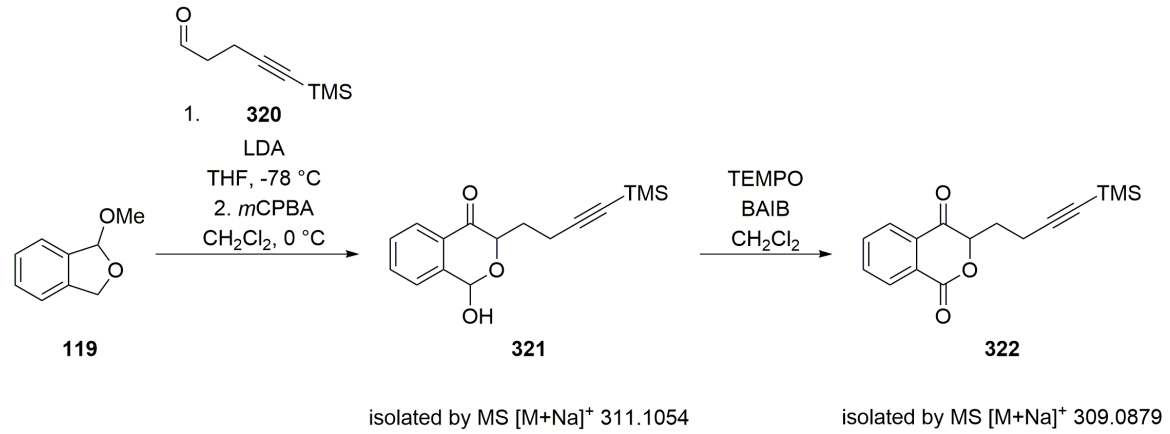
276 **319** **320**

Scheme 6.7: Synthesis of 5-(trimethylsilyl)pent-4-ynal **320**.

Entry	Conditions	Yield (%)
1	TEMPO, BAIB, CH_2Cl_2	43
2	PCC, CH_2Cl_2	52
3	IBX, DMSO, THF	62

Table 6-1. Oxidation of alcohol **319** to aldehyde **320**.

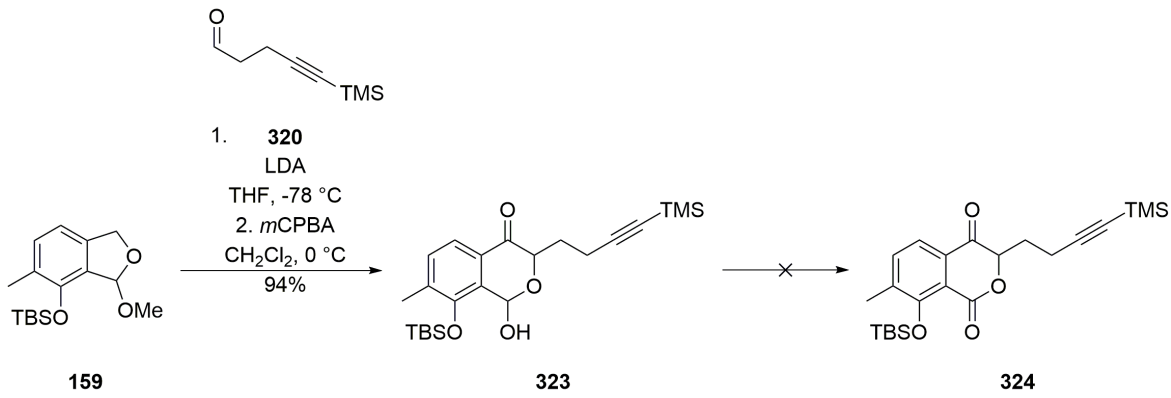
With the alkyne functionality TMS-protected, aldehyde **320** was used in the rearrangement. Pleasingly, the expected lactol product **321** was formed and an accurate mass spectra was obtained. Unfortunately, all attempts to obtain an analytically pure sample were futile, and all attempts at column chromatographic purification using silica gel led to product decomposition. Consequently, the crude lactol product **321** was then oxidised, and the keto-lactone product **322** was successfully synthesised. Again, it was not possible to obtain an analytically pure sample, due to product instability during purification, but an accurate mass spectrum was attained (scheme 6.8).



Scheme 6.8: Synthesis of keto-lactone **322**.

6.2 REARRANGEMENT WITH PHTHALAN 159 AND MODEL ALKYNE 320

Armed with this partial success, it was decided to use 5-(trimethylsilyl)pent-4-ynal **320** as a model aldehyde, with the fully functionalised phthalan precursor **159**. The rearrangement proceeded as expected and the crude residue was identified by ^{1}H NMR and mass spectrometry. Purification of the crude product using neutral alumina afforded the clean lactol **323** in excellent overall yield. Unfortunately, oxidation of lactol **323** using either TEMPO/BAIB or IBX failed to generate any of the desired keto-lactone **324** in both cases (scheme 6.9).



Scheme 6.9: Synthesis of keto-lactol **323**.

6.3 SUMMARY

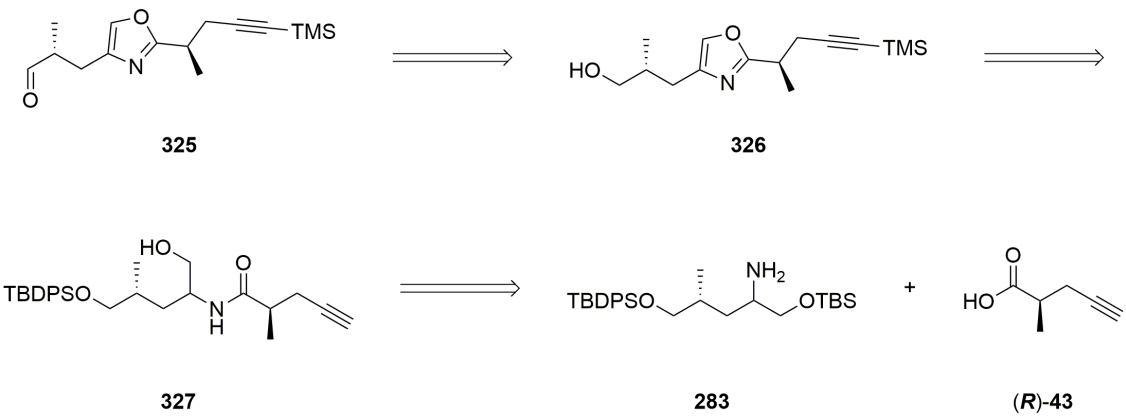
The synthesis of lactol **323** demonstrated that the isobenzofuran rearrangement can be successfully carried out in the presence of a TMS-protected acetylene. This is in marked contrast with the results previously obtained with alkene bearing substrates in which the competing Diels-Alder reactions took precedence over the oxidative rearrangement.

It was hoped this success would translate into an improved synthesis of ajudazol B, allowing the oxazole-aldehyde fragment to contain the alkyne functionality, thus, making the overall route shorter and more convergent.

7 REDESIGN OF OXAZOLE FRAGMENT

The exciting results obtained with aldehyde **320** (scheme 6.9) demonstrated that the oxidative rearrangement of isobenzofurans could tolerate the presence of a TMS-protected alkyne, thus opening the possibility of modifying the aldehyde coupling partner.

The redesigned oxazole-aldehyde **325** was envisioned as being obtained *via* oxidation of alcohol **326**. Alcohol **326** could in turn be generated from the cyclodehydration of *β*-hydroxyamide **327**, followed by introduction of the TMS group onto the alkyne unit. The key *β*-hydroxyamide **327** could be synthesised through an amide coupling between the previously generated amine **283** and (2*R*)-2-methylpent-4-ynoic acid (***R***)-**43** (scheme 7.1).

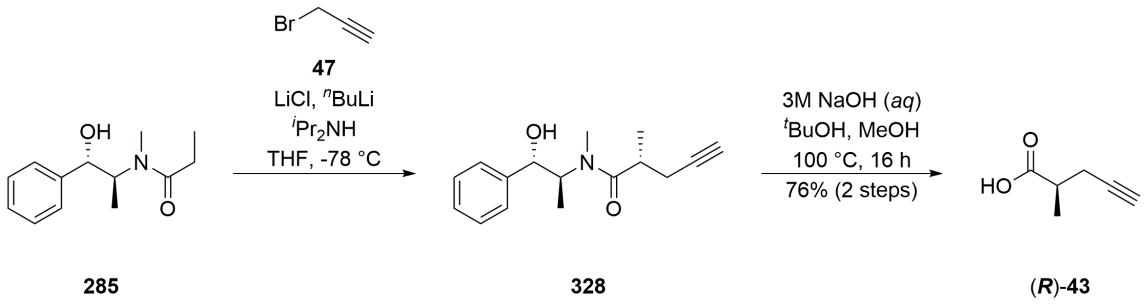


Scheme 7.1: Proposed synthesis of oxazole-aldehyde **325**.

7.1 SYNTHESIS OF OXAZOLE-ALKYNE 325

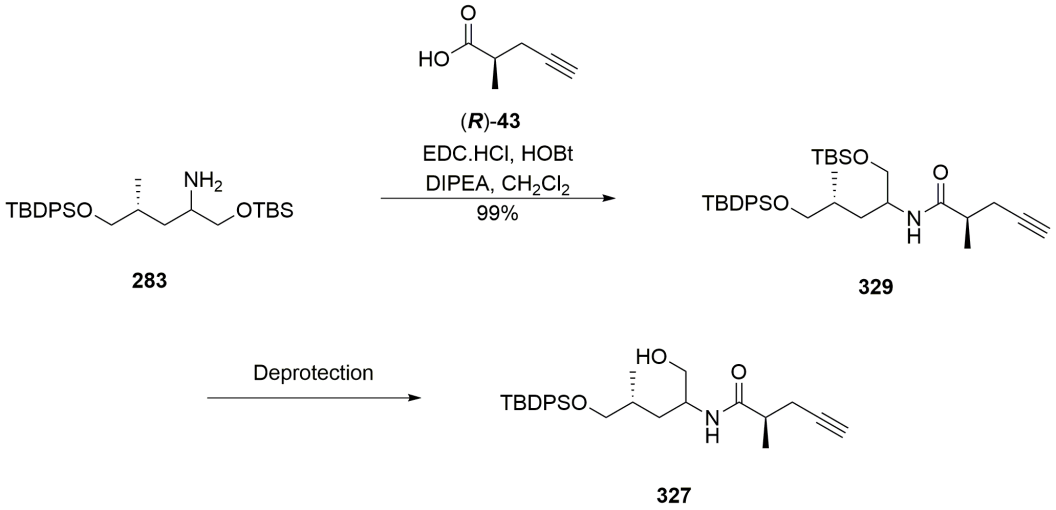
Despite its simple structure, only two literature preparations have been reported for the synthesis of (2*R*)-2-methylpent-4-ynoic acid (***R***)-**43**. Wilson and co-workers used a chiral resolution, whilst Menche used pseudoephedrine as a chiral auxiliary and 3-bromoprop-1-ynyltrimethylsilane.[23, 89]

Our approach to the synthesis of acid (***R***)-**43** began with a Myers' diastereoselective alkylation with propargyl bromide **47**, using conditions analogous to those employed in the synthesis of olefin **286** (scheme 4.3), to afford amide **328**. Amide **328** was then converted through basic hydrolysis of the amide bond to the desired enantiomerically pure acid (***R***)-**43** in 76% yield over two steps (scheme 7.2).



Scheme 7.2: Synthesis of (2*R*)-2-methylpent-4-ynoic acid (***R*)-43**.

With the desired acid (***R*)-43** in hand, an EDC mediated amide coupling with the previously generated amine **283** afforded the desired amide product **329** in excellent yield. The primary TBS group was then selectively removed in the presence of the TBDPS group, using analogous conditions to those used previously (scheme 4.8), to give the β-hydroxyamide **327**. Sadly, in the case of this substrate, these conditions gave only a 63% yield. Switching the proton source to CSA proved to be too harsh, and only 28% of the desired product was isolated, with the rest of the material decomposing. Using TMSCl, as an *in situ* source of HCl, gave the desired alcohol **327**, in 39%, together with a significant amount of the undesired diol.[90] When using TBAF at 0 °C, the reaction did not go to completion, and when allowed to warm to rt, global deprotection took place. HF in acetonitrile, on the other hand, gave global deprotection almost instantaneously. Doubling the equivalents of PPTS used, to 0.2, gave a greatly improved yield of 96% however, the reaction remained sluggish, taking 60 h to reach completion (scheme 7.3, table 7-1).



Scheme 7.3: Synthesis of β-hydroxyamide **327**.

Entry	Deprotection conditions	Time (h)	Yield (%)
1	PPTS (0.1 eq), MeOH, rt	72	63
2	CSA, MeOH, rt	16	28
3	TMSCl, H_2O, MeCN	16	39
4	TBAF, THF, 0 °C - rt	16	-
5	HF, MeCN	0.25	-
6	PPTS (0.2 eq), MeOH, rt	60	96

Table 7-1: Deprotection of **327**.

As with the synthesis of oxazole fragment **281**, the oxidation of the *β*-hydroxyamide to the *β*-formylamide proved to be challenging. Swern oxidation gave the desired formylamide **330** in very poor yield. Oxidation using TEMPO/BAIB gave no conversion, and only starting material was recovered. IBX oxidation at rt on the other hand, gave the desired aldehyde in reasonable yield. When the same IBX oxidation was executed in refluxing ethyl acetate, the yield was increased significantly. Interestingly, when the reaction time was reduced to 2 h, the desired *β*-formylamide **330** was isolated in quantitative yield (scheme 7.4, table 7-2).

327 **330**

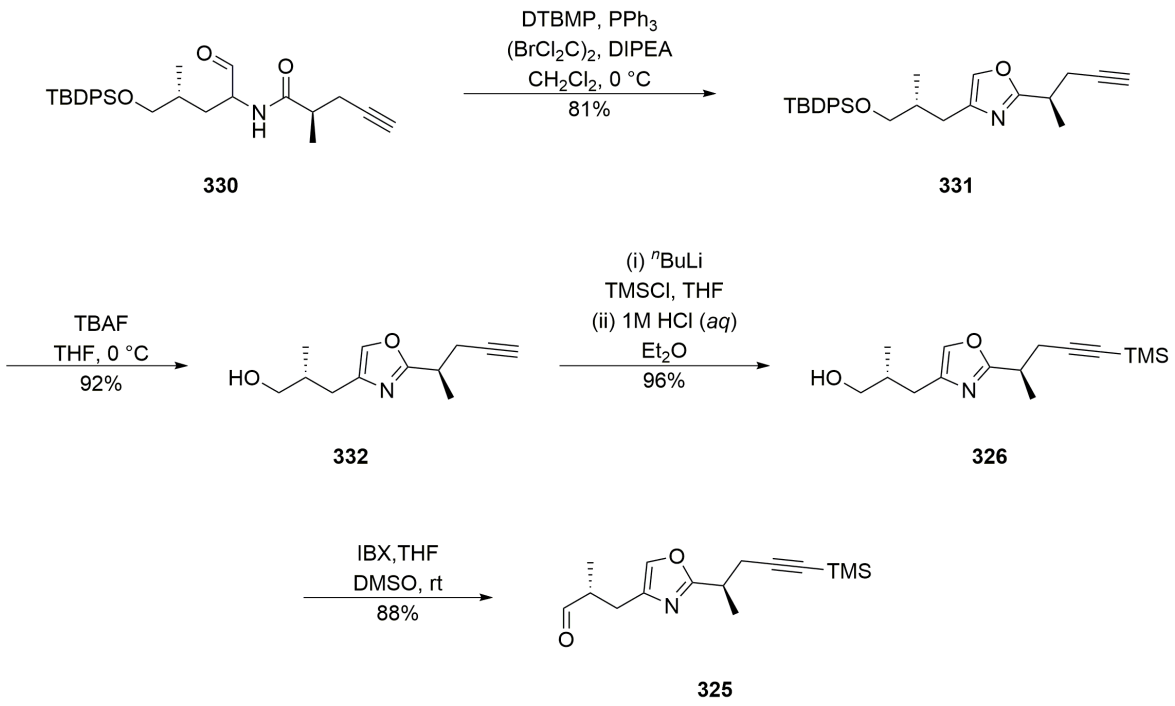
Scheme 7.4: Synthesis of aldehyde **330**.

Entry	Conditions	Yield (%)
1	Swern Oxidation	28
2	TEMPO, BAIB	-
3	IBX, DMSO, THF, rt	55
4	IBX, EtOAc, Δ (16 h)	83
5	IBX, EtOAc, Δ (2 h)	100

Table 7-2: Oxidation of **327**.

Gratifyingly, cyclodehydration of *β*-formylamide **330** using Forsyth's modification of Wipf's protocol gave the desired oxazole **331** in good yield.[35, 82] Removal of the TBDPS group was then achieved in 92% yield, to give primary alcohol **332**. Introduction of the alkynyl-TMS group was then achieved selectively to afford alcohol **326**, which upon TEMPO/BAIB oxidation generated the desired aldehyde **325** in high yield. Although the yield of the TEMPO/BAIB oxidation was 77%, the reaction required careful purification to

remove the side products, thus IBX oxidation of alcohol **326** was attempted. Excitingly, using IBX yielded aldehyde **325** in 88% yield, with minimal purification (scheme 7.5).



Scheme 7.5: Synthesis of oxazole-aldehyde **325**.

7.2 SUMMARY

The synthesis of a modified oxazole-aldehyde unit **325** containing an alkyne handle has been achieved in 16 steps and 28% yield starting from (1*S*,2*S*)-(+)-pseudoephedrine **284**. The procedure is robust and amenable to scale-up.

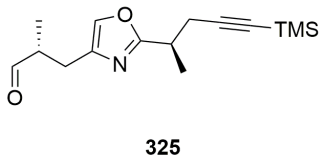
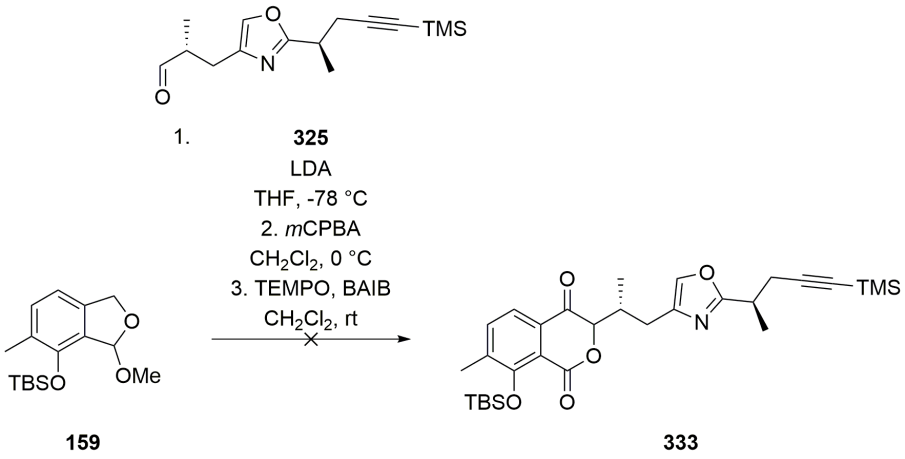


Figure 7.1: Oxazole-aldehyde **325**.

8 END-GAME STRATEGY

8.1 OXIDATIVE REARRANGEMENT

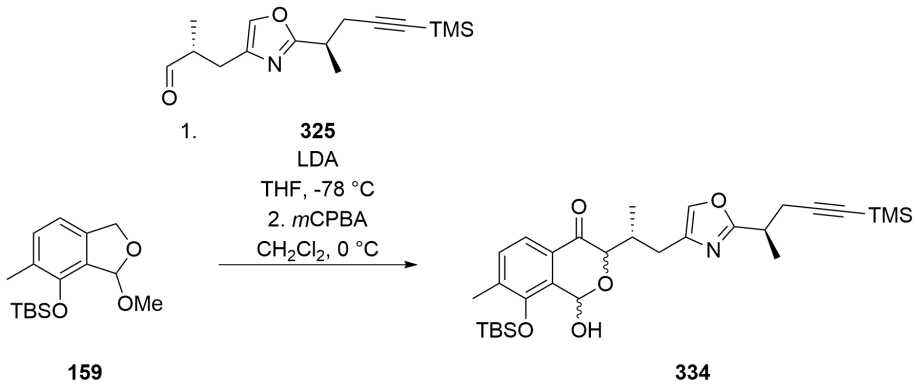
With the alkyne-aldehyde **325** and fully substituted phthalan **159** available, the oxidative rearrangement sequence was initially executed according to the standard oxidative procedure, involving flash chromatography purification of the keto-lactone unit **333**. Interestingly, whilst an accurate mass spectrum was obtained of the crude keto-lactol intermediate from the Achmatowicz rearrangement, none of the keto-lactone **333** could be identified after the TEMPO/BAIB oxidation (scheme 8.1). Therefore, it was decided to optimise the isobenzofuran rearrangement steps, and to then isolate and purify the lactol intermediate.



Scheme 8.1: Unsuccessful synthesis of keto-lactone **333**.

The initial oxidative rearrangement sequence was performed using 1.1 equivalents of the phthalan starting material **159**, however this resulted in significant amounts of unreacted aldehyde **325**. Despite this, lactol **334** was isolated as an inseparable mixture of diastereomers, in 25% yield. Unreacted aldehyde **325** was recovered making the overall yield 82%, based upon recovery of starting material.

To optimise the transformation, the equivalents of phthalan were modified initially. The phthalan, being the more easily synthesised, and therefore less valuable substrate, was increased to 1.6 equivalents resulting in an increase in yield to 34%. Further inncrease to 2.0 equivalents of phthalan **159**, translated into a much more satisfactory 65% yield (table 8-1).



159 334

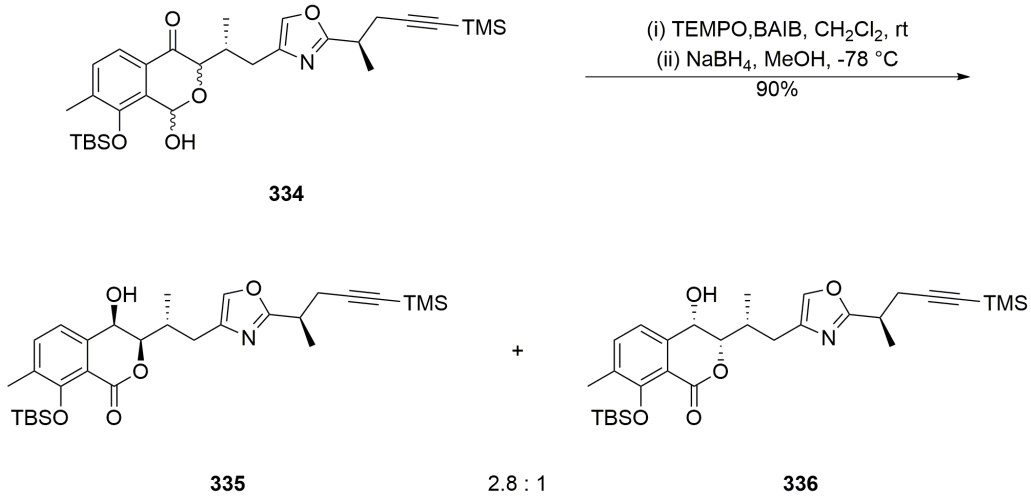
Scheme 8.2: Oxidative rearrangement utilising aldehyde **325**.

Entry	Phthalan (159) equivalents	Yield 334 (%)
1	1.1	25 (82 brsm)
2	1.6	34
3	2.0	65

Table 8-1: Oxidative rearrangement utilising aldehyde **325**.

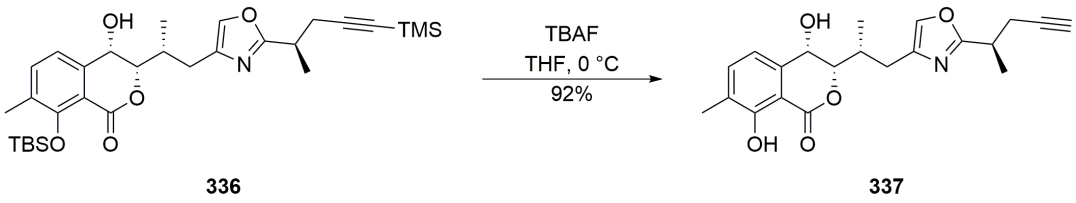
Oxidation of lactol mixture **334** to the corresponding keto-lactone **333** again proved to be problematic. Oxidation attempts using TEMPO/BAIB were unsuccessful, resulting in decomposition. Changing the oxidant to PCC afforded only starting material.

It was hypothesised that the keto-lactone **333** intermediate was highly unstable. Hence, it was decided to test whether the oxidation/reduction sequence could be carried out in a one-pot process, negating the need to isolate the putative keto-lactone unit **333**. Thus, the lactol mixture, was treated with TEMPO/BAIB, followed by the addition of $NaBH_4$ in anhydrous MeOH at -78 °C. This approach worked surprisingly well, and the *syn,anti*-isochromanone **335** and *syn,syn*-isochromanone **336** were isolated in a combined 90% yield, in a 2.8:1 ratio (scheme 8.3).



Scheme 8.3: One pot oxidation-reduction of isochromanones **335** and **336**.

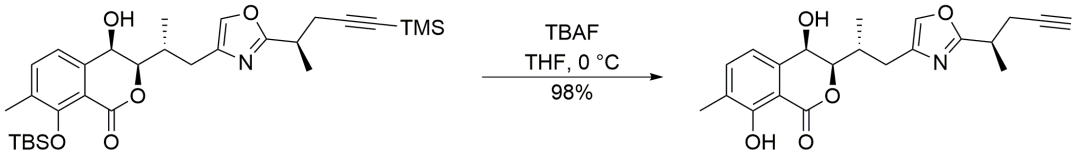
The next step was concomitant removal of the TMS and TBS protecting groups. This was initially tested on the undesired *syn*,*syn*-isochromanone **336**. Encouragingly, by using TBAF, at 0 °C, both silyl groups were removed after 10 min in excellent yield (scheme 8.4).



336 **337**

Scheme 8.4: Desilylation of *syn*,*syn*-isochromanone **336**.

The same conditions were then applied to desilylation of the desired *syn*,*anti*-isochromanone **335**. Pleasingly, both silyl groups were removed after a 10 min reaction, with the desired diol **338** being obtained in near quantitative yield (scheme 8.5).



335 **338**

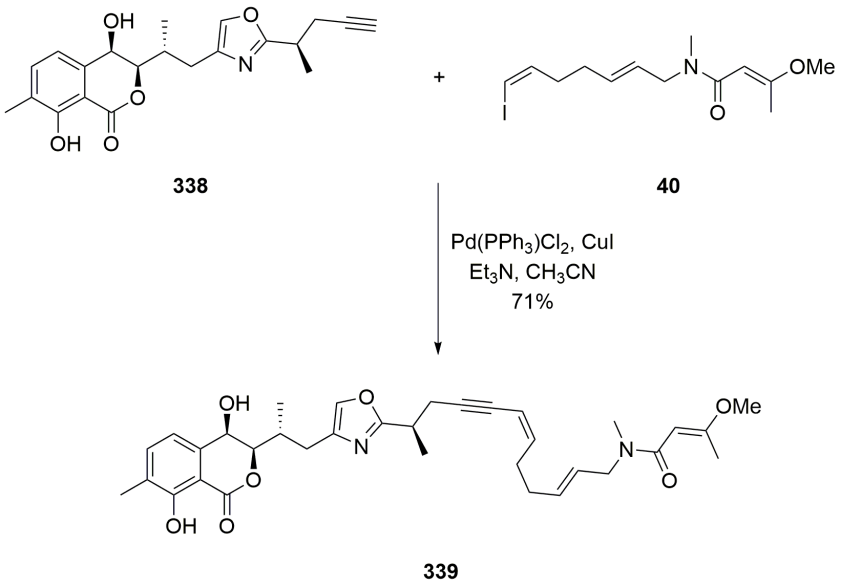
Scheme 8.5: Desilylation of *syn*,*anti*-isochromanone **335**.

Unfortunately, lactone **338** proved to be unstable, and prone to *trans*-lactonisation particularly during purification by flash chromatography. The following steps were carried out immediately after its synthesis.

8.2 COUPLING OF EASTERN AND WESTERN FRAGMENTS

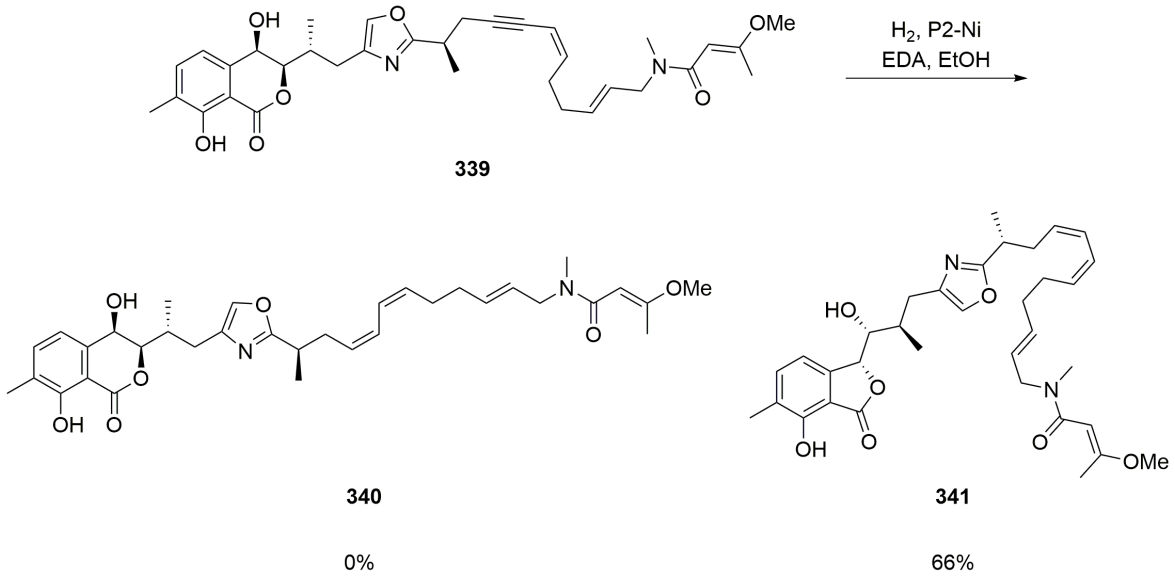
Having completed the synthesis of the western fragment **338**, efforts were then directed to achieving the pivotal coupling with the eastern fragment **40**.

Excitingly, the sp-sp^2 bond formation between acetylene **338** and vinyl iodide **40** was achieved *via* a Sonogashira coupling, completing the full ajudazol B carbon framework **339**. The amount of dissolved oxygen had a significant impact on the yield of the coupling. When the acetonitrile solvent was degassed using a stream of argon, the coupling proceeded in 57% yield. Using a freeze-pump-thaw method, the yield was successfully, and substantially, increased to 71% (scheme 8.6).



Scheme 8.6: Sonogashira coupling to synthesise enyne **339**.

Partial reduction of the enyne **339** to the *Z,Z*-diene was then attempted using Brown's P2-Ni conditions.[36] After the reaction was complete, the crude mixture was passed through a plug of celite. Unfortunately, this did not remove all the inorganic material, so the crude mixture was passed through a short plug of alumina, and likewise this also failed to remove the inorganic material. Faced with this difficulty, as a last resort the product was passed through a short plug of silica gel. A pure compound with the correct accurate mass was isolated, however, on closer inspection of the ^{1}H NMR spectrum it became apparent that the signals from the isochromanone core had shifted. Disappointingly the isolated product was the 5-membered lactone **341**.

