

A Novel Approach to the Synthesis of the FG Fragment of Pectenotoxin-4

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Table of Contents

Declaration.....	i
Abstract.....	ii
Acknowledgements.....	iii
Abbreviations and Acronyms.....	iv
Chapter 1 – Introduction.....	1
1.1 Pectenotoxin.....	2
1.1.1 Introduction to the pectenotoxin family.....	2
1.1.2 The bioactivity of the pectenotoxins.....	7
1.1.3 Previous syntheses of pectenotoxins.....	10
1.1.3.1 Evans’s total asymmetric synthesis.....	11
1.1.3.2 Murai and Fujiwara’s synthesis of the C31-C40 portion ...	16
1.1.3.3 Paquette’s synthesis of the C29-C40 fragment	20
1.1.3.4 Brimble’s synthesis of the C31-C40 portion.....	21
1.2 The formation of 2,5- <i>trans</i> -THFs.....	25
1.2.1 The cobalt-catalysed oxidative cyclisation of 5-hydroxy alkenes.....	25
Chapter 2 – Results and Discussion.....	38
2.1 Research Outline.....	39
2.2 Retrosynthetic analysis of the FG portion of PTX-4.....	42
2.3 Model studies.....	44

2.3.1	Investigations into the C5 C-O disconnection (route b).....	46
2.3.2	Investigations into the C2 C-O disconnection (route a).....	51
2.3.3	Summary of the model studies.....	58
2.4	Forward synthesis.....	59
2.4.1	Synthesis of the C31-C35 portion.....	60
2.4.2	Alkynylation of the C31-C35 aldehyde with a model alkyne.....	66
2.4.3	Oxidative cyclisation using model alkynes 122 and 130	71
2.4.4	Synthesis of the C36-C40 alkyne component.....	73
2.4.5	Coupling of aldehyde 119 with alkyne 145 and subsequent cyclisation.....	77
2.4.6	(<i>E</i>)-Selective alkyne reduction.....	79
2.4.7	Utilisation of 1,3- <i>anti</i> diastereomer (<i>R</i>)- 146	80
2.4.8	F-ring formation.....	81
2.4.9	Installation of the sulfone moiety.....	82
2.4.10	Sharpless asymmetric dihydroxylation.....	85
2.4.11	Regioselective mono-protection of 1,2-diol 159 formed by dihydroxylation.....	87
2.4.11.1	The Yamamoto protocol.....	88
2.4.11.2	Silyl ether formation.....	91
2.4.12	Completion of the synthesis of the C31-C40 fragment of PTX-4...94	
2.5	Assembly of the FG- and E-ring fragments.....	100
2.6	Conclusions	104
2.7	Future Work.....	105

Chapter 3 – Experimental Section	108
3.1 Experimental techniques.....	109
3.2 General procedures.....	111
3.3 Experimental procedures.....	112
 Appendix – X-Ray Crystal Structures	197
 References	203

Declaration

This thesis and the work of which it is a record has been carried out by myself, except where I have either acknowledged help from a named person or given reference to a published source or a thesis.

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University of Oxford, Hilary Term 2012

Abstract

A thesis submitted for the degree of Doctor of Philosophy

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The cobalt-catalysed oxidative cyclisation of 5-hydroxy alkenes has been demonstrated to be a powerful synthetic tool for the formation of *trans*-THFs with excellent diastereoselectivity. This thesis describes the utilisation of this methodology in the synthesis of the FG fragment of pectenotoxin-4, allowing the scope of the reaction to be further explored.

Introduction

This section introduces the pectenotoxins, a family of structurally complex closed-chain polyether macrolides with promising biological activities. The isolation, structural elucidation, and biological properties of the pectenotoxins are reviewed, along with a summary of previous syntheses towards the FG fragment of pectenotoxin-4. In addition, the cobalt-catalysed oxidative cyclisation of 5-hydroxy alkenes and its application in synthesis is discussed.

Results and Discussion

An outline of the synthetic strategy employed in this project and details of the novel retrosynthesis of the C31-C40 fragment of pectenotoxin-4 is described. The synthetic studies carried out towards the synthesis of the FG fragment of pectenotoxin-4 are discussed in detail, with the exploitation of a cobalt-catalysed oxidative cyclisation as the key step to form the *trans*-THF F-ring. Overall, the FG fragment, which contains six stereogenic centres, was achieved in 18 total synthetic steps (13 longest linear sequence).

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I am eternally grateful to my husband, Ga, who has been there for me during the highs and the lows. Without his endless support I wouldn’t be where I am today, and I cannot thank him enough. I look forward to completing this chapter of my life and moving on to the exciting adventures that lie ahead for us.

Thank you also to my family, in particular my Mum, Dad, Sister (Curly) and Grom. You have all been there for me and hopefully now you can see that it has been worthwhile.

Abbreviations and Acronyms

Ac	acetyl
aq.	aqueous
Bn	benzyl
br	broad
Bt	benzothiazole
°C	degrees centigrade
cat.	catalytic
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	distereomeric excess
DET	diethyl tartarate
DIAD	diisopropylazodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DSP	diarrhetic shellfish poisoning
e	electron
ee	enantiomeric excess

equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
Et ₂ O	ether
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution spectroscopy
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
ⁱ Pr	iso-propyl
IR	infrared
<i>J</i>	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LAB	lithium amidotrihydroborate
LC	lethal concentration
LDA	lithium diisopropylamide
LiDBB	lithium 4,4'-di- <i>tert</i> -butylbiphenyl
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
<i>m</i>	meta
M	molar

mCPBA	meta-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MOM	methoxymethyl
m.p	melting point
MS	mass spectrometry
MTBE	methyl <i>tert</i> -butyl ether
MTPA	methoxy(trifluoromethyl)phenylacetic acid
m/z	mass-to-charge ratio
NME	<i>N</i> -methyl ephedrine
NMO	<i>N</i> -methyl morpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
<i>p</i>	para
petrol	petroleum ether
PGME	phenylglycine methyl ester
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
PNB	<i>para</i> -nitrobenzoyl
PTX	pectenotoxin
Py	pyridine
ppm	parts per million

q	quartet
quin	quintet
R _f	retention factor
rt	room temperature
s	singlet
SA	seco acid
sat.	saturated
SEM	triethylsilylethoxymethyl
sxt	sextet
t	triplet
<i>t</i>	<i>tert</i>
TBAF	tetrabutylammonium fluoride
TBDOPS	<i>tert</i> -butoxydiphenylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
^t Bu	<i>tert</i> -butyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	triphenylsilyl

Chapter 1

Introduction

1.1 Pectenotoxin

1.1.1 Introduction to the pectenotoxin family

The pectenotoxins (PTXs) are a family of macrocyclic polyethers, named after the family of toxic scallops from which they were initially isolated.¹ The first pectenotoxins were discovered by Yasumoto and co-workers in 1985; they were isolated from the digestive glands of *Patinopecten yessoensis*, obtained from the north-eastern coast of Japan.¹ Using a combination of nuclear magnetic resonance (NMR), mass spectrometry (MS) and X-ray diffraction techniques it was possible to elucidate the full structure of PTX-1 (*Figure 1*). PTX-1 was shown to be a novel polyether lactone consisting of a forty-carbon backbone, with nineteen stereocentres and a large oxygen-rich internal cavity. Several ring systems are incorporated within the structure including *cis*- and *trans*-tetrahydrofuran (THF) rings, two spiroacetal moieties and a C33 lactone ring.¹

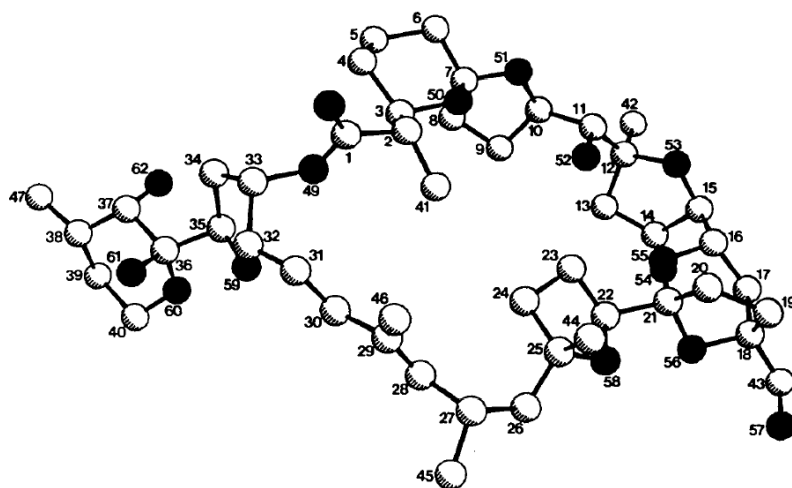


Figure 1. Computer modelled perspective of the X-ray model of PTX-1¹

The absolute configuration of PTX-1, however, was not determined until 1997 when it was proven using NMR spectroscopy, which employed the use of a chiral anisotropic reagent, phenylglycine methyl ester (PGME).² Subjecting the C43 carboxylic acid of PTX-6 to an

amide coupling with both (*R*)- and (*S*)-PGME revealed NOE correlations of the amide proton with H17, H19 and H22, allowing for the absolute configuration of the chiral carbon at C18 to be assigned as (*S*).² The remaining eighteen stereocentres were subsequently assigned according to the relative stereochemistry that had been determined from the X-ray crystallography of PTX-1 (*Figure 1 and Figure 2*).²

Since 1985, more than twenty PTXs have been isolated. The structures of the PTXs have been determined largely by comparison of their spectroscopic data. Structural diversity from PTX-1 to -4, -6 and -7 occurs firstly in the oxidation level at C43 (all levels from Me to COOH are found)³ and secondly in the stereochemistry at the C7 spiroketal ring junction (*Figure 2*). The structures of PTX-5 and -10 are yet to be determined, primarily as the amounts isolated to date have not been sufficient for a full spectral analysis.^{1,4}

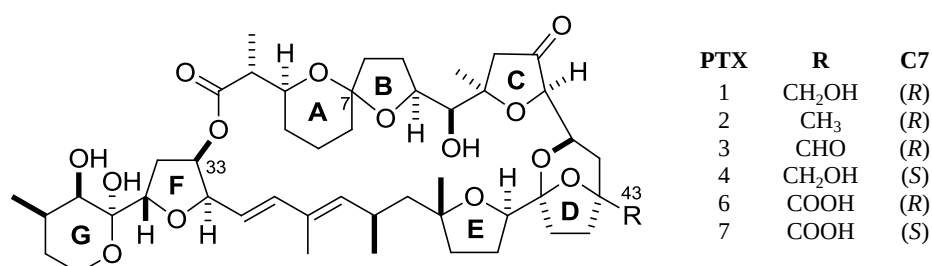
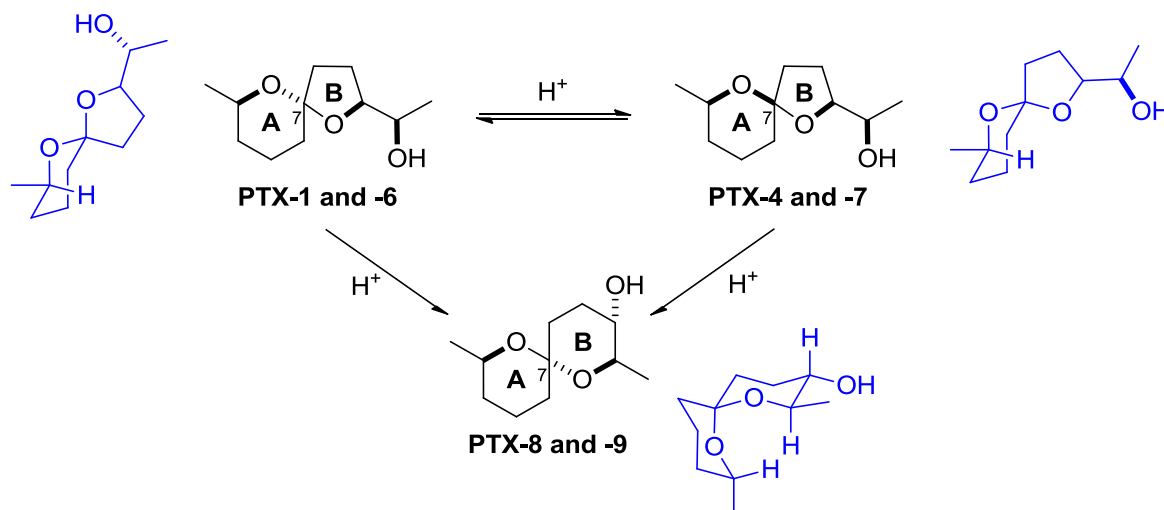


Figure 2. Structure of the pectenotoxins

Studies revealed that PTX-4 and -7 were the 7-*epi*-derivatives of PTX-1 and -6 respectively.⁴ It was demonstrated synthetically that each epimer could be interconverted through an acid-catalysed rearrangement, which also gave rise to chemical artifacts PTX-8 and -9 owing to the expansion of the B ring to a tetrahydropyran ring (*Scheme 1*).⁴



Scheme 1. Interconversion of PTXs⁴

Despite being produced synthetically, PTX-8 and PTX-9 were not found to occur naturally in the scallop extracts.⁴ Consequently, it is rationalised that the spiroketal isomerisation to produce PTX-4 and -7 occurs in the digestive gland of the scallops and is catalysed by an enzyme, as opposed to an acid-catalysed rearrangement.⁴ The biaxial orientation of the spiroketal C-O bonds in the 7-*epi*-derivatives is thought to maximise the anomeric effect, resulting in a thermodynamically more stable configuration than the alternative biequatorial arrangement present in PTX-1 and -6.^{4, 5}

Although originally isolated from the digestive glands of scallops, it was later discovered that the PTXs are produced by the toxigenic dinoflagellates *Dinophysis fortii* and *D. acuminata*, which are ingested by the shellfish.^{4, 6} PTX-2 (Figure 2) was the only PTX to be detected in *Dinophysis fortii* and therefore it was considered to be the parent compound.⁶ Further evidence to support this hypothesis came from toxicology data of the PTXs. LC_{50} values revealed the highest lethality for PTX-2 ($LC_{50} = 219 \mu\text{g/kg}$),⁷ indicating that conversion of PTX-2 into other derivatives was likely to be the result of a detoxification process. It is therefore believed that some of the PTXs are produced during

the metabolism of PTX-2, for example, oxidation at C43 within the digestive glands of scallops would produce PTX-1, -3 and -6.^{3, 4}

In 1998, two new PTX analogues were isolated from New Zealand Greenshell mussels (*Perna Canaliculus*) and their structures were identified by comparison of spectral data to that of PTXs previously reported.⁸ They were found to be seco acids (SA) of PTX-2, whereby the macrocyclic lactone ring resided in the open chain form (*Figure 3*).^{8, 9} Interestingly, it was discovered that the PTX-2 SA and 7-*epi*-PTX-2 SA possessed no cytotoxicity against human KB cells at a dose of 1.8 µg/mL, whereas PTX-2 exhibited cytotoxicity at just 0.05 µg/mL. As a result of these findings it was concluded that the closed ring system was vital to maintaining potency.⁸ Research led to the proposal that the PTX-2 SA was produced by an enzymatic hydrolysis of the PTX-2 lactone within the mussel, as part of the detoxification process.¹⁰ 7-*epi*-PTX-2 SA was shown to arise from the progressive epimerisation of PTX-2 SA to its thermodynamically more stable C7 epimer.¹⁰

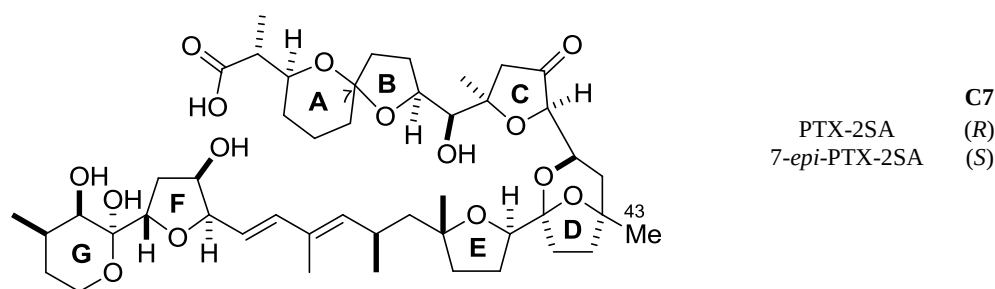


Figure 3. Structure of PTX-2 seco acids

In 2002, it was found that treatment of PTX-2 under acidic conditions (as shown with PTX-1 and -6 previously), resulted in two novel spiroketal isomers that were named PTX-2b and PTX-2c.¹¹ PTX-2b was assigned as the C7 epimer of PTX-2, and PTX-2c as the tetrahydropyran derivative of PTX-2b (c.f. PTX-8 and -9).¹¹ A novel isomer of PTX-1 was then discovered, which consisted of the core structure of PTX-2 with an additional

hydroxyl group incorporated at C34 (Figure 4).^{11, 12} The novel isomer, subsequently named PTX-11, was also shown to undergo an acid-mediated rearrangement to give PTX-11b and an additional isomer named PTX-11c.¹¹ The products were assumed to be analogous to the acid-induced rearrangement products of PTX-2, although insufficient material was available for the full spectral analysis of each compound.¹²

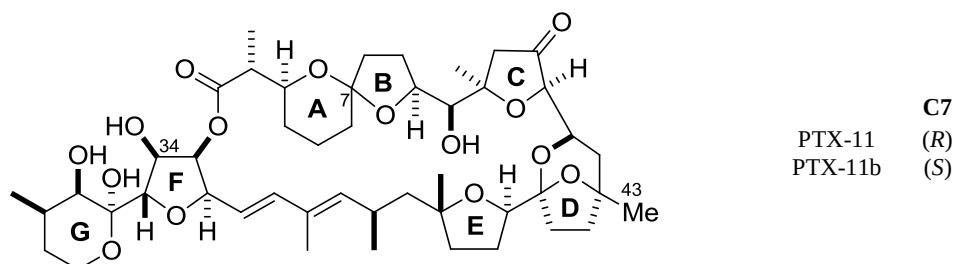


Figure 4. Structure of PTX-11

Unlike PTX-2, PTX-11 did not readily undergo enzymatic hydrolysis to afford the corresponding seco acid.¹² It was rationalised that this could be due to either the steric hindrance of the additional hydroxyl group at C34, or possibly due to hydrogen bonding between the hydroxyl group and the adjacent carbonyl group. Nonetheless, it was evident that PTX-11 was not a suitable substrate for the enzyme responsible for hydrolysing the lactone of PTX-2.¹² PTX-11 was found to display very similar toxicity to PTX-2 ($LC_{50} = 244 \mu\text{g/kg}$) and it is likely that the resistance of PTX-11 to hydrolysis could result in a greater accumulation of the toxin in mussels.^{12, 13}

Shortly after the discovery of PTX-11, PTX-12 and its C36 epimer were detected in extracts of shellfish from Norway (Figure 5).¹³ 36S-PTX-12 and 36R-PTX-12 were shown to be a pair of equilibrating diastereomers, differing from PTX-2 in that an exocyclic methylene group was present at C38, as opposed to a methyl group. LCMS analyses also revealed the presence of compounds presumed to be PTX-12 seco acids as a complex mixture of diastereomers.¹³

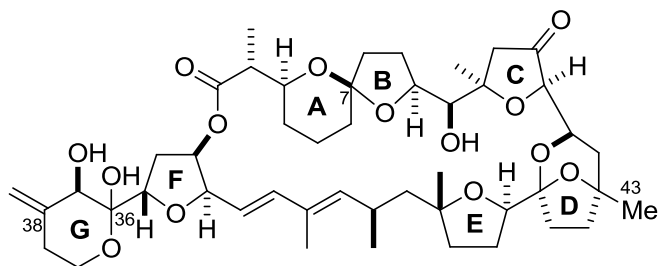


Figure 5. Structure of PTX-12

The most recent discovery of a PTX occurred in 2006 when Miles *et al.* reported the isolation of two novel PTXs from extracts of *Dinophysis acuta*.¹⁴ The compounds, subsequently named PTX-13 and -14, were identified as oxidation products of the parent toxin PTX-2, by analysis of the MS fragmentations and by comparison of the NMR spectra to those previously reported. PTX-13 was found to have an additional hydroxyl group at C32, whereas PTX-14 was identified as a spiroacetal analogue of PTX-13 (Figure 6).¹⁴ It was not clear whether PTX-14 was a natural extract or was a product of dehydration of PTX-13 on either storage or extraction.¹⁴

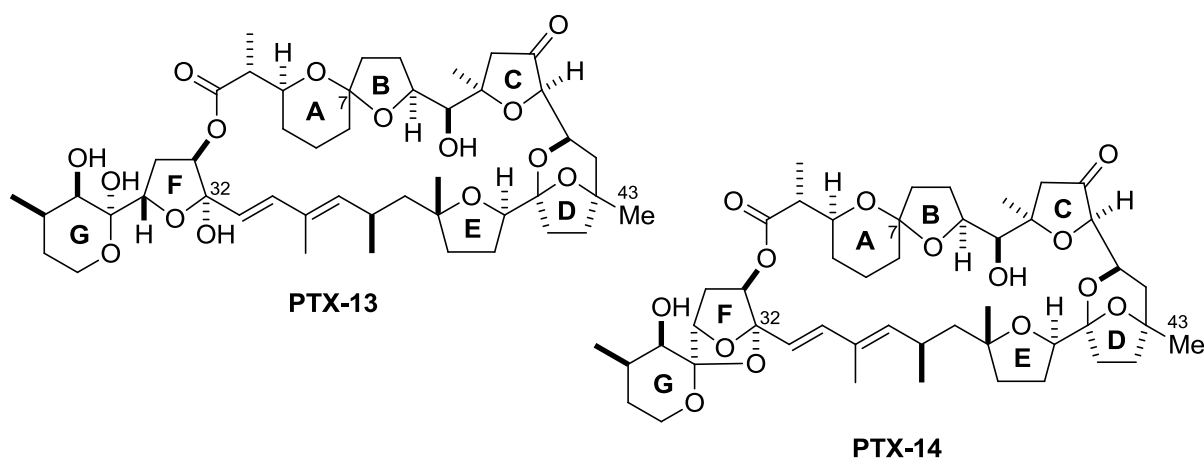


Figure 6. Structures of PTX-13 and PTX-14

1.1.2 The bioactivity of the pectenotoxins

The PTXs were formerly considered to be associated with diarrhetic shellfish poisoning (DSP).¹ However, this claim came under scrutiny when more recent studies demonstrated

that the PTXs do not inhibit protein phosphatases, nor induce diarrhoea in mammals.^{15, 16} It is likely that the origin for the original claim was due to the co-extraction of PTX with diarrhetic toxins (namely okadaic acid and dinophysistoxins), hence contaminating the samples. Following the development of improved isolation methods, it was discovered that despite the fact that PTXs exhibited potent toxicity when administered intraperitoneally in mice, only low levels of toxicity were detected following oral administration. Furthermore, subjecting mice to either route of administration did not induce diarrhoea, even at concentrations of 5000 $\mu\text{g/kg}$.^{7, 12} The particular mode of action of the PTXs is still the subject of investigations. PTXs were initially reported to be hepatotoxic,¹⁶ and PTX-2 was later shown to display selective and very potent cytotoxic activity against various cancer cell lines including lung, colon and breast.⁶ It has been reported that the PTXs interfere with the actin cytoskeleton, specifically by inhibiting actin polymerisation.^{15, 17} An X-ray crystal structure of PTX-2 bound to actin demonstrated a novel binding site between subdomain 1 and 3 (*Figure 7*).¹⁸

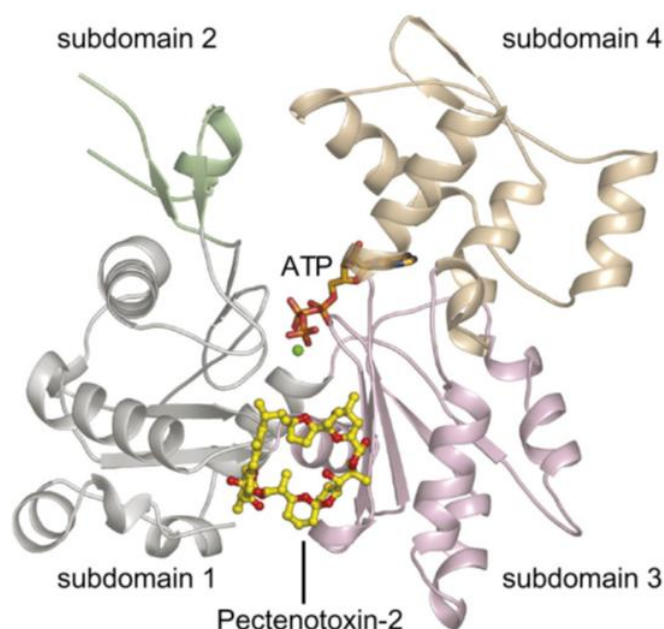


Figure 7. PTX-2 bound to actin between subdomain 1 and 3
(Diagram taken from the literature)¹⁸

The position at which PTX-2 was shown to bind to actin had not been observed previously with other small natural molecules, revealing that the PTXs possess a unique mode of action. The shape that PTX-2 adopts within the binding site consists of a distinct “ring” and “tail” moiety (*Figure 8*).

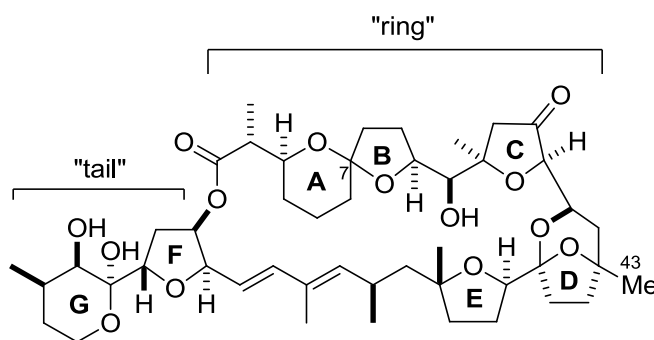


Figure 8. Distinct “ring” and “tail” shape of PTX-2

The ring portion of PTX-2 was shown to adopt a flat orientation within a shallow groove between subunit 1 and 3, interacting primarily in a hydrophobic manner. On the other hand, the tail portion of PTX-2 was shown to interact predominantly with subunit 1, whereby the polar atoms interacted with actin by means of hydrogen bonds, either with actin residues or with actin-coordinated water molecules (*Figure 9*). The cyclic hemiacetal G-ring was shown to reside within a narrow hydrophobic pocket.¹⁸ It was also noted that the conjugated diene functionality was crucial to providing conformational constraints upon the ring, ensuring that the key atoms interacted with the appropriate components of the actin surface.¹⁸

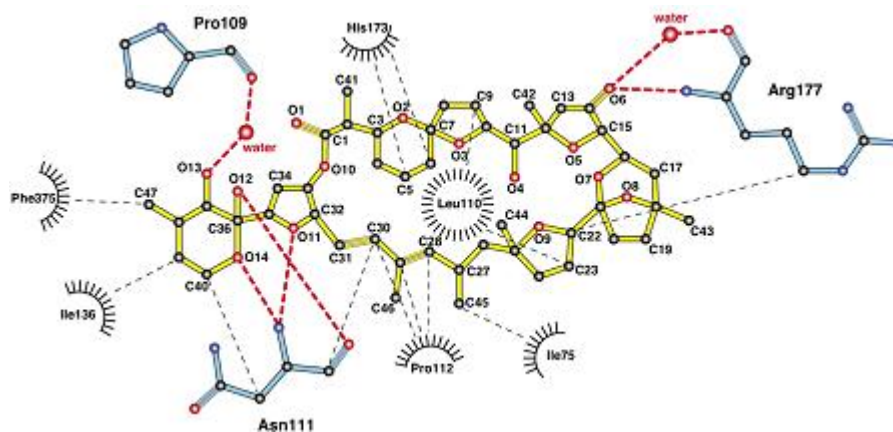


Figure 9. The interactions between PTX-2 and actin.

Hydrophobic interactions are represented by black dashes. Water molecules are depicted as red spheres with hydrogen bonding interactions shown with red dashes. Actin residues involved in polar interactions are shown in blue. (Diagram taken from the literature)¹⁸

It is envisaged that the PTXs could act as promising leads in drug discovery, with PTX-2 in particular demonstrating the potential to be used as an anti-cancer agent with a unique mode of action.¹⁹ The above binding models (*Figure 7 and Figure 9*) allow for an improved understanding of the structure-activity relationships (SAR) observed with the PTX family and could assist in the design of novel PTX analogues with improved pharmacological profiles.¹⁸ As a consequence, research groups have expressed an interest in further investigations into the mode of action of the PTXs and into the discovery of new PTX analogues.¹⁸ Since there is a low natural abundance of PTXs (e.g. only 7 mg of PTX-4 was isolated from 200 kg of toxic scallop digestive glands),¹ chemistry research groups have been prompted to investigate synthetic routes for the preparation of the PTXs.

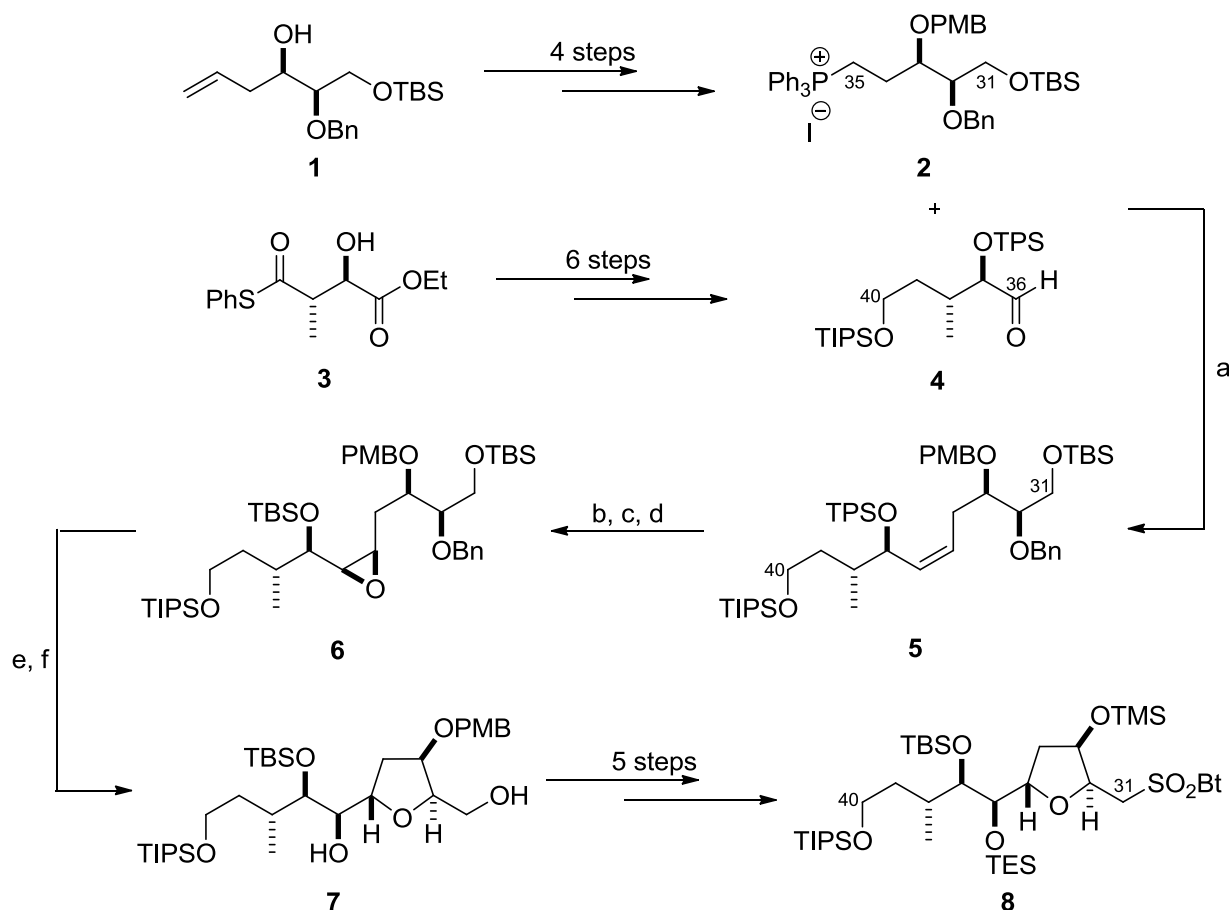
1.1.3 Previous syntheses of the pectenotoxins

Despite many research groups reporting the synthesis of specific fragments of PTX, only one total synthesis of PTX has been achieved to date,^{20, 21} highlighting the formidable synthetic challenge that exists in synthesising this family of structurally complex

polyketides. Reported herein is a summary of Evans's total asymmetric synthesis, with particular emphasis on the FG ring system, along with other significant syntheses of the FG fragment of PTX.

1.1.3.1 Evans's total asymmetric synthesis

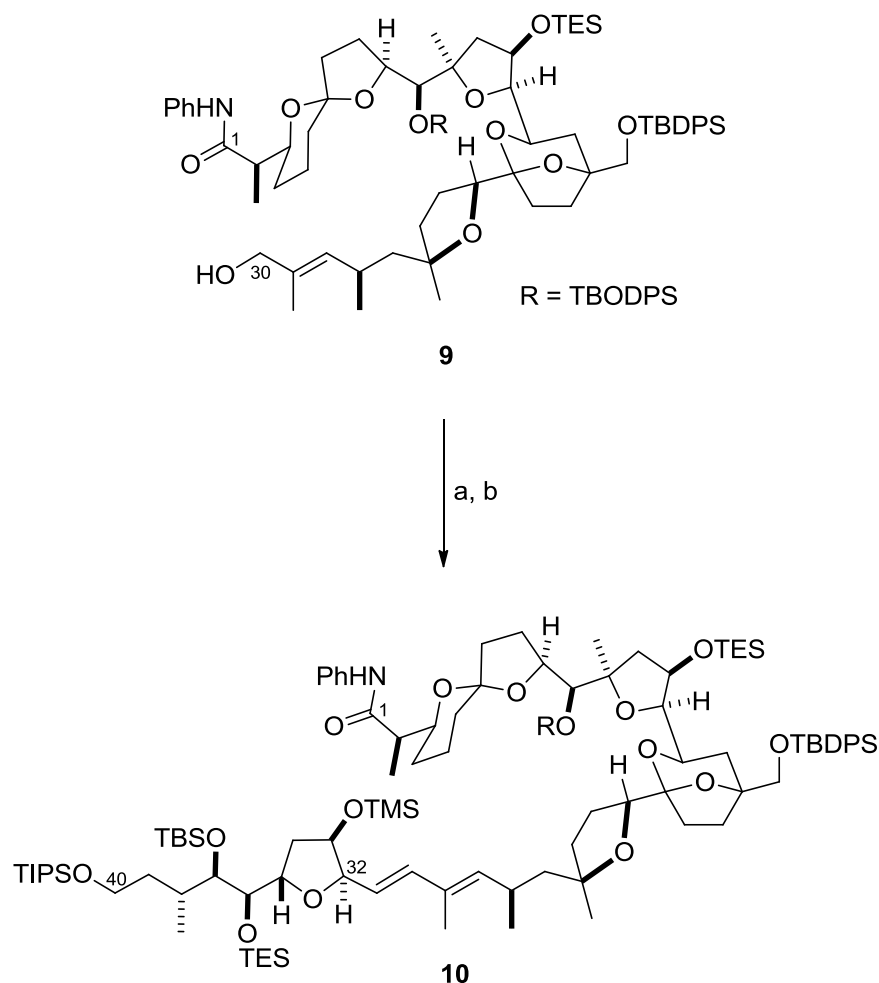
In 2002, Evans *et al.* reported the asymmetric total synthesis of PTX-4 and -8.^{20, 21} During the synthesis of the C31-C40 subunit a hydroxy-directed epoxidation²² of olefin **5** and subsequent ring closure were utilised as the key steps in the construction of the 2,5-*trans*-tetrahydrofuran F-ring (*Scheme 2*). The C31-C35 phosphonium salt **2** was accessed from known triol derivative **1** (available in 5 steps)²³ in 4 steps, and synthesis of the C36-C40 aldehyde partner **4** was accomplished from aldol adduct **3** (available in 3 steps)²⁴ in 6 steps. Union of phosphonium salt **2** and aldehyde **4** by means of a Wittig olefination afforded the desired (*Z*)-olefin **5** with high stereoselectivity (95:5). Hydroxyl-directed epoxidation of the olefin allowed access to the desired epoxide, and with subsequent protecting group manipulation furnished **6**, which possessed all of the chiral centres present in the C31-C40 subunit of PTX. Selective benzyl deprotection of **6**, followed by treatment of the resulting alcohol under acidic conditions facilitated formation of the desired 2,5-*trans*-tetrahydrofuran, with simultaneous deprotection of the primary TBS ether. Installation of the sulfone moiety and further protecting group manipulations completed the synthesis of the FG fragment of PTX-4 in 29 steps.¹⁹



Scheme 2. a) LiHMDS, THF, $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 79%; b) K_2CO_3 , MeOH/ CH_2Cl_2 (2:1), 85%; c) *m*-CPBA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 95%; d) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$, 100%; e) LiDBB, THF, $-78\text{ }^{\circ}\text{C}$, 79%; f) PPTS, MeOH/ CH_2CH_3 (1:1), 73%.

The C31-C40 fragment was joined to the C1-C30 portion of PTX-4 by means of a Julia olefination (Scheme 3).²⁵ Initial investigations into the Julia olefination on a model system revealed a significant counter-ion effect. The use of potassium bis(trimethylsilyl)amide (KHMDs) resulted in a 29:71 mixture of epimers at C32, favouring the undesired *cis*-tetrahydrofuran. Conversely, employing lithium bis(trimethylsilyl)amide (LiHMDS) resulted in a 95:5 mixture in favour of the desired *trans*-tetrahydrofuran. It was postulated that the epimerisation was a result of tetrahydrofuran ring cleavage via β -alkoxy elimination and re-addition to the intermediate vinyl sulfone.²⁶ It is assumed that the more associative lithium ion stabilises the sulfone anion such that addition to the aldehyde component is faster than β -alkoxy elimination, compared with the less associative

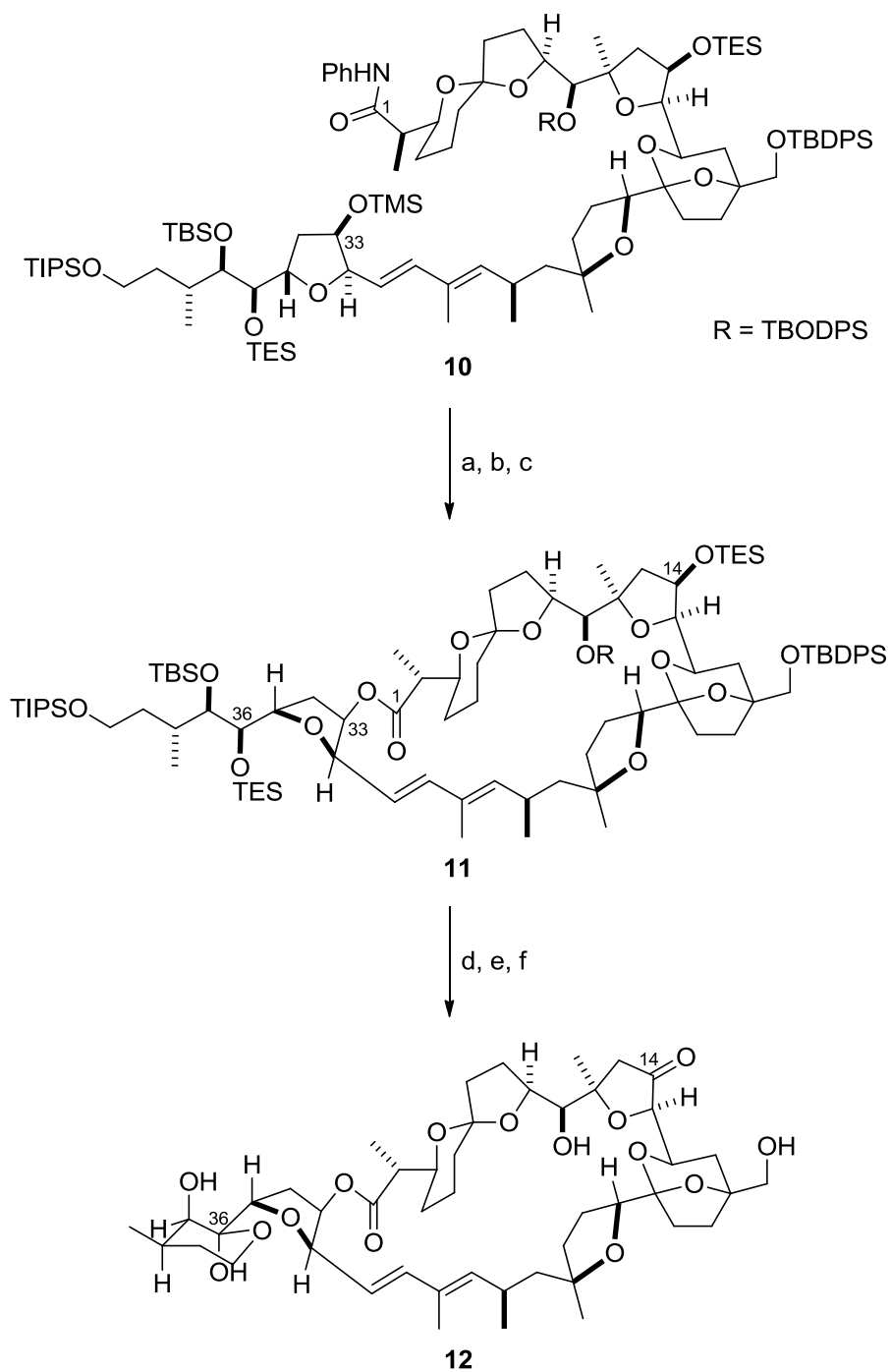
potassium ion.²⁶ Oxidation of primary alcohol **9** using the conditions of Parikh-Doering furnished the corresponding aldehyde.²⁷ The addition of LiHMDS to a pre-mixed solution of the aldehyde and sulfone **8** in THF at $-78\text{ }^{\circ}\text{C}$ allowed the successful formation of the C31-C30 bond with (*E*)-selectivity ($>95:5$) to afford the desired diene **10** as an 88:12 mixture of inseparable C32 epimers.



Scheme 3. a) $\text{SO}_3\cdot\text{Py}$, NEt_3 , $\text{CH}_2\text{Cl}_2/\text{DMSO}$, (1:1); b) sulfone **8**, LiHMDS, THF, $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 72% (two steps).

In order to effect the macrolactonisation, the *N*-phenylamide at C1 of **10** was activated by conversion to the corresponding *N*-Boc imide (Scheme 4). Exposure of the imide to LiOOH resulted in hydrolytic cleavage to the carboxylic acid with concomitant TMS ether deprotection at C33 to deliver a protected analogue of the PTX-4 seco acid. Treatment of

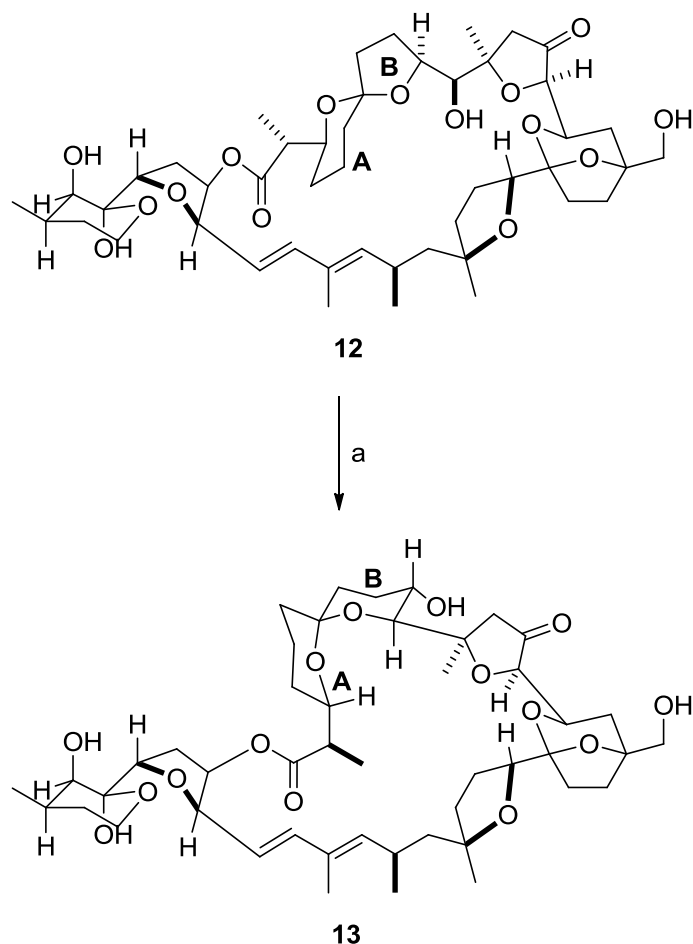
the seco acid under the mild esterification procedure developed by Yamaguchi,²⁸ afforded macrolide **11**. Formation of the hemiacetal G-ring and completion of the synthesis of PTX-4 was achieved by the selective deprotection of the C14 and C36 TES ethers, oxidation to the corresponding diketone and global silyl ether deprotection.



Scheme 4. a) Boc_2O , DMAP, MeCN, 91%; b) LiOH, H_2O_2 , THF/ H_2O (3:1); c) 2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, PhMe; d) PPTS, MeOH/ CH_2Cl_2 (1:1), 35% (three steps); e) DMP, pyridine, CH_2Cl_2 , 72%; f) TAS-F, H_2O , DMF, 85%.

The structure of synthetic PTX-4 was confirmed by comparison of ^1H NMR data with that obtained from a natural sample. In addition, the specific rotation was of the same magnitude and direction as that reported by Yasumoto, thus confirming the absolute

configuration of the synthetic PTX-4. Treatment of PTX-4 under acidic conditions mediated an isomerisation of the AB spiroketal to form PTX-8 (Scheme 5).⁴ Synthetic PTX-8 was also judged to be identical to an authentic sample PTX-8 by ¹H NMR, HPLC, TLC R_f and UV spectroscopy.²¹



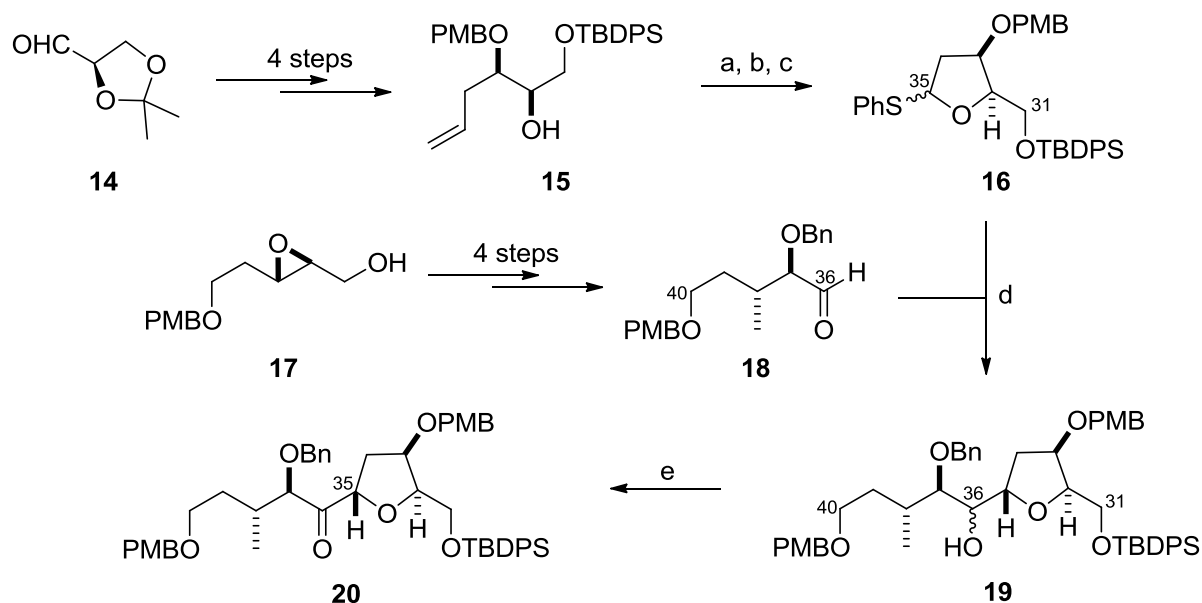
Scheme 5. a) 1% TFA (v/v), CH₃CN/H₂O (9:1), 0 °C, 40%.

The synthesis of PTX-4 was completed in a total of 93 steps (37 steps longest linear sequence) from commercially available reagents, with an overall yield of 0.3%.²¹

1.1.3.2 Murai and Fujiwara's synthesis of the C31-C40 portion

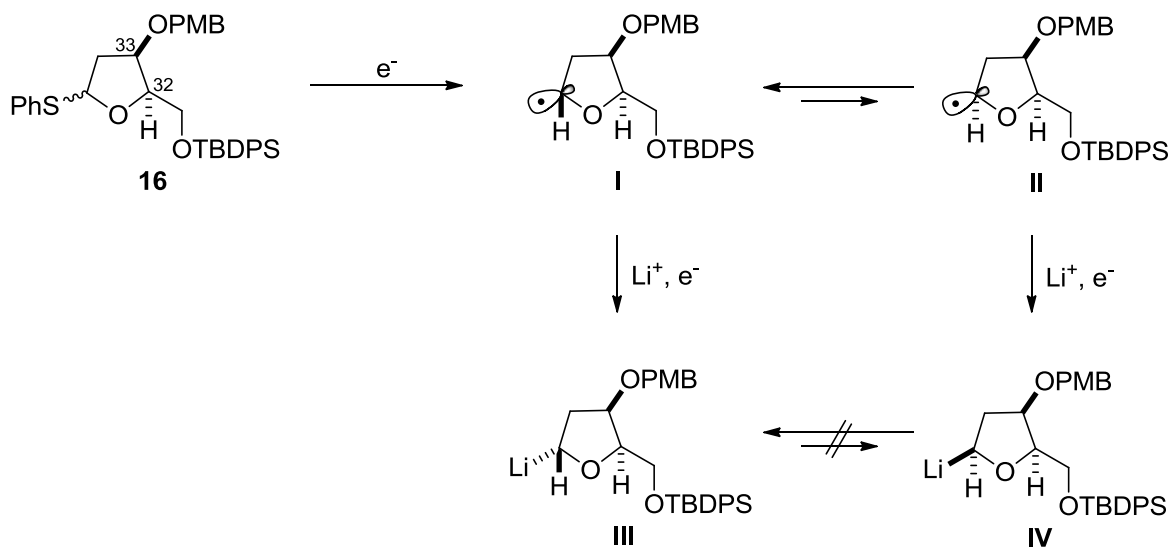
The first reported synthesis of the FG fragment of PTX was published in 1997, when Murai and co-workers reported their progress into the synthesis of PTX-2.²⁹ Their synthesis of the common C31-C40 fragment corresponded to the enantiomer of that found

in natural PTXs and consequently,² they later reported a convergent synthesis with the correct absolute configuration.³⁰ The key reaction in their synthesis was the coupling of the C31-C35 portion with C36-C40 *via* a reductive lithiation (*Scheme 6*).^{29, 31} Triol derivative **15** was synthesised from D-glyceraldehyde acetonide **14** in 4 steps,^{32, 33} and was transformed to the corresponding cyclic hemiacetal by means of an oxidative cleavage of the terminal olefin. The resultant hemiacetal was activated by acetylation and was subsequently treated with thiophenol in the presence of boron trifluoride etherate to afford the desired F-ring precursor **16** as a mixture of anomers. The synthesis of the G-ring precursor aldehyde **18** was achieved from known epoxide **17**³⁴ in 4 steps. Treatment of phenylthiotetrahydrofuran **16** with lithium 4,4'-di-*tert*-butylbiphenyl (LiDBB) resulted in the immediate generation of the corresponding anion.³⁵ Reaction of the anion with aldehyde **18** afforded alcohol **19** as an inconsequential mixture of diastereomers at C36. Subjecting the resulting secondary alcohol to a Swern oxidation³⁶ revealed a 4.2:1 mixture of diastereomers at C35, with the major diastereomer possessing the desired 2,5-*trans*-stereochemistry.³⁰



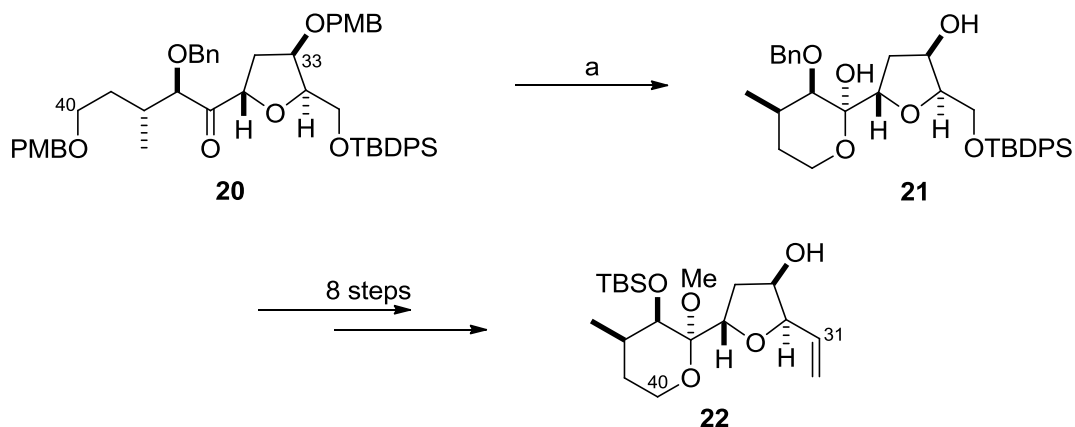
Scheme 6. a) OsO_4 , NMO, 1,4-dioxane- H_2O (3:1), then NaIO_4 , pH 7 buffer, 94%; b) Ac_2O , NEt_3 , DMAP, CH_2Cl_2 , 98%; c) PhSH , $\text{Et}_2\text{O} \cdot \text{BF}_3$, CH_2Cl_2 , -40°C , 87%; d) LiDBB, THF, -95°C , then **18**, -78°C , 71%; e) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , then NEt_3 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 98%.

Investigations into the substituent effect on the stereoselective reductive lithiation revealed that the *cis*-configuration at C33 and C32 was essential for the stereoselective generation of the 2,5-*trans*-lithiated intermediate **III** (Scheme 7).³¹ In addition, the existence of an equilibrium between radical intermediates **I** and **II** was proposed to explain the *trans*-stereoselectivity, whereby single electron transfer onto the least sterically hindered face would be favoured. It was suggested that the C33 PMB group may influence the equilibrium between **I** and **II** and/or the reaction rates of the second single electron transfer, hence favouring the formation of the 2,5-*trans*-tetrahydrofuran.³¹



Scheme 7. Proposed mechanism of the stereoselective generation of the lithiated intermediate

Bis-deprotection of the C33 and C40 *para*-methoxybenzyl groups of **20** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) allowed for the isolation of the desired diastereomer **21** as a cyclic acetal (*Scheme 8*). Following further elaboration (8 steps), the C31-C40 fragment **22** of PTX-2 was furnished with the correct stereochemistry.³⁰

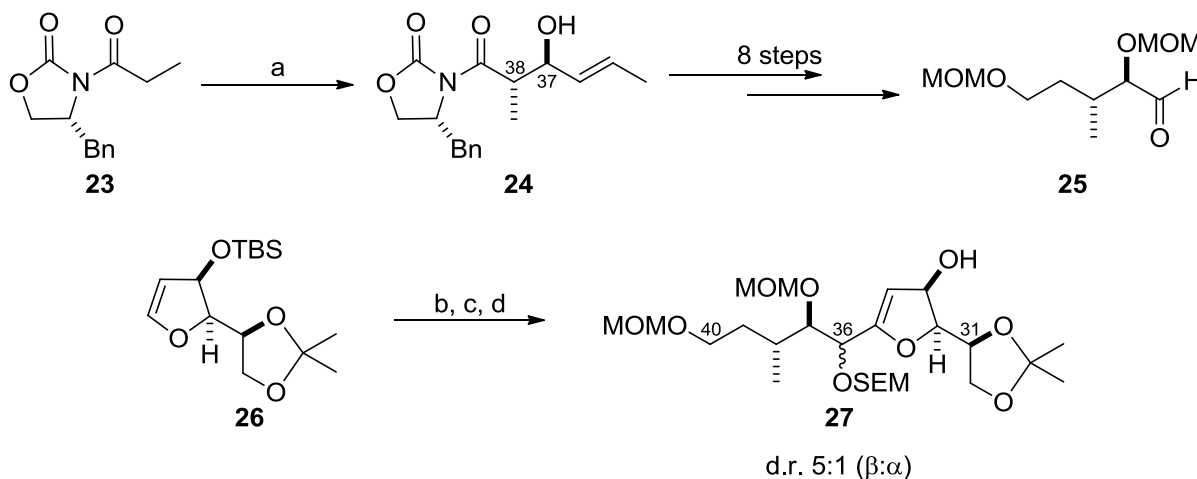


Scheme 8. a) DDQ, $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ (10:1), 0 °C, 70%.

The synthesis of the FG fragment of PTX was achieved in 22 steps from D-glyceraldehyde acetone³² and known epoxide **17**.³⁴

1.1.3.3 Paquette's synthesis of the C29-C40 fragment

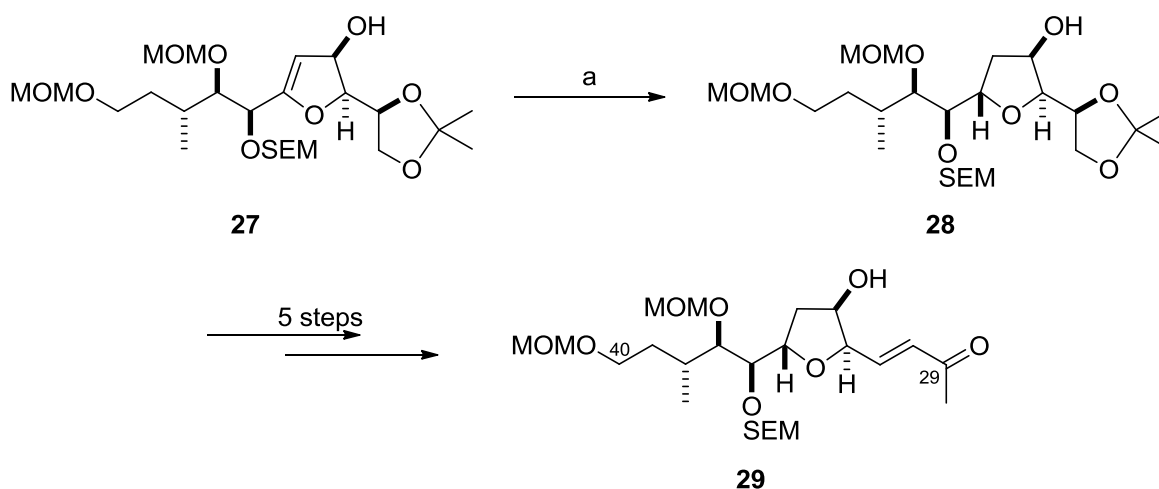
In 2002, Paquette and co-workers reported the synthesis of the C29-C40 fragment of PTX-2 in 21 steps, which utilised an alkoxide-directed hydrogenation as the key transformation to furnish the 2,5-*trans*-disubstituted tetrahydrofuran F-ring (Scheme 9).³⁷ The synthesis of aldehyde **25** was completed in 9 steps from oxazolidinone **23**,^{38, 39} with the desired stereochemistry at C37 and C38 being installed by means of an *anti*-aldol reaction employing the Heathcock modification to the Evans's aldol procedure.³⁸⁻⁴⁰ Enantiopure dihydrofuran **26**, readily available from D-mannose in 3 steps,⁴¹ was treated with *tert*-butyllithium to afford the corresponding vinyl anion, which when coupled with aldehyde **25** delivered the C31-C40 backbone of PTX as an inconsequential mixture of diastereomers (5:1) at C36. Protection of the secondary alcohol as the SEM ether,⁴² followed by chemoselective deprotection of the TBS ether with TBAF afforded **27** as a diastereomeric mixture, which was subsequently separated to give a single diastereomer.³⁷



Scheme 9. a) Crotonaldehyde, Bu_2BOTf (2 equiv.), DIPEA, Et_2O , -78°C , 62%; b) $t\text{BuLi}$, THF, -78°C , then **25**, 52%; c) SEMCl, DIPEA, CH_2Cl_2 , 85%; d) TBAF, THF, 0°C , 66%.

