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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.

![Chemical structure of Ajudazol B](image1)

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.

![Chemical structure of Synthesis](image2)

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

![Chemical structure of Isomer](image3)
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In memory of Arthur Burgoyne
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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-(Diethoxypyrophoryloxy)-1,2,3-benzotriazin-4(3H)-one

DIAD: Diisopropyl azodicarboxylate

DIBALH: Diisobutylaluminium hydride

DIPEA: N,N-Diisopropylethylamine

DMAD: Dimethyl acetylendicarb Oxylate

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-(1H-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
KHMDMS: Potassium bis(trimethylsilyl)amide
LDA: Lithium diisopropylamide
m: Multiplet
mCPBA: 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 difluorotrimethylsilylate

TBAF: Tetra-\( n \)-butylammonium fluoride

TBDPS: \textit{tert}-Butyldiphenyl silyl

TBS: \textit{tert}-Butyldimethyl silyl

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

TES: Triethyilsilyl

TESOTf: Triethyilsilyl 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

\( \mu \text{L} \): Microlitre
1 INTRODUCTION

1.1 MYXOBACTERIA

Myxobacteria are an order of Gram-negative bacteria that have been studied extensively.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[1, 3]}

![Figure 1.1: Chondromyces crocatus fruiting bodies.](image)

Myxobacteria have long been studied as a rich source of novel secondary metabolites.\textsuperscript{[4]} The microbes are attractive targets for drug discovery due to the wide assortment of metabolites they produce.\textsuperscript{[5]} \textit{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 crocains, unusual 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]

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, chondrochloren, 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.\textsuperscript{[10]} This potential was exemplified by the discovery of the crocagins, biologically active novel polycyclic peptides containing a tetrahydropyrrolo[2,3-\textit{b}] indoline core, unprecedented in bacterial natural products.\textsuperscript{[11]}

\begin{center}
\includegraphics[width=0.2\textwidth]{crocagin.png}
\end{center}

\textbf{Figure 1.3: Crocagin A.}

\section*{1.2 \textbf{AJUDAZOL A AND B}}

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

\begin{center}
\includegraphics[width=0.4\textwidth]{ajudazols.png}
\end{center}

\textbf{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. The anti,anti-configured 8-hydroxyisochroman-1-one core is unique to the ajudazols.

![Figure 1.5: Ajudazol B.](image)

### 1.3 Biological Activity

Ajudazol A, 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 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*.

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. 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.

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

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[Diagram of biosynthesis process]

- Acyl carrier protein (ACP)
- Peptidyl carrier protein (PCP)
- Subunit of Multienzyme either: Ketosynthase, Acyltransferase, O-Methyltransferase, Ketoreductase, Dehydratase, Enoyl reductase or N-Methyltransferase
- Thioesterase
- P450 type enzymes ajul and ajuI
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).

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 P₄₅₀ 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).
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.\textsuperscript{[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.\textsuperscript{[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 $R$.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ajudazol_B.png}
\caption{Ajudazol B absolute configuration.}
\end{figure}

\section*{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.\textsuperscript{[18, 23, 27-31]}

\subsection*{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.\textsuperscript{[30]}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{c12-c29.png}
\caption{C12-C29 fragment of ajudazol A.}
\end{figure}

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.
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.](image)

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. 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]
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 $\alpha,\beta$-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).

Synthesis of the racemic acetylene fragment 45, to be used as a model for ajudazol B, began with the known racemic alcohol 41. 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 $\beta$-hydroxy amide, which upon Dess-Martin oxidation, followed by cyclodehydration under Wipf’s conditions yielded oxazole 45 (scheme 1.6).
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. Rizzacasa reported the synthesis of both enantiomers of oxazole 45 to demonstrate that the synthesis could be carried out enantioselectively (scheme 1.8).
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 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.\[\text{37}\] 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 methylenation 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 \(\beta\)-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).

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).
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.

![Scheme 1.12: Rizzacasa's completion of the synthesis of 8-deshydroxyajudazol B stereoisomer 55.](image)

![Figure 1.11: 8-Deshydroxyajudazol A stereoisomer 73.](image)

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/H₂/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(PPh₃)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).
Methyl acetoacetate 93 was treated following Taylor’s and Rizzacasa’s conditions to generate 3-methoxybutenoic acid 31. 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).
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.\textsuperscript{[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 ajadazol 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\(_2\)SO\(_4\) to form the hydroxypyranone. However, several other one-pot oxidative conditions have been employed including, but not limited to: NBS in H\(_2\)O/THF; mCPBA, CH\(_2\)Cl\(_2\); iBuOOH, VO(acac)\(_2\); KBr, oxone; and photo-redox conditions using visible light.\(^{[39-44]}\)

![Scheme 1.20: Achmatowicz rearrangement.](image)

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.\cite{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)$_2$/BuOOH promoted Achmatowicz rearrangement to generate the pyranone ring in 109, in excellent yield (scheme 1.22).\cite{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.\cite{47} The $\alpha$-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 mCPBA, 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.](image)

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 isochromanones.

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

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 $\alpha$-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 $\alpha$-hydroxyisobenzofuran 132. The key $\alpha$-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.](image)

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 bond 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).

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 unsubstituted 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).\[48\]
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-methysalicylic 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 iodosicyclohexane, then re-protection of the phenol group using TBSCI 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 $\alpha,\beta$-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.](image)

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.](image)

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.](image)

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.](image)

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-isochromanone is the favoured diastereomer. Although inversion of the stereocentre to access the desired anti-isochromanone could be achieved using Mitsunobu conditions, adapting the methodology to allow for direct access of the anti-isochromanone 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-isochromanone as the major product (table 1-2).
Scheme 1.41: Reduction of keto-lactone 176.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Syn:Anti</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄, CeCl₃</td>
<td>100:0</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄</td>
<td>100:0</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>Na(CN)BH₃</td>
<td>100:0</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>L-selectride</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Me₂AlCl</td>
<td>100:0</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>Sm(OiPr)₃</td>
<td>100:0</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>BH₃</td>
<td>12:1</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>9-BBN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Alpine borane</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>(R)-CBS, BH₃</td>
<td>12:1</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>(S)-CBS, BH₃</td>
<td>12:1</td>
<td>45</td>
</tr>
</tbody>
</table>

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. 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).
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.\textsuperscript{[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.\textsuperscript{[34]} Desilylation and oxidation of the primary alcohol completed the synthesis of oxazole-aldehyde 182 (scheme 1.45).
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).

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.](image)

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).
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 \textit{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]

![Scheme 2.1](image)

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]

![Scheme 2.2](image)

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.](image)

### 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.](image)

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 Et₂O, 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]

![Scheme 2.7: Birch reduction of 220.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkali metal</th>
<th>Solvent</th>
<th>Proton source</th>
<th>Yield</th>
<th>SM : Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na</td>
<td>THF</td>
<td>'BuOH</td>
<td>-</td>
<td>1:0</td>
</tr>
<tr>
<td>2</td>
<td>Na</td>
<td>Et₂O</td>
<td>-</td>
<td>-</td>
<td>1:0</td>
</tr>
<tr>
<td>3</td>
<td>Na</td>
<td>THF</td>
<td>EtOH</td>
<td>-</td>
<td>1:0</td>
</tr>
<tr>
<td>4</td>
<td>Li</td>
<td>THF</td>
<td>'BuOH</td>
<td>-</td>
<td>5:1</td>
</tr>
<tr>
<td>5</td>
<td>Li</td>
<td>Et₂O</td>
<td>-</td>
<td>57%</td>
<td>0:1</td>
</tr>
</tbody>
</table>

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).

![Scheme 2.8: Alder-Rickert using 1-methoxy-2-methyl-1,4-cyclohexadiene 221 and DMAD 210.](image)

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.
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).

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 K**MnO**₄ under mild conditions. 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 K₂CO₃ also did not yield any of the desired products, and merely led to decomposition.

Keehn had published the use of activated MnO₂ to mediate oxidative dehydrogenations on very similar substrates. Using refluxing benzene and a Dean-Stark apparatus, treatment of diene 226 with ten equivalents of activated MnO₂ 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.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp. (°C)</th>
<th>Yield 227 (%)</th>
<th>Yield 228 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ, toluene</td>
<td>rt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DDQ, toluene</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DDQ, toluene</td>
<td>110</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>KMnO$_4$/Al$_2$O$_3$, acetone</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Pd/C, Cyclohexene, MeOH</td>
<td>rt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$CO$_3$, MeOH</td>
<td>rt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>MnO$_2$, benzene, 16 h</td>
<td>80</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>MnO$_2$, benzene, 4 h</td>
<td>80</td>
<td>70</td>
<td>4</td>
</tr>
</tbody>
</table>

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).
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).

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 H₂O₂ afforded the desired epoxide 237, albeit in low yield (scheme 2.15).

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.](image)

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.](image)

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).
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 AgSbF₆ 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]

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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>247 yield (%)</th>
<th>248 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>111</td>
<td>24</td>
<td>SM</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>160 (sealed vial)</td>
<td>24</td>
<td>SM</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>200 (MW)</td>
<td>3</td>
<td>decomposition</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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).

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).

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield 258 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>72</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>100 (MW)</td>
<td>2</td>
<td>32 (61 brsm)</td>
</tr>
</tbody>
</table>

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 nBuLi 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 alkylnones 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 acetylide 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).
Attempted synthesis of ester 261.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield 261 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS, THF, -78 °C</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>&quot;BuLi, THF, -78 °C</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$, CuI, Et$_3$N, THF, rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>(i) AgNO$_3$, H$_2$O, MeOH, NH$_4$OH (ii) CCl$_4$, 77 °C</td>
<td>-</td>
</tr>
</tbody>
</table>

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).

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. 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).

![Scheme 2.31: Phosphine-catalysed conjugate addition.](image)

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).

![Scheme 2.32: Unsuccessful cyclisation of enol ether 262.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>111</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>120 (sealed tube)</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>160 (sealed tube)</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>neat</td>
<td>160 (sealed tube)</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>170 (MW)</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

*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).
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).

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 MnO₂. 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).

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.]

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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.\cite{yu2009}

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).

\[ RCOOH + R'Cl \rightarrow RCO-R' + HCl \]

\[ RCO-R' + H2O \rightarrow RCOOR' + H2O \]

\[ RCOOR' \rightarrow RCOOR' \]

\[ RCOOR' \rightarrow RCOOH \]

**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.\cite{yu2009,huang2011} 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).

\[ RCOOH + CH2S(O)CH3 \rightarrow RCOOR' + CH3SO2H \]

**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).\cite{huang2011}
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).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>88</td>
<td>89</td>
</tr>
</tbody>
</table>

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-methysalicylic acid 87, further reducing the synthesis to two steps (scheme 2.43).
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).

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. The resulting free phenol was then TBS-protected to complete the synthesis of phthalide 158 (scheme 2.45).

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

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.

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 \( \text{o-nitrobenzenesulfonylhydrazide (NBSH)} \) 278 was investigated as an alternative \textit{in-situ} source of diimide for the reduction. NBSH 278 was synthesised according to Myers’ procedure, and used immediately for the reduction step.\footnote{71} Pleasingly, this reagent was easier to handle and the procedure more user-friendly. Furthermore, the yield was also improved, giving the desired \textit{Z}-vinyl iodide 36 with complete selectivity in 66\% yield (scheme 3.3).

\[ \text{Scheme 3.3: Synthesis of vinyl iodide 36.} \]

Oxidation of alcohol 36 using PCC followed by immediate treatment of the resultant aldehyde with methyl (triphenylphosphoranylidene)acetate 37, gave the desired \textit{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).

\[ \text{Scheme 3.4: Synthesis of bromide 279.} \]

The synthesis of \textit{(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.

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.

\((E)\)-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 $\beta$-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.](image)

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]
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, \((1S,2S)-(+)-\)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. Gratifyingly, the desired olefin 286 was isolated in quantitative yield as a single diastereomer (scheme 4.3).

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. Subsequent TBDPS-protection gave the desired silyl ether \((R)-186\) (scheme 4.4).
As an alternative approach, the reduction of amide 286 directly using lithium ammonia-borane was carried out to yield alcohol 287.\cite{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).

\[
\begin{align*}
\text{H}_2\text{N-BH}_3, \text{Li} & \quad \text{THF} \\
\text{N}=\text{O} & \quad \text{OH} \\
\text{286} & \quad \text{287} \\
\text{imid., DMF} & \quad \text{TBDPSCI} \\
67\% (2 \text{ steps}) & \quad (R)-186
\end{align*}
\]

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 (1S,2S)-(+)-pseudoephedrine 285 which was alkylated according to Myers’ procedure using the known iodide 192.\cite{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).\footnote{Synthesis of (R)-4-(benzyloxy)-2-methylbutanoic acid carried out by Dr. Colin Pearson}

\[
\begin{align*}
\text{BnO} & \quad \text{LICl, } \text{BuLi} \\
\text{N}=\text{O} & \quad \text{OH} \\
\text{285} & \quad \text{289} \\
\text{THF, } -78^\circ \text{C} & \quad \text{MsOH, LiBH}_4 \\
90\% & \quad 85\% \\
\text{O} & \quad \text{O} \\
\text{OBn} & \quad \text{OBn} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{OBn} & \quad \text{OBn} \\
\text{289} & \quad (R)-194
\end{align*}
\]

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

\[\text{Scheme 4.7: Dihydroxylation in synthesis of diol 290.}\]

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).\[80\]
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).
4.4 SUMMARY

The desired oxazole fragment was successfully synthesised starting from (2R)-3-((tert-butylidiphenylsilyl)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.

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.](image)

### 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$_2$Cl$_2$ 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 pTsOH to CSA, the yield was low. Reverting to CH₂Cl₂ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Diol</th>
<th>Yield 159 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. DIBALH, toluene, -78 °C 2. pTsOH, MeOH</td>
<td>Y</td>
<td>0 – 68</td>
</tr>
<tr>
<td>2</td>
<td>DIBALH, toluene, -78 °C, then pTsOH, MeOH</td>
<td>Y</td>
<td>0 – 54</td>
</tr>
<tr>
<td>3</td>
<td>1. DIBALH, toluene, -78 °C 2. CSA, MeOH</td>
<td>Y</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>1. DIBALH, CH₂Cl₂, -78 °C 2. pTsOH, MeOH</td>
<td>Y</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>1. DIBALH, toluene, -78 °C 2. PPTS, MeOH</td>
<td>N</td>
<td>88</td>
</tr>
</tbody>
</table>

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]
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).

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 initial 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](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>THF source</th>
<th>MeLi addition</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SPS</td>
<td>0 °C</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>SPS</td>
<td>-78 °C</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>Acros</td>
<td>0 °C</td>
<td>51</td>
</tr>
</tbody>
</table>

**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 MnO₂ 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).
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).

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.
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).

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 $\alpha$-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 $\alpha$-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.
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).

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 $\alpha$-hydroxyisobenzofuran intermediate 319 could undergo a Diels-Alder reaction with a second molecule of alkyne 318. Alternatively, the $\alpha$-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-ol 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 nBuLi, 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.\cite{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).\cite{88}

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEMPO, BAIB, CH₂Cl₂</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>PCC, CH₂Cl₂</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>IBX, DMSO, THF</td>
<td>62</td>
</tr>
</tbody>
</table>

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).
6.2 **REARRANGEMENT WITH PHTHALAN 159 AND MODEL ALKYNE 320**

Armed with this partial success, it was decided to use 5-(trimethylsilyl)pent-4-yenal 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).
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 (2R)-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 (2R)-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).
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).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Deprotection conditions</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPTS (0.1 eq), MeOH, rt</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>CSA, MeOH, rt</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl, H$_2$O, MeCN</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>TBAF, THF, 0 °C - rt</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>HF, MeCN</td>
<td>0.25</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>PPTS (0.2 eq), MeOH, rt</td>
<td>60</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 7-1: Deprotection of 327.

As with the synthesis of oxazole fragment 281, the oxidation of the $\beta$-hydroxyamide to the $\beta$-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 $\beta$-formylamide 330 was isolated in quantitative yield (scheme 7.4, table 7-2).

Scheme 7.4: Synthesis of aldehyde 330.