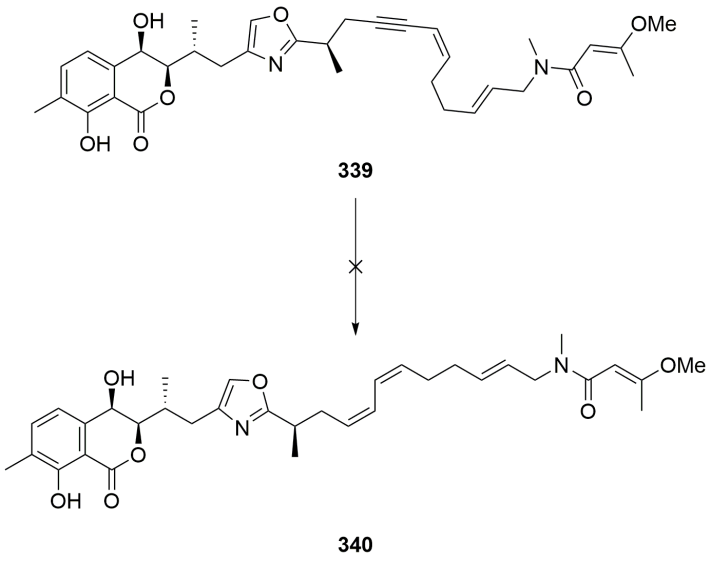


Scheme 8.7: Synthesis of **341**.

At this point, it was unclear whether the Ni in the catalyst had acted as a Lewis acid and promoted the translactonisation, or if exposure to silica had mediated the formation of the 5-membered lactone.

Therefore, different conditions were investigated for the selective, partial reduction of the enyne. Hydrogenation using Lindlar's catalyst using quinoline as a catalyst poison and a Pd loading of 5 wt. %, resulted in complete recovery of starting material after 24 h. Increasing the Pd content to 15 wt. % failed to afford any of the reduced product. Further increases in Pd content as well as solvent changes, and omission of quinoline failed to catalyse the reaction.

Switching of the palladium source to $Pd/BaSO_4$, in the presence of quinoline resulted in no reaction based on TLC monitoring on alumina plates. However, crude ^1H NMR revealed decomposition of starting material, and mass spectrometry confirmed that none of the desired product was formed (table 8-2).



Scheme 8.8: Unsuccessful partial reduction of enyne **339**.

Entry	Conditions	Pd (wt. %)	Time (h)	Yield 340 (%)
1	Lindlar's, quinoline, EtOAc	5	24	-
2	Lindlar's, quinoline, EtOAc	15	6	-
3	Lindlar's, EtOH	10	6	-
4	Lindlar's, EtOH	30	16	-
5	$PdBaSO_4$, quinoline, EtOH	10	24	decomposition

Table 8-2: Unsuccessful alternative conditions for partial reduction of enyne **339**.

Based on the lack of visible reduction using standard palladium catalysts, it was decied to revert to using P2-Ni and to try to minimise the undesired translactonisation. The treatment of enyne **339** using P2-Ni under our precisely executed conditions yielded a crude material which was filtered sequentially through celite, and neutral alumina, before being purified by preparative HPLC. Encouraginly, LCMS confirmed the presence of [M+H] and starting material. Disappointingly, after HPLC purification the quantity of product obtained with the correct [M+H] was not sufficient to obtain a ^{1}H NMR spectra.

With very limited material, and due to time constraints, the P2-Ni reduction was performed on the last of the synthesised enyne **339**. After completion of the reaction, the crude was filtered through a syringe filter, and immediately purified using preparative HPLC. LCMS confirmed the presence of starting material, and two peaks both with [M+H]. The major product appeared to be the 5-membered lactone **341**, and the minor one was postulated to be 8-*epi*-ajudazol B **340**.

An accurate mass spectrum was obtained, with $[M+Na]^{+}$ being calculated as m/z 615.3041 and observed as m/z 615.3013. Disappointingly, the quantity of material obtained after purification was insufficient to obtain an optical rotation or clear proton NMR spectrum, despite running the sample with solvent suppression and a highly extended number of scans. The spectrum obtained could not be integrated, nor could the coupling patterns be identified (figure 8.1). During the HPLC purification the eluents used contained 0.1% TFA. This could have contributed to translactonisation, and to degradation of the product.

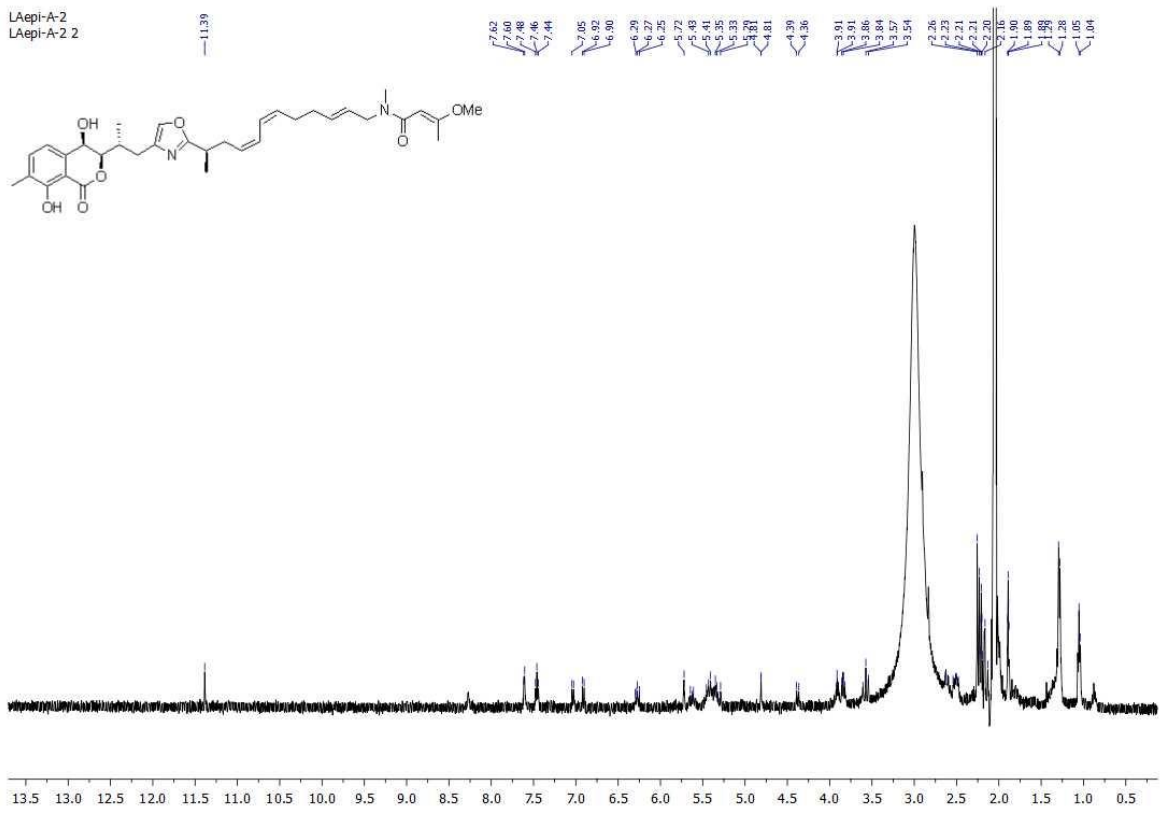
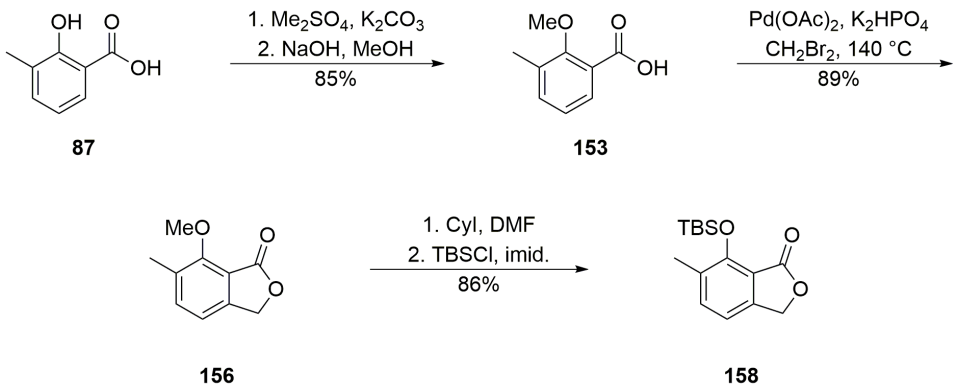


Figure 8.1: ^{1}H NMR spectrum of 8-epi-ajudazol B **340**.

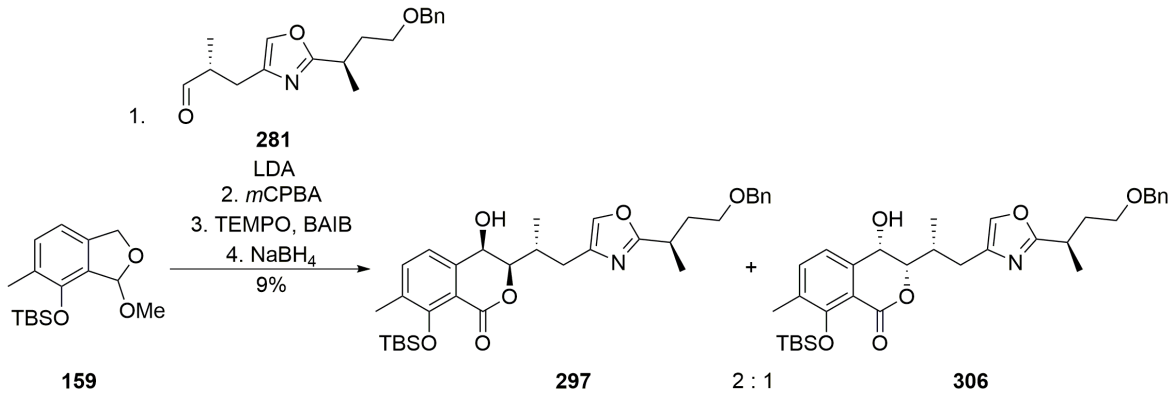
9 CONCLUSIONS

The first objective of the work presented in this thesis, was to develop an efficient synthesis of phthalide **158**. The previous synthesis was completed in 10 steps and 37% yield. This was successfully shortened to 5 steps, and the yield significantly increased to 65%.



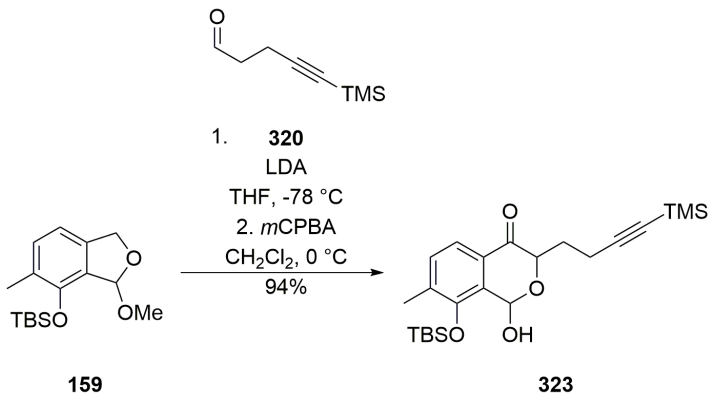
Scheme 9.1: Synthesis of phthalide **158**.

Oxazole **281** and phthalan **159** were successfully synthesised. They were then used in the oxidative rearrangement of isobenzofurans methodology to synthesise isochromanones **297** and **306**.



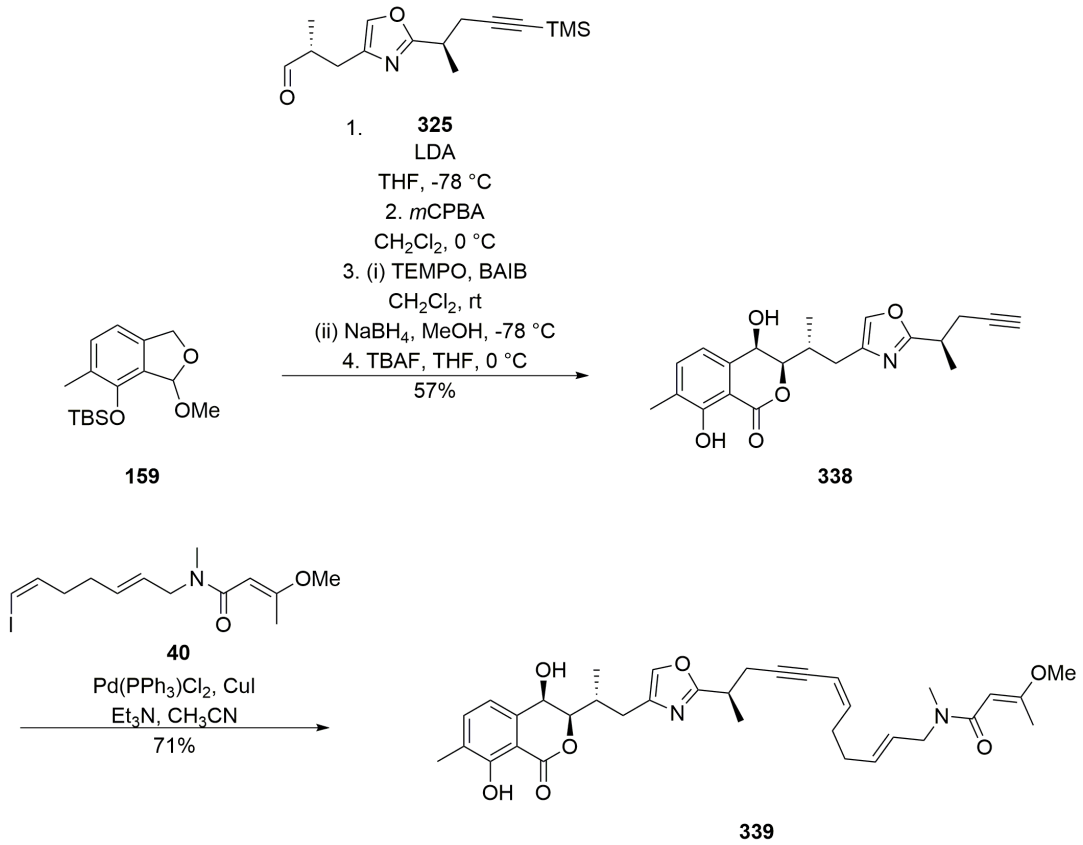
Scheme 9.2: Synthesis of isochromanones **297** and **306**.

To increase the efficiency and convergence of the route, the rearrangement was investigated to determine whether the presence of an alkyne would be tolerated. An alkyne-bearing aldehyde **320** was successfully used in the rearrangement and keto-lactol **323** was synthesised. The scope of the rearrangement was therefore expanded, increasing the synthetic utility of the methodology.



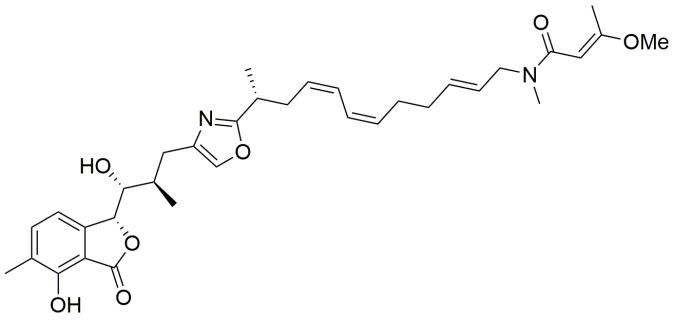
Scheme 9.3: Oxidative rearrangement of isobenzofuran in the presence of an alkyne.

A new oxazole coupling partner **325** was designed and synthesised, then successfully utilised in the oxidative rearrangement. This optimised route allowed for the efficient generation of the full ajudazol B framework in 20 steps and 11% overall yield.



Scheme 9.4: Synthesis of the ajudazol B framework.

The partial reduction of enyne **339** was unsuccessful in generating 8-*epi*-ajudazol B **340**, but a structural isomer **341** was isolated and will be tested for biological activity.



341

Figure 9.1: Isomer of ajudazol B.

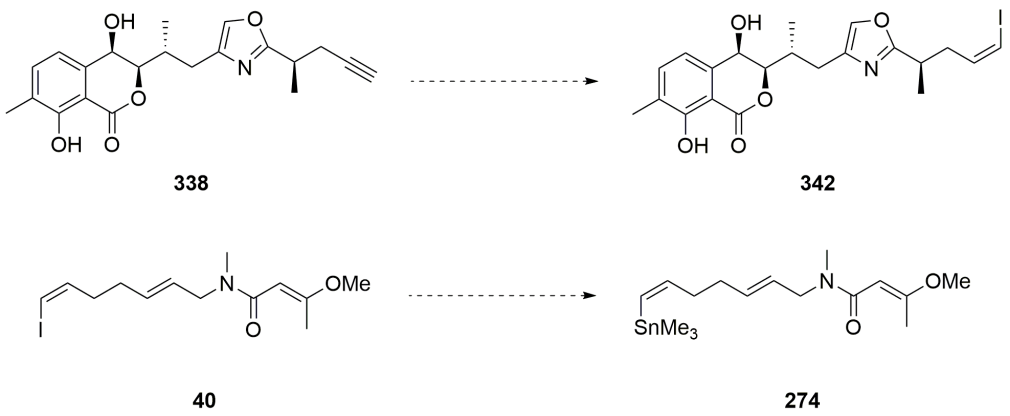
Ultimately, we were unable to complete the total synthesis of ajudazol B, though an efficient, convergent route to complete the full ajudazol B framework was developed.

10 FUTURE WORK

10.1 COMPLETION OF THE TOTAL SYNTHESIS

The first objective for any future work on this research project would be to complete the total synthesis of 8-*epi*-ajudazol B, and then focus efforts on ajudazol B.

The partial reduction of the enyne to the *Z*,*Z*-diene proved to be problematic to purify and led to translactonisation, therefore an alternative route avoiding this step could be designed. Acetylene **338** could be converted to the *Z*-vinyl iodide **342**, and the eastern fragment **40** converted to the stannane **274**. A Stille coupling, instead of the Sonogashira, could generate the desired *Z*,*Z*-diene, negating the need for the problematic partial reduction step, and completing the synthesis of 8-*epi*-ajudazol B **240**.

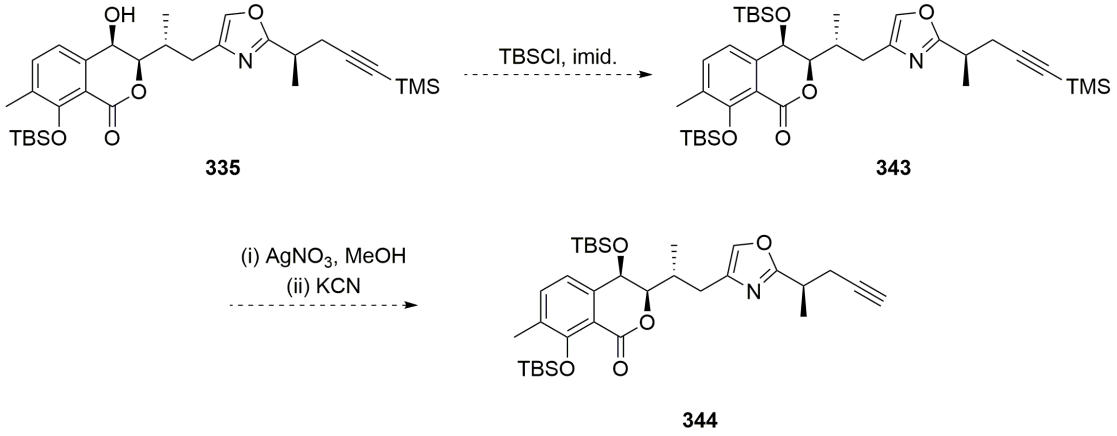


338 **342**

40 **274**

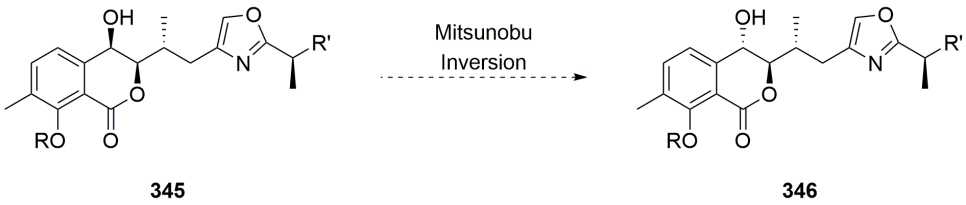
Scheme 10.1: Stille coupling partners.

Alternatively, the C8 hydroxy group could be protected to prevent translactonisation. The TMS could be selectively removed, in the presence of the TBS ethers, and the route continued as before.[91] The synthesis could then be continued as in the established route, with an added deprotection step to cleave the silyl ether protecting groups.



Scheme 10.2: Protection of C8 hydroxy group.

Work could then be focussed on achieving the *anti,anti*-relationship of the isochromanone core. Mitsunobu inversion could be attempted at several stages throughout the synthesis on various isochromanone bearing intermediates.



Scheme 10.3: Mitsunobu inversion to access *anti,anti*-isochromanone

10.2 SYNTHESIS OF ANALOGUES

The next objective would be the synthesis of analogues based on the ajudazol B framework, using the synthetic route developed. These analogues could then be tested, along with intermediates from throughout the synthesis, to establish the structure-activity relationship.

11 EXPERIMENTAL

11.1 GENERAL DETAILS

Reactions were performed in glassware that had been oven-dried and/or flame-dried prior to use. Reactions were carried out under an inert argon atmosphere unless otherwise stated. THF, Et_2O, CH_2Cl_2, MeCN, and toluene were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Liquid reagents were distilled before use where stated.

All microwave reactions were performed using a Biotage Initiator system.

NMR spectra were recorded on a Bruker AVI DPX-400 spectrometer, Bruker AVIII DPX-400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), or a Bruker AVII DPX-500 spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz). Chemical shifts (δ) are reported in parts per million (ppm). ^{1}H NMR spectra 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, m = multiplet, br = broad, or a combination of these), and (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1 Hz. DEPT135, DEPT90, and two-dimensional (COSY, NOESY, HSQC, HMBC) NMR spectroscopy were used, where appropriate, to assist with the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

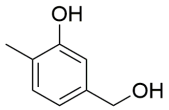
IR spectra were obtained using a Shimadzu FTIR-8400 instrument with a Golden Gate™ attachment that uses a type IIa diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) could be detected directly (thin layer).

High resolution mass spectra were recorded using ESI and CI conditions by the analytical services at the University of Glasgow.

Flash chromatography was performed using silica gel (Fluorochem silica gel 60, 40 – 63 μm) as the stationary phase, and HPLC graded solvents as the eluent. Reaction monitoring by TLC was performed on aluminium sheets pre-coated with silica (Merck Silica gel 60 F_{254}), unless otherwise stated. The plates were visualised under UV-light (λ_{max} 254 nm) and/or by staining with either anisaldehyde, potassium permanganate, or cerium ammonium molybdate dips followed by heating.

11.2 EXPERIMENTAL DETAILS

5-(Hydroxymethyl)-2-methylphenol



207

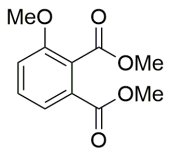
$LiAlH_4$ (250 mg, 6.58 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0 °C. 3-Hydroxy-4-methylbenzoic acid **206** (500 mg, 3.29 mmol) was dissolved in anhydrous THF (5 mL) and added dropwise to the resultant suspension *via* syringe pump over 1 h. The resultant mixture was warmed to rt and stirred for 16 h. The reaction was quenched by careful addition of EtOAc (40 mL) followed by addition of 20% Rochelle's salt solution (*aq*) (50 mL) and the resultant mixture was stirred for 16 h. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo*, to give the desired product **207** as a white solid (164 mg, 36%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (1H, d, *J* = 7.3 Hz, ^{Ar}H), 6.87 (1H, d, *J* = 7.4 Hz, ^{Ar}H) 6.86 (1H, s, ^{Ar}H), 4.66 (2H, s, CH_2), 2.28 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.0 (^{Ar}COH), 140.2 (^{Ar}CCH$_2$OH), 131.2 (^{Ar}CH), 123.2 (^{Ar}CCH$_3$), 119.3 (^{Ar}CH), 113.5 (^{Ar}CH), 65.1 (*C*H$_2$), 15.5 (*C*H$_3$).

This data is in accordance with literature values.[53]

Dimethyl 3-methoxyphthalate



216

1-Methoxy-1,3-cyclohexadiene (540 µL, 2.96 mmol) (65% by assay) was dissolved in anhydrous toluene (3 mL). DMAD (280 µL, 2.28 mmol) was added and the reaction mixture

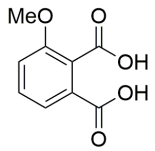
was heated to reflux (111 °C) and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and purified using flash chromatography (silica gel, 10 – 30% EtOAc in petroleum ether) to yield the desired product **216** as a yellow oil (511 mg, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (1H, dd, *J* = 7.9, 0.8 Hz, C(O)C^{Ar}C*H*), 7.48 – 7.39 (1H, m, ^{Ar}CH^{Ar}C*H*), 7.15 (1H, dd, *J* = 8.4, 0.8 Hz, C(OCH_3)^{Ar}C*H*), 3.97 (3H, s, CH_3), 3.89 (3H, s, C*H*$_3$), 3.87 (3H, s, C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.1 (*C*=O), 165.9 (*C*=O), 156.6 (^{Ar}*C*), 130.3 (^{Ar}*C*H) , 128.9 (^{Ar}*C*), 125.6 (^{Ar}*C*), 122.1 (^{Ar}*C*HCC(O)), 115.6 (^{Ar}*C*HC(OCH_3)), 56.9 (O*C*H$_3$), 52.7 (C(O)O*C*H$_3$), 52.5 (C(O)O*C*H$_3$).

This data is in accordance with literature values.[92]

3-Methoxyphthalic acid



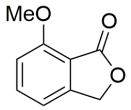
217

Dimethyl 3-methoxyphthalate **216** (1.00 g, 4.46 mmol) was dissolved in MeOH (10 mL) before addition of 2M NaOH (*aq*) (30 mL). The resultant mixture was then heated to 50 °C and stirred for 6 h. The mixture was then cooled to rt, diluted with H_2O (200 mL), and extracted with Et_2O (100 mL). The aqueous phase was then acidified with 6M HCl (aq) to pH 1, and extracted with EtOAc (200 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (silica gel, 50% EtOAc in petroleum ether) to yield the desired product **217** as a white crystalline solid (551 mg, 63%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 7.57 (1H, dd, *J* = 7.8, 0.9 Hz, C(O)C^{Ar}C*H*), 7.42 – 7.38 (1H, m, ^{Ar}CH^{Ar}C*H*), 7.24 (1H, dd, *J* = 8.3, 0.9 Hz, C(OCH_3)^{Ar}C*H*), 3.85 (3H, s, OC*H*$_3$).

This data is in accordance with literature values.[93]

7-Methoxyphthalide



218

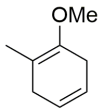
3-Methoxyphthalic acid (449 mg, 2.74 mmol) was dissolved in 12 M HCl (*aq*) (5 mL) and AcOH (11 mL). The resultant mixture was heated to 70 °C and then treated slowly with Zn dust (1 g, 15.3 mmol/h over 6 h), then stirred for 16 h. The reaction was then quenched with H_2O (5 mL), extracted with EtOAc (15 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, to give the desired product as a white solid (186 mg, 50%) which was used in the subsequent reaction without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (1H, t, *J* = 8.0 Hz, ^{Ar}H), 7.00 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 6.93 (1H, d, *J* = 8.2 Hz, ^{Ar}H), 5.23 (2H, s, CH_2), 3.99 (3H, s, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.2 (*C*=O), 158.8 (^{Ar}*C*OCH$_3$), 149.5 (^{Ar}*C*), 136.3 (^{Ar}*C*H), 113.7 (^{Ar}*C*H), 113.4 (^{Ar}*C*), 110.6 (^{Ar}*C*H), 68.7 (*C*H$_2$), 56.2 (O*C*H$_3$).

This data is in accordance with literature values.[48]

1-Methoxy-2-methylcyclohexa-1,4-diene



221

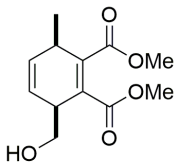
2-Methylanisole (2.55 mL, 20.6 mmol) was dissolved in Et_2O (25 mL) and cooled to -78 °C. NH_3 (*l*) (100 mL) was condensed into the flask. Li wire (2.10 g, 303 mmol) was added slowly, resulting in a deep blue metallic solution. The dry ice/acetone bath was then removed, and the mixture left to reflux and stirred for 5 h. The reaction mixture was then quenched by careful addition of MeOH, and left for 16 h for the NH_3 to evaporate. The crude reaction mixture was then diluted with H_2O (25 mL), and extracted with EtOAc (100 mL). The combined organic phases were washed with H_2O (3 × 25 mL), brine (25 mL), and concentrated *in vacuo* to yield the desired product **221** as a clear oil (1.45 g, 57%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.71 – 5.63 (2H, m, *H*C=C*H*), 3.53 (3H, s, OCH_3), 2.83 – 2.78 (2H, m, CH_2), 2.72 – 2.68 (2H, m, CH_2), 1.65 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.3 (C=*C*-OCH_3) 124.5 (H*C*=CH), 123.6 (HC=*C*H), 111.6 (H_3CC=C), 56.03 (O*C*H_3), 32.8 (*C*H_2), 26.0 (*C*H_2), 14.8 (*C*H_3).

This data is in accordance with literature values.[94]

Dimethyl 3-(hydroxymethyl)-6-methylcyclohexa-1,4-diene-1,2-dicarboxylate



226

trans,*trans*-2,4-Hexadien-1-ol (1.25 g, 12.7 mmol) and DMAD (1.53 mL, 12.4 mmol) were added to a flask and heated to 80 °C, for 16 h. The reaction mixture was then cooled and purified using flash chromatography (silica gel, 20% EtOAc in petroleum ether) to yield the desired product **226** as a pale-yellow oil (2.17 g, 73%).

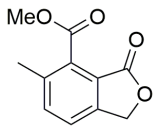
^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.89 (1H, ddd, *J* = 9.8, 4.2, 0.9 Hz, *H*C=CH), 5.69 (1H, ddd, *J* = 9.8, 4.3, 0.8 Hz, HC=C*H*), 3.80 (6H, s, OCH_3), 3.79 – 3.74 (1H, m, CH_2), 3.70 – 3.63 (1H, m, CH_2), 3.34 – 3.15 (2H, m, C*H*CH_3 + C*H*CH_2OH), 2.17 (1H, dd, *J* = 7.8, 5.5 Hz, O*H*), 1.23 (3H, d, *J* = 7.0 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 500 MHz) δ: 168.9 (*C*=O), 168.2 (*C*=O), 140.9 (*C*=CC(O)), 133.6 (*C*=CC(O)), 131.6 (H*C*=CH), 123.6 (HC=*C*H), 65.7 (*C*H_2), 52.5 (C(O)O*C*H_3), 52.2 (C(O)O*C*H_3), 41.3 (*C*HCH_2), 33.2 (*C*HCH_3), 21.8 (*C*H_3).