The key alkoxide-directed hydrogenation to establish the final chiral centre of the FG fragment ensued (Scheme 10). Difficulties arose due to the propensity for tetrahydrofuran **27** to undergo dehydration when exposed to the reaction conditions, affording the

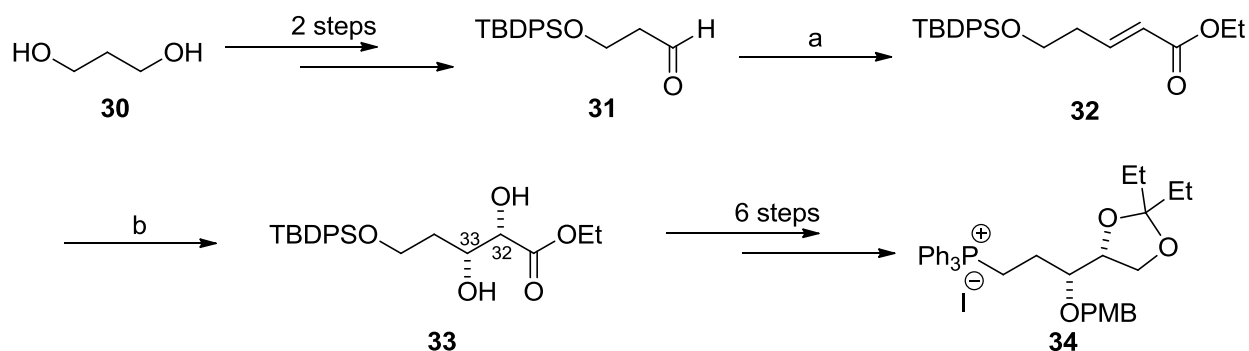
corresponding furan. This observation was attributed to the Lewis-acidic nature of the catalyst. Consequently, it was found that the inclusion of base was vital to avoid conversion to the furan. It was also discovered that ionic complexation of the sodium alkoxide salt of **27** with the cationic catalyst $[\text{Rh}(\text{NBD})(\text{DIPHOS-4})]\text{BF}_4$ ^{43, 44} was crucial for delivering the desired stereochemical outcome. A further 5 steps allowed the synthesis of the C29-C40 fragment of PTX-2 to be achieved.



Scheme 10. a) $[\text{Rh}(\text{NBD})(\text{DIPHOS-4})]\text{BF}_4$, H_2 , NaH , THF , 68%.

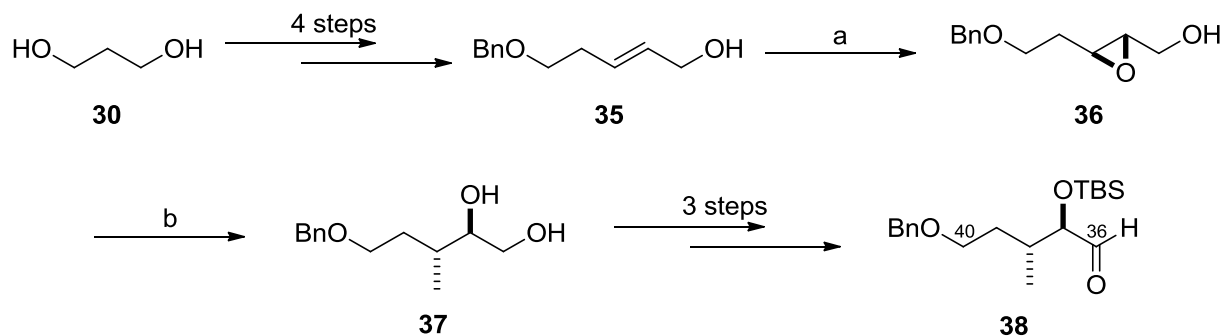
1.1.3.4 Brimble's synthesis of the C31-C40 portion

The most recent synthesis of the FG ring portion was reported by Brimble and co-workers in 2010.⁴⁵ The convergent approach centred on the union of phosphonium salt **34** and aldehyde **38** by means of a (Z)-selective Wittig olefination, in a similar fashion to Evans and co-workers.²¹ The phosphonium salt was synthesised from propane-1,3-diol **30** in 10 high yielding steps (*Scheme 11*).



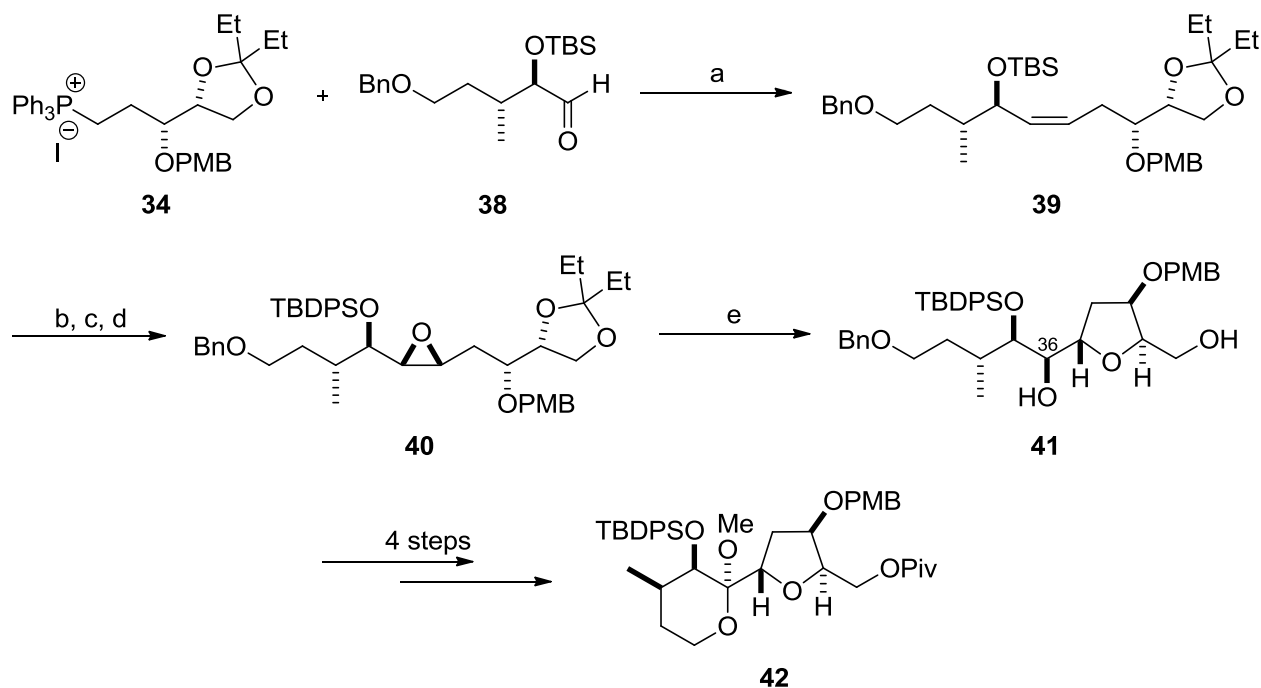
Scheme 11. *a*) (EtO)₂P(O)CH₂CO₂Et, K₂CO₃, Et₂O, H₂O, 0 °C → rt, 86%; *b*) K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, (DHQD)₂PHAL, OsO₄, ^tBuOH:H₂O (1:1), 0 °C → rt, 93%.

A Horner-Wadsworth-Emmons (HWE) olefination was utilised for the extension of the carbon backbone of aldehyde **31**. It was found that the standard HWE reaction conditions employing sodium hydride as base yielded olefin **32** in inferior yields (67%) compared to those obtained utilising the milder, optimised conditions of Villieras *et al.*⁴⁶ By performing the coupling of triethylphosphonoacetate with aldehyde **31** under biphasic aqueous conditions and changing the base to potassium carbonate, (*E*)-olefin **32** was obtained in consistently high yields (86%). Subjecting olefin **32** to a Sharpless asymmetric dihydroxylation⁴⁷ resulted in the installation of the C32 and C33 *syn*-stereocentres of the FG fragment with excellent enantioselectivity (>94% ee). Protecting group manipulation of **33**, followed by a reduction of the ester and subsequent formation of the phosphonium salt, delivered **34** in a further 6 steps. The synthesis of aldehyde **38** was also achieved from propane-1,3-diol **30** (Scheme 12). The two key stereocentres of this portion were incorporated by means of a Sharpless asymmetric epoxidation⁴⁸ of allyl alcohol **35** using (+)-diethyl tartarate (DET) as the chiral ligand. Regioselective opening of the resultant epoxy-alcohol **36** with trimethylaluminium afforded 1,2-diol **37**, which was further transformed to the desired aldehyde **38** in 3 steps.



Scheme 12. *a)* $\text{Ti}(\text{PrO})_4$, (+)-DET, 4 Å MS, CH_2Cl_2 , TBHP, 91%; *b)* AlMe_3 , CH_2Cl_2 , 0 °C → rt, 66%.

The key Wittig olefination to couple aldehyde **38** and phosphonium salt **34** in a (*Z*)-selective manner followed (Scheme 13). Treatment of phosphonium salt **34** with *n*-butyllithium afforded the corresponding phosphonium carbanion. Reaction of the carbanion with aldehyde **38**, in the presence of hexamethylphosphoramide (HMPA) as a co-solvent, delivered the desired (*Z*)-olefin **39** in an excellent yield of 93%. In order to facilitate the diastereoselective epoxidation of alkene **39**, deprotection of the TBS ether ensued. Hydroxy-directed epoxidation of the allylic alcohol provided the corresponding epoxide as the sole diastereomer (as observed by NMR analysis). Subsequent re-protection of the secondary alcohol as the TBDPS ether afforded epoxide **40**. On exposure of epoxide **40** to 50% aq. TFA, cleavage of the 1,3-dioxolane resulted, along with concomitant 5-*exo-tet*-cyclisation to afford the F-ring of PTX.



Scheme 13. a) $n\text{BuLi}$, HMPA, THF, $-78\text{ }^{\circ}\text{C}$, 93%; b) TBAF, THF, 81%; c) *m*-CPBA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 99%, >95% de; d) TBDPSCl, imid., CH_2Cl_2 , 85%; e) 50% aq. TFA, CH_2Cl_2 , 62%.

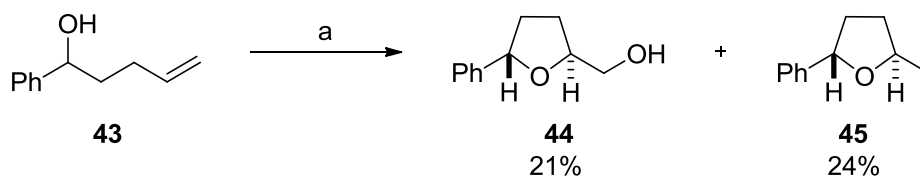
Protection of the primary alcohol as a pivalate ester, oxidation of the C36 secondary alcohol, and debenzylation in the presence of the PMB group with Raney nickel⁴⁹ facilitated a 6-*exo*-trig cyclisation to provide the hemiacetal G-ring. Subjecting the crude hemiacetal to an acid-catalysed methylation provided the corresponding methyl ketal **42** as the thermodynamically most stable anomer. The synthesis was achieved in a total of 28 steps from propane-1,3-diol.⁴⁵

1.2 The formation of 2,5-*trans* THFs

Several synthetic polyether antibiotics and biologically active natural products, including the Annonaceous acetogenins,⁵⁰ are comprised of 2,5-*trans*-disubstituted THFs, prompting the development of methodology for their convenient and diastereoselective synthesis. A variety of strategies have been developed for the synthesis of 2,5-*trans* THFs, including the oxidative cyclisation of 5-hydroxy alkenes,^{51, 52} cyclisations onto epoxides,⁵³⁻⁵⁶ ring closing metathesis,^{57, 58} and a Williamson etherification approach.^{59, 60} Reported herein is a detailed discussion about the cobalt(II) catalysed oxidative cyclisation of 5-hydroxy alkenes.

1.2.1 The cobalt-catalysed oxidative cyclisation of 5-hydroxy alkenes

In 1990, Mukaiyama and co-workers reported a diastereoselective method for the formation of *trans*-THFs, which utilised a cobalt(II) catalyst to facilitate the oxidative cyclisation of 5-hydroxy alkenes.⁵² The reaction was originally discovered during attempts to develop methodology for the hydration of olefins *via* a cobalt(II)-catalysed oxidation-reduction process.^{61, 62} It was shown that subjecting hydroxy alkene **43** to a catalytic amount of bis(trifluoroacetylacetonate)cobalt(II) (Co(tfa)₂) in 2-propanol, under an atmosphere of oxygen at 75 °C, resulted in the formation of cyclisation products **44** and **45** in yields of 21% and 24% respectively (Scheme 14). Notably, an extremely high preference was observed for the formation of *trans*-THFs (>99% de) prompting further investigations into this reaction.⁵²



Scheme 14. a) O₂, Co(tfa)₂ (20 mol%), *i*PrOH, 75 °C, 4 Å MS.

Subsequent investigations were conducted into the effect of varying the temperature of the reaction. It was discovered that a temperature of 55 °C, despite resulting in a slower reaction, led to an increase in the yield of THF **44** from 21% to 55%. Furthermore, the formation of methyl-THF **45** was not observed at this temperature. It was also found that the activity of the catalyst, and consequently the yields of the products, was greatly influenced by the structure of the ligand of the cobalt(II) complex. After screening various 1,3-diketone ligands (*Figure 10*), Co(modp)₂ was demonstrated to produce superior yields of the desired *trans*-THF product (62%). In comparison to Co(tfa)₂ and Co(acac)₂, oxidative cyclisation reactions utilising Co(modp)₂ as the catalyst also proceeded to completion in a much shorter reaction time.

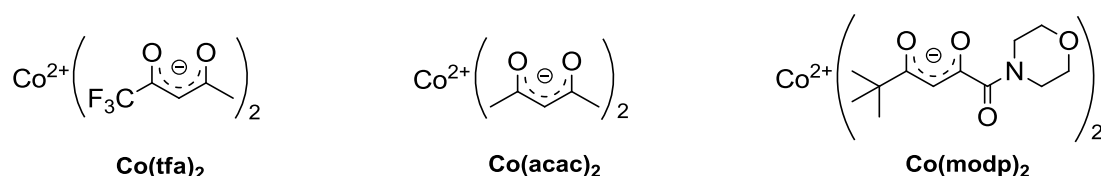
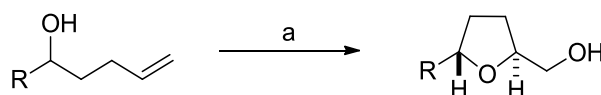


Figure 10. Cobalt(II) catalysts

Following the discovery that Co(modp)₂ acted as a more efficient catalyst for the oxidative cyclisation, an extensive investigation into the effect of the 1,3-diketone ligands present in the cobalt(II) complexes was carried out.⁶³ The redox potentials of various Co(II) complexes were measured and it was found that in order to be catalytically active, a redox potential between 0 and +0.5 V was required.⁶³ Complexes that were found to have a redox potential outside of these limits were shown to exhibit no catalytic activity. It was rationalised that the electron donating and/or electron withdrawing groups attached to the ligands affect the electrophilicity of the cobalt ion. Further work revealed that hydroperoxides could be used as an additive in the oxidative cyclisation. Utilising an equimolar amount of *tert*-butyl hydroperoxide (TBHP) resulted in the yield of the Co(modp)₂ catalysed cyclisation of **43** increasing from 62% to 73%. The optimised

conditions were then applied to a range of terminal olefins with variation at position R (Table 1). All of the reactions proceeded to form the corresponding *trans*-THF in good yields and with excellent diastereoselectivities.⁵²

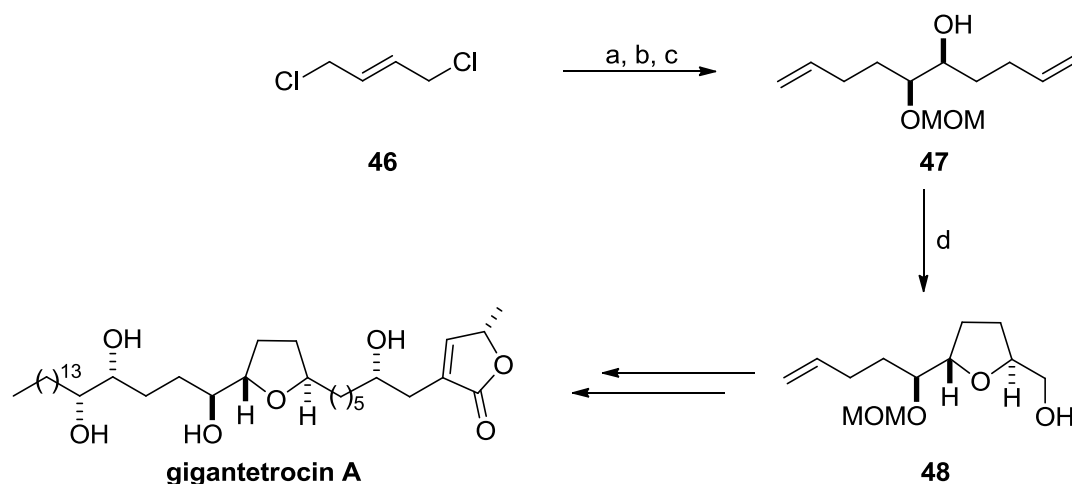


Entry	R	Yield (%)	<i>trans</i> -Selectivity (%)
1		73	99
2		69	99
3		60	99
4		53	99
5		55	>99

Table 1. a) O₂, Co(modp)₂ (25 mol%), ⁱPrOH, TBHP, 50 °C, 4 Å MS.

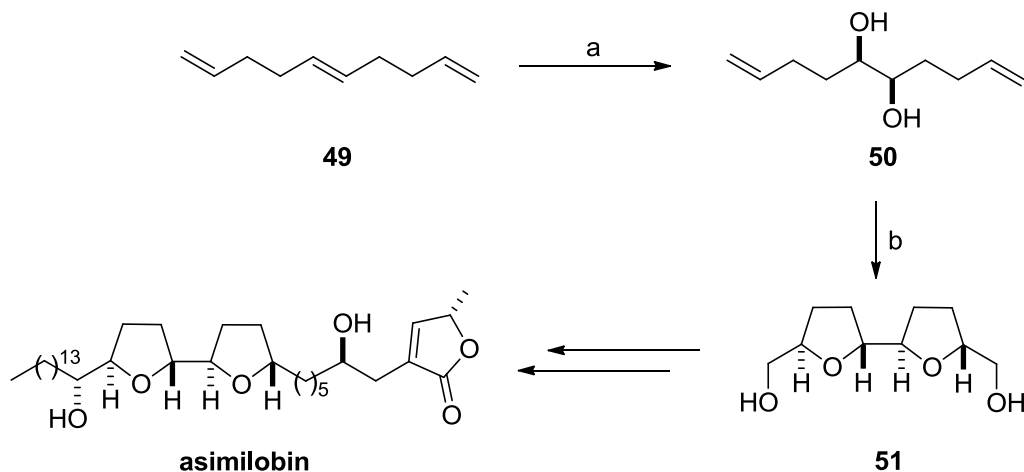
Due to the excellent diastereoselectivity of the reaction, this method has appeared in several syntheses of natural products. The successful application of this methodology was demonstrated in the first total synthesis of gigantetrocin A by Shi *et al.*⁶⁴ Mono-protected syn diol **47** was synthesised from *trans*-1,4-dichloro-2-butene in 3 steps (Scheme 15). The stereodefined diol functionality was installed by way of a Sharpless asymmetric dihydroxylation using (DHQ)₂-PHAL as the chiral ligand.⁴⁷ Treatment of the resulting diol with sodium hydride in THF afforded diepoxybutane *in situ*. The addition of allylmagnesium chloride to diepoxybutane in the presence of copper(I) iodide resulted in the selective ring-opening of both epoxides at the least hindered position to furnish the chain-extended diol. Desymmetrisation of the resulting diol was achieved by mono-protecting one of the alcohols as a MOM ether, preparing alcohol **47** for the key oxidative cyclisation. Utilising Co(modp)₂ as the cyclisation catalyst resulted in the formation of

trans-THF **48** in 74% yield and with excellent diastereoselectivity (>95%). Following the successful implementation of the oxidative cyclisation methodology, THF **48** was further manipulated to provide gigantetrocin A in a total of 19 steps from *trans*-1,4-dichloro-2-butene.⁶⁴



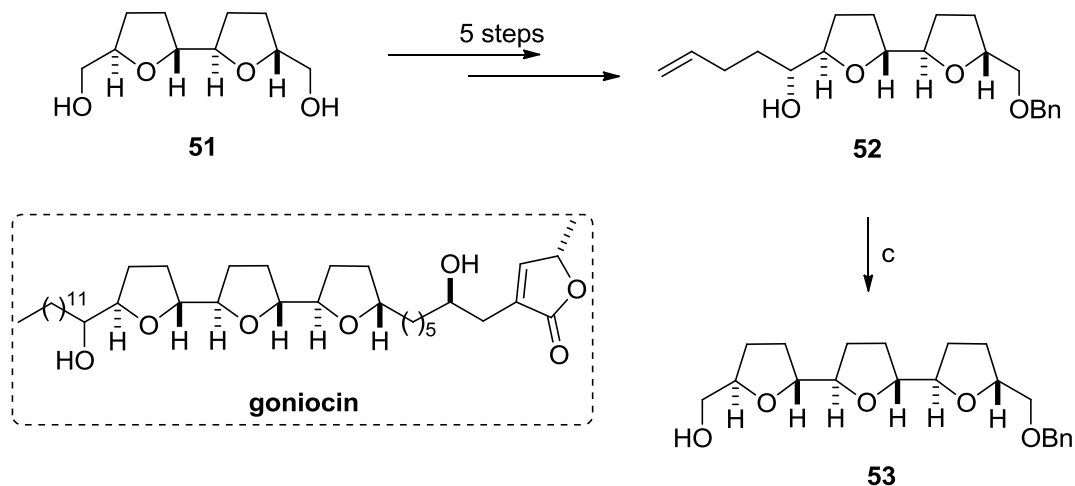
Scheme 15. a) $K_3Fe(CN)_6$, K_2CO_3 , $NaHCO_3$, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_4 \cdot 2H_2O$, $tBuOH:H_2O$ (1:1), 0 °C, 84%; b) NaH , THF, then allylmagnesium chloride, CuI , THF, -50 °C, 79%; c) NaH , $MOMCl$, THF, 67%; d) $Co(modp)_2$, $TBHP$, O_2 , $iPrOH$, 60 °C, 74%.

The cobalt-mediated oxidative cyclisation was also utilised in the efficient construction of the *trans*-bis- and *trans*-tris-THF building blocks of the annonaceous acetogenins.⁶⁵ Like gigantetrocin A, the annonaceous acetogenins are characterised by the presence of between one and three THF rings, a long hydrocarbon side-chain and a butenolide moiety.⁶⁵ Shi *et al.* demonstrated that the cobalt(II) catalysed oxidative cyclisation could be applied to the synthesis of each of the adjacent THF rings, starting from common triene **49** (Scheme 16). It was possible to selectively dihydroxylate the internal alkene of triene **49** by utilising the Sharpless asymmetric dihydroxylation reaction.⁴⁷ Subsequently, exposing unsaturated diol **50** to the oxidative cyclisation conditions led to the formation of bis-THF **51** in one transformation with excellent diastereoselectivity (>95%). The resulting bis-THF core was successfully employed in the first total synthesis of asimilobin.⁶⁶



Scheme 16. a) $K_3Fe(CN)_6$, K_2CO_3 , $NaHCO_3$, $MeSO_2NH_2$, $(DHQD)_2PHAL$, $K_2OsO_4 \cdot 2H_2O$, $tBuOH:H_2O$ (1:1), $0^\circ C$, 51%; b) $Co(modp)_2$ (40 mol%), TBHP, O_2 , $iPrOH$, $60^\circ C$, 78%.

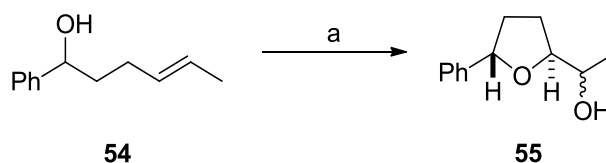
In order to allow for the formation of a further *trans*-THF ring, the side-chain of THF **51** was extended in 5 steps to form hydroxy alkene **52** (Scheme 17). The resulting hydroxy alkene was subsequently re-subjected to the oxidative cyclisation procedure in order to furnish the tris-THF **53** (>95% de), which represents the central THF core of goniocin.⁶⁵



Scheme 17. a) $Co(modp)_2$ (10 mol%), TBHP, O_2 , $iPrOH$, $60^\circ C$, 57%.

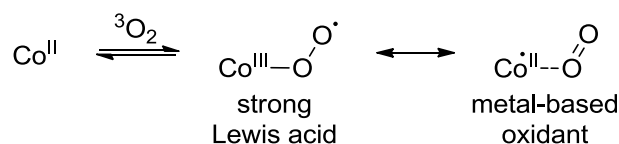
In 2002, Hartung and co-workers published their findings on extensive investigations into the cobalt(II) catalysed oxidative cyclisation.⁶⁷ It was reported that the reaction was highly dependent on substrate chain length and the substitution pattern at both the alcohol and the alkene. Upon increasing the chain length between the alcohol and the alkene by one carbon

unit, an oxidative cyclisation did not occur, even at elevated temperatures. In addition, it was found that tertiary alcohols were not favourable substrates for the cyclisation and required higher temperatures for the consumption of starting material to occur. Interestingly, when the terminal position of the alkene was substituted with a methyl group and subjected to the oxidative cyclisation reaction, a complete loss of stereochemical information from the double bond geometry was observed (*Scheme 18*).

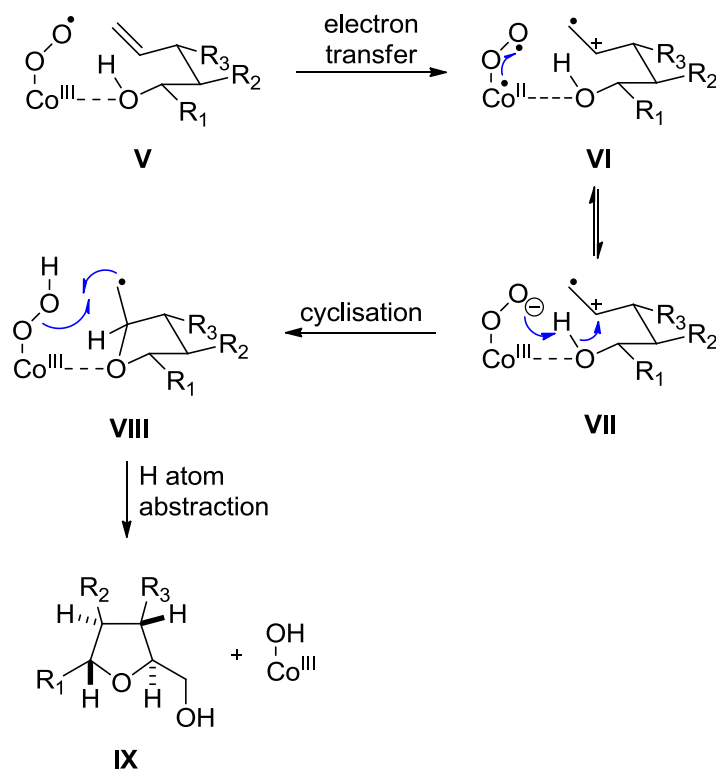


Scheme 18. a) Co(II), TBHP, O₂, *i*PrOH, 60 °C, 34%.

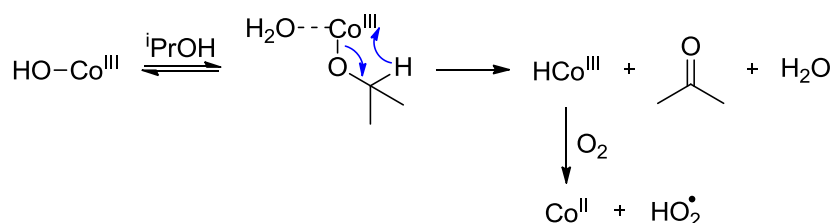
Upon inspection, it was found that *trans*-THF **55** was afforded as a 56:44 mixture of diastereomers at the newly formed hydroxy group, thus supporting the hypothesis of a mechanism involving a radical cation intermediate (see *Scheme 20*). A decrease in π -bond order would allow for free rotation about the bond, providing an explanation for the unselective hydroxylation. Subtle changes in reactivity were also observed upon varying the catalyst ligand, reaction temperature, initial catalyst concentration and solvent.⁶⁷ As a result of combining these findings with data available in the literature on related transformations, Hartung and co-workers proposed a mechanism for the oxidative cyclisation procedure.⁶⁷ In agreement with Mukaiyama's earlier investigations, it was proposed that the reaction proceeds *via* a radical mechanism. It was postulated that the paramagnetic cobalt(II) complex activates triplet oxygen by binding in a superoxo-mode (*Scheme 19*). The resultant cobalt-oxygen radical species is considered to be a strong Lewis acid and a metal-based oxidant.⁶⁷

**Scheme 19.** Activation of oxygen

The Lewis acidic complex is thought to coordinate to the hydroxy alkene, which in turn sits in a chair-like conformation with substituents lying in pseudo-equatorial positions (*Scheme 20*). Co(III) is a powerful oxidant ($E^\circ = +1.84 \text{ V}$)⁶⁸ and is consequently capable of abstracting an electron from the alkene to furnish the corresponding radical cation **VI**.⁶⁹ As a result of this, a stereoselective 5-*exo* cyclisation onto the oxidised π -bond occurs, affording the *trans*-THF, along with oxidation of Co(II) to Co(III) and the formation of cobalt hydroperoxide. The weak cobalt hydroperoxide O-O bond is readily cleaved, facilitating the formation of the desired hydroxy-THF product **IX** and, upon reduction, a cobalt(III) hydroxide species.⁷⁰

**Scheme 20.** Proposed mechanism for the cobalt-catalysed oxidative cyclisation.

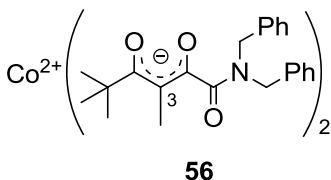
Subsequent regeneration of Co(II) is thought to occur *via* hydride shift from a coordinated 2-propanol solvent molecule, yielding acetone and water as secondary products (*Scheme 21*), which were detected by quantitative analysis of reaction mixtures.⁶⁷



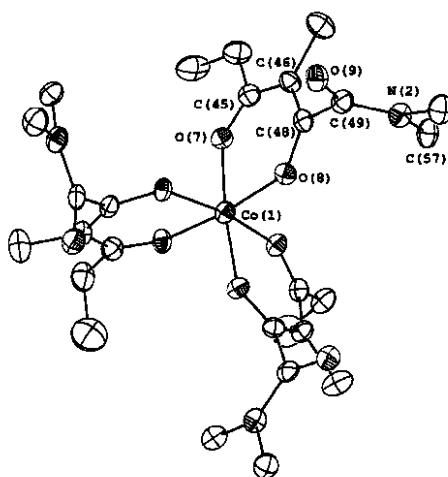
Scheme 21. Regeneration of Co(II)

In some cases, the direct abstraction of a hydrogen atom from the solvent occurs immediately after cyclisation, as opposed to hydration of the olefin, leading to the formation of a methyl-THF derivative as a side product.

The following year, the solid structure of the cobalt catalyst was elucidated by Pagenkopf and co-workers, who reported the first crystal structures of 2,4-dioxo-alkanoic acid dialkylamide Co(II) complexes.⁷¹ Various 2,4-dioxo amide complexes were synthesised in an attempt to find a ligand which would provide crystals suitable for X-ray analysis. Pleasingly, it was discovered that complex **56**, whereby the morpholine subunit of Co(mopd)₂ had been replaced with a diphenyl amide moiety, and a methyl group had been installed at the C3 position, formed red crystals that gave rise to an unexpected X-ray structure (*Figure 11*).



A unique arrangement of atoms was found, whereby a central cobalt atom was bound to water, with two flanking cobalt atoms coordinated by three dioxo amide ligands in an octahedral geometry (*Figure 12*). The central Co(II) atom with six neutral water molecules, balances the negative charge induced by the six anionic ligands which are bound to the two outer Co(II) atoms.



33

Despite the synthetic utility of Mukaiyama's oxidative cyclisation with $\text{Co}(\text{mopd})_2$, it was found that in some cases removal of the catalyst residues from the resulting *trans*-THF products by column chromatography proved extremely challenging, particularly in the case of more polar compounds.⁷² As cobalt is paramagnetic and interferes with NMR spectroscopy, characterisation of contaminated products consequently proved problematic. Pagenkopf and co-workers sought to develop a new catalyst which would retain the high efficiency of the oxidative cyclisation, yet which would display a significant increase in polarity compared to the well-established $\text{Co}(\text{modp})_2$ catalyst. By exchanging the morpholine subunit of the modp ligand with an *N*-methylpiperazine, it was found that a simplified purification procedure could be employed in order to remove the cobalt residues from the reaction mixture (Figure 13).⁷²

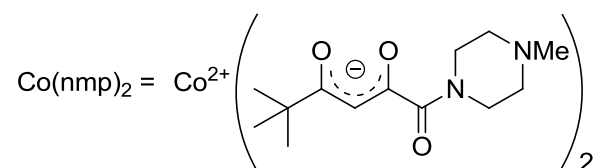
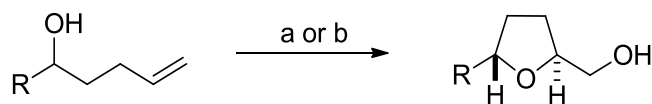


Figure 13. Second-generation cobalt(II) catalyst

Various purification methods for the removal of the catalyst residues were reported. For non-acid sensitive substrates, the cobalt residues could be removed with a pH 4 phosphate buffer wash of the organic layer. Alternatively, a neutral work-up procedure was described whereby the crude reaction mixture was treated with methyl iodide in order to methylate the tertiary amine, followed by removal of the iodide salts with a water wash. The second-generation water-soluble cobalt(II) catalyst was shown to produce improved yields for the oxidative cyclisation of a number of substrates, compared with the first generation $\text{Co}(\text{modp})_2$ catalyst (Table 2). It was also possible to cleanly isolate the more polar THF products that could not be purified effectively using the previous catalytic protocol.⁷²



Entry	R	Yield (%) ^a	Yield (%) ^b
1		47	91
2		76	91
3	PMPO-	81 ^c	90
4		57	95

Table 2. ^aCo(modp)₂ (10 mol%), TBHP, O₂, ⁱPrOH, 60 °C; ^bCo(nmp)₂ (10 mol%), TBHP, O₂, ⁱPrOH, 60 °C;
^cThis yield is artificially elevated due to the presence of cobalt residues that could not be removed after repeated chromatography.

An application of the modified procedure was demonstrated in the synthesis of the C18-C34 fragment of amphidinolide C (Figure 14).⁷³

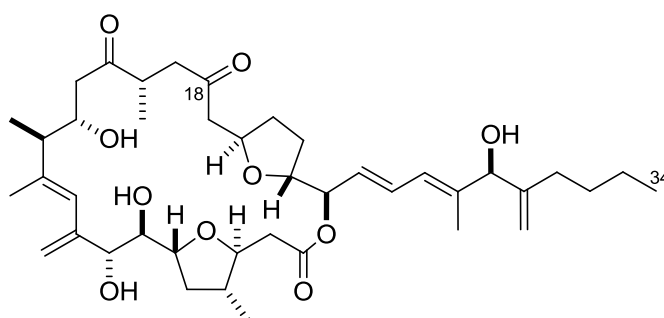
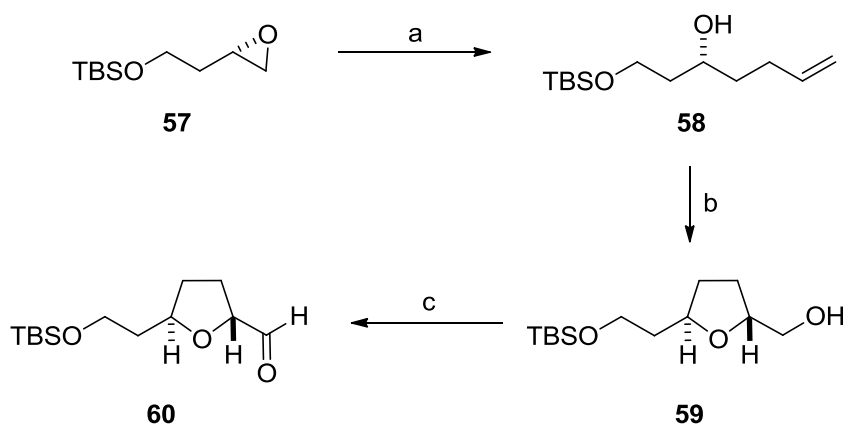


Figure 14. Amphidinolide C

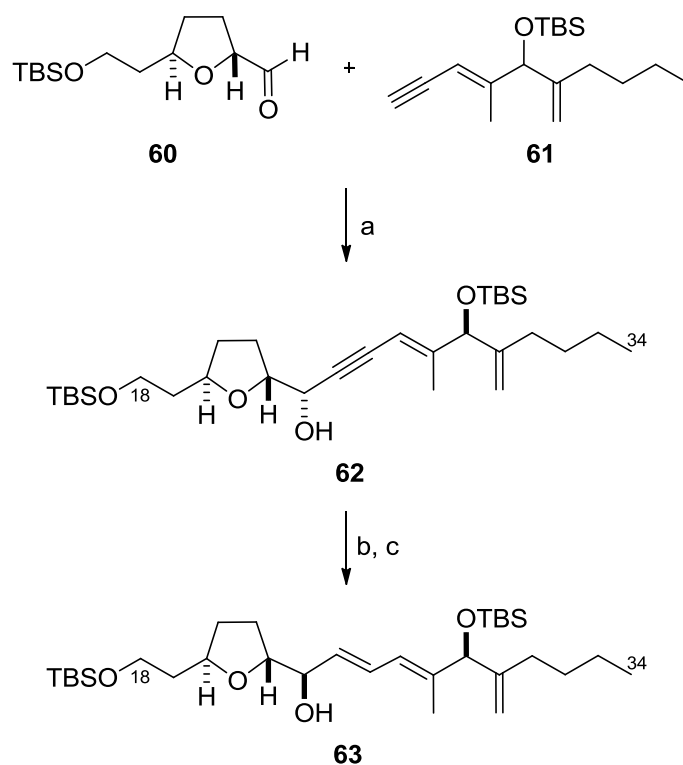
The convergent approach to the synthesis of amphidinolide C consisted of a diastereoselective alkynylation of aldehyde **60** with alkyne **61**. The synthesis of aldehyde **60** commenced with the ring-opening of known epoxide **57** using allylmagnesium bromide,⁷⁴ followed by the oxidative cyclisation of the resultant hydroxy alkene (Scheme 22). Utilising the second-generation Co(nmp)₂ catalyst in the cyclisation allowed for the formation of *trans*-THF **59** in excellent yield and diastereoselectivity. Subsequently,

subjecting *trans*-THF **59** to a Swern oxidation furnished the corresponding aldehyde **60** in an efficient three-step procedure.⁷³



Scheme 22. a) Allylmagnesium bromide, Et₂O, 0 °C → rt, 99%; b) O₂, Co(nmp)₂ (10 mol%), TBHP, ⁱPrOH, 55 °C, 97%; c) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, -78 °C → 0 °C, 85%.

It was possible to synthesise the alkyne coupling partner in 6 steps from hexanal. With alkyne **61** in hand, coupling of the alkyne portion to aldehyde **60** in a diastereoselective manner furnished alcohol **62** as a 20:1 (*anti/syn*) mixture of diastereomers in 93% yield (*Scheme 23*). Despite the diastereoselective nature of the coupling reaction, it was necessary to invert the secondary alcohol to the correct diastereomer by means of a Mitsunobu inversion. The subsequent reduction of alkyne **62** to the *trans,trans*-diene was achieved with Red-Al, which provided the C18-C34 portion of amphidinolide C in only 12 total steps.



Scheme 23. a) $n\text{BuLi}$, MTBE, $0\text{ }^{\circ}\text{C} \rightarrow -90\text{ }^{\circ}\text{C}$, 93%; b) 4-nitrobenzoic acid, DIAD, PPh_3 , 90%; c) Red-Al, Et_2O , 89%.

In summary, the cobalt(II) catalysed oxidation of 5-hydroxy alkenes has been demonstrated as a powerful synthetic tool for the formation of *trans*-THFs with excellent diastereoselectivity. The application of the reaction in the synthesis of various natural products demonstrates the synthetic utility of the reaction in complex systems. The following section describes the aims and objectives for the utilisation of this reaction in the synthesis of the *trans*-THF F-ring of PTX-4.

Chapter 2

Results and Discussion

2.1 Research outline

The pectenotoxins (PTXs) have been shown to be challenging synthetic targets, each comprising several different tetrahydrofuran (THF) rings. Despite the structural complexity of the PTXs, their interesting biological activities render them desirable synthetic targets. The development of an efficient synthetic route to the PTXs would provide an opportunity for further investigations to be conducted into the novel mode of action of the PTX family, while assessing their potential as future drug candidates. PTX-4, in particular, was considered to be a good candidate for synthesis, due to the presence of the anomerically stable spiroketal at C7 (AB ring system) (*Figure 15*). It was postulated that synthesising the thermodynamically more stable isomer would minimise the possibility of epimerisation occurring prior to the macrolactonisation step. Upon lactonisation, however, the spiroketal ring system would reside in the least stable conformation and consequently, exposure to acidic reaction conditions would need to be avoided. Evidence for this lies in the fact that upon exposing PTX-1 to 0.1% TFA, an acid-catalysed isomerisation of the AB spiroketal results, to afford an equilibrium mixture of PTX-1:4:8 (29:14:57).^{4, 5}

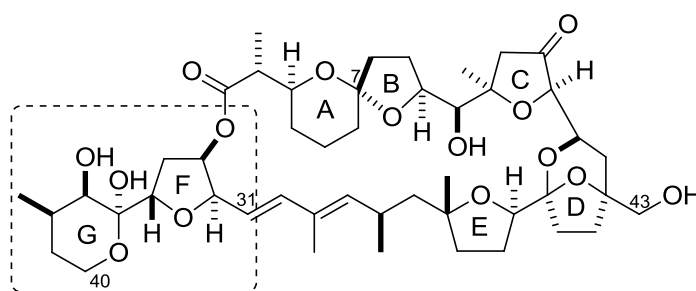
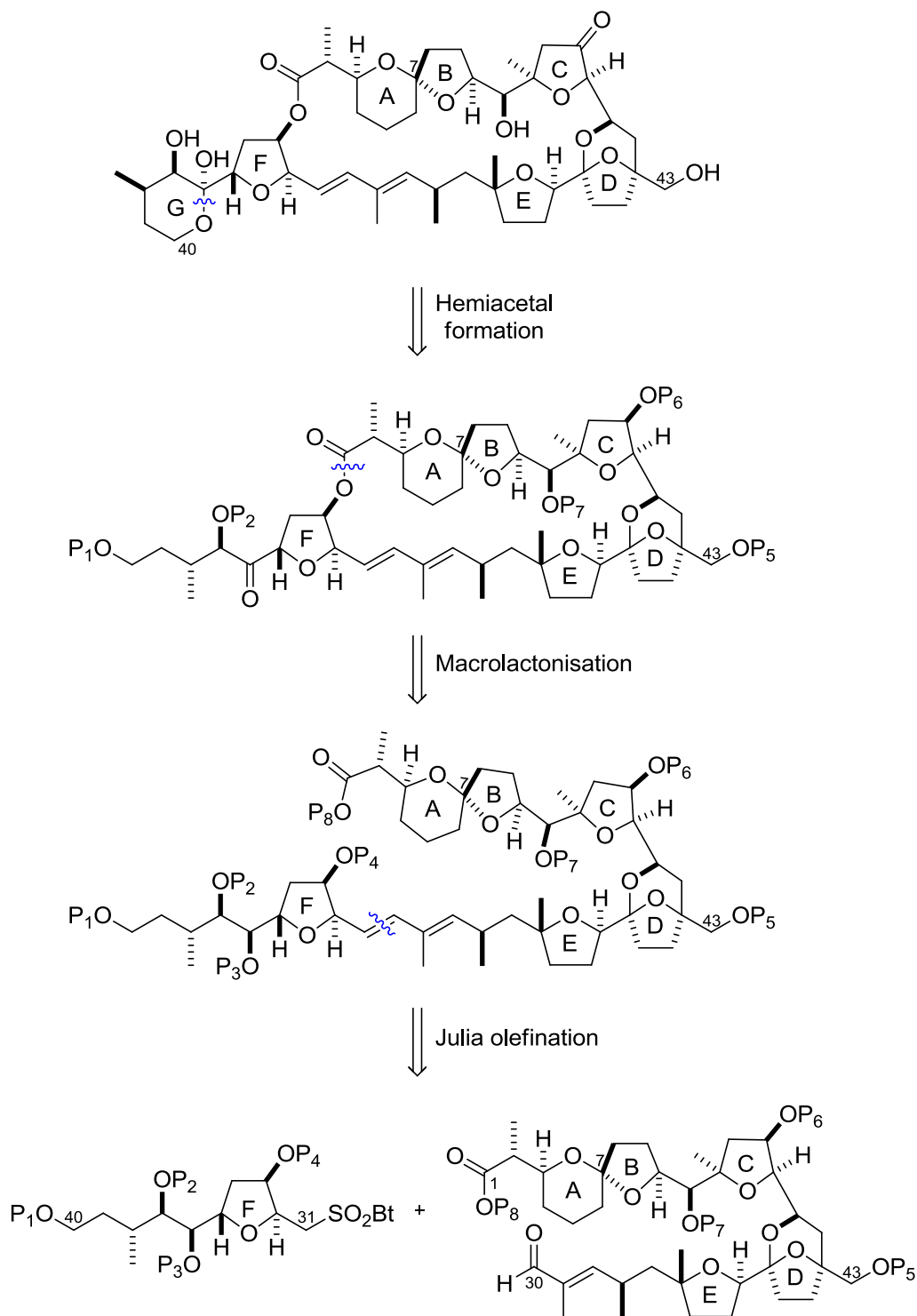


Figure 15. PTX-4

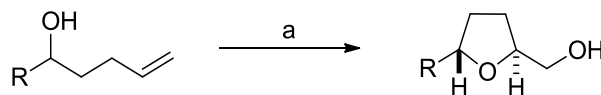
It was envisaged that methodology developed within the Donohoe group for synthesising 2,5-*cis*-substituted THFs *via* an osmium-catalysed oxidative cyclisation could be applied to the ABC and the DE ring fragments, allowing the scope and limitations of the

methodology to be truly tested and challenged.⁷⁵ However, to access the 2,5-*trans*-substituted THF portion of the FG fragment, it was anticipated that the cobalt-catalysed oxidative cyclisation protocol developed by Mukaiyama could be utilised.⁵² The aim of this research project was to design a competitive and novel route to the synthesis of the FG fragment of PTX-4, which would later be incorporated into the total synthesis of PTX-4 (*Figure 15*). The advantage of synthesising a late-stage intermediate to match that previously synthesised by Evans was recognised, as well as the utilisation of the key steps that Evans had successfully used to couple the FG fragment together with the ABCDE ring system in his total synthesis of PTX-4 (*Scheme 24*).^{20, 21}

**Scheme 24.** PTX-4 end-game

It was anticipated that existing, but under-utilised methodology developed by Mukaiyama and co-workers could provide a synthetic route for the formation of the F-ring of PTX-4. Mukaiyama's methodology entailed the combination of molecular oxygen with a cobalt(II)

catalyst in order to facilitate the oxidative cyclisation of 5-hydroxy alkenes to the corresponding 2,5-*trans* THFs (Scheme 25). These transformations have been shown to proceed in good yields and with excellent *trans* diastereoselectivities (>99:1), as discussed in Chapter 1.⁵²

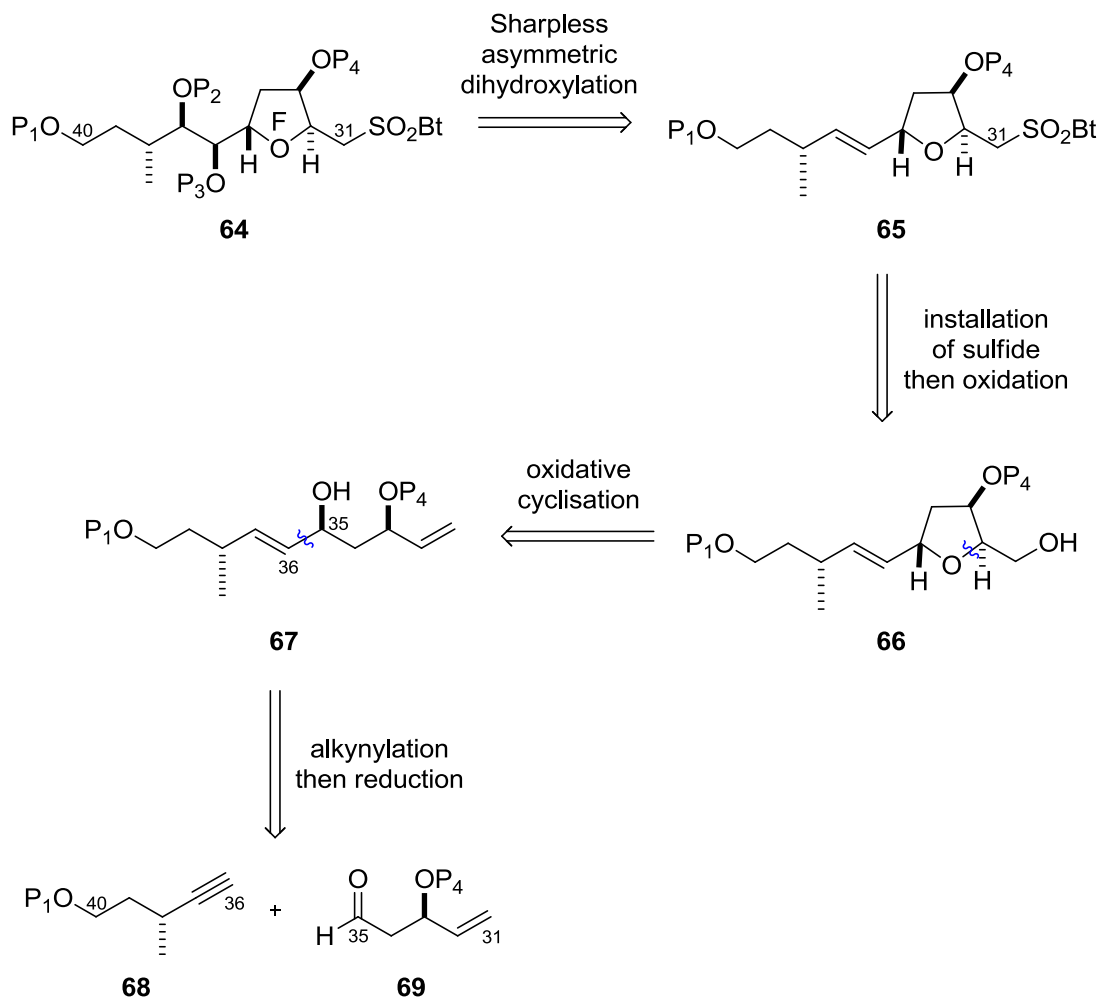


Scheme 25. a) O_2 , $Co(modp)_2$ (25 mol%), $iPrOH$, TBHP, 50 °C, 4 Å MS.

It was predicted that a short and efficient synthesis of the FG ring system of PTX-4 could be achieved by utilising this methodology as the key step in the formation of the *trans*-THF (F ring) portion. In doing so, this would provide a test of the method with respect to a complex molecule synthesis and further examine the functional group tolerance of the reaction.

2.2 Retrosynthetic analysis of the FG portion of PTX-4

A possible synthetic approach was devised for the synthesis of the C31-C40 fragment of PTX-4, which was designed around implementing Mukaiyama's oxidative cyclisation conditions as the key step to form the *trans*-THF (Scheme 26).



Scheme 26. Retrosynthetic analysis of the FG fragment of PTX-4

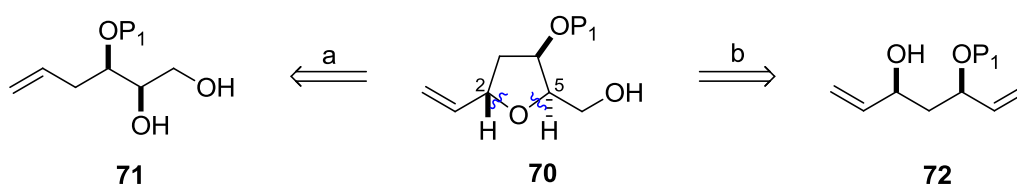
It was predicted that the 1,2-diol unit of component **64** could be installed by means of a Sharpless asymmetric dihydroxylation of the corresponding alkene **65**, with the chiral ligand controlling the relative stereochemistry.⁴⁷ A key consideration in this approach would be the ability to differentially protect the resulting secondary alcohols in order to allow for the late-stage functionalization of the C31-C40 fragment. In addition, the C31 sulfone moiety, that would prove crucial for the coupling of the FG fragment to ABCDE ring fragment, could be introduced by a Mitsunobu reaction of the primary alcohol of **66** with the appropriate thiol, followed by an oxidation to furnish the corresponding sulfone.⁷⁶ Thus, it was anticipated that by utilising the cobalt(II) catalysed oxidative cyclisation procedure as the key step in the synthesis, the *trans*-THF F-ring could be accessed from

5-hydroxy alkene **67**.⁵² Disconnection of the cyclisation precursor **67** at the C35-C36 bond could allow for the diastereoselective assembly of alkyne **68** and aldehyde **69**, followed by a hydroxyl-directed reduction of the corresponding alkyne to an (*E*)-alkene. It was rationalised that alkyne **68** could be synthesised by utilising a chiral auxiliary approach developed by Myers and co-workers,⁷⁷ allowing access to alkyne **68** in 5 steps from commercially available starting materials. Finally, the synthesis of aldehyde **69** could involve the utilisation of an enzymatic resolution, providing aldehyde **69** in 4 steps.⁷⁸

2.3 Model Studies

In order to further explore the scope of the key methodology required for the successful synthesis of the FG portion of PTX-4, it was necessary to utilise a model system to examine the key oxidative cyclisation step. Considering that the oxidative cyclisation had not previously been conducted on an alkene bearing an allylic alcohol (with or without a protecting group), it was important to demonstrate whether the cyclisation would still proceed in a high yield and diastereoselectivity. Examining the potential of the cobalt-catalysed oxidative cyclisation in the model system would therefore provide fundamental information regarding the construction of the F-ring of PTX-4, which bears a substituent at the C4 position of the THF.

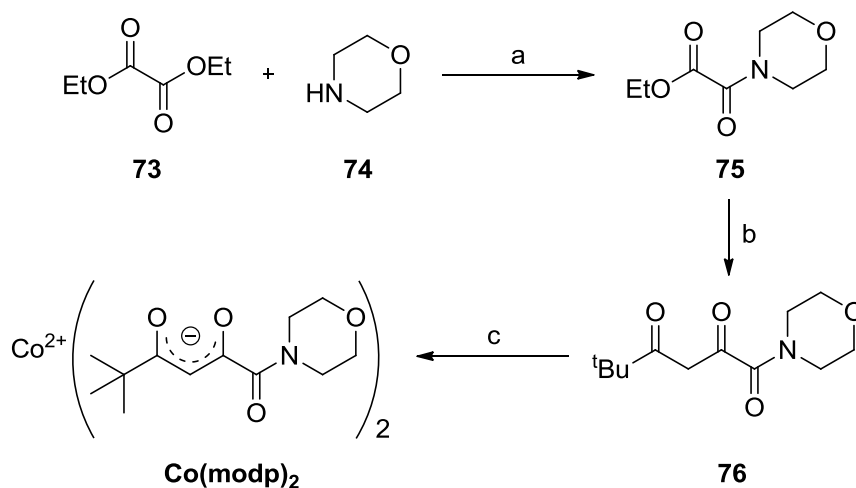
The retrosynthetic analysis of the F-ring model **70** revealed two possible disconnections that could be accessed using the cobalt catalysed oxidative cyclisation (*Scheme 27*).



Scheme 27. Retrosynthetic analysis of the model F-ring system

Disconnection of **70** at the C2 C-O bond (route a) revealed triol derivative **71**, which contains a 1,2-*syn* diol moiety. Alternatively, disconnection at the C5 C-O (route b) would give rise to the 1,3-*syn* diol derivative **72**.

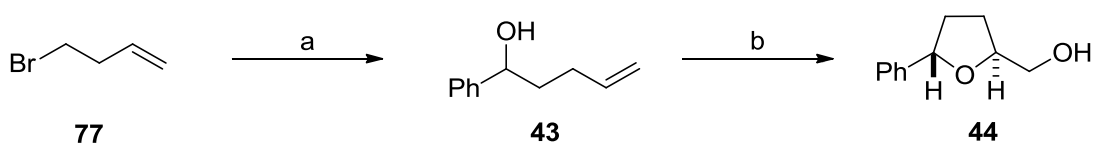
Following the reported conditions of Mukaiyama, the synthesis of the Co(modp)_2 catalyst had to be undertaken, as this catalyst is not commercially available (*Scheme 28*). The reaction between diethyl oxalate **73** and morpholine **74** was possible without the need for a base or a coupling reagent, furnishing amide **75** in excellent yield. Subsequent treatment of **75** with pinacolone in the presence of potassium *tert*-butoxide afforded the desired 1,3-diketone ligand **76** as a 1:4.7 mixture of keto-enol tautomers (as observed by ^1H NMR spectroscopy). Finally, it was possible to complex modp ligand **76** with cobalt(II) chloride in water, providing Co(modp)_2 as a fine brown powder. It was not possible to fully characterise the catalyst by NMR spectroscopy due to the paramagnetic properties of cobalt; however, the IR and MS data were consistent with those reported in the literature.⁵²



Scheme 28. a) 99%; b) pinacolone, KO^tBu , PhMe , $100\text{ }^\circ\text{C}$, 47%; c) NaOH , CoCl_2 , H_2O , $60\text{ }^\circ\text{C}$, 47%.

With the required cobalt(II) catalyst in hand, we first attempted the key oxidative cyclisation reaction on a simple substrate. Mukaiyama successfully demonstrated that hydroxy alkene **43** could cyclise to THF **44** in a yield of 73% in his original communication.⁵² Treatment of benzaldehyde with 3-butenylmagnesium bromide

(generated *in situ*) allowed for the formation of 5-hydroxy alkene **43** in one step. Upon subjecting **43** to the oxidative cyclisation conditions, the corresponding *trans*-THF product **44** was furnished in a good yield of 55% (Scheme 29). The spectroscopic data of THF **44** matched that previously reported and was consistent with the formation of a single *trans*-diastereomer.⁷⁹ This 2,5-*trans* relationship was evidenced by the PhCH doublet of doublets at 5.00 ppm in the ¹H NMR, as opposed to at 4.93 ppm where it is reported to appear for the *cis* diastereomer.⁷⁹



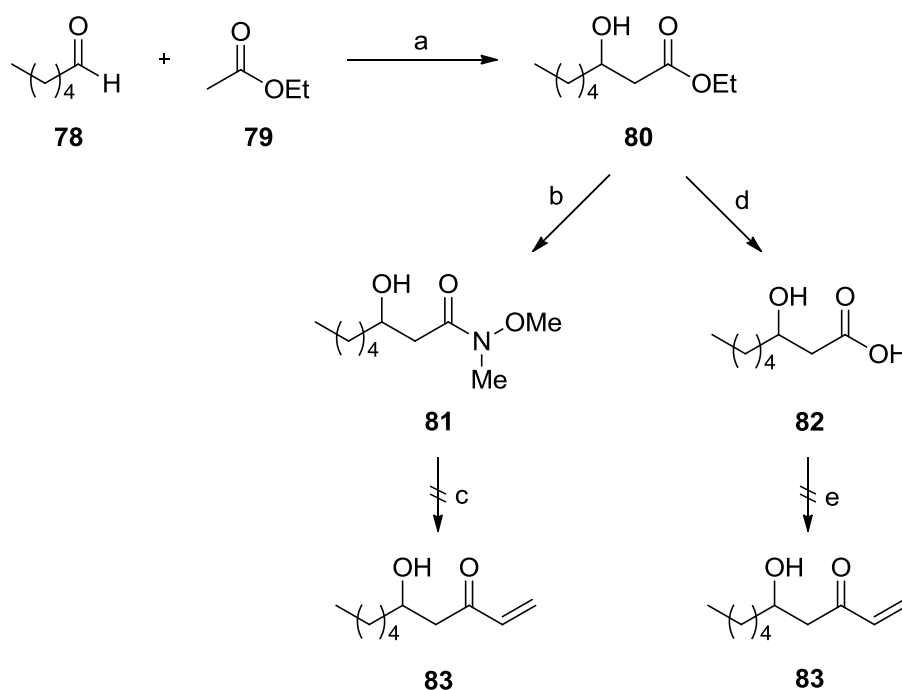
Scheme 29. a) Mg, THF, 0 °C → reflux, then benzaldehyde, THF, 0 °C → rt, 72%; b) O₂, Co(modp)₂ (20 mol%), TBHP, *i*PrOH, 60 °C, 55%.

Upon successfully replicating Mukaiyama's results, attention turned to forming a model system of the FG portion of PTX-4.

2.3.1 Investigations into the C5 C-O disconnection (route b)

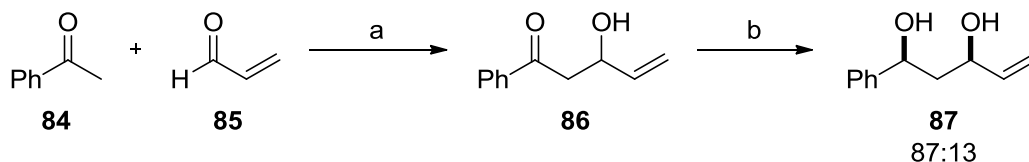
It was reasoned that a model system for 1,3-*syn* diol **72** could be accessed by utilising a Weinreb amide approach. The synthesis of the Weinreb amide commenced with an aldol reaction between ethyl acetate and hexanal, affording β-hydroxy ester **80** in a yield of 81% (Scheme 30). Evidence for the formation of the desired aldol product was confirmed by comparison of the NMR data with that reported in the literature.⁸⁰ Subsequent conversion of ester **80** to the corresponding Weinreb amide, with *N,O*-dimethylhydroxylamine in the presence of isopropylmagnesium bromide or trimethylaluminium, was poor yielding and there appeared to be significant amounts of decomposition of the substrate. However, a small amount of Weinreb amide **81** was isolated and was shown to exhibit a characteristic absorption at 1644 cm⁻¹ in the IR spectrum, corresponding to the amide carbonyl stretch.