Gratifyingly, cyclodehydration of $\beta$-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 (1S,2S)-(+)-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](image)

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 increase to 2.0 equivalents of phthalan 159, translated into a much more satisfactory 65% yield (table 8-1).
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 NaBH₄ 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 8.2: Oxidative rearrangement utilising aldehyde 325.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phthalan (159) equivalents</th>
<th>Yield 334 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>25 (82 brsm)</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>65</td>
</tr>
</tbody>
</table>

Table 8-1: Oxidative rearrangement utilising aldehyde 325.

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).

![Scheme 8.4: Desilylation of syn,syn-isochromanone 336.](image)

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).

![Scheme 8.5: Desilylation of syn,anti-isochromanone 335.](image)

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-sp² 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).
Partial reduction of the enyne 339 to the Z,Z-diene was then attempted using Brown’s P2-Ni conditions. 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 8.6: Sonogashira coupling to synthesise enyne 339.

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 trans lactonisation, 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/BaSO₄, 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](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Pd (wt. %)</th>
<th>Time (h)</th>
<th>Yield 340 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lindlar’s, quinoline, EtOAc</td>
<td>5</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Lindlar’s, quinoline, EtOAc</td>
<td>15</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Lindlar’s, EtOH</td>
<td>10</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Lindlar’s, EtOH</td>
<td>30</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>PdBaSO₄, quinoline, EtOH</td>
<td>10</td>
<td>24</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

*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 decided 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. Encouragingly, 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 1H 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-ajadazol B 340.
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.](image)

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.](image)

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.

![Figure 9.1: Isomer of ajudazol B.](image)

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 trans lactonisation, 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.

![Scheme 10.1: Stille coupling partners.](image)

Alternatively, the C8 hydroxy group could be protected to prevent trans lactonisation. 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.
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, Et₂O, CH₂Cl₂, 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 (¹H NMR at 400 MHz and ¹³C NMR at 100 MHz), or a Bruker AVII DPX-500 spectrometer (¹H NMR at 500 MHz and ¹³C NMR at 125 MHz). Chemical shifts (δ) are reported in parts per million (ppm). ¹H 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 ¹H and ¹³C 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 F₂₅₄), unless otherwise stated. The plates were visualised under UV-light (λ<sub>max</sub> 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

![Structure](image)

LiAlH₄ (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 (Na₂SO₄), filtered, and concentrated in vacuo, to give the desired product 207 as a white solid (164 mg, 36%).

1H NMR (CDCl₃, 400 MHz) δ: 7.14 (1H, d, J = 7.3 Hz, ArH), 6.87 (1H, d, J = 7.4 Hz, ArH) 6.86 (1H, s, ArH), 4.66 (2H, s, CH₂), 2.28 (3H, s, CH₃).

13C NMR (CDCl₃, 100 MHz) δ: 154.0 (ArCOH), 140.2 (ArCH₂OH), 131.2 (ArCH), 123.2 (ArCH₂), 119.3 (ArCH), 113.5 (ArCH), 65.1 (CH₂), 15.5 (CH₃).

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

Dimethyl 3-methoxyphthalate

![Structure](image)

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 \textbf{216} as a yellow oil (511 mg, quant.).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.62 (1H, dd, J = 7.9, 0.8 Hz, C(O)C\(^{\text{Ar}}\)CH), 7.48 – 7.39 (1H, m, \(^{\text{Ar}}\)CH\(^{\text{Ar}}\)CH), 7.15 (1H, dd, J = 8.4, 0.8 Hz, C(OCH\(_3\))\(^{\text{Ar}}\)CH), 3.97 (3H, s, CH\(_3\)), 3.89 (3H, s, CH\(_3\)), 3.87 (3H, s, CH\(_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 168.1 (C=O), 165.9 (C=O), 156.6 (\(^{\text{Ar}}\)C), 130.3 (\(^{\text{Ar}}\)CH), 128.9 (\(^{\text{Ar}}\)C), 125.6 (\(^{\text{Ar}}\)CHCC(O)), 115.6 (\(^{\text{Ar}}\)CHC(OCH\(_3\))), 56.9 (OCH\(_3\)), 52.7 (C(O)OCH\(_3\)), 52.5 (C(O)OCH\(_3\)).

This data is in accordance with literature values.\[^{[92]}\]

\textbf{3-Methoxyphthalic acid}

Dimethyl 3-methoxyphthalate \textbf{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\(_2\)O (200 mL), and extracted with Et\(_2\)O (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\(_2\)SO\(_4\)), 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 \textbf{217} as a white crystalline solid (551 mg, 63%).

\(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)CO) \(\delta\): 7.57 (1H, dd, J = 7.8, 0.9 Hz, C(O)C\(^{\text{Ar}}\)CH), 7.42 – 7.38 (1H, m, \(^{\text{Ar}}\)CH\(^{\text{Ar}}\)CH), 7.24 (1H, dd, J = 8.3, 0.9 Hz, C(OCH\(_3\))\(^{\text{Ar}}\)CH), 3.85 (3H, s, OCH\(_3\)).

This data is in accordance with literature values.\[^{[93]}\]
7-Methoxyphthalide

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 H₂O (5 mL), extracted with EtOAc (15 mL), washed with NaHCO₃ (10 mL), brine (10 mL), dried (Na₂SO₄), 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.

¹H NMR (CDCl₃, 400 MHz) δ: 7.62 (1H, t, J = 8.0 Hz, ArH), 7.00 (1H, d, J = 7.6 Hz, ArH), 6.93 (1H, d, J = 8.2 Hz, ArH), 5.23 (2H, s, CH₂), 3.99 (3H, s, OCH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 169.2 (C=O), 158.8 (CH₂CO), 149.5 (CH₃), 136.3 (CH₂), 113.7 (CH), 113.4 (CH), 110.6 (CH₂), 68.7 (CH₂), 56.2 (OCH₃).

This data is in accordance with literature values.⁴⁸

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

2-Methylanisole (2.55 mL, 20.6 mmol) was dissolved in Et₂O (25 mL) and cooled to -78 °C. NH₃ (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 NH₃ to evaporate. The crude reaction mixture was then diluted with H₂O (25 mL), and extracted with EtOAc (100 mL). The combined organic phases were washed with H₂O (3 × 25 mL), brine (25 mL), and concentrated in vacuo to yield the desired product 221 as a clear oil (1.45 g, 57%).
1H NMR (CDCl₃, 500 MHz) δ: 5.71 – 5.63 (2H, m, HC=CH), 3.53 (3H, s, OCH₃), 2.83 – 2.78 (2H, m, CH₂), 2.72 – 2.68 (2H, m, CH₂), 1.65 (3H, s, CH₃).

13C NMR (CDCl₃, 100 MHz) δ: 145.3 (C=OCH₃), 124.5 (H₃C=CH), 123.6 (HC=CH), 111.6 (H₃CC=CH), 56.03 (OCH₃), 32.8 (CH₂), 26.0 (CH₂), 14.8 (CH₃).

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

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

*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%).

1H NMR (CDCl₃, 500 MHz) δ: 5.89 (1H, ddd, J = 9.8, 4.2, 0.9 Hz, HC=CH), 5.69 (1H, ddd, J = 9.8, 4.3, 0.8 Hz, HC=CH), 3.80 (6H, s, OCH₃), 3.79 – 3.74 (1H, m, CH₂), 3.70 – 3.63 (1H, m, CH₂), 3.34 – 3.15 (2H, m, CHCH₃ + CHCH₂OH), 2.17 (1H, dd, J = 7.8, 5.5 Hz, OH), 1.23 (3H, d, J = 7.0 Hz, CH₃).

13C NMR (CDCl₃, 500 MHz) δ: 168.9 (C=O), 168.2 (C=O), 140.9 (C=CC(O)), 133.6 (C=CC(O)), 131.6 (HC=CH), 123.6 (HC=CH), 123.6 (HC=CH), 65.7 (CH₂), 52.5 (C(O)OCH₃), 52.2 (C(O)OCH₃), 41.3 (CHCH₂), 33.2 (CHCH₂), 21.8 (CH₃).

HRMS (ESI) calculated for C₁₂H₁₇O₅ (M+H)⁺: m/z 241.1076, observed 241.1075

IR νₘₐₓ (film)/cm⁻¹ 3385, 1717, 1636, 1435, 1256.
Methyl 5-methyl-3-oxo-1,3-dihydroisobenzofuran-4-carboxylate

Dimethyl 3-(hydroxymethyl)-6-methylcyclohexa-1,4-diene-1,2-dicarboxylate 226 (200 mg, 0.83 mmol) was dissolved in benzene. Activated MnO₂ (730 mg, 8.40 mmol) was added and the resultant solution was heated to reflux for 4 h, whilst azeotropically removing the H₂O 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%).

¹H NMR (CDCl₃, 500 MHz) δ: 7.54 (1H, d, J = 8.0 Hz, ArH), 7.44 (1H, d, J = 8.0 Hz, ArH), 5.28 (2H, s, CH₂), 4.02 (3H, s, OCH₃), 2.44 (3H, s, CH₃).

¹³C NMR (CDCl₃, 500 MHz) δ: 169.1 (C=O), 167.4 (C=O), 144.5 (ArCH₂O), 136.5 (ArCH₂), 136.3 (ArCO₂CH₂), 131.9 (ArCH), 123.2 (ArCO₂CH₂), 123.1 (ArCH), 69.3 (OCH₃), 53.1 (CH₂), 18.8 (CH₃).

HRMS (ESI) calculated for C₁₁H₁₀O₄Na (M+Na)⁺: m/z 229.0471, observed m/z 229.0473.

IR νmax (film)/cm⁻¹ 1759, 1724, 1435, 1258, 907.

Melting point: 90 – 92 °C.
**Dimethyl 3-formyl-6-methylphthalate**

(8 mg, 4%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$: 10.12 (1H, s, C(O)H), 7.92 (1H, d, $J = 8.0$ Hz, ArH), 7.49 (1H, d, $J = 8.0$ Hz, ArH), 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) $\delta$: 189.8 (C(O)H), 167.6 (C=O), 167.2 (C=O), 143.6 (ArC), 134.3 (ArCH) 133.2 (ArCH), 132.7 (ArC), 132.6 (ArC), 53.3 (OCH$_3$), 52.9 (OCH$_3$), 20.9 (CH$_3$).

HRMS (ESI) calculated for C$_{12}$H$_{13}$O$_5$ (M+H)$^+$: m/z 237.0763, observed m/z 237.0772.

IR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2955, 1730, 1701, 1593, 1273.

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

$trans,trans$-2,4-Hexadien-1-ol (2.48 g, 25.3 mmol) and DMAP (cat.) were dissolved in CH$_2$Cl$_2$ (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$_2$Cl$_2$ 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) $\delta$: 6.31 (1H, dd, $J = 10.5, 4.5$ Hz, $HC=CHCH_2$), 6.08 (1H, dd, $J = 11.0, 4.5$ Hz, $HC=CHCH_3$), 5.83 – 5.76 (1H, m, C=CHCH$_2$), 5.66 – 5.60 (1H, m, =CHCH$_3$), 4.70 (2H, d, $J = 7.0$ Hz, $CH_2$), 2.88 (1H, s, =CH), 1.78 (3H, d, $J = 7.0$ Hz, CH$_3$).

$^{13}$C NMR (CDCl$_3$, 500 MHz) $\delta$: 152.5 (C=O), 136.2 (HC=CHCH$_2$), 132.1 (HC=CHCH$_3$), 130.2 (HC=CHCH$_2$), 121.9 (HC=CHCH$_3$), 74.9 (C=CH), 74.8 (C≡CH), 66.7 (CH$_2$), 18.1 (CH$_3$).

HRMS (ESI) calculated for C$_9$H$_{10}$O$_2$Na (M+Na)$^+$: m/z 173.0573, observed m/z 173.0570.

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

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

![Structure](image)

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$_2$Cl$_2$ (0.26 mL) followed immediately by a solution of (2E,4E)-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$_2$O (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) $\delta$: 6.71 – 6.70 (m, 1H, $HC=qC$), 5.79 – 5.73 (m, 2H, $HC=CH$), 4.67 – 4.63 (m, 1H, $CH_2$), 3.85 (dd, 1H, $J = 10.4, 8.3$ Hz, $CH_2$), 3.56 – 3.48 (m, 1H, $CH$), 3.07 – 2.99 (m, 1H, $CHCH_3$), 1.27 (d, 3H, $J = 7.7$ Hz).

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

This data is in accordance with literature values.[59]
4-Methyl-2,9-dioxatricyclodec-5-en-10-one

6-Methyl-3,3a-dihydroisobenzofuran-1(6H)-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$_2$O$_2$ (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$_2$O (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$_2$SO$_4$), 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=CH), 5.73 (1H, dd $J =$ 9.3, 4.3 Hz, C=CH), 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, C$_2$H$_2$), 1.82 (3H, s, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 178.6 (C=O), 128.9 (HC=CH), 124.3 (HC=CH), 113.7 (CO), 73.5 (CH$_2$), 69.7 (HCO), 40.6 (HCCH$_2$), 34.9 (HCCH$_3$), 21.7 (CH$_3$).

HRMS (ESI) calculated for C$_9$H$_{11}$O$_3$ (M+H)$^+$: m/z 167.0708, observed 167.0709.

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

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

Freshly distilled iPr$_2$NH (0.24 mL, 1.68 mmol) was dissolved in anhydrous THF (3 mL) and cooled to -78 °C. nBuLi (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 (2E,4E)-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. TBSCI (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 NH₄Cl (aq) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H₂O (25 mL), then brine (25 mL), dried (Na₂SO₄), 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%).

1H NMR (CDCl₃, 400 MHz) δ: 6.29 (1H, dd, J = 15.2, 10.5 Hz, H=CHCH₂), 6.07 (1H, dd, J = 15.0, 10.7 Hz, H=CHCH₃), 5.86 – 5.73 (1H, m, H₂C=CH), 5.69 – 5.58 (1H, m, HC=CHCH₃), 4.67 (2H, d, J = 6.8 Hz, CH₂), 1.78 (3H, d, J = 6.7 Hz, CH₃), 0.97 (9H, s, SiC(CH₃)₃), 0.18 (6H, s, Si(CH₃)₂).

13C NMR (CDCl₃, 100 MHz) δ: 153.0 (C=O), 136.3 (HC=CHCH₂), 132.2 (HC=CHCH₃), 130.4 (H₂C=CH=CH), 122.7 (HC=CHCH₃), 95.5 (SiC=C), 92.9 (C=CC(O)), 66.6 (CH₂), 26.1 (CH₃), 18.3 (=CHCH₃), 16.7 (CH₃), -5.0 (Si(CH₃)₂).

HRMS (ESI) calculated for C₁₅H₂₄O₂SiNa (M+Na)⁺: m/z 287.1438, observed m/z 287.1424.

IR νmax (film)/cm⁻¹ 2190, 1709, 1660, 1213, 990.

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

Freshly distilled iPr₂NH (0.47 mL, 3.36 mmol) was dissolved in anhydrous THF (6 mL) and cooled to -78 °C, under an argon atmosphere. nBuLi (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 (2E,4E)-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. TIPSCI (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 NH₄Cl (aq) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H₂O (25 mL), then brine (25 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude mixture was purified using flash
chromatography (silica gel, 1% EtOAc in hexane) to yield the desired product \textbf{246} as a yellow oil (193 mg, 44%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$: 6.29 (1H, dd, $J = 15.2$, 10.5 Hz, $HC=CHCH_2$), 6.10 – 6.04 (1H, m, $HC=CHCH_3$), 5.82 – 5.75 (1H, m, C=CHCH$_2$), 5.68 – 5.62 (1H, m, C=CHCH$_3$), 4.67 (2H, d, $J = 6.8$ Hz, $CH_2$), 1.78 (3H, d, $J = 6.8$ Hz, $CH_3$), 1.12 – 1.10 (21H, m, Si(Pr)$_3$).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$: 153.1 (C=O), 136.1 (HC=CHCH$_2$), 132.0 (HC=CHCH$_3$), 130.5 (HC=CHCH$_2$), 122.9 (HC=CHCH$_3$), 96.9 (C(O)C=C), 91.5 (C(O)C=C), 66.6 ($CH_2$), 18.6 (Si(CH(CH$_3$)$_2$)$_3$), 18.3 ($CH_3$), 11.2 (Si(CH$_3$)$_2$)$_3$).

HRMS (ESI) calculated for C$_{18}$H$_{30}$O$_2$SiNa (M+Na)$^+$: m/z 329.1907, observed m/z 329.1893.

IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2170, 1711, 1663, 1462, 1207, 988.

\textit{(2E,4E)-Prop-2-yn-1-yl hexa-2,4-dienoate}

\begin{center}
\includegraphics[width=1in]{253}
\end{center}

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 anhydrous CH$_2$Cl$_2$ (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 \textbf{253} as a colourless oil (3.30 g, 100%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.34 – 7.29 (1H, m, $HC=CHC(O)$), 6.24 – 6.15 (2H, m, =CH $\times 2$), 5.81 (1H, d, $J = 15.8$ Hz, =CH), 4.76 (2H, d, $J = 2.5$ Hz, $CH_2$), 2.48 (1H, t, $J = 2.5$ Hz, =CH), 1.87 (3H, d, $J = 5.5$ Hz, $CH_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 166.3 (C=O), 146.3 (HC=CHC(O)), 140.3 (HC=CHCH$_3$), 129.7 (HC=CHCH$_3$), 117.8 (HC=CHC(O)), 77.9 ($H_2CC=CH$), 74.7 ($H_2CC=CH$), 51.7 ($CH_2$), 18.7 ($CH_3$).

This data is in accordance with literature values.$^{[59]}$
(2E,4E)-3-(tert-Butyldimethylsilyl)prop-2-yn-1-yl hexa-2,4-dienoate

Freshly distilled iPr2NH (0.47 mL, 3.36 mmol) was dissolved in anhydrous THF (6 mL) and cooled to -78 °C. nBuLi (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 (2E,4E)-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. TBSCI (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 NH4Cl (aq) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H2O (25 mL), then brine (25 mL), dried (Na2SO4), 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%).

1H NMR (CDCl3, 400 MHz) δ: 7.34 – 7.28 (1H, m, HC=CHC(O)), 6.25 – 6.13 (2H, m, HC=CH × 2), 5.83 – 5.79 (1H, m, =CHCH3), 4.77 (2H, s, CH2), 1.87 (3H, d, J = 5.4 Hz, CH3), 0.94 (9H, s, SiC(CH3)3), 0.13 (6H, s, Si(CH3)2).

13C NMR (CDCl3, 100 MHz) δ: 166.6 (C=O), 146.1 (HC=CHC(O)), 140.2 (HC=CHCH3), 129.9 (HC=CHCH3), 118.2 (HC=CHC(O)), 100.1 (C≡CCH2), 90.4 (C≡C Si), 52.8 (CH2), 26.2 (C(CH3)3), 18.9 (=CHCH3), 16.7 (C(CH3)3), -4.6 (Si(CH3)2).

This data is in accordance with literature values.[59]
4-(tert-Butyldimethylsilyl)-5-methylisobenzofuran-1(3H)-one

**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$_2$Cl$_2$ (0.26 mL), followed immediately by a solution of (2E,4E)-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$_2$O (20 mL), filtered through a celite pad, washed with Et$_2$O, 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 (2E,4E)-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$_2$O, 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) $\delta$: 7.81 (1H, d, $J = 7.8$ Hz, ArH), 7.34 (1H, d, $J = 7.8$ Hz, ArH), 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) $\delta$: 171.6 (C=O), 154.1 ($^{\Lambda}$C), 152.2 ($^{\Lambda}$C), 132.0 ($^{\Lambda}$CH), 131.1($^{\Lambda}$C), 126.4 ($^{\Lambda}$CH), 122.8($^{\Lambda}$C), 72.2 (CH$_2$), 27.1 (SiC(CH$_3$)$_3$), 25.6 (CH$_3$), 19.6 (SiC(CH$_3$)$_3$), -0.9 (Si(CH$_3$)$_2$).

This data is in accordance with literature values.$^{[59]}$
(2E,4E)-3-(Dimethyl(phenyl)silyl)prop-2-yn-1-yl hexa-2,4-dienoate

Freshly distilled \(^{t}\)Pr$_2$NH (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 (2E,4E)-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$_4$Cl (aq) (15 mL), and extracted with EtOAc (25 mL). The organic extracts were washed with H$_2$O (25 mL), then brine (25 mL), dried (Na$_2$SO$_4$), 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) $\delta$: 7.66 – 7.60 (2H, m, $^{A\text{r}}$H $\times$ 2), 7.58 – 7.52 (1H, m, $^{A\text{r}}$H), 7.43 – 7.28 (3H, m, 2 $\times$ $^{A\text{r}}$H + HC=CHC(O)), 6.26 – 6.13 (2H, m, HC=CHCH$_3$), 5.82 (1H, d, $J = 15.4$ Hz, C(O)CH=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) $\delta$: 166.6 (C=O), 146.3 (HC=CHC(O)), 140.3 (HC=CHCH$_3$), 136.6 ($^{A\text{r}}$C), 133.9 ($^{A\text{r}}$CH), 133.2 ($^{A\text{r}}$CH), 129.7 (HC=CHCH$_3$), 128.1 ($^{A\text{r}}$CH), 127.9 ($^{A\text{r}}$CH), 118.1 (HC=CHC(O)), 101.2 (C=CCCH$_3$), 90.1 (C=CSi), 52.7 (CH$_2$), 18.9 (CH$_3$), -0.9 (Si(CH$_3$)$_2$).

HRMS (ESI) calculated for C$_{17}$H$_{21}$O$_2$Si (M+H)$^+$: 285.1311, observed 285.1313

IR $v_{\text{max}}$ (film)/cm$^{-1}$ 3019, 2187, 1717, 1645, 1240, 752.
Benzyl alcohol (0.69 mL, 6.70 mmol) was dissolved in anhydrous CH₂Cl₂ (40 mL). Tri-n-butylphosphine (0.24 mL, 1.00 mmol) was added and the resultant mixture was cooled to 0 °C. (2E,4E)-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%).

¹H NMR (500 MHz, CDCl₃) δ: 7.70 (1H, d, J = 12.6 Hz, C=CHOBn), 7.42 – 7.34 (5H, m, ArH), 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, H=CH), 5.68 – 5.63 (1H, m, H=CH), 5.33 (1H, d, J = 12.6 Hz, C=HC(O)), 4.91 (2H, s, OCH₂), 4.63 (2H, d, J = 6.6 Hz, CH₂), 1.77 (3H, d, J = 6.6 Hz, CH₃).

¹³C NMR (125 MHz, CDCl₃) δ: 167.6 (C=O), 162.4 (HC=CHC(O)), 135.4 (HC=CHC(O)), 134.8 (HC=CHC(O)), 131.2 (HC=CHCH₃), 130.7 ((HC=CHCH₂), 128.9 (HC=CH), 128.8 (HC=CH), 128.7 (HC=CH), 127.9 (2 × HC=CH), 124.3 (HC=CHCH₃), 97.5 (C=CHC(O)), 73.0 (OCH₂Ph), 64.6 (CH₂), 18.3 (CH₃).

HRMS (CI) calculated for C₁₆H₁₉O₃ (M+H)^+: m/z 259.1334, observed m/z 259.1337

IR vₘₐₓ (film)/cm⁻¹ 3023, 1705, 1643, 1622, 990, 750.
(2E,4E)-Hexa-2,4-dien-1-yl 3-bromopropionate

(2E,4E)-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\textsubscript{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\textsubscript{2}O (40 mL), brine (3 × 40 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated \textit{in vacuo} to yield the desired product 264 as an orange oil (629 mg, 86%) without the need for purification.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\): 6.30 (1H, dd, \(J = 15.2, 10.5\) Hz, H\textsubscript{C}=CHCH\textsubscript{2}), 6.09 – 6.03 (1H, m, H\textsubscript{C}=CHCH\textsubscript{3}), 5.82 – 5.78 (1H, m, HC=CHCH\textsubscript{2}), 5.66 – 5.57 (1H, m, HC=CHCH\textsubscript{3}), 4.68 (2H, d, \(J = 6.8\) Hz, OCH\textsubscript{2}), 1.78 (3H, d, \(J = 6.7\) Hz, CH\textsubscript{3}).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\): 152.4 (C=O), 136.5 (HC=CHCH\textsubscript{2}), 132.4 (HC=CHCH\textsubscript{2}), 130.4 (HC=CHCH\textsubscript{3}), 122.2 (HC=CHCH\textsubscript{3}), 77.4 (C=CC(O)), 72.9 (C=CB\textsubscript{r}), 67.0 (CH\textsubscript{2}), 18.3 (CH\textsubscript{3}).

Analytical services were unable to obtain an accurate MS.

IR \(\nu_{max}\) (film)/cm\textsuperscript{-1} 2934, 2203, 1713, 1236, 990.

7-bromo-6-methyl-3,3\textsubscript{a}-dihydroisobenzofuran-1(6\textit{H})-one

A suspension of [Rh(cod)Cl\textsubscript{2}] (12.3 mg, 25.0 \mu mol, 5 mol\%) in TFE (3 mL) was treated with AgSbF\textsubscript{6} (22.3 mg, 65.0 \mu mol 13 mol\%), followed immediately by a solution of (2E,4E)-hexa-2,4-dien-1-yl 3-bromopropionate 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\textsubscript{2}O (15 mL), filtered
through celite, washed with Et₂O, 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 5.79 – 5.72 (2H, m, H=C=CH), 4.55 – 4.51 (1H, m, CH₂), 3.84 (1H, dd, J = 10.8, 8.0 Hz, CH₂), 3.72 – 3.60 (1H, m, CHCH₂), 3.33 – 3.22 (1H, m, CHCH₃), 1.46 (3H, d, J = 7.4 Hz, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 166.8 (C=O), 134.4 (C=CBr), 132.9 (C=CH), 124.7 (C=CBr), 120.9 (C=CH), 69.0 (CH₂), 42.9 (CHCH₂), 39.6 (CHCH₃), 21.5 (CH₃).

HRMS (ESI) calculated for C₉H₉O₂BrNa (M+Na)+: m/z 250.9672, observed m/z 250.9672

IR νmax (film)/cm⁻¹ 2361, 1771, 1456, 1082, 750.

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

(2E,4E)-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 MnO₂ (461 mg, 5.30 mmol) was added, and the reaction mixture was refluxed for 4 h, then filtered through celite, washed with Et₂O, and concentrated in vacuo to give the desired product 266 as a pale orange solid (186 mg, 78%).

¹H NMR (CDCl₃, 400 MHz) δ: 7.54 (1H, d, J = 7.7 Hz, ᵃᵣH), 7.33 (1H, d, J = 7.7 Hz, ᵃᵣH), 5.22 (2H, s, CH₂), 2.53 (3H, s, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 168.6 (C=O), 146.6 (ᵥᵣC), 140.2 (ᵥᵣC), 136.2 (ᵥᵣCH), 124.4 (ᵥᵣC), 123.0 (ᵥᵣC), 120.5 (ᵥᵣCH), 67.4 (CH₂), 22.3 (CH₃).

HRMS (ESI) calculated for C₉H₇O₂BrNa (M+Na)+: m/z 248.9520, observed 248.9520.

IR νmax (film)/cm⁻¹ 2361, 1751, 1578, 1082, 1016, 646.

Melting point: 140 – 142 °C.
6-Methyl-7-phenylisobenzofuran-1(3H)-one

7-Bromo-6-methylisobenzofuran-1(3H)-one (1.00 g, 4.40 mmol), phenylboronic acid (537 mg, 4.40 mmol) and Cs₂CO₃ (2.15 g, 6.6 mmol) were dissolved in toluene (60 mL) and H₂O (10 mL). The resultant mixture was treated with Pd(PPh₃)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 H₂O (100 mL), brine (100 mL), dried (Na₂SO₄), 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 7.58 (1H, d, J = 7.8 Hz, ArH), 7.50 – 7.40 (3H, m, ArH), 7.37 (1H, d, J = 7.8 Hz, ArH), 7.26 – 7.21 (2H, m, ArH), 5.25 (2H, s, CH₂), 2.22 (3H, s, CH₃).

¹³C NMR (CDCl₃, 125 MHz) δ: 169.9 (C=O), 144.9 (ArC), 141.7 (ArC), 137.9 (ArC), 136.0 (ArCH₃), 136.0 (ArC), 129.1 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 123.3 (ArC), 120.9 (ArCH₃), 68.2 (CH₂), 19.9 (CH₃).

HRMS (EI) calculated for C₁₅H₁₂O₂ (M)+: m/z 224.0837, observed 224.0838.

IR (film)/cm⁻¹ 2359, 1761, 1475, 1084, 764, 700.

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

7-Bromo-6-methylisobenzofuran-1(3H)-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 CH₂Cl₂ (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 H₂O (7 mL), brine (7 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude lactol intermediate was then dissolved in MeOH (7 mL) and TsOH·H₂O (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 NaHCO₃ (aq), diluted with Et₂O (7 mL), washed with H₂O (2 × 7 mL), brine (2 × 7 mL), dried (Na₂SO₄), 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%).

¹H NMR (400 MHz, CDCl₃) δ: 7.24 (1H, d, J = 7.6 Hz, ArH), 7.10 (1H, d, J = 7.6 Hz, ArH), 6.09 (1H, d, J = 2.1 Hz, CH₂), 5.29 – 5.23 (1H, m, CH₂), 5.03 (1H, d, J = 12.7 Hz, CH₂), 3.52 (3H, s, OCH₃), 2.43 (3H, s, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 139.4 (ArC), 138.1 (ArC), 137.4 (ArC), 131.8 (ArCH), 119.9 (ArC), 119.6 (ArCH), 108.4 (CH), 72.6 (CH₂), 55.1 (OCH₃), 22.1 (CH₃).

HRMS (EI) calculated for C₁0H₁₀O₂Br (M+H): m/z 240.9864, observed 240.9866.

IRνmax (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(3H)-one

7-Bromo-6-methylisobenzofuran-1(3H)-one 266 (100 mg, 0.44 mmol), Pd(CH₃CN)₂Cl₂ (1.5 mg, 5.8 μmol, 1 mol%), and SPhos (14.5 mg, 0.04 mmol) were dissolved in 1,4-dioxane (1 mL) and Et₃N (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 CH₂Cl₂, 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$_3$) $\delta$: 7.42 (1H, d, $J = 7.9$ Hz, $^\alpha$H), 7.33 (1H, d, $J = 7.9$ Hz, $^\alpha$H), 5.24 (2H, s, CH$_2$), 2.49 (3H, s, $^\alpha$CH$_3$), 1.46 (12H, s, $^\beta$CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 171.8 (C=O), 143.0 ($^\alpha$C), 142.4 ($^\alpha$C), 134.5 ($^\alpha$C), 129.0 ($^\alpha$C), 125.9 ($^\alpha$C), 122.2 ($^\alpha$CH), 84.8 (COB), 69.7 (OCH$_2$), 25.0 (CH$_3$), 21.5 ($^\alpha$CCH$_3$).

$^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$: 31.9 (B(OR)$_2$).

HRMS (EI) calculated for C$_{15}$H$_{19}$O$_4$B (M)$^+$: m/z 274.1379, observed 274.1374.

IR $\nu_{max}$ (film)/cm$^{-1}$: 2980, 2361, 1759, 1358, 1051.

Melting point: 176 – 178 °C.

Methyl-2-methoxy-3-methylbenzoate

![Methyl-2-methoxy-3-methylbenzoate](image)

3-Methylnsalicylic acid (20.0 g, 131 mmol), and anhydrous K$_2$CO$_3$ (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$_2$O (500 mL) and stirred for 15 min, then extracted with EtOAc (3 × 500 mL). The combined organics were then washed with H$_2$O (500 mL), brine (500 mL), dried (Na$_2$SO$_4$), 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) $\delta$: 7.64 (1H, dd, $J = 7.8$, 1.4 Hz, $^\alpha$H), 7.35 (1H, ddd, $J = 7.5$, 1.7, 0.7 Hz, $^\alpha$H), 7.06 (1H, t, $J = 7.6$ Hz, $^\alpha$H), 3.92 (3H, s, C(O)OC$_3$H$_3$), 3.84 (3H, s, OCH$_3$), 2.33 (3H, s, CH$_3$).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 166.9 (C=O), 158.4 ($^\alpha$C), 135.2 ($^\alpha$CH), 132.8 ($^\alpha$C), 129.1 ($^\alpha$CH), 124.6 ($^\alpha$C), 123.5 ($^\alpha$CH), 61.5 (OCH$_3$), 52.2 (C(O)OCH$_3$), 16.0 (CH$_3$).