HRMS (ESI) calculated for $C_{12}H_{17}O_5$ $(M+H)^+$: m/z 241.1076, observed 241.1075

IR ν_{max} (film)/cm^{-1} 3385 , 1717, 1636, 1435, 1256.

Methyl 5-methyl-3-oxo-1,3-dihydroisobenzofuran-4-carboxylate



227

Dimethyl 3-(hydroxymethyl)-6-methylcyclohexa-1,4-diene-1,2-dicarboxylate **226** (200 mg, 0.83 mmol) was dissolved in benzene. Activated MnO_2 (730 mg, 8.40 mmol) was added and the resultant solution was heated to reflux for 4 h, whilst azeotropically removing the H_2O generated using a Dean-Stark apparatus. The reaction mixture was then filtered through celite, washed with benzene (30 mL), chloroform (10 mL), and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, 20% EtOAc in pet. ether) to yield the desired lactone **227** as a white solid (116 mg, 70%) and aldehyde **228** as a clear oil (8 mg, 4%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.54 (1H, d, *J* = 8.0 Hz, ^{Ar}H), 7.44 (1H, d, *J* = 8.0 Hz, ^{Ar}H), 5.28 (2H, s, CH_2), 4.02 (3H, s, OCH_3), 2.44 (3H, s, ^{Ar}CH_3).

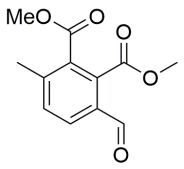
^{13}C NMR ($CDCl_3$, 500 MHz) δ: 169.1 (*C*=O), 167.4 (*C*=O), 144.5 (^{Ar}*C*CH_2O), 136.5 (^{Ar}*C*CH_3), 136.3 (^{Ar}*C*CO_2CH_3), 131.9 (^{Ar}*C*H), 123.2 (^{Ar}*C*CO_2CH_2), 123.1 (^{Ar}*C*H), 69.3 (O*C*H_3), 53.1 (*C*H_2), 18.8 (*C*H_3).

HRMS (ESI) calculated for $C_{11}H_{10}O_4Na$ $(M+Na)^+$: m/z 229.0471, observed m/z 229.0473.

IR ν_{max} (film)/cm^{-1} 1759, 1724, 1435, 1258, 907.

Melting point: 90 – 92 °C.

Dimethyl 3-formyl-6-methylphthalate



228

(8 mg, 4%).

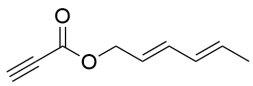
^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.12 (1H, s, C(O)*H*), 7.92 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.49 (1H, d, *J* = 8.0 Hz, Ar*H*), 3.96 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 2.52 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 189.8 (*C*(O)H), 167.6 (*C*=O), 167.2 (*C*=O), 143.6 (^{Ar}*C*), 134.3 (^{Ar}*C*H) 133.2 (^{Ar}*C*H), 132.7 (^{Ar}*C*), 132.6 (^{Ar}*C*), 132.3 (^{Ar}*C*), 53.3 (O*C*H_3), 52.9 (O*C*H_3), 20.9 (*C*H_3).

HRMS (ESI) calculated for $C_{12}H_{13}O_5$ $(M+H)^+$: m/z 237.0763, observed m/z 237.0772.

IR ν_{max} (film)/cm^{-1} 2955, 1730, 1701, 1593, 1273.

(2*E*,4*E*)-Hexa-2,4-dien-1-yl propiolate



230

trans,*trans*-2,4-Hexadien-1-ol (2.48 g, 25.3 mmol) and DMAP (cat.) were dissolved in CH_2Cl_2 (175 mL) and cooled to 0 °C. Then propiolic acid (2.33 mL, 37.9 mmol) was added followed by DCC (7.83 g, 37.9 mmol) which was added portionwise. The reaction was warmed to room temperature overnight and then the CH_2Cl_2 was removed *in vacuo*. The crude precipitate was washed with hexane (200 mL) and filtered through celite. The filtrate was then concentrated *in vacuo* and purified by column chromatography (silica gel, 5% EtOAc in hexane) to yield the desired product **230** as a clear colourless oil (2.49 g, 66%).

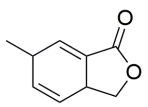
^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.31 (1H, dd, *J* = 10.5, 4.5 Hz, *H*C=CHCH$_2$), 6.08 (1H, dd, *J* = 11.0, 4.5 Hz, *H*C=CHCH$_3$), 5.83 – 5.76 (1H, m, C=C*H*CH$_2$), 5.66 – 5.60 (1H, m, =C*H*CH$_3$), 4.70 (2H, d, *J* = 7.0 Hz, C*H*$_2$), 2.88 (1H, s, ≡C*H*), 1.78 (3H, d, *J* = 7.0 Hz, CH$_3$).

^{13}C NMR ($CDCl_3$, 500 MHz) δ: 152.5 (*C*=O), 136.2 (H*C*=CHCH$_2$), 132.1 (H*C*=CHCH$_3$), 130.2 (HC=*C*HCH$_2$), 121.9 (HC=*C*HCH$_3$), 74.9 (C≡*C*H), 74.8 (*C*≡CH), 66.7 (*C*H$_2$), 18.1 (*C*H$_3$).

HRMS (ESI) calculated for $C_9H_{10}O_2Na$ $(M+Na)^+$: m/z 173.0573, observed m/z 173.0570.

This data is in accordance with literature values.[59]

6-Methyl-3,3*a*-dihydroisobenzofuran-1(6*H*)-one



234

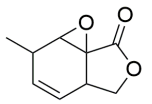
A suspension of [Rh(cod)Cl]$_2$ (12.3 mg, 5 mol%) in TFE (3 mL) was treated with $AgSbF_6$ (22.3 mg, 13 mol%) in CH_2Cl_2 (0.26 mL) followed immediately by a solution of (2*E*,4*E*)-hexa-2,4-dien-1-yl propiolate **230** (75 mg, 0.5 mmol) in TFE (2 mL). The reaction mixture was stirred for 1.5 h, then diluted with Et_2O (15 mL), and filtered through celite. The reaction mixture was concentrated *in vacuo* and the crude product was purified using flash chromatography (silica gel, 10% EtOAc in hexane) to yield the desired product **234** as a colourless oil (55.3 mg, 74%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.71 – 6.70 (m, 1H, *H*C=*q*C), 5.79 – 5.73 (m, 2H, *H*C=C*H*), 4.67 – 4.63 (m, 1H, C*H*$_2$), 3.85 (dd, 1H, *J* = 10.4, 8.3 Hz, C*H*$_2$), 3.56 – 3.48 (m, 1H, C*H*), 3.07 – 2.99 (m, 1H, C*H*CH$_3$), 1.27 (d, 3H, *J* = 7.7 Hz).

^{13}C NMR ($CDCl_3$, 500 MHz) δ: 169.5 (*C*=O), 138.7 (H*C*=C), 133.2 (H*C*=CH), 127.57 (*C*), 121.9 (HC=*C*H), 70.7 (*C*H$_2$), 37.2 (*C*H), 32.2 (*C*H), 20.5 (*C*H$_3$).

This data is in accordance with literature values.[59]

4-Methyl-2,9-dioxatricyclodec-5-en-10-one



237

6-Methyl-3,3*a*-dihydroisobenzofuran-1(6*H*)-one **234** (55 mg, 0.37 mmol) was dissolved in MeOH (3 mL) and cooled to 0 °C. 3M NaOH (*aq*) (0.37 mL), and 30% H_2O_2 (0.37 mL) were then added dropwise and the resultant mixture was warmed to rt and stirred for 5 h. The reaction mixture was then diluted with H_2O (2 mL), acidified to pH 1 with 2M HCl (*aq*), extracted with EtOAc (5 mL). The organic extracts were washed with brine (2 mL), dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified using flash chromatography (silica gel 20% EtOAc in petrol) to yield the desired product **237** as a clear oil (18.2 mg, 30%).

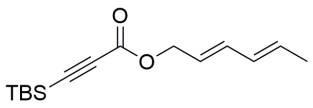
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.93 (1H, d, *J* = 9.7 Hz, C=C*H*), 5.73 (1H, dd *J* = 9.3, 4.3 Hz, C=C*H*), 5.44 (1H, br s, CH), 4.54 – 4.50 (1H, m, CH), 4.07 (1H, dd, *J* = 8.5, 6.4 Hz, CH), 3.38 – 3.28 (2H, m, CH_2), 1.82 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.6 (*C*=O), 128.9 (H*C*=CH), 124.3 (HC=*C*H), 113.7 (*C*O), 73.5 (*C*H_2), 69.7 (H*C*O), 40.6 (H*C*CH_2), 34.9 (H*C*CH_3), 21.7 (*C*H_3).

HRMS (ESI) calculated for $C_9H_{11}O_3$ $(M+H)^+$: m/z 167.0708, observed 167.0709.

IR ν_{max} (film)/cm^{-1} 2916, 1767, 1283, 907, 725.

(2*E*,4*E*)-Hexa-2,4-dien-1-yl 3-(*tert*-butyldimethylsilyl)prop-2-ynoate



245

Freshly distilled ^{i}Pr$_2$NH (0.24 mL, 1.68 mmol) was dissolved in anhydrous THF (3 mL) and cooled to -78 °C. *n*BuLi (1.6 M in hexanes, 1.05 mL, 1.7 mmol) was added dropwise and the resultant mixture stirred for 30 min. The solution was then transferred, *via* cannula, to a stirred solution of (2*E*,4*E*)-hexa-2,4-dien-1-yl propiolate **230** (250 mg, 1.66 mmol) in

anhydrous THF (3 mL) at -78 °C, and stirred for 1 h. TBSCl (253 mg, 1.68 mmol) in anhydrous THF (1 mL) was added dropwise to the resultant mixture and stirred for 3 h. The reaction was then quenched with saturated NH_4Cl (*aq*) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H_2O (25 mL), then brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (silica gel, 5% EtOAc in hexane) to yield the desired product **245** as a yellow oil (193 mg, 44%).

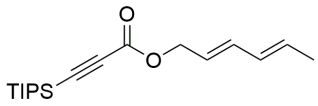
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.29 (1H, dd, *J* = 15.2, 10.5 Hz, *H*C=CHCH$_2$), 6.07 (1H, dd, *J* = 15.0, 10.7 Hz, *H*C=CHCH$_3$), 5.86 – 5.73 (1H, m, H$_2$CC*H*=CH) 5.69 – 5.58 (1H, m, HC=C*H*CH$_3$), 4.67 (2H, d, *J* = 6.8 Hz, C*H*$_2$), 1.78 (3H, d, *J* = 6.7 Hz, C*H*$_3$), 0.97 (9H, s, SiC(C*H*$_3$)$_3$), 0.18 (6H, s, Si(CH$_3$)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.0 (*C*=O), 136.3 (H*C*=CHCH$_2$), 132.2 (H*C*=CHCH$_3$), 130.4 (H$_2$C*C*H=CH), 122.7 (HC=*C*HCH$_3$), 95.5 (Si*C*≡C), 92.9 (C≡*C*C(O)), 66.6 (*C*H$_2$), 26.1 (C(*C*H$_3$)$_3$), 18.3 (=CH*C*H$_3$), 16.7 (*C*(CH$_3$)$_3$), -5.0 (Si(*C*H$_3$)$_2$).

HRMS (ESI) calculated for $C_{15}H_{24}O_2SiNa$ $(M+Na)^+$: m/z 287.1438, observed m/z 287.1424.

IR ν_{max} (film)/cm^{-1} 2190, 1709, 1660, 1213, 990.

(2*E*,4*E*)-Hexa-2,4-dien-1-yl 3-[tris(propan-2-yl)silyl]prop-2-ynoate



246

Freshly distilled ^{i}Pr$_2$NH (0.47 mL, 3.36 mmol) was dissolved in anhydrous THF (6 mL) and cooled to -78 °C, under an argon atmosphere. *n*BuLi (1.6 M in hexanes, 2.10 mL, 3.4 mmol) was added dropwise and the resultant mixture stirred for 30 min. The solution was then transferred, *via* cannula, to a stirred solution of (2*E*,4*E*)-hexa-2,4-dien-1-yl propiolate **230** (500 mg, 3.32 mmol) in anhydrous THF (6 mL) at -78 °C, and stirred for 1 h. TIPSCl (0.71 mL, 3.36 mmol) was added dropwise to the resultant mixture and stirred for 3 h. The reaction was then quenched with saturated NH_4Cl (*aq*) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H_2O (25 mL), then brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified using flash

chromatography (silica gel, 1% EtOAc in hexane) to yield the desired product **246** as a yellow oil (193 mg, 44%).

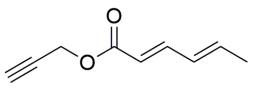
^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.29 (1H, dd, *J* = 15.2, 10.5 Hz, *H*C=CHCH$_2$), 6.10 – 6.04 (1H, m, *H*C=CHCH$_3$), 5.82 – 5.75 (1H, m, C=C*H*CH$_2$), 5.68 – 5.62 (1H, m, C=C*H*CH$_3$), 4.67 (2H, d, *J* = 6.8 Hz, C*H*$_2$), 1.78 (3H, d, *J* = 6.8 Hz, C*H*$_3$), 1.12 – 1.10 (21H, m, Si(^{i}Pr)$_3$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 153.1 (*C*=O), 136.1 (H*C*=CHCH$_2$), 132.0 (H*C*=CHCH$_3$), 130.5 (HC=*C*HCH$_2$), 122.9 (HC=*C*HCH$_3$), 96.9 (C(O)*C*≡C), 91.5 (C(O)C≡*C*), 66.6 (*C*H$_2$), 18.6 (Si(CH(*C*H$_3$)$_2$)$_3$), 18.3 (*C*H$_3$), 11.2 (Si(*C*H(CH$_3$)$_2$)$_3$).

HRMS (ESI) calculated for $C_{18}H_{30}O_2SiNa$ $(M+Na)^+$: m/z 329.1907, observed m/z 329.1893.

IR ν_{max} (film)/cm^{-1} 2170, 1711, 1663, 1462, 1207, 988.

(2*E*,4*E*)-Prop-2-yn-1-yl hexa-2,4-dienoate



253

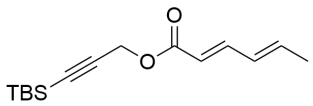
2-Propyn-1-ol (1.28 mL, 22.0 mmol), *N*,*N*'-dicyclohexylcarbodiimide (4.54 g, 22.0 mmol), and 4-(dimethylamino)pyridine (244 mg, 2.00 mmol) were dissolved in anydrous CH_2Cl_2 (40 mL) and cooled to 0 °C. 2,4-Hexadienoic acid (2.24 g, 20.0 mmol) was added and the resultant mixture was stirred for 4 h at 0 °C. The reaction mixture was then concentrated *in vacuo*, dissolved in hexane (20 mL), and filtered through a celite pad. The solvent was then removed *in vacuo* and the filtrate purified using flash chromatography (silica gel, 10% EtOAc in hexane) to yield the desired product **253** as a colourless oil (3.30 g, 100%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.29 (1H, m, *H*C=CHC(O)), 6.24 – 6.15 (2H, m, =C*H* × 2), 5.81 (1H, d, *J* = 15.8 Hz, =CH), 4.76 (2H, d, J = 2.5 Hz, C*H*$_2$), 2.48 (1H, t, *J* = 2.5 Hz, ≡C*H*), 1.87 (3H, d, *J* = 5.5 Hz, C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3 (*C*=O), 146.3 (H*C*=CHC(O)), 140.3 (H*C*=CHCH$_3$), 129.7 (HC=*C*HCH$_3$), 117.8 (HC=*C*HC(O)), 77.9 (H$_2$C*C*≡CH), 74.7 (H$_2$CC≡*C*H), 51.7 (*C*H$_2$), 18.7 (CH$_3$).

This data is in accordance with literature values.[59]

(2*E*,4*E*)-3-(*tert*-Butyldimethylsilyl)prop-2-yn-1-yl hexa-2,4-dienoate



256

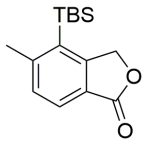
Freshly distilled $^{i}Pr_2NH$ (0.47 mL, 3.36 mmol) was dissolved in anhydrous THF (6 mL) and cooled to -78 °C. *n*BuLi (2.5 M in hexanes, 1.34 mL, 3.4 mmol) was added dropwise and the resultant mixture stirred for 30 min. The solution was then transferred, *via* cannula, to a stirred solution of (2*E*,4*E*)-prop-2-yn-1-yl hexa-2,4-dienoate **253** (500 mg, 3.33 mmol) in anhydrous THF (6 mL) at -78 °C, and stirred for 30 min. TBSCl (506 mg, 3.36 mmol) in anhydrous THF (0.5 mL) was added dropwise to the resultant mixture and stirred for 3 h. The reaction was then quenched with saturated NH_4Cl (*aq*) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H_2O (25 mL), then brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (silica gel, 1% EtOAc in hexane) to yield the desired product **256** as a yellow oil (515 mg, 59%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34 – 7.28 (1H, m, *H*C=CHC(O)), 6.25 – 6.13 (2H, m, *H*C=C × 2), 5.83 – 5.79 (1H, m, =C*H*CH_3), 4.77 (2H, s, CH_2), 1.87 (3H, d, *J* = 5.4 Hz, CH_3), 0.94 (9H, s, SiC(CH_3)$_3$), 0.13 (6H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6 (*C*=O), 146.1 (H*C*=CHC(O)), 140.2 (H*C*=CHCH$_3$), 129.9 (HC=*C*HCH$_3$), 118.2 (HC=*C*HC(O)), 100.1 (C≡*C*CH$_2$), 90.4 (C≡*C*Si), 52.8 (*C*H$_2$), 26.2 (C(*C*H$_3$)$_3$), 18.9 (=CH*C*H$_3$), 16.7 (*C*(CH$_3$)$_3$), -4.6 (Si(*C*H$_3$)$_2$).

This data is in accordance with literature values.[59]

4-(*tert*-Butyldimethylsilyl)-5-methylisobenzofuran-1(3*H*)-one



258

Method A: A suspension of $[Rh(cod)Cl]_2$ (12.3 mg, 5 mol%) in TFE (3 mL) was treated with $AgSbF_6$ (22.3 mg, 13 mol%) in CH_2Cl_2 (0.26 mL), followed immediately by a solution of (2*E*,4*E*)-3-(*tert*-butyldimethylsilyl)prop-2-yn-1-yl hexa-2,4-dienoate **256** (132 mg, 0.50 mmol) in TFE (2 mL). The resultant mixture was stirred and heated to reflux (74 °C) for 72 h. The reaction mixture was then diluted with Et_2O (20 mL), filtered through a celite pad, washed with Et_2O, concentrated *in vacuo*, and purified using flash chromatography (silica gel, 5% EtOAc in hexane) to yield the desired product **258** as a pale white solid (24.4 mg, 19%).

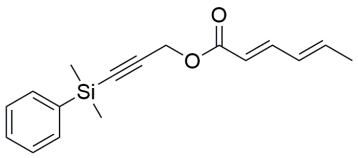
Method B: $[Rh(cod)Cl]_2$ (7.4 mg, 5 mol%) and $AgSbF_6$ (13.4 mg, 13 mol%) were added to a microwave vial, and flushed with argon. TFE (1 mL) was added, followed immediately by a solution of (2*E*,4*E*)-3-(*tert*-butyldimethylsilyl)prop-2-yn-1-yl hexa-2,4-dienoate **256** (80 mg, 0.30 mmol) in TFE (0.5 mL). The vial was placed in the microwave initiator and heated to 100 °C for 2 h. The crude reaction mixture was then filtered through celite, washed with Et_2O, concentrated *in vacuo*, and purified using flash chromatography (silica gel, 5% EtOAc in hexane) to yield the desired product **258** as a pale white solid (25.2 mg, 32%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.81 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.34 (1H, d, *J* = 7.8 Hz, Ar*H*), 5.34 (2H, s, CH_2), 2.60 (3H, s, CH_3), 0.94 (9H, s, SiC(CH_3)$_3$), 0.44 (6H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.6 (*C*=O), 154.1 (^{Ar}*C*), 152.2 (^{Ar}*C*), 132.0 (^{Ar}CH), 131.1(^{Ar}*C*), 126.4 (^{Ar}CH), 122.8(^{Ar}*C*), 72.2 (*C*H$_2$), 27.1 (SiC(*C*H$_3$)$_3$), 25.6 (*C*H$_3$), 19.6 (Si*C*(CH$_3$)$_3$), -0.9 (Si(*C*H$_3$)$_2$).

This data is in accordance with literature values.[59]

(2*E*,4*E*)-3-(Dimethyl(phenyl)silyl)prop-2-yn-1-yl hexa-2,4-dienoate



259

Freshly distilled $^{i}Pr_2NH$ (0.24 mL, 1.68 mmol) was dissolved in anhydrous THF (3 mL) and cooled to -78 °C. *n*BuLi (2.5 M in hexanes, 0.67 mL, 1.7 mmol) was added dropwise and the resultant mixture stirred for 30 min. The solution was then transferred, *via* cannula, to a stirred solution of (2*E*,4*E*)-prop-2-yn-1-yl hexa-2,4-dienoate **253** (250 mg, 1.66 mmol) in anhydrous THF (3 mL) at -78 °C, and stirred for 30 min. DMPSCl (0.28 mL, 1.68 mmol) was added dropwise to the resultant mixture, and the reaction was stirred for 3 h. The reaction was then quenched with saturated NH_4Cl (*aq*) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H_2O (25 mL), then brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (silica gel, 2.5% EtOAc in hexane) to yield the desired product **259** as a yellow oil (314 mg, 67%).

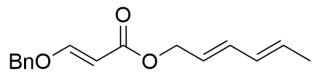
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 – 7.60 (2H, m, ^{Ar}H × 2), 7.58 – 7.52 (1H, m, ^{Ar}H), 7.43 – 7.28 (3H, m, 2 × ^{Ar}H + *H*C=CHC(O)), 6.26 – 6.13 (2H, m, *H*C=C*H*CH_3), 5.82 (1H, d, *J* = 15.4 Hz, C(O)C*H*=CH), 4.81 (2H, s, CH_2), 1.88 (3H, d, *J* = 5.3 Hz, CH_3), 0.44 (6H, s, Si$(CH_3)_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6 (*C*=O), 146.3 (H*C*=CHC(O)), 140.3 (H*C*=CHCH_3), 136.6 (^{Ar}C), 133.9 (^{Ar}CH), 133.2 (^{Ar}CH), 129.7 (HC=*C*HCH_3), 128.1 (^{Ar}CH), 127.9 (^{Ar}CH), 118.1 (HC=*C*HC(O)), 101.2 (C≡*C*CH_2), 90.1 (C≡*C*Si), 52.7 (*C*H_2), 18.9 (*C*H_3), -0.9 (Si$(CH_3)_2$).

HRMS (ESI) calculated for $C_{17}H_{21}O_2Si$ $(M+H)^+$: 285.1311, observed 285.1313

IR ν_{max} (film)/cm^{-1} 3019, 2187, 1717, 1645, 1240, 752.

(*E*)-(2*E*,4*E*)-Hexa-2,4-dien-1-yl 3-(benzyloxy)acrylate



263

Benzyl alcohol (0.69 mL, 6.70 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL). Tri-*n*-butylphosphine (0.24 mL, 1.00 mmol) was added and the resultant mixture was cooled to 0 °C. (2*E*,4*E*)-Hexa-2,4-dien-1-yl propiolate **230** (1.00 g, 6.7 mmol) was added dropwise, and the resultant mixture was warmed to rt and stirred for 30 min, before being exposed to air for 20 min. The reaction mixture was then concentrated *in vacuo* and purified using flash chromatography (silica gel, 2.5% EtOAc in hexane) to yield the desired product **263** as a clear oil (460 mg, 27%).

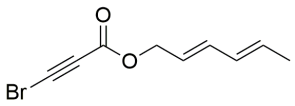
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (1H, d, *J* = 12.6 Hz, C=C*H*OBn), 7.42 – 7.34 (5H, m, Ar*H*), 6.26 (1H, dd, *J* = 15.1, 10.5 Hz, *H*C=CH), 6.07 (1H, ddd, *J* = 15.1, 10.5, 1.2 Hz, *H*C=CH), 5.79 – 5.72 (1H, m, HC=C*H*), 5.68 – 5.63 (1H, m, HC=C*H*), 5.33 (1H, d, *J* = 12.6 Hz, C=C*H*C(O)), 4.91 (2H, s, OCH_2), 4.63 (2H, d, *J* = 6.6 Hz, CH_2), 1.77 (3H, d, *J* = 6.6 Hz, CH_3).

^{13}C NMR (125 MHz. $CDCl_3$) δ: 167.6 (*C*=O), 162.4 (H*C*=CHC(O)), 135.4 (H*C*=CHC(O)), 134.8 (^{Ar}C), 131.2 (H*C*=CHCH$_3$), 130.7 ((HC=*C*HCH$_2$), 128.9 (^{Ar}CH), 128.8 (^{Ar}CH), 128.7 (^{Ar}CH), 127.9 (2 × ^{Ar}CH), 124.3 (HC=*C*HCH$_3$), 97.5 (C=*C*HC(O)), 73.0 (O*C*H$_2$Ph), 64.6 (*C*H$_2$), 18.3 (*C*H$_3$).

HRMS (CI) calculated for $C_{16}H_{19}O_3$ $(M+H)^+$: m/z 259.1334, observed m/z 259.1337

IR ν_{max} (film)/cm^{-1} 3023, 1705, 1643, 1622, 990, 750.

(2*E*,4*E*)-Hexa-2,4-dien-1-yl 3-bromopropiolate



264

(2*E*,4*E*)-Hexa-2,4-dien-1-yl prop-2-ynoate 37 **230** (477 mg, 3.18 mmol) was dissolved in acetone (38 mL) at rt. $AgNO_3$ (64.6 mg, 0.38 mmol) was added, followed by recrystallized NBS (623 mg, 3.50 mmol), and the resultant mixture was stirred for 1.5 h. The reaction mixture was then diluted with EtOAc (40 mL), washed with H_2O (40 mL), brine (3 × 40 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the desired product **264** as an orange oil (629 mg, 86%) without the need for purification.

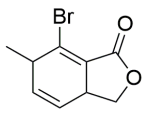
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.30 (1H, dd, *J* = 15.2, 10.5 Hz, *H*C=CHCH$_2$), 6.09 – 6.03 (1H, m, *H*C=CHCH$_3$), 5.82 – 5.78 (1H, m, HC=C*H*CH$_2$), 5.66 – 5.57 (1H, m, HC=C*H*CH$_3$), 4.68 (2H, d, *J* = 6.8 Hz, OC*H*$_2$), 1.78 (3H, d, *J* = 6.7 Hz, C*H*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 152.4 (*C*=O), 136.5 (H*C*=CHCH$_2$), 132.4 (HC=*C*HCH$_2$), 130.4 (H*C*=CHCH$_3$), 122.2 (HC=*C*HCH$_3$), 77.4 (C≡*C*C(O)), 72.9 (C≡*C*Br), 67.0 (*C*H$_2$), 18.3 (*C*H$_3$).

Analytical services were unable to obtain an accurate MS.

IR ν_{max} (film)/cm^{-1} 2934, 2203, 1713, 1236, 990.

7-bromo-6-methyl-3,3*a*-dihydroisobenzofuran-1(6*H*)-one



265

A suspension of [Rh(cod)Cl]$_2$ (12.3 mg, 25.0 μmol, 5 mol%) in TFE (3 mL) was treated with $AgSbF_6$ (22.3 mg, 65.0 μmol 13 mol%), followed immediately by a solution of (2*E*,4*E*)-hexa-2,4-dien-1-yl 3-bromopropiolate **264** (113 mg, 0.49 mmol) in TFE (2 mL). The reaction mixture was stirred at rt for 1.5 h and was then diluted with Et_2O (15 mL), filtered

through celite, washed with Et_2O, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 20% ethyl acetate in hexane) gave the desired product **265** as an orange oil (70 mg, 62%).

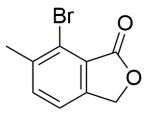
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.79 – 5.72 (2H, m, *H*C=C*H*), 4.55 – 4.51 (1H, m, CH_2), 3.84 (1H, dd, *J* = 10.8, 8.0 Hz, CH_2), 3.72 – 3.60 (1H, m, C*H*CH_2), 3.33 – 3.22 (1H, m, C*H*CH_3), 1.46 (3H, d, *J* = 7.4 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.8 (*C*=O), 134.4 (C=*C*Br), 132.9 (C=*C*H), 124.7 (*C*=CBr), 120.9 (C=*C*H), 69.0 (*C*H_2), 42.9 (*C*HCH_2), 39.6 (*C*HCH_3), 21.5 (*C*H_3).

HRMS (ESI) calculated for $C_9H_9O_2BrNa$ $(M+Na)^+$: m/z 250.9678, observed m/z 250.9672

IR ν_{max} (film)/cm^{-1} 2361, 1771, 1456, 1082, 750.

7-bromo-6-methylisobenzofuran-1(3*H*)-one



266

(2*E*,4*E*)-Hexa-2,4-dien-1-yl 3-bromoprop-2-ynoate **264** (242 mg, 1.06 mmol) was dissolved in toluene (10 mL) and heated to reflux (111 °C) for 16 h. Then MnO_2 (461 mg, 5.30 mmol) was added, and the reaction mixture was refluxed for 4 h, then filtered through celite, washed with Et_2O, and concentrated *in vacuo* to give the desired product **266** as a pale orange solid (186 mg, 78%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (1H, d, *J* = 7.7 Hz, ^{Ar}*H*), 7.33 (1H, d, *J* = 7.7 Hz, ^{Ar}*H*), 5.22 (2H, s, CH_2), 2.53 (3H, s, CH_3).

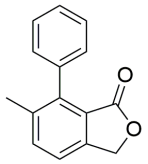
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6 (*C*=O), 146.6 (^{Ar}*C*), 140.2 (^{Ar}*C*), 136.2 (^{Ar}*C*H), 124.4 (^{Ar}*C*), 123.0 (^{Ar}*C*), 120.5 (^{Ar}*C*H), 67.4 (*C*H_2), 22.3 (*C*H_3).

HRMS (ESI) calculated for $C_9H_7O_2BrNa$ $(M+Na)^+$: m/z 248.9522, observed 248.9520.

IR ν_{max} (film)/cm^{-1} 2361, 1751, 1578, 1082, 1016, 646.

Melting point: 140 – 142 °C.

6-Methyl-7-phenylisobenzofuran-1(3*H*)-one



267

7-Bromo-6-methylisobenzofuran-1(3*H*)-one (1.00 g, 4.40 mmol), phenylboronic acid (537 mg, 4.40 mmol) and Cs_2CO_3 (2.15 g, 6.6 mmol) were dissolved in toluene (60 mL) and H_2O (10 mL). The resultant mixture was treated with $Pd(PPh_3)_4$ (153 mg, 0.13 mmol, 3 mol%). The reaction mixture was then heated to 90 °C and stirred for 16 h. The reaction mixture was then diluted with EtOAc (100 mL), washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The mixture was then purified using column chromatography (silica gel, 10% EtOAc in petroleum ether) to give the desired product **267** as a colourless solid (949 mg, 96%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (1H, d, *J* = 7.8 Hz, ^{Ar}H), 7.50 – 7.40 (3H, m, ^{Ar}H), 7.37 (1H, d, *J* = 7.8 Hz, ^{Ar}H), 7.26 – 7.21 (2H, m, ^{Ar}H), 5.25 (2H, s, CH_2), 2.22 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.9 (*C*=O), 144.9 (^{Ar}C), 141.7 (^{Ar}C), 137.9 (^{Ar}C), 136.0 ($^{Ar}CH_{phthalide}$), 136.0 (^{Ar}C), 129.1 (^{Ar}CH), 128.2 (^{Ar}CH), 128.0 (^{Ar}CH), 123.3 (^{Ar}C), 120.9 ($^{Ar}CH_{phthalide}$), 68.2 (*C*H_2), 19.9 (*C*H_3).