Unfortunately, attempting a range of conditions for the addition of vinylmagnesium bromide to Weinreb amide **81** did not result in the formation of vinyl ketone **83**, with only starting material being recovered from the reaction mixture in each case. Furthermore, attempts to form vinyl ketone **83** by the direct reaction of vinylmagnesium bromide with carboxylic acid **82** in the presence of *n*-butyl lithium were not effective.⁸¹ The NMR spectrum of the crude material was consistent with that of recovered starting material.



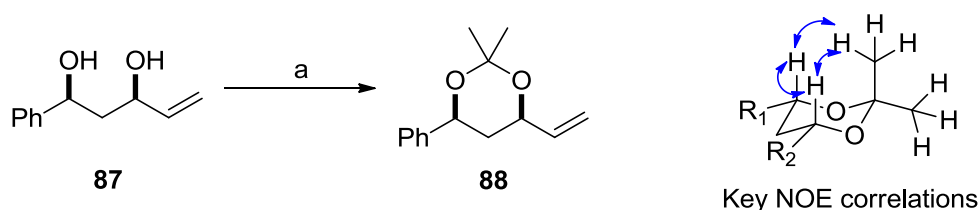
Scheme 30. a) $n\text{BuLi}$, $i\text{Pr}_2\text{NH}$, THF, $0\text{ }^\circ\text{C} \rightarrow -78\text{ }^\circ\text{C}$, 81%; b) MeNHOMe.HCl , AlMe_3 , $0\text{ }^\circ\text{C} \rightarrow \text{reflux}$, THF, 20%; c) vinylmagnesium bromide, THF, $-78\text{ }^\circ\text{C} \rightarrow \text{rt}$; d) $\text{LiOH.H}_2\text{O}$, $\text{H}_2\text{O/THF}$ (1:1), 80%; e) $n\text{BuLi}$, vinylmagnesium bromide, THF, $-78\text{ }^\circ\text{C} \rightarrow \text{rt}$.

Upon experiencing difficulties whilst attempting to afford vinyl ketone **83**, an alternative strategy was attempted. In this case, β -hydroxy ketone **86** was successfully accessed by the treatment of the enolate anion of acetophenone with acrolein. In order to access the 1,3-*syn* diol, it was necessary to diastereoselectively reduce ketone **86** with diisobutylaluminium hydride (DIBAL-H), which provided 1,3-diol **87** with good diastereoselectivity (87:13) (Scheme 31).⁸²



Scheme 31. a) $n\text{BuLi}$, $i\text{Pr}_2\text{NH}$, THF, $0\text{ }^\circ\text{C} \rightarrow -78\text{ }^\circ\text{C}$, 80%; b) DIBAL-H (2.5 equiv.), THF, $-78\text{ }^\circ\text{C}$, 85%.

The relative configuration of the major diastereomer of the 1,3-diol was unambiguously confirmed by preparation of the corresponding acetonide **88** (Scheme 32). Inspection of the ^{13}C NMR spectrum revealed peaks at 30.3 and 19.8 ppm, corresponding to the geminal methyl carbon atoms, and a peak at 99.2 ppm which is representative of the quaternary acetal carbon. According to Rychnovsky, these chemical shifts are consistent with the 1,3-acetonide existing in a chair conformation with the phenyl and vinyl substituents residing in equatorial positions.⁸³ As a result of this, it can be concluded that the diol contains a 1,3-*syn* relationship, as opposed to a 1,3-*anti* relationship which would give rise to a twist-boat conformation.⁸³ Additionally, analysis of the NOE correlations between the CHO protons and the axial CH_3 group of acetonide **88** lent further support to confirm the formation of 1,3-*syn* diastereomer **87** (Scheme 32).



Scheme 32. a) 2,2-dimethoxy propane, PTSA(cat.), 70%.

The 1,3-*syn* selectivity is understood to arise from the initial chelation of DIBAL-H to the hydroxyl group to form a 6-membered ring (Figure 16).⁸² It is assumed that the ring resides in a half-chair-like conformation with R_1 lying in a pseudo-equatorial position. It can be reasoned that hydride attack (from the second equivalent of DIBAL-H) is favoured to occur on the opposite face to the hydroxyl group via the low energy twist-chair transition state, giving rise to the observed *syn* selectivity. On the other hand, if the

approach of the external hydride were to occur from the lower face, it would proceed *via* a less stable twist-boat transition state and is consequently disfavoured.

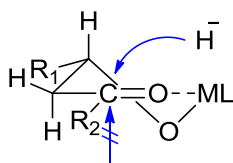
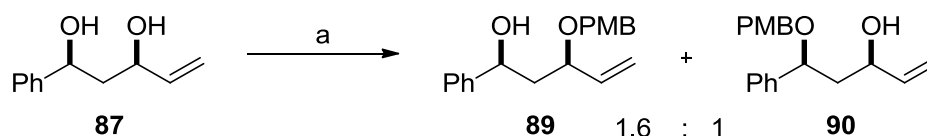


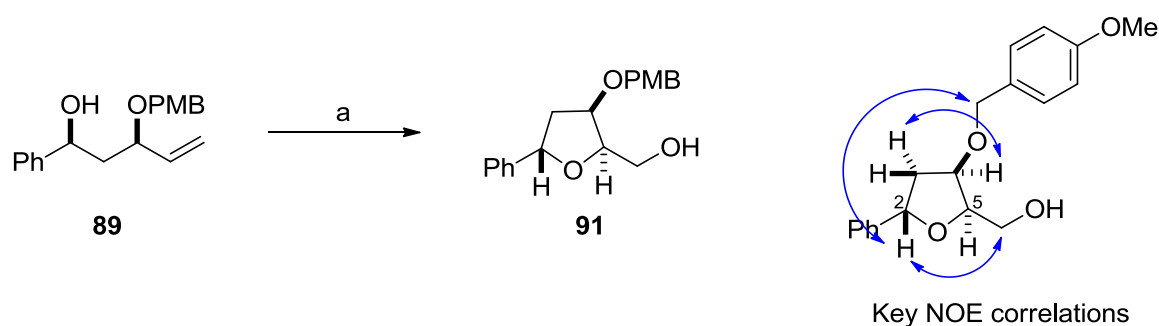
Figure 16. Model to show 1,3-syn asymmetric reduction

With 1,3-syn diol **87** in hand, mono-protection of the allylic alcohol was required. In order to be able to match a late-stage intermediate with that previously synthesised by Evans, a *para*-methoxybenzyl (PMB) group was chosen as the protecting group. Thus mono-protection of 1,3-syn diol **87**, with PMBCl in the presence of sodium hydride, was achieved in a yield of 74% and as a 1.6:1 mixture of regioisomers (*Scheme 33*). Following separation of the regioisomers by flash column chromatography and preparative TLC, it became evident that the major product was the desired allylic PMB ether **89**. Conversion of the allylic alcohol to the corresponding PMB ether was confirmed by analysis of the ^1H NMR spectrum, which showed an upfield shift of 0.3 ppm for the corresponding *CHOR* peak. In addition to this, the appearance of two distinct doublets at 4.62 and 4.35 ppm, which resembled the diastereotopic protons of OCH_2Ar , was consistent with the incorporation of a PMB group. The slight preference for the formation of the allylic ether over the bis-homoallylic ether may be attributed to the subtle difference in the steric environment of the alcohols. The literature Winstein-Holness parameter (*A*-value) for $\text{CH}=\text{CH}_2$ is 1.6 kcal/mol compared to 2.8 kcal/mol for a phenyl group, suggesting that the phenyl group would exert a larger steric effect on its neighbouring alcohol.⁸⁴



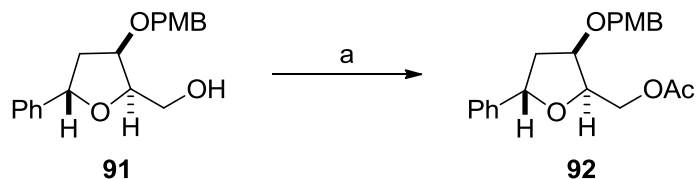
Scheme 33. a) PMBCl, NaH, DMF, 0 °C $\rightarrow$ rt, 74%.

After successfully synthesising **89**, it was possible to attempt the cobalt-catalysed oxidative cyclisation on the model system.⁵² Subjecting 5-hydroxy alkene **89** to the oxidative cyclisation conditions in the presence of a catalytic amount of Co(modp)_2 , resulted in the formation of *trans*-THF **91** as a single diastereomer, albeit in a comparatively low yield of 37% (Scheme 34). The desired 2,5-*trans* selectivity of the radical cyclisation was confirmed by NOE correlations between the PhCH and the CH_2OH . In addition to this, the 2,4-*trans* stereochemistry was confirmed by the NOE correlations between the PhCH and the OCH_2Ar (Scheme 34).



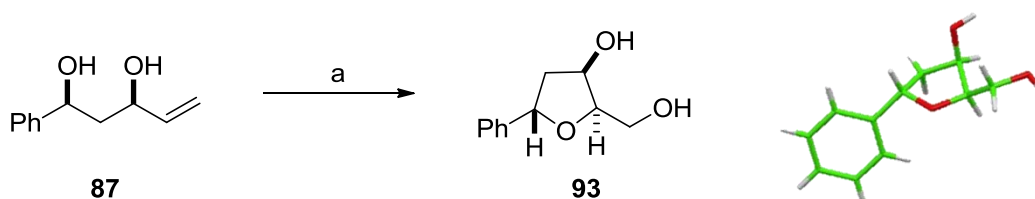
Scheme 34. a) O_2 , Co(modp)_2 (30 mol%), TBHP, $i\text{PrOH}$, 60 °C, 37%.

In an attempt to unambiguously prove the stereochemistry of **91**, efforts were made to form a crystalline derivative that would be suitable for X-ray analysis. Treatment of **91** with 3,5-dinitrobenzoyl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP) unfortunately did not result in the formation of the corresponding 3,5-dinitrobenzoate, with starting material being recovered from the reaction. Alternatively, acetylation of cyclisation product **91**, using acetic anhydride in the presence of pyridine and DMAP, did afford the corresponding acetate **92**, but this was isolated as a colourless oil and not as a crystalline solid (Scheme 35). Evidence for the formation of the acetylated compound was obtained from a strong absorption at 1737 cm^{-1} in the IR spectrum, corresponding to the C=O of the acetate group, coupled with the absence of an absorption in the alcohol region of the IR spectrum.



Scheme 35. a) Ac_2O , pyridine, DMAP, 49%.

In order to examine the feasibility of the oxidative cyclisation on an unprotected allylic alcohol, 1,3-*syn* diol **87** was reacted with a catalytic amount of $\text{Co}(\text{modp})_2$ in 2-propanol under an atmosphere of oxygen. Analysis of the reaction mixture by TLC and MS indicated that the cyclisation reaction had proceeded smoothly. However, difficulties arose whilst attempting to separate the polar product from the cobalt catalyst residues by column chromatography. Fortunately, a sufficient amount of material was successfully purified, revealing the formation of hydroxy-THF **93** as a white solid (*Scheme 36*). It was possible to recrystallise the solid from dichloromethane to provide crystals that were suitable for X-ray crystallography. Pleasingly, the X-ray crystal structure unambiguously confirmed the 2,5-*trans* stereochemical relationship of the resulting THF, and the *syn* relationship of the starting diol (*Figure 17*). In addition, it validated NOE as a method for determining the stereochemistry of the newly formed THF products.

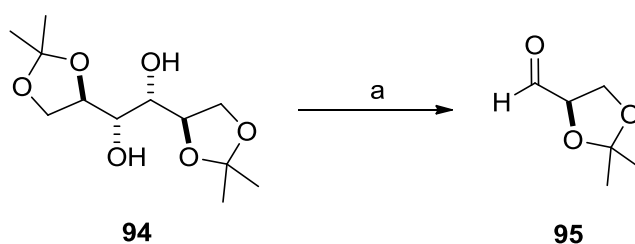


Scheme 36. a) O_2 , $\text{Co}(\text{modp})_2$ (20 mol%), TBHP, $i\text{PrOH}$, 60 $^\circ\text{C}$, 17%. **Figure 17.** X-ray structure of **93**

2.3.2 Investigations into the C5 C-O disconnection (route b)

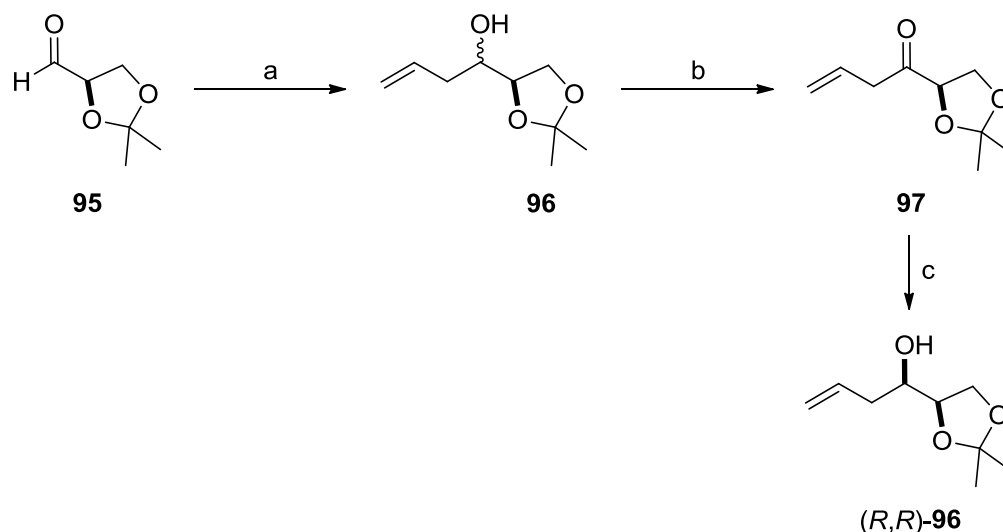
The second model substrate (see *Scheme 27*), which was required in order to examine the construction of the *trans*-THF via the formation of the C5 C-O bond was subsequently

investigated. The synthesis of triol derivative **71**, which contains a 1,2-*syn* diol moiety, began with the oxidative cleavage of D-mannitol diacetone **94** using sodium periodate (*Scheme 37*). Formation of aldehyde **95** was confirmed by the presence of a characteristic singlet at 9.72 ppm in the ^1H NMR spectrum, which corresponded to the CHO proton. Aldehyde **95** was found to be unstable to column chromatography and was consequently used in the subsequent reaction without further purification.



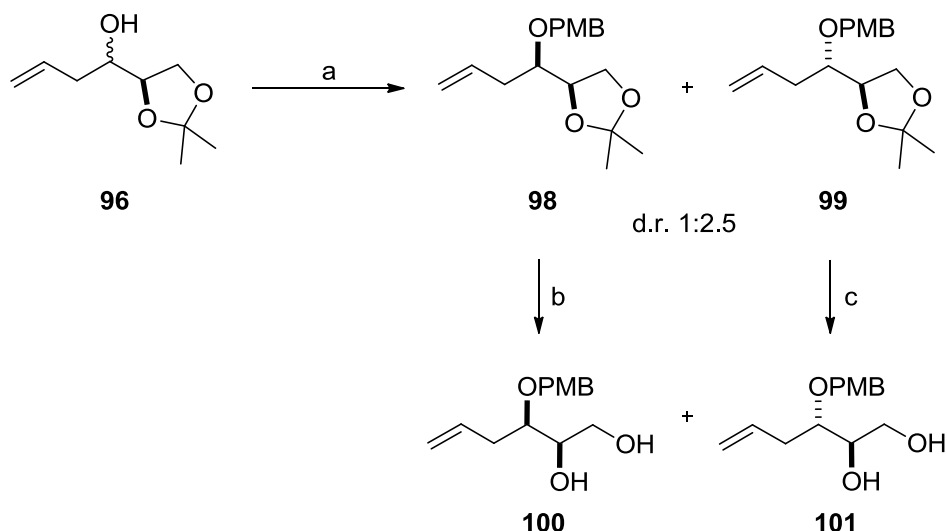
Scheme 37. a) NaIO_4 , NaHCO_3 , CH_2Cl_2 , 89%.

From aldehyde **95**, it was now possible to install the allyl side-chain, which would form part of the backbone of the THF ring and install the essential alkene functionality for the oxidative cyclisation reaction. Aldehyde **95** was treated with allylmagnesium bromide, which allowed for the formation of alcohol **96** in an excellent yield of 91%, albeit as an inseparable mixture of diastereomers (*Scheme 38*). The formation of a single diastereomer of **96** was attempted *via* an oxidation of the diastereomeric mixture of alcohols to afford the corresponding ketone, followed by a selective reduction of the carbonyl with K-Selectride[®] to afford the 1,2-*syn* alcohol (*R,R*)-**96**. Unfortunately, it was found that the sequential oxidation and reduction reactions proceeded with poor conversion. A significant amount of starting material was recovered in the attempted oxidation of alcohol **96**, and decomposition of the substrate was evident in the following reduction. However, analysis of the ^{13}C NMR spectrum of the small amount of alcohol that was obtained, revealed the desired *syn*-selectivity of the ketone reduction, and the formation of alcohol (*R,R*)-**96** as a single diastereomer.



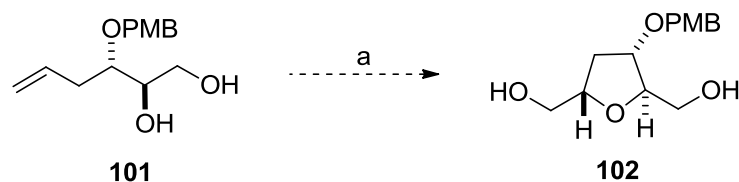
Scheme 38. a) Allylmagnesium bromide, THF, 0 °C → rt, 91%; b) Dess-Martin periodinane, CH₂Cl₂, 41%; c) K-Selectride, THF, –78 °C → rt, 14%.

As an alternative, it was found that reaction of the diastereomeric mixture of alcohols with 4-methoxybenzylchloride in the presence of sodium hydride, afforded the corresponding PMB ethers, **98** and **99**. In this case, separation of the diastereomers was possible by flash column chromatography, revealing a 2.5:1 mixture as a result of the preceding Grignard addition to aldehyde **95** (Scheme 39). At this stage, it was not possible to determine which diastereomer possessed the desired 1,2-*syn* stereochemical relationship from analysis of the ¹H NMR, and consequently acetonides **98** and **99** were cleaved under acidic conditions, resulting in the formation of the corresponding diols, **100** and **101**.



Scheme 39. a) PMBCl, NaH, DMF, 0 °C → rt, 72%; b) 2.0 M HCl, THF, 61%; c) 2.0 M HCl, THF, 66%.

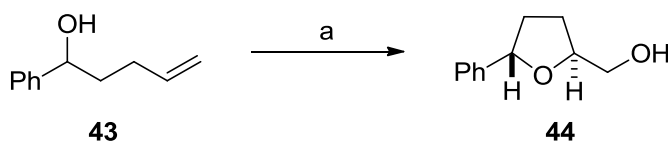
Upon revealing the bis-homoallylic hydroxyl group, 5-hydroxy alkenes **100** and **101** were ready to undergo the oxidative cyclisation. When **101** was subjected to a Co(modp)₂ catalysed oxidative cyclisation, consumption of the starting material was observed by TLC and MS (Scheme 40). In addition to this, the formation of a more polar product was detected by TLC, along with an ion in the mass spectrum that corresponded to that expected for *trans*-THF **102**. Unfortunately, as with THF **93**, difficulties were experienced when attempting to isolate the polar product from the cobalt catalyst residues by column chromatography. Consequently, due to the paramagnetic properties of the cobalt, it was not possible to use NMR spectroscopy to fully characterise the product that was isolated.



Scheme 40. a) O₂, Co(modp)₂, TBHP, ⁱPrOH, 60 °C.

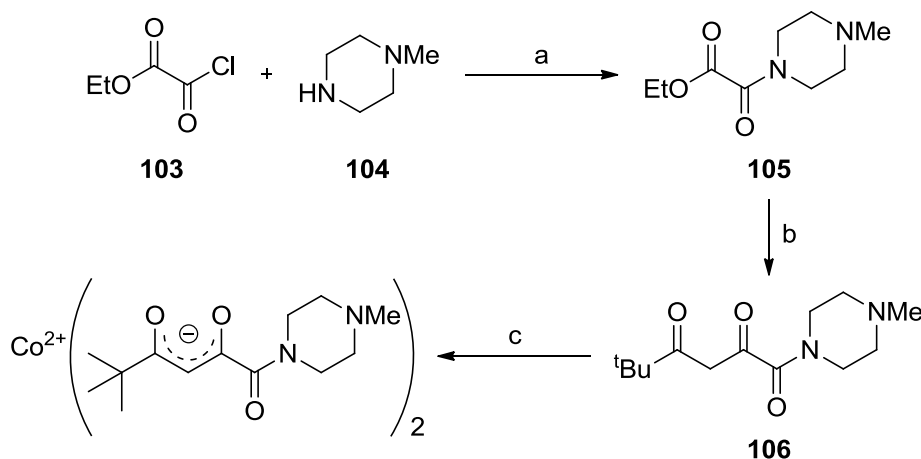
At this point in the project, Pagenkopf and co-workers reported the development of a second-generation cobalt(II) catalyst for the oxidative cyclisation of 5-hydroxy alkenes.⁷² The new catalyst had been demonstrated by Pagenkopf to result in greater yields for the

radical cyclisation, and to allow for a simplified purification process of the resulting *trans*-THFs (Scheme 41).⁷²



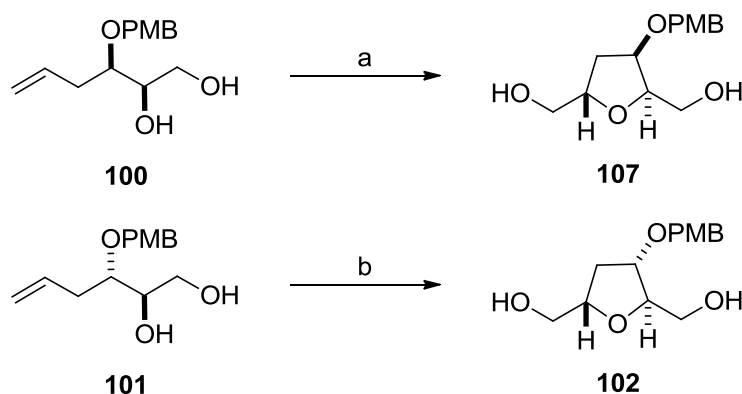
Scheme 41. a) $\text{Co}(\text{nmp})_2$ (10 mol%), TBHP, O_2 , $i\text{PrOH}$, 60 °C, 91%.

It was therefore anticipated that the new catalyst could allow for an improvement in the formation and subsequent isolation of the often polar *trans*-THF products in this synthesis. Consequently, by following the procedure detailed by Pagenkopf and co-workers, attempts were made to synthesise the second-generation cobalt(II) catalyst (Scheme 42).⁷² The synthesis commenced by reacting ethyl oxalyl chloride with *N*-methylpiperazine in the presence of triethylamine, resulting in the formation of amide **105**. A subsequent Claisen condensation with pinacolone in the presence of potassium *tert*-butoxide allowed for the formation of the nmp ligand **106** in quantitative yields. It was found that for this reaction to proceed reliably and with high yields, it was necessary to utilise sublimation-grade potassium *tert*-butoxide. With nmp ligand **106** in hand, complexation with Co(II) in aqueous benzene was achieved. Purification of the resulting fine beige powder by centrifugation afforded the desired $\text{Co}(\text{nmp})_2$ catalyst in three high yielding steps. The MS data of the catalyst was shown to be consistent with that reported by Pagenkopf and co-workers.⁷²



Scheme 42. a) NEt_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 86%; b) pinacolone, KO^tBu , THF, $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, then AcOH (1.0 M in CH_2Cl_2), 100%; c) Co(II) 2-ethylhexanoate, PhH, H_2O , 86%.

After successfully synthesising $\text{Co}(\text{nmp})_2$, hydroxy alkenes **100** and **101** were subjected to the oxidative cyclisation (Scheme 43). Pleasingly, in this case it was possible to cleanly isolate the corresponding THFs, **107** and **102**, from the second-generation cobalt catalyst residues by column chromatography, allowing the THFs to be fully characterised by NMR spectroscopy.



Scheme 43. a) O_2 , $\text{Co}(\text{nmp})_2$ (20 mol%), TBHP, $^i\text{PrOH}$, $55\text{ }^\circ\text{C}$, 45%; b) O_2 , $\text{Co}(\text{nmp})_2$ (20 mol%), TBHP, $^i\text{PrOH}$, $55\text{ }^\circ\text{C}$, 50%.

The work-up procedure reported by Pagenkopf for the isolation of the resulting *trans*-THFs, involved treatment of the reaction mixture with methyl iodide to methylate the nmp ligand, followed by a water wash to remove the iodide salt of the catalyst.⁷² However, this protocol was not found to be effective at completely removing the cobalt

catalyst residues in this case. Alternatively, separation of the cobalt residues from the crude product proved to be possible by column chromatography, which was reasoned to be aided by the increased polarity of the second-generation catalyst. Observation of the NOE correlations of **102** enabled the 2,5-*trans* THF to be identified as the 2,4-*cis* diastereomer, leading to the conclusion that diol **101** possessed the 1,2-*anti* relationship (*Figure 18*). On the other hand, 1,2-*syn* diol **100** led to the formation of the desired THF **107** with a 2,4-*trans* substitution pattern, as required in the FG fragment of PTX-4. These findings enabled the major diastereomer of the 2.5:1 mixture of alcohol **96** to be identified as the 1,2-*anti* diol.

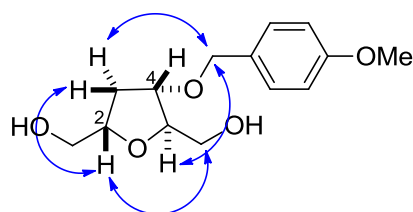
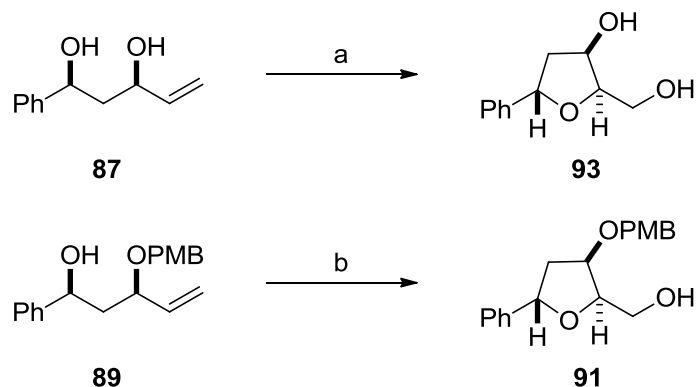


Figure 18. NOE analysis

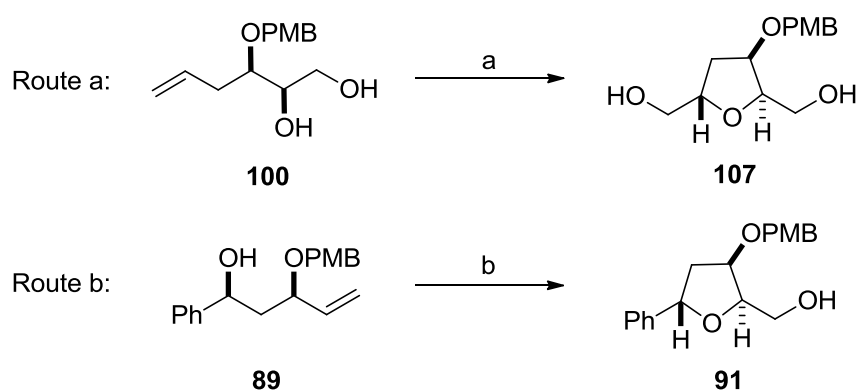
Reinvestigation into the oxidative cyclisation of 5-hydroxy alkenes **87** and **89**, revealed an improvement in the yield from 17% to 51% and 37% to 59% respectively, when $\text{Co}(\text{nmp})_2$ was used as the catalyst (*Scheme 44*). These results highlighted the advantage of utilising the more polar catalyst, with the consequence of this being an improved isolation process for the THF products.



Scheme 44. a) O_2 , $Co(nmp)_2$ (20 mol%), TBHP, $iPrOH$, 55 °C, 51%; b) O_2 , $Co(nmp)_2$ (20 mol%), TBHP, $iPrOH$, 55 °C, 59%.

2.3.3 Summary of the model studies

In order to ascertain the most efficient route to the FG fragment of PTX-4, the yields for the oxidative cyclisation of the model systems were compared (Scheme 45). It was shown that model system **89**, which resulted from disconnection of the C5 C-O bond, led to a superior yield for the formation of the desired *trans*-THF, compared to the oxidative cyclisation of **100**.



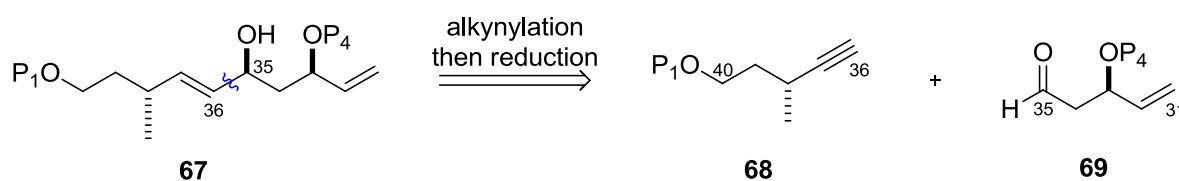
Scheme 45. a) O_2 , $Co(nmp)_2$ (20 mol%), TBHP, $iPrOH$, 55 °C, 45%; b) O_2 , $Co(nmp)_2$ (20 mol%), TBHP, $iPrOH$, 55 °C, 59%.

One explanation for this could be that the THF product contains only one hydroxyl group, in contrast to the alternative model system which contains two hydroxyl groups. As a result, THF **91** is less polar than **107**, facilitating its separation from the cobalt catalyst

residues and subsequently its isolation. In addition to this, the synthesis of model system **89** proved to be more efficient. Consequently, it was determined that the best approach to the synthesis of the *trans*-THF in the FG portion of PTX-4 would be to form the C5 C-O bond *via* the oxidative cyclisation, as opposed to the C2 C-O bond. As a result of the model studies, it was also found that a PMB group could be tolerated at the C4 position of the THF, and oxidative cyclisation in the presence of an allylic alcohol, both protected and unprotected, could proceed successfully. In addition to this, excellent 2,5-*trans* diastereoselectivity was consistently achieved. These promising preliminary results consequently led to the decision to utilise the methodology in the synthesis of the F-ring of PTX-4.

2.4 Forward synthesis

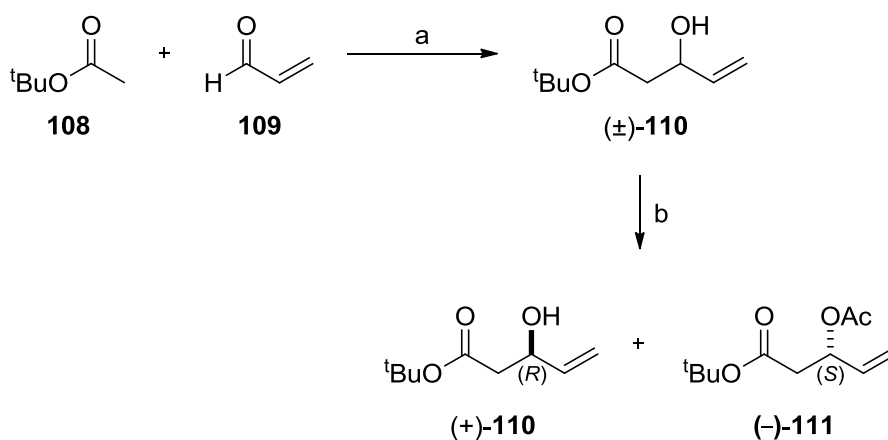
After successfully employing a model system to demonstrate the effectiveness of the cobalt(II) catalysed oxidative cyclisation, attention turned to the application of this methodology to the FG fragment of PTX-4. In order to maximise the efficiency of the synthesis, it was necessary to adopt a convergent route, with retrosynthetic analysis of cyclisation precursor **67** devised from alkyne **68** and aldehyde **69** (Scheme 46).



Scheme 46. Convergent route from alkyne **68** and aldehyde **69**

2.4.1 Synthesis of the C31-C35 aldehyde portion

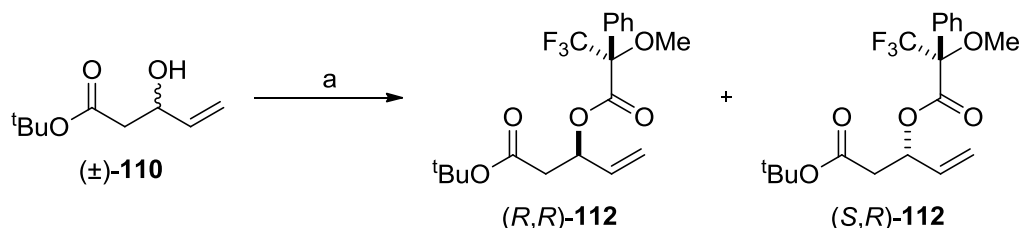
Initial studies focused on devising a short and efficient synthetic route to aldehyde **69**. It was considered that the most efficient method for forming aldehyde **69** was by utilising an enzymatic resolution, in order to provide the target in enantiopurity. The racemic β -hydroxy ester ($\pm$)-**110** was formed by the slow addition of acrolein to the lithium enolate of *tert*-butyl acetate in a yield of 85% (Scheme 47). Following literature precedent, the enzymatic resolution of ($\pm$)-**110** was attempted with Amano lipase and vinyl acetate.⁷⁸ Amano lipase was demonstrated to be selective for the conversion of only the (*S*)-alcohol to the corresponding vinyl acetate. Consequently, the (*R*)-alcohol remained unchanged, allowing access to enantiopure (+)-**110** in just 2 steps from commercially available starting materials. The formation of (+)-**110** and (–)-**111** were confirmed by comparing the spectroscopic data with that reported in the literature.⁸⁵



Scheme 47. a) $n\text{-BuLi}$, $i\text{-Pr}_2\text{NH}$, THF, $0\text{ }^\circ\text{C} \rightarrow -78\text{ }^\circ\text{C}$, 85%; b) Amano lipase PS, pentane, 4 Å MS, $35\text{ }^\circ\text{C}$, **110**: 45%, **111**: 50% .

Upon separating compounds (+)-**110** and (–)-**111** by flash column chromatography, the absolute configuration and the enantiomeric purity of the unreacted alcohol could be determined by the formation of the corresponding Mosher's ester. Firstly, racemic alcohol ($\pm$)-**110** was treated with (*R*)-Mosher's acid (MTPA) in the presence of dicyclohexylcarbodiimide (DCC) and DMAP to afford the corresponding Mosher's esters

(*R,R*)-**112** and (*S,R*)-**112** (Scheme 48).^{86, 87} Observation of the inseparable mixture of diastereomers by ¹⁹F NMR revealed a peak at -71.61 and -71.59 ppm, corresponded to the CF₃ group in each diastereomer, in a ratio of 1.1:1. Thus, the presence of two peaks confirmed that (±)-**110** was a racemic mixture, as expected.



Scheme 48. a) (*R*)-MTPA, DCC, DMAP, CH₂Cl₂, 100%.

Over the duration of the enzymatic resolution of (±)-**110**, aliquots of the reaction mixture were taken at set time intervals and the conversion of the reaction was monitored by analysis of the ¹H NMR. The reaction was deemed to have reached completion (i.e. 50%) when the integration of the new CHOAc quartet at 5.61 ppm was found to be equal to that of the multiplet at 4.56-4.43 ppm, corresponding to the CHOH of the unreacted alcohol. In addition, the enantiomeric excess of the recovered alcohol could be determined by conversion of the alcohol to the corresponding Mosher's ester. Comparison of the ¹⁹F and ¹H NMR spectrum of the Mosher's ester to that of the racemic standard, allowed the enantiopurity to be established (Table 3).

Entry	Time (h)	Conversion of reaction ^a (%)	Enantiomeric excess ^b (%)
1	16	24	46
2	24	43	67
3	48	50	87
4	60	50	≥95

Table 3. ^aas determined by ¹H NMR, ^bas determined by corresponding Mosher's ester

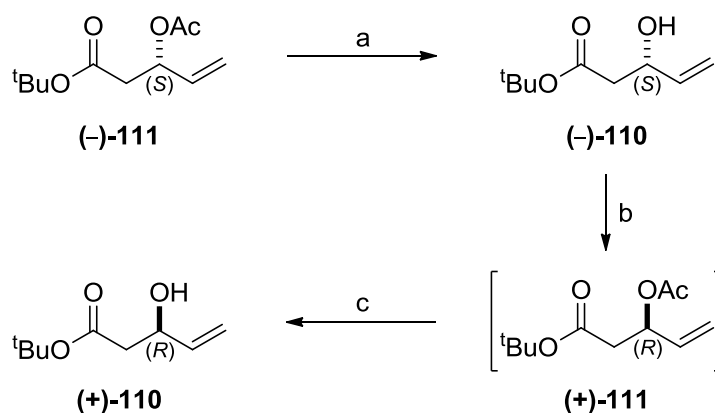
Upon assessing the enantiomeric excess of Entry 3 (Table 3), which had appeared to have proceeded to 100% conversion by ¹H NMR, the corresponding Mosher's ester was found

to have an enantiomeric excess of only 87%. As a result of this finding, it was concluded that the percentage error in integrating the ^1H NMR spectra was too large to establish whether the reaction had reached completion using NMR analysis alone. Conversion of the unreacted alcohol to the Mosher's ester, and its analysis by NMR spectroscopy, therefore proved to be essential for assessing the progress of the enzymatic resolution. In order to allow for the complete conversion of the (*S*)-alcohol to its corresponding acetate, and to obtain an enantiomeric excess of the (*R*)-alcohol of $\geq 95\%$, it was found that it was necessary to incubate the reaction at 30 °C for a minimum of 60 hours.

In addition to assessing the enantiopurity of the starting alcohol, the absolute configuration was deduced according to the Mosher ester analysis.⁸⁸ Comparison of the different chemical shifts of the protons of the two diastereomeric Mosher's esters, and analysis of the sign of $\Delta\delta^{\text{SR}}$ revealed that the absolute configuration of the secondary alcohol was (*R*), as expected.

With a view to utilising undesired (*S*)-acetate (–)-**111** in the synthesis of aldehyde **69**, efforts were made to interconvert the corresponding (*S*)-alcohol to the required (*R*)-enantiomer. In order to achieve this, it was first necessary to remove the acetate protecting group of (–)-**111**. It was deemed essential to use mildly basic conditions for this transformation in order to avoid competing elimination to the 1,3-conjugated diene. Thus, treatment of (*S*)-acetate (–)-**111** with potassium carbonate in methanol allowed for the formation of the desired (*S*)-alcohol (–)-**110** in a yield of 55%.⁸⁹ Alternatively, it was found that an improved yield of 86% was obtained when (*S*)-acetate (–)-**111** was subjected to a sodium methoxide solution in methanol (*Scheme 49*).⁹⁰ Synthesis of the corresponding Mosher's ester confirmed that (*S*)-alcohol (–)-**110** had an enantiomeric excess of $\geq 95\%$. The subsequent inversion of the (*S*)-alcohol was achieved *via* a Mitsunobu reaction to

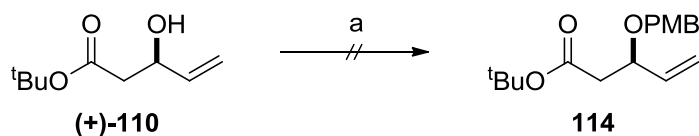
furnish acetate (+)-**111**, which was subsequently hydrolysed *in situ* to afford the corresponding (*R*)-alcohol (+)-**110**.



Scheme 49. a) NaOMe, MeOH, 0 °C, 86%; b) AcOH, PPh₃, DIAD, THF, 0 °C → rt; c) NaOMe, MeOH, 0 °C, 38% (2 steps).

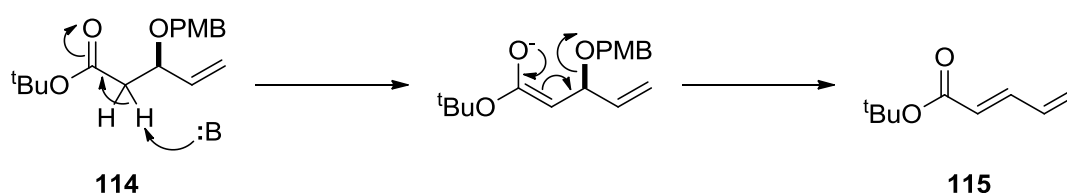
Upon examining the two-step transformation of (–)-**110** to (+)-**110**, it was discovered that the Mitsunobu reaction only afforded (*R*)-acetate (+)-**111** in approximately 40-45% yield, despite the complete consumption of starting material. However, attempts to use 4-nitrobenzoic acid as an alternative nucleophile (to afford benzoate **113**, not shown) did not provide a significant improvement to the yield. Despite this, the Mitsunobu reaction provided the capability for (*S*)-acetate (–)-**111** to be utilised in the synthesis of the key aldehyde component.

With enantiopure (*R*)-alcohol (+)-**110** in hand, conversion to the corresponding PMB ether was required. This protecting group was chosen, in order to allow for a late-stage intermediate to be matched with that previously synthesised by Evans. Consequently, protection of the secondary alcohol was attempted by utilising 4-methoxybenzyl chloride in the presence of sodium hydride (*Scheme 50*).



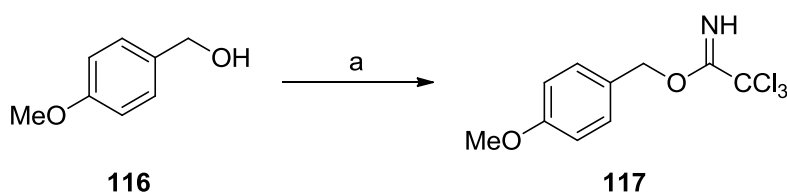
Scheme 50. a) PMBCl, NaH, DMF, 0 °C → rt.

Complete consumption of the starting material was observed by TLC, yet there was no evidence for the formation of the desired PMB-ether **114**. However, 4-methoxybenzyl alcohol was isolated from the reaction mixture following purification by column chromatography. A possible explanation for the formation of the alcohol could be that a competing elimination of the newly formed PMB ether occurs in the presence of strong base, to afford the corresponding conjugated diene **115** via an E1cB mechanism (Scheme 51).



Scheme 51. E1cB elimination

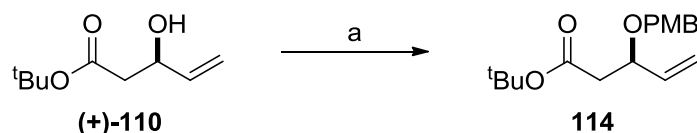
In order to avoid this undesirable elimination, an alternative strategy was sought, whereby benzylation could be performed under acidic conditions *via* the use of 4-methoxybenzyl 2,2,2-trichloroacetimidate.⁹¹ The imidate **117** was freshly prepared *via* the addition of trichloroacetonitrile to 4-methoxybenzyl alcohol **116** in the presence of a catalytic amount of sodium hydride, following a literature procedure (Scheme 52).⁹¹



Scheme 52. a) NaH (0.1 equiv.), Cl₃CCN, Et₂O, 0 °C, 76%.

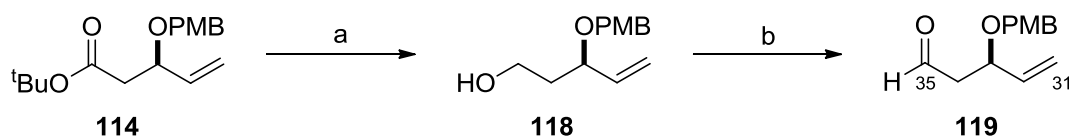
Initially, it was found that the acid-catalysed PMB-protection of (+)-**110** was unreliable, and a large excess of imidate was required to allow for the complete conversion of the alcohol. Based on this finding, it was considered that decomposition of imidate **117** could be occurring as the reaction progressed. After exploring a range of reaction conditions, it was found that adding freshly prepared **117**, in a portion-wise manner, to alcohol (+)-**110**

in the presence of a catalytic amount of camphorsulfonic acid (CSA), afforded the desired PMB ether **114** in consistently excellent yields (Scheme 53). The formation of PMB ether **114** was evident from the observation of the ^1H NMR spectrum, which displayed an upfield shift in the multiplet corresponding to the CHOR from 4.56-4.43 ppm to 4.28-4.16 ppm.



Scheme 53. a) 4-methoxybenzyl 2,2,2-trichloroacetimidate, CSA, $\text{CH}_2\text{Cl}_2/\text{cyclohexane}$ (4:1), 91%.

Following the successful formation of **114**, the reduction of the *tert*-butyl ester to the corresponding aldehyde was attempted with diisobutylaluminium hydride (DIBAL-H). Unfortunately, the reaction proved to be unreliable and an acceptable yield could not be reproduced on a large scale. In some cases, over-reduction to the corresponding alcohol was observed. This problem was overcome by using an alternative two-step reduction-oxidation procedure. Subsequently, ester **114** was reduced to alcohol **118** using lithium aluminium hydride (LiAlH_4), followed by an oxidation of the resulting alcohol with Dess-Martin periodinane (DMP), which afforded the desired C31-C35 aldehyde portion consistently in very good yields for both steps (Scheme 54).



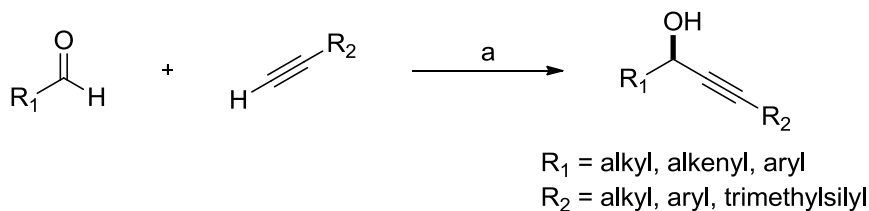
Scheme 54. a) LiAlH_4 , Et_2O , $0\text{ }^\circ\text{C}$, 80%; b) DMP, CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 82%.

The formation of aldehyde **119** was confirmed by the presence of a characteristic singlet at 9.75 ppm in the ^1H NMR spectrum, corresponding to the CHO proton of the aldehyde. In addition to this, the appearance of a peak at 201.2 ppm was observed in the ^{13}C NMR spectrum, which was representative of the aldehyde $\text{C}=\text{O}$.

After successfully synthesising aldehyde **119** in 5 steps from commercially available starting materials, attention turned to the investigation of the diastereoselective coupling of aldehyde **119** with a model alkyne.

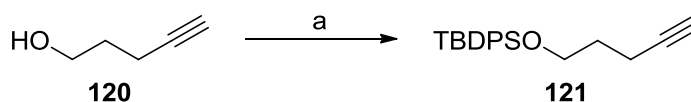
2.4.2 Alkynylation of the C31-C35 aldehyde with a model alkyne

In principle, several procedures are available for the diastereoselective assembly of aldehydes with alkynes,⁹²⁻⁹⁴ however, it was hypothesised that the enantioselective alkynylation procedure developed by Carreira and co-workers could be applied to the coupling of aldehyde **119** and alkyne **68**.⁹⁴ Carreira had reported that the addition of terminal alkynes to aldehydes, in the presence of zinc triflate and (+)- or (-)-*N*-methyl ephedrine (NME), resulted in the formation of the corresponding propargyl alcohol with good yields (67-96%) and high enantioselectivities (80-99% ee) (*Scheme 55*).



Scheme 55. a) $\text{Zn}(\text{OTf})_2$, NEt_3 , (+)-NME, *PhMe*.

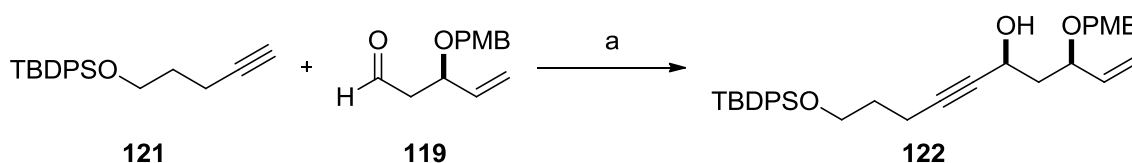
Initial studies into the application of the Carreira alkynylation to the synthesis of the FG fragment of PTX-4 were carried out on a model terminal alkyne, which was readily obtained by a silyl protection of alcohol **120** (*Scheme 56*).



Scheme 56. a) TBDPSCl , imidazole, CH_2Cl_2 , 92%.

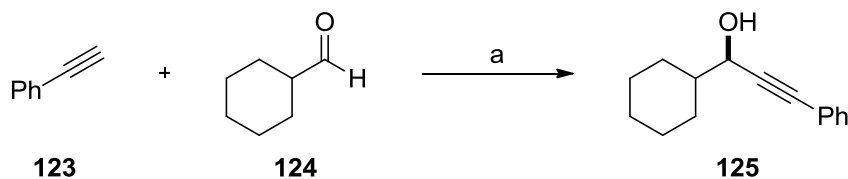
Unfortunately, subjection of alkyne **121** and aldehyde **119** to the diastereoselective alkynylation conditions reported by Carreira was unsuccessful (*Scheme 57*).⁹⁴ In each

case, only traces of propargyl alcohol **122** were isolated, along with a significant amount of unreacted alkyne **121**, and also 4-methoxybenzyl alcohol. Further investigations utilising increased equivalents of each reagent or heating the reaction to 60 °C were equally unsuccessful. Based on these observations, it was rationalised that either alkyne **121** was comparatively unreactive or that decomposition of the aldehyde coupling partner was occurring at a faster rate than the reaction could take place.



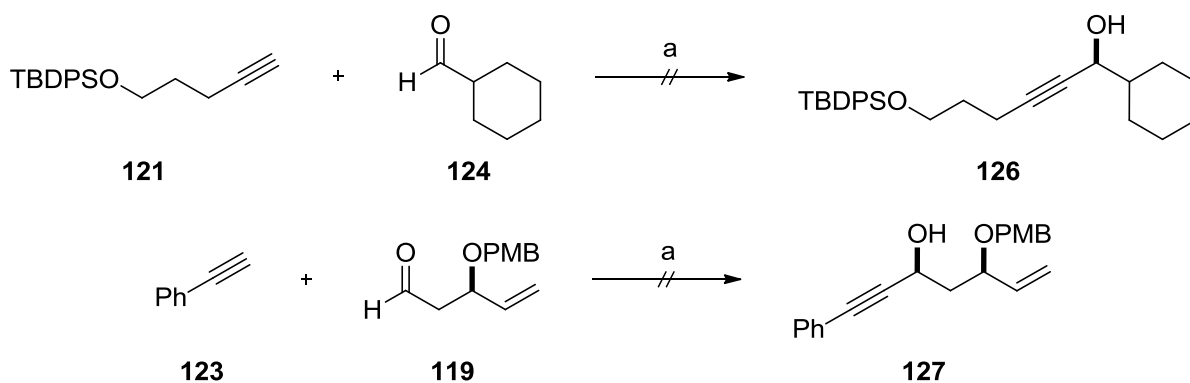
Scheme 57. Zn(OTf)₂, (-)-NME, NEt₃, PhMe, 2%.

In an effort to determine the origin of the poor conversion of the reaction, the reaction of phenyl acetylene with cyclohexanecarbaldehyde, which had been proven to be a reliable reaction in the original work of Carreira, was attempted.⁹⁴ It was anticipated that this would reveal whether the difficulties experienced were as a result of the substrate dependence of the reaction, or a wider issue relating to the general methodology. After several attempts, the reaction of alkene **123** with aldehyde **124** in the presence of zinc triflate and (+)-NME allowed for the formation of propargyl alcohol **125** in a yield of 54% (*Scheme 58*). Crucial to the success of this reaction was that all reagents were freshly distilled (where applicable) and that the zinc triflate was dried *in vacuo* at 120 °C for 16 hours prior to use. Furthermore, it was necessary to perform the reaction under rigorously anhydrous conditions in a Schlenk tube, seemingly in contrast to Carreira's report that this reaction could proceed in reagent grade toluene containing 317 ppm H₂O in a yield of 90%.⁹⁴



Scheme 58. $\text{Zn}(\text{OTf})_2$, (+)-NME, NEt_3 , PhMe, 54%.

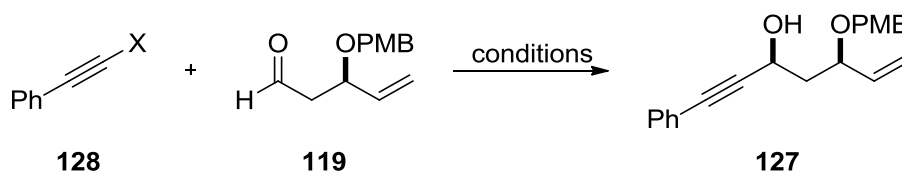
Upon successfully synthesising alcohol **125**, the coupling of alkyne **121** and aldehyde **119** was re-examined. Unfortunately, when subjected to the reaction conditions only a marginal increase in yield was observed. Consequently, a control reaction was performed between alkyne **121** and aldehyde **124**, and alkyne **123** and aldehyde **119** in an attempt to establish which coupling partner was incompatible in the reaction (Scheme 59).



Scheme 59. a) $\text{Zn}(\text{OTf})_2$, (+)-NME, NEt_3 , PhMe.

Disappointingly, in each case the reaction did not deliver the desired coupling product. In the reaction of **121** with **119** (Scheme 57) and **123** with **119** (Scheme 59), significant quantities of 4-methoxybenzyl alcohol were recovered following purification of the reaction mixture by column chromatography. This led to the speculation that an elimination of 4-methoxybenzyl alcohol from aldehyde **119** could have occurred, affording the corresponding 1,3-conjugated diene, analogous to the elimination shown in Scheme 51. As a result of these findings, it was concluded that the Carreira alkynylation protocol was not feasible for the alkynylation of **121** and **119** for the synthesis of the FG fragment of PTX-4.

Following the unsuccessful attempts to utilise Carreira's methodology, attention turned to more conventional substrate-controlled diastereoselective alkynylation reactions. Various conditions were applied to the coupling of aldehyde **119** and model alkyne **128**. Subsequent analysis of the ^1H NMR of the crude reaction mixture allowed the diastereoselectivity of the reaction to be determined (Table 4).

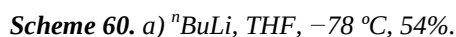


Entry	X	Conditions	Yield of 127 (%)	<i>syn:anti</i>
1	H	Zn(OTf) ₂ , (+)-NME, NEt ₃ , PhMe	-	-
2	MgBr	THF, 0 °C → rt	28	1.2:1
3	H	ⁿ BuLi, THF, -78 °C	65	1.3:1
4	Li	CeCl ₃ , THF, -40 → -78 °C	67	1.1:1

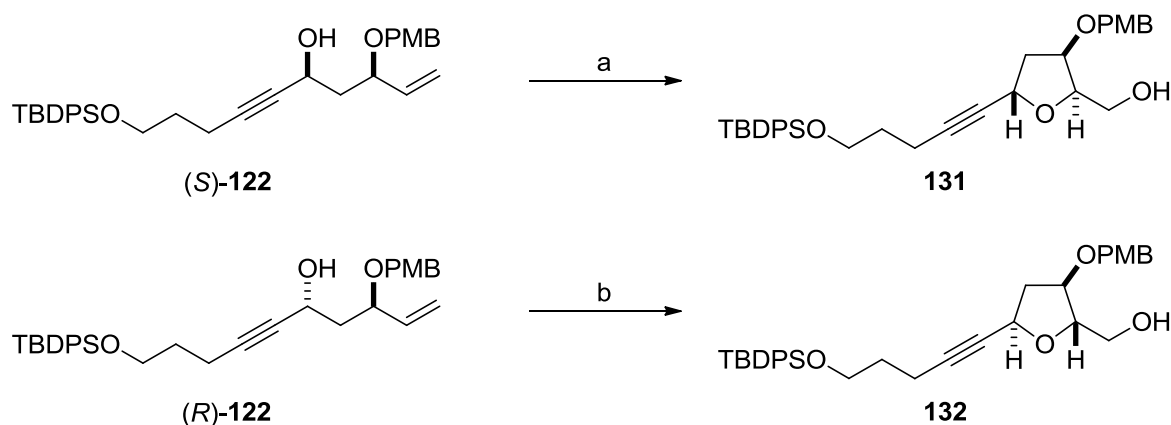
Table 4. Attempted diastereoselective alkynylation

Addition of phenylethynylmagnesium bromide to aldehyde **119** (Table 4, Entry 2) resulted in the formation of the coupled product in a poor yield of 28%. Significant amounts of decomposition (observed by TLC of the reaction mixture) could possibly account for the remainder of the mass. However, improved yields were obtained when butyllithium was utilised as the base at -78 °C (Table 4, Entry 3). One possibility for this improvement could be that the colder reaction temperatures may suppress the decomposition pathways; for example, of aldehyde **119** which has been shown to decompose under strongly basic conditions at mild temperatures (see Scheme 51). In an attempt to further improve the yield of propargyl alcohol **127**, the utilisation of a softer, less basic organocerium reagent was explored (Table 4, Entry 4). Thus, cerium(III) chloride was added to a solution of the lithium anion of phenylacetylene in order to facilitate a transmetallation of the organolithium reagent. However, despite the less basic nature of the presumed

Applying the best conditions (*Table 4*, Entry 3) to alkyne **121** and aldehyde **191**, the formation of propargyl alcohol **122** resulted in a yield of 54% as a 1.4:1 mixture of diastereomers, which were separable by flash column chromatography (*Scheme 60*). Despite the formation of two diastereomers, this result was a significant improvement in comparison to the application of Carreira's conditions.



At this stage, it was deemed necessary to attempt the coupling reaction using triisopropyl (TIPS) protected alkyne **129** (*Scheme 61*). The advantage of utilising the TIPS protecting group, as opposed to the TBDPS group, was to emulate Evans's protecting group strategy, which would subsequently lead to a more efficient end-game to the synthesis of PTX-4. Hence, alkyne **129** was synthesised by the treatment of alkynol **120** with triisopropylsilyl chloride (TIPSCl) in the presence of imidazole. The subsequent coupling of alkyne **129** with aldehyde **119** in the presence of *n*-butyl lithium proceeded in a good yield of 67% to furnish propargyl alcohol **130** as a 1.2:1 mixture of diastereomers, which were separable by flash column chromatography (*Scheme 61*).



Scheme 62. a) O_2 , $Co(nmp)_2$ (30 mol%), TBHP, $iPrOH$, 65 °C, 45%; b) O_2 , $Co(nmp)_2$ (30 mol%), TBHP, $iPrOH$, 65 °C, 54%.

The NOE correlations of **131** clearly showed that a 2,4-*trans* and 2,5-*trans* stereochemical relationship about the THF existed (Figure 19), leading to the conclusion that the starting 5-hydroxy alkene was the 1,3-*syn* diol derivative. On the other hand, the NOE correlations of **132** revealed a 2,4-*cis* relationship about the THF ring, and consequently the starting material was assigned as the 1,3-*anti* diol derivative.

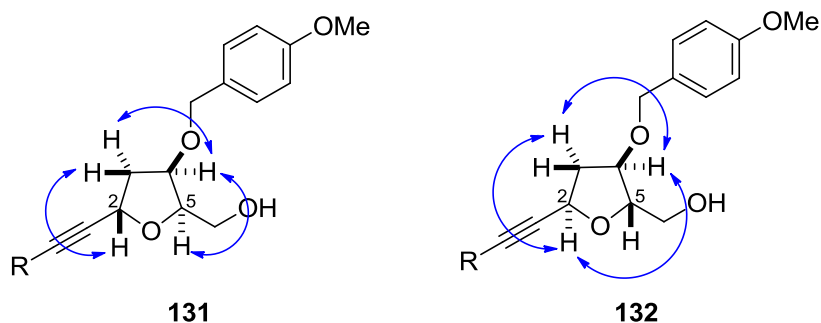
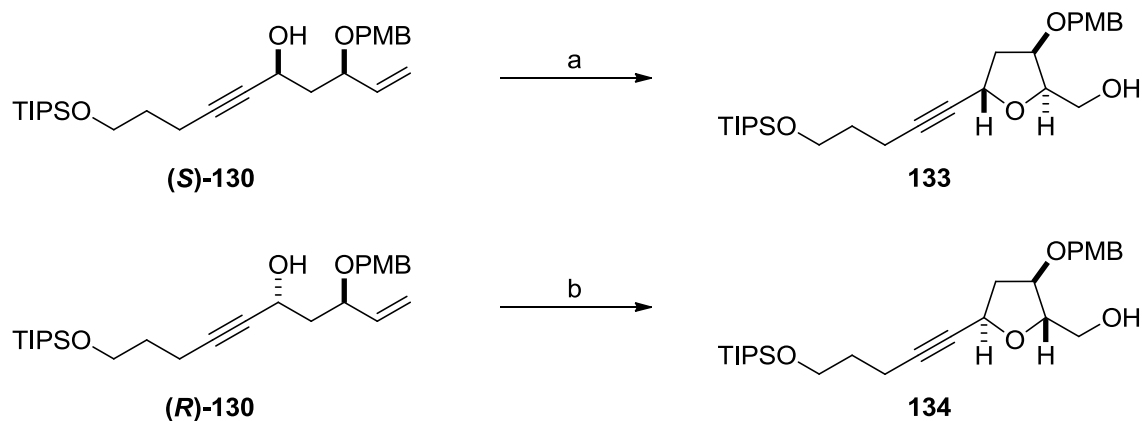


Figure 19. Key NOE correlations of the *trans*-THF products

Subjection of the corresponding TIPS ethers (S)-**130** and (R)-**130** to the oxidative cyclisation conditions also allowed for the formation of the corresponding *trans*-THFs. The stereochemistry of the starting diol derivatives were retrospectively assigned in analogy to the TBDPS ethers, by analysis of the NOE correlations (Scheme 62).