This data is in accordance with literature values.$^{[95]}$
2-Methoxy-3-methylbenzoic acid

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 H₂O (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 (Na₂SO₄), filtered, and concentrated in vacuo, to yield the desired product 153 as a white solid (18.4 g, 85%).

¹H NMR (CDCl₃, 400 MHz) δ: 7.96 (1H, dd, J = 7.8, 1.4 Hz, ArH), 7.44 (1H, dd, J = 7.5, 1.0 Hz, ArH), 7.19 (1H, t, J = 7.7 Hz, ArH), 3.93 (3H, s, OCH₃), 2.38 (3H, s, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 165.6 (C=O), 157.5 (ArCOCH₃), 137.1 (ArCH), 131.2 (ArCCH₃), 130.8 (ArCH), 125.3 (ArCH), 121.8 (ArCCOOH), 62.3 (OCH₃), 16.0 (CH₃).

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

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

2-Methoxy-3-methylbenzoic acid 153 (3.32 g, 20.0 mmol), K₂HPO₄ (10.4 g, 59.9 mmol), and Pd(OAc)₂ (900 mg, 4.01 mmol, 20 mol%) were dissolved in CH₂Br₂ (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 CH₂Cl₂ (150 mL), filtered through a celite pad, washed with CH₂Cl₂, 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) $\delta$: 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) $\delta$: 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 (CH$_2$), 62.3 (OCH$_3$), 15.6 (CH$_3$).

This data is in accordance with literature values.$^{[48]}$

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

Method A:

5-(Hydroxymethyl)-2-methylphenol 207 (1.15 g, 8.32 mmol) was dissolved in anhydrous MeCN (80 mL). Et$_3$N (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$_2$O (250 mL), washed with H$_2$O (250 mL), separated organic phase, dried (Na$_2$SO$_4$), filtered, concentrated in vacuo. The crude mixture was then purified using column chromatography (silica gel, 40 – 60% CH$_2$Cl$_2$ 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(3H)-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$_2$O$_2$ (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$_2$O (5 mL), brine (5 mL), dried (Na$_2$SO$_4$), 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(3H)-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 H₂O (50 mL), extracted with EtOAc (300 mL), washed with sat. (aq) Na₂S₂O₃ (3 × 200 mL), brine (2 × 200 mL), dried (Na₂SO₄), and concentrated in vacuo. Trituration with petroleum ether gave the desired product 157 as a white solid (2.73 g, 94%).

1H NMR (CDCl₃, 400 MHz) δ: 7.87 (1H, s, OH), 7.42 (1H, d, J = 7.5 Hz, ᾳH), 6.87 (1H, d, J = 7.5 Hz, ᾳH), 5.29 (2H, s, C₅H₈), 2.30 (3H, s, C₆H₃).

13C NMR (CDCl₃, 100 MHz) δ: 173.0 (C=O), 154.5 (ᾳC(OH)), 144.1 (ᾳC), 138.2 (ᾳCH), 124.8 (ᾳC(CH₃)), 112.8 (ᾳCH), 110.5 (ᾳC), 70.4 (CH₂), 14.6 (CH₃).

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

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

![158](image)

7-Hydroxy-6-methylisobenzofuran-1(3H)-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 Et₂O (500 mL), washed with H₂O (50 mL), brine (4 × 50 mL), dried (Na₂SO₄), 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%).

1H NMR (400 MHz, CDCl₃) δ: 7.44 (1H, d, J = 7.6 Hz, ᾳH), 6.94 (1H, d, J = 7.6 Hz, ᾳH), 5.17 (2H, s, CH₂), 2.30 (3H, s, CH₃), 1.07 (9H, s, SiC(CH₃)₃), 0.27 (6H, s, Si(CH₃)₂).
$^{13}\text{C NMR (400 MHz, CDCl}_3\text{)} \delta$: 169.1 (C=O), 153.0 ($^{\text{Ar}}$CO), 146.3 ($^{\text{Ar}}$C), 137.6 ($^{\text{Ar}}$CH), 130.2 (ArCCH$_3$), 115.9 ($^{\text{Ar}}$C), 114.3 ($^{\text{Ar}}$CH), 68.1 (CH$_2$), 26.0 (SiC(CH$_3$)$_3$), 16.8 (CH$_3$), -3.5 (Si(CH$_3$)$_2$).

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

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

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$_2$O (3 mL), and extracted with Et$_2$O (3 × 10 mL). The combined organics were washed with saturated (aq) Na$_2$S$_2$O$_3$ (3 × 20 mL), brine (20 mL), dried (Na$_2$SO$_4$), then concentrated *in vacuo* to yield the desired product 277 as a yellow oil (223 mg, 89%).

$^1\text{H NMR (CDCl}_3\text{, 400 MHz) } \delta$: 3.81 – 3.70 (2H, m, CH$_2$OH), 2.51 (2H, t, $J = 7.0$ Hz, C=CC$_2$H$_2$), 1.83 – 1.72 (2H, m, CH$_2$CH$_2$CH$_2$).

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

**o-Nitrobenzenesulfonylhydrazide**

$o$-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 (Na₂SO₄) 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 8.26 – 8.21 (1H, m, HAr), 7.94 – 7.88 (1H, m, HAr), 7.86 – 7.78 (2H, m, HAr), 6.51 (1H, br s, NH), 3.84 (2H, br s, NH₂).

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

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

5-Iodopent-4-yn-1-ol 277 (5.47 g, 26.1 mmol) was dissolved in THF:iPrOH (1:1, 150 mL), and the resultant solution treated with 2-nitrobenzenesulfonyl hydrazide 278 (7.37 g, 33.8 mmol), followed by Et₃N (9.00 mL, 64.9 mmol). The reaction mixture was stirred for 16 h and protected from light. The reaction was then diluted with H₂O (150 mL), and extracted with diethyl ether (150 mL), dried (Na₂SO₄), 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%).

¹H NMR (CDCl₃, 500 MHz) δ: 6.24 – 6.19 (2H, m, HCHI), 3.68 (2H, dd, J = 10.0, 6.6 Hz, CH₂OH), 2.24 (2H, m, CH₂), 1.70 (2H, m, CH₂).

This data is in accordance with literature values.[⁹⁶]
Methyl (2E,6Z)-7-iodohepta-2,6-dienoate

(4Z)-5-Iodopent-4-en-1-ol 36 (4.30 g, 20.3 mmol) was dissolved in anhydrous CH₂Cl₂ (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 CH₂Cl₂. 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% Et₂O in petroleum ether) to yield the desired product 38 as a colourless oil (3.03 g, 56%).

¹H NMR (C₆D₆, 500 MHz) δ: 6.85 (1H, dt, J = 15.6, 6.9 Hz, HC=CHCO₂Me), 5.82 (1H, d, J = 7.4 Hz, HHC=CH), 5.74 (1H, dt, J = 15.6, 1.6 Hz, HC=CHCO₂Me), 5.50 (1H, q, J = 6.9 Hz, HHC=CH), 3.41 (3H, s, OCH₃), 1.91 – 1.84 (2H, m, CH₂), 1.73 – 1.65 (2H, m, CH₂).

¹³C NMR (CDCl₃, 100 MHz) δ: 167.1 (C=O), 147.8 (HC=CHCO), 139.6 (HC=CHI), 122.0 (HC=CHCO), 84.0 (HC=CHI), 51.7 (OCH₃), 33.3 (CH₂), 30.6 (CH₂).

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

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

Methyl (2E,6Z)-7-iodohepta-2,6-dienoate 38 (621 mg, 2.33 mmol) was dissolved in anhydrous CH₂Cl₂ (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 CH₂Cl₂ (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$_2$SO$_4$), filtered, and concentrated *in vacuo*. The crude product was purified using flash chromatography (silica gel, 0 – 25% Et$_2$O in petroleum ether) to yield the desired product 347 as a colourless oil (505 mg, 91%).

$^1$H NMR (C$_6$D$_6$, 400 MHz) $\delta$: 5.89 (1H, dt, $J = 7.3, 1.4$ Hz, HC=CHI), 5.71 (1H, q, $J = 6.9$ Hz HC=CHI), 5.40 – 5.35 (2H, m, HC=CHCH$_2$OH), 3.78 (2H, br s, CH$_2$OH), 2.07 – 1.99 (2H, m, CH$_2$CH=CHI), 1.88 – 1.81 (2H, m, CH$_2$CH=CHCH$_2$), 0.59 (1H, br s, OH).

$^{13}$C NMR (C$_6$D$_6$, 100 MHz) $\delta$: 140.9 (HC=CHI), 131.3 (HC) 130.5 (HC), 83.2 (CHI), 63.6 (CH$_2$OH), 34.9 (H$_2$CCH=CHI), 31.0 (H$_2$CCH=CHCH$_2$).

This data is in accordance with literature values.$^{[29]}$

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

(2E,6Z)-7-Iodohepta-2,6-dien-1-ol 347 (1.00 g, 4.20 mmol) was dissolved in CH$_2$Cl$_2$ (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.
Bromide 279 (810 mg, 2.69 mmol) was dissolved in anhydrous THF (20 mL) and cooled down to 0 °C. MeNH2 (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 MeNH2 was removed in vacuo to afford the crude product. Purification using SCX ion-exchange chromatography, flushing with MeOH, followed by elution with 7M NH3 in MeOH, afforded the amine intermediate as an orange oil (490 mg, 77%). The amine was dissolved in anhydrous CH2Cl2 (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 Et2O (40 mL) and H2O (40 mL). The organic layer was then washed with sat. NaHCO3 (aq) (40 mL), 20% citric acid (aq) (40 mL), and brine (2 x 40 mL), then dried (Na2SO4), 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)

1H NMR (CDCl3, 500 MHz) δ: 6.22 (1H, d, J = 7.3 Hz, HC=CHI), 6.15 (1H, q, J = 6.8 Hz, HC=CHI), 5.59 (1H, dtt, J = 15.4, 6.5, 1.3 Hz, HC=CH2N), 5.46 (1H, dtt, J = 15.4, 5.7, 1.3 Hz, CH2CH2), 5.19* (1H, br s, HCC(O)N), 5.16 (1H, br s, CHC(O)N), 3.98* (2H, br s, CH2N), 3.89 (2H, br s, CH2N), 3.62* (3H, br s, CH3O), 3.59 (3H, br s, CH3O), 2.95 (3H, br s, NCH3), 2.34 – 2.21 (7H, m, CH3, CH2CH2).

13C NMR (CDCl3, 100 MHz) δ: 168.5 (C=O), 167.8 (HC=C(Ome)), 140.6* (HCCH2CH2), 140.2 (HCCH2CH2), 132.0* (HC=CHCH2N), 131.6 (HC=CH2N), 126.4* (HC=CHI), 125.7 (HC=CHI), 91.2 (HCC(O)N), 83.1* (HC=CHI), 82.8 (HC=CHI), 54.8 (OCH3), 52.1 (CH2N), 49.0* (CH2N), 35.1 (CH3N), 34.3 (CH2), 33.4 (CH3N), 30.5 (CH2), 18.8 (CH3).

This data is in accordance with literature values.[29]
(S)-**tert-Butyl(3-iodo-2-methylpropoxy)diphenylsilane**

(2R)-3-((**tert-Butyldiphenylsilyl**oxy)-2-methylpropan-1-ol (20.3 g, 61.8 mmol) was dissolved in CH₂Cl₂ (250 mL) and cooled to 0 °C. Imidazole (5.75 g, 84.4 mmol), PPh₃ (20.5 g, 78.0 mmol) and I₂ (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 Na₂S₂O₃ solution (250 mL) and extracted with CH₂Cl₂ (2 × 150 mL). The combined organics were then washed with saturated Na₂S₂O₃ solution (300 mL), brine (2 × 150 mL), dried (Na₂SO₄), 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 (11.7 g, 43%).

**¹H NMR** (CDCl₃, 400 MHz) δ: 7.71 – 7.65 (4H, m, ArH), 7.48 – 7.36 (6H, m, ArH), 3.59 (1H, dd, J = 10.1, 4.9 Hz, CH₂I), 3.48 (1H, dd, J = 10.1, 6.9 Hz, CH₂I), 3.40 (1H, dd, J = 9.5, 5.1 Hz, CH₂SiO), 3.34 (1H, dd, J = 9.5, 5.8 Hz, CH₂SiO), 1.80 – 1.68 (1H, m, CH(CH₃)), 1.06 (9H, s, (CH₃)₃Si), 0.97 (3H, d, J = 6.7 Hz, CH₃).

**¹³C NMR** (CDCl₃, 100 MHz) δ: 135.7 (4 × ArCH), 133.6 (2 × ArC), 129.7 (2 × ArCH), 127.7 (4 × ArCH), 67.3 (CH₂O), 37.6 (CH(CH₃)), 26.9 (SiC(CH₃)₃), 19.3 (SiC(CH₃)₃), 17.3 (CH(CH₃)₃), 13.6 (CH₂I).

[α]D²⁶ +4.1 (c = 1.66, CHCl₃), lit. [α]D²³ +3.8 (c = 0.41, CHCl₃).

This data is in accordance with literature values.[⁵¹]
**N-((1S,2S)-1-Hydroxy-1-phenylpropan-2-yl)-N-methylpropionamide**

(1S,2S)-(+-)Pseudoephedrine (24.0 g, 145 mmol) and Et₃N (25.1 mL, 181 mmol) were dissolved in anhydrous CH₂Cl₂ (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 H₂O (50 mL). The organic layer was separated and washed with saturated NaHCO₃ (aq) (2 x 100 mL), 1M HCl (aq) (2 x 100 mL), dried (Na₂SO₄), 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)

1H NMR (CDCl₃, 400 MHz) δ: 7.63 – 7.30 (5H, m, ArH), 4.63 – 4.57 (1H, m, CHOH), 4.48 – 4.51 (1H, m, H), 4.06 – 3.98* (1H, m, H), 2.94* (3H, s, NCH₃), 2.82 (3H, s, NCH₃), 2.58 – 2.47* (2H, m, CH₂), 2.44 – 2.25 (2H, m, CH₂), 2.14 (1H, d, J = 2.0 Hz, OH), 1.22 – 1.12 (6H, m, CHCH₃ + CH₃CH₂), 0.99* (3H, d, J = 6.8 Hz, CHCH₃).

13C NMR (CDCl₃, 100 MHz) δ: 176.3 (C=O), 175.0* (C=O), 142.5 (C), 141.1 (C), 128.8* (C), 128.5* (C), 128.4 (C), 127.7 (C), 126.9* (C), 126.4 (C), 76.7 (CHOH), 75.5* (CHOH), 58.8* (CCH₃), 58.3 (CCH₃), 32.9* (NCH₃), 28.7 (NCH₃), 27.6 (CH₂), 26.9* (CH₂), 15.2* (CH₃), 14.5 (CH₃), 9.6* (CH₃), 9.2 (CH₃).

[α]D³¹ +98.3 (c = 0.82, CHCl₃), lit. [α]D²⁵ +103.6 (c = 1.20, CHCl₃).

This data is in accordance with literature values.\(^{[73]}\)
(R)-N-((1S,2S)-1-Hydroxy-1-phenylpropan-2-yl)-N,2-dimethylpent-4-enamide

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. nBuLi (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-((1S,2S)-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 NH₄Cl (aq) (50 mL) and diluted with EtOAc (200 mL), and washed with saturated NH₄Cl (100 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo to yield the desired product 286 as a yellow oil (14.2 g, quant.).

Characterised fully as 287.

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

(R)-N-((1S,2S)-1-Hydroxy-1-phenylpropan-2-yl)-N,2-dimethylpent-4-enamide 286 (29.0 g, 111 mmol) was dissolved in tBuOH (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 H₂O (500 mL), and extracted with CH₂Cl₂ (4 × 300 mL). The aqueous phase was then acidified to pH < 2
using 3M HCl (aq), and extracted with CH₂Cl₂ (3 × 400 mL). The combined extracts (after acidification) were dried (Na₂SO₄), filtered, and concentrated in vacuo to give the desired product 287 as a colourless oil (12.4 g, 98%).

¹H NMR (CDCl₃, 400 MHz) δ: 11.26 (1H, br s, OH), 5.78 (1H, m H=C), 5.15 – 5.02 (2H, m, C=CH₂), 2.62 – 2.52 (1H, m, CH(CH₃)), 2.50 – 2.40 (1H, m, CH₂), 2.26 – 2.18 (1H, m CH₂).