HRMS (EI) calculated for $C_{15}H_{12}O_2$ (M)+: m/z 224.0837, observed 224.0838.

IR_{Vmax} (film)/cm^{-1} 2359, 1761, 1475, 1084, 764, 700.

7-Bromo-1-methoxy-6-methyl-1,3-dihydro-2-benzofuran

268

7-Bromo-6-methylisobenzofuran-1(3*H*)-one **266** (100 mg, 0.44 mmol) was dissolved in anhydrous toluene (7 mL), and cooled down to -78 °C. The resultant solution was then

treated with DIBALH (0.44 mL, 1M in hexanes, 0.44 mmol) via syringe pump over 1.5 h. The reaction mixture was left to warm to rt over 16 h. The reaction mixture was then cooled down to 0 °C and methanol (0.5 mL) was added, followed by CH_2Cl_2 (7 mL) and Rochelle's salt 20% (*aq*) solution (7 mL) and stirred at rt for 1 h. The organic layer was then washed with H_2O (7 mL), brine (7 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude lactol intermediate was then dissolved in MeOH (7 mL) and $TsOH.H_2O$ (5 mg, 0.03 mmol) was added. The resultant solution was left to stir at rt for 3 h. The reaction mixture was then basified with $NaHCO_3$ (*aq*), diluted with Et_2O (7 mL), washed with H_2O (2 × 7 mL), brine (2 × 7 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*, and purified using column chromatography (silica gel, 10% EtOAc in petroleum ether) to yield the desired product as a colourless oil **268** (41 mg, 19%).

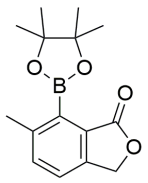
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 7.10 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 6.09 (1H, d, *J* = 2.1 Hz, C(*H*)OCH_3), 5.29 – 5.23 (1H, m, CH_2), 5.03 (1H, d, *J* = 12.7 Hz, CH_2), 3.52 (3H, s, OCH_3), 2.43 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.4 (^{Ar}C), 138.1 (^{Ar}C), 137.4 (^{Ar}C), 131.8 (^{Ar}CH), 119.9 (^{Ar}C), 119.6 (^{Ar}CH), 108.4 (*C*H), 72.6 (*C*H_2), 55.1 (O*C*H_3), 22.1 (*C*H_3).

HRMS (EI) calculated for $C_{10}H_{10}O_2Br$ $(M+H)^+$: m/z 240.9864, observed 240.9866.

IR_{Vmax} (film)/cm^{-1} 2926, 1130, 1088, 1032, 912, 731.

6-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isobenzofuran-1(3*H*)-one



269

7-Bromo-6-methylisobenzofuran-1(3*H*)-one **266** (100 mg, 0.44 mmol), $Pd(CH_3CN)_2Cl_2$ (1.5 mg, 5.8 μmol, 1 mol%), and *S*Phos (14.5 mg, 0.04 mmol) were dissolved in 1,4-dioxane (1 mL) and Et_3N (1 mL). Then pinacolborane (0.13 mL, 0.89 mmol) was added, and the resultant mixture was heated to 110 °C, and stirred for 2 h. The reaction mixture was then cooled down to rt, filtered through celite, washed with CH_2Cl_2, concentrated *in vacuo*, and

purified using flash chromatography (silica gel, 10% EtOAc in petroleum ether) to yield the desired product **269** as a colourless solid (47 mg, (59% brsm) 34 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (1H, d, *J* = 7.9 Hz, ^{Ar}H), 7.33 (1H, d, *J* = 7.9 Hz, ^{Ar}H), 5.24 (2H, s, CH_2), 2.49 (3H, s, ^{Ar}CH_3), 1.46 (12H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8 (*C*=O), 143.0 (^{Ar}C), 142.4 (^{Ar}C), 134.5 (^{Ar}C), 129.0 (^{Ar}C), 125.9 (^{Ar}C), 122.2 (^{Ar}CH), 84.8 (*C*OB), 69.7 (O*C*H$_2$), 25.0 (*C*H$_3$), 21.5 (^{Ar}C*C*H$_3$).

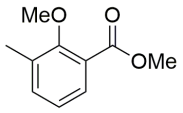
^{11}B NMR (128 MHz, $CDCl_3$) δ: 31.9 (B(OR)$_2$).

HRMS (EI) calculated for $C_{15}H_{19}O_4B$ $(M)^+$: m/z 274.1379, observed 274.1374.

IR ν_{max} (film)/cm^{-1} 2980, 2361, 1759, 1358, 1051.

Melting point: 176 – 178 °C.

Methyl-2-methoxy-3-methylbenzoate



272

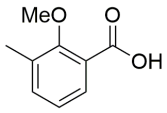
3-Methylsalicylic acid (20.0 g, 131 mmol), and anhydrous K_2CO_3 (52.7 g, 381 mmol) were dissolved in acetone (250 mL). Dimethylsulfate (36.1 mL) was added, and the resultant mixture heated to reflux and stirred for 16 h. The reaction mixture was then cooled down to rt, the solid residue removed by filtration, and the solvent removed *in vacuo*. The crude residue was then dissolved in H_2O (500 mL) and stirred for 15 min, then extracted with EtOAc (3 × 500 mL). The combined organics were then washed with H_2O (500 mL), brine (500 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*, to yield the crude product **272** as a colourless oil (23.6 g, quant.) and used without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64 (1H, dd, *J* = 7.8, 1.4 Hz, ^{Ar}H), 7.35 (1H, ddd, *J* = 7.5, 1.7, 0.7 Hz, ^{Ar}H), 7.06 (1H, t, *J* = 7.6 Hz, ^{Ar}H), 3.92 (3H, s, C(O)OCH_3), 3.84 (3H, s, OCH_3), 2.33 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.9 (*C*=O), 158.4 (^{Ar}C), 135.2 (^{Ar}CH), 132.8 (^{Ar}C), 129.1 (^{Ar}CH), 124.6 (^{Ar}C), 123.5 (^{Ar}CH), 61.5 (O*C*H$_3$), 52.2 (C(O)O*C*H$_3$), 16.0 (*C*H$_3$).

This data is in accordance with literature values.[95]

2-Methoxy-3-methylbenzoic acid



153

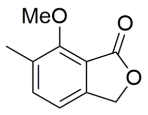
Methyl-2-methoxy-3-methylbenzoate **272** (23.6 g, 131 mmol) was dissolved in MeOH (250 mL). The resultant solution was treated with 3M NaOH (*aq*) (100 mL) and stirred for 16 h. The organics were removed *in vacuo* and the crude residue dissolved in H_2O (300 mL) and acidified using 3M HCl (*aq*). The resultant mixture was then extracted with EtOAc (3 × 200 mL), washed with brine (400 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*, to yield the desired product **153** as a white solid (18.4 g, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (1H, dd, *J* = 7.8, 1.4 Hz, ^{Ar}H), 7.44 (1H, dd, *J* = 7.5, 1.0 Hz, ^{Ar}H), 7.19 (1H, t, *J* = 7.7 Hz, ^{Ar}H), 3.93 (3H, s, OCH_3), 2.38 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.6 (*C*=O), 157.5 (^{Ar}COCH$_3$), 137.1 (^{Ar}CH), 131.2 (^{Ar}CCH$_3$), 130.8 (^{Ar}CH), 125.3 (^{Ar}CH), 121.8 (^{Ar}CCOOH), 62.3 (O*C*H$_3$), 16.0 (*C*H$_3$).

This data is in accordance with literature values.[48]

7-methoxy-6-methylisobenzofuran-1(3*H*)-one



156

2-Methoxy-3-methylbenzoic acid **153** (3.32 g, 20.0 mmol), K_2HPO_4 (10.4 g, 59.9 mmol), and $Pd(OAc)_2$ (900 mg, 4.01 mmol, 20 mol%) were dissolved in CH_2Br_2 (80 mL) in a 200 mL sealed reaction tube under an air atmosphere. The resultant mixture was then heated to 140 °C in a pre-heated oil bath and stirred for 88 h. The reaction mixture was then cooled and diluted with CH_2Cl_2 (150 mL), filtered through a celite pad, washed with CH_2Cl_2, and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (silica

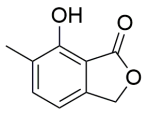
gel, 20 % EtOAc in petroleum ether) to yield the desired product **156** as a beige solid (3.16 g, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 7.06 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 5.24 (2H, s, CH_2), 4.09 (3H, s, OCH_3), 2.34 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.1 (*C*=O), 157.8 (^{Ar}C(OCH$_3$)), 146.8 (^{Ar}C), 137.5 (^{Ar}CH), 131.7 (^{Ar}C), 117.0 (^{Ar}C), 116.5 (^{Ar}CH), 68.8 (*C*H$_2$), 62.3 (O*C*H$_3$), 15.6 (*C*H$_3$).

This data is in accordance with literature values.[48]

7-Hydroxy-6-methylisobenzofuran-1(3*H*)-one



157

Method A:

5-(Hydroxymethyl)-2-methylphenol **207** (1.15 g, 8.32 mmol) was dissolved in anhydrous MeCN (80 mL). Et_3N (4.33 mL, 31.2 mmol) was added to the solution, followed by the dropwise addition of $SnCl_4$ (1.46 mL, 7.96 mmol). The resultant mixture was stirred at rt for 20 min, then paraformaldehyde (1.77 g, 59.0 mmol) was added and the mixture heated to reflux (82 °C) and stirred for 16 h. The reaction was then diluted with Et_2O (250 mL), washed with H_2O (250 mL), separated organic phase, dried (Na_2SO_4), filtered, concentrated *in vacuo*. The crude mixture was then purified using column chromatography (silica gel, 40 – 60% CH_2Cl_2 in petroleum ether) to yield the desired product **157** as a white solid (355 mg, 26%).

Method B:

6-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isobenzofuran-1(3*H*)-one **269** (43 mg, 0.16 mmol) was dissolved in anhydrous THF (3 mL). Then 1M NaOH (0.47 mL) was added, followed by (*aq*) 30% H_2O_2 (0.16 mL), and the resultant mixture stirred for 2 h. The reaction mixture was then diluted with EtOAc (5 mL), acidified with 1M HCl (0.60 mL), washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo*. The

crude product was purified using flash column chromatography (silica gel, 20% EtOAc in petroleum ether) to give the desired product **157** as a colourless solid (12 mg, 46%).

Method C

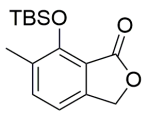
7-Methoxy-6-methylisobenzofuran-1(3*H*)-one **156** (3.16 g, 17.7 mmol) was dissolved in anhydrous DMF (100 mL). The resultant solution was treated with iodocyclohexane (16.1 mL, 124 mmol), and the reaction mixture was heated to 153 °C and stirred for 80 h. The reaction mixture was then diluted with H_2O (50 mL), extracted with EtOAc (300 mL), washed with sat. (*aq*) $Na_2S_2O_3$ (3 × 200 mL), brine (2 × 200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Trituration with petroleum ether gave the desired product **157** as a white solid (2.73 g, 94%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (1H, s, OH), 7.42 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 6.87 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 5.29 (2H, s, CH_2), 2.30 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.0 (*C*=O), 154.5 (^{Ar}C(OH)), 144.1 (^{Ar}C), 138.2 (^{Ar}CH), 124.8 (^{Ar}C(CH_3)), 112.8 (^{Ar}CH), 110.5 (^{Ar}C), 70.4 (*C*H_2), 14.6 (*C*H_3).

This data is in accordance with literature values.[48]

7-((*tert*-Butyldimethylsilyl)oxy)-6-methylisobenzofuran-1(3*H*)-one



158

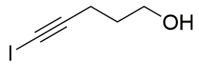
7-Hydroxy-6-methylisobenzofuran-1(3*H*)-one **157** (355 mg, 2.16 mmol) and imidazole (349 mg, 5.12 mmol) were dissolved in anhydrous DMF (10 mL). TBSCl (463 mg, 3.07 mmol) was added, and the resultant mixture was stirred for 16 h. The reaction was then diluted with Et_2O (500 mL), washed with H_2O (50 mL), brine (4 × 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was then purified using flash chromatography (silica gel, 5% EtOAc in petroleum ether) to give the desired product **158** as a white solid (551 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 6.94 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 5.17 (2H, s, CH_2), 2.30 (3H, s, CH_3), 1.07 (9H, s, SiC(CH_3)$_3$), 0.27 (6H, s, Si(CH_3)$_2$).

^{13}C NMR (400 MHz, $CDCl_3$) δ: 169.1 (*C*=O), 153.0 (^{Ar}*C*O), 146.3 (^{Ar}*C*), 137.6 (^{Ar}*C*H), 130.2 (Ar*C*CH_3), 115.9 (^{Ar}*C*), 114.3 (^{Ar}*C*H), 68.1 (*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.8 (Si*C*(CH_3)$_3$), 16.8 (*C*H_3), -3.5 (Si(*C*H_3)$_2$).

This data is in accordance with literature values.[48]

5-Iodopent-4-yn-1-ol



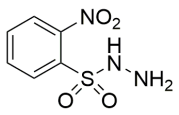
277

A 0 °C solution of pent-4-yn-1-ol (100 mg, 1.19 mmol) in MeOH (3 mL) was treated with 12.5 M (*aq*) NaOH (0.24 mL), and the resultant solution stirred for 10 min. I_2 (332 mg, 1.31 mmol) was then added, and the reaction was warmed to rt and stirred for 3 h. The reaction mixture was then diluted with H_2O (3 mL), and extracted with Et_2O (3 × 10 mL). The combined organics were washed with saturated (*aq*) $Na_2S_2O_3$ (3 × 20 mL), brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to yield the desired product **277** as a yellow oil (223 mg, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.81 – 3.70 (2H, m, C*H*$_2$OH), 2.51 (2H, t, *J* = 7.0 Hz, C≡CC*H*$_2$), 1.83 – 1.72 (2H, m, CH_2C*H*$_2$$CH_2$).

This data is in accordance with literature values.[70]

***o*-Nitrobenzenesulfonylhydrazide**



278

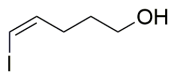
o-Nitrobenzenesulfonyl chloride (10.0 g, 45.1 mmol) was dissolved in anhydrous THF (100 mL) and cooled to -30 °C. Hydrazine monohydrate (5.46 mL, 112 mmol) was added dropwise, and the resultant mixture was stirred for 30 min. The reaction was then diluted

with EtOAc (200 mL), and washed with ice-cold brine (5 × 100 mL). The organics were then dried (Na_2SO_4) at 0 °C, then added slowly to a stirring solution of hexane (500 mL) at rt. The precipitate was then collected by vacuum filtration, washed with hexane, and dried *in vacuo*, to afford the desired product **278** as a white powder (8.87 g, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.26 – 8.21 (1H, m, ^{Ar}H), 7.94 – 7.88 (1H, m, ^{Ar}H), 7.86 – 7.78 (2H, m, ^{Ar}H), 6.51 (1H, br s, N*H*), 3.84 (2H, br s, NH_2).

This data is in accordance with literature values.[71]

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



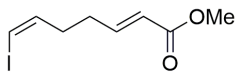
36

5-Iodopent-4-yn-1-ol **277** (5.47 g, 26.1 mmol) was dissolved in THF:^{i}PrOH (1:1, 150 mL), and the resultant solution treated with 2-nitrobenzenesulfonyl hydrazide **278** (7.37 g, 33.8 mmol), followed by Et_3N (9.00 mL, 64.9 mmol). The reaction mixture was stirred for 16 h and protected from light. The reaction was then diluted with H_2O (150 mL), and extracted with diethyl ether (150 mL), dried (Na_2SO_4), filtered, concentrated *in vacuo*, and purified by flash chromatography (5 – 25% EtOAc in hexane) to yield the desired product **36** as a colourless oil (3.66 g, 66%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.24 – 6.19 (2H, m, *H*C=C*H*I), 3.68 (2H, dd, *J* = 10.0, 6.6 Hz, CH_2OH), 2.24 (2H, m, CH_2), 1.70 (2H, m, CH_2).

This data is in accordance with literature values.[96]

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



38

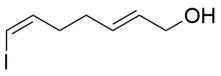
(4*Z*)-5-Iodopent-4-en-1-ol **36** (4.30 g, 20.3 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) at 0 °C. PCC (4.81 g, 22.3 mmol) was added, and the resultant mixture was stirred for 2 h, then warmed to rt and stirred for 3 h. The reaction mixture was then filtered through Florisil® and washed with CH_2Cl_2. The solvent was carefully concentrated *in vacuo*, until approximately 75 mL remained, then the flask was flushed with argon and treated with methyl (triphenylphosphoranylidene)acetate (7.46 g, 22.3 mmol) and stirred at rt for 24 h. The crude mixture was concentrated *in vacuo*, then purified using flash chromatography (silica gel, 5% Et_2O in petroleum ether) to yield the desired product **38** as a colourless oil (3.03 g, 56%).

^{1}H NMR (C_6D_6, 500 MHz) δ: 6.85 (1H, dt, *J* = 15.6, 6.9 Hz, *H*C=CHCO$_2$Me), 5.82 (1H, d, *J* = 7.4 Hz, I*H*C=CH), 5.74 (1H, dt, *J* = 15.6, 1.6 Hz, HC=C*H*CO$_2$Me), 5.50 (1H, q, *J* = 6.9 Hz, IHC=C*H*), 3.41 (3H, s, C*H*$_3$), 1.91 – 1.84 (2H, m, C*H*$_2$), 1.73 – 1.65 (2H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.1 (*C*=O), 147.8 (H*C*=CHCO), 139.6 (H*C*=CHI), 122.0 (HC=*C*HCO), 84.0 (HC=*C*HI), 51.7 (O*C*H$_3$), 33.3 (*C*H$_2$), 30.6 (*C*H$_2$).

This data is in accordance with literature values.[29]

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



347

Methyl (2*E*,6*Z*)-7-iodohepta-2,6-dienoate **38** (621 mg, 2.33 mmol) was dissolved in anhydrous CH_2Cl_2 (16 mL) and cooled to 0 °C. The resultant solution was then treated with DIBALH (5.13 mL, 1M in hexanes, 5.13 mmol), warmed to rt, and stirred for 16 h. The reaction mixture was quenched with MeOH (5 mL), diluted with CH_2Cl_2 (20 mL), and Rochelle's salt 20% (*aq*) solution (40 mL) was added. The resultant mixture was stirred for

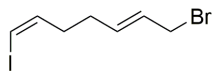
4 h, the organic separated, washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 0 – 25% Et_2O in petroleum ether) to yield the desired product **347** as a colourless oil (505 mg, 91%).

^{1}H NMR (C_6D_6, 400 MHz) δ: 5.89 (1H, dt, *J* = 7.3, 1.4 Hz, *H*C=CHI), 5.71 (1H, q, *J* = 6.9 Hz HC=C*H*I), 5.40 – 5.35 (2H, m, *H*C=C*H*CH_2OH), 3.78 (2H, br s, C*H*$_2$OH), 2.07 – 1.99 (2H, m, C*H*$_2$CH=CHI), 1.88 – 1.81 (2H, m, C*H*$_2$CH=CHCH_2), 0.59 (1H, br s, O*H*).

^{13}C NMR (C_6D_6, 100 MHz) δ: 140.9 (H*C*=CHI), 131.3 (H*C*) 130.5 (H*C*), 83.2 (*C*HI), 63.6 (*C*H_2OH), 34.9 (H_2*C*CH=CHI), 31.0 (H_2*C*CH=CHCH_2).

This data is in accordance with literature values.[29]

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

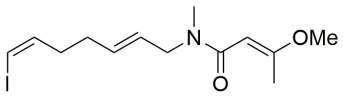


279

(2*E*,6*Z*)-7-Iodohepta-2,6-dien-1-ol **347** (1.00 g, 4.20 mmol) was dissolved in CH_2Cl_2 (50 mL). The resultant solution was then treated sequentially with PPh_3 (2.20 g, 8.39 mmol) and CBr_4 (2.79 g, 8.41 mmol), and stirred for 1 h. The solvent was removed *in vacuo* and the crude reaction mixture purified using flash chromatography (silica gel, 5% EtOAc in petroleum ether) to yield the desired product **279** as a pale orange oil (1.26 g, 100%).

Fully characterised as **40**.

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



40

Bromide **279** (810 mg, 2.69 mmol) was dissolved in anhydrous THF (20 mL) and cooled down to 0 °C. $MeNH_2$ (2M in THF, 6.73 mL, 13.5 mmol) was added, and the reaction mixture stirred at 0 °C for 1 h, before being warmed to rt and stirred for a further 1 h. The solvent and excess $MeNH_2$ was removed *in vacuo* to afford the crude product. Purification using SCX ion-exchange chromatography, flushing with MeOH, followed by elution with 7M NH_3 in MeOH, afforded the amine intermediate as an orange oil (490 mg, 77%). The amine was dissolved in anhydrous CH_2Cl_2 (40 mL) and cooled down to 0 °C. (*E*)-3-Methoxybutenoic acid **31** (250 mg, 2.15 mmol), and HBTU (963 mg, 2.54 mmol) were added, followed by the dropwise addition of DIPEA (0.71 mL, 4.08 mmol). The resultant mixture was stirred at 0 °C for 20 min, then warmed to rt and stirred for an additional 2 h. The solvent was removed *in vacuo*, and the resultant slurry was partitioned between Et_2O (40 mL) and H_2O (40 mL). The organic layer was then washed with sat. $NaHCO_3$ (*aq*) (40 mL), 20% citric acid (*aq*) (40 mL), and brine (2 × 40 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was then purified using flash chromatography (silica gel, 10 – 20% EtOAc in petroleum ether) to yield the desired product **40** as a pale-yellow oil (229 mg, 34%).

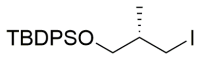
(*3:2 mixture of rotamers. * denotes minor rotamer*)

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.22 (1H, d, *J* = 7.3 Hz, HC=C*H*I), 6.15 (1H, q, *J* = 6.8 Hz, *H*C=CHI), 5.59 (1H, dtt, *J* = 15.4, 6.5, 1.3 Hz, HC=C*H*CH_2N), 5.46 (1H, dtt, *J* = 15.4, 5.7, 1.3 Hz, C*H*CH_2CH_2), 5.19* (1H, br s, *H*CC(O)N), 5.16 (1H, br s, C*H*C(O)N), 3.98* (2H, br s, C*H*$_2$N), 3.89 (2H, br s, C*H*$_2$N), 3.62* (3H, br s, C*H*$_3$O), 3.59 (3H, br s, C*H*$_3$O), 2.95 (3H, br s, NC*H*$_3$), 2.34 – 2.21 (7H, m, C*H*$_3$, C*H*$_2$C*H*$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.5 (*C*=O), 167.8 (HC=*C*(OMe)), 140.6* (H*C*CH_2CH_2), 140.2 (H*C*CH_2CH_2), 132.0* (HC=*C*HCH_2N), 131.6 (HC=*C*HCH_2N), 126.4* (H*C*=CHI), 125.7 (H*C*=CHI), 91.2 (H*C*C(O)N), 83.1* (HC=*C*HI), 82.8 (HC=*C*HI), 54.8 (OCH_3), 52.1 (*C*H_2N), 49.0* (*C*H_2N), 35.1 (*C*H_3N), 34.3 (*C*H_2), 33.4 (*C*H_3N), 30.5 (*C*H_2), 18.8 (*C*H_3).

This data is in accordance with literature values.[29]

(*S*)-*tert*-Butyl(3-iodo-2-methylpropoxy)diphenylsilane



(***S***)-**185**

(2*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (20.3 g, 61.8 mmol) was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C. Imidazole (5.75 g, 84.4 mmol), PPh_3 (20.5 g, 78.0 mmol) and I_2 (19.8 g, 78.0 mmol) were added sequentially and the resultant solution was stirred for 10 min, then warmed to rt and stirred for 1 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (250 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined organics were then washed with saturated $Na_2S_2O_3$ solution (300 mL), brine (2 × 150 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified using flash chromatography (silica gel, petroleum ether) to yield the desired product (***S***)-**185** as a colourless oil (11.7g, 43%).

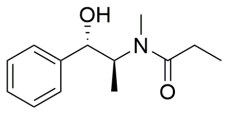
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71 – 7.65 (4H, m, ^{Ar}H), 7.48 – 7.36 (6H, m, ^{Ar}H), 3.59 (1H, dd, *J* = 10.1, 4.9 Hz, CH_2I), 3.48 (1H, dd, *J* = 10.1, 6.9 Hz, CH_2I), 3.40 (1H, dd, *J* = 9.5, 5.1 Hz, CH_2SiO), 3.34 (1H, dd, *J* = 9.5, 5.8 Hz, CH_2SiO), 1.80 – 1.68 (1H, m, CH(CH_3)), 1.06 (9H, s, (CH_3)$_3$Si), 0.97 (3H, d, *J* = 6.7 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 135.7 (4 × ^{Ar}CH), 133.6 (2 × ^{Ar}C), 129.7 (2 × ^{Ar}CH), 127.7 (4 × ^{Ar}CH), 67.3 (CH_2O), 37.6 (CH(CH_3)), 26.9 (SiC(CH_3)$_3$), 19.3 (SiC(CH_3)$_3$), 17.3 (CH(CH_3)$_3$), 13.6 (CH_2I).

$[\alpha]_D^{26}$ +4.1 (c = 1.66, $CHCl_3$), lit. $[\alpha]_D^{23}$ +3.8 (c = 0.41, $CHCl_3$).

This data is in accordance with literature values.[51]

***N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide**



285

(1*S*,2*S*)-(+)-Pseudoephedrine (24.0 g, 145 mmol) and Et_3N (25.1 mL, 181 mmol) were dissolved in anhydrous CH_2Cl_2 (300 mL). The resultant solution was then treated by the dropwise addition of propionic anhydride (20.4 mL, 160 mmol) and the reaction mixture was stirred for 30 min before being quenched with H_2O (50 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (*aq*) (2 × 100 mL), 1M HCl (*aq*) (2 × 100 mL), dried (Na_2SO_4), and filtered. The solvent was removed *in vacuo* to yield the desired compound **285** as a white crystalline solid (29.87 g, 93%).

(*3:1 mixture of rotamers*. * *denotes minor rotamer*)

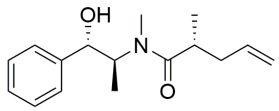
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 – 7.30 (5H, m, ^{Ar}H), 4.63 – 4.57 (1H, m, C*H*OH), 4.48 – 4.51 (1H, m, *H*), 4.06 – 3.98* (1H, m, *H*), 2.94* (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.58 – 2.47* (2H, m, CH_2), 2.44 – 2.25 (2H, m, CH_2), 2.14 (1H, d, *J* = 2.0 Hz, O*H*), 1.22 – 1.12 (6H, m, CHCH_3 + CH_2CH_3), 0.99* (3H, d, *J* = 6.8 Hz, CHCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.3 (*C*=O), 175.0* (*C*=O), 142.5 (^{Ar}C), 141.1 (^{Ar}C), 128.8* (^{Ar}CH), 128.5* (^{Ar}CH), 128.4 (^{Ar}CH), 127.7 (^{Ar}CH), 126.9* (^{Ar}CH), 126.4 (^{Ar}CH), 76.7 (*C*HOH), 75.5* (*C*HOH), 58.8* (*C*CH_3), 58.3 (*C*CH_3), 32.9* (N*C*H_3), 28.7 (N*C*H_3), 27.6 (*C*H_2), 26.9* (*C*H_2), 15.2* (*C*H_3), 14.5 (*C*H_3), 9.6* (*C*H_3), 9.2 (*C*H_3).

$[\alpha]_D^{31}$ +98.3 (c = 0.82, $CHCl_3$), lit. $[\alpha]_D^{25}$ +103.6 (c = 1.20, $CHCl_3$).

This data is in accordance with literature values.[73]

(*R*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide

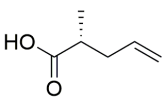


286

LiCl (13.79 g, 325 mmol) (heated to 230 °C under vacuum for 16 h) and freshly distilled DIPA (17.3 mL, 123 mmol) were added to a flame-dried flask. THF (100 mL) was added and the resultant mixture was cooled down to -78°C. *n*BuLi (2.5 M in hexanes, 45.6 mL, 114 mmol) was added and the reaction mixture was warmed to 0 °C for 5 min, then cooled down to -78 °C. An ice cooled solution of *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide **285** (12.0 g, 54.2 mmol) in THF (50 mL) was added dropwise *via* cannula. The reaction mixture was stirred at -78 °C for 1 h, warmed to 0 °C for 15 min, rt for 5 min, and cooled back down to -78 °C. Allyl bromide (7.03 mL, 81.3 mmol) was added dropwise *via* syringe pump and the resultant mixture was stirred at -78 °C for 4 h, then the dry ice/acetone bath was removed and the mixture stirred for 16 h. The reaction was quenched with saturated NH_4Cl (*aq*) (50 mL) and diluted with EtOAc (200 mL), and washed with saturated NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the desired product **286** as a yellow oil (14.2 g, quant.).

Characterised fully as **287**.

(2*R*)-2-Methylpent-4-enoic acid



287

(*R*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide **286** (29.0 g, 111 mmol) was dissolved in ^{t}BuOH (100 mL), MeOH (100 mL), and 3M NaOH (*aq*) (100 mL). The resultant solution was heated to reflux and stirred for 16 h. The reaction mixture was then cooled to rt, and concentrated *in vacuo*, before being diluted with H_2O (500 mL), and extracted with CH_2Cl_2 (4 × 300 mL). The aqueous phase was then acidified to pH < 2

using 3M HCl (*aq*), and extracted with CH_2Cl_2 (3 × 400 mL). The combined extracts (after acidification) were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the desired product **287** as a colourless oil (12.4 g, 98%).

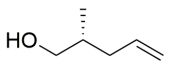
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.26 (1H, br s, O*H*), 5.78 (1H, m *H*C=C), 5.15 – 5.02 (2H, m, C=CH_2), 2.62 – 2.52 (1H, m, C*H*(CH_3)), 2.50 – 2.40 (1H, m, CH_2), 2.26 – 2.18 (1H, m CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.7 (*C*=O), 135.1 (H*C*=CH_2), 117.2 (HC=*C*H_2), 39.0 (*C*H_2), 37.5 (*C*H), 16.3 (*C*H_3).

$[\alpha]_D^{26}$ −32.4 (c = 1.30, $CHCl_3$), lit. $[\alpha]_D^{20}$ −20.9 (c = 1.11, $CHCl_3$).