Scheme 63. a) O_2 , $Co(nmp)_2$ (30 mol%), TBHP, $iPrOH$, 60 °C, 52%; b) O_2 , $Co(nmp)_2$ (25 mol%), TBHP, $iPrOH$, 60 °C, 48%.

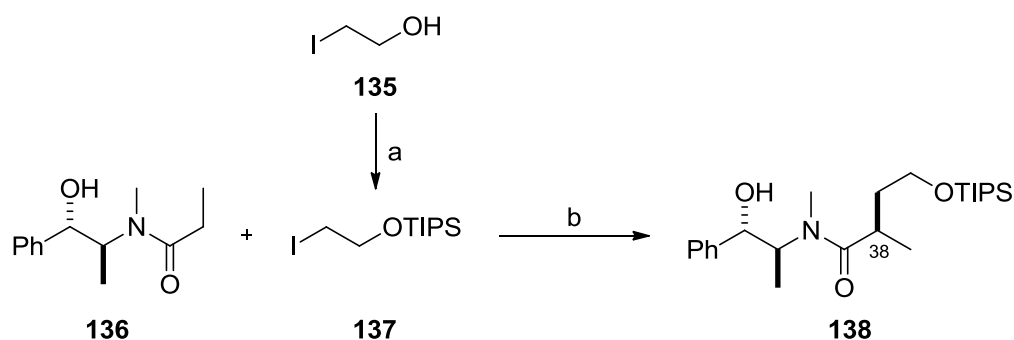
It was found that the cyclisation reactions proceeded in similar yields to the previous model systems, indicating that a pendant alkyne bore little or no influence on the oxidative cyclisation of the 5-hydroxy alkene.

Having achieved promising results with the alkynylation and subsequent cyclisation reactions using a model alkyne, attention turned to the synthesis of the desired C36-C40 alkyne component of PTX-4.

2.4.4 Synthesis of the C36-C40 alkyne component

It was proposed that the synthesis of terminal alkyne **68** could be achieved by following an analogous procedure to that reported by Fürstner and co-workers in the synthesis of amphidinolide G1.⁹⁵ Central to the strategy for the synthesis of alkyne **68** was the utilisation of a chiral auxiliary approach developed by Myers and co-workers,^{77, 96} which would allow for the construction of the chiral methyl group at C38. Accordingly, the synthesis of alkyl halide **137** commenced with the reaction of iodoethanol with triisopropylsilyl chloride (TIPSCl) in the presence of imidazole. Deprotonation of pseudoephedrine propionamide **136** and the subsequent reaction of the resulting enolate

anion with alkyl halide **137** allowed for the formation of **138** in an excellent yield of 97% (Scheme 64).



Scheme 64. a) TIPSCl, imidazole, CH_2Cl_2 , 91%; b) $^n\text{BuLi}$, $^i\text{Pr}_2\text{NH}$, LiCl, THF, $0\text{ }^\circ\text{C} \rightarrow -78\text{ }^\circ\text{C}$, 97%.

The formation of **138** was confirmed by comparison of the ^1H and ^{13}C NMR data with that reported in the literature.⁹⁶ However, the NMR spectra were complicated due to restricted rotation about the amide bond giving rise to a 6:1 mixture of rotamers. Consequently, determination of the diastereomeric ratio of the product by ^1H NMR spectroscopy was not feasible. As the spectroscopic data of **138** was a good match with the literature, it was anticipated that the diastereomeric ratio of **138** was comparatively high (i.e. $\geq 95\%$ de). The enantopurity at C38 was confirmed at a later stage (see Scheme 66).

It has been postulated by Myers, that the diastereoselectivity for the alkylation reaction arises from the aggregation of solvent molecules with the intermediate lithium alkoxide, which causes steric hindrance on the lower face of the (Z)-enolate and thus forces electrophilic attack to occur from the top face.⁹⁶ As a consequence, a 1,4-syn relationship results between the methyl group that is bound to the chiral auxiliary and the incoming electrophile (Figure 20).⁹⁶

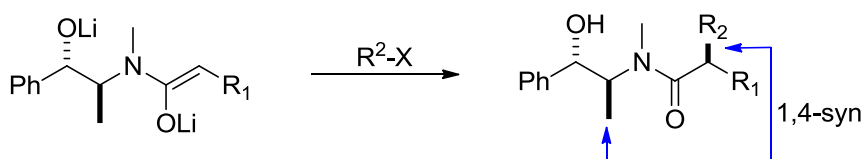
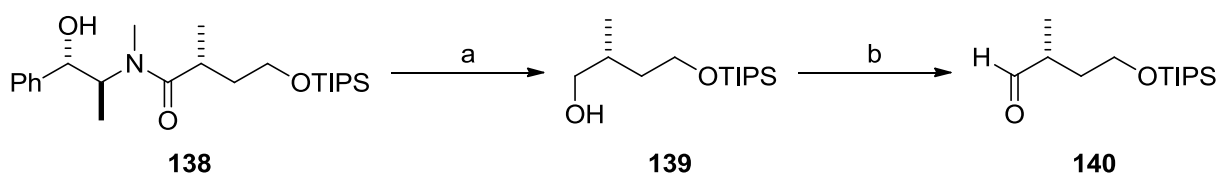


Figure 20. Mnemonic for pseudoephedrine amide enolate alkylation

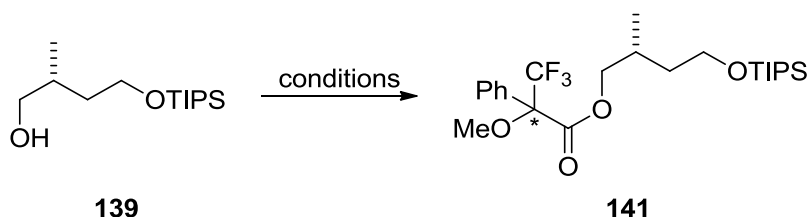
The role of lithium chloride in the alkylation remains unclear, however, Myers and co-workers found it to be essential in order to accelerate the rate of the reaction. It was postulated that this could be due to an alteration in the aggregation state of the enolate in solution, and consequently to its reactivity.⁹⁶ In addition to this, the inclusion of lithium chloride was shown to suppress the competing *O*-alkylation of the secondary hydroxyl group of the chiral auxiliary.⁹⁶

With the desired stereocentre in place, attempts were made to remove the chiral auxiliary by means of a reductive cleavage of the amide bond. It was rationalised that a highly nucleophilic hydride source, known as lithium amidotrihydroborate (LAB) could be utilised for the transformation, since it has been demonstrated to cause little or no base-induced epimerisation α to the intermediate aldehyde centre. Thus, the hydride source was generated *in situ* by deprotonation of the commercial borane-ammonia complex.⁹⁷ Upon adding **138** to the solution of LAB, the amide bond was cleaved and the aldehyde intermediate was subsequently reduced *in situ* to deliver primary alcohol **139** in a good yield of 88% (Scheme 65). A Swern oxidation of the primary alcohol followed in a quantitative yield, providing access to aldehyde **140**, which displayed a distinct peak at 9.68 ppm in the ^1H NMR spectrum, corresponding to the *CHO* proton.³⁶



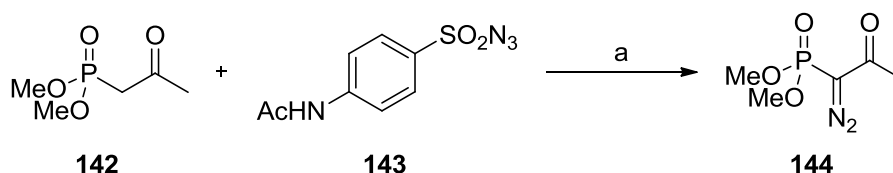
Scheme 65. a) $n\text{-BuLi}$, $i\text{-Pr}_2\text{NH}$, $\text{BH}_3\cdot\text{NH}_3$, THF , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 88%; b) $(\text{COCl})_2$, DMSO , NEt_3 , CH_2Cl_2 , 100%.

The enantiomeric purity of **139** was examined by synthesising the corresponding Mosher's esters (Scheme 66).⁸⁶ Comparison of the ^1H NMR spectra of the resulting Mosher's esters, established that alcohol **139** was $\geq 95\%$ ee.



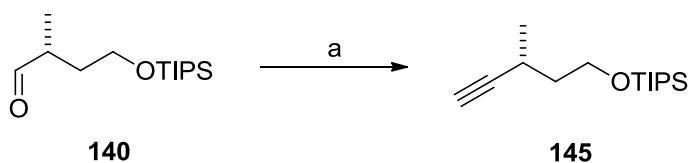
Scheme 66. a) (*R*)-MTPA, DCC, DMAP, CH₂Cl₂, 96%; b) (*S*)-MTPA, DCC, DMAP, CH₂Cl₂, 100%.

In order to access terminal alkyne **145**, it was necessary to perform a one-carbon chain extension of aldehyde **140**, which we envisaged by means of a Seyferth-Gilbert homologation.^{98, 99} However, in order to minimise the risk of epimerisation at the chiral methyl centre, the Bestmann-Ohira modification was applied, allowing the reaction to proceed under milder, less basic reaction conditions by the utilisation of phosphonate **144**.¹⁰⁰ Although phosphonate **144** is commercially available, it is considered to be susceptible to decomposition and is reasonably expensive. Consequently, the Bestmann-Ohira reagent was freshly prepared by the diazotisation of phosphonate **142** using azide **143** in the presence of potassium carbonate, and was used immediately in the subsequent homologation (*Scheme 67*).



Scheme 67. a) K₂CO₃, MeCN, 98%.

Treatment of aldehyde **140** with phosphonate **144** in the presence of sodium methoxide, allowed for the formation of alkyne **145** in a very good yield of 76% (*Scheme 68*). The conversion of **140** to **145** was evident from the IR spectra, which showed a strong absorption at 3313 cm⁻¹, and from the ¹H NMR spectrum, which displayed a distinct doublet at 2.03 ppm, both of which corresponded to the terminal alkyne C≡C-H.

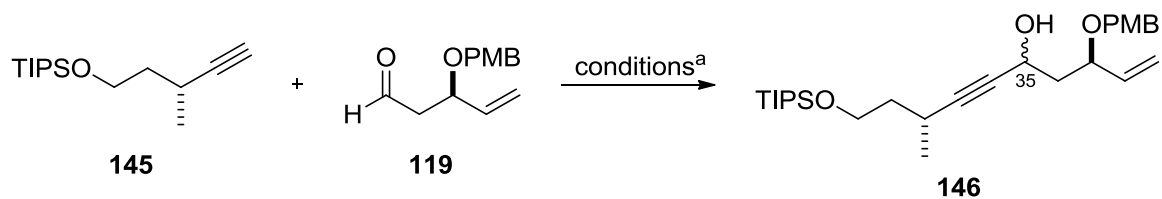


Scheme 68. a) **144**, NaOMe, THF, $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 76%.

In summary, access to terminal alkyne **145** was successfully achieved in just 5 steps from iodoethanol in high enantiopurity. With both aldehyde **119** and alkyne **145** now in hand, investigations into their diastereoselective assembly ensued.

2.4.5 Coupling of aldehyde **119** with alkyne **145** and subsequent cyclisation

The convergent approach to the synthesis of the C31-C40 fragment of PTX-4, required the assembly of aldehyde **119** and alkyne **145**. Model studies on the alkynylation of model alkyne **128** with aldehyde **119** revealed that the most promising reaction conditions were *n*-butyllithium in THF at $-78\text{ }^{\circ}\text{C}$. As such, these conditions were also to be employed for the coupling of aldehyde **119** and alkyne **145**. Thus, treatment of alkyne **145** with *n*-butyllithium in THF at $-78\text{ }^{\circ}\text{C}$, followed by the slow addition of aldehyde **119**, furnished alcohol **146** (*Scheme 69*). A 1.4:1 mixture of diastereomers at C35 was identified by analysis of the ^1H NMR spectrum of the crude reaction. The mixture was subsequently separated by column chromatography, affording alcohol (*R*)-**146** and (*S*)-**146** in a combined yield of 72%. The major diastereomer was later assigned as the desired 1,3-*syn* diastereomer (see *Scheme 70*).

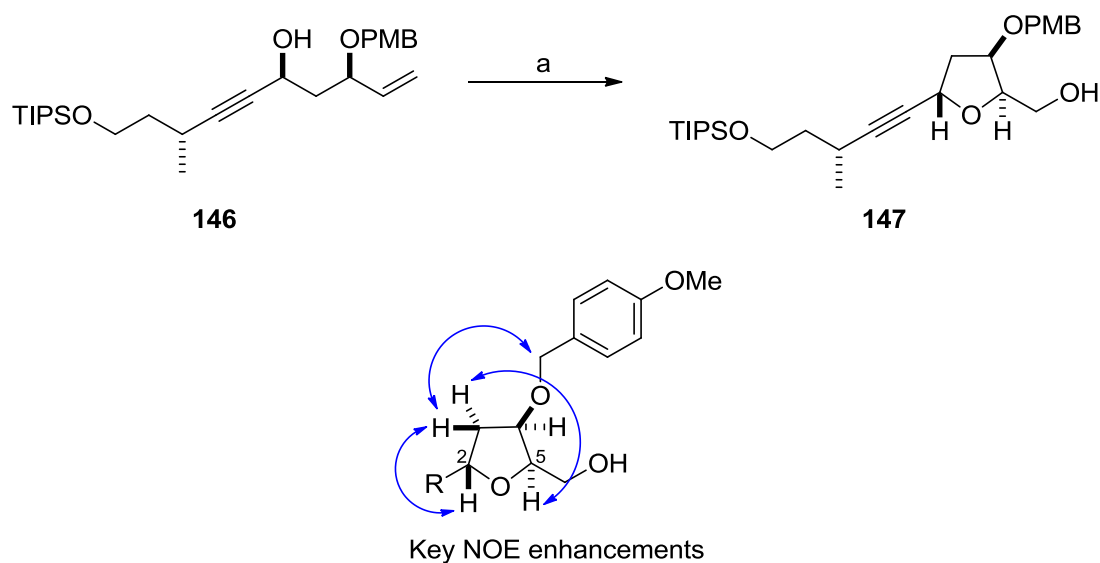


Entry	Solvent ^a	syn:anti
1	THF	1.4:1
2	Et ₂ O	0.7:1
3	PhMe	0.9:1
4	MTBE	0.8:1

Scheme 69. a) ⁿBuLi, solvent, −78 °C.

In an attempt to improve the diastereoselectivity of the addition, a range of solvents were screened (Scheme 69). However, it was found that THF was the only solvent which demonstrated a preference for the formation of the desired 1,3-syn diastereomer.

After successfully assembling the C31-C40 backbone of PTX-4, the precursor to the oxidative cyclisation, attempts were made to construct the F-ring. Upon exposing a solution of hydroxy alkene **146** to a catalytic amount of Co(nmp)₂ under an oxygen atmosphere, the radical cyclisation proceeded to deliver *trans*-THF **147** in a yield of 49% (Scheme 70).

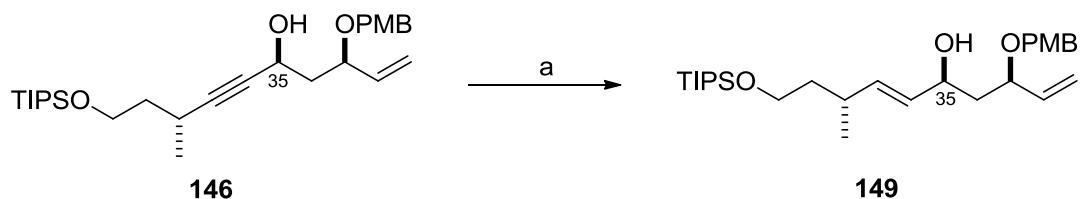


Scheme 70. a) O₂, Co(nmp)₂ (25 mol%), TBHP, ⁱPrOH, 60 °C, 49%.

Analysis of the NOE correlations of **147** confirmed the expected 2,5-*trans* stereochemistry of the newly formed THF ring, along with the 2,4-*trans* relationship, thus allowing the starting 5-hydroxy alkene **146** to be identified as the 1,3-*syn* diastereomer (*Scheme 70*). In addition, the 1,3-*anti* diastereomer of **146** was cyclised to furnish the corresponding *trans*-THF with a 2,4-*cis* relationship (compound **148**, not shown).

2.4.6 (*E*)-Selective alkyne reduction

In order to allow for the subsequent formation of the 1,2-diol unit of the FG fragment, which was proposed *via* a Sharpless asymmetric dihydroxylation, it was necessary to perform a selective reduction of alkyne **147** to the (*E*)-alkene. However, methods that facilitate a *trans*-selective delivery of two hydrogen atoms across an un-functionalised triple bond are limited.¹⁰¹ On the other hand, the treatment of propargyl alcohols with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al[®]) is known to allow for the selective formation of the corresponding (*E*)-allylic alcohol.¹⁰²⁻¹⁰⁵ This stereoselective reduction can be accounted for by the initial chelation of the aluminium-based reducing reagent with the hydroxyl group, followed by an intramolecular delivery of the hydride.¹⁰⁴ Consequently, it was rationalised that modifying the synthetic strategy, such that the reduction of the alkyne occurred prior to the oxidative cyclisation, could prove to be the most efficient method for forming the desired (*E*)-alkene. Accordingly, it was found that treatment of alkyne **146** with Red-Al[®] provided alkene **149** in a very good yield of 81% (*Scheme 71*).



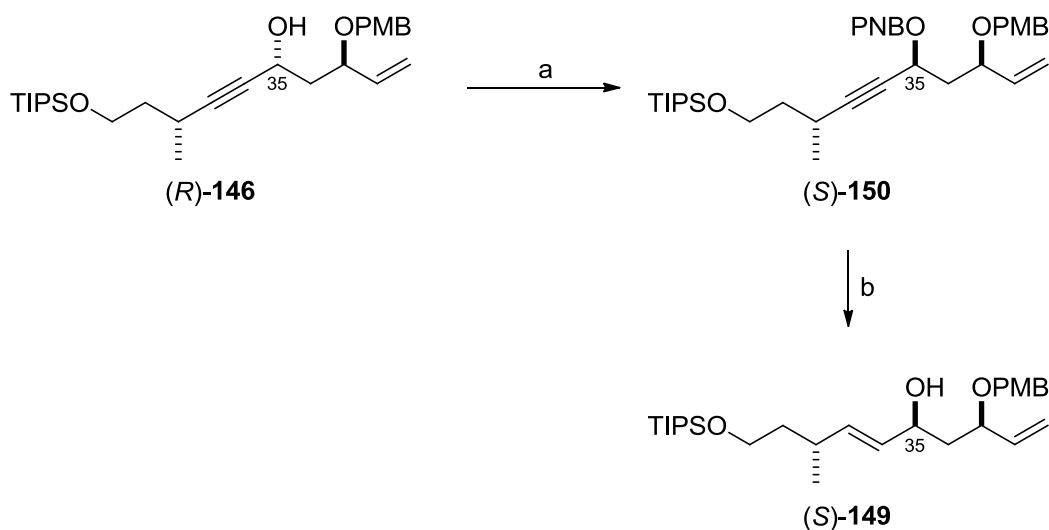
Scheme 71. a) Red-Al[®], Et₂O, 0 °C → rt, 81%.

Reduction of the alkyne was verified by analysis of the ¹H NMR spectrum. The presence of the newly formed alkene was noticeable by the appearance of two doublets of doublets at 5.55 and 5.41 ppm, corresponding to the CH=CH. Furthermore, the geometry of the alkene was established by the measurement of the CH=CH coupling constant, which was measured as 15.5 Hz, characteristic of a *trans*-double bond. Consequently, the (*E*)-selectivity of the alkyne reduction, owing to the participation of the C35 hydroxyl group, was confirmed. As expected, there was no evidence in the ¹H NMR spectrum to suggest the formation of any of the (*Z*)-alkene isomer.

2.4.7 Utilisation of 1,3-*anti* diastereomer (*R*)-146

As discussed previously, the addition of alkyne **145** to aldehyde **119** resulted in the formation of propargyl alcohol **146** as a 1.4:1 mixture of diastereomers at C35, which were separable by flash column chromatography (see *Scheme 69*). A paper published by Pagenkopf and co-workers on the synthesis of amphidinolide C,⁷³ prompted investigations into the utilisation of the undesired 1,3-*anti* diastereomer (*R*)-**146**. In an analogous procedure to Pagenkopf, the secondary alcohol stereocentre of (*R*)-**146** was inverted by means of a Mitsunobu reaction with 4-nitrobenzoic acid (*Scheme 72*). The subsequent reaction of (*S*)-**150** with 5 equivalents of Red-Al[®] at 0 °C, resulted firstly in cleavage of the *para*-nitrobenzoyl (PNB) group to expose the C35 hydroxyl, as noted by consumption of

the starting material by TLC, and secondly, upon warming the reaction to room temperature, facilitated the selective reduction of the alkyne to the desired (*E*)-alkene.

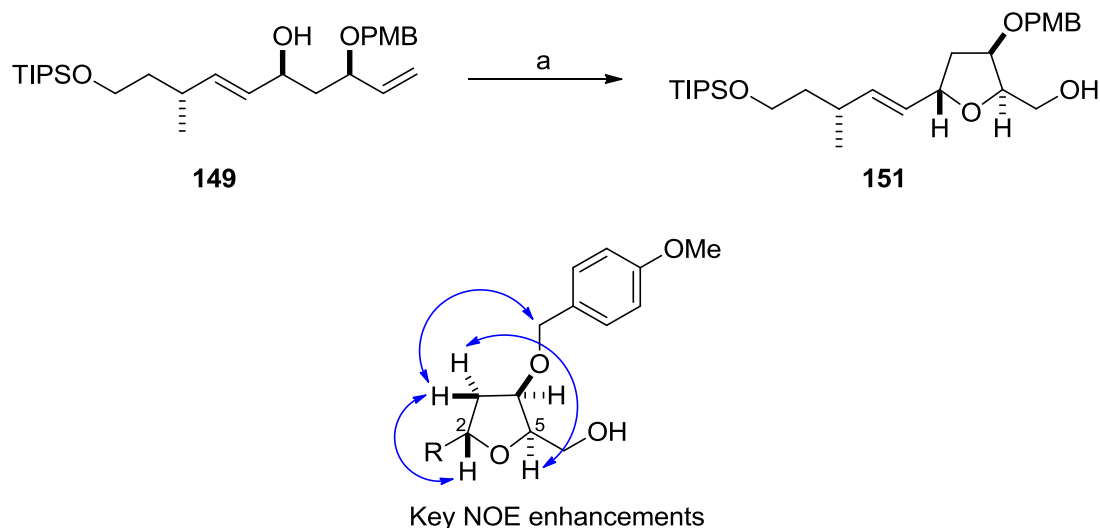


Scheme 72. a) 4-Nitrobenzoic acid, PPh_3 , DIAD, THF, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 86%; b) Red-Al[®], Et_2O , $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 71%.

The spectroscopic data of (S)-149 was identical to that of the product obtained by the direct reduction of alkyne 146 (see Scheme 71). Pleasingly, this two-step procedure provided an efficient method for utilising the undesired 1,3-*anti* diastereomer in the synthesis of the C31-C40 fragment of PTX-4.

2.4.8 F-ring formation

With the required (*E*)-alkene 149 in hand, it was anticipated that the *trans*-THF F-ring of PTX-4 could be furnished. Pleasingly, upon subjecting 149 to the cobalt-catalysed oxidative cyclisation, the F-ring of PTX-4 was successfully obtained in a good yield of 57% (Scheme 73).



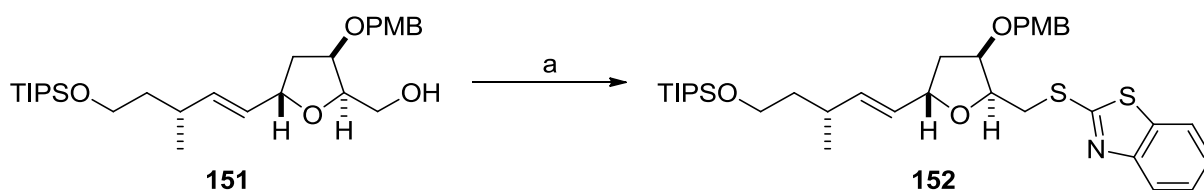
Scheme 73. a) O_2 , $Co(nmp)_2$ (25 mol%), TBHP, $iPrOH$, 70 °C, 57%.

The formation of the oxidative cyclisation product was confirmed by the disappearance of the peaks corresponding to the terminal alkene of **149** in the ^1H NMR spectrum centred at 5.77 and 5.26 ppm, along with a shift of the $CHOH$ peak of the starting material from 4.26 to 4.62 ppm. In addition to this, analysis of the NOE correlations confirmed that the expected 2,5- and 2,4-*trans* stereochemistry was in place about the THF ring of **151** (Scheme 73). The successful formation of **151** demonstrated the effectiveness of utilising the oxidative cyclisation protocol as the key step in this synthesis, allowing excellent levels of diastereoselectivity to be achieved in the formation of the F-ring of PTX-4.

2.4.9 Installation of the sulfone moiety

Upon synthesising the F-ring of PTX-4, it was necessary to exchange the primary alcohol for a benzothiazole sulfone. This would prove essential in allowing the FG fragment to be coupled to the ABCDE ring system by a modified Julia olefination at a later stage. It was anticipated that a Mitsunobu reaction could be utilised for this transformation. Hence, alcohol **151** was treated with benzothiazole thiol in the presence of triphenylphosphine and

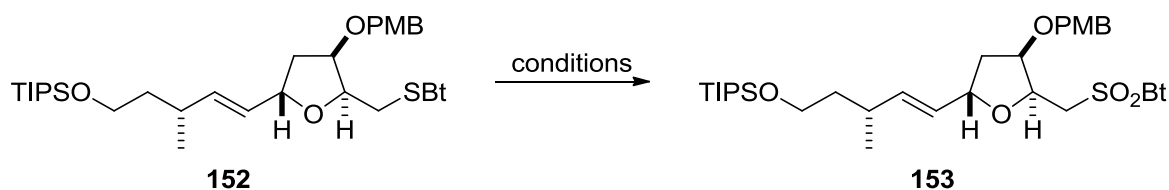
diisopropylazodicarboxylate (DIAD), to afford sulfide **152** in an excellent yield of 91% (Scheme 74).



Scheme 74. a) *BtSH*, *PPh₃*, *DIAD*, *THF*, 0 °C → *rt*, 91%.

Substitution of the primary alcohol was verified by the disappearance of the broad O-H stretch at 3439 cm⁻¹ in the IR spectrum. Furthermore, the appearance of additional peaks in the aromatic region of the ¹H NMR spectrum confirmed the presence of the benzothiazole group.

A range of conditions were attempted for the subsequent chemoselective oxidation of thioether **152** in the presence of the *trans*-disubstituted alkene (Table 5).



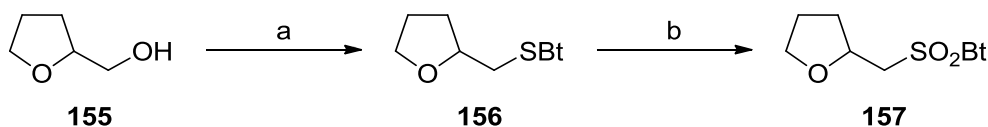
Entry	Conditions	Yield (%)
1	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0 °C	24
2	H ₂ O ₂ , Na ₂ WO ₄ (10 mol%), MeOH	57
3	H ₂ O ₂ , (NH ₄) ₆ Mo ₇ O ₂₄ (25 mol%), EtOH	72

Table 5. Oxidation of sulfide **152**

Initially, the oxidation was attempted with 2 equivalents of *meta*-chloroperoxybenzoic acid (*m*-CPBA). Upon monitoring the reaction by TLC, it was evident that the initial oxidation of the sulfide to the sulfoxide (**154**) proceeded rapidly (<1 hour), allowing for the full consumption of the starting material. However, subsequent oxidation to the corresponding sulfone was comparatively slow and proved difficult to achieve. As a result of this, sulfone **153** was obtained in a yield of just 24%, along with the corresponding sulfoxide

intermediate in a yield 56%. Alternatively, it was believed that the oxidation of thioether **152** could be accomplished by utilising hydrogen peroxide in the presence of a transition metal catalyst. By using sodium tungstate as a catalyst (*Table 5*, Entry 2),¹⁰⁶ it was possible to obtain sulfone **153** in a more optimistic yield of 57%. However, this reaction proved to be extremely slow, taking approximately 48 hours for the full conversion of the starting material to the intermediate sulfoxide. On the other hand, it was found that the treatment of sulfide **152** with hydrogen peroxide in the presence of a catalytic amount of ammonium molybdate,¹⁰⁷ allowed for the formation of sulfone **153** in a yield of 72% after just 16 hours. The formation of sulfone **153** was apparent from the characteristic S=O stretches in the IR spectrum at 1329 and 1147 cm^{-1} . Interestingly, there was no evidence to suggest that epoxidation of the alkene had occurred in any case.

Despite the promising result with the use a catalytic amount of ammonium molybdate (*Table 5*, Entry 3), the yield for the oxidation of **152** with hydrogen peroxide proved to be unreliable. The issue with the reaction appeared to be the incomplete conversion of the intermediate sulfoxide to the desired sulfone **153**, with the reaction appearing to stall before reaching completion. Consequently, a more thorough investigation into the reaction was required before continuing with the synthesis on a large scale. In the interest of conserving sulfide **152**, a model system was utilised to examine the oxidation. Thus, reaction of tetrahydrofurfuryl alcohol with benzothiazole thiol, under Mitsunobu conditions, allowed for the formation of sulfide **156** (*Scheme 75*). The effect of altering the catalyst loading on the subsequent oxidation of **156** was investigated, and it was found that 10 mol% of ammonium molybdate was optimal, allowing for the full conversion of the starting thioether to the sulfoxide, and its subsequent oxidation to sulfone **157** within 18 hours.

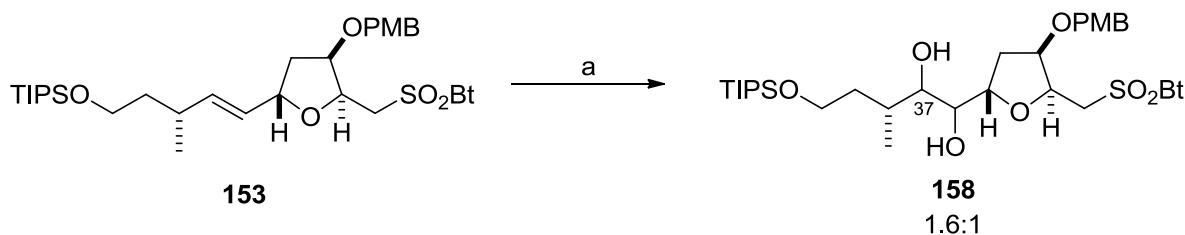


Scheme 75. a) *BtSH*, *PPh₃*, *DIAD*, *THF*, 0 → 10 °C, 69%, b) *H₂O₂*, *(NH₄)₆Mo₇O₂₄* (10 mol%), *EtOH*, 93%.

Interestingly, it was found that increasing the catalyst loading up to 50 mol% had a detrimental effect on the progress of the reaction, with starting material still visible by TLC after 18 hours, and no evidence for the formation of sulfone **157**. On the other hand, when the catalyst loading was decreased further to 5 mol%, full consumption of the intermediate sulfoxide was possible, although the rate of the reaction was significantly reduced. Pleasingly, when the optimised conditions were applied to the oxidation of sulfide **152**, the reaction was found to proceed reliably in very good yields.

2.4.10 Sharpless asymmetric dihydroxylation

In order to access the 1,2 diol from the corresponding alkene, it was anticipated that a Sharpless asymmetric dihydroxylation could be employed.⁴⁷ However, prior to attempting the asymmetric variant, it was reasoned that subjecting alkene **153** to an Upjohn dihydroxylation, would provide an insight as to whether there was a fundamental substrate bias for the dihydroxylation to occur on one face in preference to the other. Thus, treatment of alkene **153** with a catalytic amount of osmium tetroxide in the presence of *N*-methyl morpholine-*N*-oxide (NMO) allowed for the *syn*-selective dihydroxylation to proceed in an excellent yield of 84%. A 1.6:1 mixture of inseparable diastereomers was afforded, which was later revealed to be slightly in favour of the undesired stereoisomer (*Scheme 76*).¹⁰⁸



Scheme 76. a) OsO_4 (8 mol%), NMO, $\text{H}_2\text{O}/\text{THF}/\text{BuOH}$ (1:10:8), 2.5 h, 84%.

Following the success of the dihydroxylation using the racemic protocol, investigations into the Sharpless asymmetric dihydroxylation ensued. According to the mnemonic developed by Sharpless, it was predicted that the use of $(\text{DHQD})_2\text{PHAL}$ as the chiral quinidine ligand, would allow for the formation of the desired (*R*)-alcohol at C37, as a result of a *syn* addition across the top face of the *trans*-disubstituted alkene (*Figure 21*).¹⁰⁹

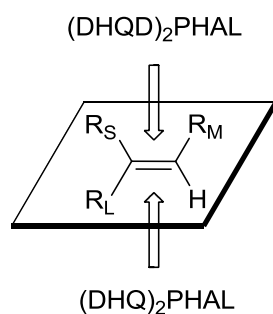
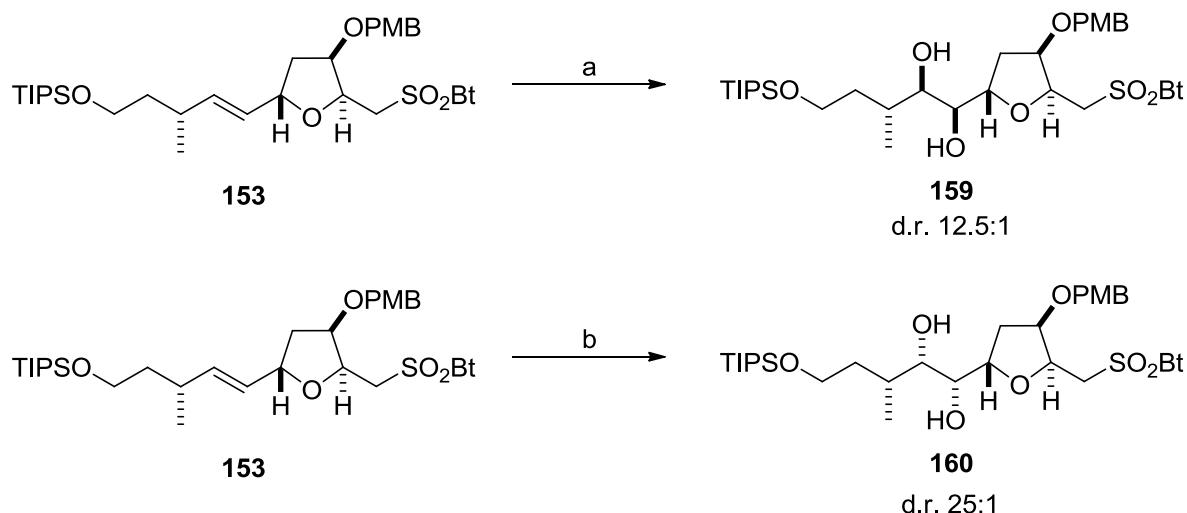


Figure 21. Sharpless mnemonic for predicting the stereochemical outcome¹⁰⁹

Thus subjection of alkene **153** to the Sharpless asymmetric dihydroxylation conditions with $(\text{DHQD})_2\text{PHAL}$ afforded desired 1,2-*syn* diol **159** in a yield of 84% and a 12.5:1 diastereoselectivity (*Scheme 77*). On the other hand, the addition of osmium tetroxide to the lower face was achieved by the use of $(\text{DHQ})_2\text{PHAL}$ as the chiral ligand, furnishing 1,2-*syn* diol **160** in a comparative yield and as a 25:1 mixture of diastereomers. The stereoselectivity of the asymmetric dihydroxylations have been assumed to conform to the Sharpless mnemonic (*Figure 21*).



Scheme 77. a) $K_2OsO_4 \cdot 2H_2O$ (5 mol%), $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3 , $MeSO_2NH_2$, $tBuOH:H_2O$ (1:1), $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 84%; b) $K_2OsO_4 \cdot 2H_2O$ (5 mol%), $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3 , $MeSO_2NH_2$, $tBuOH:H_2O$ (1:1), $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 78%.

These results demonstrated the ability of the chiral ligands to influence the diastereoselectivity of the dihydroxylation to occur on either face of the *trans*-disubstituted alkene. The asymmetric dihydroxylations were found to proceed slowly at $0\text{ }^\circ\text{C}$, and consequently, the reactions were allowed to warm to room temperature. It was found that the reactions required a minimum of 72 hours at room temperature in order to proceed to completion, compared to just 2.5 hours at $0\text{ }^\circ\text{C}$ in the case of the Upjohn dihydroxylation. This was despite the presence of methane sulfonamide in the asymmetric variant, which has been demonstrated to accelerate the rate of dihydroxylation of non-terminal alkenes by enhancing the hydrolysis of the intermediate osmate ester.¹⁰⁹

2.4.11 Regioselective mono-protection of 1,2-diol **159** formed by dihydroxylation

In order to allow for the late-stage functionalisation of the C31-C40 fragment of PTX-4, it was essential to be able to distinguish between the C36 and C37 secondary alcohols within **159** (Figure 22).

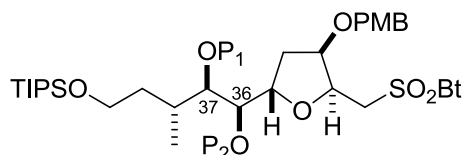
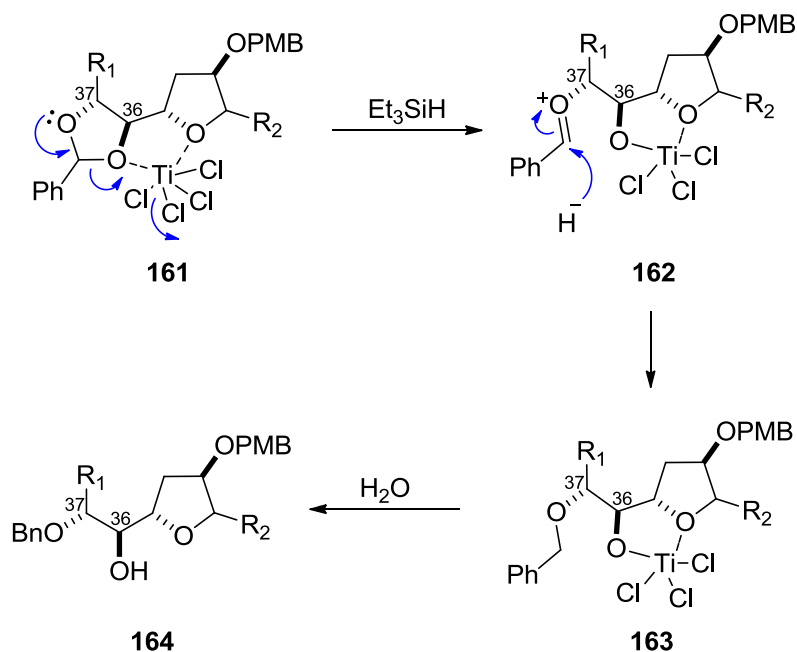


Figure 22. Differential protection of the C36 and C37 alcohols

It was anticipated that a subtle difference in the steric and electronic environment of the alcohols would potentially allow for the regioselective mono-protection of the 1,2-diol, enabling the remaining alcohol functionality to be protected differentially.

2.4.11.1 The Yamamoto protocol

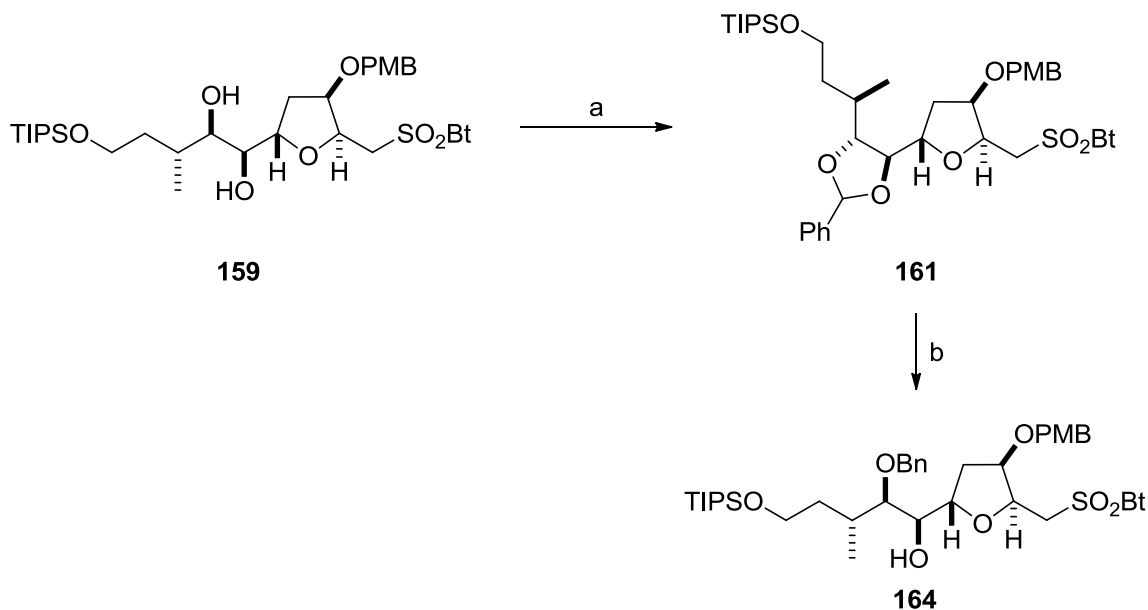
Initially, application of Yamamoto's regioselective mono-protection protocol was investigated, as it was considered to be the most promising strategy for the mono-protection of the 1,2-diol, whilst avoiding bis-protection of the hydroxyl groups.⁴¹ The protocol involves converting a 1,n-diol (n=2,3) to its corresponding benzylidene acetal, followed by selectively cleaving the acetal to afford the resultant mono-protected benzyl ether.^{110, 111} It was reasoned that on subjecting 1,2-diol **159** to the Yamamoto protocol, the reductive cleavage of the corresponding acetal could occur regioselectively by utilising titanium tetrachloride in the presence of triethylsilane (*Scheme 78*).



Scheme 78. Proposed mechanism for regioselective reductive cleavage of acetal **161**

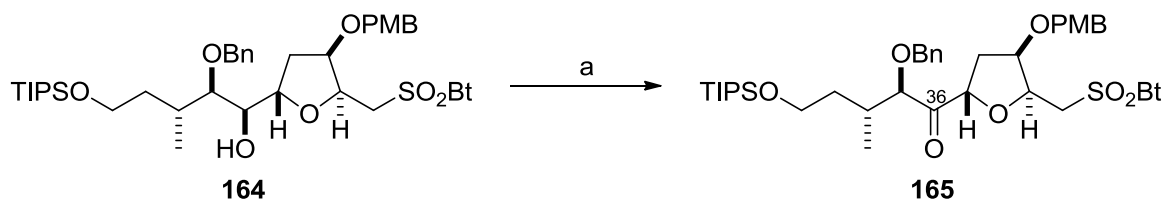
The titanium-based Lewis acid could act by coordinating with both the C36 oxygen atom and the oxygen atom of the adjacent THF ring to form titanium chelate **161**.¹¹¹ Participation of the C37 oxygen lone pair could subsequently facilitate cleavage of the acetal at the C36 oxygen, resulting in the formation of oxocarbenium ion **162**. Finally, a hydride attack on the newly formed oxocarbenium ion by triethylsilane, would afford benzyl ether **163**, which upon hydrolysis would furnish mono-protected diol **164**.

Thus, treatment of diol **159** with benzaldehyde dimethyl acetal in the presence of a catalytic amount of camphorsulfonic acid (CSA) afforded benzylidene acetal **161** as an inconsequential mixture of diastereomers at the acetal carbon (*Scheme 79*). Pleasingly, subsequent exposure of acetal **161** to triethylsilane in the presence of titanium tetrachloride, resulted in a reductive cleavage of the benzylidene acetal to afford mono-protected 1,2-diol **164**.



Scheme 79. a) Benzaldehyde dimethyl acetal, CSA, CH_2Cl_2 , 79%; b) Et_3SiH , TiCl_4 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 23%.

Unfortunately, the reductive cleavage of acetal **161** was poor yielding. As the reaction progressed, there was evidence to suggest that decomposition of the substrate was occurring, and a significant amount of starting material was recovered from the reaction (40%). However, a sufficient quantity of the mono-protected diol was obtained, allowing the regioselectivity of the reductive cleavage to be determined. Analysis of the ^1H NMR spectrum revealed the disappearance of the C37 CHOH doublet at 3.24 ppm in the starting diol. In addition, the COSY NMR spectrum showed that the C37 CH no longer coupled to an OH atom. On the other hand, the C36 CH did show a coupling interaction to an OH atom. This NMR evidence showed that the regioselectivity of the reductive cleavage was as predicted by the mechanism shown in *Scheme 78*, thus resulting in the selective benzyl-protection of the C37 hydroxyl. Further clarification of the regioselectivity was achieved by treating **164** with Dess Martin periodinane (DMP) to afford ketone **165** in a very good yield of 80% (*Scheme 80*).



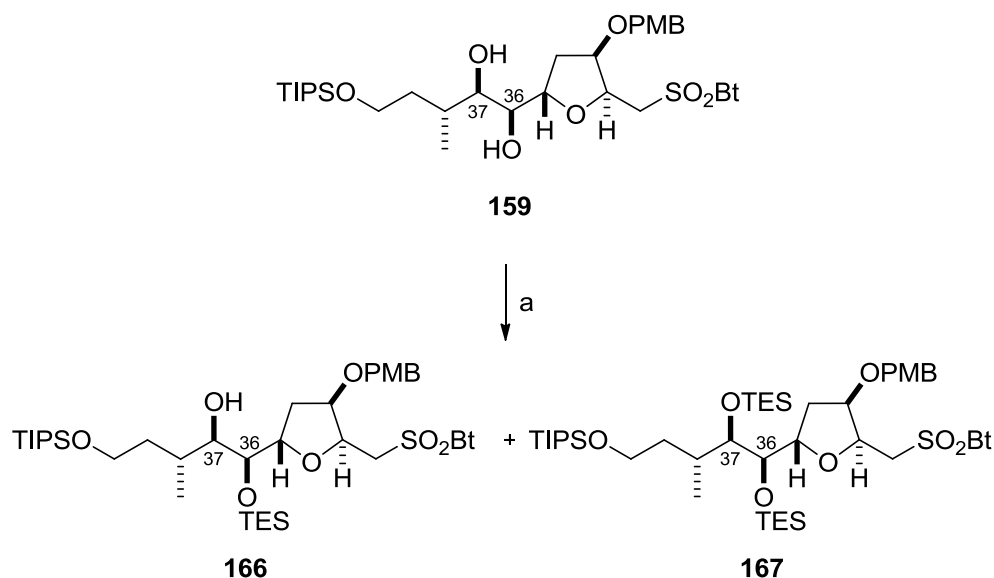
Scheme 80. a) DMP, NaHCO_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 80%.

Oxidation at the C36 hydroxyl group resulted in the disappearance of the C36 CHOH multiplet at 3.44-3.37 ppm in the ^1H NMR spectrum. In addition, the appearance of a strong C=O stretch at 1724 cm^{-1} in the IR spectrum, confirmed that the C36 hydroxyl group had undergone an oxidation to the corresponding ketone. However, the poor yields obtained whilst attempting to apply Yamamoto's protocol to the regioselective mono-protection of diol **159** meant that attention turned to an alternative protocol.

2.4.11.2 Silyl ether formation

Upon re-evaluating the protecting group strategy, it was anticipated that a regioselective silyl protection of diol **159** could be achieved. An advantage of installing a silyl ether at C36 or C37, would be that an intermediate could be prepared that was common to that synthesised in Evans's strategy. Initially, the incorporation of a trimethylsilyl (TMS) group was attempted by the treatment of diol **159** with trimethylsilyl chloride (TMSCl) in the presence of triethylamine. Analysis of the reaction mixture by TLC revealed that the starting material had been rapidly consumed, and that two new products with similar R_f values had been formed. Furthermore, the mass spectrum revealed a strong ion peak corresponding to the mass of the mono-protected silyl ether. It was reasoned that the two products observed by TLC were the regioisomers of mono-TMS protected **159**. Unfortunately, the presumed TMS ethers were not stable to purification by column chromatography and starting material was recovered. Due to the lability of the trimethylsilyl group, attention turned to installing a more robust silyl protecting group,

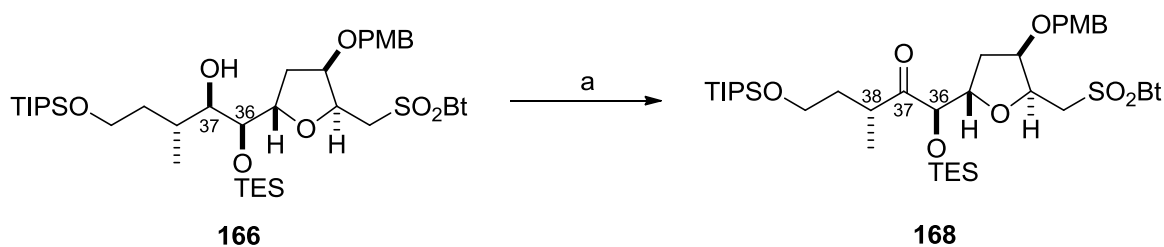
which would not only be able to withstand purification by column chromatography, but would remain intact during the remaining transformations of the synthesis. In view of this, a regioselective mono-protection of diol **159** was attempted using triethylsilyl chloride (TESCl) in the presence of imidazole (*Scheme 81*).



Scheme 81. a) TESCl (4 eq.), imidazole, CH_2Cl_2 , 0 °C, **166**: 48%, **167**: 44%.

It was found that an excess of reagents were required to achieve full consumption of the starting material; however, this resulted in the unavoidable formation of the bis-TES protected product **167** in a yield of 44%, along with the desired C36 mono-TES protected ether **166** in a yield of 48%. Interestingly, there was no evidence of mono-TES protection at the C37 hydroxyl. The mono-protection of **159** was assigned to the C36 hydroxyl, as opposed to the C37 hydroxyl, by analysis of the COSY spectrum. It was clear that the C37 CH showed a coupling interaction with an adjacent OH. On the other hand, the C36 CH no longer showed an observable coupling to an OH atom, confirming that the C36 OH had reacted. The rationale behind the regioselectivity for the reaction remains unclear. Factors taken into consideration include the steric environment of the C36 and C37 hydroxyl groups, a possible inductive effect from the THF oxygen, and hydrogen bonding; however there appears to be no obvious argument to explain the selectivity.

To provide further evidence that the hydroxyl at C36 had been regioselectively protected, compound **166** was treated with Dess-Martin periodinane (*Scheme 82*).



Scheme 82. a) DMP, NaHCO_3 , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt}$, 59%.

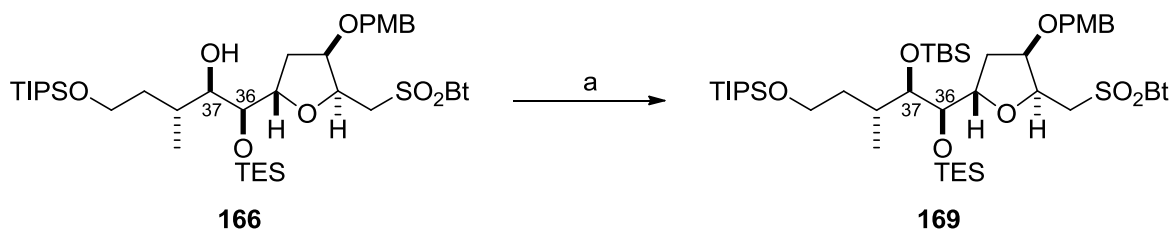
The disappearance of the OH doublet at 2.56 ppm in the ^1H NMR spectrum, along with the appearance of a peak at 212.6 ppm in the ^{13}C NMR spectrum, characteristic of a ketone C=O functionality, confirmed that an oxidation of the hydroxyl had taken place. A downfield shift of the C38 CH peak from 1.86 to 2.08 ppm and the C36 CH peak from 3.51 to 4.10 ppm were also observed in the ^1H NMR spectrum, which can be accounted for by the deshielding effect of the C37 ketone functionality. Furthermore, the COSY spectrum revealed that there was no longer a coupling interaction between the C38 or C36 CH with the C37 CH. These findings provided strong evidence for the regioselective silyl protection at the C36 hydroxyl of diol **159**.

In order to avoid the formation of undesired bis-protected product **167**, an attempt was made to perform the regioselective silylation of the secondary alcohol using triethylsilyl trifluoromethanesulfonamide (TESOTf) in the presence of triethylamine. It was anticipated that because TESOTf is a more reactive silylating reagent, fewer equivalents would be required to allow for the full consumption of the starting diol, minimising the formation of **167**. However, a non-selective reaction resulted upon treating diol **159** with 1.5 equivalents of TESOTf in the presence of triethylamine, furnishing bis-protected product **167** along with both mono-protected regioisomers, which proved difficult to separate by flash column chromatography. It is reasoned that the enhanced reactivity of TESOTf gave rise to the poor selectivity. Despite the formation of undesired bis-protected product **167**, treating diol

159 with TESCl, as opposed to TESOTf, proved to be a more efficient procedure, as the C37 regioisomer was not formed. With compound **166** in hand, it was anticipated that the C37 hydroxyl group could be converted to the desired TBS ether.

2.4.12 Completion of the synthesis of the C31-C40 fragment of PTX-4

In order to complete the synthesis of the FG fragment of PTX-4, and to match an intermediate to one that was previously synthesised by Evans, a *tert*-butyldimethylsilyl (TBS) group needed to be incorporated at the C37 hydroxyl. Initially, attempts were made to access **169** by the treatment of **166** with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in dichloromethane. Despite our best efforts to achieve the transformation by using a large excess of TBSCl, or by adding DMAP as an additional activator, the reaction was unsuccessful. In each case, there was no evidence to suggest the formation of **169**, and when exposed to the more forcing reaction conditions, indications of O-silyl migration to the adjacent C37 hydroxyl were observed. Following unsuccessful attempts at utilising TBSCl for the formation of **169**, attention turned to the use of the more reactive silylating reagent, *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). In the presence of TBSOTf and triethylamine in dichloromethane, compound **166** was successfully converted to the desired C31-C40 fragment of PTX-4 in an excellent yield of 92% (*Scheme 83*).



Scheme 83. a) TBSOTf (3.75 eq.), NEt₃, CH₂Cl₂, 92%.

The formation of the silyl ether was confirmed by the disappearance of the C36 OH doublet at 2.56 ppm in the ^1H NMR spectrum, along with the appearance of peaks between 0.98 and -0.04 ppm that corresponded to the TBS group. Furthermore, the structure of the C21-C30 fragment of PTX-4 was confirmed by comparison of the ^1H (not shown) and ^{13}C NMR spectroscopic data of **169** with that reported by Evans (*Table 6*).²⁶ In addition, the specific rotation was of the same magnitude and direction as described in the literature ($[\alpha]_{\text{D}}^{20} -9.7$ ($c = 1$, CH_2Cl_2), literature $[\alpha]_{\text{D}}^{20} -11.4$ ($c = 0.83$, CH_2Cl_2)), thus confirming the absolute configuration of the fragment.²⁶

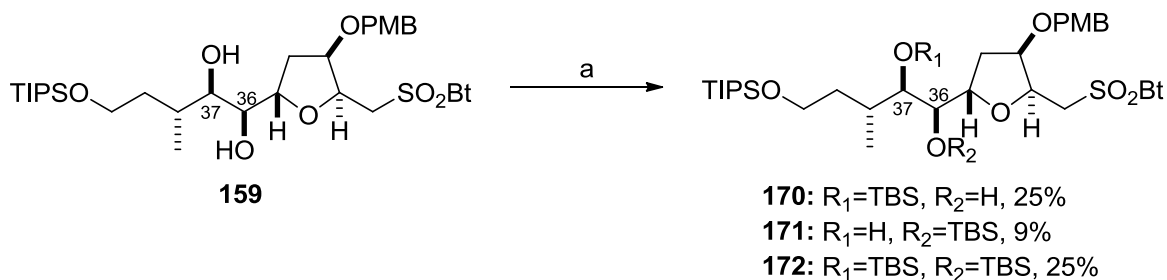
Literature ²⁶	Compound 169	Δ ppm	Assignment
166.5	166.3	-0.2	ArC
159.4	159.2	-0.2	ArC
152.9	152.7	-0.2	ArC
137.1	136.8	-0.3	ArC
130.0	129.9	-0.1	ArC
129.6	129.4	-0.2	ArC
128.2	127.9	-0.3	ArC
127.8	127.6	-0.2	ArC
125.7	125.5	-0.2	ArC
122.5	122.3	-0.2	ArC
113.8	113.7	-0.1	ArC
79.2	79.0	-0.2	CHOTBS
79.1	78.92	-0.2	CHOPMB
-	78.85	-	CHOTES
78.4	78.1	-0.3	CHOTESCH
75.2	74.9	-0.3	CHCH ₂ S
71.5	71.2	-0.3	OCH ₂ Ar
61.9	61.7	-0.2	SiOCH ₂
55.5	55.2	-0.3	OCH ₃
54.5	54.2	-0.3	SCH ₂
36.7	36.6	-0.1	SiOCH ₂ CH ₂
34.6	34.4	-0.2	CH ₂ CHOPMB
32.5	32.3	-0.2	CHCH ₃
26.2	26.0	-0.2	OSi(Me) ₂ C(CH ₃) ₃
18.4	18.2	-0.2	OSi(Me) ₂ C(Me) ₃
18.3	18.1	-0.2	((CH ₃) ₂ CH) ₃ SiO
17.3	17.1	-0.2	CHCH ₃
12.2	12.0	-0.2	((Me ₃) ₂ CH) ₃ SiO
7.2	7.0	-0.2	OSi(CH ₂ CH ₃) ₃
6.8	-	-	-
6.0	-	-	-
5.4	5.2	-0.2	OSi(CH ₂ CH ₃) ₃
-3.5	-3.7	-0.2	OSi(CH ₃) ₂ (^t Bu)
-4.3	-4.5	-0.2	OSi(CH ₃) ₂ (^t Bu)

Table 6. Comparison of ¹³C NMR data (100 MHz, CDCl₃) of **169** with that reported in the literature²⁶

The ^1H and ^{13}C NMR spectroscopic data for compound **169** both gave a very good match to the data reported by Evans.²⁶ However, two additional carbon peaks at 6.8 and 6.0 ppm were reported in Evans's ^{13}C NMR data that did not appear in the ^{13}C NMR spectrum of **169**. Upon counting the number of carbon peaks that are expected for compound **169**, it was realised that Evans had reported an additional two peaks (assuming that Evans also had two peaks coinciding at 79.1 ppm). As Evans did not assign the carbon NMR peaks in his data, it was not clear which carbons atoms the peaks at 6.8 and 6.0 ppm referred to. In addition, it should be noted that all carbon atoms of **169** can be accounted for exclusive of the peaks at 6.8 and 6.0 ppm. Further to this, the precursor to **169** in Evans's synthesis (the C36 unprotected analogue), did not have peaks at 6.8 and 6.0 ppm in the ^{13}C NMR data, which would indicate that the peaks at 6.8 and 6.0 ppm resulted from the subsequent TES-protection step. However, one would assume that the incorporation of a triethylsilyl group would result in an additional two carbon peaks in the silyl region, and not an additional four as reported. Also, when Evans subjected **169** to a C33 PMB-deprotection, despite no modification to the silyl ether functionalities, the ^{13}C NMR data of the resulting compound no longer contained the peaks at 6.8 or 6.0 ppm. Consequently, it was rationalised that the additional peaks in the silyl region of the ^{13}C NMR spectrum may have been reported in error, or were due to an impurity in the sample. However, to address any ambiguity we sought to match the characterisation data of a second compound, which had been synthesised by Evans.

The regioselective incorporation of a TBS ether at C37 was investigated. Initial attempts to protect diol **159** using TBSCl were unsuccessful, with starting material consistently being returned. However, it was found that the treatment of diol **159** with TBSOTf and triethylamine in dichloromethane, allowed for the full consumption of the starting material, along with the formation of three compounds (*Scheme 84*). These compounds were

assigned as the two mono-TBS protected regioisomers **170** and **171**, in yields of 25% and 9% respectively, along with bis-protected product **172** in a yield of 25%. Interestingly, the major regioisomer in this case was the C37 silyl ether, as opposed to the C36 silyl ether, which was the major regioisomer when diol **159** was treated with TESCl (see *Scheme 81*). However, the differences in the observed regioselectivity are not fully understood.



Scheme 84. a) TBSOTf (2.5 equiv.), NEt₃, CH₂Cl₂.

Despite the poor selectivity of the reaction, and the difficulty in separating regioisomers **170** and **171**, it was possible to obtain a sufficient quantity of the desired C37 TBS ether **170** to allow comparison of the ¹H (not shown) and ¹³C NMR (*Table 7*) data with that reported by Evans. Silyl ether formation at C37 was confirmed by analysis of the COSY NMR spectrum, which showed that the C37 CH no longer coupled to an OH atom, whereas the C36 CH did show a coupling interaction an OH atom.