¹³C NMR (CDCl₃, 100 MHz) δ: 181.7 (C=O), 135.1 (HC=CH₂), 117.2 (HC=CH₂), 39.0 (CH₂), 37.5 (CH), 16.3 (CH₃).

[α]D²⁶ −32.4 (c = 1.30, CHCl₃), lit. [α]D²⁰ −20.9 (c = 1.11, CHCl₃).

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

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

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 nBuLi (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-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N₂'-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 Et₂O (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 (Na₂SO₄), 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 Et₂O (100 mL). The resultant solution was transferred dropwise via cannula to a rapidly stirred suspension of LiAlH₄ (3.47 g, 91.3 mmol) in anhydrous Et₂O (150 mL) at 0 °C. The reaction mixture was warmed to rt, and stirred for 16 h before being cooled to 0 °C. H₂O (3.5 mL) was added dropwise, followed by 15% NaOH (aq) (3.5 mL), then H₂O (10.4 mL), and the resultant mixture stirred for 15 min. Na₂SO₄ 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 5.88 – 5.77 (1H, m, HC=CH₂), 5.10 – 5.00 (2H, m, HC=CH₂), 3.55 – 3.45 (2H, m, CH₂OH), 2.23 – 2.14(1H, m, CH₂CH=CH₂), 2.00 -1.91 (1H, m, CH₂CH=CH₂), 2.00 – 1.92 (1H, m, CH(CH₃)), 1.33 (1H, br s, OH), 0.94 (3H, d, J = 0.94 Hz, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 137.0 (HC=CH₂), 116.1(HC=CH₂), 67.9 (OCH₂), 37.9 (CH₂), 35.6 (CH), 16.4 (CH₃).

[α]D⁺³¹ +6.8 (c = 1.01, CHCl₃), lit. [α]D⁺¹⁹ +4.3 (c = 1.00, CHCl₃).

This data is in accordance with literature values.⁹⁸

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

Method A:

(S)-tert-Butyl(3-iodo-2-methylpropoxy)diphenylsilane  (S)-185 (500mg, 1.14 mmol) was dissolved in Et₂O (8 mL) and cooled to -78 °C. '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 ZnBr₂ (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(PPh₃)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 Et₂O (10 mL), washed with water (2 × 25 mL), then brine (2 × 25 mL), dried (Na₂SO₄), filtered, and concentrated \textit{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:**

\((2R)\)-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). TBDPSCI (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 H₂O (250 mL), brine (4 × 250 mL), dried (Na₂SO₄), filtered, and concentrated \textit{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 (CDCl₃, 400 MHz) \(\delta\): 7.73 – 7.62 (4H, m, \(^{1}H\)), 7.48 – 7.33 (6H, m, \(^{1}H\)), 5.84 – 5.71 (1H, m, HC=CH₂), 5.08 – 4.92 (2H, m, HC=CH₂), 3.50 (2H, dd, \(J = 6.0, 2.6\) Hz, CH₃SiO), 2.30 – 2.23 (1H, m, CH₂CH=CH₂), 1.95 – 1.88 (1H, m, CH₂CH=CH₂), 1.80 – 1.72 (1H, m, CH(CH₃)), 1.06 (9H, s, (CH₃)₃Si), 0.92 (3H, d, \(J = 6.7\) Hz, CH₃).

\(^{13}\)C NMR (CDCl₃, 100 MHz) \(\delta\): 137.3 (HC=CH₂), 135.6 (4 × \(^{13}C\)), 134.2 (\(^{13}C\)), 134.0 (\(^{13}C\)), 129.5 (2 × \(^{13}C\)), 127.6 (4 × \(^{13}C\)), 115.7 (HC=CH₂), 68.4 (CH₂), 37.6 (CH₂), 35.7 (CH(CH₃)), 26.9 (C(CH₃)₃), 19.3 (C(CH₃)₃), 16.4 (CH₃).

\([\alpha]D^{22} +6.8\) (c = 1.96, CHCl₃), lit. \([\alpha]D^{20} +3.1\) (c = 1.14, CHCl₃).

This data is in accordance with literature values.\[^{[99]}\]
(4R)-5-((tert-Butyldiphenylsilyl)oxy)-4-methylpentane-1,2-diol

(R)-tert-Butyl((2-methylpent-4-en-1-yl)oxy)diphenylsilane (R)-186 (10.68 g, 31.54 mmol) was dissolved in MeCN (80 mL) and cooled to 0 °C. H₂O (20 mL), and NMO (7.26 g, 62.0 mmol) were added, followed by OsO₄ (2.5% w/w in tBuOH, 0.30 mmol). The reaction mixture was warmed to rt, and stirred for 16 h. The reaction mixture was quenched with Na₂SO₃ (aq) (100 mL), diluted with Et₂O (200 mL), washed with water (200 mL), then brine (2 × 200 mL), dried (Na₂SO₄), 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)

¹H NMR (CDCl₃, 400 MHz) δ: 7.68 – 7.64 (4H, m, ArH), 7.47 – 7.34 (6H, m, ArH), 3.88 – 3.76 (1H, m, CH(OH)), 3.65 – 3.38 (4H, m, OCH₂), 3.34 (1H, d, J = 3.4 Hz, OH), 2.83* (1H, d, J = 4.1 Hz, OH), 1.99 (1H, dd, J = 6.8, 4.9 Hz, OH(CH)), 1.92* (1H, dd, J = 7.2, 5.0 Hz, OH(CH)), 1.91 – 1.83 (1H, m, CH(CH₃)), 1.56 – 1.44 (3H, m, CH₂ + SiOCH₂), 1.36 (1H, dd, J = 14.3, 6.4, 2.9 Hz, CH₂), 1.06 (9H, s, SiC(CH₃)₃), 0.92* (3H, d, J = 6.9 Hz, CH₃), 0.86 (3H, d, J = 6.9 Hz, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 135.7* (ArCH), 135.6(ArCH), 135.6* (ArCH), 133.3* (ArC), 133.3* (ArC), 133.2 (ArC), 133.2 (ArC), 129.8 (ArCH), 127.8 (ArCH), 70.7 (CH(OH)), 70.0 (CH₂OSi), 69.8* (CH(OH)), 68.9* (CH₂OSi), 67.4 (CH₂OH), 67.1* (CH₂OH), 38.8* (CH₂), 37.8 (CH₂), 33.7 (CH(CH₃)), 32.2* (CH(CH₃)), 26.9* (SiC(CH₃)₃), 26.8 (SiC(CH₃)₃), 19.2 (SiC(CH₃)), 17.7 (CH₃), 17.6* (CH₃).

HRMS (ESI) calculated for C₂₂H₃₂O₃SiNa (M+Na)*: m/z 395.2013, observed 395.1996.

IR v_max (film)/cm⁻¹ 3383, 2957, 2930, 2857, 1471, 1427.
(4R)-1-((tert-Butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-pentanol

\[
\text{TBDPSO} \quad \text{OH} \quad \text{OTBS}
\]

348

(4R)-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 TBSCI (4.85 g, 32.2 mmol) was added. The reaction mixture was stirred for 1 h before being quenched with H₂O (100 mL), extracted with Et₂O (200 mL), washed with brine (4 × 100 mL), dried (Na₂SO₄), 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.

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

\[
\text{TBDPSO} \quad \text{OMs} \quad \text{OTBS}
\]

291

(4R)-1-((tert-Butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-pentanol 348 (15.1 g, 32.2 mmol) was dissolved in anhydrous CH₂Cl₂ (200 mL) and cooled to 0 °C. Et₃N (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 H₂O (100 mL). The organics were then washed with H₂O (2 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo to give the desired product 291 as a yellow oil (18.2 g, 100% crude).

Fully characterised as 292.
(4R)-1-((tert-Butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl azide

(4R)-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). NaN₃ (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 H₂O (150 mL), extracted with Et₂O (300 mL), washed with brine (4 × 100 mL), dried (Na₂SO₄), 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.

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

(4R)-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 H₂ 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 CH₂Cl₂) 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)
1H NMR (CDCl₃, 400 MHz) δ: 7.68 – 7.62 (4H, m, ṼH), 7.45 – 7.34 (6H, m, ṼH), 3.66 (1H, td, J = 9.4, 3.7 Hz, SiOCH₂), 3.56 – 3.41 (3H, m, SiOCH₂), 3.08 (1H, m, CH(NH₂)), 1.92 – 1.79 (1H, m, CH₂), 1.66 – 1.59 (1H, m, CH(CH₃)), 1.56 – 1.48* (1H, m, CH(CH₃)), 1.37 – 1.29 (1H, m, CH₂), 1.05 (9H, s, Si(CH₃)₃), 0.96 (3H, d, J = 6.6 Hz, CH₃), 0.94* (3H, d, J = 6.6 Hz, CH₃), 0.90 (9H, s, Si(CH₃)₃), 0.89 (9H, s, Si(CH₃)₂), 0.07 (6H, s, Si(CH₃)₂).

13C NMR (CDCl₃, 100 MHz) δ: 135.6 (ṼCH), 135.6* (ṼCH), 133.8 (ṼC), 133.7 (ṼC), 129.6 (ṼCH), 129.6 (ṼCH), 127.7 (ṼCH), 69.3 (SiOCH₂), 68.6 (SiOCH₂), 51.2 (CH₂(NH₂)), 50.9* (CH(NH₂)), 38.3 (CH₂), 37.5* (CH₂), 32.5 (CH(CH₃)), 32.4* (CH(CH₃)), 26.9* (SiC(CH₃)₂), 25.9 (SiC(CH₃)₃), 19.3* (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), 17.5 (CH₃), 16.8* (CH₃), -5.33* (Si(CH₃)₂), -5.38 (Si(CH₃)₂).

HRMS (CI) calculated for C₁₆H₂₅O₃NNa (M+H)+: m/z 486.3224, observed 486.3207.

IR νmax (film)/cm⁻¹ 3017, 2957, 2930, 2857, 2359, 1472.

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

(4R)-1-((tert-Butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl amine 292 (6.19 g, 12.7 mmol) and (2R)-4-(benzoyloxy)-2-methylbutanoic acid (R)-194 (2.65 g, 12.7 mmol) were dissolved in anhydrous CH₂Cl₂ (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 Et₂O (200 mL), washed with water (150 mL), NaHCO₃ (aq) (100 mL), 10% HCl (aq) (100 mL), brine (2 × 100 mL), dried (Na₂SO₄), then filtered, and concentrated in vacuo to give the desired crude amide product 350 (8.43 g, 98% crude).

Fully characterised as 295.
(2R)-4-(Benzyloxy)-N-((4R)-5-((tert-butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide

(2R)-4-Benzylxoy-N-((4R)-((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. NEt₃ (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.

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

Method A:

CH₂Cl₂ (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 CH₂Cl₂ (5 mL) was added dropwise over 20 min and the resultant solution was stirred for 30 min. (2R)-4-(Benzyloxy)-N-((4R)-5-((tert-butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide 293 (2.50 g, 4.45 mmol) in CH₂Cl₂ (5 mL) was added dropwise over 30 min and the reaction mixture was stirred for 30 min. Et₃N (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 CH₂Cl₂ (100 mL), washed with
NH₄Cl (100 mL), H₂O (2 × 100 mL), brine (2 × 100 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to give the desired crude product 351 as an orange oil (1.57 g, 63%).

Method B:

(2R)-4-(Benzyloxy)-N-((4R)-5-((tert-butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylbutanamide 293 (6.09 g, 10.8 mmol) was dissolved in anhydrous CH₂Cl₂ (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 CH₂Cl₂ (75 mL), washed with NaHCO₃ (aq) (100 mL), Na₂S₂O₃ (aq) (100 mL), and brine (100 mL). The organic was then dried (Na₂SO₄), 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

(2R)-4-(Benzyloxy)-N-((4R)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-1-oxopentan-2-yl)-2-methylbutanamide 351 (1.57 g, 2.80 mmol) dissolved in CH₂Cl₂ (60 mL) and cooled down to 0 °C. PPh₃ (2.05 g, 7.82 mmol), DTBMP (2.01 g, 9.79 mmol), and (BrCCl₂)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 % Et₂O in petroleum ether) to yield the desired product 295 (795 mg, 61% brsm 225 mg).

¹H NMR (500 MHz, CDCl₃) 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, OCH₃Ph), 3.58 – 3.41 (4H, m, OCH₂Si, CH₂OBn), 3.19 – 3.14 (1H, m, (CH₃)CH(Ar)), 2.67 (1H, dd, J = 14.6, 5.5 Hz, CH₂Ar), 2.33 (1H, dd, J = 14.6, 7.8 Hz, CH₂Ar), 2.16 – 2.02 (2H, m, CH(CH₂Ar), CH₂(CH₂OBn)), 1.91 – 1.85 (1H, m,
1H NMR (CDCl₃, 400 MHz) δ: 7.37 – 7.27 (6H, m, ArH), 4.47 (2H, s, OCH₂), 3.58 – 3.41 (4H, m, CH₂OH + CH₂OBn), 3.23 – 3.14 (1H, m, CH(CH₃)), 2.60 – 2.46 (2H, m, CH₂), 2.16 – 2.08 (1H, m, CH₂), 2.04 – 1.96 (1H, m, CH₂), 1.93 – 1.85 (1H, m, CH(CH₃)), 1.32 (3H, d, J = 7.1 Hz, CH₃), 0.91 (3H, d, J = 6.9 Hz, CH₃).

13C NMR (100 MHz, CDCl₃) δ: 168.0 (Ar-CN), 138.4 (Ar CHO), 138.0 (Ar-C), 134.2 (Ar-C), 128.3 (Ar CH), 127.6 (Ar CH), 127.5 (Ar CH), 73.0 (OCH₂Ph), 67.7 (CH₂OBn), 67.4 (CH₂OH),
35.0 (CH(CH₃)), 34.9 (CH₂), 30.6 (CH(CH₃)), 30.1 (CH₂), 18.5 (CH(CH₃)), 16.9 (CH(CH₃)).

HRMS (ESI) calculated for C₁₈H₂₅O₃NNa (M+Na)^+: m/z 326.1727, observed 326.1716.

IR ν_max (film)/cm⁻¹ 3370, 2870, 1566, 1094, 1038, 750.

[α]D^26 -22.6 (c = 1.31, CHCl₃).

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

(R)-3-((R)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)-2-methylpropan-1-ol 296 (176 mg, 0.58 mmol) was dissolved in CH₂Cl₂ (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%).

¹H NMR (CDCl₃, 400 MHz) δ: 9.72 (1H, d, J = 1.3 Hz, C(O)H), 7.36 – 7.27 (6H, m, ArH), 4.47 (2H, s, OCH₂Ph), 3.55 – 3.40 (2H, m, CH₂OBn), 3.23 – 3.12 (1H, m, CH(CH₃)), 2.92 (1H, ddd, J = 14.7, 6.6, 1.0 Hz, CH₂Ar), 2.83 – 2.71 (1H, m, CH(CH₃)), 2.54 (1H, ddd, 14.7, 7.1, 0.9 Hz, CH₂Ar), 2.18 – 2.05 (1H, m, CH₂), 1.93 – 1.85 (1H, m, CH₂), 1.32 (3H, d, J = 7.1 Hz, CH₃), 1.11 (3H, d, J = 7.1 Hz, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 204.1 (HC=O), 168.1 (ArC), 138.4 (ArC), 137.3 (ArC), 134.3 (ArCH), 128.3 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 73.0 (OCH₂Ph), 67.8 (OCH₂CH₃), 45.4 (CH(CH₃)C(O)H), 35.0 (CH₂), 30.7 (CH(CH₃)), 27.2 (CH₂), 18.6 (CH₃), 13.3 (CH₃).

HRMS (ESI) calculated for C₁₈H₂₃O₃NNa (M+Na)^+: m/z 324.1570, observed 324.1554.

IR ν_max (film)/cm⁻¹ 2972, 2874, 2861, 1722, 1570, 1440, 1036.