This data is in accordance with literature values.[97]

(2*R*)-2-Methylpent-4-en-1-ol



288

Method A:

Freshly distilled DIPA (32.1 mL, 228 mmol) was dissolved in anhydrous THF (200 mL) and cooled to -78 °C. The resultant solution was treated with *n*BuLi (2.5 M in hexanes, 86.8 mL, 217 mmol) and stirred at -78 °C for 10 min, then 0 °C for 10 min. Borane-ammonia complex (6.72 g, 217 mmol) was added in one portion and the reaction mixture was stirred at 0 °C for 15 min, then rt for 15 min, then cooled to 0 °C. (*R*)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2′-dimethylpent-4-enamide **286** (14.2 g, 54.3 mmol) was added in anhydrous THF (150 mL) dropwise, *via* cannula, and the reaction mixture was warmed up to rt and stirred for 4 h. The reaction mixture was then cooled to 0 °C and quenched using 1M HCl (*aq*) (300 mL) and stirred for 30 min. The phases were then separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic phases were then washed with 1M HCl (*aq*) (300 mL), 1M NaOH (*aq*) (300 mL), and brine (300 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give the desired alcohol **288** as a clear oil. Used without further purification.

Method B:

(2R)-2-Methylpent-4-enoic acid **287** (9.92 g, 86.9 mmol) was dissolved in anhydrous Et_2O (100 mL). The resultant solution was transferred dropwise *via* cannula to a rapidly stirred suspension of $LiAlH_4$ (3.47 g, 91.3 mmol) in anhydrous Et_2O (150 mL) at 0 °C. The reaction mixture was warmed to rt, and stirred for 16 h before being cooled to 0 °C. H_2O (3.5 mL) was added dropwise, followed by 15% NaOH (*aq*) (3.5 mL), then H_2O (10.4 mL), and the resultant mixture stirred for 15 min. Na_2SO_4 was added and the mixture stirred for 15 min, filtered, and concentrated *in vacuo* to give the desired product **288** as a clear oil (6.76 g, 76%).

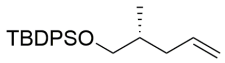
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.88 – 5.77 (1H, m, *H*C=CH_2), 5.10 – 5.00 (2H, m, HC=C*H*$_2$), 3.55 – 3.45 (2H, m, C*H*$_2$OH), 2.23 – 2.14(1H, m, C*H*$_2$CH=CH_2), 2.00 -1.91 (1H, m, C*H*$_2$CH=CH_2), 2.00 – 1.92 (1H, m, C*H*(CH_3)), 1.33 (1H, br s, O*H*), 0.94 (3H, d, *J* = 0.94 Hz, C*H*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.0 (HC=C*H*$_2$), 116.1(H*C*=CH_2), 67.9 (O*C*H$_2$), 37.9 (*C*H$_2$), 35.6 (*C*H), 16.4 (*C*H$_3$).

$[\alpha]_D^{31}$ +6.8 (c = 1.01, $CHCl_3$), lit. $[\alpha]_D^{19}$ +4.3 (c = 1.00, $CHCl_3$).

This data is in accordance with literature values.[98]

(*R*)-*tert*-Butyl((2-methylpent-4-en-1-yl)oxy)diphenylsilane



(***R***)-**186**

Method A:

(*S*)-*tert*-Butyl(3-iodo-2-methylpropoxy)diphenylsilane (***S***)-**185** (500mg, 1.14 mmol) was dissolved in Et_2O (8 mL) and cooled to -78 °C. ^{t}BuLi (1.41 mL, 1.7 M in hexanes, 2.40 mmol) was added slowly and the resultant solution was stirred for 30 min. In a separate flask $ZnBr_2$ (166 mg, 0.74 mmol), was dried at 230 °C, under high vacuum for 24 h and dissolved in anhydrous THF (1.6 mL), cooled to 0 °C then added dropwise to the lithiated intermediate, and stirred for 45 min at -78 °C, then warmed up to 0 °C and stirred for 20 min. $Pd(PPh_3)_4$ (40 mg, 3 mol%, 34.6 μmol) and vinyl bromide (3.42 mL, 1M in THF, 3.42 mmol) were

added to a flask and the resultant suspension added dropwise to the organozinc intermediate. The reaction mixture was then warmed up to rt and stirred for 16 h then diluted with Et_2O (10 mL), washed with water (2 × 25 mL), then brine (2 × 25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was then purified using flash chromatography (silica gel, petroleum ether) to yield the desired product (***R***)-**186** as a colourless oil (277 mg, 72%).

Method B:

(2*R*)-2-Methylpent-4-en-1-ol **288** (6.76 g, 67.5 mmol) and imidazole (9.19 g, 135 mmol) were dissolved in anhydrous DMF (200 mL). TBDPSCl (19.2 mL, 74.0 mmol) was then added and the resultant mixture was stirred at rt for 16 h. The reaction was then diluted with EtOAc (500 mL), washed with H_2O (250 mL), brine (4 × 250 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was then purified using flash chromatography (silica gel, 5% EtOAc in petroleum ether) to yield the desired product (***R***)-**186** as a colourless oil (20.3 g, 89%).

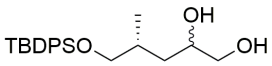
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 – 7.62 (4H, m, ^{Ar}H), 7.48 – 7.33 (6H, m, ^{Ar}H), 5.84 – 5.71 (1H, m, $HC{=}CH_2$), 5.08 – 4.92 (2H, m, $HC{=}CH_2$), 3.50 (2H, dd, *J* = 6.0, 2.6 Hz, CH_2SiO), 2.30 – 2.23 (1H, m, $CH_2CH{=}CH_2$), 1.95 – 1.88 (1H, m, $CH_2CH{=}CH_2$), 1.80 – 1.72 (1H, m, $CH(CH_3)$), 1.06 (9H, s, $(CH_3)_3CSi$), 0.92 (3H, d, *J* = 6.7 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.3 ($HC{=}CH_2$), 135.6 (4 × ^{Ar}CH), 134.2 (^{Ar}C), 134.0 (^{Ar}C), 129.5 (2 × ^{Ar}CH), 127.6 (4 × ^{Ar}CH), 115.7 ($HC{=}CH_2$), 68.4 (CH_2), 37.6 (CH_2), 35.7 ($CH(CH_3)$), 26.9 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 16.4 (CH_3).

$[\alpha]_D^{22}$ +6.8 (c = 1.96, $CHCl_3$), lit. $[\alpha]_D^{20}$ +3.1 (c = 1.14, $CHCl_3$).

This data is in accordance with literature values.[99]

(4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpentane-1,2-diol



290

(*R*)-*tert*-Butyl((2-methylpent-4-en-1-yl)oxy)diphenylsilane (***R*)-186** (10.68g, 31.54 mmol) was dissolved in MeCN (80 mL) and cooled to 0 °C. H_2O (20 mL), and NMO (7.26 g, 62.0 mmol) were added, followed by OsO_4 (2.5% w/w in ^{t}BuOH, 0.30 mmol). The reaction mixture was warmed to rt, and stirred for 16 h. The reaction mixture was quenched with Na_2SO_3 (*aq*) (100 mL), diluted with Et_2O (200 mL), washed with water (200 mL), then brine (2 × 200 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo* to give the desired product **290** as a yellow oil (11.75 g, 100%).

(*1.3:1 mixture of diastereomers. * denotes minor diastereomer*)

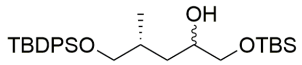
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 – 7.64 (4H, m, ^{Ar}H), 7.47 – 7.34 (6H, m, ^{Ar}H), 3.88 – 3.76 (1H, m, C*H*(OH)), 3.65 – 3.38 (4H, m, OCH_2), 3.34 (1H, d, *J* = 3.4 Hz, O*H*), 2.83* (1H, d, *J* = 4.1 Hz, O*H*), 1.99 (1H, dd, *J* = 6.8, 4.9 Hz, O*H*(CH)), 1.92* (1H, dd, *J* = 7.2, 5.0 Hz, O*H*(CH)), 1.91 – 1.83 (1H, m, C*H*(CH_3), 1.56 – 1.44 (3H, m, CH_2 + SiOCH_2), 1.36 (1H, dd, *J* = 14.3, 6.4, 2.9 Hz, CH_2), 1.06 (9H, s, SiC(CH_3)$_3$), 0.92* (3H, d, *J* = 6.9 Hz, CH_3), 0.86 (3H, d, *J* = 6.9 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 135.7* (^{Ar}*C*H), 135.6(^{Ar}*C*H), 135.6*(^{Ar}*C*H), 133.3* (^{Ar}*C*), 133.3* (^{Ar}*C*), 133.2 (^{Ar}*C*), 133.2 (^{Ar}*C*), 129.8 (^{Ar}*C*H), 127.8 (^{Ar}*C*H), 70.7 (*C*H(OH)), 70.0 (*C*H_2OSi), 69.8* (*C*H(OH)), 68.9* (*C*H_2OSi), 67.4 (*C*H_2OH), 67.1* (*C*H_2OH), 38.8* (*C*H_2), 37.8 (*C*H_2), 33.7 (*C*H(CH_3)), 32.2* (*C*H(CH_3)), 26.9* (SiC(*C*H_3)$_3$), 26.8 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)), 17.7 (*C*H_3), 17.6* (*C*H_3).

HRMS (ESI) calculated for $C_{22}H_{32}O_3SiNa$ $(M+Na)^+$: m/z 395.2013, observed 395.1996.

IR ν_{max} (film)/cm^{-1} 3383, 2957, 2930, 2857, 1471, 1427.

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentanol

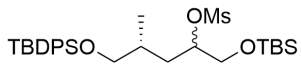


348

(4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpentane-1,2-diol **290** (12.0 g, 32.2 mmol) was dissolved in anhydrous DMF (150 mL) and cooled to 0 °C. Imidazole (4.39 g, 64.5 mmol), then TBSCl (4.85 g, 32.2 mmol) was added. The reaction mixture was stirred for 1 h before being quenched with H_2O (100 mL), extracted with Et_2O (200 mL), washed with brine (4 × 100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was then purified using flash chromatography (silica gel, 20% EtOAc in petroleum ether) to yield the desired compound **348** as a colourless oil (15.0 g, 99%).

Fully characterised as **292**.

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl mesylate

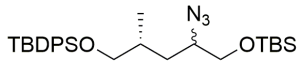


291

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentanol **348 (**15.1 g, 32.2 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) and cooled to 0 °C. Et_3N (8.93 mL, 64.4 mmol) was added, followed by MsCl (2.74 mL, 35.4 mmol), and the resultant mixture was stirred for 1 h. The reaction mixture was then quenched with H_2O (100 mL). The organics were then washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give the desired product **291** as a yellow oil (18.2 g, 100% crude).

Fully characterised as **292**.

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl azide

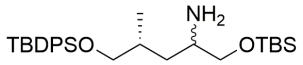


349

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl mesylate **291** (18.2 g, 32.2 mmol) was dissolved in anhydrous DMF (150 mL). NaN_3 (6.28 g, 96.6 mmol) was added and the resultant solution heated to 80 °C and stirred for 16 h. The reaction was then quenched with H_2O (150 mL), extracted with Et_2O (300 mL), washed with brine (4 × 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane) to yield the desired product **349** as a yellow oil (14.74 g, 89%).

Fully characterised as **292**.

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl amine



292

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl azide **349** (5.48 g, 10.7 mmol) was dissolved in EtOH (120 mL), and charged with 10% activated Pd/C (335 mg, 3.15 mmol). The resultant suspension was stirred under an atmosphere of H_2 for 16 h. The suspension was then filtered through celite, washed with EtOH, and the filtrate concentrated *in vacuo*. The crude product was then purified using flash chromatography (silica gel, 0 – 10 % MeOH in CH_2Cl_2) to yield the desired product **292** as a colourless oil (4.38 g, 84%) (66% from (*R*)-*tert*-butyl((2-methylpent-4-en-1-yl)oxy)diphenylsilane (***R***)-**186**).

(*1.3:1 mixture of diastereomers*. * *denotes minor diastereomer*)

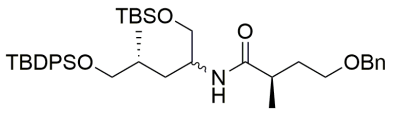
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 – 7.62 (4H, m, ^{Ar}H), 7.45 – 7.34 (6H, m, ^{Ar}H), 3.66 (1H, td, *J* = 9.4, 3.7 Hz, SiOCH_2), 3.56 – 3.41 (3H, m, SiOCH_2), 3.08 (1H, m, *CH*(NH_2)), 1.92 – 1.79 (1H, m, CH_2), 1.66 – 1.59 (1H, m, C*H*(CH_3)), 1.56 – 1.48* (1H, m, C*H*(CH_3)), 1.37 – 1.29 (1H, m, CH_2), 1.05 (9H, s, Si(CH_3)$_3$), 0.96 (3H, d, *J* = 6.6 Hz, CH_3), 0.94* (3H, d, *J* = 6.6 Hz, CH_3), 0.90 (9H, s, Si(CH_3)$_3$), 0.89 (9H, s, Si(CH_3)$_2$), 0.07 (6H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 135.6 (^{Ar}*C*H), 135.6* (^{Ar}*C*H), 133.8 (^{Ar}*C*), 133.7 (^{Ar}*C*), 129.6 (^{Ar}*C*H), 129.6 (^{Ar}*C*H), 127.7 (^{Ar}*C*H), 69.3 (SiO*C*H_2), 68.6 (SiO*C*H_2), 51.2 (*C*H_2(NH_2)), 50.9* (*C*H(NH_2)), 38.3 (*C*H_2), 37.5* (*C*H_2), 32.5 (*C*H(CH_3)), 32.4* (*C*H(CH_3)), 26.9* (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 19.3* (Si*C*(CH_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 17.5 (*C*H_3), 16.8* (*C*H_3), -5.33* (Si(CH_3)$_2$), -5.38 (Si(CH_3)$_2$).

HRMS (CI) calculated for $C_{18}H_{25}O_3NNa$ $(M+H)^+$: m/z 486.3224, observed 486.3207.

IR ν_{max} (film)/cm^{-1} 3017, 2957, 2930, 2857, 2359, 1472.

(2*R*)-4-Benzyloxy-*N*-((4*R*)-((*tert*-butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyloxy)-4-methylpentan-2-yl)-2-methyl butanamide

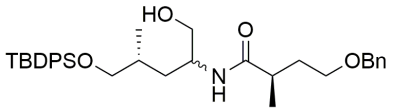


350

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl amine **292 (**6.19 g, 12.7 mmol) and (2*R*)-4-(benzyloxy)-2-methylbutanoic acid (***R***)-**194** (2.65 g, 12.7 mmol) were dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled to 0 °C. EDC.HCl (2.93 g, 15.3 mmol) and HOBt (172 mg, 1.27 mmol) were added, followed by the dropwise addition of DIPEA (4.44 mL, 25.5 mmol). The reaction mixture was stirred at 0 °C for 2 h, then warmed to rt and stirred for 16 h. The solvent was then removed *in vacuo* and the crude mixture dissolved in Et_2O (200 mL), washed with water (150 mL), $NaHCO_3$ (*aq*) (100 mL), 10% HCl (*aq*) (100 mL), brine (2 × 100 mL), dried (Na_2SO_4), then filtered, and concentrated *in vacuo* to give the desired crude amide product **350** (8.43 g, 98% crude).

Fully characterised as **295**.

(2*R*)-4-(Benzyloxy)-*N*-((4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide

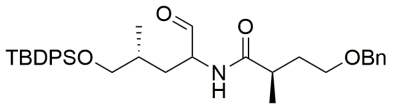


293

(2*R*)-4-Benzyloxy-*N*-((4*R*)-((*tert*-butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyloxy)-4-methylpentan-2-yl)-2-methyl butanamide **350** (8.43 g, 12.7 mmol) was dissolved in ethanol (110 mL), and the resultant solution was treated with PPTS (313 mg, 1.25 mmol) then stirred at rt for 72 h. NEt_3 (5 mL) was added and the solvent was removed *in vacuo*. The crude product was then purified using flash chromatography (silica gel, 50 - 100% EtOAc in petroleum ether) to give the desired product **293** as a colourless oil (6.19 g, 88%).

Fully characterised as **295**.

(2*R*)-4-(Benzyloxy)-*N*-((4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-1-oxopentan-2-yl)-2-methylbutanamide



351

Method A:

CH_2Cl_2 (90 mL) was added to a flame dried flask and cooled to -78 °C. before adding oxalyl chloride (0.60 mL, 7.09 mmol). Then a solution of DMSO (0.85 mL, 12.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 20 min and the resultant solution was stirred for 30 min. (2*R*)-4-(Benzyloxy)-*N*-((4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide **293** (2.50 g, 4.45 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 30 min and the reaction mixture was stirred for 30 min. Et_3N (3.70 mL, 12.0 mmol) was then added dropwise over 30 min before the reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with

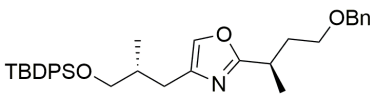
NH_4Cl (100 mL), H_2O (2 × 100 mL), brine (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the desired crude product **351** as an orange oil (1.57 g, 63%).

Method B:

(2*R*)-4-(Benzyloxy)-*N*-((4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide **293** (6.09 g, 10.8 mmol) was dissolved in anhydrous CH_2Cl_2 (75 mL). DMP (6.90 g, 16.3 mmol) was added, and the resultant solution stirred for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (75 mL), washed with $NaHCO_3$ (*aq*) (100 mL), $Na_2S_2O_3$ (*aq*) (100 mL), and brine (100 mL). The organic was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*, and the crude purified using flash chromatography (silica gel, 40 – 50% EtOAc in petroleum ether) to give the desired product **351** as a yellow oil (4.21 g, 69%).

Fully characterised as **295**.

2-((*R*)-4-(Benzyloxy)butan-2-yl)-4-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)oxazole



295

(2*R*)-4-(Benzyloxy)-*N*-((4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-1-oxopentan-2-yl)-2-methylbutanamide **351** (1.57 g, 2.80 mmol) dissolved in CH_2Cl_2 (60 mL) and cooled down to 0 °C. PPh_3 (2.05 g, 7.82 mmol), DTBMP (2.01 g, 9.79 mmol), and $(BrCCl_2)_2$ were added sequentially. The resultant mixture was stirred at 0 °C for a further 10 min, before the reaction was allowed to warm up to rt and stirred for 45 min. DIPEA (2.43 mL, 14.0 mmol) was then added dropwise and the reaction was stirred for 16 h. The reaction mixture was concentrated *in vacuo*, before being purified by flash chromatography (silica gel, 0 – 5 % Et_2O in petroleum ether) to yield the desired product **295** (795 mg, 61% brsm 225 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (4H, dt, *J* = 8.0, 1.5 Hz, ^{Ar}H), 7.45 – 7.28 (10H, m, ^{Ar}H), 7.16 (1H, s, ^{Ar}H), 4.46 (2H, s, OCH_2Ph), 3.58 – 3.41 (4H, m, OCH_2Si, CH_2OBn), 3.19 – 3.14 (1H, m, (CH_3)C*H*(Ar)), 2.67 (1H, dd, *J* = 14.6, 5.5 Hz, CH_2Ar), 2.33 (1H, dd, *J* = 14.6, 7.8 Hz, CH_2Ar), 2.16 – 2.02 (2H, m, CH(CH_2Ar), CH_2(CH_2OBn)), 1.91 – 1.85 (1H, m,

CH_2(CH_2OBn)), 1.31 (3H, d, *J* = 7.1 Hz, CH_3(CHAr)), 1.06 (9H, s, (CH_3)$_3$CSi), 0.96 (3H, d, *J* = 6.7 Hz, CH_3(CHCH_2Ar).

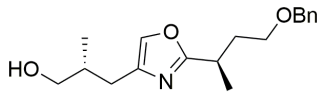
^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0 (^{Ar}*C*N), 139.1 (^{Ar}*C*), 138.6 (^{Ar}*C*H), 135.6 (^{Ar}*C*H), 134.2 (^{Ar}*C*), 134.0 (^{Ar}*C*H), 129.7 (^{Ar}*C*H), 128.4 (^{Ar}*C*H), 127.8 (^{Ar}*C*H), 127.7 (^{Ar}*C*H), 73.0 (O*C*H_2Ph), 68.3 (SiO*C*H_2), 68.1 (BnO*C*H_2), 35.3 (*C*H(CH_3)), 35.1 (*C*H_2), 30.9 (*C*H(CH_3)), 30.0 (*C*H_2), 27.0 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH_3)$_3$), 18.7 (*C*H_3), 16.8 (*C*H_3).

HRMS (ESI) calculated for $C_{34}H_{43}O_3SiNa$ $(M+Na)^+$: m/z 564.2904, observed 564.2888

IR ν_{max} (film)/cm^{-1} 2970, 2361, 1738, 1366, 912, 743.

$[\alpha]_D^{26}$ -4.6 (c = 0.87, $CHCl_3$).

(*R*)-3-(2-((*R*)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)-2-methylpropan-1-ol



296

2-((*R*)-4-(Benzyloxy)butan-2-yl)-4-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)oxazole **295** (795 mg, 1.47 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0 °C. The resultant solution was then treated with TBAF (1M in THF, 7.31 mL, 7.31 mmol), and stirred at 0 °C for 30 min, before being warmed to rt and stirred for 16 h. The reaction mixture was then quenched with H_2O (5 mL), diluted with Et_2O (20 mL), washed with H_2O (2 × 10 mL), brine (20 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*. The crude product was then purified using flash chromatography (silica gel, 0 – 60% Et_2O in petroleum ether) to yield the desired product **296** as a pale yellow oil (345 mg, 77%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37 – 7.27 (6H, m, ^{Ar}*H*), 4.47 (2H, s, OCH_2), 3.58 – 3.41 (4H, m, CH_2OH + CH_2OBn), 3.23 – 3.14 (1H, m, C*H*(CH_3)), 2.60 – 2.46 (2H, m, CH_2), 2.16 – 2.08 (1H, m, CH_2), 2.04 – 1.96 (1H, m, CH_2), 1.93 – 1.85 (1H, m, C*H*(CH_3)), 1.32 (3H, d, *J* = 7.1 Hz, CH_3), 0.91 (3H, d, *J* = 6.9 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0 (^{Ar}*C*N), 138.4 (^{Ar}*C*HO), 138.0 (^{Ar}*C*), 134.2 (^{Ar}*C*), 128.3 (^{Ar}*C*H), 127.6 (^{Ar}*C*H), 127.5 (^{Ar}*C*H), 73.0 (O*C*H_2Ph), 67.7 (*C*H_2OBn), 67.4 (*C*H_2OH),

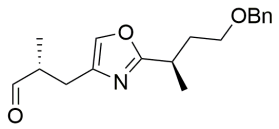
35.0 (*C*H(CH_3)), 34.9 (*C*H_2), 30.6 (*C*H(CH_3)), 30.1 (*C*H_2), 18.5 (CH(*C*H_3)), 16.9 (CH(*C*H_3)).

HRMS (ESI) calculated for $C_{18}H_{25}O_3NNa$ $(M+Na)^+$: m/z 326.1727, observed 326.1716.

IR ν_{max} (film)/cm^{-1} 3370, 2870, 1566, 1094, 1038, 750.

$[\alpha]_D^{26}$ -22.6 (c = 1.31, $CHCl_3$).

(2*R*)-3-(2-((2*R*)-4-(Benzyloxy)butan-2-yl)-1,3-oxazol-4-yl)-2-methylpropanal



281

(*R*)-3-(2-((*R*)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)-2-methylpropan-1-ol **296** (176 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (10 mL). The resultant solution was then treated sequentially with BAIB (0.60 g, 1.86 mmol) and TEMPO (18 mg, 0.12 mmol). The reaction mixture was then stirred for 16 h. The solvent was removed *in vacuo* and the crude product was purified using flash chromatography (silica gel, 20% EtOAc in petroleum ether) to give the desired product **281** as a colourless oil (127 mg, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.72 (1H, d, *J* = 1.3 Hz, C(O)*H*), 7.36 – 7.27 (6H, m, ^{Ar}*H*), 4.47 (2H, s, OCH_2Ph), 3.55 – 3.40 (2H, m, CH_2OBn), 3.23 – 3.12 (1H, m, C*H*(CH_3)), 2.92 (1H, ddd, *J* = 14.7, 6.6, 1.0 Hz, CH_2Ar), 2.83 – 2.71 (1H, m, C*H*(CH_3)), 2.54 (1H, ddd, 14.7, 7.1, 0.9 Hz, CH_2Ar), 2.18 – 2.05 (1H, m, CH_2), 1.93 – 1.85 (1H, m, CH_2), 1.32 (3H, d, *J* = 7.1 Hz,CH_3), 1.11 (3H, d, *J* = 7.1 Hz, CH_3).

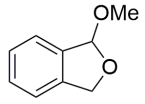
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.1 (H*C*=O), 168.1 (^{Ar}*C*), 138.4 (^{Ar}*C*), 137.3 (^{Ar}*C*), 134.3 (^{Ar}*C*H), 128.3 (^{Ar}*C*H), 127.6 (^{Ar}*C*H), 127.5 (^{Ar}*C*H), 73.0 (O*C*H_2Ph), 67.8 (O*C*H_2CH_2), 45.4 (*C*H(CH_3)C(O)H), 35.0 (*C*H_2), 30.7 (*C*H(CH_3)), 27.2 (*C*H_2), 18.6 (*C*H_3), 13.3 (*C*H_3).

HRMS (ESI) calculated for $C_{18}H_{23}O_3NNa$ $(M+Na)^+$: m/z 324.1570, observed 324.1554.

IR ν_{max} (film)/cm^{-1} 2972, 2874, 2861, 1722, 1570, 1440, 1036.

$[\alpha]_D^{26}$ -20.5 (c = 1.12, $CHCl_3$).

1-Methoxy-1,3-dihydroisobenzofuran



119

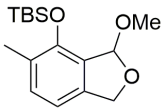
Phthalide (6.70 g, 50.0 mmol) was dissolved in anhydrous toluene (500 mL) and cooled to -78 °C. The resultant solution was then treated with DIBALH (50.0 mL, 1M in hexanes, 50.0 mmol) added *via* syringe pump over 1.5 h. The reaction mixture was warmed to rt, then MeOH (20 mL) and *p*-TsOH.H_2O (150 mg, 0.79 mmol) were added. The resultant mixture was stirred for 3 h then diluted with EtOAc (500 mL) and Rochelle's salt 20 % (*aq*) solution (600 mL) was added and stirred for 16 h. The organic phase was separated, washed with saturated $NaHCO_3$ (*aq*) solution (400 mL), brine (400 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in petroleum ether) to yield the desired product **119** as a colourless oil (4.66 g, 62%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44 – 7.28 (4H, m, ^{Ar}H), 6.20 (1H, d, *J* = 2.2 Hz, C*H*OCH_3), 5.23 (1H, d, *J* = 12.7 Hz, CH_2), 5.06 (1H, d, *J* = 12.7 Hz, CH_2), 3.45 (3H, s, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 140.0 (^{Ar}C), 137.3 (^{Ar}C), 129.2 (^{Ar}CH), 127.7 (^{Ar}CH), 123.0 (^{Ar}CH), 121.0 (^{Ar}CH), 107.6 (*C*HOCH_3), 72.4 (*C*H_2), 54.3 (O*C*H_3).

This data is in accordance with literature values.[27]

***tert*-Butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yl)oxy)dimethylsilane**



159

7-((*tert*-Butyldimethylsilyl)oxy)-6-methyl-1,3-dihydro-2-benzofuran-1-one **158** (1.67 g, 6.00 mmol) was dissolved in anhydrous toluene (90 mL) and cooled to -78 °C. The resultant solution was then treated with DIBALH (6.00 mL, 1M in hexanes, 6.00 mmol) added *via* syringe pump over 1.5 h. The reaction was then quenched with MeOH (6 mL), and then diluted with Et_2O (100 mL). Rochelle's salt 20% (*aq*) solution (100 mL) was then added,

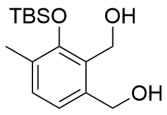
and then stirred for 16 h. The layers were then separated, and the organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude lactol intermediate was then dissolved in anhydrous MeOH (100 mL), and treated with PPTS (150 mg, 0.60 mmol). The reaction mixture was stirred for 2 h, then basified with saturated $NaHCO_3$ (*aq*) solution, diluted with Et_2O (150 mL), and the aqueous phase extracted with (150 mL). The combined organics were then washed with H_2O (2 × 100 mL), brine (2 × 100 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in petroleum ether) to yield the desired product **159** as a colourless oil (1.55 g, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 6.77 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 6.16 (1H, d, *J* = 1.9 Hz, C*H*), 5.14 (1H, d, *J* = 12.4 Hz, CH_2), 4.94 (1H, d, *J* = 12.4 Hz, CH_2), 3.41 (3H, s, CH_3), 2.23 (3H, s, CH_3), 1.03 (9H, s, C(CH_3)$_3$), 0.21 (6H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.2 (^{Ar}C), 139.9 (^{Ar}C), 132.9 (^{Ar}CH), 128.3 (^{Ar}C), 128.2 (^{Ar}C), 113.8 (^{Ar}CH), 106.4 (*C*H(OCH$_3$)), 72.1 (*C*H$_2$), 54.2 (O*C*H$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 18.6 (^{Ar}*C*H$_3$), 17.2 (Si*C*(CH$_3$)$_3$, -3.4 (Si(*C*H$_3$)$_2$), -3.5 (Si(*C*H$_3$)$_2$).

This data is in accordance with literature values.[48]

(3-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-1,2-phenylene)dimethanol



303

Procedure as per synthesis of *tert*-butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yl)oxy)dimethylsilane **159**. Compound isolated as a yellow oil.

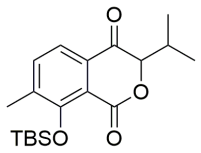
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 6.92 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 4.80 (2H, s, CH_2), 4.69 (2H, s, CH_2), 2.79 (2H, br s, O*H*), 2.23 (3H, s, CH_3), 1.05 (9H, s, C(CH_3)$_3$), 0.20 (6H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.9 (^{Ar}C), 139.1 (^{Ar}C), 130.9 (^{Ar}CH), 130.5 (^{Ar}C), 129.7 (^{Ar}C), 123.3 (^{Ar}CH), 64.7 (HO*C*H$_2$), 57.3 (HO*C*H$_2$), 26.1 (SiC(*C*H$_3$)$_3$), 18.7 (Si*C*), 18.0 (*C*H$_3$), -3.5 (Si(*C*H$_3$)$_2$).

HRMS (ESI) calculated for $C_{15}H_{26}O_3SiNa$ $(M+Na)^+$: m/z 305.1543, observed m/z 305.1539.