Literature ²⁶	Compound 170	Δ ppm	Assignment
166.3	166.3	0.0	ArC
159.3	159.3	0.0	ArC
152.7	152.7	0.0	ArC
136.8	136.8	0.0	ArC
129.7	129.8	-0.1	ArC
129.4	129.4	0.0	ArC
127.9	127.9	0.0	ArC
127.7	127.6	0.0	ArC
125.5	125.5	0.0	ArC
122.3	122.3	0.0	ArC
113.8	113.8	0.0	ArC
79.5	79.5	0.0	CHOTBS
78.9	79.0	+0.1	CHOPMB
78.2	-	-	-
76.2	76.2	0.0	CHOHCH
76.1	76.1	0.0	CHCH ₂ S
72.0	72.0	0.0	CHOH
71.4	71.4	0.0	OCH ₂ Ar
61.0	61.0	0.0	SiOCH ₂
55.3	55.3	0.0	OCH ₃
54.6	54.6	0.0	SCH ₂
35.0	35.0	0.0	SiOCH ₂ CH ₂
33.6	33.63	0.0	CH ₂ CHOPMB
-	33.59	-	CHCH ₃
25.9	25.9	0.0	OSi(Me) ₂ C(CH ₃) ₃
18.2	18.2	0.0	OSi(Me) ₂ C(Me) ₃
18.0	18.0	0.0	((CH ₃) ₂ CH) ₃ SiO
15.0	15.0	0.0	CHCH ₃
11.9	11.9	0.0	(Me) ₂ CH) ₃ SiO
-4.2	-4.2	0.0	OSi(CH ₃) ₂ (tBu)
-4.5	-4.5	0.0	OSi(CH ₃) ₂ (tBu)

Table 7. Comparison of ¹³C NMR data (100 MHz, CDCl₃) of **170** with that reported in the literature²⁶

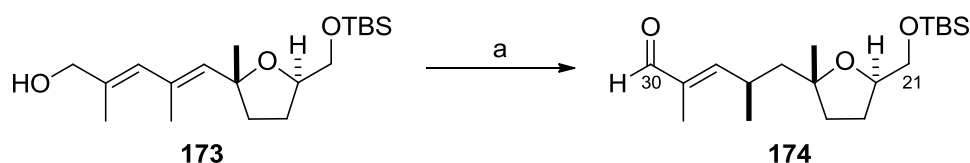
Once again, a very good match of the ¹H and ¹³C NMR data was observed. However, it should be noted that an additional peak at 78.2 ppm was reported by Evans that was not

present in the ^{13}C NMR spectrum of **170**. Upon counting the number of carbon atoms that would be expected to appear in the 50-100 ppm region, it was found that Evans had reported an additional peak. Once again, all of the carbons atoms of **170** can be accounted for exclusive of the peak at 78.2 ppm, and therefore it was postulated that the peak at 78.2 ppm may have also been reported in error. Promisingly, the peaks in the silyl region of the ^{13}C NMR spectrum, which was the area of inconsistency with **169**, matched perfectly in this case. Consequently, it was concluded that aside from minor discrepancies, the C31-C40 fragment of PTX-4 was a very good match with that synthesised by Evans, and attention turned to the assembly of the FG fragment with the E-ring portion of PTX-4.

2.5 Assembly of the FG- and E-ring fragments

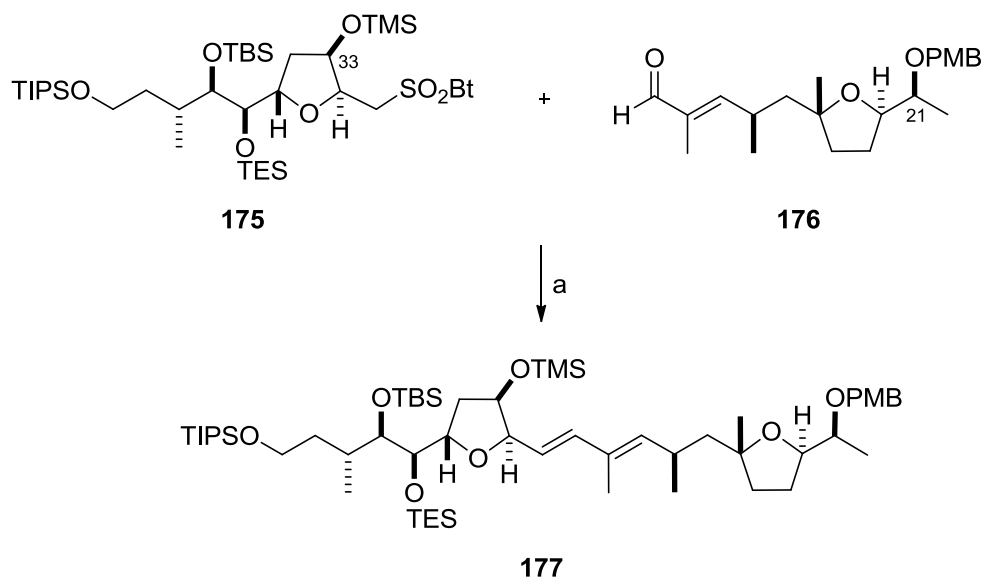
Following the successful synthesis of the C21-C40 fragment of PTX-4, it was anticipated that a modified Julia olefination could be carried out in order to join the FG portion with the E-ring aldehyde, in an analogous fashion to that used in Evans's synthesis. The C30-C21 fragment **173** was synthesised by a co-worker in 12 steps from commercially available starting materials.¹¹² The fragment was provided as a 2:1 mixture of diastereomers, which were unfortunately inseparable at this stage, and it was not possible to determine which chiral centre of the C30-C21 fragment had epimerised during the synthesis. However, investigation into the Julia olefination ensued. In order to prepare fragment **173** for the modified Julia olefination, it was necessary to oxidise the alcohol to the corresponding aldehyde. It was rationalised that a Parikh-Doering oxidation could be utilised for the transformation (*Scheme 85*).²⁷ Thus, treatment of alcohol **173** with dimethylsulfoxide (DMSO) in the presence of SO_3 -pyridine and triethylamine, provided

the desired Julia olefination coupling partner **174** in an excellent yield of 84% (Scheme 85).



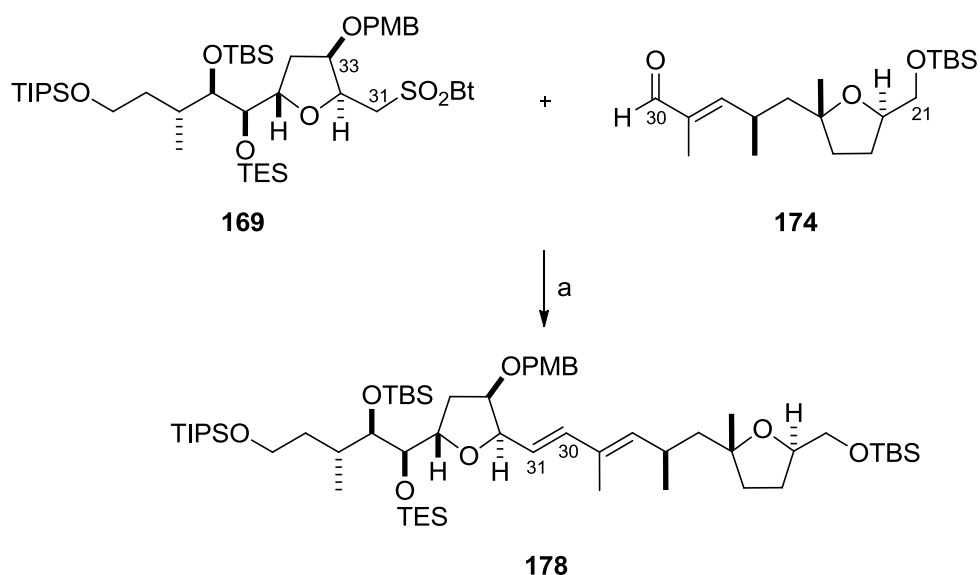
Scheme 85. a) $\text{SO}_3\cdot\text{py}$, NEt_3 , CH_2Cl_2 , DMSO , $-10\text{ }^\circ\text{C}$, 84%.

The formation of aldehyde **174** was confirmed by the presence of a distinct singlet at 9.39 ppm in the ^1H NMR spectrum, corresponding to the CHO proton. With the desired aldehyde in hand, the construction of the C31-C30 bond was attempted via a modified Julia olefination.¹¹³ It has been shown that the benzothiazole sulfone moiety plays a crucial role in the mechanism of the olefination, influencing both the selectivity of the reaction and acting as a leaving group to allow for the formation of the corresponding alkene.¹¹³ Julia and co-workers found that the olefination is best performed under Barbier-type conditions, where the base is added to a pre-mixed solution of the aldehyde and sulfone.¹¹³ This is necessary to avoid the possibility of the sulfonyl carbanion, produced upon treating the sulfone with base, undergoing self-condensation with a second equivalent of sulfone, which could occur in the absence of the aldehyde coupling partner. It is also known that the geometry of the resulting alkene, which is required to be (*E*) in this case, can be influenced by the choice of base and solvent.¹¹⁴ Following extensive model studies by Evans, it was found that the optimal conditions for the formation of the desired coupled adduct **177** were lithium bis(trimethylsilyl)amide (LiHMDS) in THF at $-78\text{ }^\circ\text{C}$ (Scheme 86).²⁶



Scheme 86. Evans's Julia olefination strategy: *a*) LiHMDS, THF, -78 °C → 0 °C, 100%.

It was anticipated that application of the above conditions to the reaction of sulfone **169** and aldehyde **174**, which differ from Evans at C21 and C33, would allow for the formation of the desired (*E*)-alkene C21-C40 fragment of PTX-4. Pleasingly, treatment of a solution of sulfone **169** and aldehyde **174** in THF at -78 °C with LiHMDS, allowed for the rapid formation of diene **178** in a quantitative yield (Scheme 87).



Scheme 87. *a*) LiHMDS, THF, -78 °C → 0 °C, 100%.

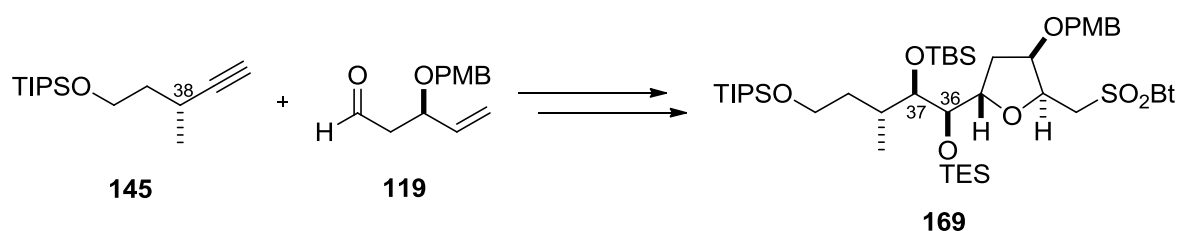
The formation of the C30-C31 alkene of **178** was confirmed by the appearance of peaks at 6.24 and 5.77 ppm in the ^1H NMR spectrum corresponding to the 1,2-disubstituted $\text{CH}=\text{CH}$. In addition to this, the geometry of the alkene was identified by the observation of the coupling constant of $\text{CH}=\text{CH}$. This was measured as 15.4 Hz, which is characteristic of a *trans*-alkene and confirms the formation of the desired (*E*)-alkene as the major product. However, examination of the ^1H NMR spectrum revealed that **178** had been obtained as a mixture of diastereomers. Due to the diastereomeric mixture of the starting aldehyde, it was difficult to fully establish the efficiency of the reaction. In the meantime, a co-worker was able to provide a small amount of aldehyde **174** as an improved 4:1 mixture of diastereomers, allowing the Julia olefination to be re-attempted on material of a higher diastereomeric purity. Unfortunately, upon subjecting aldehyde **174** and sulfone **169** to the modified Julia olefination, a mixture of diastereomers was obtained once again. Several explanations could account for the mixture, including the diastereomeric mixture of the starting aldehyde, and poor *E/Z*-selectivity or epimerisation at C32, which was also witnessed by Evans.²¹ During his initial investigations into the Julia olefination of **175** and **176**, Evans found that there was a significant counter-ion effect.²⁶ The use of potassium bis(trimethylsilyl)amide (KHMDs) resulted in a 29:71 mixture of epimers at C32, favouring the undesired *cis*-tetrahydrofuran, whereas employing LiHMDs as the base resulted in a 95:5 mixture in favour of the desired *trans*-tetrahydrofuran.²⁶ It was postulated that the epimerisation was a result of tetrahydrofuran ring cleavage *via* β -alkoxy elimination and re-addition to the intermediate vinyl sulfone.²⁶ Evidently, the success of the Julia olefination is very dependent on the base used, and consequently it was realised that once aldehyde **174** can be produced as a single diastereomer, further optimisation of the Julia olefination of sulfone **169** and aldehyde **174** could potentially provide a highly efficient method for the formation of the C21-C40 fragment of PTX-4. The potential for

the utilisation of the Julia olefination strategy as the key step in the assembly of the FG portion and E-ring portion of PTX-4 has been demonstrated, with the synthesis of the C21-C40 fragment of PTX-4 being achieved, albeit as a mixture of diastereomers. Further investigations into the selectivity of this reaction are on-going in the laboratory.

2.6 Conclusions

In summary, a short and efficient synthesis of the C31-C40 fragment of PTX-4 was accomplished in 18 total synthetic steps (13 steps longest linear sequence), which is the shortest known synthesis to date (

Scheme 88).

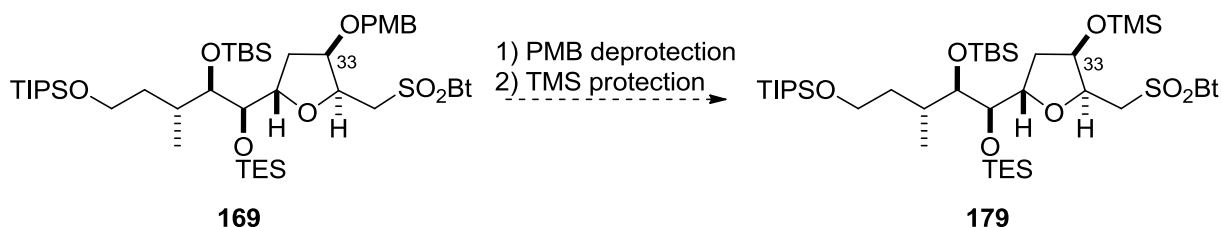


Scheme 88. Synthesis of C31-C40 fragment of PTX-4

The key transformations in this synthesis include an enzymatic resolution for the synthesis of aldehyde **119**, a diastereoselective alkylation to incorporate the C38 chiral methyl group of alkyne **145**, a cobalt-catalysed oxidative cyclisation to furnish the F-ring of PTX-4, and a selective silyl protection of 1,2-diol **159**. The synthesis of compound **169** was achieved in an overall yield of 1.8% from commercially available starting materials, and the full spectroscopic data proved to be a very good match with that reported in the literature.²⁶ After achieving access to the C31-C40 fragment of PTX-4, it was demonstrated that a modified Julia olefination could be utilised for the assembly of the FG and E-ring fragments, providing the C21-C40 fragment of PTX-4.

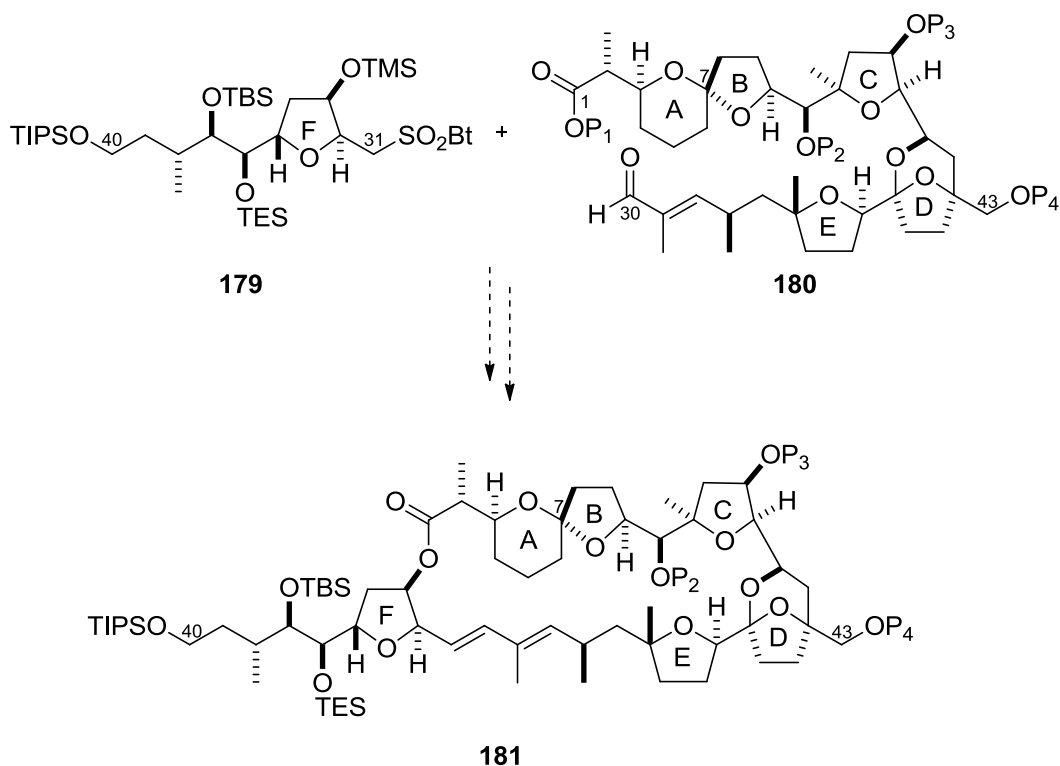
2.7 Future work

It is anticipated that in the total synthesis of PTX-4, C31-C40 fragment **169** would be incorporated by means of a modified Julia olefination to the ABCDE aldehyde, in an analogous manner to the strategy employed by Evans.²¹ In order to allow for the subsequent macrolactonisation onto the C33 hydroxyl group, it would be essential to exchange the C33 PMB ether to a more labile protecting group e.g. TMS, which would be readily cleaved prior to lactonisation (*Scheme 89*).



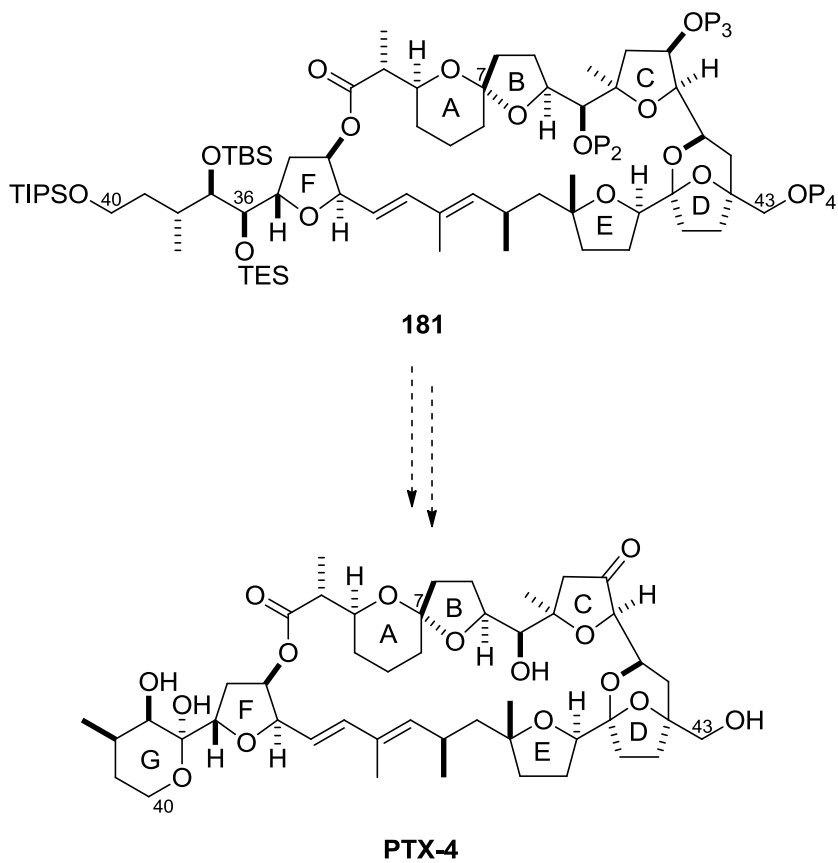
Scheme 89. Protecting group manipulation of 169

From this point, it was predicted that subjecting **179** and **180** to the Julia olefination would install the *trans*-alkene at C31-C30, resulting in the construction of the C1-C40 backbone of PTX-4. Subsequent deprotection of the C33 TMS ether and exposure of the C1 carboxylic acid would prepare the fragment for lactonisation. Employing similar conditions to Evans, the formation of macrocycle **181** could be achieved (*Scheme 90*).



Scheme 90. Formation of macrocycle

Following the successful macrolactonisation to form **181**, formation of the hemiacetal G-ring and the completion of the synthesis of PTX-4 would be achieved by a selective deprotection and oxidation at C14 and C36, followed by a global deprotection (*Scheme 91*). Upon revealing the C40 hydroxyl group, cyclisation onto the C36 ketone would result in the construction of the G-ring to deliver PTX-4, as demonstrated by Evans.²¹



Scheme 91. Completion of the synthesis of PTX-4

Chapter 3

Experimental Section

3.1 Experimental Techniques

^1H NMR spectra were recorded using a Bruker AC 200 (200 MHz), Bruker AVANCE AV400 (400 MHz) or a Bruker AVANCE AV 500 (500 MHz) spectrometer in CDCl_3 or C_6D_6 . Chemical shifts (δ) were quoted in parts per million (ppm) relative to residual solvent peaks or to tetramethylsilane (SiMe_4) as an internal standard. Signal splittings are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), m (multiplet), and br. (broad). Coupling constants (J) are quoted in Hertz (Hz). Assignments were aided by correlation spectroscopy (COSY) and heteronuclear multiple-quantum correlation (HMQC) where necessary.

^{13}C NMR spectra were recorded using a Bruker AVANCE AV400 (100 MHz) or a Bruker AVANCE AV 500 (125 MHz) spectrometer in CDCl_3 or C_6D_6 and were referenced to the corresponding deuterated solvent. ^1H and ^{13}C NMR spectra were recorded at room temperature. NOE spectra were obtained on a Bruker DRX-500 (500 MHz) spectrometer.

Infrared (IR) spectra were recorded on a Bruker Tensor 27 Fourier Transform-Infrared spectrometer, analysing compounds as thin films. Absorption maxima, ν_{max} , are quoted in wavenumbers (cm^{-1}).

High resolution mass spectroscopy (HRMS) were recorded on a Bruker MicroTof spectrometer under the conditions of electrospray ionization (ESI). Values are reported as a ratio of mass to charge in Daltons.

Specific optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter using the sodium D line (589.3 nm), and are quoted in the units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ with solution concentration given in units of $10^{-2} \text{ g cm}^{-3}$.

Melting points were measured using a Leica VMTG melting point apparatus and are recorded uncorrected.

Flash column chromatography was performed according to the method described by Still *et al.*¹¹⁵ using Merck silica gel (60 Å, 40-63 µm) with the specified solvent system and head pressure by means of bellows. The column fractions and reactions were monitored by thin-layer chromatography (TLC) using Merck Kieselgel 60 F₂₅₄ 0.25mm pre-coated aluminium-backed silica plates. Compounds were visualised under UV light ($\lambda_{\text{max}} = 254 \text{ nm}$) and/or by staining with potassium permanganate, vanillin or phosphomolybdic acid solution as appropriate, followed by vigorous heating.

Reagents obtained from Acros, Aldrich, Alfa, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly as supplied or purified according to the procedures outlined by Perrin and Amarego.¹¹⁶

Reactions were carried out under an atmosphere of argon using flame-dried glassware where anhydrous conditions were required.

Acetonitrile, dichloromethane, diethyl ether, methanol, pentane, tetrahydrofuran and toluene were purified prior to use by filtration through two activated alumina columns,

employing the method of Grubbs *et al.*¹¹⁷ Petrol refers to the fraction of light petroleum ether that boils in the range of 30-60 °C. Ether refers to diethyl ether.

3.2 General Procedures

General Procedure A: Co(modp)₂ oxidative cyclisation⁵²

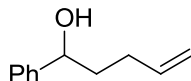
To a solution of *alcohol* (0.617 mmol) in ⁱPrOH (6.0 mL) was added Co(modp)₂ (as stated) and *tert*-butyl hydroperoxide (5.5 M in decane, amount as stated). The reaction was stirred at 60 °C (unless otherwise stated) under a stationary oxygen atmosphere (balloon) until all starting material had been consumed (monitored by TLC). The reaction mixture was allowed to cool to room temperature and was quenched by the addition of a saturated aqueous solution of Na₂SO₃ (6 mL). The organic layer was washed with a saturated aqueous solution of Na₂SO₃ (3 x 6 mL) and the combined aqueous fractions were extracted with Et₂O (4 x 5 mL). The combined organic fractions were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified as stated.

General Procedure B: Co(nmp)₂ oxidative cyclisation⁷²

To a flask containing Co(nmp)₂ (as stated) under a stationary oxygen atmosphere (balloon), was added a solution of *alcohol* (0.617 mmol) in ⁱPrOH (6.0 mL) followed by *tert*-butyl hydroperoxide (5.5 M in decane, amount as stated). The reaction was stirred at 60 °C (unless otherwise stated) until all starting material had been consumed (monitor by TLC). The reaction mixture was allowed to cool to room temperature and was concentrated *in vacuo*. The crude product was then purified as stated.

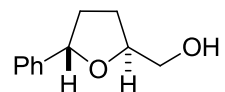
3.3 Experimental Procedures

(±)-1-Phenylpent-4-en-1-ol (43)



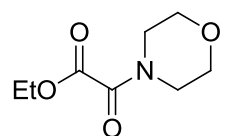
To a stirred mixture of magnesium turnings (360 mg, 14.8 mmol) in THF (6.0 mL) at 0 °C was dropwise added 4-bromo-1-butene (750 μ L, 7.41 mmol), and the mixture was heated to reflux for 2 h. The reaction mixture was cooled to 0 °C and added to a solution of benzaldehyde (350 μ L, 2.96 mmol) in THF (3.0 mL), and allowed to stir at room temperature for 2 h. The reaction mixture was then cooled to 0 °C and was quenched carefully by the addition of a saturated solution of NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 x 25 mL) and the combined organic fractions were dried over MgSO_4 , filtered and concentrated *in vacuo* to afford a pale yellow oil. Purification by flash column chromatography (0-10% Et_2O /petrol) afforded the title compound as a colourless oil (343 mg, 72%).

δ_{H} (400 MHz, CDCl_3) 7.37-7.27 (m, 5H, ArCH), 5.86 (tdd, 1H, J 17.0, 10.3, 6.3, $\text{CH}=\text{CH}_2$), 5.08-4.99 (m, 2H, $\text{CH}=\text{CH}_2$), 4.74 (dd, 1H, J 7.4, 5.9, CHOH), 2.21-2.07 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.96-1.77 (m, 2H, CHOH CH_2); δ_{C} (100 MHz, CDCl_3) 144.6 (ArC), 138.2 ($\text{CH}=\text{CH}_2$), 128.5 (ArC), 127.6 (ArC), 125.9 (ArC), 115.0 ($\text{CH}=\text{CH}_2$), 74.0 (CHOH), 38.1 (CHOH CH_2), 30.1 ($\text{CH}_2\text{CH}=\text{CH}_2$). Spectroscopic data consistent with that reported in literature.¹¹⁸

(±)-((2S,5S)-5-Phenyltetrahydrofuran-2-yl)methanol (44)

Alcohol 43 (100 mg, 0.617 mmol) was subjected to **General Procedure A** (4 h) using Co(modp)_2 (67 mg, 0.12 mmol, 20 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 70 μL , 0.37 mmol). Purification by flash column chromatography (10-40% Et_2O /petrol) afforded the title compound as a colourless oil (61 mg, 55 %).

δ_{H} (400 MHz, CDCl_3) 7.35 (d, 4H, J 4.3, ArCH), 7.28 (dq, 1H, J 8.7, 4.1, ArCH), 5.00 (dd, 1H, J 8.0, 6.1, PhCH), 4.42-4.35 (m, 1H, CHCH₂OH), 3.75 (dd, 1H, J 11.6, 3.1, CH_AH_BOH), 3.60 (dd, 1H, J 11.6, 6.1, CH_AH_BOH), 2.41-2.35 (m, 1H, CH_AH_BCH₂), 2.12-2.04 (m, 2H, CH_AH_BCH₂ and OH), 1.95-1.79 (m, 2H, CH₂CH₂); δ_{C} (100 MHz, CDCl_3) 142.9 (ArC), 128.4 (ArC), 128.1 (ArC), 127.4 (ArC), 125.6 (ArC), 80.9 (PhCH), 80.1 (CHCH₂OH), 65.1 (CH₂OH), 35.4 (CH₂CH₂), 27.9 (CH₂CH₂). Spectroscopic data consistent with that reported in literature.⁷⁹

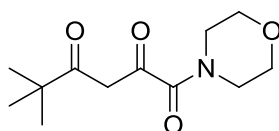
Ethyl 2-morpholino-2-oxoacetate (75)

Morpholine (1.00 mL, 11.5 mmol) and diethyl oxalate (2.00 mL, 11.5 mmol) were stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and was purified by flash column chromatography (20-40% EtOAc/petrol) to afford the title compound as a colourless oil (2.13 g, 99%).

δ_{H} (400 MHz, CDCl_3) 4.33 (q, 2H, J 7.2, CH₃CH₂O), 3.74-3.70 (m, 4H, 2 x CH₂O), 3.66-3.63 (m, 2H, NCH₂), 3.48-3.45 (m, 2H, NCH₂), 1.36 (t, 3H, J 7.1, CH₃CH₂O); δ_{C} (100 MHz, CDCl_3) 162.4 (C=O), 160.1 (CH₂OC=O), 66.6 (CH₂O), 66.4 (CH₂O), 62.3

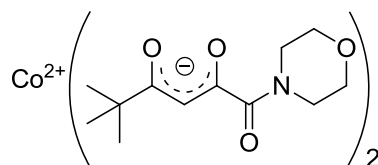
(CH₃CH₂O), 46.4 (NCH₂), 41.7 (NCH₂), 14.0 (CH₃CH₂O). Spectroscopic data consistent with that reported in literature.¹¹⁹

5,5-Dimethyl-1-morpholinohexane-1,2,4-trione (76)



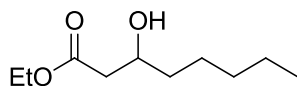
To a suspension of potassium *tert*-butoxide (648 mg, 5.77 mmol) in toluene (10 mL) was added a toluene solution (2.0 mL) of 3,3-dimethylbutan-2-one (720 μ L, 5.77 mmol) and ester **75** (900 mg, 4.81 mmol). The reaction mixture was stirred for 1.5 h at 100 °C before being allowed to cool to room temperature. The reaction mixture was quenched by the addition of 10% aq. HCl (10 mL) and stirred for 30 minutes. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic fractions were washed with brine, dried over Na₂SO₄, filtered, and solvents removed *in vacuo* to afford the crude material as a viscous yellow oil. Purification by flash column chromatography (0-15% EtOAc/petrol) afforded the title compound as a pale yellow oil (548 mg, 47%) as a mixture of keto-enol tautomers (1:4.7).

δ_{H} (400 MHz, CDCl₃) (* denotes minor tautomer peak) 6.03 (d, 1H, *J* 3.9, C=CH), 4.05* (d, 2H, *J* 3.8, COCH₂CO), 3.75-3.63 (m, 8H, 4 x CH₂), 1.23-1.17 (m, 9H, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 201.2 (C=O), 184.7 (C=O), 163.9 (C=O), 95.5 (C=CH), 67.0 (CH₂O), 66.6 (CH₂O), 46.7 (NCH₂), 42.3 (NCH₂), 39.1 (C(CH₃)₃), 27.2 (CH₃), 26.8 (CH₃), 26.0 (CH₃). Spectroscopic data consistent with that reported in literature.⁶³

Co^{II}(modp)₂

To an aqueous solution (2.0 mL) of NaOH (17 mg, 0.42 mmol) and *modp ligand 76* (100 mg, 0.415 mmol) was slowly added an aqueous solution (50 μ L) of cobalt(II) chloride (49 mg, 0.21 mmol). After the mixture had been stirred at 60 $^{\circ}$ C for 2 h, the precipitate was separated by filtration, washed with water, and dried *in vacuo* to afford the title compound as a light brown powder (53 mg, 47%).

HRMS (ESI⁺) C₂₄H₃₇N₂O₈Co requires 540.1876, found [M+H]⁺ 540.1875; **IR** ν_{max} (film)/cm⁻¹ 2964, 1596, 1521, 1114, 1067. Spectroscopic data consistent with that reported in literature.⁶³

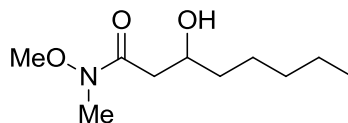
(±)-Ethyl 3-hydroxyoctanoate (80)

To a stirred solution of diisopropylamine (4.3 mL, 31 mmol) in THF (77 mL) at 0 $^{\circ}$ C was added *n*-butyllithium (1.6 M in hexanes, 19.3 mL, 30.9 mmol). The reaction mixture was stirred for 20 minutes before being cooled to -78° C. Freshly distilled ethyl acetate (2.9 mL, 30 mmol) was added dropwise and the mixture stirred for 30 minutes at -78° C. Hexanal (1.2 mL, 10 mmol) was then added dropwise and the reaction mixture was then stirred at -78° C for 4.5 h. The reaction was quenched by the dropwise addition of a saturated solution of NH₄Cl and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to

afford a yellow oil. Purification by flash column chromatography (10-25% Et₂O/petrol) furnished the title compound as a pale yellow oil (1.53 g, 81%).

δ_{H} (400 MHz, CDCl₃) 4.17 (q, 2H, *J* 7.1, CH₃CH₂O), 4.07-3.90 (m, 1H, CHOH), 2.55-2.46 (m, 1H, COCH_AH_BCHOH), 2.45-2.35 (m, 1H, COCH_AH_BCHOH), 1.62-1.37 (m, 3H, CH₃CH₂O), 1.37-1.21 (m, 8H, 4 x (CH₂)₄CH₃), 0.96-0.80 (m, 3H, (CH₂)₄CH₃); δ_{C} (100 MHz, CDCl₃) 173.2 (C=O), 68.0 (CHOH), 60.7 (CH₂O), 41.3 (COCH₂), 36.5 (CHOHCH₂), 31.7 (CHOH(CH₂)₂CH₂), 25.2 (CHOHCH₂CH₂), 22.6 (CHOH(CH₂)₃CH₂), 14.2 (CH₃CH₂O), 14.0 ((CH₂)₄CH₃). Spectroscopic data consistent with that reported in literature.⁸⁰

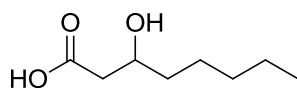
(±)-3-Hydroxy-*N*-methoxy-*N*-methyloctanamide (81)



To a suspension of *N,O*-dimethylhydroxylamine hydrochloride (389 mg, 3.98 mmol) in THF (4.0 mL) at 0 °C was dropwise added trimethylaluminium (2.0 M in hexanes, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at 0 °C for 1 h. After this time, ester **80** (300 mg, 1.60 mmol) in THF (1.0 mL) was added and the reaction mixture heated to reflux for 19 h. The reaction mixture was then cooled to 0 °C and carefully quenched by the dropwise addition of 1.0 M HCl (3.0 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), and the combined organic fractions were dried over MgSO₄, filtered and concentrated *in vacuo* to afford an orange oil. Purification by flash column chromatography (10-20% EtOAc/petrol) provided the title compound as a yellow oil (63 mg, 20%).

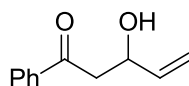
δ_{H} (400 MHz, CDCl_3) 4.07-3.97 (m, 1H, CHOH), 3.80 (br. s, 1H, OH), 3.69 (s, 3H, CH_3O), 3.19 (s, 3H, NCH_3), 2.66 (d, 1H, J 16.7, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.44 (dd, 1H, J 16.7, 9.6, $\text{COCH}_\text{A}\text{H}_\text{B}$), 1.61-1.22 (m, 8H, 4 x CH_2), 0.89 (t, 3H, J 6.4, $(\text{CH}_2)_4\text{CH}_3$); δ_{C} (100 MHz, CDCl_3) 173.9 ($\text{C}=\text{O}$), 67.9 (CHOH), 61.2 (CH_3O), 38.2 (COCH_2), 36.5 (CHOHCH_2), 31.8 (NCH_3), 25.2 (CH_2), 25.2 (CH_2), 22.6 (CH_2CH_3), 14.0 ($(\text{CH}_2)_4\text{CH}_3$); **HRMS** (ESI^+) $\text{C}_{10}\text{H}_{21}\text{NNaO}_3$ requires 226.1414, found $[\text{M}+\text{Na}]^+$ 226.1416; **IR** ν_{max} (film)/ cm^{-1} 3444 br., 2932, 2859, 1644, 1464, 1388.

($\pm$)-3-Hydroxyoctanoic acid (82**)**



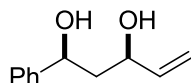
To a solution of *ester* **80** (250 mg, 1.33 mmol) in THF (2.7 mL) and water (2.7 mL) at 0 °C was added lithium hydroxide monohydrate (167 mg, 3.98 mmol). The reaction mixture was stirred for 1.5 h whilst warming to room temperature and was then washed with EtOAc (2 x 5 mL). The aqueous layer was acidified to pH 2 by the dropwise addition of conc. HCl and was extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a pale yellow oil, which was purified by flash column chromatography (10-40% EtOAc/petrol). The title compound was isolated as a pale yellow oil (170 mg, 80%).

δ_{H} (400 MHz, CDCl_3) 4.07-4.02 (m, 1H, CHOH), 2.58 (dd, 1H, J 16.6, 3.0, $\text{COCH}_\text{A}\text{H}_\text{B}\text{CHOH}$), 2.47 (dd, 1H, J 16.4, 9.0, $\text{COCH}_\text{A}\text{H}_\text{B}\text{CHOH}$), 1.59-1.27 (m, 8H, 4 x CH_2), 0.90 (t, 3H, J 6.4, $(\text{CH}_2)_4\text{CH}_3$); δ_{C} (100 MHz, CDCl_3) 177.8 ($\text{C}=\text{O}$), 68.1 (CHOH), 41.1 (COCH_2), 36.4 (CHOHCH_2), 31.7 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 25.1 ($\text{CHOHCH}_2\text{CH}_2$), 22.6 (CH_2CH_3), 14.0 ($(\text{CH}_2)_4\text{CH}_3$). Spectroscopic data consistent with that reported in literature.¹²⁰

(±)-3-Hydroxy-1-phenylpent-4-en-1-one (86)

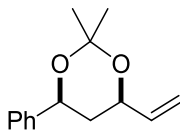
To a solution of diisopropylamine (3.9 mL, 28 mmol) in THF (70 mL) at 0 °C was dropwise added *n*-butyllithium (1.6 M in hexanes, 17.3 mL, 27.7 mmol) and the mixture stirred at 0 °C for 30 minutes. After being cooled to −78 °C, acetophenone (3.1 mL, 27 mmol) was added dropwise and the reaction mixture stirred at −78 °C for 30 minutes. Acrolein (600 μL, 8.92 mmol) was added and after stirring for 3 h at −78 °C, the reaction was quenched by the addition of a saturated solution of NH₄Cl (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), the combined organic fractions washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated to afford a yellow oil. Purification by flash column chromatography (10-40% Et₂O/petrol) provided the title compound as a pale yellow oil (1.26 g, 80%).

δ_{H} (400 MHz, CDCl₃) 8.01-7.93 (m, 2H, ArCH), 7.63-7.54 (m, 1H, ArCH), 7.53-7.44 (m, 2H, ArCH), 5.98 (ddd, 1H, *J* 17.2, 10.6, 5.6, CH=CH₂), 5.42-5.33 (m, 1H, CH=CH_AH_B), 5.23-5.15 (m, 1H, CH=CH_AH_B), 4.82-4.73 (m, 1H, CHOH), 3.34 (d, 1H, *J* 3.8, COCH_AH_B), 3.24-3.18 (m, 2H, COCH_AH_B and OH); δ_{C} (100 MHz, CDCl₃) 200.1 (C=O), 139.1 (CH=CH₂), 136.6 (ArC), 133.6 (ArC), 128.7 (ArC), 128.1 (ArC), 115.2 (CH=CH₂), 68.8 (CHOH), 44.8 (CH₂). Spectroscopic data consistent with that reported in literature.¹²¹

(±)-(1*S*,3*R*)-1-Phenylpent-4-ene-1,3-diol (87)

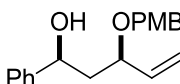
To a solution of β -hydroxyketone **86** (0.50 g, 2.8 mmol) in THF (43 mL) at $-78\text{ }^{\circ}\text{C}$ was dropwise added diisobutylaluminium hydride (1.0 M in hexanes, 7.1 mL, 7.1 mmol) and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. The reaction was quenched by the sequential addition of MeOH (1.5 mL), a saturated solution of Rochelle's salt (20 mL) and Et₂O (10 mL). The cold bath was removed and the mixture was stirred vigorously whilst warming to room temperature. The two layers were separated and the aqueous layer extracted with Et₂O (3 x 40 mL). The combined organic fractions were dried over Na₂SO₄, filtered and concentrated to afford a colourless oil. Purification by flash column chromatography (5-25% EtOAc/petrol) delivered the title compound as a colourless oil (431 mg, 85%), consisting of a mixture of diastereomers (87:13, *syn:anti*).

δ_{H} (400 MHz, CDCl₃) (*denotes minor diastereomer) 7.43-7.25 (m, 5H, ArCH), 5.94-5.83 (m, 1H, CH=CH₂), 5.27 (dd, 1H, *J* 17.2, 1.3, CH=CH_AH_B), 5.11 (dd, 1H, *J* 10.4, 1.3, CH=CH_AH_B), 5.03* (dd, 1H, *J* 8.8, 2.3, PhCHOH), 4.96 (dd, 1H, *J* 9.9, 2.0, PhCHOH), 4.48-4.40 (m, 1H, CHOHCH=CH₂), 3.08 (br. s, 2H, 2 x OH), 1.99-1.79 (m, 2H, CH₂); δ_{C} (100 MHz, CDCl₃) 144.2 (ArC), 140.4 (CH=CH₂), 128.5 (ArC), 125.7 (ArC), 125.6 (ArC), 114.7 (CH=CH₂), 74.7 (CHOH), 73.4 (PhCHOH), 45.2 (CH₂). Spectroscopic data consistent with that reported in literature.¹²²

(±)-(4*S*,6*R*)-2,2-Dimethyl-4-phenyl-6-vinyl-1,3-dioxane (88)

A solution of *1,3-diol* **87** (50 mg, 0.28 mmol) and *p*-toluenesulfonic acid monohydrate (cat.) in 2,2-dimethoxy propane (1.0 mL) was stirred at room temperature for 1 h. After dilution with EtOAc (10 mL), the mixture was washed with a saturated solution of NaHCO₃ (10 mL) and brine (10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford a yellow oil. Purification by flash column chromatography (10% Et₂O/petrol) provided the title compound as a colourless oil (43 mg, 70%).

δ_{H} (400 MHz, CDCl₃) 7.45-7.33 (m, 4H, ArCH), 7.33-7.24 (m, 1H, ArCH), 5.88 (ddd, 1H, *J* 17.0, 10.8, 5.8, CH=CH₂), 5.32 (d, 1H, *J* 17.4, CH=CH_AH_B), 5.17 (d, 1H, *J* 10.6, CH=CH_AH_B), 4.97 (dd, 1H, *J* 11.7, 2.4, PhCHO), 4.54 (dd, 1H, *J* 11.0, 6.2, OCHCH=CH₂), 1.81 (dt, 1H, *J* 13.1, 2.5, CH_AH_B), 1.67-1.60 (m, 4H, CH_AH_B and CH₃), 1.56 (s, 3H, CH₃); δ_{C} (100 MHz, CDCl₃); 142.2 (ArC), 138.5 (CH=CH₂), 128.5 (ArC), 127.7 (ArC), 126.0 (ArC), 115.7 (CH=CH₂), 99.2 (C(CH₃)₂), 71.3 (PhCHO), 70.4 (OCHCH=CH₂), 39.0 (CH₂), 30.3 (CH₃), 19.8 (CH₃). Spectroscopic data consistent with that reported in literature.¹²³

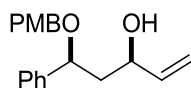
(±)-(1*S*,3*R*)-3-((4-Methoxybenzyl)oxy)-1-phenylpent-4-en-1-ol (89)

A solution of *1,3-diol* **87** (500 mg, 2.81 mmol) in DMF (3.0 mL) was added dropwise to a vigorously-stirred solution of sodium hydride (60% dispersion in mineral oil, 135 mg, 3.37 mmol) in DMF (7.0 mL) at 0 °C under Ar. After 30 minutes, a solution of 4-methoxybenzyl chloride (460 μ L, 3.37 mmol) in DMF (4.0 mL) was added dropwise and

the reaction mixture was stirred for 1.5 h whilst warming to room temperature. After this time the reaction was quenched by the addition of ice-cold water, and the aqueous phase extracted with Et₂O (3 x 10 mL). The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford a yellow oil, which was purified by flash column chromatography (40% Et₂O/petrol). The title compound was furnished as a colourless oil (385 mg, 46%), along with its undesired regioisomer (235 mg, 28%).

δ_{H} (400 MHz, CDCl₃) 7.37-7.24 (m, 7H, ArCH), 6.91 (d, 2H, *J* 8.3, ArCH), 5.77 (ddd, 1H, *J* 17.4, 9.7, 8.2, CH=CH₂), 5.33-5.25 (m, 2H, CH=CH₂), 4.89 (dd, 1H, *J* 9.6, 2.8, CHOH), 4.62 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.35 (d, 1H, *J* 11.4, OCH_AH_BAr), 4.15-4.07 (m, 1H, CHOPMB), 3.83 (s, 3H, OCH₃), 2.08 (dt, 1H, *J* 14.5, 9.8, CH_AH_B), 1.82 (dt, 1H, *J* 14.5, 3.0, CH_AH_B); δ_{C} (100 MHz, CDCl₃) 159.3 (ArC), 144.3 (ArC), 137.9 (CH=CH₂), 129.8 (ArC), 129.7 (ArC), 128.3 (ArC), 127.3 (ArC), 125.7 (ArC), 117.8 (CH=CH₂), 113.9 (ArC), 80.8 (CHOPMB), 73.8 (CHOH), 69.9 (OCH₂Ar), 55.3 (OCH₃), 45.0 (CH₂); **HRMS** (ESI⁺) C₁₉H₂₂NaO₃ requires 321.1467, found [M+Na]⁺ 321.1469; **IR** ν_{max} (film)/cm⁻¹ 3443 br., 2916, 2850, 1613, 1514, 1249, 1064, 1035.

(±)-(3*R*,5*S*)-5-((4-Methoxybenzyl)oxy)-5-phenylpent-1-en-3-ol (90)



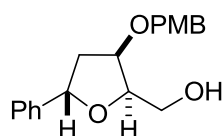
Compound **90** was isolated in the synthesis of compound **89**.

δ_{H} (400 MHz, CDCl₃) 7.46-7.29 (m, 5H, ArCH), 7.22 (d, 2H, *J* 8.3, ArCH), 6.89 (d, 2H, *J* 8.2, ArCH), 5.90-5.76 (m, 1H, CH=CH₂), 5.25 (dd, 1H, *J* 17.2, 1.4, CH=CH_AH_B), 5.07 (dd, 1H, *J* 10.5, 1.3, CH=CH_AH_B), 4.61 (dd, 1H, *J* 10.1, 3.4, CHOH), 4.42 (d, 1H, *J* 11.2, OCH_AH_BAr), 4.33-4.30 (m, 1H, CHOPMB), 4.20 (d, 1H, *J* 11.2, OCH_AH_BAr), 3.82 (s, 3H, OCH₃), 2.04 (dt, 1H, *J* 14.6, 9.8, CH_AH_B), 1.79 (dt, 1H, *J* 14.6, 3.2, CH_AH_B);

δ_{C} (100 MHz, CDCl_3) 159.4 (ArC), 141.4 (ArC), 140.3 ($\text{CH}=\text{CH}_2$), 129.6 (ArC), 128.7 (ArC), 128.0 (ArC), 126.6 (ArC), 114.3 ($\text{CH}=\text{CH}_2$), 81.3 (CHOPMB), 72.4 (CHOH), 70.1 (OCH_2Ar), 55.3 (OCH_3), 45.3 (CH_2); **HRMS** (ESI^+) $\text{C}_{19}\text{H}_{22}\text{NaO}_3$ requires 321.1467, found $[\text{M}+\text{Na}]^+$ 321.1471; **IR** ν_{max} (film)/ cm^{-1} 3463 br., 2916, 2850, 1613, 1514, 1249, 1064, 1035.

($\pm$)-((2*R*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy-5-phenyltetrahydrofuran-2-yl)methanol

(91)



General Procedure A:

Alcohol 89 (100 mg, 0.335 mmol) was subjected to **General Procedure A** (6 h) using $\text{Co}(\text{modp})_2$ (54 mg, 0.10 mmol, 30 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 60 μL , 0.034 mmol). Purification by flash column chromatography (10-65% Et_2O /petrol) afforded the title compound as a colourless oil (39 mg, 37%).

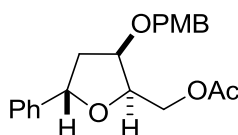
δ_{H} (400 MHz, CDCl_3) 7.35 (d, 4H, J 4.2, ArCH), 7.28 (d, 3H, J 8.3, ArCH), 6.91 (d, 2H, J 8.2, ArCH), 5.25 (dd, 1H, J 9.5, 5.9, PhCH), 4.64 (d, 1H, J 11.5, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.42 (d, 1H, J 11.5, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.36 (m, 2H, CHCH_2OH and CHOPMB), 4.01-3.86 (m, 2H, CH_2OH), 3.83 (s, 3H, OCH_3), 2.54 (dd, 1H, J 13.3, 5.9, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 2.03-1.93 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$); δ_{C} (100 MHz, CDCl_3) 159.4 (ArC), 142.3 (ArC), 132.3 (ArC), 129.7 (ArC), 129.2 (ArC), 128.5 (ArC), 127.5 (ArC), 125.7 (ArC), 114.0 (ArC), 113.7 (ArC), 81.9 (CHCH_2OH), 80.4 (CHOPMB), 79.5 (PhCH), 71.5 (OCH_2Ar), 62.3 (CH_2OH), 55.3 (OCH_3), 40.9 (CH_2CHOPMB); **HRMS** (ESI^+) $\text{C}_{19}\text{H}_{22}\text{NaO}_4$ requires 337.1421, found

$[M+Na]^+$ 331.1410; **IR** $\nu_{\max}$ (film)/ cm^{-1} 3442 br., 2934, 1611, 1513, 1249, 1172, 1064, 1036.

General Procedure B:

Alcohol 89 (100 mg, 0.335 mmol) was subjected to **General Procedure B** (24 h) using $\text{Co}(\text{nmp})_2$ (38 mg, 0.067 mmol, 20 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 60 μL , 0.034 mmol). The reaction was cooled to room temperature and purged of oxygen with argon. Methyl iodide (0.1 mL, 1.68 mmol) was added and the reaction mixture was allowed to stir for 15 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water (5 mL) and EtOAc (5 mL). The layers were separated and aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine, dried over MgSO_4 , filtered and concentrated. Purification of the crude product by flash column chromatography (40-60% EtOAc/petrol) afforded the title compound as a colourless oil (62 mg, 59%).

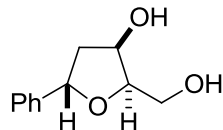
(±)-((2*R*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-phenyltetrahydrofuran-2-yl)methyl acetate (**92**)



To a solution of *alcohol 91* (25 mg, 0.080 mmol) in pyridine (64 μL) was added acetic anhydride (38 μL , 0.40 mmol), followed by a catalytic amount of 4-(dimethylamino)pyridine. The reaction was stirred for 6 h and was then concentrated *in vacuo*. Purification by flash column chromatography (20-25% Et_2O /petrol) afforded the title compound as a colourless oil (14 mg, 49%).

δ_{H} (400 MHz, CDCl_3) 7.35 (d, 4H, J 4.3, ArCH), 7.28 (d, 3H, J 8.6, ArCH), 6.91 (d, 2H, J 8.5, ArCH), 5.23 (dd, 1H, J 9.9, 5.8, PhCH), 4.61 (d, 1H, J 11.6, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.49-4.40 (m, 3H, $\text{OCH}_A\text{H}_B\text{Ar}$, CHOPMB and CHCH_2OAc), 4.37-4.26 (m, 2H, CH_2OAc), 3.83 (s, 3H, ArOCH_3), 2.52 (dd, 1H, J 13.3, 5.8, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 2.09 (s, 3H, COCH_3), 1.97-1.88 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$); δ_{C} (100 MHz, CDCl_3) 171.1 ($\text{C}=\text{O}$), 159.3 (ArC), 141.4 (ArC), 131.2 (ArC), 129.9 (ArC), 129.2 (ArC), 128.4 (ArC), 127.5 (ArC), 125.8 (ArC), 113.9 (ArC), 82.6 (CHCH_2OAc), 80.2 (CHOPMB), 79.2 (PhCH), 71.3 (OCH_2Ar), 64.0 (CH_2OAc), 55.3 (OCH_3), 40.8 (CH_2CHOPMB), 21.1 (COCH_3); **HRMS** (ESI^+) $\text{C}_{21}\text{H}_{24}\text{NaO}_5$ requires 379.1516, found $[\text{M}+\text{Na}]^+$ 379.1520; **IR** ν_{max} (film)/ cm^{-1} 2917, 1737, 1612, 1514, 1370, 1248, 1174, 1040.

(+)-((2R,3R,5S)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3-ol (93)



General Procedure A:

Alcohol 87 (100 mg, 0.561 mmol) was subjected to **General Procedure A** (5 h) using $\text{Co}(\text{modp})_2$ (61 mg, 0.11 mmol, 20 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 100 μL , 0.561 mmol). Purification by flash column chromatography (10-75% EtOAc/petrol) afforded a brown oil, which was further purified by flash column chromatography (50% EtOAc/petrol) to remove the remaining cobalt residues, affording the title compound as a white solid (19 mg, 17%).

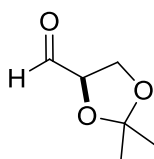
m.p. 76-78 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} +21.8$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.39-7.32 (m, 4H, ArCH), 7.31-7.26 (m, 1H, ArCH), 5.32 (dd, 1H, J 10.0, 5.7, PhCH), 4.65 (m, 1H, CHOH), 4.23 (d, 1H, J 3.8, CHCH_2OH), 4.05 (m, 2H, CH_2OH), 3.08 (br. s, 2H, 2 x OH), 2.42 (dd,

1H, *J* 13.3, 5.7, CH_AH_BCHOH), 2.11-1.99 (m, 1H, CH_AH_BCHOH); δ_{C} (100 MHz, CDCl₃) 142.4 (ArC), 128.5 (ArC), 127.6 (ArC), 125.6 (ArC), 81.6 (CHCH₂OH), 80.0 (PhCH), 74.7 (CHOH), 62.0 (CH₂OH), 45.2 (CH₂CHOH); **HRMS** (ESI⁺) C₁₁H₁₄NaO₃ requires 217.0835, found [M+Na]⁺ 217.0835; **IR** ν_{max} (film)/cm⁻¹ 3386 br., 2932, 1451, 1041.

General Procedure B:

Alcohol 87 (100 mg, 0.561 mmol) was subjected to **General Procedure B** (48 h) using Co(nmp)₂ (63 mg, 0.11 mmol, 20 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 100 μ L, 0.561 mmol). Purification by flash column chromatography (50-75% EtOAc/petrol) afforded the title compound as a pale yellow crystalline solid (55 mg, 51%).

(+)-(R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (95)

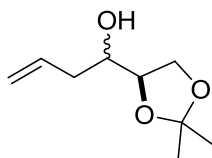


To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol (1.50 g, 5.72 mmol) in CH₂Cl₂ (15 mL) was added sodium periodate (2.45 g, 11.4 mmol), followed by the addition of a saturated solution of NaHCO₃ (60 μ L). The reaction mixture was stirred vigorously at room temperature for 2 h, then MgSO₄ (900 mg) was added, and stirring continued for 20 minutes. The slurry was filtered through a plug of Celite[®] and the solvents evaporated *in vacuo* to afford the crude title compound as a yellow oil (1.33 g, 89%), which was used without further purification.

$[\alpha]_{\text{D}}^{20}$ +62.5 (*c* = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 9.72 (d, 1H, *J* 1.9, CHO), 4.41-4.39 (m, 1H, OCH₂CHO), 4.18-4.09 (m, 2H, OCH₂CHO), 1.49 (s, 3H, CH₃), 1.42 (s, 3H, CH₃); δ_{C} (100 MHz, CDCl₃) 201.9 (CHO), 111.3 (C(CH₃)₂), 79.8 (OCH₂CHO), 65.6

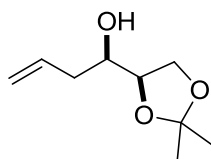
(OCH₂CHO), 26.2 (CH₃), 25.1 (CH₃). Spectroscopic data consistent with that reported in literature.¹²⁴

(±)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (96)



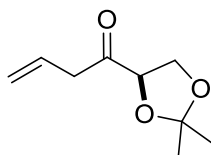
To a solution of *aldehyde 95* (1.25 g, 9.60 mmol) in THF (96 mL) at 0 °C was added allylmagnesium bromide (16.3 mL, 16.3 mmol). The reaction mixture was allowed to stir for 18 h whilst warming to room temperature. After this time, the reaction mixture was cooled to 0 °C and was quenched by the addition of a saturated solution of NH₄Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic fractions were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to afford a yellow oil (1.50 g, 91%), which was used without further purification. NMR of the title compound showed a 2.5:1 mixture of diastereomers (*anti:syn*).

δ_{H} (400 MHz, CDCl₃) (*denotes minor diastereomer) 5.90-5.80 (m, 1H, CH=CH₂), 5.18-5.11 (m, 2H, CH=CH₂), 4.07-3.98 (m, 2H, OCH₂), 3.97-3.89 (m, 1H, OCH₂CHO), 3.83-3.71 (m, 1H, CHOH), 3.63-3.56* (m, 1H, CHOH), 2.42-2.13 (m, 2H, CHOHCH₂), 1.44 (s, 3H, CH₃), 1.37 (s, 3H, CH₃); δ_{C} (100 MHz, CDCl₃) (*denotes minor diastereomer) 134.0 (CH=CH₂), 118.4 (CH=CH₂), 117.9* (CH=CH₂), 109.1 (C(CH₃)₂), 78.1 (OCH₂CHO), 71.6* (CHOH), 70.4 (CHOH), 66.0* (OCH₂), 65.2 (OCH₂), 38.3* (CHOHCH₂), 37.6 (CHOHCH₂), 26.6 (CH₃), 25.3 (CH₃). Spectroscopic data consistent with that reported in literature.¹²⁵

(+)-(R)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (96)

To a stirred solution of *ketone* **97** (180 mg, 1.06 mmol) in THF (5.3 mL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of K-Selectride[®] (1.0 M in THF, 2.1 mL, 2.1 mmol). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2h, then was gradually brought to room temperature and quenched by the dropwise addition of water. The mixture was diluted with EtOAc (5 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), the combined organic extracts washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Flash column chromatography of the residue (10-25% Et_2O /petrol) afforded the title compound as a colourless oil (25 mg, 14%).

$[\alpha]_{\text{D}}^{20} +14.7$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 5.93-5.80 (m, 1H, $\text{CH}=\text{CH}_2$), 5.18-5.09 (m, 2H, $\text{CH}=\text{CH}_2$), 4.08-3.96 (m, 2H, OCH_2), 3.79-3.71 (m, 1H, CHOH), 3.64-3.56 (m, 1H, OCH_2CHO), 2.25 (t, 2H, J 6.6, CHOHCH_2), 1.44 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); δ_{C} (100 MHz, CDCl_3) 134.0 ($\text{CH}=\text{CH}_2$), 117.9 ($\text{CH}=\text{CH}_2$), 109.4 ($\text{C}(\text{CH}_3)_2$), 78.5 (OCH_2CHO), 71.6 (CHOH), 66.0 (OCH_2), 38.3 (CHOHCH_2), 26.6 (CH_3), 25.3 (CH_3). Spectroscopic data consistent with that reported in literature.¹²⁶

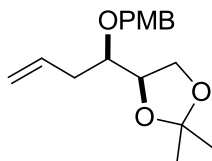
(+)-(R)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-one (97)

To a solution of *alcohol* **96** (500 mg, 2.90 mmol) in CH_2Cl_2 (30 mL) at room temperature, was added Dess-Martin periodinane (1.36 g, 3.19 mmol) and the reaction mixture was

stirred at room temperature for 2 h. A saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) was added and the mixture stirred vigorously for 10 minutes. The two layers were separated, the organic layer washed with a saturated solution of NaHCO_3 (20 mL), then dried over Na_2SO_4 , filtered and concentrated to afford a dark yellow oil. Purification by flash column chromatography (0-5% Et_2O /petrol) delivered the title compound as a colourless oil (201 mg, 41%).