[α]D^26 -20.5 (c = 1.12, CHCl₃).
1-Methoxy-1,3-dihydroisobenzofuran

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.H₂O (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 NaHCO₃ (aq) solution (400 mL), brine (400 mL), dried (Na₂SO₄), 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 7.44 – 7.28 (4H, m, ArH), 6.20 (1H, d, J = 2.2 Hz, CHOCH₃), 5.23 (1H, d, J = 12.7 Hz, CH₂), 5.06 (1H, d, J = 12.7 Hz, CH₂), 3.45 (3H, s, OC₃H₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 140.0 (ArC), 137.3 (ArC), 129.2 (ArCH), 127.7 (ArCH), 123.0 (ArCH), 121.0 (ArCH), 107.6 (CHOCH₃), 72.4 (CH₂), 54.3 (OCH₃).

This data is in accordance with literature values.²⁷

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

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 Et₂O (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\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated \textit{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\textsubscript{3} (aq) solution, diluted with Et\textsubscript{2}O (150 mL), and the aqueous phase extracted with (150 mL). The combined organics were then washed with H\textsubscript{2}O (2 × 100 mL), brine (2 × 100 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, then concentrated \textit{in vacuo}. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in petroleum ether) to yield the desired product \textbf{159} as a colourless oil (1.55 g, 88%).

\begin{align*}
{^1}\text{H NMR} & \quad (\text{CDCl}_3, \quad 400 \text{ MHz}) \quad \delta: \quad 7.14 \ (1\text{H, d, } J = 7.6 \text{ Hz, } \text{ArH}), \quad 6.77 \ (1\text{H, d, } J = 7.6 \text{ Hz, } \text{ArH}), \\
& \quad 6.16 \ (1\text{H, d, } J = 1.9 \text{ Hz, CH}), \quad 5.14 \ (1\text{H, d, } J = 12.4 \text{ Hz, CH}_2), \quad 4.94 \ (1\text{H, d, } J = 12.4 \text{ Hz, CH}_2), \\
& \quad 3.41 \ (3\text{H, s, CH}_3), \quad 2.23 \ (3\text{H, s, CH}_3), \quad 1.03 \ (9\text{H, s, C(CH}_3)_3), \quad 0.21 \ (6\text{H, s, Si(CH}_3)_2).
\end{align*}

\begin{align*}
{^{13}}\text{C NMR} & \quad (\text{CDCl}_3, \quad 100 \text{ MHz}) \quad \delta: \quad 149.2 \ (\text{ArC}), \quad 139.9 \ (\text{ArC}), \quad 132.9 \ (\text{ArCH}), \quad 128.3 \ (\text{ArC}), \quad 128.2 \\
& \quad (\text{ArC}), \quad 113.8 \ (\text{ArCH}), \quad 106.4 \ (\text{CH(OCH}_3)_3), \quad 72.1 \ (\text{CH}_2), \quad 54.2 \ (\text{OCH}_3), \quad 25.9 \ (\text{SiC(CH}_3)_3), \quad 18.6 \\
& \quad (\text{ArCH}_3), \quad 17.2 \ (\text{SiC(CH}_3)_3), \quad -3.4 \ (\text{Si(CH}_3)_2), \quad -3.5 \ (\text{Si(CH}_3)_2).
\end{align*}

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

\textbf{3-((tert-Butyldimethylsilyl)oxy)-4-methyl-1,2-phenylene}dimethanol

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{303.png}
\caption{3-((tert-Butyldimethylsilyl)oxy)-4-methyl-1,2-phenylene}dimethanol
\end{figure}

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

\begin{align*}
{^1}\text{H NMR} & \quad (\text{CDCl}_3, \quad 400 \text{ MHz}) \quad \delta: \quad 7.09 \ (1\text{H, d, } J = 7.5 \text{ Hz, } \text{ArH}), \quad 6.92 \ (1\text{H, d, } J = 7.5 \text{ Hz, } \text{ArH}), \\
& \quad 4.80 \ (2\text{H, s, CH}_2), \quad 4.69 \ (2\text{H, s, CH}_2), \quad 2.79 \ (2\text{H, br s, OH}), \quad 2.23 \ (3\text{H, s, CH}_3), \quad 1.05 \ (9\text{H, s, C(CH}_3)_3), \quad 0.20 \ (6\text{H, s, Si(CH}_3)_2).
\end{align*}

\begin{align*}
{^{13}}\text{C NMR} & \quad (\text{CDCl}_3, \quad 100 \text{ MHz}) \quad \delta: \quad 151.9 \ (\text{ArC}), \quad 139.1 \ (\text{ArC}), \quad 130.9 \ (\text{ArCH}), \quad 130.5 \ (\text{ArC}), \quad 129.7 \\
& \quad (\text{ArC}), \quad 123.3 \ (\text{ArCH}), \quad 64.7 \ (\text{HOCH}_2), \quad 57.3 \ (\text{HOCH}_2), \quad 26.1 \ (\text{SiC(CH}_3)_3), \quad 18.7 \ (\text{SiC}), \quad 18.0 \\
& \quad (\text{CH}_3), \quad -3.5 \ (\text{Si(CH}_3)_2).
\end{align*}
HRMS (ESI) calculated for C_{15}H_{26}O_{3}SiNa (M+Na)^+: m/z 305.1543, observed m/z 305.1539.

IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3384, 2955, 2930, 2859, 1580, 1416, 1265

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

![Chemical Structure](image)

*tert*-Butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yloxy)dimethylsilane (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 iPr$_2$NH (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$_2$O at 0 °C, diluted with Et$_2$O (10 mL), washed with H$_2$O (10 mL), brine (10 mL), then dried (Na$_2$SO$_4$). The solvent was removed in vacuo to give the $\alpha$-hydroxy-isobenzofuran intermediate. This intermediate was then immediately dissolved in anhydrous CH$_2$Cl$_2$ (6 mL) and cooled to 0 °C. The resultant solution was then treated with mCPBA (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$_2$Cl$_2$ (2 × 10 mL), and dried (Na$_2$SO$_4$). The solvent was removed in vacuo to give the crude keto-lactol intermediate. This intermediate was then dissolved in anhydrous CH$_2$Cl$_2$ (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$_2$Cl$_2$ (20 mL), washed with Na$_2$S$_2$O$_3$ (aq) (2 × 10 mL), water (2 × 10 mL), brine (10 mL), dried (Na$_2$SO$_4$), 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) $\delta$: 7.63 (1H, d, $J = 7.8$ Hz, $^\text{Ar}H$), 7.57 (1H, d, $J = 7.8$ Hz, $^\text{Ar}H$), 4.75 (1H, d, $J = 4.9$ Hz, C(O)CH), 2.42 – 2.33 (4H, m, CH$_3$ & CH(CH$_3$)$_2$), 1.10 (3H, d, $J =
6.9 Hz, CH(CH₃)₂, 1.07 (9H, s, SiC(CH₃)₃), 0.99 (3H, d, J = 6.8 Hz, CH(CH₃)₂), 0.24 (3H, s, SiCH₃), 0.21 (3H, s, SiCH₃).

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

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

![Chemical structure](image)

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 NaBH₄ (16 mg, 0.43 mmol) and the reaction mixture was warmed to rt and stirred for 16 h. The reaction was then quenched with H₂O, and 10% (aq) citric acid solution (10 mL). The aqueous was extracted with CH₂Cl₂ (2 × 10 mL), and the combined organics washed with H₂O (10 mL), brine (10 mL), dried (Na₂SO₄), 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%).

**¹H NMR** (CDCl₃, 400 MHz) δ: 7.38 (1H, dd, J = 7.5, 0.7 Hz, ArH), 6.96 (1H, d, J = 7.5 Hz, ArH), 4.67 (1H, dd, J = 7.3, 1.1 Hz, HC(OH)), 3.88 (1H, dd, J = 9.8, 1.4 Hz, HC(OH)), 2.33 – 2.22 (1H, m, HC(CH₃)₂), 2.27 (3H, s, SiCH₃), 1.95 (1H, d, J = 7.4 Hz, OH), 1.17 (3H, d, J = 6.6 Hz, HC(CH₃)₂), 1.07 (3H, d, J = 6.6 Hz, HC(CH₃)₂), 1.04 (9H, s, SiC(CH₃)₃), 0.19 (3H, s, Si(CH₃)₂), 0.11 (3H, s, Si(CH₃)₂).

**¹³C NMR** (CDCl₃, 100 MHz) δ: 163.0 (C=O), 155.4 (ArC), 139.6 (ArC), 136.3 (ArCH), 132.8 (ArC), 120.4 (ArCH), 115.8 (ArC), 85.7 (CHCH(CH₃)₂), 66.1 (CHOH), 28.4 (CH(CH₃)₂), 25.9 (SiC(CH₃)₃), 19.3 (CH₃), 18.7 (SiC), 18.2 (CH₃), 17.5 (ArCH), -3.7 (Si(CH₃)₂), -3.7 (Si(CH₃)₂).

This data is in accordance with literature values.[48]
1-Hydroxy-3-isopropylisochroman-4-one

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 Pr2NH (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 H2O at 0 °C, diluted with Et2O (60 mL), washed with water (60 mL), brine (60 mL), then dried (Na2SO4). The solvent was removed in vacuo to give the α-hydroxy-isobenzofuran intermediate. This intermediate was then immediately dissolved in anhydrous CH2Cl2 (30 mL) and cooled to 0 °C. The resultant solution was then treated with mCPBA (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 NaHCO3 (aq) (30 mL), extracted with CH2Cl2 (2 × 30 mL), and dried (Na2SO4). The solvent was removed in vacuo to give the crude keto-lactol 305 (1.03 g, 100%) which was used in the subsequent reaction without further purification.

3-Isopropylisochroman-1,4-dione

1-Hydroxy-3-isopropylisochroman-4-one 305 (343 mg, 1.67 mmol) was dissolved in anhydrous CH2Cl2 (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\(_3\)) \(\delta\): 8.33 – 8.28 (1H, m, \(^{\text{Ar}}\)H), 8.11 – 8.07 (1H, m, \(^{\text{Ar}}\)H), 7.86 (2H, m, \(^{\text{Ar}}\)H), 4.96 (1H, d, \(J = 3.7\) Hz, OCH), 2.51 (1H, m, H(C\(_3\)H)\(_2\)), 1.16 (3H, d, \(J = 7.0\) Hz, CH\(_3\)), 0.94 (3H, d, \(J = 6.8\) Hz, CH\(_3\)).

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 192.5 (\(\text{C}=\text{O}\)), 162.0 (\(\text{C}=\text{O(O)}\)), 135.6 (\(^{\text{Ar}}\)CH), 134.5 (\(^{\text{Ar}}\)CH), 132.0 (\(^{\text{Ar}}\)C), 130.6 (\(^{\text{Ar}}\)CH), 128.1 (\(^{\text{Ar}}\)C), 125.6 (\(^{\text{Ar}}\)CH), 88.9 (CHO), 33.4 (CH(CH\(_3\))\(_2\)), 18.9 (CH\(_3\)), 16.3 (CH\(_3\)).

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

(3R,4R)-4-hydroxy-3-isopropylisochroman-1-one

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\(_2\)Cl\(_2\) (2 \(\times\) 10 mL), and the combined organics washed with H\(_2\)O (10 mL), brine (10 mL), dried (Na\(_2\)SO\(_4\)), 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\(_3\)) \(\delta\): 8.16 (1H, dd, \(J = 7.8, 1.1\) Hz, \(^{\text{Ar}}\)H), 7.67 (1H, td, \(J = 7.5, 1.3\) Hz, \(^{\text{Ar}}\)H), 7.55 (1H, td, \(J = 7.6, 1.2\) Hz, \(^{\text{Ar}}\)H), 7.48 (1H, d, \(J = 7.5\) Hz, \(^{\text{Ar}}\)H), 4.78 (1H, d, \(J = 6.2\) Hz, CHO\(_{\text{OH}}\)), 4.03 (1H, dd, \(J = 9.8, 1.5\) Hz, CH\(_{\text{CH(CH\(_3\))}}\)), 2.41 – 2.34 (1H, m, CH\(_{\text{CH(CH\(_3\))}}\)), 1.80 (1H, d, \(J = 7.1\) Hz, OH), 1.23 (3H, d, \(J = 6.6\) Hz, CH\(_{\text{CH(CH\(_3\))}}\)), 1.13 (3H, d, \(J = 6.6\) Hz, CH\(_{\text{CH(CH\(_3\))}}\)).
13C NMR (100 MHz, CDCl3) 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 (CHOC), 65.2 (CHOH), 28.7 (CH(CH3)2), 19.3 (CH3), 18.2 (CH3).

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

(3R,4R)-3-((R)-1-2-((R)-4-(Benzyloxy)butan-2-yl)oxazol-4-yl)propan-2-yl)-8-(tert-butyldimethylsilyloxy)-4-hydroxy-7-methylicoschroman-1-one

tert-Butyl((3-methoxy-5-methyl-1,3-dihydro-2-benzofuran-4-yl)oxy)dimethylsilane (159 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 Et2O, 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. (2R)-3-((2R)-4-(Benzyloxy)butan-2-yl)-1,3-oxazol-4-yl)-2-methylpropanal (281 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. H2O (1 mL) was added, then the reaction mixture was diluted with Et2O (10 mL), washed with H2O (10 mL), brine (10 mL), the organic dried (Na2SO4), filtered, and concentrated in vacuo to yield the α-hydroxy-isobenzofuran intermediate. The crude intermediate was then immediately dissolved in anhydrous CH2Cl2 (10 mL), and cooled to 0 °C, under an argon atmosphere. mCPBA (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 NaHCO3 (aq) (10 mL), extracted with CH2Cl2 (2 × 10 mL), and dried (Na2SO4). The solvent was removed in vacuo, and the lactol intermediate was immediately dissolved in anhydrous CH2Cl2 (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 CH2Cl2 (3 mL) under an argon atmosphere, and cooled to -78 °C. CeCl3.7H2O
(66 mg, 0.18 mmol) in MeOH (3 mL) was added, and the resultant mixture stirred for 10 min. NaBH₄ (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 H₂O (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 CH₂Cl₂ (3 × 3 mL). The combined organics were washed with brine (3 mL), dried (Na₂SO₄), 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

1H NMR (CDCl₃, 400 MHz) δ: 7.37 (1H, dd, J = 7.5, 0.7 Hz, ArH), 7.36 – 7.22 (6H, m, ArH), 6.95 (1H, d, J = 7.6 Hz, ArH), 4.66 (1H, d, J = 1.3 Hz, CH(OH)), 4.45 (2H, s, OCH₂Ph), 4.06 (1H, dd, J = 9.3, 1.5 Hz, CH(O₂C)), 3.53 – 3.42 (2H, m, CH₂OBn), 3.22 – 3.13 (1H, m, CH(CH₃)), 3.04 (1H, dd, J = 14.6, 2.6 Hz, CH₂), 2.60 (1H, dd, J = 14.6, 7.8 Hz, CH₂), 2.51 – 2.43 (1H, m, CH(CH₃)), 2.27 (3H, s, ArCCH₃), 2.14 – 2.05 (1H, m, CH₂CH₂OBn), 1.92 – 1.83 (1H, m, CH₂CH₂OBn), 1.30 (3H, d, J = 7.3 Hz, CH₃), 1.21 (3H, d, J = 6.7 Hz), 1.04 (9H, s, SiC(CH₃)₃), 0.20 (3H, s, Si(CH₃)₂), 0.12 (3H, s, Si(CH₃)₂).

13C NMR (CDCl₃, 100 MHz) δ: 167.7 (C=O), 163.0 (C=N), 155.4 (ArC), 139.7 (ArC), 138.4 (ArC), 137.9 (ArC), 136.3 (ArCH), 134.7 (ArCH), 132.7 (ArC), 128.3 (ArCH), 127.6 (ArC), 127.5 (ArCH), 120.4 (ArCH), 115.8 (ArC), 83.0 (CH(O₂C)), 73.0 (OCH₂Ph), 67.8 (CH₂OBn), 66.3 (CH(OH)), 35.0 (CH₂CH₂OBn), 33.2 (CH(CH₃)), 30.7 (CH(CH₃)), 28.1 (CH₃), 26.0 (SiC(CH₃)₃), 18.6 (SiC(CH₃)₃), 18.4 (CH₃), 17.5 (ArCCH₃), 15.4 (CH₃), -3.6 (Si(CH₃)₂), -3.7 (Si(CH₃)₂).