IR ν_{max} (film)/cm^{-1} 3384, 2955, 2930, 2859, 1580, 1416, 1265

8-((*tert*-Butyldimethylsilyl)oxy)-3-isopropyl-7-methylisochroman-1,4-dione



352

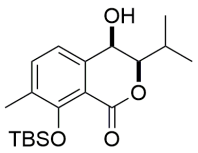
tert-Butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yl)oxy)dimethylsilane **159** (295 mg, 1.00 mmol) was dissolved in anhydrous THF (6 mL) and cooled to 0 °C. The resultant solution was then treated with freshly distilled $^{i}Pr_2NH$ (0.28 mL, 1.99 mmol) and stirred for 10 min. MeLi (1.25 mL, 1.6 M, 1.25 mmol) was then added slowly, then stirred for 30 min before the reaction mixture was cooled to -78 °C. Freshly distilled isobutyraldehyde (0.11 mL, 1.21 mmol) was then added and the reaction stirred for 1.5 h. The reaction was then quenched with H_2O at 0 °C, diluted with Et_2O (10 mL), washed with H_2O (10 mL), brine (10 mL), then dried (Na_2SO_4). The solvent was removed *in vacuo* to give the α-hydroxy-isobenzofuran intermediate. This intermediate was then immediately dissolved in anhydrous CH_2Cl_2 (6 mL) and cooled to 0 °C. The resultant solution was then treated with *m*CPBA (77% w/w, 246 mg, 1.10 mmol) and the reaction mixture was stirred at 0 °C for 2 h. The reaction was then quenched with $NaHCO_3$ (*aq*) (10 mL), extracted with CH_2Cl_2 (2 × 10 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* to give the crude keto-lactol intermediate. This intermediate was then dissolved in anhydrous CH_2Cl_2 (6 mL) and cooled to 0 °C. BAIB (1.03 g, 3.2 mmol), then TEMPO (31 mg, 0.20 mmol) were added and the reaction mixture stirred at rt for 45 min, then diluted with CH_2Cl_2 (20 mL), washed with $Na_2S_2O_3$ (*aq*) (2 × 10 mL), water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was then purified using flash column chromatography (silica gel, 20% EtOAc in petroleum ether) to yield the desired product **352** as a clear oil (124 mg, 35%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.63 (1H, d, *J* = 7.8 Hz, ^{Ar}H), 7.57 (1H, d, *J* = 7.8 Hz, ^{Ar}H), 4.75 (1H, d, *J* = 4.9 Hz, C(O)C*H*), 2.42 – 2.33 (4H, m, CH_3 & C*H*(CH_3)$_2$), 1.10 (3H, d, *J* =

6.9 Hz, CH(CH_3)$_2$), 1.07 (9H, s, SiC(CH_3)$_3$), 0.99 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.24 (3H, s, SiCH_3), 0.21 (3H, s, SiCH_3).

This data is in accordance with literature values.[48]

(3*R*,4*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-3-isopropyl-7-methylisochroman-1-one



160

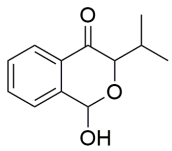
8-((*tert*-Butyldimethylsilyl)oxy)-3-isopropyl-7-methylisochroman-1,4-dione **352** (124 mg, 0.36 mmol) was dissolved in anhydrous MeOH (5 mL) and cooled to -78 °C. The resultant solution was then treated with $NaBH_4$ (16 mg, 0.43 mmol) and the reaction mixture was warmed to rt and stirred for 16 h. The reaction was then quenched with H_2O, and 10% (*aq*) citric acid solution (10 mL). The aqueous was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organics washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 20% EtOAc in petroleum ether) to yield the desired product **160** as a white solid (54 mg, 43%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38 (1H, dd, *J* = 7.5, 0.7 Hz, ^{Ar}H), 6.96 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 4.67 (1H, dd, *J* = 7.3, 1.1 Hz, *H*C(OH)), 3.88 (1H, dd, *J* = 9.8, 1.4 Hz, *H*C(OC(O)), 2.33 – 2.22 (1H, m, *H*C(CH$_3$)$_2$), 2.27 (3H, s, ^{Ar}CH_3), 1.95 (1H, d, *J* = 7.4 Hz, O*H*), 1.17 (3H, d, *J* = 6.6 Hz, HC(CH_3)$_2$), 1.07 (3H, d, *J* = 6.6 Hz, HC(CH_3)$_2$), 1.04 (9H, s, SiC(CH_3)$_3$), 0.19 (3H, s, Si(CH_3)$_2$), 0.11 (3H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.0 (*C*=O), 155.4 (^{Ar}C), 139.6 (^{Ar}C), 136.3 (^{Ar}C*H*), 132.8 (^{Ar}C), 120.4 (^{Ar}C*H*), 115.8 (^{Ar}C), 85.7 (*C*HCH(CH$_3$)$_2$), 66.1 (*C*HOH), 28.4 (*C*H(CH$_3$)$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 19.3 (*C*H$_3$), 18.7 (Si*C*), 18.2 (*C*H$_3$), 17.5 (^{Ar}C*H*$_3$), -3.7 (Si(*C*H$_3$)$_2$), -3.7 (Si(*C*H$_3$)$_2$).

This data is in accordance with literature values.[48]

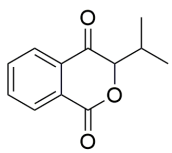
1-Hydroxy-3-isopropylisochroman-4-one



305

1-Methoxy-1,3-dihydro-2-benzofuran **119** (750 mg, 5.00 mmol) was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. The resultant solution was then treated with freshly distilled $^{i}Pr_2NH$ (1.40 mL, 9.96 mmol) and stirred for 10 min. MeLi (6.25 mL, 1.6 M, 6.25 mmol) was then added slowly and the solution stirred for 30 min before the reaction mixture was cooled to -78 °C. Freshly distilled isobutyraldehyde (0.55 mL, 6.03 mmol) was then added and the reaction mixture stirred for 1.5 h. The reaction was then quenched with H_2O at 0 °C, diluted with Et_2O (60 mL), washed with water (60 mL), brine (60 mL), then dried (Na_2SO_4). The solvent was removed *in vacuo* to give the α-hydroxy-isobenzofuran intermediate. This intermediate was then immediately dissolved in anhydrous CH_2Cl_2 (30 mL) and cooled to 0 °C. The resultant solution was then treated with *m*CPBA (77% w/w, 1.23 g, 7.13 mmol) and the reaction mixture was left to stir at 0 °C for 2 h. The reaction was then quenched with $NaHCO_3$ (*aq*) (30 mL), extracted with CH_2Cl_2 (2 × 30 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* to give the crude keto-lactol **305** (1.03 g, 100%) which was used in the subsuquent reaction without further purification.

3-Isopropylisochroman-1,4-dione



176

1-Hydroxy-3-isopropylisochroman-4-one **305** (343 mg, 1.67 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL) and cooled to 0 °C. BAIB (1.67 g, 5.18 mmol), then TEMPO (52 mg, 0.33 mmol) were added and the reaction mixture stirred at rt for 1.5 h. The reaction mixture was then concentrated *in vacuo*, and then purified using flash column

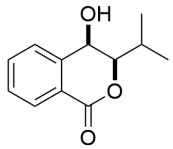
chromatography (silica gel, 20% EtOAc in petroleum ether) to yield the desired product **176** as a yellow oil (204 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 – 8.28 (1H, m, ^{Ar}H), 8.11 – 8.07 (1H, m, ^{Ar}H), 7.86 (2H, m, ^{Ar}H), 4.96 (1H, d, *J* = 3.7 Hz, OC*H*), 2.51 (1H, m, *H*C(CH_3)$_2$), 1.16 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.94 (3H, d, *J* = 6.8 Hz, C*H*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 192.5 (*C*=O), 162.0 (C=O(O)), 135.6 (^{Ar}CH), 134.5 (^{Ar}CH), 132.0 (^{Ar}C), 130.6 (^{Ar}CH), 128.1 (^{Ar}C), 125.6 (^{Ar}CH), 88.9 (*C*HO), 33.4 (*C*H(CH_3)$_2$), 18.9 (*C*H$_3$), 16.3 (*C*H$_3$).

This data is in accordance with literature values.[27]

(3R,4R)-4-hydroxy-3-isopropylisochroman-1-one



177

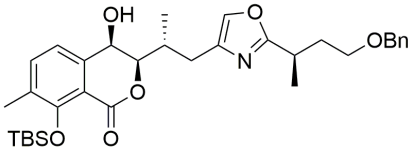
3-Isopropylisochroman-1,4-dione **176** (200 mg, 0.98 mmol) was dissolved in anhydrous MeOH (10 mL) and cooled to -78 °C. The resultant solution was then treated with $NaBH_4$ (45 mg, 1.19 mmol), and stirred at -78 °C for 3 h. The reaction mixture was then quenched with water, and 10% (*aq*) citric acid solution. The aqueous was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organics washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 20% EtOAc in petroleum ether) to give the desired product **177** as a pale yellow solid (145 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (1H, dd, *J* = 7.8, 1.1 Hz, ^{Ar}H), 7.67 (1H, td, *J* = 7.5, 1.3 Hz, ^{Ar}H), 7.55 (1H, td, *J* = 7.6, 1.2 Hz, ^{Ar}H), 7.48 (1H, d, *J* = 7.5 Hz, ^{Ar}H), 4.78 (1H, d, *J* = 6.2 Hz, C*H*OH), 4.03 (1H, dd, *J* = 9.8, 1.5 Hz, C*H*CH(CH_3)$_3$), 2.41 – 2.34 (1H, m, C*H*(CH_3)$_3$), 1.80 (1H, d, *J* = 7.1 Hz, O*H*), 1.23 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)$_3$, 1.13 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9 (*C*=O), 140.3 (^{Ar}C), 134.3 (^{Ar}CH), 130.5 (^{Ar}CH), 130.0 (^{Ar}CH), 128.0 (^{Ar}CH), 124.3 (^{Ar}C), 86.5 (*C*HOC), 65.2 (*C*HOH), 28.7 (*C*H(CH_3)$_2$), 19.3 (*C*H_3), 18.2 (*C*H_3).

This data is in accordance with literature values.[27]

(3*R*,4*R*)-3-((*R*)-1-(2-((*R*)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)propan-2-yl)-8-(*tert*-butyldimethylsilyloxy)-4-hydroxy-7-methylisochroman-1-one



297

tert-Butyl((3-methoxy-5-methyl-1,3-dihydro-2-benzofuran-4-yl)oxy)dimethylsilane **159** (100 mg, 0.34 mmol) was dissolved in anhydrous THF (6 mL), and cooled to 0 °C. Freshly distilled DIPA (0.10 mL, 0.71 mmol) was added, and the resultant solution stirred for 10 min. MeLi (1.6 M in Et_2O, 0.43 mL, 0.69 mmol) was added dropwise, and the resultant mixture was stirred for 30 min at 0 °C before being cooled to -78 °C. (2*R*)-3-(2-((2*R*)-4-(Benzyloxy)butan-2-yl)-1,3-oxazol-4-yl)-2-methylpropanal **281** (100 mg, 0.33 mmol) in anhydrous THF (0.20 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h at -78 °C, before being warmed to 0 °C. H_2O (1 mL) was added, then the reaction mixture was diluted with Et_2O (10 mL), washed with H_2O (10 mL), brine (10 mL), the organic dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the α-hydroxy-*iso*benzofuran intermediate. The crude intermediate was then immediately dissolved in anhydrous CH_2Cl_2 (10 mL), and cooled to 0 °C, under an argon atmosphere. *m*CPBA (77% w/w, 82 mg, 0.37 mmol) was added and the resultant solution stirred at 0 °C for 2 h. The reaction was then quenched with $NaHCO_3$ (*aq*) (10 mL), extracted with CH_2Cl_2 (2 × 10 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the lactol intermediate was immediately dissolved in anhydrous CH_2Cl_2 (6 mL) and cooled to 0 °C. BAIB (1.03 g, 3.2 mmol), then TEMPO (31 mg, 0.20 mmol) were added and the reaction mixture was stirred at rt for 4 h, and then concentrated *in vacuo*. The crude product was then purified using flash column chromatography (silica gel, 20% EtOAc in petroleum ether) to yield the keto-lactone intermediate as a yellow oil (34 mg, 0.06 mmol, 18%). The intermediate was then dissolved in anhydrous CH_2Cl_2 (3 mL) under an argon atmosphere, and cooled to -78 °C. $CeCl_3.7H_2O$

(66 mg, 0.18 mmol) in MeOH (3 mL) was added, and the resultant mixture stirred for 10 min. $NaBH_4$ (3.1 mg, 0.08 mmol) was added and the reaction mixture was stirred for 30 min at -78 °C. The reaction was then quenched with H_2O (3 mL) and 10% (*aq*) citric acid solution (3 mL), and the resultant biphasic mixture stirred for 20 min at rt. The organic phase was separated and the aqueous was extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were washed with brine (3 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude products were purified using flash chromatography (silica gel, 20 – 50% EtOAc in petroleum ether) to give the desired product **297**, an inseparable mixture of diastereomers, as a colourless oil (17.8 mg, 9%).

*NMR data major diastereomer reported only

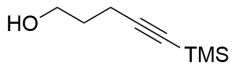
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37 (1H, dd, *J* = 7.5, 0.7 Hz, ^{Ar}H), 7.36 – 7.22 (6H, m, ^{Ar}H), 6.95 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 4.66 (1H, d, *J* = 1.3 Hz, C*H*(OH)), 4.45 (2H, s, OCH_2Ph), 4.06 (1H, dd, *J* = 9.3, 1.5 Hz, C*H*(O_2C)), 3.53 – 3.42 (2H, m, CH_2OBn), 3.22 – 3.13 (1H, m, C*H*(CH_3)), 3.04 (1H, dd, *J* = 14.6, 2.6 Hz, CH_2), 2.60 (1H, dd, *J* = 14.6, 7.8 Hz, CH_2), 2.51 – 2.43 (1H, m, C*H*(CH_3)), 2.27 (3H, s, ^{Ar}CCH_3), 2.14 – 2.05 (1H, m, CH_2CH_2OBn), 1.92 – 1.83 (1H, m, CH_2CH_2OBn), 1.30 (3H, d, *J* = 7.3 Hz, CH_3), 1.21 (3H, d, *J* = 6.7 Hz), 1.04 (9H, s, SiC(CH_3)$_3$), 0.20 (3H, s, Si(CH_3)$_2$), 0.12 (3H, s, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.7 (*C*=O), 163.0 (*C*=N), 155.4 (^{Ar}C), 139.7 (^{Ar}C), 138.4 (^{Ar}C), 137.9 (^{Ar}C), 136.3 (^{Ar}CH), 134.7 (^{Ar}CH), 132.7 (^{Ar}C), 128.3 (^{Ar}CH), 127.6 (^{Ar}C), 127.5 (^{Ar}CH), 120.4 (^{Ar}CH), 115.8 (^{Ar}C), 83.0 (*C*H(O_2C)), 73.0 (O*C*H_2Ph), 67.8 (*C*H_2OBn), 66.3 (*C*H(OH), 35.0 (*C*H_2CH_2OBn), 33.2 (*C*H(CH_3)), 30.7 (*C*H(CH_3)), 28.1 (*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.6 (Si*C*(CH_3)$_3$), 18.4 (*C*H_3), 17.5 (^{Ar}C*C*H3), 15.4 (*C*H_3), -3.6 (Si(*C*H_3)$_2$), -3.7 (Si(*C*H_3)$_2$).

HRMS (ESI) calculated for $C_{33}H_{45}O_6NSiNa$ $(M+Na)^+$: m/z 602.2908, observed 602.2880.

IR vmax (film)/cm^{-1} 3380, 2951, 2930, 2858, 1723, 1597, 1585, 1472, 1417, 1254

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



319

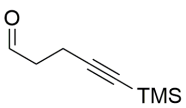
4-Pentyn-1-ol (0.94 mL, 10.1 mmol) was dissolved in anhydrous THF (30 mL) and the solution cooled to -78 °C. *n*BuLi (2.5 M in hexanes, 8.06 mL, 20.2 mmol) was added slowly and the resultant mixture stirred for 45 min at -78 °C, then the dry ice/acetone bath was removed and the reaction stirred for 15 min. The reaction mixture was then cooled back down to -78 °C and TMSCl (2.54 mL, 20.1 mmol) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C, then rt for 1 h. A mixture of Et_2O:1 M HCl (1:1, 50 mL) was added and the reaction stirred for 3 h, before being diluted with Et_2O (100 mL). The organic phase was separated and the aqueous layer extracted with Et_2O (50 mL). The organic extracts were then washed with sat. $NaHCO_3$ (*aq*) (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 10% EtOAc in petroleum ether) gave the desired product **319** as a colourless oil (1.45 g, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.80 – 3.75 (2H, m, OCH_2), 2.36 (2H, t, J = 6.9 Hz, CH_2), 1.82 – 1.75 (2H, m, CH_2), 1.57 (1H, s, O*H*), 0.16 (9H, s, Si(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 106.6 (*C*≡CSi), 85.3 (C≡*C*Si), 61.9 (O*C*H$_2$), 31.1 (*C*H$_2$), 16.5 (*C*H$_2$), 0.0 (Si(*C*H$_3$)$_3$).

This data is in accordance with literature values.[87]

5-(Trimethylsilyl)pent-4-ynal



320

IBX (1.25 g, 4.46 mmol) was dissolved in DMSO (8 mL). 5-(Trimethylsilyl)pent-4-yn-1-ol **319** (350 mg, 2.24 mmol) in anhydrous THF (15 mL) was then added and the resultant mixture was stirred for 20 h, at rt. H_2O (20 mL) was added to the reaction and the mixture was stirred for 4 h, forming a white precipitate. The reaction was then filtered, and the

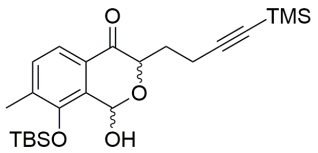
precipitate washed thoroughly with Et_2O (75 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (50 mL). The organic extracts were then washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 5% Et_2O in pentane) gave the desired product **320** as a colourless oil (214 mg, 62%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.80 (1H, t, *J* = 1.1 Hz, C(O)*H*), 2.73 – 2.65 (2H, m, CH_2), 2.58 – 2.53 (2H, m, CH_2), 0.15 (9H, s, Si(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 200.4 (*C*(O)H), 104.7 (*C*≡CSi), 85.8 (C≡*C*Si), 42.5 (*C*H_2), 13.1 (*C*H_2), 0.0 (Si(*C*H_3)$_3$.

This data is in accordance with literature values.[100]

8-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-7-methyl-3-(4-(trimethylsilyl)but-3-yn-1-yl)isochroman-4-one



323

tert-Butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yl)oxy)dimethylsilane **159** (507 mg, 1.72 mmol) was dissolved in anhydrous THF (10 mL), and cooled to 0 °C. Freshly distilled ^{i}Pr$_2$NH (0.48 mL, 3.42 mmol) was added, and the resultant solution stirred for 10 min. MeLi (1.6 M in Et_2O, 2.15 mL, 3.44 mL) was added dropwise, and the resultant mixture was stirred for 30 min at 0 °C before being cooled to -78 °C. 5-(Trimethylsilyl)pent-4-ynal **320** (266 mg, 1.72 mmol) in anhydrous THF (0.20 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h at -78 °C, before being warmed to 0 °C. H_2O (1 mL) was added, then the reaction mixture was diluted with Et_2O (25 mL), washed with H_2O (20 mL), and brine (20 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the α-hydroxy-isobenzofuran intermediate. The crude intermediate was then immediately dissolved in anhydrous CH_2Cl_2 (10 mL), and cooled to 0 °C. *m*CPBA (77% w/w, 423 mg, 1.87 mmol) was added and the resultant solution stirred at 0 °C for 2 h. The reaction was then quenched with $NaHCO_3$ (*aq*) (10 mL), extracted with CH_2Cl_2 (2 × 10 mL),

and dried (Na_2SO_4). The solvent was removed *in vacuo*. Purification using flash chromatography (neutral alumina, 5% EtOAc in petroleum ether) gave the desired product **323** (701 mg, 94%).

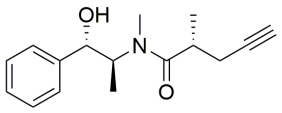
^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.59 (1H, d, *J* = 7.9 Hz, ^{Ar}H), 7.27 (1H, d, *J* = 7.9 Hz, ^{Ar}H), 6.36 (1H, br s, C*H*OH), 4.95 (1H, dd, *J* = 8.9, 3.6 Hz, C(O)C*H*), 2.78 (1H, d, *J* = 3.6 Hz, O*H*), 2.46 – 2.41 (2H, m, CH_2CH_2), 2.36 – 2.31 (1H, m, CH_2), 2.31 (3H, s, CH_3), 1.97 – 1.88 (1H, m, CH_2), 1.06 (OSiC(CH_3)$_3$), 0.30 (3H, s, SiCH_3), 0.26 (3H, s, SiCH_3), 0.14 (9H, s, CSiC(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 195.5 (*C*=O), 149.8 (^{Ar}C), 136.4 (^{Ar}C), 132.0 (^{Ar}CH), 131.4 (^{Ar}C), 128.0 (^{Ar}C), 119.7 (^{Ar}CH), 103.4 (*C*≡C), 88.0 (*C*H(CO)), 85.5 (*C*≡C), 71.2 (*C*H(OH)), 29.3 (*C*H_2), 26.1 (SiC(*C*H_3)$_3$), 25.7 (Si*C*(CH$_3$)$_3$), 18.6 (*C*H_2), 15.8 (*C*H_3), 0.13 (Si(*C*H_3)$_3$), -3.12 (Si(*C*H_3)$_2$), -3.58 (Si(*C*H_3)$_2$).

HRMS (ESI) calculated for $C_{23}H_{36}O_4Si_2Na$ $(M+Na)^+$: m/z 455.2044, observed 455.2027.

IR ν_{max} (film)/cm^{-1} 3391, 2957, 2930, 2857, 2357, 2178, 1694, 1472, 1252.

(*R*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-ynamide

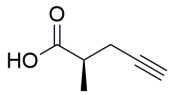


328

LiCl (11.4 g, 268 mmol) was dried under vacuum at 230 °C for 16 h, then allowed to cool to rt under a flow of argon. Anhydrous THF (80 mL) and freshly distilled DIPA (1.59 mL, 11.3 mmol) were added and the resultant mixture was cooled to -78°C. *n*BuLi (2.5 M in hexanes, 37.9 mL, 94.8 mmol) was added and the reaction mixture was warmed to 0 °C for 5 min and cooled to -78 °C. An ice cooled solution of *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide **285** (10.0 g, 45.2 mmol) in THF (100 mL) was added dropwise *via* cannula. The reaction mixture was stirred at -78 °C for 1 h, warmed to 0 °C for 15 min, rt for 5 min, and cooled to -78 °C. Propargyl bromide (80% w/w in toluene, 7.55 mL, 68.0 mmol) was added dropwise *via* syringe pump and the resultant mixture was stirred at -78 °C for 2 h, then the dry ice/acetone bath was removed and the mixture stirred for 16 h. The reaction was quenched with saturated NH_4Cl (*aq*) (250 mL) and diluted with

EtOAc (300 mL), and washed with saturated NH_4Cl (300 mL). The aqueous layer was extracted with EtOAc (2 × 300 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the desired product **328** as a yellow oil (11.7 g, 100%) which was used in the subsequent reaction without further purification.

(2*R*)-2-Methylpent-4-ynoic acid



(***R***)-**43**

(*R*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-ynamide **328** (11.7 g, 45.2 mmol) was dissolved in ^{t}BuOH (60 mL), MeOH (60 mL), and 3M NaOH (*aq*) (60 mL). The resultant solution was heated to reflux and stirred for 16 h. The reaction mixture was then cooled to rt, and concentrated *in vacuo*, before being diluted with H_2O (300 mL), and extracted with CH_2Cl_2 (4 × 200 mL). The aqueous was then acidified to pH < 2 using 3M HCl (*aq*), and extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts (after acidification) were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the desired product (***R***)-**43** as an orange oil (4.05 mg, 80%).

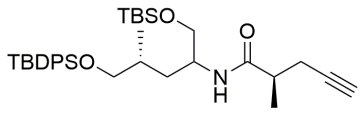
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.72 (1H, m, C*H*CH_3), 2.58 (1H, ddd, *J* = 16.8, 6.0, 2.6 Hz, C*H*$_2$), 2.41 (1H, ddd, *J* = 16.8, 7.6, 2.6 Hz, C*H*$_2$), 2.03 (1H, t, *J* = 2.6 Hz, C≡C*H*), 1.33 (3H, d, *J* = 7.1 Hz, C*H*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 180.3 (*C*=O), 81.1 (*C*≡CH), 70.1 (C≡*C*H), 38.4 (*C*H), 22.3 (*C*H_2), 16.1 (*C*H_3).

$[\alpha]_D^{26}$ +7.6 (c = 1.38, $CHCl_3$), lit. $[\alpha]_D^{23}$ +4.2 (c = 1.00, $CHCl_3$).

This data is in accordance with literature values.[23]

(2*R*)-*N*-((4*R*)-1-((*tert*-butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-pentant-2-yl)-2-methyl-4-pentynamide

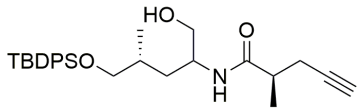


329

(4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(-*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl amine **292 (**8.36 g, 17.2 mmol) and (2*R*)-2-methylpent-4-ynoic acid (***R***)-**43** (1.93 g, 17.2 mmol) were dissolved in anhydrous CH_2Cl_2 (110 mL) and cooled to 0 °C. Then EDC.HCl (3.95 g, 20.6 mmol) and HOBt (232 mg, 1.72mmol) were added, followed by the dropwise addition of DIPEA (6.00 mL, 34.4 mmol). The reaction mixture was stirred at 0 °C for 2 h, then warmed to rt and stirred for 16 h. The solvent was then removed *in vacuo* and the crude mixture dissolved in Et_2O (300 mL), washed with water (300 mL), $NaHCO_3$ (*aq*) (200 mL), 10% HCl (*aq*) (200 mL), brine (2 × 200 mL), dried (Na_2SO_4), then filtered, and concentrated *in vacuo* to give the desired crude amide product **329** (9.84 g, 99%).

Fully characterised as **331**.

(2*R*)-*N*-((4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylpent-4-ynamide

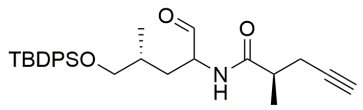


327

(2*R*)-*N*-((4*R*)-1-((*tert*-butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-pentant-2-yl)-2-methyl-4-pentynamide **329** (9.84 g, 17.0 mmol) was dissoved in EtOH (115 mL). PPTS (427 mg, 1.70 mmol) was added and the resultant solution stirred for 72 h. Et_3N (2 mL) was added and the reaction mixture concentrated *in vacuo*, and purified using flash chromatography (silica gel 25 – 50% EtOAc in petroleum ether) to yield the desired product **327** as a colourless oil (7.60 g, 96%).

Fully characterised as **331**.

(2*R*)-*N*-((4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-oxopentan-2-yl)-2-methylpent-4-ynamide

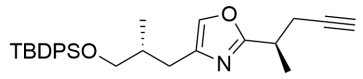


330

(2*R*)-*N*-((4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylpent-4-ynamide **327** (3.53 g, 7.58 mmol) was dissolved in EtOAc (215 mL). IBX (6.37 g, 22.8 mmol) was added and the resultant mixture was heated to reflux and stirred for 3 h. The reaction was then cooled and filtered through a plug of silica using EtOAc/petroleum ether (1:2) as eluent. The eluent was removed *in vacuo* to yield the desired product **330** as a colourless oil (3.51 g, 100%).

Fully characterised as **331**.

4-((*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropyl)-2-((*R*)-pent-4-yn-2-yl)oxazole



331

(2*R*)-*N*-((4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-oxopentan-2-yl)-2-methylpent-4-ynamide **330** (2.04 g, 4.40 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) and cooled to 0 °C. PPh_3 (5.77 g, 22.0 mmol), DTBMP (3.55 g, 17.3 mmol), and $(Cl_2BrC)_2$ (7.16 g, 22.0 mmol) were added and the resultant solution stirred at 0 °C for 4 h. The reaction mixture was then warmed to rt then stirred for 45 min, then DIPEA (7.67 mL, 44.0 mmol) was added dropwise. The reaction mixture was then stirred for 16 h, before being diluted with CH_2Cl_2 (200 mL), washed with NH_4Cl (2 × 100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 5% EtOAc in petroleum ether) gave the desired product **331** as a pale yellow oil (1.60 g, 81%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 – 7.63 (4H, m, ^{Ar}H), 7.45 – 7.35 (6H, m, ^{Ar}H), 7.19 (1H, s, ^{Ar}H), 3.59 – 3.49 (2H, m, OCH_2), 3.19 – 3.09 (1H, m, $CH(CH_3)_3$), 2.72 – 2.63 (2H, m,

CH_2), 2.50 (1H, ddd, *J* = 16.7, 8.3, 2.7 Hz, CH_2), 2.35 (1H, dd, *J* = 14.3, 7.5 Hz, CH_2), 2.11 – 2.03 (1H, m, CH(CH_3)), 1.97 (1H, t, *J* = 2.7 Hz, C≡CH), 1.43 (3H, d, *J* = 7.0 Hz, CH_3), 1.06 (9H, s, SiC(CH_3)$_3$), 0.98 (3H, d, *J* = 6.7 Hz, CH_3).

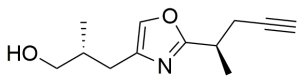
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.0 (N=*C*), 139.24 (^{Ar}C), 135.6 (^{Ar}CH), 134.3 (^{Ar}CH$_{oxazole}$), 134.0 (^{Ar}C), 133.9 (^{Ar}C), 129.5 (^{Ar}CH), 127.6 (^{Ar}CH), 81.5 (*C*≡CH), 70.0 (C≡*C*H), 68.1 (O*C*H$_2$), 35.1 (*C*H), 33.2 (*C*H), 29.8 (*C*H$_2$), 26.9 (SiC(*C*H$_3$)$_3$), 24.3 (*C*H$_2$), 19.3 (Si*C*), 17.5 (*C*H$_3$), 16.7 (*C*H$_3$).

HRMS (ESI) calculated for $C_{28}H_{35}O_2NSiNa$ $(M+Na)^+$: m/z 468.2329, observed 468.2308.

IR ν_{max} (film)/cm^{-1} 3308, 2961, 2932, 2857, 1566, 1462, 1427

$[\alpha]_D^{26}$ +13.8 (c = 1.05, $CHCl_3$).

(*R*)-2-methyl-3-(2-((*R*)-pent-4-yn-2-yl)oxazol-4-yl)propan-1-ol



332

4-((*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropyl)-2-((*R*)-pent-4-yn-2-yl)oxazole **331** (100 mg, 0.22 mmol) was dissolved in anhydrous THF (4 mL), and cooled to 0 °C. TBAF (1M in THF, 0.90 mL, 0.90 mmol) was added slowly, and the resultant solution stirred for 1 h, then warmed to rt and stirred for 16 h. The reaction was quenched with H_2O (10 mL), and extracted with Et_2O (10 mL). The organic extracts were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 50% EtOAc in petroleum ether) gave the desired product **332** as a colourless oil (42 mg, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32 (1H, t, *J* = 0.8 Hz, ^{Ar}H), 3.59 – 3.55 (1H, m, OCH_2), 3.48 – 3.42 (1H, m, OCH_2), 3.20 – 3.12 (1H, m, CH(CH_3)), 2.68 (1H, ddd, *J* = 16.7, 5.9, 2.7 Hz, CH_2C≡C), 2.61 – 2.48 (3H, m, CH_2C≡C + CH_2), 2.06 – 1.98 (1H, m, CH(CH_3)$_3$), 2.00 (1H, t, *J* = 2.7 Hz, C≡CH), 1.44 (3H, d, *J* = 7.0 Hz, CH_3), 0.92 (3H, d, *J* = 6.9 Hz, CH_3).

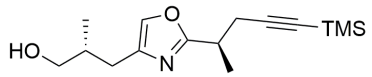
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.3 (^{Ar}CN), 138.3 (^{Ar}CH), 134.6 (^{Ar}C), 81.2 (*C*≡CH), 70.2 (C≡*C*H), 67.3 (O*C*H_2), 35.1 (N=C*C*H(CH_3)), 33.1 (*C*H(CH_3)), 30.0 (*C*H_2), 24.2 (*C*H_2), 17.4 (*C*H_3), 16.8 (*C*H_3).