$[\alpha]_{\text{D}}^{20} +21.0$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 5.99-5.90 (m, 1H, $\text{CH}=\text{CH}_2$), 5.23-5.14 (m, 2H, $\text{CH}=\text{CH}_2$), 4.49-4.56 (m, 1H, CHO), 4.21 (ddd, 1H, J 8.8, 7.8, $\text{OCH}_\text{A}\text{H}_\text{B}$), 4.04-4.00 (m, 1H, $\text{OCH}_\text{A}\text{H}_\text{B}$), 3.43-3.39 (m, 2H, COCH_2), 1.50 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); δ_{C} (100 MHz, CDCl_3) 208.7 ($\text{C}=\text{O}$), 129.7 ($\text{CH}=\text{CH}_2$), 119.2 ($\text{CH}=\text{CH}_2$), 111.0 ($\text{C}(\text{CH}_3)_2$), 80.0 (OCH_2CHO), 66.5 (OCH_2), 43.4 (COCH_2), 26.1 (CH_3), 25.0 (CH_3); **HRMS** (ESI^+) $\text{C}_9\text{H}_{14}\text{NaO}_3$ requires 193.0835, found $[\text{M}+\text{Na}]^+$ 193.0835; **IR** ν_{max} (film)/ cm^{-1} 2989, 1720, 1375, 1261, 1214, 1153, 1070.

(R)-4-((R)-1-((4-Methoxybenzyl)oxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (98)

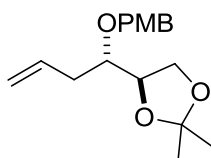


A solution of *alcohol* ($\pm$)-**96** (420 mg, 2.36 mmol) in DMF (12 mL) was added dropwise to a vigorously-stirred solution of sodium hydride (60% dispersion in mineral oil, 94 mg, 2.4 mmol) in DMF (6.0 mL) at 0 °C under Ar. After 30 minutes, a solution of 4-methoxybenzyl chloride (0.32 mL, 2.4 mmol) in DMF (3.0 mL) was added dropwise and the reaction was stirred for 16 h whilst warming to room temperature. The reaction mixture was cooled to 0 °C and was quenched by the addition of ice-cold water. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined

organics fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (0-15% Et_2O /petrol) and subsequent preparative TLC (20% Et_2O /petrol) afforded the title compound as a colourless oil (197 mg, 20%), along with its diastereomer (512 mg, 52%).

δ_{H} (400 MHz, CDCl_3) 7.36-7.20 (m, 2H, ArCH), 6.93-6.84 (m, 2H, ArCH), 5.96-5.78 (m, 1H, CHCH₂), 5.17-5.02 (m, 2H, CHCH₂), 4.68-4.56 (m, 2H, OCH₂Ar), 4.20 (q, 1H, *J* 6.7, OCH₂CHO), 3.98 (dd, 1H, *J* 8.2, 6.6, OCH_AH_B), 3.81 (s, 3H, OCH₃), 3.70 (t, 1H, *J* 7.8, OCH_AH_B), 3.50 (td, 1H, *J* 6.8, 4.6, CHOPMB), 2.36-2.15 (m, 2H, CHOPMBCH₂), 1.44 (s, 3H, CH₃), 1.37 (s, 3H, CH₃); δ_{C} (100 MHz, CDCl_3) 159.1 (ArC), 134.6 (CH=CH₂), 130.7 (ArC), 129.5 (ArC), 128.7 (ArC), 117.2 (CH=CH₂), 113.7 (ArC), 109.3 (C(CH₃)₂), 78.8 (CHOPMB), 77.9 (CHO), 72.2 (OCH₂Ar), 65.8 (OCH₂), 55.3 (OCH₃), 35.3 (CHOPMBCH₂), 26.5 (CH₃), 25.4 (CH₃). Spectroscopic data consistent with that reported in literature.¹²⁷

(R)-4-((S)-1-((4-Methoxybenzyl)oxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (99)

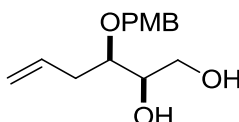


Compound **99** was isolated in the synthesis of compound **98**.

δ_{H} (400 MHz, CDCl_3) 7.27 (d, 2H, *J* 8.1, ArCH), 6.89 (d, 2H, *J* 8.3, ArCH), 5.91 (ddt, 1H, *J* 17.1, 9.9, 7.3, CH=CH₂), 5.20-5.08 (m, 2H, CH=CH₂), 4.65-4.47 (m, 2H, OCH₂Ar), 4.13-4.01 (m, 2H, OCH_AH_B and OCH₂CHO), 3.88 (dd, 1H, *J* 8.0, 6.3, OCH_AH_B), 3.82 (s, 3H, OCH₃), 3.56 (q, 1H, *J* 5.6, CHOPMB), 2.49-2.39 (m, 1H, CHOPMBCH_AH_B), 2.39-2.30 (m, 1H, CHOPMBCH_AH_B), 1.44 (s, 3H, CH₃), 1.36 (s, 3H, CH₃); δ_{C} (100 MHz, CDCl_3) 159.2 (ArC), 134.3 (CH=CH₂), 130.5 (ArC), 129.5 (ArC), 117.5 (CH=CH₂), 113.8

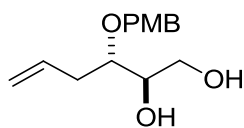
(ArC), 109.1 (C(CH₃)₂), 78.5 (CHOPMB), 77.2 (CHO), 72.1 (OCH₂Ar), 66.5 (OCH₂), 55.3 (OCH₃), 35.6 (CHOPMBCH₂), 26.7 (CH₃), 25.4 (CH₃). Spectroscopic data consistent with that reported in literature.¹²⁷

(2*R*,3*R*)-3-((4-Methoxybenzyl)oxy)hex-5-ene-1,2-diol (100)



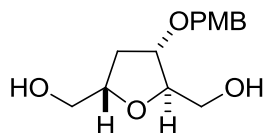
A solution of *dioxolane* **98** (140 mg, 0.479 mmol) in 2 M aq. HCl in THF (2:1, 2.9 mL) was stirred at room temperature for 17 h. The reaction mixture was diluted with EtOAc (5 mL), the layers were separated, and the organic layer was washed with a saturated solution of NaHCO₃ (5 mL). The aqueous phase was then extracted with EtOAc (3 x 5 mL) and the combined organic fractions were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford an oil. Purification by flash column chromatography (20-50% EtOAc/petrol) provided the title compound as a colourless oil (74 mg, 61%).

δ_{H} (400 MHz, CDCl₃) 7.30-7.21 (m, 2H, ArCH), 6.89 (d, 2H, *J* 8.5, ArCH), 5.93-5.79 (m, 1H, CH=CH₂), 5.21-5.10 (m, 2H, CH=CH₂), 4.65 (d, 1H, *J* 11.0, OCH_AH_BAr), 4.41 (d, *J* 11.0, 1H, OCH_AH_BAr), 3.81 (s, 3H, OCH₃), 3.79-3.57 (m, 3H, OCH₂ and CHOH), 3.53 (d, 1H, *J* 5.4, CHOPMB), 2.50 (dq, 1H, *J* 13.8, 6.8, CHOPMBCH_AH_B), 2.45-2.29 (m, 3H, CHOPMBCH_AH_B and 2 x OH); δ_{C} (100 MHz, CDCl₃) 159.5 (ArC), 133.9 (CH=CH₂), 129.9 (ArC), 129.7 (ArC), 129.5 (ArC), 117.9 (CH=CH₂), 114.0 (ArC), 113.9 (ArC), 78.6 (CHOPMB), 72.4 (CHOH), 71.7 (OCH₂Ar), 63.8 (OCH₂), 55.3 (OCH₃), 34.7 (CHOPMBCH₂). Spectroscopic data consistent with that reported in literature.²⁹

(+)-(2*R*,3*S*)-3-((4-Methoxybenzyl)oxy)hex-5-ene-1,2-diol (101)

A solution of *dioxolane* **99** (360 mg, 1.23 mmol) in 2 M aq. HCl in THF (2:1, 7.5 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc (5 mL) and was washed with a saturated solution of NaHCO₃ (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and washed with brine (5 mL). The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford an oil, which was purified by flash column chromatography (20-45% EtOAc/petrol) to furnish the title compound as a colourless oil (205 mg, 66%).

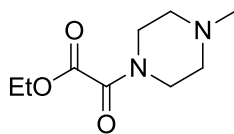
$[\alpha]_D^{20} +18.7$ ($c = 1$, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 7.26 (d, 2H, J 8.6, ArCH), 6.89 (d, 2H, J 8.6, ArCH), 5.94-5.80 (m, 1H, CH=CH₂), 5.21-5.08 (m, 2H, CH=CH₂), 4.61 (d, 1H, J 11.1, OCH_AH_BAr), 4.45 (d, 1H, J 11.1, OCH_AH_BAr), 3.81 (s, 3H, OCH₃), 3.79-3.66 (m, 3H, OCH₂O and CHOH), 3.61 (q, 1H, J 5.6, CHOPMB), 2.51-2.41 (m, 1H, CHOPMBCH_AH_B), 2.41-2.30 (m, 3H, CHOPMBCH_AH_B and 2 x OH); δ_C (100 MHz, CDCl₃) 159.4 (ArC), 134.2 (CHCH₂), 130.1 (ArC), 129.5 (ArC), 117.7 (CHCH₂), 113.9 (ArC), 80.2 CHOPMB), 72.3 (CHOH), 72.2 (OCH₂Ar), 63.3 (OCH₂), 55.3 (OCH₃), 35.1 (CH₂). Spectroscopic data consistent with that reported in literature.¹²⁸

(+)-((2*R*,3*S*,5*S*)-3-((4-Methoxybenzyl)oxy)tetrahydrofuran-2,5-diyl)methanol (102)

To a flask containing Co(nmp)₂ (45 mg, 0.079 mmol, 20 mol%) under a stationary oxygen atmosphere (balloon) was added a solution of *alcohol* **101** (100 mg, 0.397 mmol) in ⁱPrOH

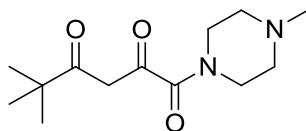
(4.0 mL), followed by *tert*-butyl hydroperoxide (5.5 M in decane, 7.0 μ L, 0.040 mmol). The reaction was stirred at 55 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was purged of oxygen with argon. Methyl iodide (120 μ L, 1.98 mmol) was then added and the reaction mixture stirred at room temperature for 1.5 days. The reaction mixture was concentrated *in vacuo* and the residue re-dissolved in water (1 mL) and EtOAc (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic fractions were washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to afford a dark green oil. Purification by flash column chromatography (50-100% EtOAc/petrol) delivered the desired product as a pale yellow viscous oil (53 mg, 50%).

$[\alpha]_{\text{D}}^{20}$ +59.8 (*c* = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 7.25 (d, 2H, *J* 8.1, ArCH), 6.89 (d, 2H, *J* 8.6, ArCH), 4.51-4.41 (m, 2H, OCH₂Ar), 4.30-4.21 (m, 1H, HOCH₂CH), 4.13-4.07 (m, 1H, CHCH₂OH), 4.07-4.01 (m, 1H, CHOPMB), 3.81 (s, 3H, OCH₃), 3.73-3.62 (m, 3H, CH₂OH and CH_AH_BOH), 3.61-3.51 (m, 1H, CH_AH_BOH), 2.72 (br. s, 1H, OH), 2.42 (br. s, 1H, OH), 2.29-2.20 (m, 1H, CH_AH_BOPMB), 1.91-1.81 (m, 1H, CH_AH_BOPMB); δ_{C} (100 MHz, CDCl₃) 159.3 (ArC), 129.6 (ArC), 129.3 (ArC), 113.9 (ArC), 83.7 (CHCH₂OH), 79.3 (CHOPMB), 79.2 (HOCH₂CH), 71.4 (OCH₂Ar), 65.1 (HOCH₂), 62.9 (CH₂OH), 55.3 (OCH₃), 33.8 (CH₂OPMB); HRMS (ESI⁺) C₁₄H₂₀NaO₅ requires 291.1203, found [M+Na]⁺ 291.1204; IR ν_{max} (film)/cm⁻¹ 3393 br., 2933, 1611, 1513, 1462, 1247, 1172, 1031, 820.

Ethyl 2-(4-methylpiperazin-1-yl)-2-oxoacetate (105)

To a solution of *N*-methylpiperazine (0.55 mL, 5.0 mmol) and triethylamine (0.70 mL, 5.0 mmol) in CH₂Cl₂ (5.0 mL) at 0 °C was added ethyl oxalyl chloride (0.56 mL, 5.0 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 20 h before being treated with a saturated solution of NaHCO₃ (5 mL). The two layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic fractions were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford a yellow oil (856 mg, 86%), which was used without further purification.

δ_{H} (400 MHz, CDCl₃) 4.32 (q, 2H, *J* 7.2, CH₂O), 3.66-3.64 (m, 2H, NCH₂), 3.46-3.43 (m, 2H, NCH₂), 2.44 (t, 4H, *J* 5.05, 2 x CH₂N), 2.32 (s, 3H, NCH₃), 1.35 (t, 3H, *J* 7.1, CH₃ CH₂O); δ_{C} (100 MHz, CDCl₃) 162.7 (C=O), 160.1 (C=O), 62.1 (CH₂O), 54.8 (NCH₂), 54.1 (NCH₂), 45.9 (2 x CH₂N), 41.2 (NCH₃), 14.0 (CH₃). Spectroscopic data consistent with that reported in literature.⁷²

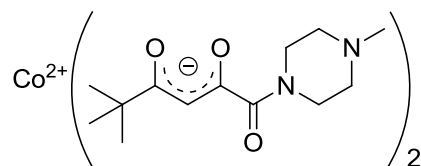
5,5-Dimethyl-1-(4-methylpiperazine-1-yl)hexane-1,2,4-trione (106)

A solution of sublimation-grade potassium *tert*-butoxide (421mg, 3.75 mmol) in THF (9.0 mL) was added to a solution of *amide* **105** (375 mg, 1.87 mmol) and 3,3-dimethylbutan-2-one (0.23 mL, 1.9 mmol) in THF (2.0 mL) at 0 °C and stirred for 17 h whilst warming to room temperature. Freshly prepared acetic acid (1.0 M in CH₂Cl₂, 3.5

mL) was added and the mixture stirred for 30 minutes before it was filtered through Celite[®]. The solvents were evaporated *in vacuo* to afford the title compound as an orange syrup (0.476 g, 100%), which was used without further purification.

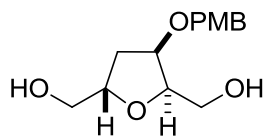
δ_{H} (400 MHz, CDCl_3) (1:5.6 mixture of keto-enol tautomers) (*denotes minor tautomer peak) 5.99 (s, 1H, CHCHOH), 4.04* (s, 2H, COCH_2CO), 3.78-3.58 (m, 4H, 2 x NCH_2), 2.52 (q, 4H, J 4.5, 2 x CH_2N), 2.34 (s, 3H, NCH_3), 1.27-1.11 (m, 9H, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 201.1 ($\text{C}=\text{O}$), 185.1 (COH), 163.9 ($\text{C}=\text{O}$), 95.4 ($\text{CH}=\text{C}$), 54.8 (NCH_2), 54.1 (NCH_2), 45.6 (NCH_3), 45.5 (CH_2N), 41.3 (CH_2N), 39.1 ($\text{C}(\text{CH}_3)_3$), 27.2 ($\text{C}(\text{CH}_3)_3$). Spectroscopic data consistent with that reported in literature.⁷²

$\text{Co}^{\text{II}}(\text{nmp})_2$



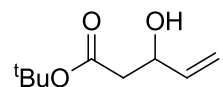
To a solution of *nmp ligand 106* (1.0 g, 3.9 mmol) in benzene (20 mL) was added cobalt(II) ethylhexanoate (65 wt% in mineral spirits, 1.1 mL, 2.0 mmol). After 10 minutes water (105 μL , 7.88 mmol) was added and the reaction mixture stirred for 20 h. Hexanes (80 mL) was then added and the solids were separated by centrifugation. The solvent was decanted and the catalyst was triturated with hexanes. The remaining solvent was removed under reduced pressure to afford the $\text{Co}(\text{nmp})_2$ catalyst (0.95 g, 86%) as a beige solid.

HRMS (ESI^+) $\text{C}_{26}\text{H}_{42}\text{CoN}_4\text{NaO}_6$ requires 588.2329, found $[\text{M}+\text{Na}]^+$ 588.2332; **IR** ν_{max} (film)/ cm^{-1} 2955, 2791, 1646, 1581, 1521, 1430, 1362, 1295, 1257, 1147, 1001, 962, 838, 777, 657.

(-)-((2R,3R,5S)-3-((4-Methoxybenzyl)oxy)tetrahydrofuran-2,5-diyl)methanol (107)

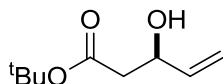
To a flask containing $\text{Co}(\text{nmp})_2$ (27 mg, 0.048 mmol, 20 mol%) under a stationary oxygen atmosphere (balloon) was added a solution of *alcohol 100* (60 mg, 0.24 mmol) in $i\text{PrOH}$ (2.4 mL), followed by *tert*-butyl hydroperoxide (5.5 M in decane, 4.0 μL , 0.024 mmol). The reaction was stirred at 55 $^\circ\text{C}$ for 18 h. The reaction mixture was allowed to cool to room temperature and was purged of oxygen with argon. Methyl iodide (75 μL , 1.2 mmol) was then added and the reaction mixture stirred at room temperature for 17 h. The reaction mixture was concentrated *in vacuo* and the residue re-dissolved in water (0.5 mL) and EtOAc (0.5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 0.5 mL). The combined organic fractions were washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo*. Purification by flash column chromatography (50-100% EtOAc/petrol) afforded the title compound as a pale yellow oil (29 mg, 45%).

$[\alpha]_{\text{D}}^{20}$ -18.9 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.30-7.18 (m, 2H, ArCH), 6.97-6.84 (m, 2H, ArCH), 4.58 (d, 1H, J 11.6, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.37 (d, 2H, J 11.1, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$ and HOCH_2CH), 4.25 (br. s, 1H, CHOPMB), 4.10 (d, 1H, J 4.3, CHCH_2OH), 3.92-3.73 (m, 5H, CH_2OH and OCH_3), 3.73-3.46 (m, 2H, HOCH_2), 2.69 (br. s, 2H, 2 x OH), 2.13 (dd, 1H, J 13.3, 6.2, $\text{CH}_\text{A}\text{H}_\text{B}\text{OPMB}$), 1.90 (dt, 1H, J 13.0, 6.4, $\text{CH}_\text{A}\text{H}_\text{B}\text{OPMB}$); δ_{C} (100 MHz, CDCl_3) 159.3 (ArC), 129.7 (ArC), 129.3 (ArC), 129.1 (ArC), 113.9 (ArC), 81.7 (CHCH_2OH), 80.1 (CHOPMB), 78.5 (HOCH_2CH), 71.2 (OCH_2Ar), 64.3 (HOCH_2), 62.1 (CH_2OH), 55.3 (OCH_3), 33.8 (CH_2OPMB); **HRMS** (ESI^+) $\text{C}_{14}\text{H}_{20}\text{NaO}_5$ requires 291.1203, found $[\text{M}+\text{Na}]^+$ 291.1205; **IR** ν_{max} (film)/ cm^{-1} 3398 br., 2932, 1611, 1513, 1247, 1171, 1031.

(±)-tert-Butyl 3-hydroxypent-4-enoate (110)

To a solution of diisopropylamine (9.8 mL, 70.0 mmol) in THF (220 mL) at 0 °C was dropwise added *n*-butyllithium (1.6 M in hexanes, 43.8 mL, 70.0 mmol). The mixture was stirred at 0 °C for 30 minutes and was then cooled to −78 °C. *tert*-Butyl acetate (8.5 mL, 64 mmol) was added dropwise and the mixture stirred at −78 °C for 50 minutes. A solution of acrolein (4.3 mL, 64 mmol) in THF (30 mL) was slowly added and the reaction mixture stirred at −78 °C for 15 minutes. The reaction was quenched by the rapid addition of a saturated solution of NH₄Cl (20 mL), poured into a separating funnel containing Et₂O (130 mL), and the two layers were separated. The organic layer was washed with brine (2 x 100 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography (10-15% EtOAc/petrol) furnished the desired product as a pale yellow oil (9.36 g, 85%).

δ_{H} (400 MHz, CDCl₃) 5.93-5.83 (m, 1H, CH=CH₂), 5.36-5.27 (m, 1H, CH=CH_AH_B), 5.15 (d, 1H, *J* 10.6, CH=CH_AH_B), 4.53-4.46 (m, 1H, CHOH), 3.16 (d, 1H, *J* 3.8, OH), 2.55-2.40 (m, 2H, COCH₂), 1.47 (s, 9H, (CH₃)₃). δ_{C} (100 MHz, CDCl₃) 172.1 (C=O), 139.3 (CH=CH₂), 115.6 (CH=CH₂), 81.9 (C(CH₃)₃), 69.4 (CHOH), 42.5 (CH₂CHOH), 28.5 (C(CH₃)₃). Spectroscopic data consistent with that reported in literature.¹²⁹

(+)-(R)-tert-Butyl 3-hydroxypent-4-enoate (110)**From ester (±)-110:**

To a suspension of β -hydroxy ester (±)-**110** (5.0 g, 29 mmol), Amino Lipase PS (2.6 g) and crushed molecular sieves (4 Å, 4.35 g) in pentane (135 mL) was added vinyl acetate (2.7 mL, 29 mmol). The mixture was incubated at 35 °C for 4 days and was then filtered through a short plug of Celite[®] and the solvents evaporated *in vacuo*. Purification by flash column chromatography (5-10% Et₂O/petrol) afforded the desired product as a colourless oil (2.26 g, 45%), along with the corresponding acetate as a colourless oil (3.09 g, 50%).

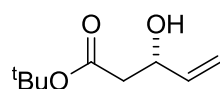
$[\alpha]_D^{20}$ +6.2 ($c = 1$, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 5.88 (ddd, 1H, J 16.9, 10.8, 5.4, CH=CH₂), 5.31 (d, 1H, J 17.2 CH=CH_AH_B), 5.15 (d, 1H, J 10.4, CH=CH_AH_B), 4.56-4.43 (m, 1H, CHOH), 3.16 (d, J 4.6, 1H, OH), 2.58-2.37 (m, 2H, COCH₂), 1.47 (s, 9H, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 172.1 (C=O), 139.3 (CH=CH₂), 115.6 (CH=CH₂), 81.9 (C(CH₃)₃), 69.4 (CHOH), 42.5 (CH₂CHOH), 28.5 (C(CH₃)₃). Spectroscopic data consistent with that reported in literature.⁸⁵

From alcohol (S)-110:

To a solution of *alcohol* (S)-**110** (2.07 g, 12.0 mmol) in THF (56.5 mL) was added triphenylphosphine (6.29 g, 24.0 mmol) and glacial acetic acid (1.0 mL, 18 mmol). The mixture was cooled to 0 °C, then diethylazodicarboxylate (4.7 mL, 24 mmol) was added dropwise. The reaction mixture was stirred for 2 h at room temperature, then was concentrated *in vacuo*. The residue was re-dissolved in MeOH and cooled to 0 °C. Sodium methoxide (25 wt% in methanol, 2.7 mL, 12 mmol) was added dropwise and the resultant mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by the addition of acetic

acid (1.2 mL) and was then concentrated *in vacuo*. The residue was re-dissolved in a saturated solution of NaHCO₃ (20 mL), the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification of the crude product by flash column chromatography (10-20% Et₂O/petrol) afforded the title compound as a pale yellow oil (780 mg, 38%). Spectroscopic data consistent with that reported above for *alcohol (+)-110*.

(-)-(S)-tert-Butyl 3-hydroxypent-4-enoate (110)

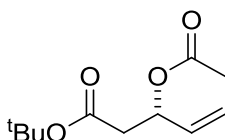


To a solution of (*S*)-*acetate* **111** (3.0 g, 14 mmol) in methanol (42 mL) at 0 °C was dropwise added sodium methoxide (25 wt% in methanol, 3.2 mL, 14 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then the reaction was quenched by the addition of acetic acid (1.4 mL). The mixture was concentrated *in vacuo* then the residue was re-dissolved in a saturated solution of NaHCO₃ (20 mL). The aqueous was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (15% Et₂O/petrol) to afford the desired product as a colourless oil (2.08 g, 86%).

$[\alpha]_D^{20}$ -5.9 (*c* = 1, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 5.98-5.84 (m, 1H, CH=CH₂), 5.41-5.28 (m, 1H, CH=CH_AH_B), 5.24-5.12 (m, 1H, CH=CH_AH_B), 4.54 (br. s, 1H, CHOH), 3.19 (d, 1H, *J* 4.4, OH), 2.62-2.41 (m, 2H, CH₂CHOH), 1.52 (s, 9H, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 171.7 (C=O), 138.9 (CH=CH₂), 115.2 (CH=CH₂), 81.5 (C(CH₃)₃), 69.0 (CHOH),

42.0 (CH₂CHOH), 28.1 (C(CH₃)₃). Spectroscopic data consistent with that reported in literature.⁹⁰

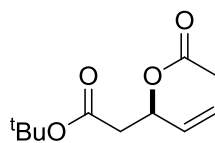
(-)-(S)-tert-Butyl 3-acetoxypent-4-enoate (111)



Acetate (S)-**111** was isolated in the synthesis of *alcohol* (R)-**110** from *ester* (±)-**110**.

[α]_D²⁰ -4.7 (c = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 5.83 (ddd, 1H, *J* 17.1, 10.7, 6.3, CH=CH₂), 5.61 (q, 1H, *J* 6.5, CHOAc), 5.31 (d, 1H, *J* 17.2, CH=CH_AH_B), 5.21 (d, 1H, *J* 10.6, CH=CH_AH_B), 2.66-2.48 (m, 2H, CH₂CHOAc), 2.06 (s, 3H, COCH₃), 1.44 (s, 9H, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 170.2 (C=O), 169.4 (C=O), 135.6 (CH=CH₂), 117.7 (CH=CH₂), 81.4 (C(CH₃)₃), 71.5 (CHOAc), 41.1 (CH₂CHOAc), 28.4 (C(CH₃)₃), 21.4 (COCH₃). Spectroscopic data consistent with that reported in literature.⁸⁵

(+)-(R)-tert-Butyl 3-acetoxypent-4-enoate (111)

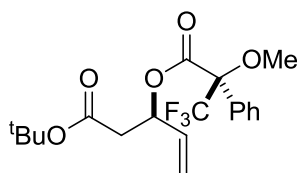


To a solution of (S)-*alcohol* **110** (0.320 g, 1.85 mmol) in THF (8.7 mL) at 0 °C was added triphenylphosphine (0.976 g, 3.72 mmol) and acetic acid (0.16 mL, 2.8 mmol), followed by the dropwise addition of diisopropyl azodicarboxylate (0.73 mL, 3.7 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then was concentrated *in vacuo*. The residue was re-dissolved in a saturated solution of NaHCO₃ (10 mL) and was extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered

and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2-4% EtOAc/petrol) to afford a colourless oil (0.170 g, 43%).

$[\alpha]_D^{20} +4.2$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 5.83 (ddd, 1H, J 17.1, 10.6, 6.2, $\text{CH}=\text{CH}_2$), 5.64-5.56 (m, 1H, CHOAc), 5.30 (d, J 17.2, 1H, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.20 (d, J 10.4, 1H, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 2.65-2.48 (m, 2H, CH_2CHOAc), 2.05 (s, 3H, COCH_3), 1.44 (s, 9H, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 169.8 ($\text{C}=\text{O}$), 168.9 ($\text{C}=\text{O}$), 135.2 ($\text{CH}=\text{CH}_2$), 117.3 ($\text{CH}=\text{CH}_2$), 81.0 ($\text{C}(\text{CH}_3)_3$), 71.1 (CHOAc), 40.7 (CH_2CHOAc), 28.0 ($\text{C}(\text{CH}_3)_3$), 21.0 (COCH_3).

(+)-(R)-tert-Butyl 3-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)pent-4-enoate (112)

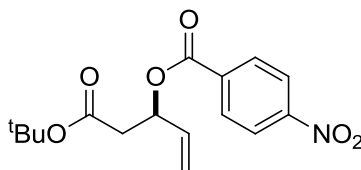


To a solution of (*R*)-alcohol **110** (20 mg, 0.12 mmol) in CH_2Cl_2 (1.7 mL) was added *R*-(+)- α -methoxy- α -trifluoromethylphenylacetic acid (84 mg, 0.360 mmol), dicyclohexylcarbodiimide (74 mg, 0.36 mmol) and 4-(dimethylamino)pyridine (44 mg, 0.36 mmol). The reaction mixture was stirred at room temperature for 18 h, then filtered through a short plug of Celite[®] and the solvent evaporated *in vacuo*. Purification by flash column chromatography (2-4% Et_2O /petrol) afforded the desired product as a colourless oil (45 mg, 100%).

$[\alpha]_D^{20} +28.4$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.58-7.47 (m, 2H, ArCH), 7.45-7.33 (m, 3H, ArCH), 5.97-5.82 (m, 2H, $\text{CH}=\text{CH}_2$ and CHOCO), 5.45 (d, 1H, J 15.9, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.33 (d, 1H, J 9.6, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.54 (s, 3H, OCH_3), 2.71 (dd, 1H, J 16.2, 7.8, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHO}$), 2.56 (dd, 1H, J 16.0, 4.7, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHO}$), $(\text{CH}_3)_3$; δ_{C} (100 MHz, CDCl_3)

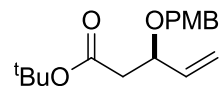
168.4 (C=O), 165.5 (C=O), 133.8 (CH=CH₂), 132.2 (ArC), 129.5 (ArC), 128.3 (ArC), 127.5 (ArC), 119.6 (CH=CH₂), 81.4 (C(CH₃)₃), 73.5 (CHOCO), 55.4 (OCH₃), 40.0 (CH₂CHO), 27.9 (C(CH₃)₃); δ_F (376 MHz, CDCl₃) -71.6 (CF₃).

(-)-(R)-5-(*tert*-Butoxy)-5-oxopent-1-en-3-yl 4-nitrobenzoate (113)



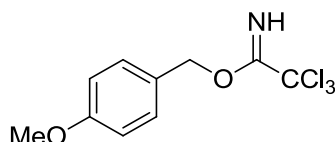
To a solution of (*S*)-*alcohol* **110** (100 mg, 0.581 mmol) in THF (4.5 mL) was added 4-nitrobenzoic acid (388 mg, 2.32 mmol) and triphenylphosphine (609 mg, 2.32 mmol) and the mixture cooled to 0 °C. Diisopropyl azodicarboxylate (0.46 μ L, 2.3 mmol) was added dropwise and the ice bath removed. The reaction mixture was stirred at room temperature for 1.5 h, then poured into a half-saturated aqueous solution of NaHCO₃ (20 mL). The two layers were separated and the aqueous extracted with EtOAc (3 x 20 mL). The organic phases were combined and washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo* to provide a yellow oil. The crude product was purified by flash column chromatography (5-8% EtOAc/petrol) to afford the desired product as a yellow oil (87 mg, 47%).

$[\alpha]_D^{20}$ -14.4 (c = 1, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 8.29 (m, 2H, *J* 8.8, ArCH), 8.22 (m, 2H, *J* 8.8 ArCH), 6.01-5.85 (m, 2H, CH=CH₂ and CHOCO), 5.42 (d, 1H, *J* 16.7, CH=CH_AH_B), 5.30 (d, 1H, *J* 9.9, CH=CH_AH_B), 2.84-2.65 (m, 2H, CH₂CHOPNB), 1.40 (s, 9H, (CH₃)₃); δ_C (100 MHz, CDCl₃) 168.7 (C=O), 163.5 (C=O), 154.7 (ArC), 150.6 (ArC), 135.5 (CH=CH₂), 134.5 (ArC), 130.7 (ArC), 123.6 (ArC), 118.3 (CH=CH₂), 81.4 (C(CH₃)₃), 72.8 (CHOPNB), 40.7 (CH₂CHOPNB), 28.0 (C(CH₃)₃); **IR** ν_{max} (film)/cm⁻¹ 2980, 1727, 1528, 1270, 1102.

(+)-(R)-tert-Butyl 3-((4-methoxybenzyl)oxy)pent-4-enoate (114)

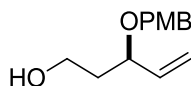
To a solution of (*R*)-alcohol **110** (2.29 g, 13.3 mmol) in a mixture of CH₂Cl₂ (62.5 mL) and cyclohexane (16 mL) was dropwise added *imide* **117** (1.4 mL, 6.6 mmol), followed by camphorsulfonic acid (0.309 g, 1.33 mmol). The resulting mixture was stirred for 1 h before a further portion of *imide* **117** (1.4 mL, 6.6 mmol) was slowly added. After stirring for a further 18 h, a third portion of 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.4 mL, 6.6 mmol) was dropwise added. After 18 h, a saturated solution of NaHCO₃ was added (50 mL) and the two layers separated. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic phases washed with brine, dried over MgSO₄, filtered and the solvent evaporated *in vacuo*. The crude product was then purified by flash column chromatography (2-3% EtOAc/petrol) to afford the desired product as a colourless oil (3.55 g, 91%).

[α]_D²⁰ +7.3 (c = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 7.30-7.22 (m, 2H, ArCH), 6.87 (d, 2H, *J* 8.6, ArCH), 5.79 (ddd, 1H, *J* 17.3, 10.0, 7.6, CH=CH₂), 5.36-5.21 (m, 2H, CH=CH₂), 4.52 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.35 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.28-4.16 (m, 1H, CHOPMB), 3.81 (s, 3H, OCH₃), 2.59 (dd, 1H, *J* 14.9, 8.1, CH_AH_BCHOPMB), 2.42 (dd, 1H, *J* 14.8, 5.7, CH_AH_BCHOPMB), 1.45 (s, 9H, (CH₃)₃); δ_{C} (100 MHz, CDCl₃) 170.2 (C=O), 159.1 (ArC), 137.5 (CH=CH₂), 130.4 (ArC), 129.4 (ArC), 117.7 (CH=CH₂), 113.7 (ArC), 80.5 (OC(CH₃)₃), 77.2 (CHOPMB), 70.3 (OCH₂Ar), 55.3 (OCH₃), 42.1 (CH₂CHOPMB), 28.1 (C(CH₃)₃); **HRMS** (ESI⁺) C₁₇H₂₄NaO₄ requires 315.1567, found [M+Na]⁺ 315.1567; **IR** ν_{max} (film)/cm⁻¹ 2978, 1729, 1613, 1514, 1367, 1301, 1248, 1159, 1125, 1066, 1036, 931, 822, 765.

4-Methoxybenzyl 2,2,2-trichloroacetimidate (117)⁹¹

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.576 g, 6.00 mmol) in Et₂O (50 mL) at 0 °C was slowly added a solution of 4-methoxybenzyl alcohol (7.3 mL, 60 mmol). After effervescence had ceased, the mixture was stirred for 30 minutes, then neat trichloroacetonitrile (6.3 mL, 60 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C then was concentrated *in vacuo*. The residue was treated with pentane (47 mL) and MeOH (0.2 mL) and the mixture stirred for 10 minutes before being filtered through Celite[®] and the solid residues washed with pentane (40 mL). The filtrate was concentrated *in vacuo* to provide the crude product as a yellow oil (12.8 g, 76%).

δ_{H} (400 MHz, CDCl₃) 8.37 (br. s, 1H, NH), 7.38 (d, *J* 8.6, 2H, ArCH), 6.92 (d, *J* 8.6, 2H, ArCH), 5.29 (s, 2H, CH₂O), 3.83 (s, 3H, CH₃O); δ_{C} (100 MHz, CDCl₃) 162.6 (C=NH), 159.7 (ArC), 129.7 (ArC), 127.5 (ArC), 113.9 (ArC), 91.5 (CCl₃), 70.7 (CH₂O), 55.3 (CH₃O). Spectroscopic data consistent with that reported in literature.¹³⁰

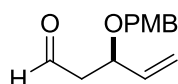
(+)-(R)-3-((4-Methoxybenzyl)oxy)pent-4-en-1-ol (118)¹³¹

To a solution of lithium aluminium hydride (1.0 M in THF, 10.6 mL, 10.6 mmol) in Et₂O (17 mL) at 0 °C was dropwise added a solution of *ester 114* (2.39 g, 8.18 mmol) in Et₂O (3.0 mL). The reaction mixture was stirred at 0 °C for 2 h before it was quenched by the

addition of ice water (0.4 mL), followed by 15% aqueous NaOH solution (0.4 mL) and water (1.2 mL). The mixture was stirred vigorously whilst warming to room temperature and was then filtered through Celite[®] (Et₂O rinse), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification of the crude product by flash column chromatography (15-25% EtOAc/petrol) afforded the desired product as a colourless oil (1.45 g, 80%).

$[\alpha]_{\text{D}}^{20} +43.5$ ($c = 1$, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 7.26 (m, 2H, J 8.3, ArCH), 6.89 (m, 2H, J 8.6, ArCH), 5.80 (ddd, 1H, J 17.6, 9.7, 7.8, CH=CH₂), 5.34-5.21 (m, 2H, CH=CH₂), 4.57 (d, 1H, J 11.4, OCH_AH_BAr), 4.31 (d, 1H, J 11.4, OCH_AH_BAr), 4.02 (td, 1H, J 7.6, 4.7, CHOPMB), 3.82 (s, 3H, OCH₃), 3.80-3.67 (m, 2H, OCH₂), 2.48 (br. s, 1H, OH), 1.95-1.73 (m, 2H, CH₂CHOPMB); δ_{C} (100 MHz, CDCl₃) 159.2 (ArC), 138.2 (CH=CH₂), 130.2 (ArC), 129.4 (ArC), 117.4 (CH=CH₂), 113.9 (ArC), 79.6 (CHOPMB), 69.9 (OCH₂Ar), 60.7 (OCH₂), 55.3 (OCH₃), 37.7 (CH₂CHOPMB); **HRMS** (ESI⁺) C₁₃H₁₈NaO₃ requires 245.1148, found $[M+Na]^+$ 245.1149; **IR** ν_{max} (film)/cm⁻¹ 3418 br., 2937, 1613, 1514, 1464, 1421, 1302, 1248, 1174, 1034, 929, 821.

(+)-(R)-3-((4-Methoxybenzyl)oxy)pent-4-enal (119)

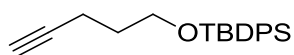


To a solution of *alcohol* **118** (1.45 g, 6.53 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added Dess-Martin periodinane (3.60 g, 8.49 mmol), and the reaction stirred for 3 h whilst slowly warming towards room temperature. The reaction mixture was then diluted with Et₂O and poured into a saturated solution of Na₂S₂O₃ (45 mL). The mixture was stirred vigorously until all solids dissolved, the two layers were separated, and the organic layer was washed with a saturated solution of NaHCO₃ (45 mL). The organics were dried over Na₂SO₄,

filtered and concentrated. Purification by flash column chromatography (10-12% Et₂O/petrol) afforded the desired product as a colourless oil (1.18 g, 82%).

$[\alpha]_D^{20} +31.0$ ($c = 1$, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 9.75 (s, 1H, CHO), 7.35-7.08 (m, 2H, ArCH), 6.89 (d, 2H, J 8.6, ArCH), 5.81 (ddd, 1H, J 17.3, 10.0, 7.6, CH=CH₂), 5.43-5.22 (m, 2H, CH=CH₂), 4.56 (d, 1H, J 11.4, OCH_AH_BAr), 4.43-4.19 (m, 2H, OCH_AH_BAr and CHOPMB), 3.82 (s, 3H, OCH₃), 2.74 (ddd, 1H, J 16.3, 8.2, 2.5, CH_AH_BCHOPMB), 2.63-2.36 (m, 1H, CH_AH_BCHOPMB); δ_C (100 MHz, CDCl₃) 201.2 (CHO), 159.7 (ArC), 137.5 (CH=CH₂), 130.4 (ArC), 129.9 (ArC), 118.6 (CH=CH₂), 114.2 (ArC), 75.4 (CHOPMB), 70.4 (OCH₂Ar), 55.7 (OCH₃), 49.5 (CH₂CHOPMB); **HRMS** (ESI⁺) C₁₃H₁₆NaO₃ requires 243.0992, found $[M+Na]^+$ 243.0991; **IR** ν_{max} (film)/cm⁻¹ 2935, 2838, 1726, 1613, 1514, 1465, 1248, 1174, 1078, 1035, 933, 822.

***tert*-Butyl(pent-4-yn-1-yloxy)diphenylsilane (121)**

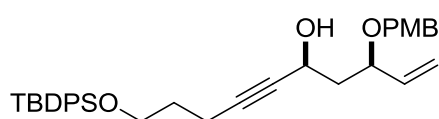


To a solution of pent-4-yn-1-ol (930 μ L, 10.0 mmol) and *tert*-butylchlorodiphenylsilane (2.86 g, 11.0 mmol) in CH₂Cl₂ (6.7 mL) was dropwise added a solution of imidazole (1.02 g, 15.0 mmol) in CH₂Cl₂ (13.3 mL). The reaction mixture was stirred at room temperature for 18 h, then was poured into HCl (1 M, 13 mL). The two layers were separated and the organic layer was dried over MgSO₄, filtered, and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (0-2.5% Et₂O/petrol) to afford the title compound as a colourless oil (2.96 g, 92%).

δ_H (400 MHz, CDCl₃) 7.69 (d, 4H, J 6.6, ArCH), 7.49-7.36 (m, 6H, ArCH), 3.77 (t, 2H, J 6.1, CH₂O), 2.37 (td, 2H, J 7.1, 2.5, CH₂CH₂O), 1.94 (t, 1H, J 2.4, HC $\equiv$ C), 1.80 (t, 2H, J 6.4, HC $\equiv$ CCH₂) 1.08 (s, 9H, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 136.0 (ArC), 134.2 (ArC),

130.0 (ArC), 128.0 (ArC), 84.7 (HC≡C), 68.7 (HC≡C), 62.7 (CH₂O), 31.8 (HC≡CCH₂), 27.3 (C(CH₃)₃), 19.7 ((C(CH₃)₃), 15.4 (CH₂CH₂O). Spectroscopic data consistent with that reported in literature.¹³²

(+)-(3*R*,5*S*)-10-((*tert*-Butyldiphenylsilyl)oxy)-3-((4-methoxybenzyl)oxy)dec-1-en-6-yn-5-ol (122)

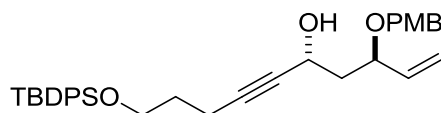


To a solution of *alkyne* **121** (366 mg, 1.14 mmol) in THF (3.5 mL) cooled to $-78\text{ }^{\circ}\text{C}$ was dropwise added *n*-butyllithium (1.6 M in hexanes, 0.6 mL, 1.1 mmol). After 10 minutes, a solution of *aldehyde* **119** (50 mg, 0.23 mmol) in THF (1.1 mL) was added dropwise. The reaction mixture was stirred for 2.5 h at $-78\text{ }^{\circ}\text{C}$ before being quenched by the addition of MeOH (0.7 mL) and allowed to warm to room temperature. A saturated solution of NH₄Cl (0.7 mL) was added and the aqueous layer was extracted with Et₂O (3 x 1.5 mL). The combined organics were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to provide the crude product. Purification by flash column chromatography (20-30% Et₂O/petrol) afforded the desired product as a colourless oil (40 mg, 32%) along with the *anti* diastereomer (27 mg, 22%).

$[\alpha]_{\text{D}}^{20} +38.8$ ($c = 1$, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 7.72-7.64 (m, 4H, ArCH), 7.47-7.35 (m, 6H, ArCH), 7.24 (d, 2H, J 8.6, ArCH), 6.88 (d, 2H, J 8.3, ArCH), 5.82-5.71 (m, 1H, CH=CH₂), 5.32-5.23 (m, 2H, CH=CH₂), 4.55 (m, 2H, OCH_AH_BAr and CHOH), 4.28 (d, 1H, J 11.4, OCH_AH_BAr), 4.01 (td, 1H, J 8.6, 4.0, CHOPMB), 3.80 (s, 3H, OCH₃), 3.73 (t, 2H, J 5.9, SiOCH₂), 2.91 (d, 1H, J 3.0, OH), 2.40-2.32 (m, 2H, CH₂C≡C), 2.06 (dt, 1H, J 14.1, 8.8, CH_AH_BCHOPMB), 1.84-1.70 (m, 3H, CH_AH_BCHOPMB and SiOCH₂CH₂),

1.06 (s, 9H, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 159.2 (ArC), 137.8 (CH=CH₂), 135.5 (ArC), 133.8 (ArC), 130.0 (ArC), 129.5 (ArC), 127.6 (ArC), 117.8 (CH=CH₂), 113.8 (ArC), 84.8 (CH₂C≡C), 80.8 (CH₂C≡C), 79.2 (CHOPMB), 69.9 (OCH₂Ar), 62.4 (SiOCH₂), 61.4 (CHOH), 55.2 (OCH₃), 43.6 (CH₂CHOPMB), 31.5 (SiOCH₂CH₂), 26.8 (C(CH₃)₃), 19.2 ((C(CH₃)₃), 15.2 (CH₂C≡C); **HRMS** (ESI⁺) C₃₄H₄₂NaO₄Si requires 565.2745, found [M+Na]⁺ 565.2736; **IR** ν_{max} (film)/cm⁻¹ 3435 br., 2953, 2931, 2858, 1613, 1514, 1471, 1428, 1302, 1248, 1174, 1110, 1033, 931, 823, 742, 703, 614.

(+)-(3*R*,5*R*)-10-((*tert*-Butyldiphenylsilyl)oxy)-3-((4-methoxybenzyl)oxy)dec-1-en-6-yn-5-ol (122)

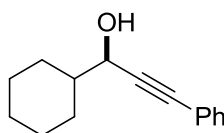


(*R*)-Alcohol **122** was isolated in the synthesis of (*S*)-alcohol **122**.

$[\alpha]_{\text{D}}^{20} +13.4$ (c = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 7.79-7.59 (m, 4H, ArCH), 7.49-7.32 (m, 6H, ArCH), 7.26 (d, 2H, *J* 8.8, ArCH), 6.86 (2H, d, *J* 8.8, ArCH), 5.78 (ddd, 1H, *J* 17.4, 10.2, 7.4, CH=CH₂), 5.36-5.14 (m, 2H, CH=CH₂), 4.53 (m, 2H, OCH_AH_BAr and CHOH), 4.31 (d, 1H, *J* 11.0, OCH_AH_BAr), 4.29-4.23 (m, 1H, CHOPMB), 3.79 (s, 3H, OCH₃), 3.73 (t, 2H, *J* 6.0, SiOCH₂), 3.24 (d, 1H, *J* 5.9, OH), 2.36 (t, 2H, *J* 6.6, CH₂C≡C), 2.06-1.88 (m, 1H, CH_AH_BCHOPMB), 1.84-1.78 (m, 1H, CH_AH_BCHOPMB), 1.75 (quin, 2H, *J* 6.8, SiOCH₂CH₂), 1.05 (s, 9H, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 159.2 (ArC), 137.7 (CH=CH₂), 135.5 (ArC), 133.8 (ArC), 129.6 (ArC), 127.6 (ArC), 117.4 (CH=CH₂), 113.8 (ArC), 85.0 (CH₂C≡C), 80.9 (CH₂C≡C), 78.2 (CHOPMB), 70.3 (OCH₂Ar), 62.4 (SiOCH₂), 60.5 (CHOH), 55.3 (OCH₃), 42.4 (CH₂CHOPMB), 31.7 (SiOCH₂CH₂), 26.8 (C(CH₃)₃), 19.2 ((C(CH₃)₃), 15.3 (CH₂C≡C); **HRMS** (ESI⁺) C₃₄H₄₂NaO₄Si requires

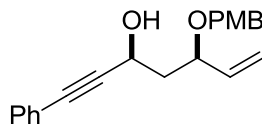
565.2745, found $[M+Na]^+$ 565.2746; **IR** $\nu_{\max}$ (film)/ cm^{-1} 3470 br., 2931, 2858, 1613, 1514, 1464, 1428, 1302, 1248, 1174, 1110, 1036, 931, 822, 743, 704, 614.

(-)-(R)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol (125)



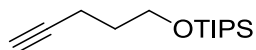
A Schlenk tube containing $\text{Zn}(\text{OTf})_2$ (200 mg, 0.550 mmol) was heated to 120 °C in vacuo for 16 hours. To this was added (+)-*N*-methylephedrine (108 mg, 0.600 mmol) and the Schlenk tube was purged with argon for 15 minutes. Freshly distilled NEt_3 (84 μL , 0.90 mmol) and toluene (1.5 mL) were added and the resulting mixture was stirred for 2.5 h. Freshly distilled phenylacetylene (73 μL , 0.60 mmol) was added and after stirring for 15 minutes, freshly distilled cyclohexanecarbaldehyde (55 μL , 0.50 mmol) was added. The reaction mixture was stirred for 2.5 h before being quenched by the addition of a saturated solution of NH_4Cl (3 mL). The reaction mixture was poured into a separation funnel containing Et_2O (10 mL). The two layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2-10% EtOAc /petrol) to afford a colourless oil (85 mg, 54%).

$[\alpha]_{\text{D}}^{20}$ -10.8 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.53-7.40 (m, 2H, ArCH) 7.38-7.30 (m, 3H, ArCH) 4.40 (d, 1H, J 6.1, CHOH), 1.95 (d, 2H, d, J 12.4, OH and cyCH), 1.82 (d, 3H, J 12.4, cyCH) 1.72 (d, 2H, J 12.6, cyCH) 1.09-1.03 (m, 5H, cyCH); δ_{C} (100 MHz, CDCl_3) 132.7 (ArC), 128.3 (ArC), 122.7 (ArC), 89.2 ($\text{PhC}\equiv\text{C}$), 85.7 ($\text{PhC}\equiv\text{C}$), 67.7 (CHOH), 44.3 (cyC), 28.6 (cyC), 28.2 (cyC), 26.4 (cyC), 25.9 (cyC). Spectroscopic data consistent with that reported in literature.¹³³

(+)-(3*S*,5*R*)-5-((4-Methoxybenzyl)oxy)-1-phenylhept-6-en-1-yn-3-ol (127)

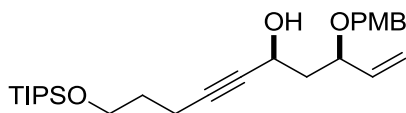
To a solution of phenylacetylene (140 μ L, 1.14 mmol) in THF (3.5 mL) cooled to -78 $^{\circ}$ C was dropwise added *tert*-butyllithium (1.9 M in pentane, 0.6 mL, 1.1 mmol). After the reaction was stirred at -78 $^{\circ}$ C for 10 minutes, a solution of *aldehyde* **119** (50 mg, 0.23 mmol) in THF (1.0 mL) was dropwise added. The reaction mixture was stirred for 2 h at -78 $^{\circ}$ C and was then quenched by the addition of MeOH (1.0 mL) and allowed to warm to room temperature. A saturated solution of NH_4Cl (1.0 mL) was added and the aqueous layer was extracted with Et_2O (3 x 1.5 mL), the combined organics washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to provide the crude product. Purification by flash column chromatography (10-25% Et_2O /petrol) afforded the desired product as a colourless oil (17.5 mg, 24%) along with the *anti* diastereomer (14.0 mg, 19%).

$[\alpha]_{\text{D}}^{20} +79.4$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.47-7.35 (m, 2H, ArCH) 7.35-7.23 (m, 5H, ArCH), 6.88 (d, 2H, J 8.3, ArCH), 5.82 (ddd, 1H, J 17.4, 10.0, 8.0, $\text{CH}=\text{CH}_2$), 5.38-5.26 (m, 2H, $\text{CH}=\text{CH}_2$), 4.83 (dd, 1H, J 7.8, 5.3, CHOH), 4.59 (d, 1H, J 11.4, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.33 (d, 1H, J 11.1, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.17-4.06 (m, 1H, CHOPMB), 3.79 (s, 3H, OCH_3), 2.22 (dt, 1H, J 14.1, 8.7, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.98 (dt, 1H, J 14.1, 4.6, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$); δ_{C} (100 MHz, CDCl_3) 159.2 (ArC), 137.8 ($\text{CH}=\text{CH}_2$), 131.7 (ArC), 129.5 (ArC), 128.2 (ArC), 122.6 (ArC), 118.0 ($\text{CH}=\text{CH}_2$), 113.9 (ArC), 89.5 ($\text{PhC}\equiv\text{C}$), 84.7 ($\text{PhC}\equiv\text{C}$), 79.0 (CHOPMB), 69.9 (OCH_2Ar), 61.7 (CHOH), 55.2 (OCH_3), 43.3 (CHOCH_2); **HRMS** (ESI^+) $\text{C}_{21}\text{H}_{22}\text{NaO}_3$ requires 345.1461, found $[\text{M}+\text{Na}]^+$ 345.1458; **IR** ν_{max} (film)/ cm^{-1} 3418, 1613, 1514, 1249, 1070, 1034.

Triisopropyl(pent-4-yn-1-yloxy)silane (129)

To a solution of pent-4-yn-1-ol (930 μ L, 10.0 mmol) and triisopropylchlorosilane (2.4 mL, 11 mmol) in CH_2Cl_2 (7.0 mL) was dropwise added a solution of imidazole (1.02 g, 15.0 mmol) in CH_2Cl_2 (13 mL). The reaction mixture was stirred at room temperature for 18 h and was then poured into a saturated solution of NaHCO_3 (10 mL). The two layers were separated and the aqueous extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried over MgSO_4 , filtered, concentrated, and the resultant colourless oil purified by flash column chromatography (0-1.6% Et_2O /petrol) to afford the desired product (2.2 g, 93%).

δ_{H} (400 MHz, CDCl_3) 3.78 (t, 2H, J 6.1, CH_2O), 2.32 (td, 2H, J 7.1, 2.5, $\text{C}\equiv\text{CCH}_2$), 1.93 (t, 1H, J 2.7, $\text{HC}\equiv\text{C}$), 1.76 (quin, 2H, J 6.6, $\text{C}\equiv\text{CCH}_2\text{CH}_2$), 1.10-1.02 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_{C} (100 MHz, CDCl_3) 84.4 ($\text{HC}\equiv\text{C}$), 68.1 ($\text{HC}\equiv\text{C}$), 61.7 (CH_2O), 31.8 ($\text{C}\equiv\text{CCH}_2\text{CH}_2$), 18.0 ($(\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$), 14.9 ($\text{C}\equiv\text{CCH}_2$), 12.0 ($(\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$). Spectroscopic data consistent with that reported in literature.¹³⁴

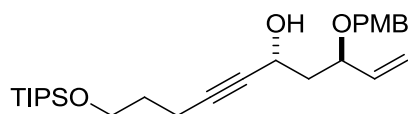
(+)-(3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-10-((triisopropylsilyl)oxy)dec-1-en-6-yn-5-ol (130)

To a solution of *alkyne* **129** (655 mg, 2.72 mmol) in THF (13.7 mL) cooled to -78°C was dropwise added *tert*-butyllithium (1.9 M in pentane, 1.4 mL, 2.7 mmol). After 10 minutes, a solution of *aldehyde* **119** (200 mg, 0.908 mmol) in THF (4.3 mL) was added dropwise.

The reaction mixture was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$ before being quenched by the addition of MeOH (2.7 mL) and allowed to warm to room temperature. A saturated solution of NH_4Cl (2.7 mL) was added and the aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organics were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to provide the crude product. Purification by flash column chromatography (10-20% Et_2O /petrol) afforded the desired product as a colourless oil (0.155 g, 37%) along with (*R*)-**130** as a colourless oil (0.125 g, 30%).

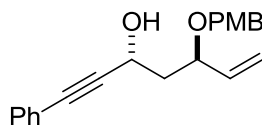
$[\alpha]_{\text{D}}^{20} +52.2$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.24 (d, 2H, J 8.6, ArCH), 6.88 (d, 2H, J 8.6, ArCH), 5.77 (ddd, 1H, J 17.6, 9.9, 7.8, $\text{CH}=\text{CH}_2$), 5.34-5.22 (m, 2H, $\text{CH}=\text{CH}_2$), 4.55 (d, 2H, J 11.1, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$ and CHOH), 4.29 (d, 1H, J 11.4, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.08-3.96 (m, 1H, CHOPMB), 3.81 (s, 3H, OCH_3), 3.74 (t, 2H, J 6.1, SiOCH_2), 2.93 (br. s, 1H, OH), 2.31 (td, 2H, J 7.1, 1.8, $\text{CH}_2\text{C}\equiv\text{C}$), 2.08 (dt, 1H, J 14.1, 8.8, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.83 (dt, 1H, J 14.1, 4.4, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.72 (quin, 2H, J 6.6, $\text{SiOCH}_2\text{CH}_2$), 1.14-0.98 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_{C} (100 MHz, CDCl_3) 159.2 (ArC), 137.9 ($\text{CH}=\text{CH}_2$), 130.0 (ArC), 129.5 (ArC), 117.8 ($\text{CH}=\text{CH}_2$), 113.8 (ArC), 85.1 ($\text{CH}_2\text{C}\equiv\text{C}$), 80.7 ($\text{CH}_2\text{C}\equiv\text{C}$), 79.3 (CHOPMB), 69.9 (OCH_2Ar), 61.9 (SiOCH_2), 61.4 (CHOH), 55.3 (OCH_3), 43.7 (CH_2CHOPMB), 31.9 ($\text{SiOCH}_2\text{CH}_2$), 18.0 $((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 15.2 ($\text{CH}_2\text{C}\equiv\text{C}$), 12.0 $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{27}\text{H}_{44}\text{NaO}_4\text{Si}$ requires 483.2901, found $[\text{M}+\text{Na}]^+$ 483.2890; **IR** ν_{max} (film)/ cm^{-1} 3423 br., 2943, 2866, 1614, 1514, 1464, 1248, 1108, 1068, 1037.

(+)-(3*R*,5*R*)-3-((4-Methoxybenzyl)oxy)-10-((triisopropylsilyl)oxy)dec-1-en-6-yn-5-ol
(130)



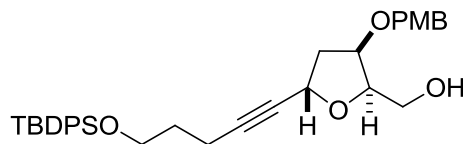
(*R*)-Alcohol **130** was isolated in the synthesis of alcohol (*S*)-**130**.

$[\alpha]_D^{20} +50.7$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.27 (d, 2H, J 8.6, ArCH), 6.88 (d, 2H, J 8.6, ArCH), 5.80 (ddd, 1H, J 17.4, 10.1, 7.3, $\text{CH}=\text{CH}_2$), 5.35-5.22 (m, 2H, $\text{CH}=\text{CH}_2$), 4.60-4.55 (m, 1H, CHOH), 4.55 (d, 1H, J 11.1, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.34-4.27 (m, 1H, CHOPMB), 4.33 (d, 1H, J 11.1, $\text{OCH}_A\text{H}_B\text{Ar}$), 3.81 (s, 3H, OCH_3), 3.76 (t, 2H, J 6.1, SiOCH_2), 3.30 (d, 1H, J 7.3, OH), 2.33 (td, 2H, J 7.2, 1.8, $\text{CH}_2\text{C}\equiv\text{C}$), 2.08-1.94 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.83 (ddd, 1H, J 14.5, 6.6, 3.4, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.73 (quin, 2H, J 6.6, $\text{SiOCH}_2\text{CH}_2$), 1.15-1.01 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_{C} (100 MHz, CDCl_3) 159.2 (ArC), 137.7 ($\text{CH}=\text{CH}_2$), 130.0 (ArC), 129.6 (ArC), 117.5 ($\text{CH}=\text{CH}_2$), 113.8 (ArC), 85.2 ($\text{CH}_2\text{C}\equiv\text{C}$), 80.8 ($\text{CH}_2\text{C}\equiv\text{C}$), 78.2 (CHOPMB), 70.3 (OCH_2Ar), 61.9 (SiOCH_2), 60.6 (CHOH), 55.3 (OCH_3), 42.4 (CH_2CHOPMB), 32.0 ($\text{SiOCH}_2\text{CH}_2$), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 15.2 ($\text{CH}_2\text{C}\equiv\text{C}$), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{27}\text{H}_{44}\text{NaO}_4\text{Si}$ requires 483.2901, found $[\text{M}+\text{Na}]^+$ 483.2888; **IR** ν_{max} (film)/ cm^{-1} 3443 br., 2943, 2866, 1514, 1248, 1108, 1067.

(+)-(3*R*,5*R*)-5-((4-Methoxybenzyl)oxy)-1-phenylhept-6-en-1-yn-3-ol (127)

(*R*)-Alcohol **127** was isolated in the synthesis of alcohol (*S*)-**127**.

$[\alpha]_D^{20} +76.0$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.48-7.35 (m, 2H, ArCH), 7.35-7.24 (m, 5H, ArCH), 6.86 (d, 2H, J 8.6, ArCH), 5.84 (ddd, 1H, J 17.3, 10.0, 7.6, $\text{CH}=\text{CH}_2$), 5.43-5.23 (m, 2H, $\text{CH}=\text{CH}_2$), 4.89-4.75 (br. s, 1H, CHOH), 4.60 (d, 1H, J 11.1, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.46-4.39 (m, 1H, CHOPMB), 4.39 (d, 1H, J 11.1, $\text{OCH}_A\text{H}_B\text{Ar}$), 3.77 (s, 3H, OCH_3), 2.21-2.10 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.97 (ddd, 1H, J 14.5, 6.2, 3.3, $\text{CH}_A\text{H}_B\text{CHOPMB}$); δ_{C} (100 MHz, CDCl_3) 159.3 (ArC), 137.6 ($\text{CH}=\text{CH}_2$), 131.7 (ArC), 129.7 (ArC), 128.2 (ArC), 122.8 (ArC), 117.8 ($\text{CH}=\text{CH}_2$), 113.9 (ArC), 89.7 ($\text{PhC}\equiv\text{C}$), 84.9 ($\text{PhC}\equiv\text{C}$), 78.2 (CHOPMB), 70.3 (OCH_2Ar), 61.1 (CHOH), 55.2 (OCH_3), 42.0 (CH_2CHOPMB); **HRMS** (ESI^+) $\text{C}_{21}\text{H}_{22}\text{NaO}_3$ requires 345.1461, found $[\text{M}+\text{Na}]^+$ 345.1459; **IR** ν_{max} (film)/ cm^{-1} 3443, 2930, 1613, 1514, 1249, 1069, 1035.