HRMS (ESI) calculated for C₃₃H₄₅O₇NSiNa (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

![Structure 319](image)

4-Pentyn-1-ol (0.94 mL, 10.1 mmol) was dissolved in anhydrous THF (30 mL) and the solution cooled to -78 °C. nBuLi (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 Et₂O:1 M HCl (1:1, 50 mL) was added and the reaction stirred for 3 h, before being diluted with Et₂O (100 mL). The organic phase was separated and the aqueous layer extracted with Et₂O (50 mL). The organic extracts were then washed with sat. NaHCO₃ (aq) (100 mL), brine (100 mL), dried (Na₂SO₄), 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 3.80 – 3.75 (2H, m, OC₂H₂), 2.36 (2H, t, J = 6.9 Hz, CH₂), 1.82 – 1.75 (2H, m, CH₂), 1.57 (1H, s, OH), 0.16 (9H, s, Si(CH₃)₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 106.6 (C≡Si), 85.3 (C≡Si), 61.9 (OCH₂), 31.1 (CH₂), 16.5 (CH₂), 0.0 (Si(CH₃)₃).

This data is in accordance with literature values. [87]

5-(Trimethylsilyl)pent-4-ynal

![Structure 320](image)

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. H₂O (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 Et₂O (75 mL). The organic phase was separated, and the aqueous phase extracted with Et₂O (50 mL). The organic extracts were then washed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification using flash chromatography (silica gel, 5% Et₂O in pentane) gave the desired product 320 as a colourless oil (214 mg, 62%).

1H NMR (CDCl₃, 400 MHz) δ: 9.80 (1H, t, J = 1.1 Hz, C(O)H), 2.73 – 2.65 (2H, m, CH₂), 2.58 – 2.53 (2H, m, CH₂), 0.15 (9H, s, Si(CH₃)₃).

13C NMR (CDCl₃, 100 MHz) δ: 200.4 (C(O)H), 104.7 (C≡CSi), 85.8 (C≡CSi), 42.5 (CH₂), 13.1 (CH₂), 0.0 (Si(CH₃)₃).

This data is in accordance with literature values.[100]

8-((tert-Butyldimethylsilyloxy)-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)dimethysilane 159 (507 mg, 1.72 mmol) was dissolved in anhydrous THF (10 mL), and cooled to 0 °C. Freshly distilled Pr₂NH (0.48 mL, 3.42 mmol) was added, and the resultant solution stirred for 10 min. MeLi (1.6 M in Et₂O, 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. H₂O (1 mL) was added, then the reaction mixture was diluted with Et₂O (25 mL), washed with H₂O (20 mL), and brine (20 mL). The organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo to yield the α-hydroxy-isobenzofuran intermediate. The crude intermediate was then immediately dissolved in anhydrous CH₂Cl₂ (10 mL), and cooled to 0 °C. mCPBA (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 NaHCO₃ (aq) (10 mL), extracted with CH₂Cl₂ (2 × 10 mL),
and dried (Na$_2$SO$_4$). The solvent was removed \textit{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) $\delta$: 7.59 (1H, d, $J = 7.9$ Hz, $^\alpha$H), 7.27 (1H, d, $J = 7.9$ Hz, $^\beta$H), 6.36 (1H, br s, CHOH), 4.95 (1H, dd, $J = 8.9, 3.6$ Hz, C(O)CH$_2$), 2.78 (1H, d, $J = 3.6$ Hz, OH), 2.46 – 2.41 (2H, m, CH$_2$CH$_2$), 2.36 – 2.31 (1H, m, CH$_2$), 2.31 (3H, s, CH$_3$), 1.97 – 1.88 (1H, m, CH$_2$), 1.06 (OSi(CH$_3$)$_3$), 0.30 (3H, s, SiCH$_3$), 0.26 (3H, s, SiCH$_3$), 0.14 (9H, s, CSi(CH$_3$)$_3$).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$: 195.5 (C=O), 149.8 ($^\alpha$C), 136.4 ($^\beta$C), 132.0 ($^\gamma$C), 131.4 ($^\delta$C), 128.0 ($^\epsilon$C), 119.7 ($^\zeta$CH), 103.4 (C=C), 88.0 (CH(CO)), 85.5 (C=C), 71.2 (CH(OH)), 29.3 (CH$_3$), 26.1 (SiC(CH$_3$)$_3$), 25.7 (SiC(CH$_3$)$_3$), 18.6 (CH$_2$), 15.8 (CH$_3$), 0.13 (Si(CH$_3$)$_3$), -3.12 (Si(CH$_3$)$_2$), -3.58 (Si(CH$_3$)$_2$).

HRMS (ESI) calculated for C$_{23}$H$_{36}$O$_4$Si$_2$Na (M+Na)$^+$: m/z 455.2044, observed 455.2027.

IR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3391, 2957, 2930, 2857, 2357, 2178, 1694, 1472, 1252.

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

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. nBuLi (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-((1S,2S)-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$_4$Cl (aq) (250 mL) and diluted with
EtOAc (300 mL), and washed with saturated NH₄Cl (300 mL). The aqueous layer was extracted with EtOAc (2 × 300 mL), and the combined organic extracts were dried (Na₂SO₄), 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.

(2R)-2-Methylpent-4-ynoic acid

(R)-N-((1S,2S)-1-Hydroxy-1-phenylpropan-2-yl)-N,2-dimethylpent-4-ynamide 328 (11.7 g, 45.2 mmol) was dissolved in tBuOH (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 H₂O (300 mL), and extracted with CH₂Cl₂ (4 × 200 mL). The aqueous was then acidified to pH < 2 using 3M HCl (aq), and extracted with CH₂Cl₂ (3 × 200 mL). The combined extracts (after acidification) were dried (Na₂SO₄), filtered, and concentrated in vacuo to give the desired product (R)-43 as an orange oil (4.05 mg, 80%).

¹H NMR (CDCl₃, 400 MHz) δ: 2.72 (1H, m, CHCH₃), 2.58 (1H, ddd, J = 16.8, 6.0, 2.6 Hz, CH₂), 2.41 (1H, ddd, J = 16.8, 7.6, 2.6 Hz, CH₂), 2.03 (1H, t, J = 2.6 Hz, C≡CH), 1.33 (3H, d, J = 7.1 Hz, CH₃).

¹³C NMR (CDCl₃, 100 MHz) δ: 180.3 (C=O), 81.1 (C≡CH), 70.1 (C≡CH), 38.4 (CH), 22.3 (CH₂), 16.1 (CH₃).

[α]D²⁶ +7.6 (c = 1.38, CHCl₃), lit. [α]D²³ +4.2 (c = 1.00, CHCl₃).

This data is in accordance with literature values.²³
(2R)-N-((4R)-1-((tert-butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-pentant-2-yl)-2-methyl-4-pentynamide

(4R)-1-((tert-Butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-pentyl amine 292 (8.36 g, 17.2 mmol) and (2R)-2-methylpent-4-ynoic acid (R)-43 (1.93 g, 17.2 mmol) were dissolved in anhydrous CH₂Cl₂ (110 mL) and cooled to 0 °C. Then EDC.HCl (3.95 g, 20.6 mmol) and HOBt (232 mg, 1.72 mmol) 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 Et₂O (300 mL), washed with water (300 mL), NaHCO₃ (aq) (200 mL), 10% HCl (aq) (200 mL), brine (2 × 200 mL), dried (Na₂SO₄), then filtered, and concentrated in vacuo to give the desired crude amide product 329 (9.84 g, 99%).

Fully characterised as 331.

(2R)-N-((4R)-5-((tert-Butyldiphenylsilyl)oxy)-1-hydroxy-4-methylpentan-2-yl)-2-methylpent-4-yname

(2R)-N-((4R)-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 dissolved in EtOH (115 mL). PPTS (427 mg, 1.70 mmol) was added and the resultant solution stirred for 72 h. Et₃N (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.
(2R)-N-((4R)-5-((tert-Butyldiphenylsilyl)oxy)-4-methyl-1-oxopentan-2-yl)-2-methylpent-4-ynamide

(2R)-N-((4R)-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

(2R)-N-((4R)-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 CH₂Cl₂ (40 mL) and cooled to 0 °C. PPh₃ (5.77 g, 22.0 mmol), DTBMP (3.55 g, 17.3 mmol), and (Cl₂BrC)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 CH₂Cl₂ (200 mL), washed with NH₄Cl (2 × 100 mL), brine (100 mL), dried (Na₂SO₄), 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%).

¹H NMR (CDCl₃, 400 MHz) δ: 7.69 – 7.63 (4H, m, ArH), 7.45 – 7.35 (6H, m, ArH), 7.19 (1H, s, ArH), 3.59 – 3.49 (2H, m, OCH₂), 3.19 – 3.09 (1H, m, CH(CH₃)₃), 2.72 – 2.63 (2H, m,
$\text{CH}_2$, 2.50 (1H, ddd, $J = 16.7, 8.3, 2.7$ Hz, $\text{CH}_2$), 2.35 (1H, dd, $J = 14.3, 7.5$ Hz, $\text{CH}_2$), 2.11 – 2.03 (1H, m, $\text{CH}(\text{CH}_3)$), 1.97 (1H, t, $J = 2.7$ Hz, $\text{C}≡\text{CH}$), 1.43 (3H, d, $J = 7.0$ Hz, $\text{CH}_3$), 1.06 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.98 (3H, d, $J = 6.7$ Hz, $\text{CH}_3$).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 166.0 (N=$\text{C}$), 139.24 (Ar$\text{C}$), 135.6 (Ar$\text{C}$H), 134.3 (Ar$\text{C}$H$_{\text{oxazole}}$), 134.0 (Ar$\text{C}$), 133.9 (Ar$\text{C}$), 129.5 (Ar$\text{C}$H$_{\text{oxazole}}$), 127.6 (Ar$\text{C}$H), 81.5 (Ar$\text{C}$H), 70.0 (Ar$\text{C}$H), 68.1 (OCH$_2$), 35.1 (CH), 33.2 (CH), 29.8 (CH$_2$), 26.9 (SiC(CH$_3$)$_3$), 24.3 (CH$_2$), 19.3 (SiC), 17.5 (CH$_3$), 16.7 (CH$_3$).

HRMS (ESI) calculated for C$_{28}$H$_{35}$O$_2$NSiNa ($\text{M}+$Na)$^+$: m/z 468.2329, observed 468.2308.

IR $\nu_{\text{max}}$ (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

\[
\text{HO-} \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\quad \begin{array}{c}
\text{CH}_3 \\
\text{C≡C}
\end{array}
\]

4-((R)-3-((tert-Butylidiphenylsilyl)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$_2$O (10 mL), and extracted with Et$_2$O (10 mL). The organic extracts were washed with H$_2$O (10 mL), brine (10 mL), dried (Na$_2$SO$_4$), 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) $\delta$: 7.32 (1H, t, $J = 0.8$ Hz, $^\text{Ar}H$), 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$_2$C≡C), 2.61 – 2.48 (3H, m, CH$_2$C≡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) $\delta$: 166.3 ($^{\text{Ar}}$CN), 138.3 ($^{\text{Ar}}$CH), 134.6 ($^{\text{Ar}}$C), 81.2 (C=CH), 70.2 (C=CH), 67.3 (OCH$_2$), 35.1 (N=CCH(CH$_3$)), 33.1 (CH(CH$_3$)), 30.0 (CH$_2$), 24.2 (CH$_2$), 17.4 (CH$_3$), 16.8 (CH$_3$), 16.8 (CH$_3$), 0.0 (Si(CH$_3$)$_3$).

HRMS (ESI) calculated for C$_{12}$H$_{17}$O$_2$NNa (M+Na)$^+$: m/z 230.1151, observed 230.1147.

IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3304, 2932, 2364, 1568, 1458, 1096.

[$\alpha$]$^D_{26}$ +10.5 (c = 1.05, CHCl$_3$).

(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$_2$O (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$_2$O (15 mL), the organic phase separated, washed with NaHCO$_3$ (aq), dried (Na$_2$SO$_4$), 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) $\delta$: 7.32 (1H, s, $^{\text{Ar}}$H), 3.62 – 3.51 (1H, m, OCH$_2$), 3.50 – 3.35 (1H, m, OCH$_2$), 3.22 – 3.04 (2H, m, OH + CH(CH$_3$)), 2.71 (1H, dd, $J = 16.9$, 5.7 Hz, CH$_2$C≡C), 2.62 – 2.43 (3H, m, CH$_2$C≡C + CH$_2$), 2.08 – 1.92 (1H, m, CH(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) $\delta$: 166.4 ($^{\text{Ar}}$C=N), 138.2 ($^{\text{Ar}}$C), 134.5 ($^{\text{Ar}}$CH), 103.9 (C=C), 86.6 (C=CH), 67.2 (OCH$_2$), 35.0 (CH(CH$_3$)), 33.3 (CH(CH$_3$)), 29.9 (CH$_2$), 25.7 (CH$_2$), 17.4 (CH$_3$), 16.8 (CH$_3$), 0.0 (Si(CH$_3$)$_3$).
HRMS (ESI) calculated for C_{15}H_{25}O_{2}SiNa (M+Na)^+: m/z 302.1547, observed 302.1542.

IR \nu_{\text{max}} \text{ (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

(2R)-2-Methyl-3-(2-(((2R)-5-(trimethylsilyl)pent-4-yn-2-yl)-1,3-oxazol-4-yl)propan1-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%).

\[^1^H\text{NMR (CDCl}_3, 500\text{MHz) }\delta:\] 9.73 (1H, d, J = 1.0 Hz, C(O)H), 7.32 (1H, s, \text{^A^r}C), 3.18 – 3.09 (1H, m, CH(CH_3)), 2.93 (1H, ddd, J = 14.8, 6.5, 0.7 Hz, CH_2), 2.83 – 2.75 (1H, m, CH(CH_3)), 2.70 (1H, ddd, 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, CH_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).

\[^1^3C\text{NMR (CDCl}_3, 125\text{MHz) }\delta:\] 204.0 (C=O), 166.6 (\text{^A^r}C), 137.5 (\text{^A^r}C), 134.6(\text{^A^r}CH), 103.4 (C=CSi), 86.6 (C=CSi), 45.4 (CH), 33.4 (CH), 27.1 (CH_2), 25.7 (CH_2), 17.5 (CH_3), 13.3 (CH_3), 0.0 (Si(CH_3)_3).

HRMS (ESI) calculated for C_{15}H_{25}O_{2}SiNa (M+Na)^+: m/z 302.1390, observed 302.1378.

IR \nu_{\text{max}} \text{ (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

![Chemical Structure](image)

**334**

*tert*-Butyl((3-methoxy-5-methyl-1,3-dihydroisobenzofuran-4-yl)oxy)dimethylsilane (444 mg, 1.51 mmol) was dissolved in anhydrous THF (10 mL), and cooled to 0 °C. Freshly distilled Pr$_2$NH (0.42 mL, 3.02 mmol) was added, and the resultant solution stirred for 10 min. MeLi (1.60 M in Et$_2$O, 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 (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$_2$O (1 mL) was added, then the reaction mixture was diluted with Et$_2$O (10 mL), washed with H$_2$O (10 mL), brine (10 mL), the organic dried (Na$_2$SO$_4$), filtered, and concentrated *in vacuo* to yield the α-hydroxy-isobenzofuran intermediate. The crude intermediate was then immediately dissolved in anhydrous CH$_2$Cl$_2$ (10 mL), and cooled to 0 °C. mCPBA (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$_2$Cl$_2$ (2 × 10 mL), and dried (Na$_2$SO$_4$). 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$_5$NSi$_2$Na (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

![Image of the chemical structure]

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$_2$Cl$_2$ (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$_2$O (1 mL) and 10% (aq) citric acid solution (1 mL). The resultant mixture was then extracted with CH$_2$Cl$_2$ (3 × 5 mL), and the combined organic extracts washed with brine (10 mL), dried (Na$_2$SO$_4$), 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%).

(3R,4R)-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

![Image of the chemical structure]

(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, $^\alpha$Ar-H), 6.95 (1H, d, $J = 7.6$ Hz, $^\alpha$Ar-H), 4.68 (1H, d, $J = 6.4$ Hz, CH(OH)), 4.09 (1H, dd, $J = 9.2$, 3.2 Hz, CH(O$_2$C)), 3.17 – 3.08 (1H, m, CH(CH$_3$)), 3.02 (1H, dd, $J = 14.7$, 3.3 Hz, CH$_2$C≡C), 2.74 – 2.66 (2H,
m, CH(CH₃), CH₂), 2.56 – 2.42 (2H, m, CH₂C≡C, CH₂), 2.28 (3H, s, \(^{13}C\)CH₃), 2.18 (1H, dd, \(J = 11.2, 7.2\) Hz, H), 1.41 (3H, d, \(J = 7.0\) Hz, CH₃), 1.13 (3H, d, \(J = 6.9\) Hz, CH₃), 1.06 (9H, s, SiC(CH₃)₃), 0.22 (3H, s, Si(CH₃)₂), 0.13 (3H, s, Si(CH₃)₂), 0.11 (9H, s, Si(CH₃)₃).