HRMS (ESI) calculated for $C_{12}H_{17}O_2NNa$ $(M+Na)^+$: m/z 230.1151, observed 230.1147.

IR ν_{max} (film)/cm^{-1} 3304, 2932, 2364, 1568, 1458, 1096.

$[\alpha]_D^{26}$ +10.5 (c = 1.05, $CHCl_3$).

(2*R*)-2-Methyl-3-(2-((2*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)-1,3-oxazol-4-yl)propan-1-ol



326

(*R*)-2-methyl-3-(2-((*R*)-pent-4-yn-2-yl)oxazol-4-yl)propan-1-ol **332** (410 mg, 1.98 mmol) was dissolved in anhydrous THF (15 mL) and cooled to -78 °C. *n*BuLi (2.3 M in hexanes, 1.73 mL, 3.98 mmol) was added dropwise and the resultant solution stirred for 45 min. The dry ice/acetone bath was removed, and the reaction stirred for 10 min. The reaction was cooled down to -78 °C and then TMSCl (0.53 mL, 4.20 mmol) was added dropwise. The reaction was allowed to warm up to rt and was stirred for 16 h. Et_2O (10 mL) and 1M HCl (*aq*) (10 mL) were added and the resultant biphasic mixture stirred for 3 h. The reaction mixture was diluted with Et_2O (15 mL), the organic phase separated, washed with $NaHCO_3$ (*aq*) (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 10 – 40% EtOAc in petroleum ether) to yield the desired product **326** as a pale yellow oil (408 mg, 74% (94% brsm)).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32 (1H, s, ^{Ar}H), 3.62 – 3.51 (1H, m, OCH_2), 3.50 – 3.35 (1H, m, OCH_2), 3.22 – 3.04 (2H, m, O*H* + C*H*(CH_3)), 2.71 (1H, dd, *J* = 16.9, 5.7 Hz, CH_2C≡C), 2.62 – 2.43 (3H, m, CH_2C≡C + CH_2), 2.08 – 1.92 (1H, m, C*H*(CH_3)), 1.43 (3H, d, *J* = 7.0 Hz, CH_3), 0.92 (3H, d, *J* = 6.9 Hz, CH_3), 0.13 (9H, s, Si(CH_3)$_3$).

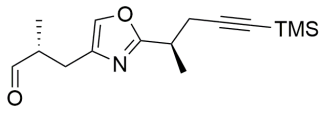
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.4 (^{Ar}C=N), 138.2 (^{Ar}C), 134.5 (^{Ar}CH), 103.9 (*C*≡C), 86.6 (*C*≡C), 67.2 (O*C*H_2), 35.0 (*C*H(CH_3)), 33.3 (*C*H(CH_3), 29.9 (*C*H_2), 25.7 (*C*H_2), 17.4 (*C*H_3), 16.8 (*C*H_3), 0.0 (Si(*C*H_3)$_3$).

HRMS (ESI) calculated for $C_{15}H_{25}O_2NSiNa$ $(M+Na)^+$: m/z 302.1547, observed 302.1542.

IR ν_{max} (film)/cm^{-1} 2960, 2359, 2178, 1724, 1570, 1458, 1250.

$[\alpha]_D^{27}$ +9.8 (c = 1.28, $CHCl_3$).

(*R*)-2-Methyl-3-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propanal



325

(2*R*)-2-Methyl-3-(2-((2*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)-1,3-oxazol-4-yl)propan-1-ol **326** (408 mg, 1.46 mmol) was dissolved in anhydrous THF (11 mL). IBX (824 mg, 2.94 mmol) and DMSO (6 mL) were added and the resultant mixture was stirred for 16 h. H_2O (6 mL) was added and the reaction mixture stirred for 4 h, a white precipitate was formed. The reaction mixture was then filtered, washed with Et_2O (50 mL) and the aqueous phase extracted with Et_2O (30 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified *via* flash chromatography (silica gel, 15% EtOAc in petroleum ether) to yield the desired product **325** as a colourless oil (357 mg, 88%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.73 (1H, d, *J* = 1.0 Hz, C(O)*H*), 7.32 (1H, s, ^{Ar}H), 3.18 – 3.09 (1H, m, C*H*(CH_3)), 2.93 (1H, ddd, *J* = 14.8, 6.5, 0.7 Hz, CH_2), 283 – 2.75 (1H, m, C*H*(CH_3)), 2.70 (1H, dd, *J* = 16.8, 5.7 Hz, CH_2), 2.57 (1H, ddd, *J* = 14.8, 7.2, 0.8 Hz, CH_2), 2.52 (1H, dd, *J* = 16.8, 8.3 Hz, *C*H_2), 1.42 (3H, d, *J* = 7.0 Hz, CH_3), 1.13 (3H, d, *J* = 7.1 Hz, CH_3), 0.12 (9H, s, Si(CH_3)$_3$).

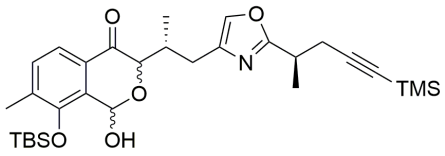
^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.0 (*C*=O), 166.6 (^{Ar}CN), 137.5 (^{Ar}C), 134.6(^{Ar}CH), 103.4 (*C*≡CSi), 86.6 (C≡*C*Si), 45.4 (*C*H), 33.4 (*C*H), 27.1 (*C*H_2), 25.7 (*C*H_2), 17.5 (*C*H_3), 13.3 (*C*H_3), 0.0 (Si(*C*H_3)$_3$).

HRMS (ESI) calculated for $C_{15}H_{23}O_2NSiNa$ $(M+Na)^+$: m/z 300.1390, observed 300.1378.

IR ν_{max} (film)/cm^{-1} 2963, 2178, 1724, 1569, 1250.

$[\alpha]_D^{27}$ -8.2 (c = 0.63, $CHCl_3$).

8-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-4-one



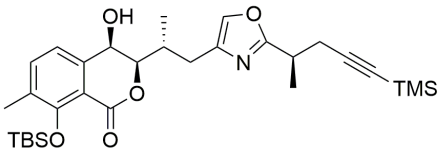
334

tert-Butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yl)oxy)dimethylsilane **159** (444 mg, 1.51 mmol) was dissolved in anhydrous THF (10 mL), and cooled to 0 °C. Freshly distilled $^{i}Pr_2NH$ (0.42 mL, 3.02 mmol) was added, and the resultant solution stirred for 10 min. MeLi (1.60 M in Et_2O, 1.89 mL, 3.02 mmol) was added dropwise, and the resultant mixture was stirred for 30 min at 0 °C before being cooled down to -78 °C. (*R*)-2-Methyl-3-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propanal **325** (208 mg, 0.75 mmol) in anhydrous THF (0.20 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h at -78 °C, before being warmed to 0 °C. H_2O (1 mL) was added, then the reaction mixture was diluted with Et_2O (10 mL), washed with H_2O (10 mL), brine (10 mL), the organic dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the α-hydroxy-isobenzofuran intermediate. The crude intermediate was then immediately dissolved in anhydrous CH_2Cl_2 (10 mL), and cooled to 0 °C. *m*CPBA (77% w/w, 168 mg, 0.75 mmol) was added and the resultant solution stirred at 0 °C for 2 h. The reaction was then quenched with $NaHCO_3$ (*aq*) (10 mL), extracted with CH_2Cl_2 (2 × 10 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*. Purification *via* flash column chromatography (silica gel 10 – 40% EtOAc in petroleum ether) gave the desired lactol product **334** as an orange oil (269 mg, 65%) as a mixture of diastereomers which were carried through to the subsequent step.

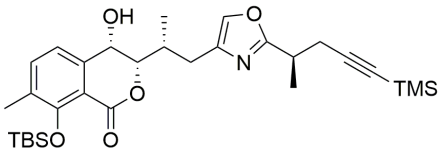
HRMS (ESI) calculated for $C_{30}H_{45}O_5NSi_2Na$ $(M+Na)^+$: m/z 578.2728, observed 578.2700

Fully characterised as **335** and **336**.

8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one



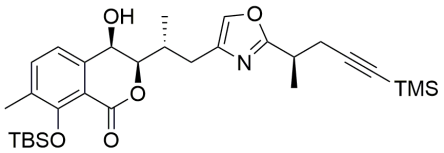
335



336

8-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-4-one **334** (130 mg, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL). The resultant solution was treated with BAIB (238 mg, 0.74 mmol) then TEMPO (3.6 mg, 23 µmol) and stirred for 16 h. The reaction mixture was then cooled to -78 °C and $NaBH_4$ (11.3 mg, 0.30 mmol) in anhydrous MeOH (0.5 mL) was added. The resultant mixture was stirred for 1 h, then warmed to 0 °C, and quenched with H_2O (1 mL) and 10% (*aq*) citric acid solution (1 mL). The resultant mixture was then extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel 10 – 40 % EtOAc in petroleum ether) gave the desired products as pale yellow oils in a separable mixture of diastereomers (2.8:1, **335**:**336**) (115mg, 90%).

(3*R*,4*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one



335

(85 mg, 67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 7.36 (1H, s, ^{Ar}H), 6.95 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 4.68 (1H, d, *J* = 6.4 Hz, C*H*(OH)), 4.09 (1H, dd, *J* = 9.2, 3.2 Hz, C*H*(O_2C)), 3.17 – 3.08 (1H, m, C*H*(CH_3)), 3.02 (1H, dd, *J* = 14.7, 3.3 Hz, CH_2C≡C), 2.74 – 2.66 (2H,

m, C*H*(CH_3), C*H*$_2$), 2.56 – 2.42 (2H, m, C*H*$_2$C≡C, C*H*$_2$), 2.28 (3H, s, ^{Ar}C*H*$_3$), 2.18 (1H, dd, *J* = 11.2, 7.2 Hz, *H*), 1.41 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 1.13 (3H, d, *J* = 6.9 Hz, *C*H$_3$), 1.06 (9H, s, SiC(C*H*$_3$)$_3$), 0.22 (3H, s, Si(C*H*$_3$)$_2$), 0.13 (3H, s, Si(C*H*$_3$)$_2$), 0.11 (9H, s, Si(C*H*$_3$)$_3$).

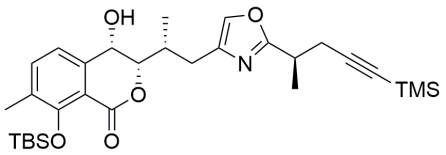
^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2 (*C*=O), 162.9 (^{Ar}*C*N), 155.3 (^{Ar}*C*), 139.6 (^{Ar}*C*), 138.0 (^{Ar}*C*), 136.3 (^{Ar}*C*H), 134.9 (^{Ar}*C*H$_{ox}$), 132.7 (^{Ar}*C*), 120.4 (^{Ar}*C*H), 115.8 (^{Ar}*C*H), 104.1 (*C*≡C), 86.4 (*C*≡C), 82.3 (*C*H(O$_2$C)), 66.3 (*C*H(OH)), 33.3 (*C*H), 33.1 (*C*H), 28.0 (*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 25.7 (*C*H$_2$), 18.6 (*C*H$_3$), 17.5 (*C*H$_3$), 0.00 (Si(*C*H$_3$)$_3$), -3.66 (Si(*C*H$_3$)$_2$), -3.69 (Si(*C*H$_3$)$_2$).

HRMS (ESI) calculated for $C_{30}H_{45}O_5NSi_2Na$ $(M+Na)^+$: m/z 578.2728, observed 578.2704

IR ν_{max} (film)/cm^{-1} 2965, 2932, 2363, 1734, 1719, 1558, 1251

$[\alpha]_D^{28}$ -3.9 (c = 1.86, $CHCl_3$).

(3*S*,4*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one



336

(30 mg, 23%)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (1H, d, *J* = 7.9 Hz, ^{Ar}*H*), 7.38 (1H, s, ^{Ar}*H*), 7.28 (1H, d, *J* = 7.9 Hz, ^{Ar}*H*), 4.72 (1H, d, *J* = 10.4 Hz, C*H*(OH)), 4.10 (1H, dd, *J* = 10.5, 2.1 Hz, C*H*(O$_2$C)), 3.22 – 3.14 (1H, m, C*H*(CH_3)), 3.05 (1H, dd, *J* = 16.1, 6.8 Hz, C*H*$_2$C≡C), 2.73 – 2.66 (1H, m, C*H*$_2$), 2.61 – 2.51 (2H, m, C*H*$_2$C≡C, C*H*(CH_3)), 2.40 (1H, dd, *J* = 16.3, 3.6 Hz, C*H*$_2$), 2.27 (3H, s, ^{Ar}C*H*$_3$), 1.47 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 1.25 (3H, d, *J* = 7.7 Hz, C*H*$_3$), 1.05 (9H, s, SiC(C*H*$_3$)$_3$), 0.21 (3H, s, Si(C*H*$_3$)$_2$), 0.14 (3H, s, Si(C*H*$_3$)$_2$), 0.13 (9H, s, Si(C*H*$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3 (*C*=O), 163.4 (^{Ar}*C*N), 154.7 (^{Ar}*C*), 142.5 (^{Ar}*C*), 139.1 (^{Ar}*C*), 136.2 (^{Ar}*C*H), 134.2 (^{Ar}*C*H$_{ox}$), 130.2 (^{Ar}*C*), 116.7 (^{Ar}*C*H), 115.0 (^{Ar}*C*), 103.4 (*C*≡C), 87.2 (*C*≡C), 85.5 (*C*H(O$_2$C)), 65.4 (*C*H(OH)), 33.4 (*C*H), 31.6 (*C*H), 26.0 (SiC(*C*H$_3$)$_3$), 25.6

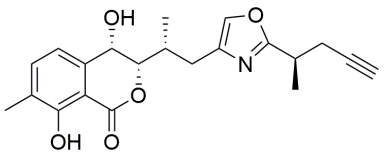
(CH_2), 25.4 (CH_2), 18.6 (CH_3), 17.3 (CH_3), 0.00 ($Si(CH_3)_3$), -3.66 ($Si(CH_3)_2$), -3.69 ($Si(CH_3)_2$).

HRMS (ESI) calculated for $C_{30}H_{45}O_5NSi_2Na$ $(M+Na)^+$: 578.2728, observed 578.2705

IR ν_{max} (film)/cm^{-1} 3021, 2359, 1753, 1736, 1726, 1366

$[\alpha]_D^{29}$ -61.9 (c = 0.91, $CHCl_3$).

(3*S*,4*S*)-4,8-Dihydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one



337

(3*S*,4*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one **336** (30 mg, 54.0 µmol) was dissolved in anhydrous THF (3 mL) and cooled to 0 °C. TBAF (1M in THF, 108 µL, 108 µmol) was added dropwise, and the resultant mixture stirred for 10 min. H_2O (2 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 3 mL), the combined organic extracts washed with brine (3 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 40% EtOAc in petroleum ether) gave the desired product **337** as a colourless oil (17 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.05 (1H, s, ^{Ar}OH), 7.40 (1H, d, *J* = 7.7 Hz, ^{Ar}H), 7.39 (1H, s, ^{Ar}H), 7.12 (1H, d, *J* = 7.6 Hz, ^{Ar}H), 6.05 (1H, d, *J* = 6.1 Hz, O*H*), 4.86 (1H, dd, *J* = 10.3, 5.9 Hz, C*H*(OH)), 4.31 (1H, dt, *J* = 10.8, 2.5 Hz, C*H*(O_2C)), 3.23 – 3.15 (1H, m, C*H*(CH_3)), 3.00 (1H, ddd, *J* = 16.0, 7.7, 1.1 Hz, CH_2C≡C), 2.69 – 2.59 (2H, m, CH_2, C*H*(CH_3)), 2.58 – 2.52 (1H, m, CH_2), 2.50 – 2.44 (1H, m, CH_2C≡C), 2.27 (3H, s, $^{Ar}CH_3$), 1.93 (1H, t, *J* = 2.6 Hz, C≡C*H*), 1.45 (3H, d, *J* = 7.0 Hz, CH_3), 1.26 (3H, d, *J* = 7.2 Hz, CH_3).

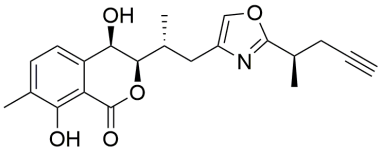
^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1 (*C*=O), 167.0 (^{Ar}CN), 160.1 (^{Ar}C(OH)), 141.2 (^{Ar}C), 138.8 (^{Ar}C), 137.4 (^{Ar}CH), 134.5 (^{Ar}CH), 125.6 (^{Ar}C), 114.3 (^{Ar}CH), 105.9 (^{Ar}C), 86.6 (*C*H(O_2C)), 80.7 (*C*≡CH), 70.5 (C≡*C*H), 64.7 (*C*H(OH)), 33.1 (*C*H(CH_3)), 32.4 (*C*H(CH_3)), 26.0 (*C*H_2C≡C), 24.1 (*C*H_2), 18.2 (*C*H_3), 17.4 (*C*H_3), 15.5 ($^{Ar}CCH_3$).

HRMS (ESI) calculated for $C_{21}H_{23}O_5NNa$ (M+Na)+: m/z 392.1468, observed 392.1455.

IR vmax (film)/cm-1 3298, 2934, 1676, 1424, 1250, 1136.

$[\alpha]_D^{29}$ -52.0 (c = 0.23, $CHCl_3$).

(3*R*,4*R*)-4,8-Dihydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one



338

(3*R*,4*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((*R*)-1-(2-((*R*)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one **335** (44 mg, 79.2 µmol) was dissolved in anhydrous THF (3 mL) and cooled to 0 °C. TBAF (1M in THF, 0.16 mL, 0.16 mmol) was added dropwise, and the resultant mixture stirred for 10 min. H_2O (2 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 3 mL), the combined organic extracts washed with brine (3 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 40% EtOAc in petroleum ether) gave the desired product **338** as a colourless oil (29 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.26 (1H, s, ^{Ar}OH), 7.39 (1H, d, *J* = 7.2 Hz, ^{Ar}H), 7.38 (1H, s, ^{Ar}H), 6.83 (1H, d, *J* = 7.4 Hz, ^{Ar}H), 4.73 (1H, d, *J* = 5.0 Hz, C*H*(OH)), 4.24 (1H, dd, *J* = 8.6, 1.5 Hz, C*H*(O_2C)), 3.17 – 3.06 (2H, m, C*H*(CH_3), CH_2), 2.69 – 2.53 (3H, m, CH_2C≡C, C*H*(CH_3), CH_2), 2.49 (1H, ddd, *J* = 16.7, 8.0, 2.6 Hz, CH_2C≡C), 2.29 (3H, s, ^{Ar}CCH_3), 1.95 (1H, br s, C≡C*H*), 1.67 (1H, br s, O*H*), 1.42 (3H, d, *J* = 7.0 Hz, CH_3), 1.12 (3H, *J* = 6.6 Hz, CH_3).

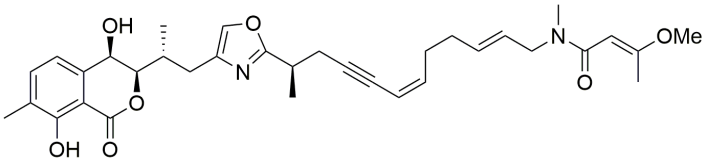
^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6 (*C*=O), 166.2 (^{Ar}*C*N), 160.5 (^{Ar}*C*), 138.2 (^{Ar}*C*), 138.1 (^{Ar}*C*), 137.3 (^{Ar}*C*H), 135.0 (^{Ar}*C*H), 128.0 (^{Ar}*C*), 117.8 (^{Ar}*C*H), 106.5 (^{Ar}*C*), 85.1 (*C*H(O_2C)), 81.4 (*C*≡CH), 70.0 (C≡*C*H), 65.3 (*C*H(OH)), 33.5 (*C*H(CH_3)), 33.1 (*C*H(CH_3)), 28.2 (*C*H_2), 24.3 (*C*H_2C≡C), 17.5 (*C*H_3), 15.7 (^{Ar}C*C*H3), 15.5 (*C*H_3).

HRMS (ESI) calculated for $C_{21}H_{23}O_5NNa$ $(M+Na)^+$: m/z 392.1468, observed 392.1456

IR ν_{max} (film)/cm^{-1} 3641, 3300, 2951, 2854, 1729, 1668, 1483

$[\alpha]_D^{29}$ +16.2 (c = 0.64, $CHCl_3$).

(*E*)-*N*-((*R*,2*E*,6*Z*)-11-(4-((*R*)-2-((3*R*,4*R*)-4,8-Dihydroxy-7-methyl-1-oxoisochroman-3-yl)propyl)oxazol-2-yl)dodeca-2,6-dien-8-yn-1-yl)-3-methoxy-*N*-methylbut-2-enamide



339

Acetylene **338** (15 mg, 40.6 µmol) and vinyl iodide **40** (17 mg, 48.7 µmol) were azeotroped with toluene, then dissolved in anhydrous, degassed MeCN (1.5 mL) in the absence of light, and cooled to 0 °C. $Pd(PPh_3)_2Cl_2$ (2.8 mg, 4.0 µmol) and CuI (1.4 mg, 7.4 µmol) were added, followed by dropwise addition of Et_3N (25 µL, 180 µmol). The resultant mixture was stirred for 1 h at 0 °C, then warmed to rt and stirred for 19 h. The reaction mixture was diluted with EtOAc (5 mL), washed with H_2O (2 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification using flash chromatography (silica gel, 50 – 80% EtOAc in petroleum ether) gave the desired product as a yellow oil (17 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.28 (1H, s, ^{Ar}OH), 7.38 (1H, d, *J* = 7.4 Hz, ^{Ar}H), 7.38 (1H, s, ^{Ar}H), 6.84 (1H, d, *J* = 7.4 Hz, ^{Ar}H), 5.77 (1H, dd, *J* = 15.0, 7.2 Hz, *H*C=CH), 5.57 (1H, dt, *J* = 15.4, 6.5 Hz, *H*C=CH), 5.49 – 5.37 (2H, m, *H*C=CH), 5.15 (1H, s, *H*C=C), 4.73 (1H, br s, C*H*(OH)), 4.22 (1H, d, *J* = 8.7 Hz, C*H*(O_2C)), 3.98 (1H, br s, CH_2N), 3.88 (1H, br s, CH_2N), 3.59 (3H, br s, OCH_3), 3.22 – 3.08 (2H, m, C*H*(CH_3) + CH_2), 2.94 (3H, s, NCH_3), 2.80 (1H, dd, *J* = 16.9, 5.6 Hz, CH_2C≡C), 2.75 – 2.65 (1H, m, CH_2C≡C), 2.62 – 2.48 (2H, m, C*H*(CH_3) + CH_2), 2.33 – 2.25 (2H, m, CH_2), 2.28 (3H, s, ^{Ar}CCH_3), 2.20 – 2.05 (5H, m, C=C(CH_3) + CH_2), 1.43 (3H, d, *J* = 7.0 Hz, CH_3), 1.12 (3H, d, *J* = 6.7 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6 (*C*=O), 168.6 (*C*=O), 166.3 (HC=*C*(OMe)), 160.3 (*C*), 142.2 (H*C*=C), 138.4 (^{Ar}C), 138.3 (^{Ar}C), 137.2 (^{Ar}CH), 134.8 (^{Ar}CH), 132.8 (H*C*=C), 127.6 (^{Ar}C), 125.8 (^{Ar}CH), 125.1 (H*C*=C), 117.9 (^{Ar}CH), 109.6 (H*C*=C), 106.6 (^{Ar}C), 91.2 (H*C*=C(OMe)), 85.3 (*C*H(O_2C)), 78.9 (*C*≡C), 77.7 (*C*≡C), 65.1 (*C*H(OH)), 54.9 (O*C*H_3), 52.2 (*C*H_2N), 33.6 (*C*H(CH_3)), 33.5 (*C*H(CH_3)), 31.4 (*C*H_2), 29.6 (*C*H_2), 28.4 (*C*H_2), 25.6 (*C*H_2), 18.7 (*C*H_3), 17.7 (*C*H_3), 15.7 (*C*H_3), 15.4 (*C*H_3).

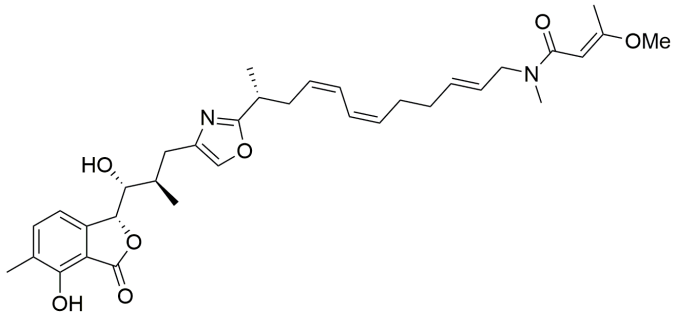
N.B. *C*H_3N *not observed*

IR ν_{max} (film)/cm^{-1} 3664, 2916, 2849, 2359, 1726, 1691, 1631, 1583, 1427.

HRMS (ESI) calculated for $C_{34}H_{42}O_7N_2Na$ $(M+Na)^+$: m/z 613.2884, observed 613.2866.

$[\alpha]_D^{29}$ +11.8 (c = 0.88, $CHCl_3$).

(*E*)-*N*-((R,2*E*,6*Z*,8*Z*)-11-(4-((2*R*,3*R*)-3-Hydroxy-3-((*R*)-4-hydroxy-5-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2-methylpropyl)oxazol-2-yl)dodeca-2,6,8-trien-1-yl)-3-methoxy-*N*-methylbut-2-enamide



341

$Ni(OAc)_2.4H_2O$ (21.5 mg, 86.4 µmol) was dissolved in degassed EtOH (2 mL), under an argon atmosphere. $NaBH_4$ (2.8 mg, 74.0 µmol) was added and the reaction mixture turned black, and was stirred for 2 min, before being placed under a hydrogen atmosphere. EDA (57.8 µL, 0.86 mmol) was added, followed by a solution of enyne **339** (14.1 mg, 23.9 µmol) in degassed EtOH (0.5 mL). The resultant mixture was stirred for 30 min, under a hydrogen atmosphere, then filtered through celite, and washed with EtOH (10 mL). then filtered through a plug of silica uing 5% MeOH in CH_2Cl_2 as eluent. The solvent was removed *in vacuo* to give the title compound **341** as a clear oil (9.4 mg, 66%).

^{1}H NMR (400 MHz, acetone-d_6) δ: 8.23 (1H, br s, ^{Ar}O*H*), 7.59 (1H, s, ^{Ar}*H*), 7.46 (1H, d, *J* = 7.4 Hz, ^{Ar}*H*), 7.03 (1H, d, *J* = 7.4 Hz, ^{Ar}*H*), 6.34 – 6.23 (2H, m, C*H*=CH), 5.71 (1H, s, C*H*(CO)N), 5.63 – 5.55 (1H, m, C*H*=CH), 5.49 – 5.32 (3H, m, C*H*=H), 4.34 (1H, d, *J* = 7.2 Hz, C*H*(O_2C)), 3.90 (2H, d, *J* = 5.4 Hz, CH_2N), 3.82 (1H, t, *J* = 7.2 Hz, C*H*(OH)), 3.59 (3H, br s, OCH_3), 3.04 – 2.99 (1H, m, C*H*(CH_3)), 2.95 – 2.82 (4H, m, CH_2), 2.78 (3H, s, NCH_3), 2.66 – 2.57 (1H, m, C*H*(CH_3)), 2.53 – 2.47 (2H, m, CH_2), 2.31 – 2.23 (2H, m, CH_2), 2.24 (3H, s, ^{Ar}CH_3), 2.12 (3H, s, C=CCH_3), 1.29 (3H, d, *J* = 6.7 Hz, CH_3), 1.03 (3H, d, *J* = 6.6 Hz, CH_3).

^{13}C NMR (100 MHz, acetone-d_6) δ: 172.8 (*C*), 171.0 (*C*), 168.1 (*C*), 155.0 (*C*), 148.1 (*C*), 139.6 (*C*), 138.5 (*C*H), 135.9 (*C*H), 135.9 (*C*), 132.5 (*C*H), 129.3 (*C*H), 127.0 (*C*), 126.4 (*C*H), 125.2 (*C*), 124.8 (*C*H), 123.0 (*C*H), 114.3 (*C*H), 112.9 (*C*), 92.3 (*C*H(CO)N), 83.6 (*C*H(O_2C)), 76.0 (*C*H(OH)), 55.4 (O*C*H_3), 49.9 (N*C*H_2), 37.0 (*C*H(CH_3)), 34.7 (*C*H(CH_3)), 33.7 (*C*H_2), 33.0 (*C*H_2), 28.0 (*C*H_2), 27.8 (*C*H_2), 18.8 (*C*H_3), 18.4 (*C*H_3), 16.7 (*C*H_3), 14.9 (*C*H_3).

N.B. *C*H_3N *not observed*

HRMS (ESI) calculated for $C_{34}H_{44}O_7N_2Na$ $(M+Na)^+$: m/z 615.3041, observed 615.3014.

IR ν_{max} (film)/cm^{-1} 3422, 2970, 2930, 2860, 2367, 2340, 1732, 1643, 1601, 1574, 1454, 1439, 1381, 1240, 1107.

$[\alpha]_D^{23}$ -8.8 (c = 0.68, $CHCl_3$).