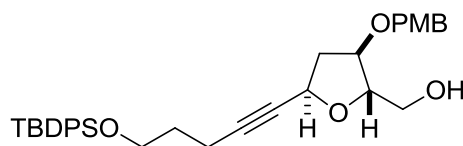
(-)-((2*R*,3*R*,5*S*)-5-(5-((*tert*-Butyldiphenylsilyl)oxy)pent-1-yn-1-yl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methanol (131)

Bis-homoallylic alcohol (*S*)-**122** (92 mg, 0.17 mmol) was subjected to **General Procedure B** (24 h) using $\text{Co}(\text{nmp})_2$ (48 mg, 0.085 mmol, 50 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 3.0 μL , 0.017 mmol). The temperature was then increased to 65 $^\circ\text{C}$ for 5.5 h until all starting material had been consumed. Purification by flash column

chromatography (20-50% EtOAc/petrol) afforded the desired product as a colourless oil (43 mg, 45%).

$[\alpha]_D^{20}$ -18.8 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.72-7.62 (m, 4H, ArCH), 7.46-7.35 (m, 6H, ArCH), 7.24 (d, 2H, J 8.6, ArCH), 6.90 (d, 2H, J 8.6, ArCH), 4.84 (t, 1H, J 6.9, $\text{C}\equiv\text{CCH}$), 4.55 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.35 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.31 (td, 1H, J 5.3, 3.0, CHOPMB), 4.15 (q, 1H, J 5.0, CHCH_2OH), 3.90-3.83 (m, 2H, CH_2OH), 3.82 (s, 3H, OCH_3), 3.73 (t, 2H, J 5.9, SiOCH_2), 2.37 (td, 2H, J 7.1, 1.6, $\text{CH}_2\text{C}\equiv\text{C}$), 2.34-2.27 (ddd, 1H, J 13.1, 6.6, 2.8, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 2.07 (ddd, 1H, J 13.0, 7.3, 5.7, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.76 (quin, 2H, J 6.6, $\text{SiOCH}_2\text{CH}_2$), 1.05 (s, 9H, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 159.4 (ArC), 135.5 (ArC), 133.8 (ArC), 129.6 (ArC), 127.6 (ArC), 114.0 (ArC), 85.7 ($\text{CH}_2\text{C}\equiv\text{C}$), 80.5 ($\text{C}\equiv\text{CCH}$), 79.7 (CHCH_2OH), 79.2 (CHOPMB), 71.4 (OCH_2Ar), 67.3 ($\text{C}\equiv\text{CCH}$), 62.4 (SiOCH_2), 61.9 (CH_2OH), 55.3 (OCH_3), 39.9 (CH_2CHOPMB), 31.4 ($\text{SiOCH}_2\text{CH}_2$), 26.8 ($\text{C}(\text{CH}_3)_3$), 19.2 ($\text{C}(\text{CH}_3)_3$), 15.3 ($\text{CH}_2\text{C}\equiv\text{C}$); **HRMS** (ESI^+) $\text{C}_{34}\text{H}_{42}\text{NaO}_5\text{Si}$ requires 581.2694, found $[\text{M}+\text{Na}]^+$ 581.2699; **IR** ν_{max} (film)/ cm^{-1} 3423 br., 2932, 1514, 1428, 1249, 1110.

(-)-((2S,3R,5R)-5-(5-((*tert*-Butyldiphenylsilyl)oxy)pent-1-yn-1-yl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methanol (132)

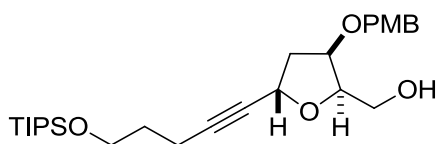


Bis-homoallylic alcohol (R)-122 (78 mg, 0.14 mmol) was subjected to **General Procedure B** (45 h) using $\text{Co}(\text{nmp})_2$ (16 mg, 0.029 mmol, 40 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 3.0 μL , 0.014 mmol) at 55 $^\circ\text{C}$. Purification by flash column

chromatography (5-60% EtOAc/petrol) afforded the desired product as a pale yellow oil (42 mg, 54%).

$[\alpha]_D^{20}$ -9.6 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.68 (dd, 4H, J 7.7, 1.4, ArCH), 7.47-7.34 (m, 6H, ArCH), 7.25 (d, 1H, J 8.6, ArCH), 7.28 (d, 1H, J 8.6, ArCH), 6.88 (d, 2H, J 8.6, ArCH), 4.72 (t, 1H, J 6.7, $\text{C}\equiv\text{CCH}$), 4.50 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.43 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.15-4.08 (m, 1H, CHCH_2OH), 4.08-4.00 (m, 1H, CHOPMB), 3.80 (s, 3H, OCH_3), 3.77 (d, 1H, J 3.0, $\text{CH}_A\text{H}_B\text{OH}$), 3.73 (t, 2H, J 6.1, SiOCH_2), 3.61 (dd, 1H, J 11.9, 4.3, $\text{CH}_A\text{H}_B\text{OH}$), 2.44-2.35 (m, 3H, $\text{CH}_2\text{C}\equiv\text{C}$ and $\text{CH}_A\text{H}_B\text{CHOPMB}$), 2.09 (dt, 1H, J 12.5, 6.1, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.77 (quin, 2H, J 6.6, $\text{SiOCH}_2\text{CH}_2$), 1.06 (s, 9H, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 159.3 (ArC), 135.5 (ArC), 133.8 (ArC), 129.6 (ArC), 129.2 (ArC), 127.6 (ArC), 113.8 (ArC), 86.0 ($\text{CH}_2\text{C}\equiv\text{C}$), 83.0 (CHCH_2OH), 79.4 ($\text{C}\equiv\text{C}$), 78.4 (CHOPMB), 71.6 (OCH_2Ar), 67.8 ($\text{C}\equiv\text{CCH}$), 62.5 (SiOCH_2), 62.5 (CH_2OH), 55.3 (OCH_3), 39.3 (CH_2CHOPMB), 31.5 ($\text{SiOCH}_2\text{CH}_2$), 26.8 ($\text{C}(\text{CH}_3)_3$), 19.2 ($\text{C}(\text{CH}_3)_3$), 15.4 ($\text{CH}_2\text{C}\equiv\text{C}$); **HRMS** (ESI^+) $\text{C}_{34}\text{H}_{42}\text{NaO}_5\text{Si}$ requires 581.2694, found $[\text{M}+\text{Na}]^+$ 581.2693; **IR** ν_{max} (film)/ cm^{-1} 3443 br., 2931, 2857, 1514, 1428, 1250.

(-)-((2*R*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)tetrahydrofuran-2-yl)methanol (**133**)

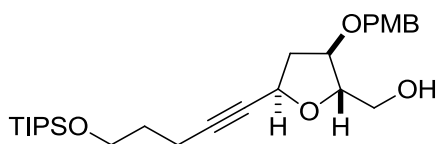


Bis-homoallylic alcohol (*R*)-**130** (120 mg, 0.261 mmol) was subjected to **General Procedure B** (29 h) using $\text{Co}(\text{nmp})_2$ (29 mg, 0.052 mmol, 20 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 5.0 μL , 0.026 mmol). After 6 h, a further 10 mol%

catalyst (14.7 mg, 0.0261 mmol) was added. Purification by flash column chromatography (10-30% Et₂O/petrol) afforded the desired product as a colourless oil (65 mg, 52%).

$[\alpha]_D^{20}$ -20.6 ($c = 1$, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 7.24 (d, 2H, J 8.6, ArCH), 6.89 (d, 2H, J 8.6, ArCH), 4.86 (t, 1H, J 6.9, C $\equiv$ CCH), 4.56 (d, 1H, J 11.6, OCH_AH_BAr), 4.40-4.30 (m, 2H, OCH_AH_BAr and CHOPMB), 4.17 (q, 1H, J 5.1, CHCH₂OH), 3.88-3.77 (m, 2H, CH₂OH), 3.82 (s, 3H, OCH₃), 3.75 (t, 2H, J 6.1, SiOCH₂), 2.36-2.28 (m, 3H, CH₂C $\equiv$ C and CH_AH_BCHOPMB), 2.12 (ddd, 1H, J 13.0, 7.2, 5.6, CH_AH_BCHOPMB), 1.73 (quin, 2H, J 6.6, SiOCH₂CH₂), 1.13-0.99 (m, 21H, ((CH₃)₂CH)₃SiO); δ_C (100 MHz, CDCl₃) 159.4, 129.2 (ArC), 114.0 (ArC), 85.9, 80.5, 79.8 (CHOPMB), 71.4 (OCH₂Ar), 67.3 (C $\equiv$ CCH), 61.9 (CH₂OH), 61.8 (SiOCH₂), 55.3 (OCH₃), 39.9 (CH₂CHOPMB), 31.8 (SiOCH₂CH₂), 18.0 ((CH₃)₂CH)₃SiO), 15.2 (CH₂C $\equiv$ C), 12.0 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₂₇H₄₄NaO₅Si requires 499.2850, found [M+Na]⁺ 499.2845; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3443 br., 2943, 2866, 1613, 1514, 1463, 1249, 1107, 1068, 1039.

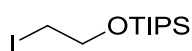
(-)-((2S,3R,5R)-3-((4-Methoxybenzyl)oxy)-5-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)tetrahydrofuran-2-yl)methanol (134)



Bis-homoallylic alcohol (*S*)-**130** (100 mg, 0.217 mmol) was subjected to **General Procedure B** (24 h) using Co(nmp)₂ (31 mg, 0.054 mmol, 25 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 4.0 μ L, 0.022 mmol). Purification by flash column chromatography (10-40% Et₂O/petrol) afforded the desired product as a colourless oil (50 mg, 48%).

$[\alpha]_D^{20}$ -18.0 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.27 (d, 2H, J 8.3, ArCH), 6.89 (d, 2H, J 8.6, ArCH), 4.74 (t, 1H, J 6.8, $\text{C}\equiv\text{CCH}$), 4.52 (d, 1H, J 11.4, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.45 (d, 1H, J 11.4, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.17-4.09 (m, 1H, CHCH_2OH), 4.09-4.00 (m, 1H, CHOPMB), 3.85-3.79 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$), 3.82 (s, 3H, OCH_3), 3.79-3.70 (m, 2H, SiOCH_2), 3.61 (dd, 1H, J 12.0, 4.2, $\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$), 2.47-2.39 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 2.39-2.32 (td, 2H, J 7.1, 1.5, $\text{CH}_2\text{C}\equiv\text{C}$), 2.11 (dt, 1H, J 12.5, 6.1, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.74 (quin, 2H, J 13.1, 6.6, $\text{SiOCH}_2\text{CH}_2$), 1.07 (s, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_{C} (100 MHz, CDCl_3) 159.3 (ArC), 130.0 (ArC), 129.2 (ArC), 113.8 (ArC), 86.1 ($\text{CH}_2\text{C}\equiv\text{C}$), 83.0 (CHCH_2OH), 79.3 ($\text{C}\equiv\text{C}$), 78.4 (CHOPMB), 71.6 (OCH_2Ar), 67.9 ($\text{C}\equiv\text{CCH}$), 62.4 (CH_2OH), 61.9 (SiOCH_2), 55.3 (OCH_3), 39.8 (CH_2CHOPMB), 31.8 ($\text{SiOCH}_2\text{CH}_2$), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 15.3 ($\text{CH}_2\text{C}\equiv\text{C}$), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{27}\text{H}_{44}\text{NaO}_5\text{Si}$ requires 499.2850, found $[\text{M}+\text{Na}]^+$ 499.2840; **IR** ν_{max} (film)/ cm^{-1} 3424 br., 2943, 2866, 1514, 1250, 1068.

(2-Iodoethoxy)triisopropylsilane (137)

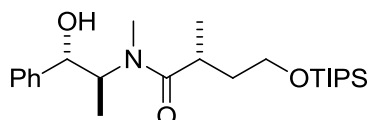


A solution of 2-iodoethanol (3.1 mL, 40 mmol), triisopropylchlorosilane (10.3 mL, 48.0 mmol) and imidazole (3.27 g, 48.0 mmol) in CH_2Cl_2 (48 mL) was stirred at room temperature for 18 h. Water (12 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (0-3% Et_2O /petrol) to yield the title compound as a colourless oil (11.9 g, 91%).

δ_{H} (400 MHz, CDCl_3) 3.93 (t, 2H, J 7.2, CH_2O), 3.24 (t, J 7.1, ICH_2), 1.16-1.00 (m, 21H, $\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$); δ_{C} (100 MHz, CDCl_3) 64.9 (CH_2O), 18.4 ($\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$), 12.4

(OSi(CH(CH₃)₂)₃), 7.4 (ICH₂). Spectroscopic data consistent with that reported in literature.¹³⁵

(+)-(R)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N,2-dimethyl-4-((triisopropylsilyl)oxy)butanamide (138)

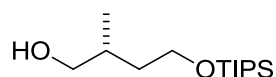


n-Butyllithium (1.6 M in hexanes, 18.0 mL, 45.2 mmol) was added to a suspension of flame-dried LiCl (4.1 g, 97 mmol) and diisopropylamine (6.8 mL, 48 mmol) in THF (45 mL) at 0 °C. The resulting slurry was stirred at 0 °C for 15 minutes, then at room temperature for 20 minutes before it was cooled to −78 °C. A solution of *N*-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide (5.0 g, 23 mmol) in THF (125 mL) was added dropwise and the reaction mixture was stirred for 45 minutes at −78 °C, warmed to 0 °C for 15 minutes and then stirred at room temperature for 15 minutes. The reaction mixture was then cooled back down to −78 °C. *Alkyl halide 137* (5.3 g, 16 mmol) was added neat and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 18 h. The reaction was quenched by the addition of a saturated solution of NH₄Cl (120 mL) and the aqueous phase extracted with EtOAc (2 x 120 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (25-35% EtOAc/petrol), giving the desired amide as a colourless oil (6.58 g, 97%).

[α]_D²⁰ +32.3 (*c* = 1, CH₂Cl₂); δ_{H} (400 MHz, C₆D₆) (6:1 mixture of rotamers) (major rotamer) 7.31 (d, 2H, *J* 7.6, ArCH), 7.25-7.05 (m, 3H, ArCH), 4.54 (t, 1H, *J* 7.1, CHOH), 4.28-4.10 (m, 1H, CHCH₃), 3.64-3.44 (m, 2H, CH₂OSi), 2.91-2.80 (m, 1H, CHCH₃), 2.46

(s, 3H, NCH_3), 2.02-1.91 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2\text{OSi}$), 1.56-1.46 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2\text{OSi}$), 1.17-0.99 (m, 27H, CHOHCHCH_3 , COCHCH_3 and $\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$); δ_C (100 MHz, CDCl_3) (major rotamer) 179.2 (C=O), 142.5 (ArC), 128.3 (ArC), 127.6 (ArC), 126.3 (ArC), 76.6 (CHOH), 60.6 (CH_2OSi), 37.1 (CHCH_3CH_2), 32.7 (NCH_3 and CHCH_3), 32.4 (COCHCH_3), 18.0 ($\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$), 17.0 (COCHCH_3), 14.4 (CHOHCHCH_3), 11.9 ($\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$). Spectroscopic data consistent with that reported in literature.⁹⁶

(+)-(R)-2-Methyl-4-((triisopropylsilyl)oxy)butan-1-ol (139)

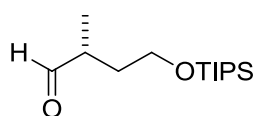


n-Butyllithium (1.6 M in hexanes, 29.3 mL, 46.9 mmol) was added dropwise to a solution of diisopropylamine (6.9 mL, 49 mmol) in THF (52 mL) at 0 °C. The mixture was stirred at room temperature for 10 minutes before it was cooled to 0 °C. $\text{BH}_3\cdot\text{NH}_3$ (1.45 g, 46.9 mmol) was added portion-wise and the resulting slurry was allowed to warm to room temperature over 1 h. The mixture was cooled back down to 0 °C and a solution of *amide* **138** (4.95 g, 11.7 mmol) in THF (8.0 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature over a period of 2 h once addition was complete. The reaction was then quenched at 0 °C by the addition of HCl (1.0 M, 7.6 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (7% EtOAc/petrol) afforded *alcohol* **139** as a colourless oil (2.67 g, 88%).

$[\alpha]_\text{D}^{20}$ +6.7 ($c = 1$, CH_2Cl_2); δ_H (400 MHz, CDCl_3) 3.85 (dt, 1H, J 10.4, 5.2, $\text{CH}_\text{A}\text{H}_\text{B}\text{OSi}$), 3.78-3.70 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{OSi}$), 3.59-3.48 (m, 1H, $\text{HOCH}_\text{A}\text{H}_\text{B}$), 3.48-3.38 (m, 1H, $\text{HOCH}_\text{A}\text{H}_\text{B}$), 3.13 (br. s, 1H, OH), 1.90-1.77 (m, 1H, CHCH_3), 1.59 (q, 2H, J 6.1,

CHCH₃CH₂) 1.19-1.00 (m, 21H, OSi(CH(CH₃)₂)₃), 0.93 (d, 3H, *J* 6.8, CHCH₃); δ_C (100 MHz, CDCl₃) 68.3 (OCH₂), 62.0 (CH₂OSi), 37.8 (CHCH₃CH₂), 34.6 (CHCH₃), 17.9 (OSi(CH(CH₃)₂)₃), 17.5 (CHCH₃), 11.9 (OSi(CH(CH₃)₂)₃); **HRMS** (ESI⁺) C₁₄H₃₂NaO₂Si requires 283.2064, found [M+Na]⁺ 283.2059; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3334 br., 2943, 2867, 1463, 1384, 1248, 1099, 997.

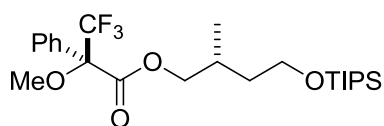
(-)-(R)-2-Methyl-4-((triisopropylsilyl)oxy)butanal (140)



To a solution of oxalyl chloride (0.81 mL, 9.4 mmol) in CH₂Cl₂ (27 mL) cooled to -78 °C was dropwise added a solution of dimethylsulfoxide (1.4 mL, 20 mmol) in CH₂Cl₂ (9.0 mL). After stirring for 10 minutes, a solution of *alcohol* **139** (1.88 g, 7.22 mmol) in CH₂Cl₂ (14.0 mL) was added. The reaction mixture was stirred for 1 h at -78 °C, after which NEt₃ (7.1 mL, 51 mmol) was added and the reaction mixture allowed to warm to room temperature. After 1 h, the reaction was quenched by the addition of brine (36 mL), and the aqueous layer extracted with Et₂O (2 x 40 mL). The combined organic fractions were dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (1.87 g, 100%), which was used without further purification.

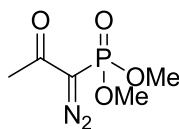
$[\alpha]_D^{20}$ -4.8 (*c* = 1, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 9.68 (d, 1H, *J* 1.3, CHO), 3.85-3.70 (2H, m, CH₂O), 2.60-2.52 (m, 1H, CHCH₃), 2.05-1.93 (m, 1H, CHCH₃CH_AH_B), 1.70-1.57 (m, 1H, CHCH₃CH_AH_B), 1.13 (d, 3H, *J* 7.1, CHCH₃), 1.10-0.99 (m, 21H, OSi(CH(CH₃)₂)₃); δ_C (100 MHz, CDCl₃) 204.9 (C=O), 60.6 (CH₂OSi), 43.5 (CHCH₃), 33.9 (CHCH₃CH₂), 18.0 ((OSi(CH(CH₃)₂)₃), 13.1 (CHCH₃), 11.9 ((OSi(CH(CH₃)₂)₃). Spectroscopic data consistent with that reported in literature.¹³⁶

(R)-(R)-2-Methyl-4-((triisopropylsilyl)oxy)butyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (141)



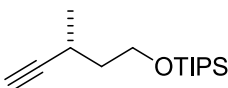
To a solution of *alcohol 139* (20 mg, 0.077 mmol) in CH_2Cl_2 (1.2 mL) was added *R*-(+)- α -methoxy- α -trifluoromethylphenylacetic acid (56 mg, 0.25 mmol), dicyclohexylcarbodiimide (49 mg, 0.25 mmol) and 4-(dimethylamino)pyridine (29 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 7 h, then was filtered through Celite[®] and the solvents evaporated *in vacuo*. Purification by flash column chromatography (1-2% Et_2O /petrol) afforded the title compound as a colourless oil (35 mg, 96%).

$[\alpha]_{\text{D}}^{20} +30.1$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.56-7.49 (m, 2H, ArCH), 7.44-7.38 (m, 3H, m, ArCH), 4.30 (dd, 1H, J 10.6, 5.3, $\text{OCH}_\text{A}\text{H}_\text{B}$), 4.14 (dd, 1H, J 10.6, 6.6, $\text{OCH}_\text{A}\text{H}_\text{B}$), 3.79-3.68 (m, 2H, CH_2OSi), 3.56 (s, 3H, OCH_3), 2.10 (dq, 1H, J 13.1, 6.5, CHCH_3), 1.64 (1 H, dq, J 13.3, 6.6, $\text{CHCH}_3\text{CH}_\text{A}\text{H}_\text{B}$), 1.46-1.36 (m, 1H, $\text{CHCH}_3\text{CH}_\text{A}\text{H}_\text{B}$), 1.13-1.01 (m, 21H, $\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$), 0.96 (d, 3H, J 6.8, CHCH_3); δ_{C} (100 MHz, CDCl_3) 166.6 (C=O), 132.4 (ArC), 129.6 (ArC), 128.4 (ArC), 127.4 (ArC), 71.4 (OCH_2), 60.9 (CH_2OSi), 55.4 (OCH_3), 36.2 (CHCH_3CH_2), 29.5 (CHCH_3), 18.0 ($\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$), 16.7 (CHCH_3), 11.9 ($\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$); δ_{F} (376 MHz, CDCl_3) -71.6 (CF_3); **HRMS** (ESI^+) $\text{C}_{24}\text{H}_{39}\text{F}_3\text{NaO}_4\text{Si}$ requires 499.2462, found $[\text{M}+\text{Na}]^+$ 499.2449; **IR** ν_{max} (film)/ cm^{-1} 2943, 2867, 2120, 1750, 1464, 1389, 1245, 1169, 1105, 1024.

Dimethyl (1-diazo-2-oxopropyl)phosphonate (144)

To a suspension of 4-acetamidobenzenesulfonyl azide (10.4 g, 43.4 mmol) and potassium carbonate (13.2 g, 95.5 mmol) in MeCN (430 mL) was added dimethyl (2-oxopropyl)phosphonate (6.0 mL, 43 mmol). The reaction was stirred at room temperature for 16 h, was filtered, and the solvents evaporated *in vacuo*. The residue was re-dissolved in CH₂Cl₂ and filtered through Celite[®]. The filtrate was concentrated *in vacuo* to afford the title compound as a yellow oil (8.17 g, 98%).

δ_{H} (400 MHz, CDCl₃) 3.86 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 2.27 (s, 3H, CH₃CO); δ_{C} (100 MHz, CDCl₃) 189.8 (C=O), 53.6 (OCH₃), 53.5 (OCH₃), 27.1 (CH₃).

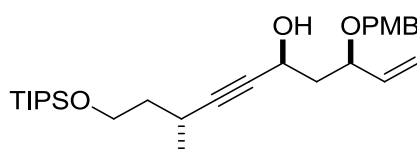
(-)-(R)-Triisopropyl((3-methylpent-4-yn-1-yl)oxy)silane (145)

To a solution of *phosphonate* **144** (2.2 mL, 15 mmol) in THF (28 mL) at -78 °C was added sodium methoxide solution (25 wt% in methanol, 3.3 mL, 15 mmol). After stirring for 30 minutes, a solution of *aldehyde* **140** (1.87 g, 7.24 mmol) in THF (17 mL) was added dropwise. The reaction mixture was stirred for 18 h whilst slowly warming to room temperature. Water (17.5 mL) was added, and the mixture extracted with Et₂O (3 x 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated *in vacuo*. Purification by flash column chromatography afforded the title compound as a colourless oil (1.40 g, 76%).

$[\alpha]_{\text{D}}^{20}$ -31.9 (c = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 3.87-3.79 (m, 2H, CH₂O), 2.68 (sxtld, 1H, *J* 7.1, 2.5, CHCH₃), 2.03 (d, 1H, *J* 2.5, HC≡C), 1.68 (q, 2H, *J* 6.7, CHCH₃CH₂), 1.22

(d, 3H, J 7.1, CHCH₃), 1.16-1.01 (m, 21H, OSi(CH(CH₃)₂)₃); δ_C (100 MHz, CDCl₃) 88.9 (HC≡C), 68.2 (HC≡C), 61.0 (CH₂O), 39.8 (CHCH₃), 22.1 (CHCH₃), 20.9 (CHCH₃CH₂), 18.0 ((OSi(CH(CH₃)₂)₃), 12.0 ((OSi(CH(CH₃)₂)₃); **IR** $\nu_{\max}$ (film)/cm⁻¹ 3313, 2942, 2867, 1463, 1111.

(+)-(3*R*,5*S*,8*R*)-3-((4-Methoxybenzyl)oxy)-8-methyl-10-((triisopropylsilyl)oxy)dec-1-en-6-yn-5-ol (146)

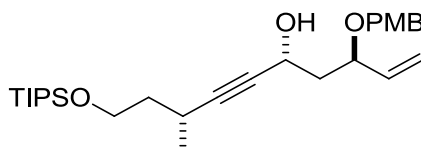


To a solution of *alkyne* **145** (867 mg, 3.41 mmol) in THF (35 mL) cooled to -78 °C was dropwise added *n*-butyllithium (1.6 M in hexanes, 1.8 mL, 3.4 mmol). After 10 minutes, a solution of *aldehyde* **119** (500 mg, 2.27 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 2.5 h at -78 °C before being quenched by the addition of MeOH (6.7 mL) and allowed to warm to room temperature. A saturated solution of NH₄Cl (6.7 mL) was added and the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organics were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to provide the crude product. Purification by flash column chromatography (10-30% Et₂O/petrol) afforded the desired product as a colourless oil (0.46 g, 42%) along with diastereomer (*R*)-**146** as a pale yellow oil (0.33 g, 30%).

$[\alpha]_D^{20} +15.5$ ($c = 1$, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 7.24 (m, 2H, J 8.6, ArCH), 6.87 (m, 2H, J 8.6, ArCH), 5.78 (ddd, 1H, J 17.6, 9.9, 7.7, CH=CH₂), 5.33-5.21 (m, 2H, CH=CH₂), 4.58-4.54 (m, 1H, CHOH), 4.55 (d, 1H, J 11.4, OCH_AH_BAr), 4.29 (d, 1H, J 11.1, OCH_AH_BAr), 4.03 (td, 1H, J 8.5, 4.2, CHOPMB), 3.81 (s, 3H, OCH₃), 3.80 (t, 2H, J 6.3, SiOCH₂), 2.87 (d, 1H, J 3.5, OH), 2.68 (sxttd, 1H, J 7.1, 1.3, CHCH₃), 2.08 (dt, 1H, J 14.1,

8.8, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.82 (dt, 1H, J 14.1, 4.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.64 (d, 2H, J 6.5, $\text{SiOCH}_2\text{CH}_2$), 1.17 (d, 3H, J 7.1, CHCH_3), 1.13-0.98 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_C (100 MHz, CDCl_3) 159.2 (ArC), 154.1 (ArC), 138.0 ($\text{CH}=\text{CH}_2$), 130.0 (ArC), 129.4 (ArC), 117.7 ($\text{CH}=\text{CH}_2$), 113.8 (ArC), 89.4 ($\text{CHCH}_3\text{C}\equiv\text{C}$), 80.9 ($\text{C}\equiv\text{CCHOH}$), 79.3 (CHOPMB), 70.0 (OCH_2Ar), 61.4 (SiOCH_2), 61.1 (CHOH), 55.3 (OCH_3), 43.8 (CH_2CHOPMB), 39.9 ($\text{SiOCH}_2\text{CH}_2$), 22.2 (CHCH_3), 21.0 (CHCH_3), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{28}\text{H}_{46}\text{NaO}_4\text{Si}$ requires 497.3058, found $[\text{M}+\text{Na}]^+$ 497.3062; **IR** ν_{max} (film)/ cm^{-1} 3480 br., 2942, 2866, 1514, 1248.

(+)-(3*R*,5*R*,8*R*)-3-((4-Methoxybenzyl)oxy)-8-methyl-10-((triisopropylsilyl)oxy)dec-1-en-6-yn-5-ol (146)

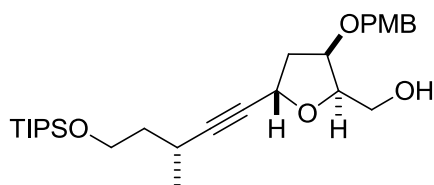


Alcohol (*R*)-**146** was isolated in the synthesis of alcohol (*S*)-**146**.

$[\alpha]_\text{D}^{20} +13.6$ ($c = 1$, CH_2Cl_2); δ_H (400 MHz, CDCl_3) 7.27 (d, 2H, J 8.6, ArCH), 6.88 (d, 2H, J 8.6, ArCH), 5.80 (ddd, 1H, J 17.4, 10.2, 7.6, $\text{CH}=\text{CH}_2$), 5.37-5.21 (m, 2H, $\text{CH}=\text{CH}_2$), 4.62-4.55 (m, 1H, CHOH), 4.55 (d, 1H, J 10.9, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.33 (d, 1H, J 10.9, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.34-4.27 (m, 1H, CHOPMB), 3.81 (s, 3H, OCH_3), 3.81 (t, 2H, J 6.3, SiOCH_2), 3.23 (d, 1H, J 7.6, OH), 2.70 (sxttd, 1H, J 6.8, 1.0, CHCH_3), 2.08-1.95 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.83 (ddd, 1H, J 14.5, 6.6, 3.4, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.66 (q, 2H, J 6.5, $\text{SiOCH}_2\text{CH}_2$), 1.20 (d, 3H, J 6.8, CHCH_3), 1.15-0.99 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_C (100 MHz, CDCl_3) 159.2 (ArC), 137.8 ($\text{CH}=\text{CH}_2$), 130.1 (ArC), 129.5 (ArC), 117.3 ($\text{CH}=\text{CH}_2$), 113.9 (ArC), 89.5 ($\text{CHCH}_3\text{C}\equiv\text{C}$), 81.0 ($\text{C}\equiv\text{CCHOH}$), 78.4 (CHOPMB), 70.4 (OCH_2Ar), 61.1 (SiOCH_2), 60.5 (CHOH), 55.2 (OCH_3), 42.5 (CH_2CHOPMB), 40.0 ($\text{SiOCH}_2\text{CH}_2$),

22.3 (CHCH₃), 21.1 (CHCH₃), 18.0 ((CH₃)₂CH)₃SiO), 12.0 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₂₈H₄₆NaO₄Si requires 497.3058, found [M+Na]⁺ 497.3056; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3480 br., 2942, 2866, 1514, 1248, 1109.

(-)-((2*R*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-((*R*)-3-methyl-5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)tetrahydrofuran-2-yl)methanol (**147**)

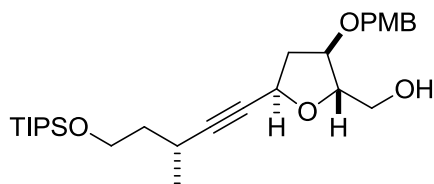


Bis-homoallylic alcohol (*S*)-**146** (58 mg, 0.12 mmol) was subjected to **General Procedure B** (21 h) using Co(nmp)₂ (17 mg, 0.031 mmol, 25 mol%) and *tert*-butyl hydroperoxide (5.5 M in decane, 2.0 μ L, 0.012 mmol). Purification by flash column chromatography (10-20% EtOAc/petrol) afforded the desired product as a colourless oil (29 mg, 49%).

$[\alpha]_D^{20}$ -47.5 (*c* = 1, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 7.24 (d, 2H, *J* 8.3, ArCH), 6.89 (d, 2H, *J* 8.6, ArCH), 4.87 (t, 1H, *J* 7.3, C $\equiv$ CCH), 4.56 (d, 1H, *J* 11.4, OCH_AH_BAr), 4.36 (d, 1H, *J* 11.6, OCH_AH_BAr), 4.36-4.30 (m, 1H, CHOPMB), 4.17 (q, 1H, *J* 4.9, CHCH₂OH), 3.88-3.81 (m, 2H, CH₂OH), 3.82 (s, 3H, OCH₃), 3.79 (t, 2H, *J* 6.3, SiOCH₂), 2.69 (sxt, 1H, *J* 6.9, CHCH₃), 2.34 (ddd, 1H, *J* 12.9, 6.5, 2.8, CH_AH_BCHOPMB), 2.11 (ddd, 1H, *J* 13.0, 7.2, 5.8, CH_AH_BCHOPMB), 1.65 (q, 2H, *J* 6.3, SiOCH₂CH₂), 1.18 (d, 3H, *J* 6.8, CHCH₃), 1.15-1.00 (m, 21H, ((CH₃)₂CH)₃SiO); δ_C (100 MHz, CDCl₃) 159.6 (ArC), 153.2 (ArC), 129.5 (ArC), 129.2 (ArC), 127.3 (ArC), 114.0 (ArC), 90.2 (CHCH₃C $\equiv$ C), 80.4 (CHCH₂OH), 79.8 (CHOPMB), 71.4 (OCH₂Ar), 67.3 (C $\equiv$ CCH), 61.9 (CH₂OH), 61.1 (SiOCH₂), 55.3 (OCH₃), 40.0 (CH₂CHOPMB), 39.8 (SiOCH₂CH₂), 22.3 (CHCH₃), 20.9 (CHCH₃), 18.0 ((CH₃)₂CH)₃SiO), 12.0 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₂₈H₄₆NaO₅Si

requires 513.3007, found $[M+Na]^+$ 513.2998; **IR** $\nu_{\max}$ (film)/ cm^{-1} 3418 br., 2942, 2866, 1514, 1249, 1068.

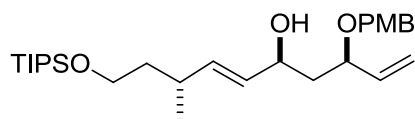
(–)-((2*S*,3*R*,5*R*)-3-((4-Methoxybenzyl)oxy)-5-((*R*)-3-methyl-5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)tetrahydrofuran-2-yl)methanol (148)



Bis-homoallylic alcohol (R)-**146** (40 mg, 0.084 mmol) was subjected to **General Procedure B** (25 h) using $\text{Co}(\text{nmp})_2$ (12 mg, 0.021 mmol, 35 mol%) at 60 °C. Purification by flash column chromatography (10-20% EtOAc/petrol) afforded the desired product as a pale green oil (19 mg, 48%).

$[\alpha]_D^{20}$ –48.2 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.26 (d, 2H, J 8.3, ArCH), 6.88 (d, 2H, J 8.6, ArCH), 4.73 (td, 1H, J 6.8, 1.3, $\text{C}\equiv\text{CCH}$), 4.51 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.43 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.13-4.08 (m, 1H, CHCH_2OH), 4.08-4.01 (m, 1H, CHOPMB), 3.82-3.77 (m, 3H, $\text{CH}_A\text{H}_B\text{OH}$ and SiOCH_2), 3.81 (s, 3H, OCH_3), 3.61 (dd, 1H, J 11.9, 4.3, $\text{CH}_A\text{H}_B\text{OH}$), 2.71 (sxt, 1H, J 6.7, CHCH_3), 2.46-2.36 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 2.16-2.04 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.66 (q, 2H, J 6.5, $\text{SiOCH}_2\text{CH}_2$), 1.19 (d, 3H, J 6.8, CHCH_3), 1.13-0.99 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_{C} (100 MHz, CDCl_3) 153.9 (ArC), 129.2 (ArC), 113.8 (ArC), 90.4 ($\text{CHCH}_3\text{C}\equiv\text{C}$), 83.0 (CHCH_2OH), 79.5 ($\text{CHCH}_3\text{C}\equiv\text{C}$), 78.4 (CHOPMB), 71.6 (OCH_2Ar), 67.8 ($\text{C}\equiv\text{CCH}$), 62.4 (CH_2OH), 61.1 (SiOCH_2), 55.3 (OCH_3), 40.0 (CH_2CHOPMB), 39.9 ($\text{SiOCH}_2\text{CH}_2$), 22.4 (CHCH_3), 20.8 (CHCH_3), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{28}\text{H}_{46}\text{NaO}_5\text{Si}$ requires 513.3007, found $[M+Na]^+$ 513.3008; **IR** $\nu_{\max}$ (film)/ cm^{-1} 3443 br., 2941, 2866, 1612, 1514, 1463, 1249, 1104, 1067.

(+)-(3*R*,5*S*,8*R*,*E*)-3-((4-Methoxybenzyl)oxy)-8-methyl-10-((triisopropylsilyl)oxy)deca-1,6-dien-5-ol (149)



From alkyne 146:

To a solution of *alkyne* **146** (0.20 g, 0.42 mmol) in Et₂O (4.2 mL) at 0 °C was dropwise added Red-Al[®] (65 wt% in toluene, 0.260 mL, 0.84 mmol). The ice bath was removed and the reaction was stirred for 3.5 h at room temperature. The reaction mixture was slowly poured into a half-saturated solution of NH₄Cl (8 mL), and a saturated solution of Rochelle's salt was added (8 mL). The slurry was stirred vigorously for 30 minutes, and then the aqueous layer was extracted with Et₂O (2 x 15 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (8-10% EtOAc/petrol) to furnish the title compound as a colourless oil (162 mg, 81%).

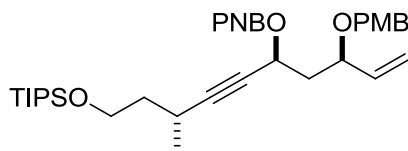
$[\alpha]_{\text{D}}^{20} +23.6$ (c = 1, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 7.25 (d, 2H, *J* 8.6, ArCH), 6.88 (d, 2H, *J* 8.6, ArCH), 5.83-5.70 (m, 1H, CH=CH₂) 5.55 (dd, 1H, *J* 15.5, 7.5, CH=CHCHOH), 5.41 (dd, 1H, *J* 15.5, 6.2, CHCH₃CH=CH), 5.31-5.21 (m, 2H, CH=CH₂), 4.57 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.29 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.30-4.23 (m, 1H, CHOH), 4.05-3.96 (m, 1H, CHOPMB), 3.81 (s, 3H, OCH₃), 3.71-3.64 (m, 2H, SiOCH₂), 3.28 (s, 1H, OH), 2.31 (dt, 1H, *J* 13.8, 6.9, CHCH₃), 1.84 (dt, 1H, *J* 14.4, 9.5, COCH_AH_BCO), 1.63 (dt, 1H, *J* 14.4, 3.5, COCH_AH_BCO), 1.53 (dq, 2H, *J* 14.0, 6.9, SiOCH₂CH₂), 1.14-1.02 (m, 21H, ((CH₃)₂CH)₃SiO), 0.98 (d, 3H, *J* 6.8, CHCH₃); δ_{C} (100 MHz, CDCl₃) 159.3 (ArC), 138.2 (CH=CH₂), 136.7 (CH=CH), 130.7 (ArC), 130.0 (ArC), 129.6 (CH=CH), 129.5 (ArC), 117.5 (CH=CH₂), 113.9 (ArC), 80.3 (CHOPMB), 71.8 (CHOH), 69.9

(OCH₂Ar), 61.4 (SiOCH₂), 55.3 (OCH₃), 43.1 (CH₂CHOPMB), 39.8 (SiOCH₂CH₂), 32.7 (CHCH₃), 20.4 (CHCH₃), 18.0 ((CH₃)₂CH)₃SiO), 12.0 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₂₈H₄₈NaO₄Si requires 499.3214, found [M+Na]⁺ 499.3201; **IR** ν_{max} (film)/cm⁻¹ 3455 br., 2942, 2866, 1614, 1514.

From alkyne **150**:

To a solution of alkyne **150** (0.70 g, 1.1 mmol) in Et₂O (22 mL) cooled to 0 °C, was dropwise added Red-Al[®] (65% w/w in toluene, 1.7 mL, 5.6 mmol). The ice bath was removed and the reaction was stirred for 18 h at room temperature. The reaction mixture was slowly poured into a half-saturated solution of NH₄Cl (50 mL), and a saturated solution of Rochelle's salt was added (50 mL). The slurry was stirred vigorously for 30 minutes, and then the aqueous layer was extracted with Et₂O (2 x 100 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% EtOAc/petrol) to furnish the title compound as a pale yellow oil (0.378 g, 71%). Spectroscopic data consistent with that reported above for *alkene 149*.

(-)-(3*R*,5*S*,8*R*)-3-((4-Methoxybenzyl)oxy)-8-methyl-10-((triisopropylsilyl)oxy)dec-1-en-6-yn-5-yl 4-nitrobenzoate (**150**)

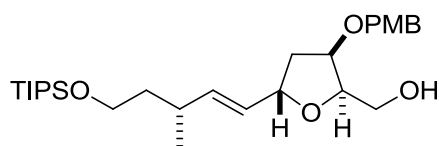


To a solution of *alcohol (R)*-**146** (0.320 g, 0.675 mmol) in THF (20 mL) was added 4-nitrobenzoic acid (0.451 g, 2.70 mmol) and triphenylphosphine (0.708 g, 2.70 mmol). The mixture was cooled to 0 °C before diisopropyl azodicarboxylate (0.53 mL, 2.7 mmol)

was added dropwise. The ice bath was removed and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was slowly poured into a half-saturated solution of NaHCO_3 (23 mL) and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (3-5% EtOAc/petrol) afforded the title compound as a pale yellow oil (0.359 g, 86%).

$[\alpha]_{\text{D}}^{20} -4.2$ ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 8.26 (d, 2H, J 8.3, ArCH), 8.15 (d, 2H, J 8.3, ArCH), 7.23 (d, 2H, J 8.1, ArCH), 6.84 (d, 2H, J 8.3, ArCH), 5.87-5.72 (m, 2H, $\text{CH}=\text{CH}_2$ and CHOPNB), 5.35-5.20 (m, 2H, $\text{CH}=\text{CH}_2$), 4.54 (d, 1H, J 11.1, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.26 (d, 1H, J 11.1, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.08-3.97 (m, 1H, CHOPMB), 3.79 (s, 3H, OCH_3) 3.77 (t, 2H, J 5.8, SiOCH_2), 2.76-2.64 (m, 1H, CHCH_3), 2.36-2.24 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 2.08-1.97 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.70-1.53 (m, 2H, $\text{SiOCH}_2\text{CH}_2$), 1.17 (d, 3H, J 6.8, CHCH_3), 1.11-0.93 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); δ_{C} (75 MHz, CDCl_3) 163.4 ($\text{C}=\text{O}$), 159.1 (ArC), 150.5 (ArC), 137.8 ($\text{CH}=\text{CH}_2$), 135.6 (ArC), 130.8 (ArC), 130.3 (ArC), 129.4 (ArC), 123.4 (ArC), 118.0 ($\text{CH}=\text{CH}_2$), 113.7 (ArC), 91.4 ($\text{CHCH}_3\text{C}\equiv\text{C}$), 77.5 (CHOPMB), 70.0 (OCH_2Ar), 63.9 (CHOPNB), 61.0 (SiOCH_2), 55.2 (OCH_3), 41.2 (CH_2CHOPMB), 39.7 ($\text{SiOCH}_2\text{CH}_2$), 22.3 (CHCH_3), 20.8 (CHCH_3), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 11.9 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{35}\text{H}_{49}\text{NaO}_7\text{Si}$ requires 646.3171, found $[\text{M}+\text{Na}]^+$ 646.3168; **IR** ν_{max} (film)/ cm^{-1} 2942, 2866, 1730, 1530, 1269, 1248, 1100.

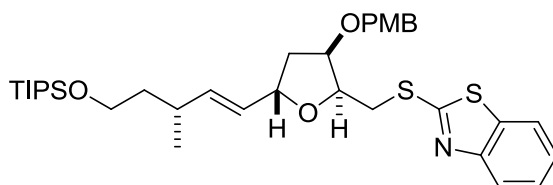
(-)-2-((((2R,3R,5S)-3-((4-Methoxybenzyl)oxy)-5-((R,E)-3-methyl-5-((triisopropylsilyl)oxy)pent-1-en-1-yl)tetrahydrofuran-2-yl)methanol (151)



Bis-homoallylic alcohol **149** (865 mg, 1.82 mmol) was subjected to **General Procedure B** using $\text{Co}(\text{nmp})_2$ (0.257 g, 0.454 mmol, 25 mol%) at 70 °C. Purification by flash column chromatography (10-16% EtOAc/petrol) afforded the desired product as a colourless oil (513 mg, 57%).

$[\alpha]_{\text{D}}^{20}$ -42.9 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.25 (d, 2H, J 8.6, ArCH), 6.90 (d, 2H, J 8.6, ArCH), 5.66 (dd, 1H, J 15.4, 7.3, $\text{CHCH}_3\text{CH}=\text{CH}$), 5.43 (dd, 1H, J 15.4, 7.1, $\text{CH}=\text{CHCH}$), 4.65-4.58 (m, 1H, $\text{CH}=\text{CHCH}$), 4.59 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.37 (d, 1H, J 11.4, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.31-4.24 (m, 1H, CHOPMB), 4.13 (q, 1H, J 5.1, CHCH_2OH), 3.88-3.78 (m, 2H, CH_2OH), 3.82 (s, 3H, OCH_3), 3.69 (t, 2H, J 6.7, SiOCH_2), 2.35 (dt, 1H, J 13.8, 6.9, CHCH_3), 2.26 (ddd, 1H, J 13.1, 5.8, 1.8, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.76 (ddd, 1H, J 13.6, 8.9, 5.1, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.64-1.45 (m, 2H, $\text{SiOCH}_2\text{CH}_2$), 1.15-1.02 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 1.01 (d, 3H, J 6.8, CHCH_3); δ_{C} (100 MHz, CDCl_3) 159.4 (ArC), 138.9 ($\text{CH}=\text{CH}$), 129.7 (ArC), 129.2 (ArC), 128.1 ($\text{CH}=\text{CH}$), 114.0 (ArC), 80.9 (CHCH_2OH), 80.4 (CHOPMB), 78.8 ($\text{CH}=\text{CHCH}$), 71.3 (OCH_2Ar), 62.3 (CH_2OH), 61.3 (SiOCH_2), 55.3 (OCH_3), 39.6 ($\text{SiOCH}_2\text{CH}_2$), 38.6 (CH_2CHOPMB), 32.5 (CHCH_3), 20.0 (CHCH_3), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{28}\text{H}_{48}\text{NaO}_5\text{Si}$ requires 515.3163, found $[\text{M}+\text{Na}]^+$ 513.3163; **IR** ν_{max} (film)/ cm^{-1} 3439 br., 2941, 2866, 1613, 1514, 1463, 1248, 1173, 1103, 1068, 1038.

(-)-2-(((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-((*R*,*E*)-3-methyl-5-((triisopropylsilyl)oxy)pent-1-en-1-yl)tetrahydrofuran-2-yl)methyl)thio)benzo[*d*]thiazole (152)

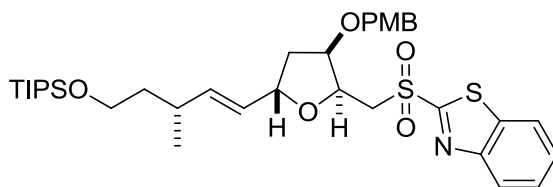


To a solution of *alcohol* **151** (0.487 g, 0.984 mmol) in THF (25 mL) at 0 °C was added 2-benzothiazolethiol (0.496 g, 2.96 mmol) and triphenylphosphine (0.778 g, 2.96 mmol). Diisopropyl azodicarboxylate (590 μ L, 2.96 mmol) was added dropwise and the reaction mixture stirred for 3 h whilst warming to room temperature. The reaction mixture was concentrated *in vacuo* and the crude material purified by flash column chromatography (4-4.5% EtOAc/petrol) to afford the title compound as a yellow oil (0.58 g, 91%).

$[\alpha]_D^{20}$ -69.1 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 7.85 (d, 1H, J 8.1, BtCH), 7.75 (d, 1H, J 7.8, BtCH), 7.41 (t, 1H, J 7.7, BtCH), 7.31 (d, 3H, J 8.6, ArCH and BtCH), 6.90 (d, 2H, J 8.3, ArCH), 5.66 (dd, 1H, J 15.4, 7.3, CH=CH), 5.43 (dd, 1H, J 15.4, 7.3, CH=CH), 4.68-4.61 (m, 1H, CH=CHCH), 4.59 (d, 1H, J 11.6, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.50-4.45 (m, 1H, CHCH₂S), 4.45 (d, 1H, J 11.1, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.25 (t, 1H, J 3.8, CHOPMB), 3.82 (s, 3H, OCH₃), 3.76-3.64 (m, 3H, SiOCH₂ and CH_AH_BS), 3.64-3.54 (m, 1H, CH_AH_BS), 2.41-2.32 (m, 1H, CHCH₃), 2.28 (dd, 1H, J 13.3, 5.4, CH_AH_BCHOPMB), 1.72 (ddd, 1H, J 13.5, 9.7, 4.4, CH_AH_BCHOPMB), 1.61-1.46 (m, 2H, SiOCH₂CH₂), 1.14-1.03 (m, 21H, ((CH₃)₂CH)₃SiO), 1.01 (d, 3H, J 6.8, CHCH₃); δ_{C} (100 MHz, CDCl_3) 159.3 (ArC), 153.3 (ArC), 139.0 (CH=CH), 135.3 (ArC), 130.1 (ArC), 129.3 (ArC), 128.1 (CH=CH), 126.0 (ArC), 124.1 (ArC), 121.5 (ArC), 120.9 (ArC), 113.8 (ArC), 80.2 (CHCH₂S), 79.3 (CH=CHCH), 79.2 (CHOPMB), 71.4 (OCH₂Ar), 61.3 (SiOCH₂), 55.3 (OCH₃), 39.6 (SiOCH₂CH₂), 38.4 (CH₂CHOPMB), 32.5 (CH₂S), 32.5 (CHCH₃), 20.0 (CHCH₃), 18.1

$((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 12.0 $((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{35}\text{H}_{51}\text{NNaO}_4\text{S}_2\text{Si}$ requires 664.2921, found $[\text{M}+\text{Na}]^+$ 664.2929; **IR** ν_{max} (film)/ cm^{-1} 2940, 2865, 1613, 1514, 1461, 1428, 1248, 1102.

(-)-2-(((2S,3R,5S)-3-((4-Methoxybenzyl)oxy)-5-((R,E)-3-methyl-5-((triisopropylsilyl)oxy)pent-1-en-1-yl)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole (153)

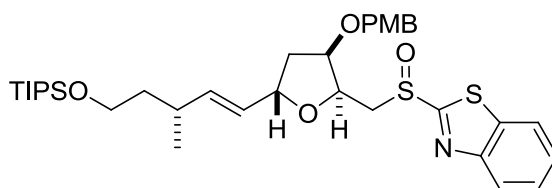


Ammonium molybdate (34.4 mg, 0.0279 mmol) was added to H_2O_2 (30 wt% in H_2O , 114 μL , 1.12 mmol) at 0 °C to produce a bright yellow solution. In a separate flask, *thioether* **152** (0.179 g, 0.279 mmol) was dissolved in EtOH (1.7 mL) and cooled to 0 °C. The molybdate solution was then added to the thioether solution and the cloudy yellow mixture stirred for 2.5 days at room temperature. The reaction mixture was diluted with a saturated solution of NaHCO_3 (1 mL) and the aqueous layer was extracted with Et_2O (2 x 2 mL). (The aqueous layer was carefully quenched by the addition of Na_2SO_3 (s) until starch/iodine paper showed that no more peroxides were present). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (10-14% EtOAc/petrol) afforded the desired *sulfone* **153** as a colourless oil (0.137 g, 73%).

$[\alpha]_{\text{D}}^{20}$ -23.3 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 8.21 (d, 1H, J 8.1, BtCH), 7.99 (d, 1H, J 8.1, BtCH), 7.67-7.53 (m, 2H, BtCH), 7.23 (d, 2H, J 8.1, ArCH), 6.88 (d, 2H, J 8.1, ArCH), 5.31 (dd, 1H, J 15.4, 7.1, CH=CH), 5.21 (dd, 1H, J 15.4, 6.8, CH=CH), 4.65 (d, 1H, J 5.8, CHCH₂S), 4.51 (d, 1H, J 11.1, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.37-4.32 (m, 1H, CH=CHCH),

4.36 (d, 1H, J 11.1, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.26 (t, 1H, J 4.3, CHOPMB), 3.99 (dd, 1H, J 14.8, 6.7, $\text{CH}_A\text{H}_B\text{S}$), 3.89 (dd, 1H, J 14.9, 5.8, $\text{CH}_A\text{H}_B\text{S}$), 3.82 (s, 3H, OCH_3), 3.63-3.55 (m, 2H, SiOCH_2), 2.24-2.14 (m, 2H, CHCH_3 and $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.74-1.61 (m, 1H, $\text{CH}_A\text{H}_B\text{CHOPMB}$), 1.45-1.33 (m, 2H, $\text{SiOCH}_2\text{CH}_2$), 1.13-0.98 (m, 21H, $((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 0.88 (d, 3H, J 6.8, CHCH_3); δ_{C} (100 MHz, CDCl_3) 166.6 (ArC), 159.3 (ArC), 152.7 (ArC), 139.0 ($\text{CH}=\text{CH}$), 137.0 (ArC), 129.7 (ArC), 129.3 (ArC), 127.8 (ArC), 127.4 (ArC), 127.3 ($\text{CH}=\text{CH}$), 125.4 (ArC), 122.3 (ArC), 113.9 (ArC), 79.3 (CHOPMB), 78.4 ($\text{CH}=\text{CHCH}$), 75.3 (CHCH_2S), 71.4 (OCH_2Ar), 61.2 (SiOCH_2), 55.3 (OCH_3), 54.8 (CH_2S), 39.5 ($\text{SiOCH}_2\text{CH}_2$), 38.2 (CH_2CHOPMB), 32.4 (CHCH_3), 19.8 (CHCH_3), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$); **HRMS** (ESI^+) $\text{C}_{35}\text{H}_{51}\text{NNaO}_6\text{S}_2\text{Si}$ requires 696.2819, found $[\text{M}+\text{Na}]^+$ 696.2810; **IR** ν_{max} (film)/ cm^{-1} 2919, 2865, 1734, 1613, 1514, 1464, 1329, 1248, 1147, 1099, 883, 820, 760, 730, 687.

(-)-2-(((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-((*R*,*E*)-3-methyl-5-((triisopropylsilyl)oxy)pent-1-en-1-yl)tetrahydrofuran-2-yl)methyl)sulfinyl)benzo[*d*]thiazole (**154**)

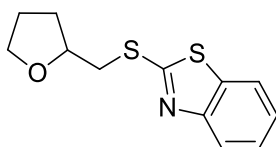


Sulfoxide **154** was isolated as a minor product in the synthesis of sulfone **153**.

$[\alpha]_{\text{D}}^{20}$ -28.0 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 8.08 (d, 1H, J 8.1, BtCH), 8.01 (d, 1H, J 7.8, BtCH), 7.57 (t, 1H, J 7.3, BtCH), 7.50 (t, 1H, J 7.3, BtCH), 7.20 (d, 2H, J 8.3, ArCH), 6.83 (d, 2H, J 8.6, ArCH), 5.66 (dd, 1H, J 15.4, 7.1, $\text{CH}=\text{CH}$), 5.45 (dd, 1H, J 15.3, 7.2, $\text{CH}=\text{CH}$), 4.59 - 4.71 (m, 2H, $\text{CH}=\text{CHCH}$ and CHCH_2S), 4.52 (d, 1H, J 11.6, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.33 (d, 1H, J 11.6, $\text{OCH}_A\text{H}_B\text{Ar}$), 4.14 (t, 1H, J 3.8, CHOPMB), 3.78 (s, 3H,

OCH₃), 3.70 (t, 2H, *J* 6.6, SiOCH₂), 3.56 (dd, 1H, *J* 13.1, 9.1, CH_AH_BS), 3.35 (dd, 1H, *J* 13.1, 3.8, CH_AH_BS), 2.37 (dt, 1H, *J* 13.8, 6.9, CHCH₃), 2.28 (dd, 1H, *J* 12.5, 6.2, CH_AH_BCHOPMB), 1.79 (ddd, 1H, *J* 13.5, 9.2, 4.8, CH_AH_BCHOPMB), 1.65-1.47 (m, 2H, SiOCH₂CH₂), 1.14-1.03 (m, 21H, ((CH₃)₂CH)₃SiO), 1.02 (d, 3H, *J* 6.6, CHCH₃); δ_C (100 MHz, CDCl₃) 159.9 (ArC) 139.0 (CH=CH), 129.3 (ArC), 126.8 (ArC), 126.1 (ArC), 122.3 (ArC), 113.8 (ArC), 79.7 (CHOPMB), 79.0 (CH=CHCH), 71.2 (OCH₂Ar), 61.3 (SiOCH₂), 59.1 (CH₂S), 55.3 (OCH₃), 39.7 (SiOCH₂CH₂), 38.6 (CH₂CHOPMB), 32.6 (CHCH₃), 20.0 (CHCH₃), 18.1 ((CH₃)₂CH)₃SiO, 12.0 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₃₅H₅₁NNaO₅S₂Si requires 680.2870, found [M+Na]⁺ 680.2875; **IR** $\nu_{\max}$ (film)/cm⁻¹ 2926, 2864, 1613, 1513, 1462, 1426, 1312, 1248, 1173, 1062, 883, 820, 758, 729, 680.

(±)-2-(((tetrahydrofuran-2-yl)methyl)thio)-benzo[d]thiazole (155)

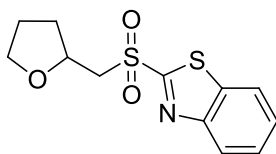


To a solution of tetrahydrofurfuryl alcohol (0.50 mL, 5.2 mmol) in THF (100 mL) at 0 °C was added 2-benzothiazolethiol (1.73 g, 10.3 mmol), triphenylphosphine (2.7 g, 10 mmol), followed the dropwise addition of diisopropyl azodicarboxylate (2.0 mL, 10 mmol). The reaction mixture was stirred for 3.5 h whilst slowly warming to 10 °C, and then was concentrated *in vacuo*. The residue was purified by flash column chromatography (10-15% EtOAc/petrol) to afford a pale yellow oil (0.9 g, 69%).

δ_H (400 MHz, CDCl₃) 7.86 (d, 1H, *J* 8.1, BtCH), 7.75 (d, 1H, *J* 7.8, BtCH), 7.42 (t, 1H, *J* 7.6, BtCH), 7.30 (t, 1H, *J* 7.8, BtCH), 4.30 (quin, 1H, *J* 6.4, CHCH₂S), 4.00-3.92 (m, 1H, CH_AH_BO), 3.85-3.77 (m, 1H, CH_AH_BO), 3.64-3.50 (m, 2H, CH₂S), 2.19-2.09 (m, 1H, CH_AH_BCH), 2.06-1.88 (m, 2H, CH₂CH₂CH), 1.81-1.71 (m, 1H, CH_AH_BCH); δ_C (100 MHz,

CDCl₃) 153.1 (BtC), 135.3 (BtC), 126.0 (BtC), 124.2 (BtC), 121.4 (BtC), 121.0 (BtC), 77.2 (CHCH₂S), 68.5 (CH₂O), 38.1 (CH₂S), 30.8 (CH₂CH), 25.9 (CH₂CH₂CH).

(±)-2-(((tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole (156)

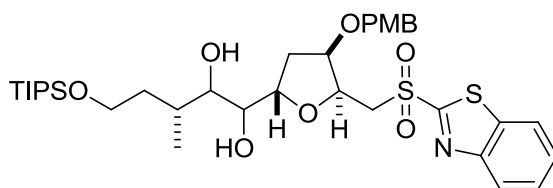


Ammonium molybdate (24.6 mg, 0.0199 mmol) was added to H₂O₂ (30 wt% in H₂O, 82 μL, 0.80 mmol) at 0 °C to produce a bright yellow solution. In a separate flask, *thioether* **155** (50 mg, 0.20 mmol) was dissolved in EtOH (1.2 mL) and cooled to 0 °C. The molybdate solution was then added to the thioether solution and the reaction mixture stirred for 18 hours at room temperature. The reaction mixture was diluted with a saturated solution of NaHCO₃ (1 mL) and the aqueous layer was extracted with Et₂O (2 x 2 mL). (The aqueous layer was carefully quenched by the addition of Na₂SO₃ (s) until starch/iodine paper showed that no more peroxides were present). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/petrol) afforded the desired *sulfone* **156** as a colourless oil (52.3 mg, 93%).