\(^{13}C\) NMR (100 MHz, CDCl₃) δ: 166.2 (C=O), 162.9 (\(^{13}C\)CN), 155.3 (\(^{13}C\)N), 139.6 (\(^{13}C\)N), 138.0 (\(^{13}C\)N), 136.3 (\(^{13}C\)CH), 134.9 (\(^{13}C\)CH₉), 132.7 (\(^{13}C\)CH), 115.8 (\(^{13}C\)CH), 104.1 (C≡C), 86.4 (C≡C), 82.3 (CH(O₂C)), 66.3 (CH(OH)), 33.3 (CH), 33.1 (CH), 28.0 (CH₂), 25.9 (SiC(CH₃)₃), 25.7 (CH₂), 18.6 (CH₃), 17.5 (CH₃), 0.00 (Si(CH₃)₃), -3.66 (Si(CH₃)₂), -3.69 (Si(CH₃)₂).

HRMS (ESI) calculated for C₂₀H₂₈O₃N₅Si₂Na (M+Na): m/z 578.2728, observed 578.2704

IR \(v_{\text{max}}\) (film)/cm\(^{-1}\) 2965, 2932, 2363, 1734, 1719, 1558, 1251

[\(\alpha\)]\(_{D}\) = -3.9 (c = 1.86, CHCl₃).

\((35S,4S)-8-\text{(tert-Butyldimethylsilyl)oxy}-4\text{-hydroxy-7-methyl-3-\text{((R)-1-((R)-5-\text{trimethysilyl})pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl}isochroman-1-one}

(30 mg, 23%)

\(^{1}H\) NMR (400 MHz, CDCl₃) δ: 7.40 (1H, d, \(J = 7.9\) Hz, \(^{1}H\)H), 7.38 (1H, s, \(^{1}H\)H), 7.28 (1H, d, \(J = 7.9\) Hz, \(^{1}H\)H), 4.72 (1H, d, \(J = 10.4\) Hz, CH(OH)), 4.10 (1H, dd, \(J = 10.5, 2.1\) Hz, CH(O₂C)), 3.22 – 3.14 (1H, m, CH(CH₃)), 3.05 (1H, dd, \(J = 16.1, 6.8\) Hz, CH₂C≡C), 2.73 – 2.66 (1H, m, CH₂), 2.61 – 2.51 (2H, m, CH₂C≡C, CH(CH₃)), 2.40 (1H, dd, \(J = 16.3, 3.6\) Hz, CH₂), 2.27 (3H, s, \(^{1}CH\)CH₃), 1.47 (3H, d, \(J = 7.0\) Hz, CH₃), 1.25 (3H, d, \(J = 7.7\) Hz, CH₃), 1.05 (9H, s, SiC(CH₃)₃), 0.21 (3H, s, Si(CH₃)₂), 0.14 (3H, s, Si(CH₃)₂), 0.13 (9H, s, Si(CH₃)₃).

\(^{13}C\) NMR (100 MHz, CDCl₃) δ: 167.3 (C=O), 163.4 (\(^{13}CN\)), 154.7 (\(^{13}CN\)), 142.5 (\(^{13}CN\)), 139.1 (\(^{13}CN\)), 136.2 (\(^{13}CN\)), 134.2 (\(^{13}CN\), 130.2 (\(^{13}CN\)), 116.7 (\(^{13}CN\)), 115.0 (\(^{13}CN\)), 103.4 (C≡C), 87.2 (C≡C), 85.5 (CH(O₂C)), 65.4 (CH(OH)), 33.4 (CH), 31.6 (CH), 26.0 (SiC(CH₃)₃), 25.6

180
(CH₂), 25.4 (CH₂), 18.6 (CH₃), 17.3 (CH₂), 0.00 (Si(CH₃)₃), -3.66 (Si(CH₃)₂), -3.69 (Si(CH₃)₂).

HRMS (ESI) calculated for C_{30}H_{45}O_{5}NSi₂Na (M+Na)^+: 578.2728, observed 578.2705

IR ν max (film)/cm⁻¹ 3021, 2359, 1753, 1736, 1726, 1366

[α]D^29 -61.9 (c = 0.91, CHCl₃).

(3S,4S)-4,8-Dihydroxy-7-methyl-3-((R)-1-((R)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one

(3S,4S)-8-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((R)-1-((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. H₂O (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 (Na₂SO₄), 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%).

¹H NMR (400 MHz, CDCl₃) δ: 11.05 (1H, s, ArOH), 7.40 (1H, d, J = 7.7 Hz, ArH), 7.39 (1H, s, ArH), 7.12 (1H, d, J = 7.6 Hz, ArH), 6.05 (1H, d, J = 6.1 Hz, OH), 4.86 (1H, dd, J = 10.3, 5.9 Hz, CH(OH)), 4.31 (1H, dt, J = 10.8, 2.5 Hz, CH(O₂C)), 3.23 – 3.15 (1H, m, CH₂C≡C), 2.69 – 2.59 (2H, m, CH₂, CH(CH₃)), 2.50 – 2.44 (1H, m, CH₂C≡C), 2.27 (3H, s, CH₂), 1.93 (1H, t, J = 2.6 Hz, C≡CH), 1.45 (3H, d, J = 7.0 Hz, CH₂), 1.26 (3H, d, J = 7.2 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 170.1 (C=O), 167.0 (ÅC), 160.1 (ÅC(OH)), 141.2 (ÅC), 138.8 (ÅC), 137.4 (ÅC), 134.5 (ÅC), 125.6 (ÅC), 114.3 (ÅC), 105.9 (ÅC), 86.6 (CH(O₂C)), 80.7 (C≡CH), 70.5 (C≡CH), 64.7 (CH(OH)), 33.1 (CH(CH₃)), 32.4 (CH(CH₃)), 26.0 (CH₂C≡C), 24.1 (CH₂), 18.2 (CH₂), 17.4 (CH₃), 15.5 (ÅCCH₃).
HRMS (ESI) calculated for C_{21}H_{25}O_{5}N_{Na} (M+Na)^+: m/z 392.1468, observed 392.1455.

IR \text{v}_{\text{max}} \text{ (film)/cm}^{-1} 3298, 2934, 1676, 1424, 1250, 1136.

[\alpha]_{D}^{29} -52.0 \text{ (c = 0.23, CHCl}_3\text{).}

(3R,4R)-4,8-Dihydroxy-7-methyl-3-((R)-1-(2-((R)-pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one

(3R,4R)-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 \mu\text{mol}) 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_{2}O (2 mL) was added, and the reaction mixture was extracted with EtOAc (3 \times 3 mL), the combined organic extracts washed with brine (3 mL), dried (Na_{2}SO_{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\text{H NMR} (400 MHz, CDCl\textsubscript{3}) \delta: 11.26 (1H, s, \text{^3}\text{H}O\text{H}), 7.39 (1H, d, \text{J}=7.2 \text{ Hz,} \text{^4}\text{H}), 7.38 (1H, s, \text{^5}\text{H}), 6.83 (1H, d, \text{J}=7.4 \text{ Hz,} \text{^6}\text{H}), 4.73 (1H, d, \text{J}=5.0 \text{ Hz,} \text{CH(OH)}), 4.24 (1H, dd, \text{J}=8.6, 1.5 \text{ Hz,} \text{CH(O}_{2}\text{C})\text{)}, 3.17 – 3.06 (2H, m, \text{CH(CH}3\text{)}\text{)}, \text{CH}2\text{)}, 2.69 – 2.53 (3H, m, \text{CH}_{2}\text{C}=\text{C, \text{CH(CH}3\text{)}\text{)}, \text{CH}2\text{)}, 2.49 (1H, ddd, \text{J}=16.7, 8.0, 2.6 \text{ Hz,} \text{CH}_{2}\text{C}=\text{C, \text{CH(CH}3\text{)}\text{)}, \text{CH}2\text{)}, 2.29 (3H, s, \text{^8}\text{CCH}3\text{)}, 1.95 (1H, br s, \text{C}=\text{CH}), 1.67 (1H, br s, \text{O\text{H}}), 1.42 (3H, d, \text{J}=7.0 \text{ Hz,} \text{CH}3\text{)}, 1.12 (3H, J = 6.6 Hz, \text{CH}3\text{)}.

^13\text{C NMR} (100 MHz, CDCl\textsubscript{3}) \delta: 169.6 (\text{C}=\text{O}), 166.2 (\text{^3}\text{CN}), 160.5 (\text{^4}\text{C}), 138.2 (\text{^5}\text{C}), 138.1 (\text{^6}\text{C}), 137.3 (\text{^7}\text{CH}), 135.0 (\text{^8}\text{CH}), 128.0 (\text{^9}\text{C}), 117.8 (\text{^10}\text{CH}), 106.5 (\text{^11}\text{C}), 85.1 (\text{CH(O}_{2}\text{C})\text{)}, 81.4 (\text{C}=\text{CH}), 70.0 (\text{C}=\text{CH}), 65.3 (\text{CH(OH)}), 33.5 (\text{CH(CH}3\text{)}\text{)}, 33.1 (\text{CH(CH}3\text{)}\text{)}, 28.2 (\text{CH}2\text{)}, 24.3 (\text{CH}_{2}\text{C}=\text{C, 17.5 (CH}3\text{)}, 15.7 (\text{^4}\text{CCH}3\text{)}, 15.5 (\text{CH}3\text{)}.

HRMS (ESI) calculated for C_{21}H_{25}O_{5}N_{Na} (M+Na)^+: m/z 392.1468, observed 392.1456.

IR \text{v}_{\text{max}} \text{ (film)/cm}^{-1} 3641, 3300, 2951, 2854, 1729, 1668, 1483.

[\alpha]_{D}^{29} +16.2 \text{ (c = 0.64, CHCl}_3\text{).}
(E)-N-((R,2E,6Z)-11-(4-((R)-2-((3R,4R)-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

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(Ph3)2Cl2 (2.8 mg, 4.0 µmol) and CuI (1.4 mg, 7.4 µmol) were added, followed by dropwise addition of Et3N (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 H2O (2 mL), brine (2 mL), dried (Na2SO4), 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%).

1H NMR (400 MHz, CDCl3) δ: 11.28 (1H, s, °OH), 7.38 (1H, d, J = 7.4 Hz, °H), 7.38 (1H, s, °H), 6.84 (1H, d, J = 7.4 Hz, °H), 5.77 (1H, dd, J = 15.0, 7.2 Hz, HC=CH), 5.57 (1H, dt, J = 15.4, 6.5 Hz, HC=CH), 5.49 – 5.37 (2H, m, HC=CH), 5.15 (1H, s, HC=C), 4.73 (1H, br s, CH(OH)), 4.22 (1H, d, J = 8.7 Hz, CH(O2C)), 3.98 (1H, br s, CH2N), 3.88 (1H, br s, CH2N), 3.59 (3H, br s, OCH3), 3.22 – 3.08 (2H, m, CH(CH3) + CH2), 2.94 (3H, s, NCH3), 2.80 (1H, dd, J = 16.9, 5.6 Hz, CH2C=C), 2.75 – 2.65 (1H, m, CH2C=C), 2.62 – 2.48 (2H, m, CH(CH3) + CH2), 2.33 – 2.25 (2H, m, CH2), 2.28 (3H, s, °CH2CH2), 2.20 – 2.05 (5H, m, C=C(CH3) + CH2), 1.43 (3H, d, J = 7.0 Hz, CH3), 1.12 (3H, d, J = 6.7 Hz, CH3).

13C NMR (100 MHz, CDCl3) δ: 169.6 (C=O), 168.6 (C=O), 166.3 (HC=C(O)(Me)), 160.3 (C), 142.2 (HC=C), 138.4 (°C), 138.3 (°C), 137.2 (°CH), 134.8 (°CH), 132.8 (HC=C), 127.6 (°C), 125.8 (°CH), 125.1 (HC=C), 117.9 (°CH), 109.6 (HC=C), 106.6 (°C), 91.2 (HC=C(O)(Me)), 85.3 (CH(O2C)), 78.9 (C=O), 77.7 (C=O), 65.1 (CH(OH)), 54.9 (OCH3), 52.2 (CH2N), 33.6 (CH(CH3)), 33.5 (CH(CH3)), 31.4 (CH2), 29.6 (CH2), 28.4 (CH2), 25.6 (CH2), 18.7 (CH3), 17.7 (CH3), 15.7 (CH3), 15.4 (CH3).

N.B. CH3N not observed

IR v_max (film)/cm⁻¹: 3664, 2916, 2849, 2359, 1726, 1691, 1631, 1583, 1427.

HRMS (ESI) calculated for C34H42O7N2Na (M+Na)⁺: m/z 613.2884, observed 613.2866.

[α]D²⁹ +11.8 (c = 0.88, CHCl₃).

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(E)-N-(((R,2E,6Z,8Z)-11-(4-((2R,3R)-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

Ni(OAc)$_2$.4H$_2$O (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 using 5% MeOH in CH$_2$Cl$_2$ 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, $^\alpha$OH), 7.59 (1H, s, $^\alpha$H), 7.46 (1H, d, $J = 7.4$ Hz, $^\alpha$H), 7.03 (1H, d, $J = 7.4$ Hz, $^\alpha$H), 6.34 – 6.23 (2H, m, CH=CH), 5.71 (1H, s, CH(CO)N), 5.63 – 5.55 (1H, m, CH=CH), 5.49 – 5.32 (3H, m, CH=H), 4.34 (1H, d, $J = 7.2$ Hz, CH(O$_2$C)), 3.90 (2H, d, $J = 5.4$ Hz, CH$_3$N), 3.82 (1H, t, $J = 7.2$ Hz, CH(OH)), 3.59 (3H, br s, OCH$_3$), 3.04 – 2.99 (1H, m, CH(CH$_3$)), 2.95 – 2.82 (4H, m, CH$_2$), 2.78 (3H, s, NCH$_3$), 2.66 – 2.57 (1H, m, CH(CH$_3$)), 2.53 – 2.47 (2H, m, CH$_2$), 2.31 – 2.23 (2H, m, CH$_2$), 2.24 (3H, s, $^\alpha$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$_3$).

$^1$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 (CH), 135.9 (CH), 135.9 (C), 132.5 (CH), 129.3 (CH), 127.0 (C), 126.4 (CH), 125.2 (C), 124.8 (CH), 123.0 (CH), 114.3 (CH), 112.9 (C), 92.3 (CH(CO)N), 83.6 (CH(O$_2$C)), 76.0 (CH(OH)), 55.4 (OCH$_3$), 49.9 (NCH$_3$), 37.0 (CH(CH$_3$)), 34.7 (CH(CH$_3$)), 33.7 (CH$_3$), 33.0 (CH$_2$), 28.0 (CH$_2$), 27.8 (CH$_2$), 18.8 (CH$_3$), 18.4 (CH$_3$), 16.7 (CH$_3$), 14.9 (CH$_3$).

N.B. CH$_3$N not observed
HRMS (ESI) calculated for $C_{34}H_{44}O_7N_2Na$ (M+Na)$^+$: $m/z$ 615.3041, observed 615.3014.

IR $\nu_{\text{max}}$ (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$_3$).
12 REFERENCES

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(2R)-3-((2R)-4-(Benzyloxy)butan-2-yl)-1,3-oxazol-4-yl)-2-methylpropanal 281
8-((tert-Butyldimethylsilyl)oxy)-1-hydroxy-7-methyl-3-(4-(trimethylsilyl)but-3-yn-1-yl)isochroman-4-one 323
(R)-2-Methyl-3-((R)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propanal
(3R,4R)-8-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-3-((R)-1-((R)-5-(trimethylsilyl)pent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one 335
(3R,4R)-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
(E)-N-((R,2E,6Z)-11-((4-((R)-2-((3R,4R)-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
(E)-N-((R,2E,6Z,8Z)-11-((4-((2R,3R)-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