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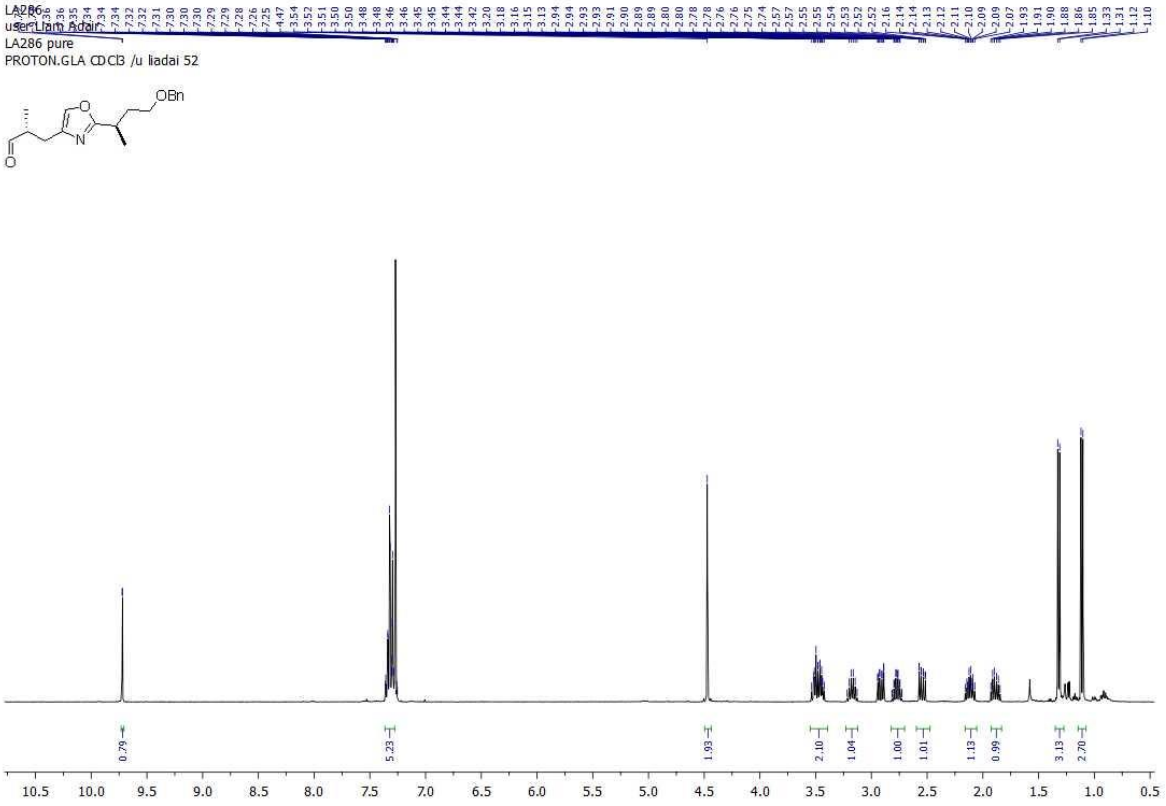
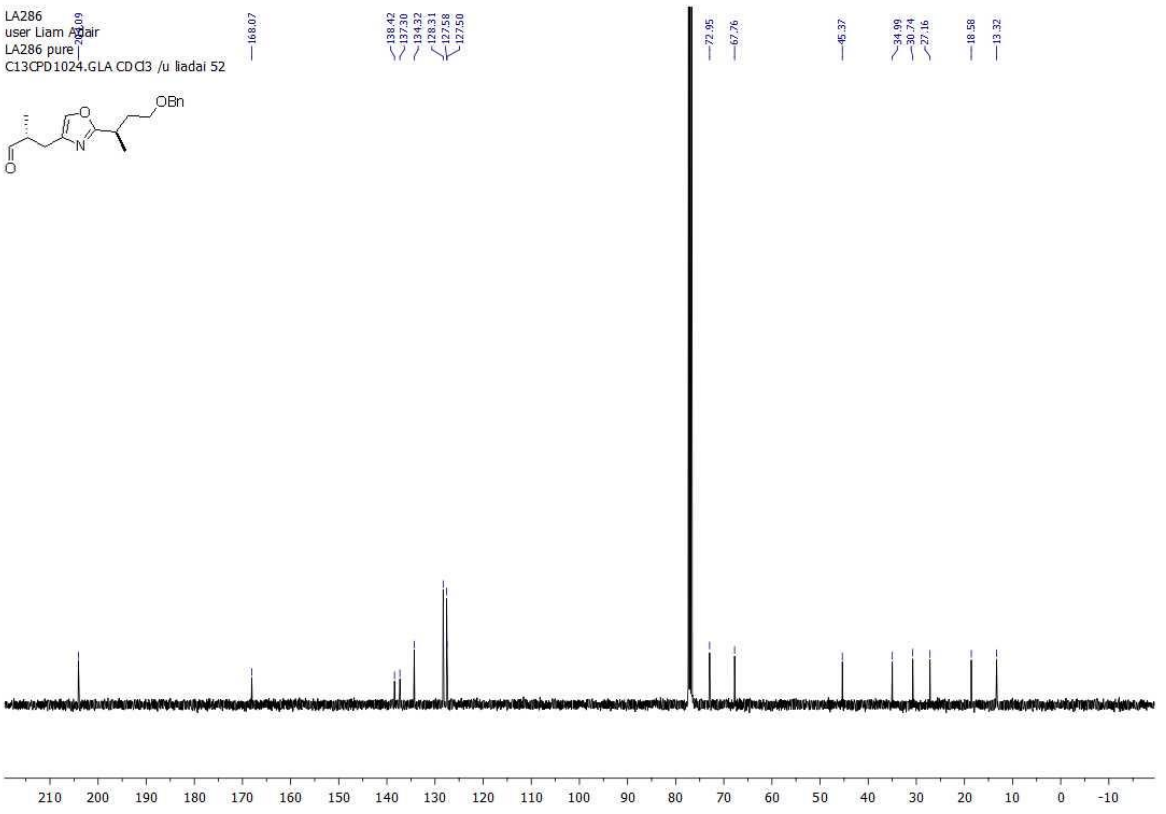
13 APPENDICES

(2*R*)-3-(2-((2*R*)-4-(Benzyloxy)butan-2-yl)-1,3-oxazol-4-yl)-2-methylpropanal 281





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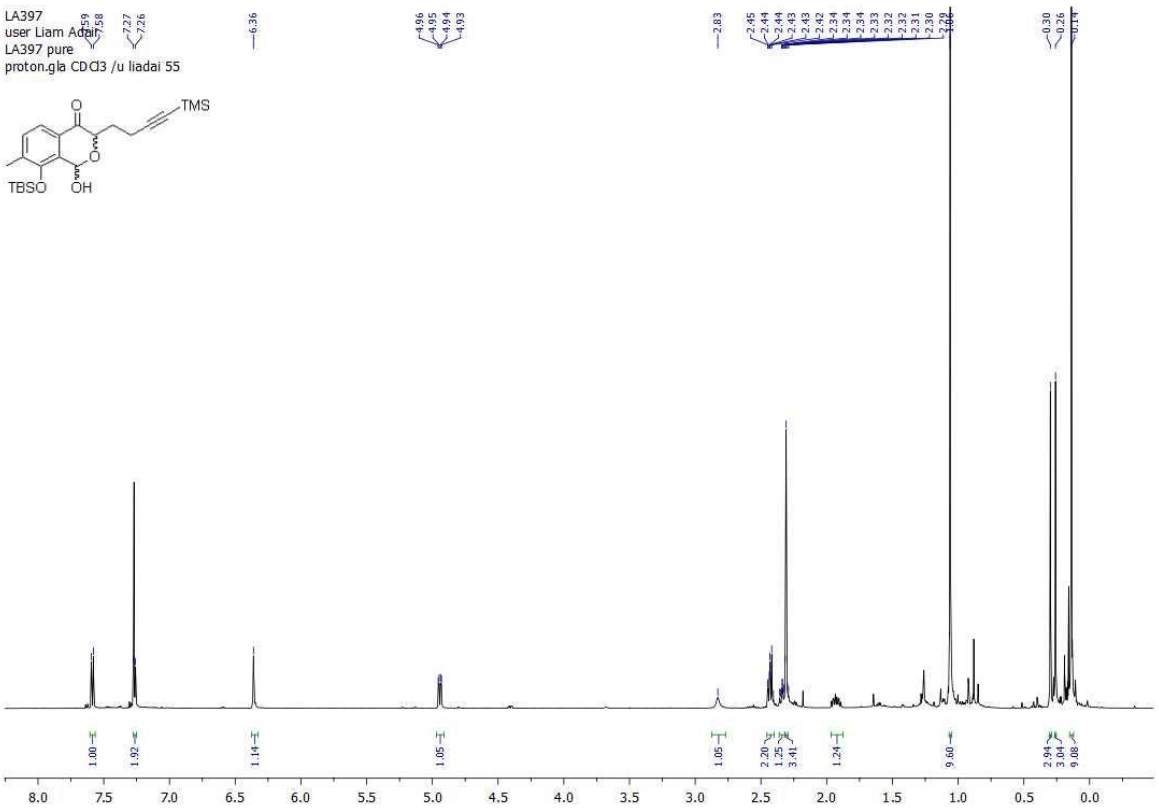

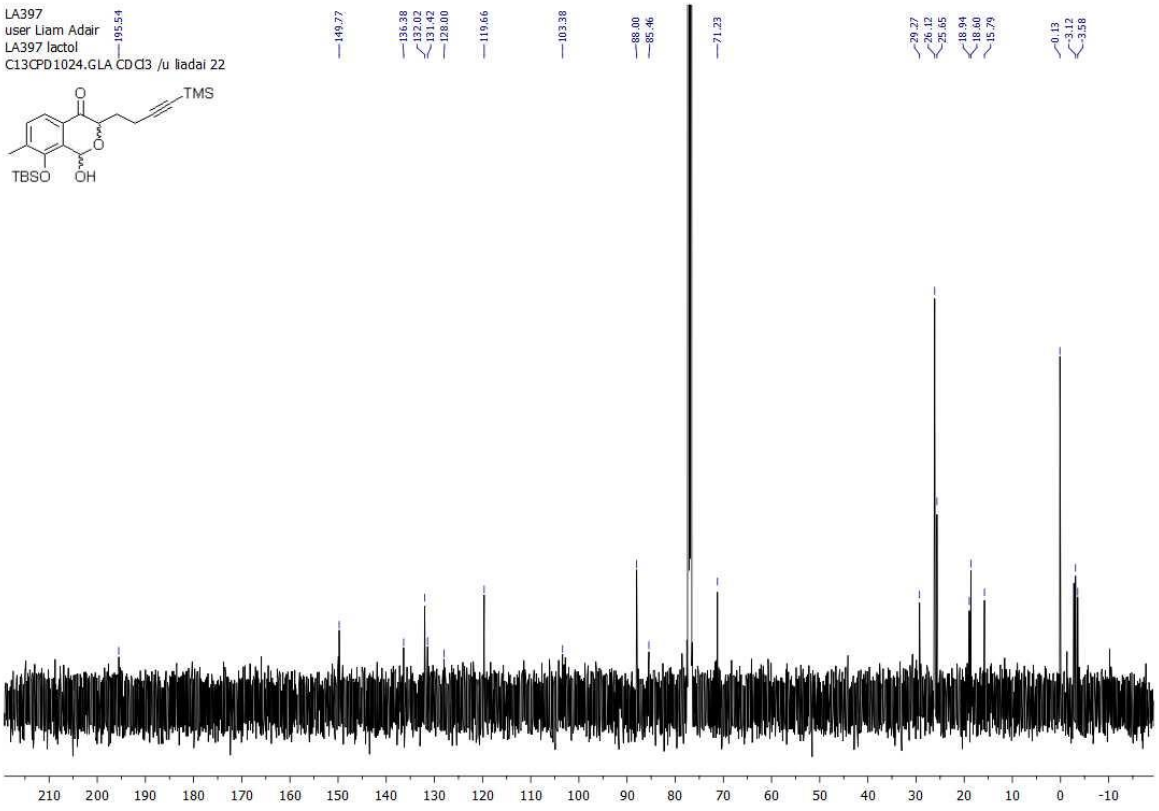

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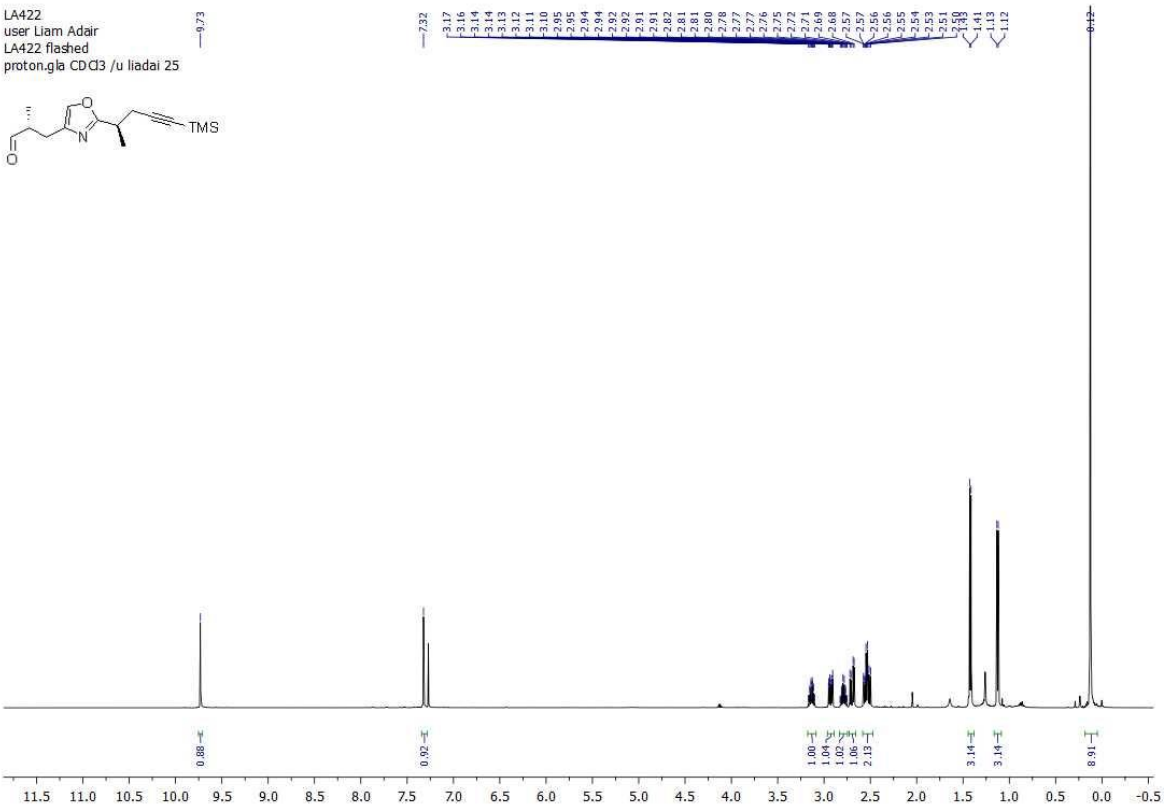

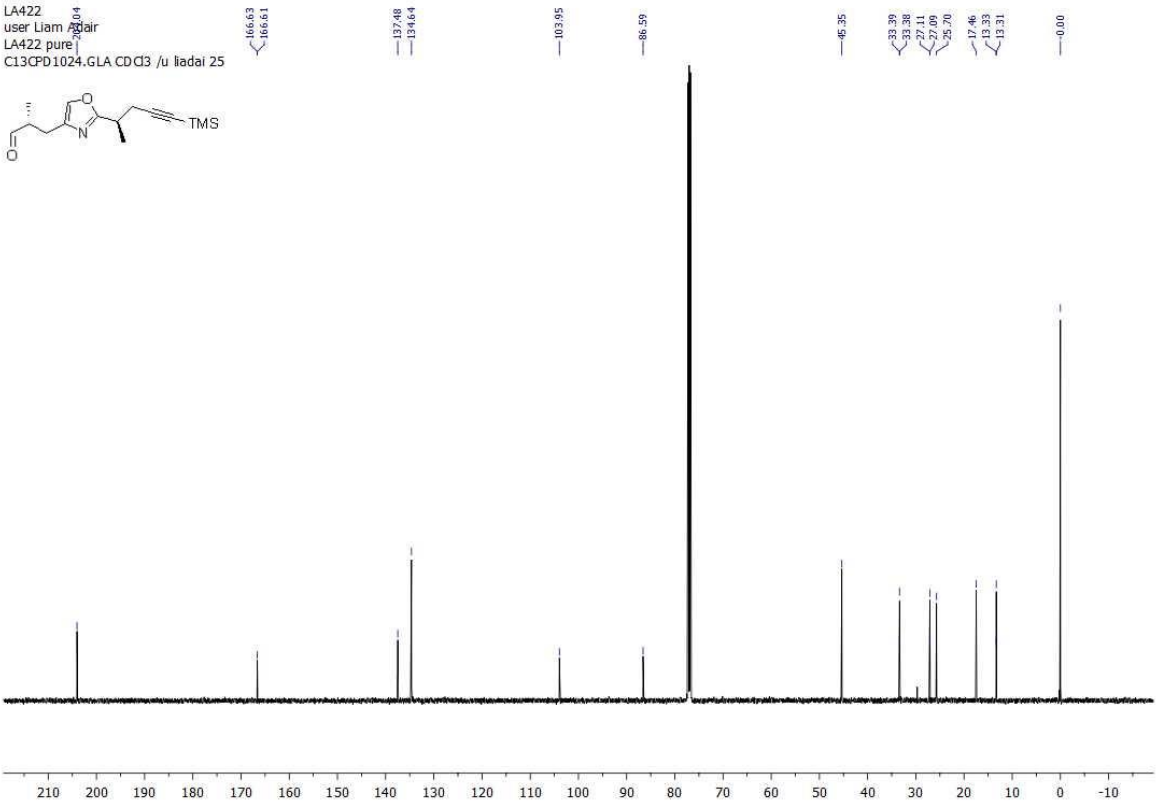

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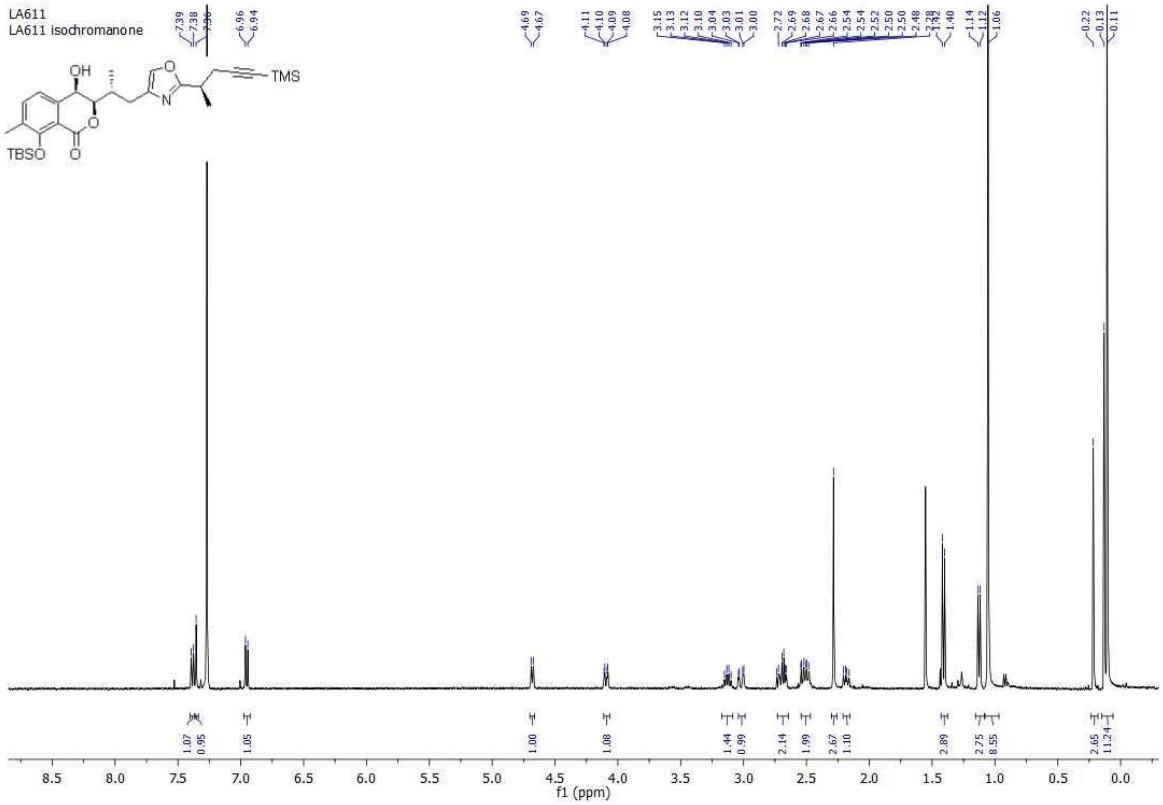

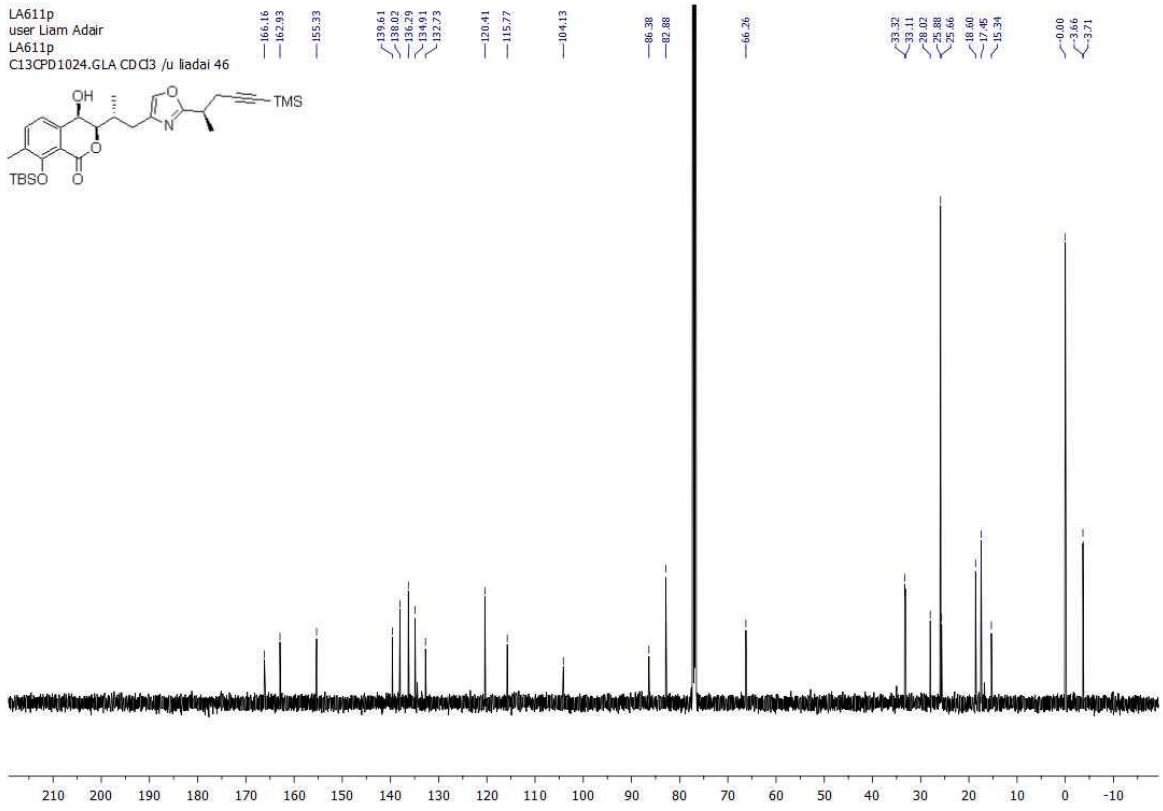

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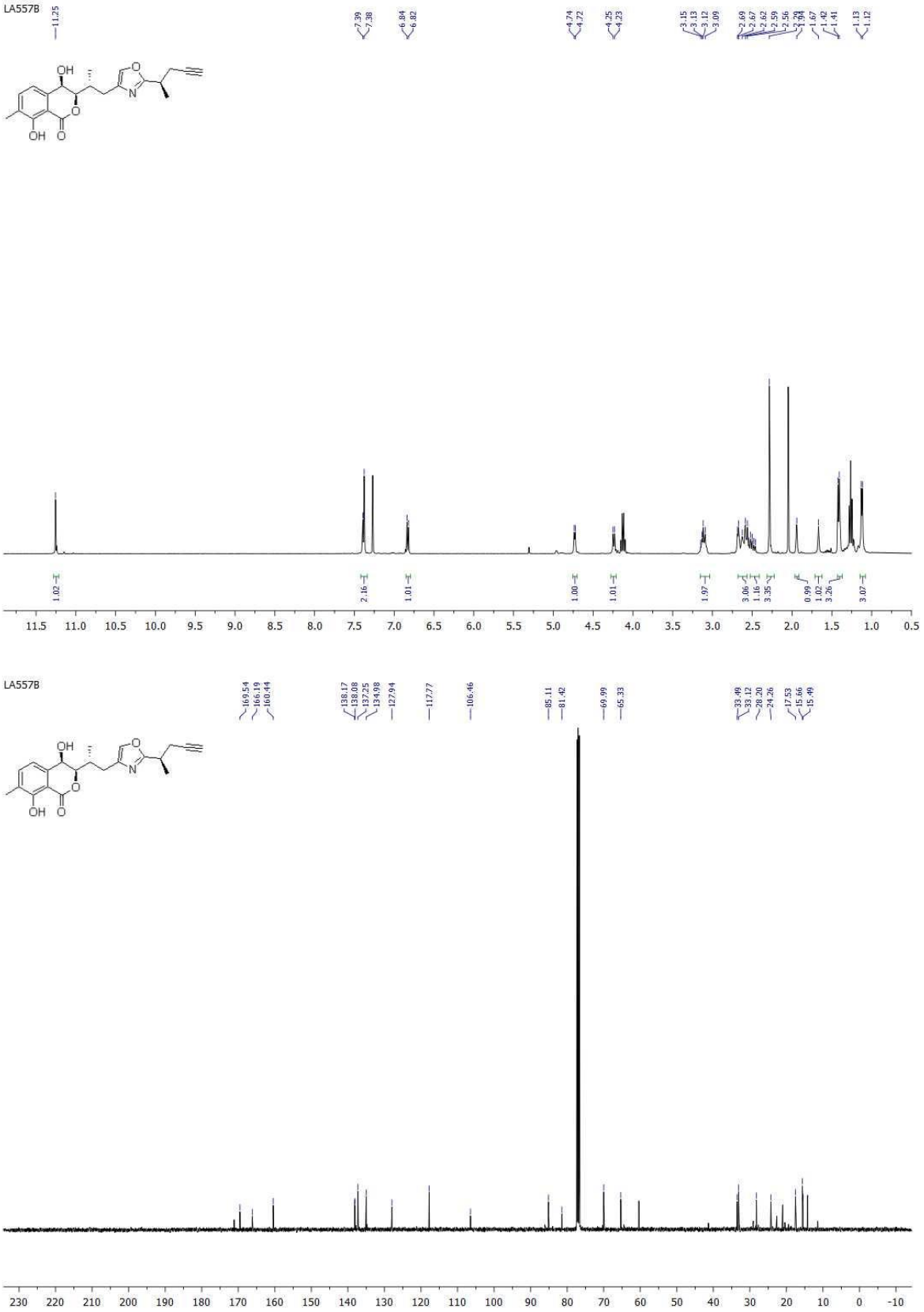

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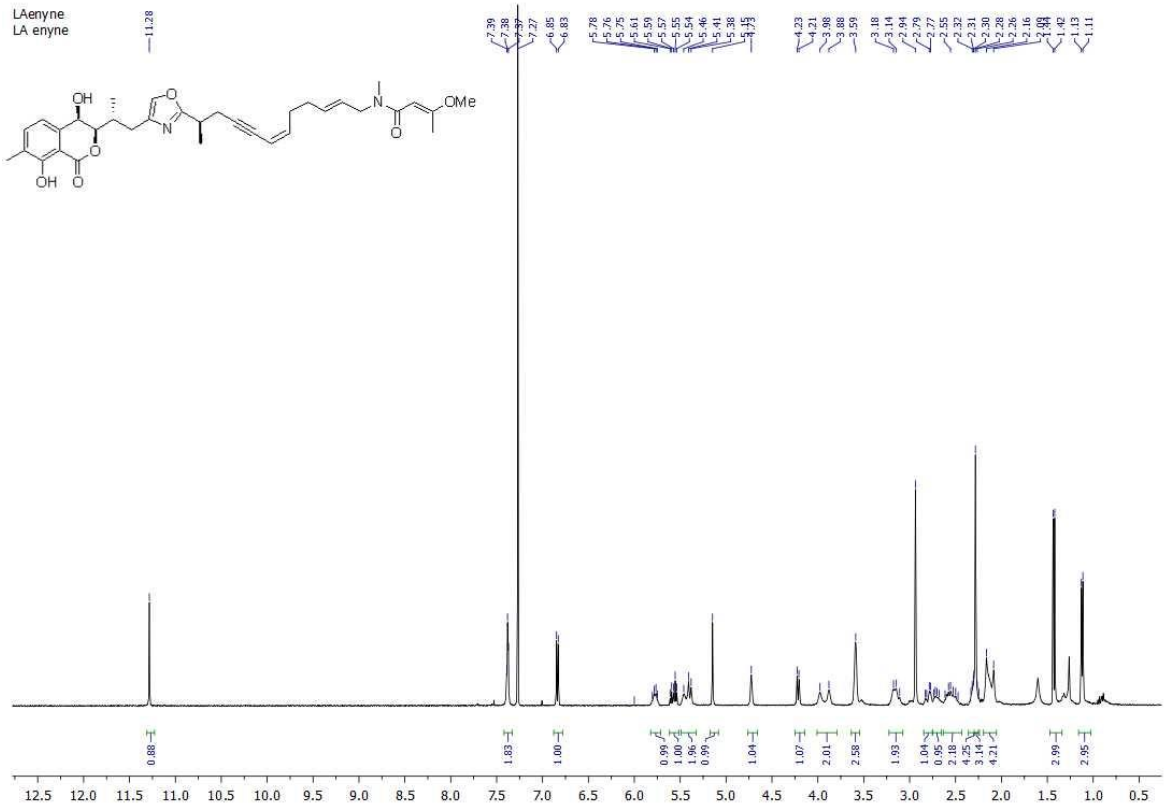
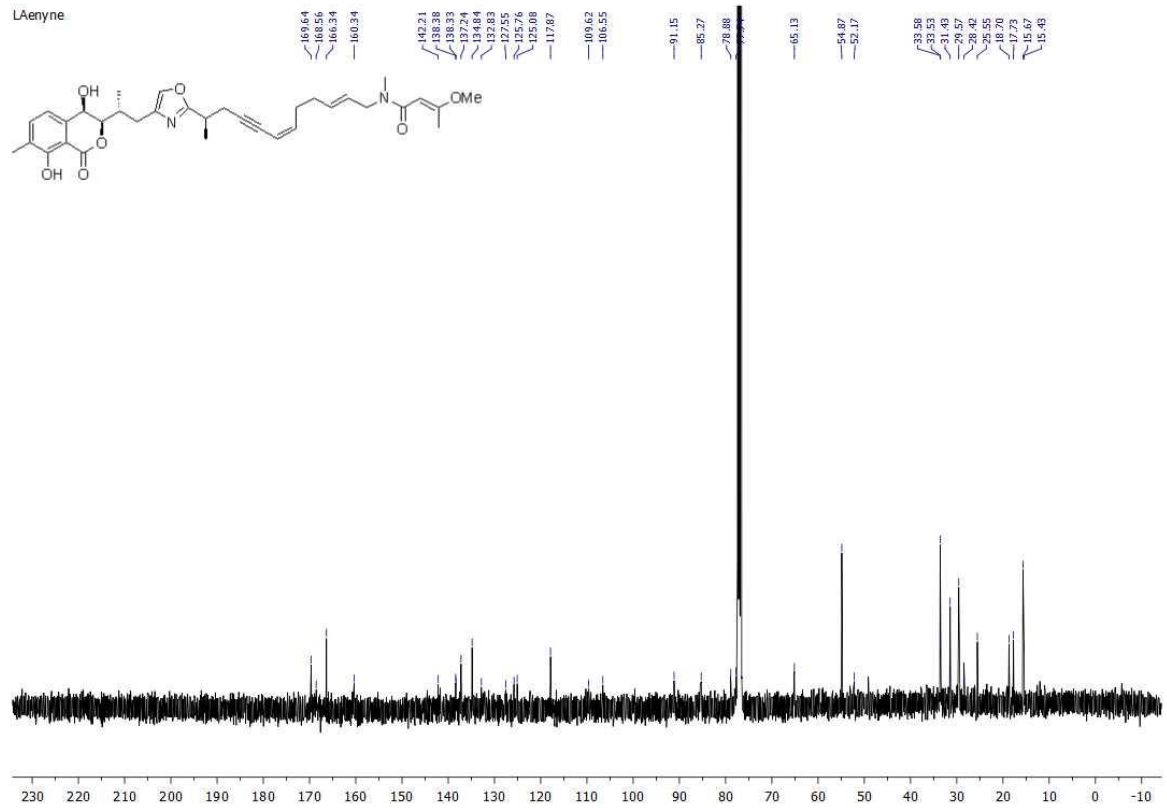
339





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