δ_{H} (400 MHz, CDCl₃) 8.22 (d, 1H, *J* 8.1, BtCH), 8.02 (d, 1H, *J* 7.6, BtCH), 7.67-7.56 (m, 2H, BtCH), 4.47 (quin, 1H, *J* 6.6, OCH), 3.88 (dd, 1H, *J* 14.6, 5.5, CH_AH_BS), 3.78-3.64 (m, 2H, CH₂O), 3.62 (dd, 1H, *J* 14.7, 5.3, CH_AH_BS), 2.19 (sxt, 1H, CH₂CH_AH_B), 1.99-1.83 (m, 2H, CH₂CH₂), 1.80-1.69 (m, 1H, CH₂CH_AH_B); δ_{C} (100 MHz, CDCl₃) 166.5 (BtC), 152.6 (BtC), 136.8 (BtC), 127.9 (BtC), 127.5 (BtC), 125.4 (BtC), 122.3 (BtC), 72.6 (CHCH₂S), 68.2 (CH₂O), 59.4 (CH₂S), 31.5 (CH₂CH), 25.2 (CH₂CH₂CH); **HRMS** (ESI⁺)

$C_{12}H_{13}NNaO_3S_2$ requires 306.0229, found $[M+Na]^+$ 306.0220; **IR** $\nu_{\max}$ (film)/ cm^{-1} 2975, 2876, 1472, 1323, 1238, 1143, 1025, 946, 852, 762, 730.

(±)-(3R)-1-((2S,4R,5S)-5-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methyl-5-((triisopropylsilyl)oxy)pentane-1,2-diol (158)

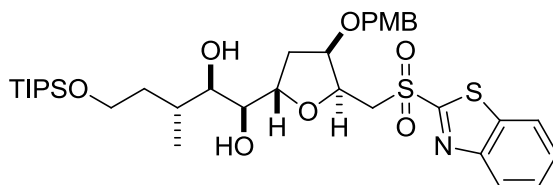


To a solution of *alkene* **153** (45 mg, 0.067 mmol) and *N*-methylemorpholine *N*-oxide (15.7 mg, 0.134 mmol) in water (13.4 μ L), THF (0.13 mL) and *tert*-butanol (107 μ L) was added osmium tetroxide (1.4 mg, 0.0033 mmol). The reaction was stirred at room temperature for 2.5 h before being quenched by the addition of Na_2SO_3 (2.7 mg) and stirred for 30 minutes. Water (0.5 mL) and EtOAc (0.5 mL) were added and the two layers separated. The aqueous phase was extracted with EtOAc (3 x 0.5 mL) and the combined organic phases were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (30-35% EtOAc/petrol) to afford the desired product as a pale orange gum (39 mg, 84%) as a 1.6:1 mixture of diastereomers.

δ_H (400 MHz, $CDCl_3$) (*denotes minor diastereomer) 8.29-8.17 (m, 1H, BtCH), 8.01 (d, 1H, *J* 8.1, BtCH), 7.70-7.53 (m, 2H, BtCH), 7.22 (d, 2H, *J* 8.3, ArCH), 6.88 (d, 2H, *J* 8.3, ArCH), 4.67-4.59 (m, 1H, CHCH₂S), 4.52 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.33 (dd, 1H, *J* 11.1, 4.8, OCH_AH_BAr), 4.24-4.20 (m, 1H, CHOPMB), 4.16-4.10* (m, 1H, CHOHCH), 4.04-3.97 (m, 1H, CHOHCH), 3.97-3.91 (m, 1H, CH_AH_BS), 3.82 (s, 3H, OCH₃), 3.79-3.72 (m, 2H, CH_AH_BS and SiOCH_AH_B), 3.72-3.61 (m, 1H, SiOCH_AH_B), 3.44 (q, 1H, *J* 4.5,

CHOHCH), 3.41-3.36* (m, 1H, CHOHCH), 3.23 (d, 1H, J 3.8, CHCH₃CHOH), 3.13-3.08* (m, 1H, CHCH₃CHOH), 2.92 (d, 1H, J 3.8, CHCH₃CHOH), 2.54 (d, 1H, J 5.3, CHOHCH), 2.15-2.04 (m, 1H, CH_AH_BCHOPMB), 2.04-1.92 (m, 1H, CH_AH_BCHOPMB), 1.82-1.71* (m, 1H, CHCH₃), 1.71-1.64 (m, 1H, CHCH₃), 1.65-1.54 (m, 1H, SiOCH₂CH_AH_B), 1.44-1.33 (m, 1H, SiOCH₂CH_AH_B), 1.15-1.00 (m, 21H, ((CH₃)₂CH)₃SiO), 0.83* (3H, d, J 6.6, CHCH₃), 0.77 (3H, d, J 6.6, CHCH₃); δ_C (100 MHz, CDCl₃) (*denotes minor diastereomer) 166.4 (ArC), 159.3 (ArC), 152.6 (ArC), 136.9 (ArC), 129.3 (ArC), 127.9 (ArC), 127.6 (ArC), 125.4 (ArC), 122.3 (ArC), 113.9 (ArC), 81.3* (CHOHCH), 79.3 (CHOPMB), 78.8 (CHOHCH), 76.4* (CHCH₂S), 75.8 (CHCH₂S), 73.5 (CHCH₃CHOH), 72.7 (CHOHCH), 71.1 (OCH₂Ar), 61.6* (SiOCH₂), 61.0 (SiOCH₂), 55.4 (CH₂S), 55.3 (OCH₃), 36.7 (SiOCH₂CH₂), 35.4* (SiOCH₂CH₂), 32.9 (CHCH₃), 32.0 (CH₂CHOPMB), 18.0 ((CH₃)₂CH)₃SiO), 16.4* (CHCH₃), 13.7 (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₃₅H₅₃NNaO₈S₂Si requires 730.2874, found [M+Na]⁺ 730.2870; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3504 br., 2940, 2865, 1613, 1514, 1465, 1424, 1383, 1328, 1247, 1173, 1146, 1098, 1068, 1037, 996.

(+)-(1S,2R,3R)-1-((2S,4R,5S)-5-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methyl-5-((triisopropylsilyl)oxy)pentane-1,2-diol (159)



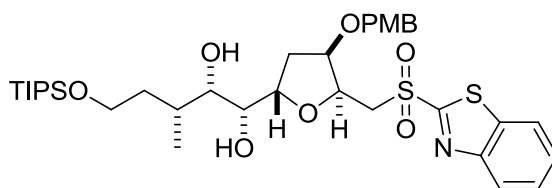
To a stirred solution of alkene **153** (0.200 g, 0.297 mmol) in *tert*-butanol (1.8 mL) and water (1.6 mL) was added potassium ferricyanide (0.293 g, 0.891 mmol), potassium carbonate (0.123 g, 0.891 mmol), methanesulfonamide (28 mg, 0.30 mmol), then

(DHQD)₂PHAL (17.4 mg, 0.0223 mmol). The resultant mixture was stirred vigorously until all reagents had dissolved and then cooled to 0 °C. Potassium osmate (5.5 mg, 0.015 mmol) in water (0.2 mL) was added and the reaction mixture allowed to warm to room temperature and stirred for 4.5 days. The reaction mixture was quenched by the addition of Na₂SO₃ (17 mg) and the mixture stirred vigorously for 30 minutes. EtOAc (7.5 mL) was added and the two layers were separated. The organic phase was washed with water (7.5 mL) and the combined aqueous phases extracted with EtOAc (2 x 8 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30-35% EtOAc/petrol) afforded the title compound as a colourless oil (0.176 g, 84%) as a 12.5:1 mixture of diastereomers.

$[\alpha]_D^{20} +4.0$ (c = 1, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 8.24 (d, 1H, *J* 7.6, BtCH), 8.01 (d, 1H, *J* 7.3, BtCH), 7.67-7.57 (m, 2H, BtCH), 7.22 (d, 2H, *J* 8.6, ArCH), 6.88 (d, 2H, *J* 8.6, ArCH), 4.63 (dt, 1H, *J* 8.2, 4.0, CHCH₂S), 4.53 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.34 (d, 1H, *J* 11.4, OCH_AH_BAr), 4.24-4.18 (m, 1H, CHOPMB), 4.16-4.09 (m, 1H, CHOHCH), 3.95 (dd, 1H, *J* 15.2, 8.3, CH_AH_BS), 3.82 (s, 3H, OCH₃), 3.79-3.75 (m, 1H, CH_AH_BS), 3.75-3.63 (m, 2H, SiOCH₂), 3.38 (dd, 1H, *J* 3.7, 2.4, CHOHCH), 3.24 (d, 1H, *J* 4.3, CHCH₃CHOH), 3.13-3.08 (m, 1H, CHCH₃CHOH), 2.55 (d, 1H, *J* 7.1, CHOHCH), 2.15-2.02 (m, 2H, CH₂CHOPMB), 1.82-1.70 (m, 1H, CHCH₃), 1.46-1.28 (m, 2H, SiOCH₂CH₂), 1.15-1.00 (m, 21H, ((CH₃)₂CH)₃SiO), 0.83 (d, 3H, *J* 6.6, CHCH₃); δ_C (100 MHz, CDCl₃) 166.3 (ArC), 159.4 (ArC), 152.7 (ArC), 136.9 (ArC), 130.3 (ArC), 129.4 (ArC), 128.1 (ArC), 127.6 (ArC), 125.5 (ArC), 122.4 (ArC), 113.9 (ArC), 81.3 (CHOHCH), 79.2 (CHOPMB), 76.4 (CHCH₂S), 76.1 (CHCH₃CHOH), 71.2 (CHOHCH), 71.2 (OCH₂Ar), 61.6 (SiOCH₂), 55.7 (CH₂S), 55.3 (OCH₃), 35.5 (SiOCH₂CH₂), 33.1 (CHCH₃), 32.8 (CH₂CHOPMB), 18.0 ((CH₃)₂CH)₃SiO), 16.4 (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺)

$C_{35}H_{53}NNaO_8S_2Si$ requires 730.2874, found $[M+Na]^+$ 730.2874; **IR** ν_{max} (film)/ cm^{-1} 3507 br., 2940, 2865, 1613, 1514, 1465, 1328, 1248, 1147, 1092.

(+)-(1*R*,2*S*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methyl-5-((triisopropylsilyl)oxy)pentane-1,2-diol (160)

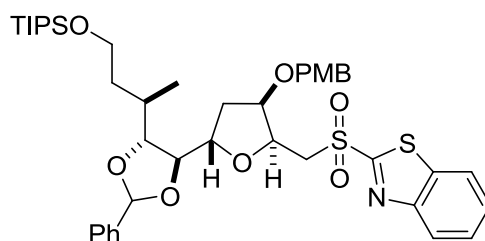


To a stirred solution of alkene **153** (20 mg, 0.030 mmol) in *tert*-butanol/water (0.36 mL, 1:1 mixture) was added potassium ferricyanide (29.3 mg, 0.0891 mmol), potassium carbonate (12.3 mg, 0.0891 mmol), methanesulfonamide (2.83 mg, 0.0297 mmol), then (DHQ)₂PHAL (1.7 mg, 0.0022 mmol). The resultant mixture was stirred vigorously until all reagents had dissolved and then cooled to 0 °C. Potassium osmate (0.55 mg, 0.0015 mmol) was added and the reaction mixture stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of Na₂SO₃ (1.7 mg) and the mixture stirred vigorously for 30 minutes. EtOAc (0.75 mL) was added and the two layers were separated. The organic phase was washed with water (0.75 mL) and the combined aqueous phases extracted with EtOAc (3 x 1 mL). The combined organics were dried over Na₂SO₄, filtered and evaporated *in vacuo*. Purification by flash column chromatography (35% EtOAc/petrol) afforded the title compound as a colourless oil (16.3 mg, 78%) as a 25:1 mixture of diastereomers.

$[\alpha]_D^{20} +1.36$ ($c = 0.5$, CH₂Cl₂); δ_H (400 MHz, CDCl₃) 8.22 (d, 1H, *J* 8.3, BtCH), 8.01 (d, 1H, *J* 7.6, BtCH), 7.67-7.53 (m, 2H, BtCH), 7.22 (d, 2H, *J* 8.6, ArCH), 6.88 (d, 2H, *J* 8.6, ArCH), 4.68-4.59 (m, 1H, CHCH₂S), 4.52 (d, 1H, *J* 11.4, OCH_AH_BAr), 4.32 (d, 1H, *J* 11.1,

OCH_AH_BAr), 4.22 (t, 1H, *J* 3.7, CHOPMB), 4.06-3.97 (m, 1H, CHOHCH), 3.94 (d, 1H, *J* 7.6, CH_AH_BS), 3.82 (s, 3H, OCH₃), 3.85-3.80 (1H, m, CH_AH_BS), 3.79-3.71 (m, 1H, SiOCH_AH_B), 3.69-3.59 (m, 1H, SiOCH_AH_B), 3.47-3.42 (m, 1H, CHOHCH), 3.25-3.21 (m, 1H, CHCH₃CHOH), 2.95-2.88 (m, 1H, CHCH₃CHOH), 2.60-2.51 (m, 1H, CHOHCH), 2.15-2.07 (m, 1H, CH_AH_BCHOPMB), 2.04-1.93 (m, 1H, CH_AH_BCHOPMB), 1.72-1.64 (m, 1H, CHCH₃), 1.61-1.54 (m, 1H, SiOCH₂CH_AH_B), 1.45-1.33 (m, 1H, SiOCH₂CH_AH_B), 1.14-0.98 (m, 21H, ((CH₃)₂CH)₃SiO), 0.77 (d, 3H, *J* 6.8, CHCH₃); δ_c (100 MHz, CDCl₃) 166.5 (ArC), 152.7 (ArC), 129.6 (ArC), 129.3 (ArC), 127.9 (ArC), 127.6 (ArC), 125.5 (ArC), 122.4 (ArC), 122.3 (ArC), 113.9 (ArC), 79.3 (CHOPMB), 78.8 (CHOHCH), 75.8 (CHCH₂S), 73.5 (CHCH₃CHOH), 72.7 (CHOHCH), 71.2 (OCH₂Ar), 61.0 (SiOCH₂), 55.4 (CH₂S), 55.3 (OCH₃), 36.7 (SiOCH₂CH₂), 32.9 (CHCH₃), 32.1 (CH₂CHOPMB), 18.0 ((CH₃)₂CH)₃SiO), 13.7 (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₃₅H₅₃NNaO₈S₂Si requires 730.2874, found [M+Na]⁺ 730.2876; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3503 br., 2939, 2865, 1613, 1514, 1464, 1424, 1383, 1328, 1248, 1173, 1147, 1088, 1068, 1038, 996, 969.

(+)-2-(((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-((4*R*,5*R*)-2-phenyl-5-((*R*)-4-((triisopropylsilyl)oxy)butan-2-yl)-1,3-dioxolan-4-yl)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[*d*]thiazole (161)



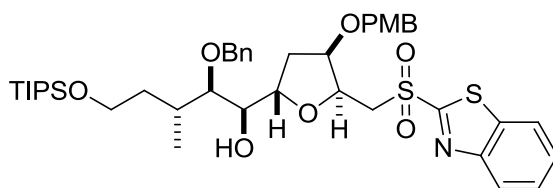
To a solution of *diol* **159** (32 mg, 0.045 mmol) in CH₂Cl₂ (0.7 mL) was added benzaldehyde dimethyl acetal (13.5 μ L, 0.0905 mmol) and camphorsulfonic acid (0.10 mg,

0.00045 mmol). The reaction mixture was stirred at room temperature for 18 h before water (1 mL) and CH₂Cl₂ (1 mL) were added. The two layers were separated and the aqueous extracted with CH₂Cl₂ (1 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20% EtOAc/petrol) afforded the title compound as a as a colourless oil (28 mg, 79%). The ¹H NMR revealed a 2.4:1 mixture of diastereomers at the acetal carbon.

[α]_D²⁰ +10.5 (c = 0.6, CH₂Cl₂); **δ_H** (500 MHz, CDCl₃) (*denotes the minor diastereomer) 8.22 (d, 1H, *J* 8.5, BtCH), 7.98 (d, 1H, *J* 8.2, BtCH), 7.94* (d, 1H, *J* 8.2, BtCH), 7.64-7.52 (m, 2H, BtCH), 7.50-7.44 (m, 2H, ArCH), 7.42-7.32 (m, 3H, ArCH), 7.26-7.21 (m, 2H, ArCH), 6.92-6.87 (m, 2H, ArCH), 5.83 (s, 1H, OCHPh), 5.74* (s, 1H, OCHPh), 4.66-4.60 (m, 1H, CHCH₂S), 4.54 (d, 1H, *J* 11.3, OCH_AH_BAr), 4.37-4.32 (m, 1H, OCH_AH_BAr), 4.23-4.19 (m, 1H, CHOPMB), 4.16-4.03 (m, 2H, CH₂S), 3.98 (t, 1H, *J* 7.7, CHOCH), 3.83 (s, 3H, OCH₃), 3.82* (s, 3H, OCH₃), 3.78* (dd, 1H, *J* 5.7, 2.2, CHOCH), 3.74-3.59 (m, 3H, SiOCH₂ and CHOCH), 3.39 (t, 1H, *J* 5.8, CHCH₃CHO), 3.32* (dd, 1H, *J* 7.6, 6.0, CHCH₃CHO), 2.23-2.08 (m, 1H, CH₂CHOPMB), 1.76-1.63 (m, 1H, CHCH₃), 1.13-0.97 (m, 23H, ((CH₃)₂CH)₃SiO and SiOCH₂CH₂), 0.74 (d, 3H, *J* 6.9, CHCH₃), 0.65* (d, 3H, *J* 6.6, CHCH₃); **δ_C** (125 MHz, CDCl₃) (*denotes minor diastereomer) 166.6* (ArC), 166.4 (ArC), 159.4 (ArC), 152.8 (ArC), 137.9* (ArC), 137.4 (ArC), 137.1* (ArC), 136.9 (ArC), 129.5* (ArC), 129.4 (ArC), 128.3 (ArC), 127.9 (ArC), 127.7* (ArC), 127.5 (ArC), 127.4* (ArC), 127.1 (ArC), 125.5 (BtC), 125.4* (BtC), 122.4* (BtC), 122.3 (BtC), 114.0 (ArC), 113.9* (ArC), 104.4 (OCHPh), 103.3* (OCHPh), 82.7 (CHO), 82.1* (CHO), 81.3* (CHO), 80.1 (CHO), 79.7 (CHOPMB), 79.4* (CHOCH), 79.1 (CHOCH), 77.5 (CHCH₂S), 71.3* (OCH₂Ar), 71.1 (OCH₂Ar), 61.1 (SiOCH₂), 56.0 (CH₂S), 55.3 (OCH₃), 35.6* (CHCH₃), 35.2 (CHCH₃), 33.3 (SiOCH₂CH₂), 32.2 (CH₂CHOPMB), 18.0 ((CH₃)₂CH)₃SiO), 15.9 (CHCH₃), 15.3* (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺)

$C_{42}H_{57}NNaO_8S_2Si$ requires 818.3187, found $[M+Na]^+$ 818.3197; **IR** $\nu_{\max}$ (film)/ cm^{-1} 2941, 2865, 1613, 1514, 1461, 1328, 1248, 1147, 1092, 1065, 1029.

(1*R*,2*R*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-2-(benzyloxy)-3-methyl-5-((triisopropylsilyl)oxy)pentan-1-ol (164)

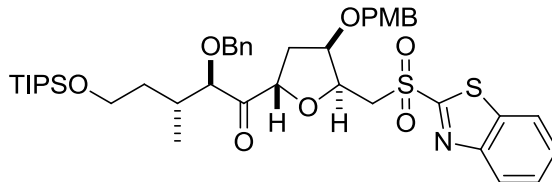


To a solution of *acetal* **161** (24 mg, 0.030 mmol) in CH_2Cl_2 (0.3 mL) cooled to $-78\text{ }^{\circ}C$ was added triethylsilane (20 μ L, 0.12 mmol) followed by the dropwise addition of titanium tetrachloride (46 μ L, 0.45 mmol). The reaction was stirred at $-78\text{ }^{\circ}C$ for 2h, and then was quenched by the addition of water (1 mL). The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 1 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-24% EtOAc/petrol) afforded the desired product as a colourless oil (5.5 mg, 23%) along with recovered starting material (9.5 mg).

δ_H (400 MHz, $CDCl_3$) 8.20 (d, 1H, *J* 8.3, BtCH), 7.98 (d, 1H, *J* 7.8, BtCH), 7.66-7.54 (m, 2H, BtCH), 7.37-7.28 (m, 5H, ArCH), 7.23 (d, 2H, *J* 8.6, ArCH), 6.88 (d, 2H, *J* 8.6, ArCH), 4.69-4.61 (m, 1H, CHCH₂S), 4.55-4.46 (m, 3H, OCH₂Ph and OCH_AH_BAr), 4.32 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.27-4.22 (m, 1H, CHOPMB), 4.17-4.06 (m, 1H, CHOHCH), 4.01-3.92 (m, 1H, CH_AH_BS), 3.89-3.81 (m, 1H, CH_AH_BS), 3.82 (s, 3H, OCH₃), 3.75-3.67 (m, 1H, SiOCH_AH_B), 3.67-3.57 (m, 1H, SiOCH_AH_B), 3.44-3.37 (m, 1H, CHOH), 3.13-3.07 (m, 1H, CHOBn), 2.47 (d, 1H, *J* 5.6, CHOH), 2.03-1.96 (m, 2H, CH₂CHOPMB), 1.87 (ddd, 1H, *J* 9.4, 6.4, 3.4, CHCH₃), 1.66-1.56 (m, 1H, SiOCH₂CH_AH_B), 1.35-1.36 (m, 1H,

SiOCH₂CH_AH_B), 1.12-0.99 (m, 21H, ((CH₃)₂CH)₃SiO), 0.84 (d, 3H, *J* 6.8, CHCH₃); δ_C (100 MHz, CDCl₃) 166.4 (ArC), 152.7 (ArC), 138.4 (ArC), 129.3 (ArC), 128.4 (ArC), 127.9 (ArC), 127.6 (ArC), 125.6 (ArC), 122.3 (ArC), 121.7 (ArC), 113.9 (ArC), 113.6 (ArC), 82.3 (CHOBn), 80.2 (CHOPMB), 79.1 (CHOHCH), 76.9 (CHCH₂S), 73.7 (OCH₂Ph), 71.2 (CHOH), 69.2 (OCH₂Ar), 61.3 (SiOCH₂), 55.3 (OCH₃), 33.2 (CH₂CHOPMB), 18.0 ((CH₃)₂CH)₃SiO), 14.0 (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₄₂H₅₉NNaO₈S₂Si requires 820.3344, found [M+Na]⁺ 820.3347; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3531 br., 2940, 2865, 1613, 1514, 1464, 1329, 1248, 1147, 1094.

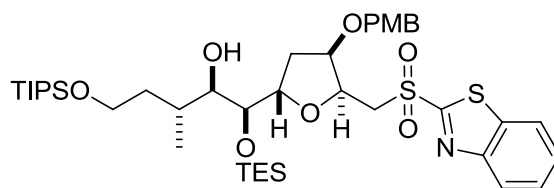
(2*R*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-2-(benzyloxy)-3-methyl-5-((triisopropylsilyl)oxy)pentan-1-one (165)



To a slurry of Dess-Martin periodinane (5.3 mg, 0.013 mmol) in CH₂Cl₂ (0.12 mL) at 0 °C was added NaHCO₃ (7.9 mg, 0.094 mmol). The mixture was stirred for 30 minutes before a solution of *alcohol* **164** (5.0 mg, 0.0063 mmol) in CH₂Cl₂ (0.1 mL) was added. The reaction mixture was stirred at room temperature for 18 h. More Dess-Martin periodinane (13.3 mg, 0.0314 mmol) was added over 3 days until TLC showed that all starting material had been consumed. The reaction mixture was diluted with Et₂O (0.5 mL) and poured into a saturated solution of Na₂S₂O₃ (0.2 mL). The mixture was stirred until all solids had dissolved, then the two layers were separated and the organics washed with a saturated solution of NaHCO₃ (0.5 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to provide the title compound as a colourless substance (4 mg, 80%).

δ_{H} (400 MHz, CDCl_3) 8.20 (d, 1H, J 7.9, BtCH), 7.96 (d, 1H, J 7.5, BtCH), 7.65-7.54 (m, 2H, BtCH), 7.37-7.28 (m, 5H, ArCH), 7.20 (m, 2H, J 8.5, ArCH), 6.87 (m, 2H, J 8.5, ArCH), 5.02 (s, 1H, CHOBn), 4.65 (t, 1H, J 8.0, COCH), 4.58-4.52 (m, 1H, CHCH₂S), 4.52-4.43 (m, 2H, OCH_AH_BAr and OCH_AH_BPh), 4.31 (dd, 2H, J 11.3, 3.4, OCH_AH_BAr and OCH_AH_BPh), 4.19 (t, 1H, J 3.6, CHOPMB), 4.02-3.84 (m, 2H, CH₂S), 3.82 (s, 3H, OCH₃), 3.68-3.51 (m, 2H, SiOCH₂), 2.32-2.23 (m, 1H, CH_AH_BCHOPMB), 2.13-2.03 (m, 1H, CHCH₃), 1.97 (ddd, 2H, J 13.5, 8.7, 4.8, CH_AH_BCHOPMB), 1.71-1.49 (m, 2H, SiOCH₂CH₂), 1.09-0.97 (m, 21H, ((CH₃)₂CH)₃SiO), 0.75 (d, 3H, J 6.8, CHCH₃); δ_{C} (125 MHz, C_6D_6) 209.2 (C=O), 167.9 (ArC), 160.0 (ArC), 153.2 (ArC), 138.7 (ArC), 137.1 (ArC), 130.0 (ArC), 129.7 (ArC), 127.5 (ArC), 127.3 (ArC), 125.5 (ArC), 122.4 (ArC), 114.3 (ArC), 87.0 (CHOBn), 80.1 (CHOCH), 79.2 (CHOPMB), 77.4 (CHCH₂S), 72.8 (OCH₂Ph), 71.4 (OCH₂Ar), 61.4 (SiOCH₂), 55.0 (OCH₃), 54.9 (CH₂S), 34.9 (CHCH₃), 33.9 (SiOCH₂CH₂), 31.9 (CH₂CHOPMB), 18.4 ((CH₃)₂CH)₃SiO, 16.7 (CHCH₃), 12.3 ((CH₃)₂CH)₃SiO); **HRMS** (ESI⁺) C₄₂H₅₇NNaO₈S₂Si requires 818.3187, found [M+Na]⁺ 818.3195; **IR** ν_{max} (film)/cm⁻¹ 2920, 2865, 1724, 1613, 1514, 1463, 1331, 1259, 1148, 1092, 908, 799, 729.

(-)-(5*S*,6*R*,7*R*)-5-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3,3-diethyl-11,11-diisopropyl-7,12-dimethyl-4,10-dioxo-3,11-disilatridecan-6-ol (166)

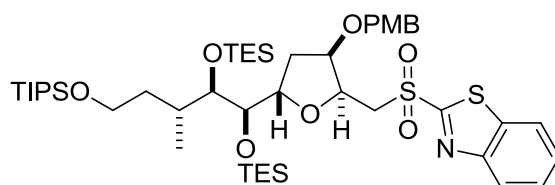


To a solution of *diol* **159** (40 mg, 0.057 mmol) in CH_2Cl_2 (0.57 mL) at 0 °C was added imidazole (15.4 mg, 0.226 mmol) and triethylchlorosilane (37.9 μL , 0.226 mmol). The

reaction mixture was stirred at 0 °C for 1.5 h, before it was quenched by the addition of water (0.5 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 0.5 mL), the combined organic phases dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc/petrol) afforded the desired mono-TES protected product as a colourless oil (22 mg, 48%), along with the corresponding bis-TES protected product as a colourless oil (23.3 mg, 44%).

[α]_D²⁰ -16.5 (c = 1, CH₂Cl₂); **δ _H** (400 MHz, CDCl₃) 8.21 (d, 1H, *J* 8.1, BtCH), 8.00 (d, 1H, *J* 8.1, BtCH), 7.68-7.54 (m, 2H, BtCH), 7.21 (d, 2H, *J* 8.6 ArCH), 6.86 (d, 2H, *J* 8.6, ArCH), 4.62-4.52 (m, 1H, CHCH₂S), 4.49 (d, 1H, *J* 10.9, OCH_AH_BAr), 4.31 (d, 1H, *J* 10.9, OCH_AH_BAr), 4.23 (t, 1H, *J* 3.7, CHOPMB), 4.20-4.10 (m, 1H, CHOSiCH), 4.01 (dd, 1H, *J* 14.8, 6.4, CH_AH_BS), 3.87 (dd, 1H, *J* 14.8, 5.7, CH_AH_BS), 3.81 (s, 3H, OCH₃), 3.79-3.64 (m, 2H, SiOCH₂), 3.51 (d, 1H, *J* 5.8, CHOSi), 3.00 (t, 1H, *J* 8.3, CHOH), 2.56 (d, 1H, *J* 8.6, OH), 2.17 (dd, 1H, *J* 13.3, 5.9, CH_AH_BCHOPMB), 1.96-1.85 (m, 1H, SiOCH₂CH_AH_B), 1.85-1.76 (m, 1H, CH_AH_BCHOPMB), 1.73-1.65 (m, 1H, CHCH₃), 1.36-1.25 (m, 1H, SiOCH₂CH_AH_B), 1.15-0.97 (m, 21H, ((CH₃)₂CH)₃SiO), 0.87 (t, 9H, *J* 8.0, OSi(CH₂CH₃)₃), 0.76 (d, 3H, *J* 6.8, CHCH₃), 0.54 (qd, 6H, *J* 7.9, 2.9, OSi(CH₂CH₃)₃); **δ _C** (100 MHz, CDCl₃) 166.3 (ArC), 159.3 (ArC), 152.6 (ArC), 136.8 (ArC), 129.6 (ArC), 129.4 (ArC), 127.9 (ArC), 127.5 (ArC), 125.4 (ArC), 122.3 (ArC), 113.8 (ArC), 79.7 (CHOSiCH), 78.9 (CHOPMB), 75.5 (CHCH₂S), 74.9 (CHOH), 73.9 (CHOSi), 71.2 (OCH₂Ar), 61.5 (SiOCH₂), 55.2 (OCH₃), 54.7 (CH₂S), 35.4 (SiOCH₂CH₂), 33.2 (CH₂CHOPMB), 33.0 (CHCH₃), 18.0 ((CH₃)₂CH)₃SiO), 16.3 (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO), 6.9 (OSi(CH₂CH₃)₃), 5.2 (OSi(CH₂CH₃)₃); **HRMS** (ESI⁺) C₄₁H₆₇NNaO₈S₂Si₂ requires 844.3739, found [M+Na]⁺ 844.3764; **IR** ν_{max} (film)/cm⁻¹ 3538 br., 2942, 2867, 1613, 1514, 1464, 1382, 1332, 1248, 1148, 1094, 1010, 883, 761, 730, 687.

(-)-2-(((2*S*,3*R*,5*S*)-5-((5*R*,6*R*,7*R*)-3,3-Diethyl-11,11-diisopropyl-7,12-dimethyl-6-((triethylsilyl)oxy)-4-10-dioxo-3,11-disilatridecan-5-yl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole (**167**)

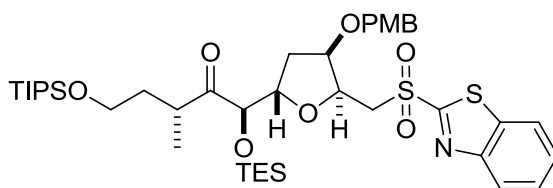


Compound **167** was isolated in the synthesis of **166**.

$[\alpha]_D^{20}$ -9.5 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 8.20 (d, 1H, J 7.8, BtCH), 8.00 (d, 1H, J 7.8, BtCH), 7.66-7.56 (m, 2H, BtCH), 7.22 (d, 2H, J 8.6, ArCH), 6.85 (d, 2H, J 8.6, ArCH), 4.53-4.46 (m, 2H, CHCH_2S and $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.33 (d, 1H, J 10.9, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.28-4.20 (m, 2H, CHOSiCH and CHOPMB), 4.14 (dd, 1H, J 14.7, 7.8, $\text{CH}_\text{A}\text{H}_\text{B}\text{S}$), 3.85-3.78 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{S}$), 3.81 (s, 3H, OCH_3), 3.76-3.69 (m, 1H, $\text{SiOCH}_\text{A}\text{H}_\text{B}$), 3.69-3.60 (m, 1H, $\text{SiOCH}_\text{A}\text{H}_\text{B}$), 3.45 (dd, 1H, J 6.2, 3.4, CHOSiCH), 3.36 (dd, 1H, J 6.8, 3.3, $\text{CHCH}_3\text{CHOSi}$), 2.17 (dd, 1H, J 13.5, 6.2, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$), 1.93-1.78 (m, 3H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOPMB}$ and CHCH_3 and $\text{SiOCH}_2\text{CH}_\text{A}\text{H}_\text{B}$), 1.18-1.00 (m, 22H, $\text{SiOCH}_2\text{CH}_\text{A}\text{H}_\text{B}$ and $((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 0.94 (t, 15H, J 8.0, $\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 0.90-0.83 (m, 6H, CHCH_3 and $\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 0.62-0.47 (m, 12H, 2 x $\text{SiO}(\text{CH}_2\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 159.2 (ArC), 152.7 (ArC), 136.8 (ArC), 129.3 (ArC), 127.9 (ArC), 127.5 (ArC), 125.5 (ArC), 122.3 (ArC), 113.7 (ArC), 78.9 ($\text{CHCH}_3\text{CHOTES}$), 78.8 (CHOTESCH), 78.2 (CHOPMB), 78.1 (CHOTESCH), 75.0 (CHCH_2S), 71.2 (OCH_2Ar), 61.7 (SiOCH_2), 55.3 (OCH_3), 54.2 (CH_2S), 36.5 ($\text{SiOCH}_2\text{CH}_2$), 34.2 (CH_2CHOPMB), 32.5 (CHCH_3), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 17.0 (CHCH_3), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 7.0 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 7.0 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 6.8 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 6.4 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 5.3 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 5.2 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$); **HRMS** (ESI^+) $\text{C}_{47}\text{H}_{81}\text{NNaO}_8\text{S}_2\text{Si}_3$ requires 958.4604, found $[\text{M}+\text{Na}]^+$

958.4609; **IR** $\nu_{\max}$ (film)/ cm^{-1} 2954, 2914, 2875, 1615, 1515, 1461, 1335, 1246, 1151, 1070, 1005.

(-)-(5*S*,7*R*)-5-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3,3-diethyl-11,11-diisopropyl-7,12-dimethyl-4,10-dioxo-3,11-disilatridecan-6-one (168)

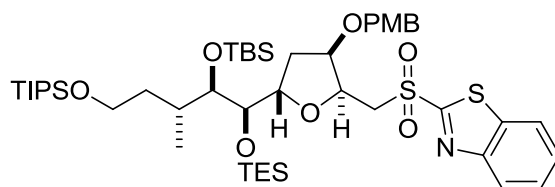


To a slurry of Dess-Martin periodinane (20.2 mg, 0.0478 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C was added NaHCO_3 (24.1 mg, 0.287 mmol). The mixture was stirred for 30 minutes before a solution of *alcohol* **166** (15.7 mg, 0.0191 mmol) in CH_2Cl_2 (0.1 mL) was added. The reaction mixture was stirred for 4.5 h whilst slowly warming to room temperature, then was diluted with Et_2O (0.5 mL) and poured into a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (0.6 mL). The mixture was stirred until all solids had dissolved and the layers were separated. The organics were washed with a saturated solution of NaHCO_3 (0.6 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (12% EtOAc /petrol) afforded the title compound as a colourless oil (9.2 mg, 59%).

$[\alpha]_{\text{D}}^{20}$ -17.9 ($c = 0.8$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 8.19 (d, 1H, J 7.6, BtCH), 8.02 (d, 1H, J 7.6, BtCH), 7.66-7.55 (m, 2H, BtCH), 7.25 (d, 2H, J 8.3, ArCH), 6.88 (d, 2H, J 8.6, ArCH), 4.57-4.46 (m, 3H, CHOSiCH and CHCH₂S and OCH_AH_BAr), 4.39 (d, 1H, J 11.0, OCH_AH_BAr), 4.29 (q, 1H, J 3.5, CHOPMB), 4.10 (d, 1H, J 3.2, CHOSi), 3.97-3.90 (m, 1H, CH_AH_BS), 3.87-3.80 (m, 1H, CH_AH_BS), 3.82 (s, 3H, OCH₃), 3.66-3.54 (m, 2H, SiOCH₂), 2.95 (sxt, 1H, J 6.7, CHCH₃), 2.10 (dd, 2H, J 7.3, 3.3, CH₂CHOPMB), 1.73 (dq,

^1H , J 13.2, 6.4, $\text{SiOCH}_2\text{CH}_A\text{H}_B$), 1.48-1.35 (m, ^1H , $\text{SiOCH}_2\text{CH}_A\text{H}_B$), 1.13-0.97 (m, ^{21}H , $((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 0.95-0.82 (m, ^9H , $\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 0.77 (d, ^3H , J 6.8, CHCH_3), 0.63-0.47 (m, ^6H , $\text{OSi}(\text{CH}_2\text{CH}_3)_3$); δ_{C} (125 MHz, CDCl_3) 212.6 ($\text{C}=\text{O}$), 171.2 (ArC), 166.1 (ArC), 159.4 (ArC), 152.7 (ArC), 137.1 (ArC), 129.7 (ArC), 129.5 (ArC), 127.8 (ArC), 127.5 (ArC), 125.5 (ArC), 122.4 (ArC), 113.9 (ArC), 79.8 (CHOSi), 79.0 (CHOPMB), 78.4 (CHOSiCH), 76.4 (CHCH_2S), 71.4 (CH_2OAr), 60.7 (SiOCH_2), 60.4, 55.3 (CH_2S), 54.6 (OCH_3), 37.2 (CHCH_3), 36.5 ($\text{SiOCH}_2\text{CH}_2$), 33.2 (CH_2CHOPMB), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 15.5 (CHCH_3), 11.9 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 6.8 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$), 4.9 ($\text{OSi}(\text{CH}_2\text{CH}_3)_3$); **HRMS** (ESI^+) $\text{C}_{41}\text{H}_{65}\text{NNaO}_8\text{S}_2\text{Si}_2$ requires 842.3582, found $[\text{M}+\text{Na}]^+$ 842.3591; **IR** ν_{max} (film)/ cm^{-1} 2924, 2867, 1727, 1613, 1514, 1463, 1332, 1248, 1148, 1103, 1069, 1009, 883, 822, 761, 730, 687.

(-)-2-((((2S,3R,5S)-5-((5R,6R,7R)-6-((*tert*-Butyldimethylsilyl)oxy)-3,3-diethyl-11,11-diisopropyl-7,12-dimethyl-4,10-dioxo-3,11-disilatridecan-5-yl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole (169)

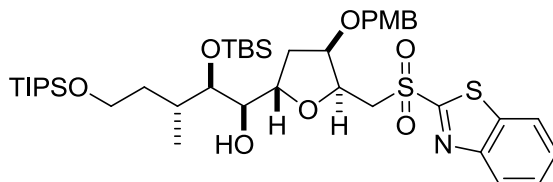


To a solution of *alcohol* **166** (22 mg, 0.027 mmol) in CH_2Cl_2 (0.16 mL) at $0\text{ }^\circ\text{C}$ was added NEt_3 (22.4 μL , 0.161 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (23.1 μL , 0.107 mmol). The reaction was stirred for 30 minutes at $0\text{ }^\circ\text{C}$ before the mixture was quenched by the addition of a saturated solution of NH_4Cl (0.5 mL). After warming to room temperature, the mixture was diluted with EtOAc (0.5 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 0.5 mL) and the combined organic phases were washed with brine, dried over MgSO_4 , filtered, and concentrated

in vacuo. Purification by flash column chromatography (10% EtOAc/petrol) afforded the desired product as a colourless oil (23 mg, 92%).

$[\alpha]_D^{20}$ -9.7 ($c = 1$, CH_2Cl_2); δ_{H} (500 MHz, CDCl_3) 8.20 (d, 1H, J 8.2, BtCH), 8.00 (d, 1H, J 8.2, BtCH), 7.67-7.56 (m, 2H, BtCH), 7.21 (d, 2H, J 8.2, ArCH), 6.85 (d, 2H, J 8.5, ArCH), 4.55-4.45 (m, 1H, CHCH₂S), 4.48 (d, 1H, J 11.3, OCH_AH_BAr), 4.33 (d, 1H, J 10.7, OCH_AH_BAr), 4.27 (dt, 1H, J 15.7, 6.8, CHOTESCH), 4.24-4.19 (m, 1H, CHOPMB), 4.15 (dd, 1H, J 14.7, 7.7, CH_AH_BS), 3.85-3.78 (m, 1H, CH_AH_BS), 3.81 (s, 1H, OCH₃), 3.76-3.69 (m, 1H, SiOCH_AH_B), 3.69-3.61 (m, 1H, SiOCH_AH_B), 3.49-3.43 (m, 1H, CHOTES), 3.39-3.33 (m, 1H, CHOTBS), 2.17 (dd, 1H, J 13.2, 5.4, CH_AH_BCHOPMB), 1.96-1.82 (m, 3H, CH_AH_BCHOPMB, CHCH₃ and SiOCH₂CH_AH_B), 1.09-1.01 (m, 22H, SiOCH₂CH_AH_B and ((CH₃)₂CH)₃SiO), 0.98-0.84 (m, 21H, CHCH₃, OSi(CH₂CH₃)₃, OSi(CH₃)₂(CH₃)₃), 0.62-0.45 (m, 6H, OSi(CH₂CH₃)₃), 0.07--0.04 (m, 6H, OSi(CH₃)₂C(CH₃)₃); δ_{C} (100 MHz, CDCl_3) 166.3 (ArC), 159.2 (ArC), 152.7 (ArC), 136.8 (ArC), 129.9 (ArC), 129.4 (ArC), 127.9 (ArC), 127.6 (ArC), 125.5 (ArC), 122.3 (ArC), 113.7 (ArC), 79.0 (CHOTBS), 78.9 (CHOPMB), 78.9 (CHOTES), 78.1 (CHOTESCH), 74.9 (CHCH₂S), 71.2 (OCH₂Ar), 61.7 (SiOCH₂), 55.2 (OCH₃), 54.2 (SCH₂), 36.6 (SiOCH₂CH₂), 34.4 (CH₂CHOPMB), 32.3 (CHCH₃), 26.0 (OSi(CH₃)₂C(CH₃)₃), 18.2 OSi(CH₃)₂C(CH₃)₃, 18.1 ((CH₃)₂CH)₃SiO), 17.1 (CHCH₃), 12.0 ((CH₃)₂CH)₃SiO), 7.0 (OSi(CH₂CH₃)₃), 5.2 (OSi(CH₂CH₃)₃), -3.7 (OSi(CH₃)₂C(CH₃)₃), -4.5 (OSi(CH₃)₂C(CH₃)₃); **HRMS** (ESI⁺) C₄₇H₈₁NNaO₈S₂Si₃ requires 958.4604, found [M+Na]⁺ 958.4619; **IR** ν_{max} (film)/cm⁻¹ 2953, 2865, 1613, 1514, 1463, 1334, 1249, 1149, 1096, 1007, 881, 761, 729, 682.

(–)-(1*R*,2*R*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-3-methyl-5-((triisopropylsilyl)oxy)pentan-1-ol (170)

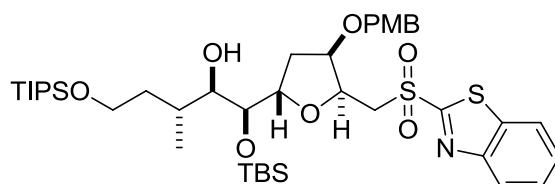


To a solution of *diol* **159** (18 mg, 0.025 mmol) in CH₂Cl₂ (0.15 mL) at 0 °C was added NEt₃ (14.2 μL, 0.102 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (14.6 μL, 0.0636 mmol). The reaction was stirred at 0 °C for 1 h and was then quenched by the addition of a saturated solution of NH₄Cl (0.5 mL). After warming to room temperature, the aqueous layer was extracted with EtOAc (2 x 0.5 mL). The combined organic phases were washed with brine, dried over MgSO₄ and evaporated. Purification by flash column chromatography (10-15% EtOAc/petrol) afforded the title compound as a pale yellow oil (5.2 mg, 25%) along with its regioisomer as a colourless oil (1.9 mg, 9%) and the corresponding bis-protected product as a pale yellow oil (5.9 mg, 25%).

[α]_D²⁰ –3.8 (c = 0.4, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 8.21 (d, 1H, *J* 7.8, BtCH), 8.00 (d, 1H, *J* 7.6, BtCH), 7.67-7.55 (m, 2H, BtCH), 7.24 (d, 2H, *J* 8.6, ArCH), 6.88 (d, 2H, *J* 8.6, ArCH), 4.63-4.57 (m, 1H, CHCH₂S), 4.50 (d, 1H, *J* 11.1, OCH_AH_BAr), 4.37 (d, 1H, *J* 10.9, OCH_AH_BAr), 4.29 (m, 1H, CHOPMB), 4.07-3.99 (m, 1H, CHOHCH), 3.95 (t, 2H, *J* 5.7, CH₂S), 3.82 (s, 3H, OCH₃), 3.73-3.64 (m, 1H, SiOCH_AH_B), 3.59 (td, 1H, *J* 9.1, 5.8, SiOCH_AH_B), 3.45 (t, 1H, *J* 3.5, CHOSi), 3.31-3.28 (m, 1H, CHOH), 2.50 (d, 1H, *J* 6.8, CHOH), 2.09-1.95 (m, 2H, CH₂CHOPMB), 1.78-1.67 (m, 1H, CHCH₃), 1.51-1.39 (m, 1H, SiOCH₂CH_AH_B), 1.25-1.16 (m, 1H, SiOCH₂CH_AH_B), 1.12-0.97 (m, 21H, ((CH₃)₂CH)₃SiO), 0.86 (s, 9H, OSi(CH₃)₂(CH₃)₃), 0.78 (d, 3H, *J* 6.8, CHCH₃), 0.05 (s, 3H, OSi(CH₃)₂(CH₃)₃), 0.04 (s, 3H, OSi(CH₃)₂(CH₃)₃); δ_{C} (125 MHz, CDCl₃) 166.3 (ArC),

159.3 (ArC), 152.7 (ArC), 136.8 (ArC), 129.8 (ArC), 129.4 (ArC), 127.9 (ArC), 127.6 (ArC), 125.5 (ArC), 122.3 (ArC), 113.8 (ArC), 79.5 (CHOTBS), 79.0 (CHOPMB), 76.2 (CHOHCH), 76.1 (CHCH₂S), 72.0 (CHOH), 71.4 (CH₂OAr), 61.0 (SiOCH₂), 55.3 (OCH₃), 54.6 (SCH₂), 35.0 (SiOCH₂CH₂), 33.6 (CH₂CHOPMB), 33.6 (CHCH₃), 25.9 (OSi(CH₃)₂C(CH₃)₃), 18.2 (OSi(CH₃)₂C(CH₃)₃), 18.0 ((CH₃)₂CH)₃SiO), 15.0 (CHCH₃), 11.9 ((CH₃)₂CH)₃SiO), -4.2 (OSi(CH₃)₂C(CH₃)₃), -4.5 (OSi(CH₃)₂C(CH₃)₃); **HRMS** (ESI⁺) C₄₁H₆₇NNaO₈S₂Si₂ requires 844.3739, found [M+Na]⁺ 844.3742; **IR** $\nu_{\max}$ (film)/cm⁻¹ 3529 br., 2929, 2864, 1613, 1514, 1463, 1330, 1249, 1148, 1096, 882, 835, 762, 730, 686.

(-)-(5*S*,6*R*,7*R*)-5-((2*S*,4*R*,5*S*)-5-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-11,11-diisopropyl-2,2,3,3,7,12-hexamethyl-4,10-dioxo-3,11-disilatridecan-6-ol (171)

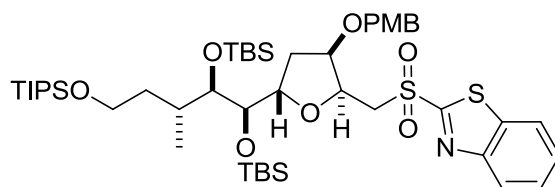


Compound **171** was isolated in the synthesis of *alcohol 170*.

[α]_D²⁰ -7.5 (c = 0.16, CH₂Cl₂); **δ_{H}** (400 MHz, CDCl₃) 8.21 (d, 1H, *J* 7.8, BtCH), 8.00 (d, 1H, *J* 7.8, BtCH), 7.68-7.55 (m, 2H, BtCH), 7.21 (d, 2H, *J* 8.6, ArCH), 6.86 (d, 2H, *J* 8.3, ArCH), 4.61-4.55 (m, 1H, CHCH₂S), 4.49 (d, 1H, *J* 11.1, OCH₂Ar), 4.31 (d, 1H, *J* 11.1, OCH₂Ar), 4.25-4.13 (m, 2H, CHOSiCH and CHOPMB), 4.02 (dd, 1H, *J* 14.8, 6.2, SCH_AH_B), 3.87 (dd, 1H, *J* 14.8, 5.7, SCH_AH_B), 3.81 (s, 3H, OCH₃), 3.80-3.62 (m, 2H, SiOCH₂), 3.53 (d, 1H, *J* 5.8, CHOSi), 3.00 (t, 1H, *J* 8.8, CHOH), 2.42 (d, 1H, *J* 9.1, OH), 2.18 (dd, 0.7H, *J* 13.3, 5.9, CH_AH_BOPMB), 1.99-1.88 (m, 1H, SiOCH₂CH_AH_B), 1.85-1.75 (m, 1H, CH_AH_BOPMB), 1.75-1.63 (m, 1H, CHCH₃), 1.14-1.01 (m, 21H,

$((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 0.84 (s, 9H, $\text{OSi}(\text{CH}_3)_2(\text{CH}_3)_3$), 0.75 (d, 3H, J 6.6, CHCH_3), 0.07–0.04 (m, 6H, $\text{OSi}(\text{CH}_3)_2(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 166.4 (ArC), 159.3 (ArC), 152.7 (ArC), 136.9 (ArC), 129.6 (ArC), 129.4 (ArC), 129.2 (ArC), 127.9 (ArC), 127.6 (ArC), 125.5 (ArC), 122.3 (ArC), 113.8 (ArC), 79.8 (CHOTBS), 79.0 (CHOPMB), 75.5 (CHCH_2S), 75.2 (CHOTBSCH), 74.0 (CHOH), 71.2 (OCH_2Ar), 61.6 (SiOCH_2), 55.3 (OCH_3), 54.7 (SCH_2), 35.7 ($\text{SiOCH}_2\text{CH}_2$), 33.3 (CH_2CHOPMB), 33.1 (CHCH_3), 26.0 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.3 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 16.2 (CHCH_3), 11.9 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), -4.0 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -5.0 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$); **HRMS** (ESI^+) $\text{C}_{41}\text{H}_{67}\text{NNaO}_8\text{S}_2\text{Si}_2$ requires 844.3739, found $[\text{M}+\text{Na}]^+$ 844.3745; **IR** ν_{max} (film)/ cm^{-1} 3527 br., 2926, 2864, 1613, 1515, 1464, 1332, 1249, 1148, 1095, 883, 835, 778, 762, 731, 686.

(-)-2-((((2S,3R,5S)-5-((5R,6R,7R)-6-((tert-Butyldimethylsilyl)oxy)-11,11-diisopropyl-2,2,3,3,7,12-hexamethyl-4,10-dioxo-3,11-disilatridecan-5-yl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole (172)

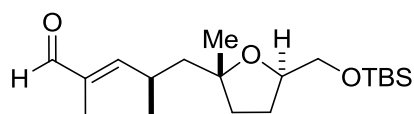


Compound **172** was isolated in the synthesis of *alcohol 170*.

$[\alpha]_{\text{D}}^{20}$ -4.8 ($c = 0.5$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 8.20 (d, 1H, J 7.6, BtCH), 8.00 (d, 1H, J 7.3, BtCH), 7.67–7.56 (m, 2H, BtCH), 7.21 (m, 2H, J 8.3, ArCH), 6.85 (d, 2H, J 8.6, ArCH), 4.53–4.45 (m, 2H, CHCH_2S and $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.35–4.27 (m, 2H, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ar}$ and CHOTBSCH), 4.25–4.11 (m, 2H, CHOPMB and $\text{CH}_\text{A}\text{H}_\text{B}\text{S}$), 3.85–3.78 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{S}$), 3.81 (s, 3H, OCH_3), 3.77–3.69 (m, 1H, $\text{SiOCH}_\text{A}\text{H}_\text{B}$), 3.69–3.61 (m, 1H, $\text{SiOCH}_\text{A}\text{H}_\text{B}$), 3.45 (dd, 1H, J 6.6, 3.3, CHOTBSCH), 3.35 (dd, 1H, J 7.3, 3.3, $\text{CHCH}_3\text{CHOTBS}$), 2.17 (dd,

^1H , J 13.5, 6.2, $\text{CH}_\text{A}\text{H}_\text{B}\text{OPMB}$), 1.98-1.84 (m, 3H, $\text{CH}_\text{A}\text{H}_\text{B}\text{OPMB}$, CHCH_3 and $\text{SiOCH}_2\text{CH}_\text{A}\text{H}_\text{B}$), 1.13-1.00 (m, 22H, $\text{SiOCH}_2\text{CH}_\text{A}\text{H}_\text{B}$ and $((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 0.95-0.86 (m, 12H, CHCH_3 and $\text{OSi}(\text{CH}_3)_2(\text{CH}_3)_3$), 0.79 (s, 9H, $\text{OSi}(\text{CH}_3)_2(\text{CH}_3)_3$), 0.07-0.02 (m, 6H, $\text{OSi}(\text{CH}_3)_2(\text{CH}_3)_3$), -0.02 (d, 6H, J 3.3, $\text{OSi}(\text{CH}_3)_2(\text{CH}_3)_3$); δ_C (100 MHz, CDCl_3) 166.3 (ArC), 159.2 (ArC), 152.7 (ArC), 136.8 (ArC), 129.9 (ArC), 129.4 (ArC), 127.9 (ArC), 127.5 (ArC), 125.5 (ArC), 122.3 (ArC), 113.7 (ArC), 79.2 (CHOTBS), 79.0 (CHOTBS), 78.5 (CHOPMB), 78.0 (CHOTBSCH), 74.9 (CHCH_2S), 71.2 (OCH_2Ar), 61.6 (SiOCH_2), 55.3 (OCH_3), 54.2 (SCH_2), 36.6 ($\text{SiOCH}_2\text{CH}_2$), 34.2 (CH_2CHOPMB), 32.1 (CHCH_3), 26.0 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.1 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), 17.3 (CHCH_3), 12.0 ($((\text{CH}_3)_2\text{CH})_3\text{SiO}$), -3.7 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -4.5 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -4.6 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -4.7 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$); **HRMS** (ESI^+) $\text{C}_{47}\text{H}_{81}\text{NNaO}_8\text{S}_2\text{Si}_3$ requires 958.4604, found $[\text{M}+\text{Na}]^+$ 958.4634; **IR** ν_max (film)/ cm^{-1} 2928, 2861, 1613, 1515, 1471, 1334, 1250, 1096, 908, 882, 834, 775, 730, 680.

(-)-(R,E)-5-((2R,5R)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enal (174)

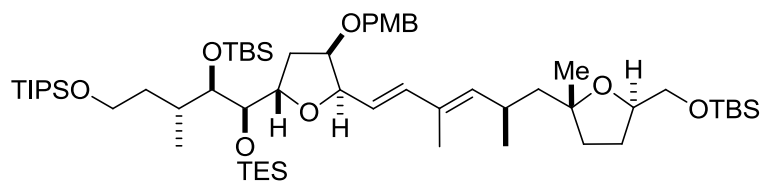


To a stirred solution of **173** (23 mg, 0.067 mmol) in CH_2Cl_2 (670 μL) and dimethyl sulfoxide (220 μL) cooled to $-10\text{ }^\circ\text{C}$ was added NEt_3 (93.6 μL , 0.672 mmol). After 5 minutes, a solution of sulfur trioxide pyridine complex (0.107 g, 0.672 mmol) in dimethyl sulfoxide (450 μL) was added. The reaction mixture was stirred for 40 minutes at $-10\text{ }^\circ\text{C}$ before it was quenched by the addition of brine and diluted with Et_2O (10 mL) and water (5 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered

and concentrated *in vacuo*. The crude product was purified by flash column chromatography (7.5% EtOAc/petrol) to afford the title compound as a colourless oil (19.2 mg, 84%).

$[\alpha]_D^{20}$ -10.5 ($c = 1$, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 9.39 (s, 1H, CHO), 6.41 (d, 1H, J 9.1, C=CH), 3.89-3.81 (m, 1H, CHCH₂OSi), 3.59 (dd, 1H, J 10.5, 4.4, CH_AH_BOSi), 3.52 (dd, 1H, J 10.5, 5.2, CH_AH_BOSi), 2.98-2.86 (m, 1H, CHCH₃), 1.95-1.79 (m, 2H, CH₂CH), 1.77 (s, 3H, CH₃CO), 1.74-1.60 (m, 4H, CHCH₃CH₂ and CCH₂CH₂), 1.19-1.14 (m, 3H, CHOCCH₃), 1.12-1.05 (m, 3H, CHCH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.09-0.01 (m, 6H, Si(CH₃)₂C(CH₃)₃); δ_{C} (100 MHz, CDCl_3) 195.7 (CHO), 161.9 (C=CH), 136.2 (C=CH), 82.9 (CH₃CO), 79.5 (CHCH₂OSi), 66.0 (CH₂OSi), 48.0 (CHCH₃CH₂), 37.1 (CH₂CH₂CH), 30.3 (CHCH₃), 28.2 (CH₂CH₂CH), 27.1 (CCH₃), 25.9 (OSi(CH₃)₂C(CH₃)₃), 21.2 (CHCH₃), 18.4 (OSi(CH₃)₂C(CH₃)₃), 9.1 (CHOCCH₃), -5.3 (OSi(CH₃)₂C(CH₃)₃), -5.4 (OSi(CH₃)₂C(CH₃)₃); **HRMS** (ESI^+) $\text{C}_{19}\text{H}_{36}\text{NaO}_3\text{Si}$ requires 363.2326, found $[\text{M}+\text{Na}]^+$ 363.2329; **IR** ν_{max} (film)/ cm^{-1} 2958, 2928, 2857, 1687, 1462, 1253, 1103, 1017, 835, 776, 675.

(-)-(7R,8R,9R)-8-((tert-Butyldimethylsilyl)oxy)-9-((2S,4R,5R)-5-((R,1E,3E)-6-((2R,5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-11,11-diethyl-3,3-diisopropyl-2,7-dimethyl-4,10-dioxo-3,11-disilatridecane (178)



To a solution of *sulfone* **169** (23.9 mg, 0.0255 mmol) and *aldehyde* **174** (3.5 mg, 0.010 mmol) in THF (0.1 mL) at -78 °C was added lithium bis(trimethylsilyl)amide (1.0 M in

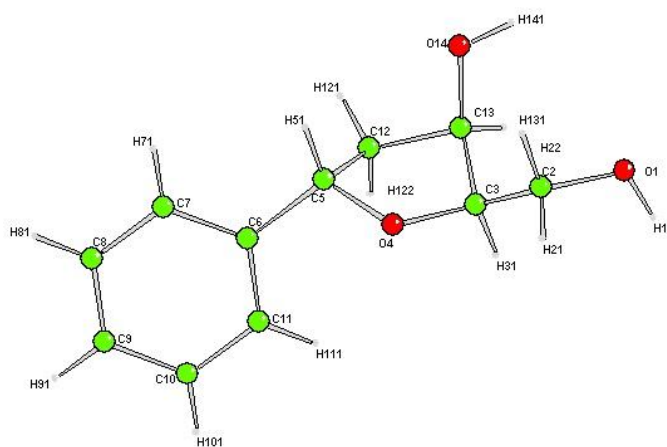
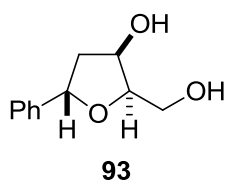
THF, 38.3 μ L, 0.0383 mmol). The reaction mixture was stirred at -78 $^{\circ}$ C for 25 minutes and was then allowed to warm to 0 $^{\circ}$ C for 20 minutes. The reaction was quenched by the addition of a saturated solution of NH_4Cl (0.3 mL) and diluted with EtOAc (10 mL) and water (5 mL). The two layers were separated and the aqueous phase extracted with Et_2O (2 x 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography delivered the title compound as a colourless oil (12 mg, 100%).

$[\alpha]_{\text{D}}^{20}$ -10.1 ($c = 1$, CH_2Cl_2); δ_{H} (500 MHz, CDCl_3) (major diastereomer) 7.26-7.19 (m, 2H, ArCH), 6.90-6.82 (m, 2H, ArCH), 6.24 (d, 1H, J 15.8, CH=CH), 5.77 (dd, 1H, J 15.4, 7.3, CH=CH), 5.35-5.26 (m, 1H, $\text{CH}_3\text{C}=\text{CH}$), 4.54-4.32 (m, 3H, CH_2OAr and CHOTESCH), 4.30 (dd, 1H, J 7.3, 3.8, CHCH=CH), 4.01-3.91 (m, 2H, CHOPMB and CHCH₂OSi), 3.80 (s, 3H, OCH₃), 3.79-3.72 (m, 1H, SiOCH_AH_B), 3.72-3.65 (m, 1H, SiOCH_AH_B), 3.65-3.59 (m, 1H, CH_AH_BOSi), 3.56-3.49 (m, 2H, CH_AH_BOSi and CHOTES), 3.41 (dd, 1H, J 6.3, 2.5, CHOTBS), 2.74-2.61 (m, 1H, CHCH₃CH₂), 2.19-2.11 (m, 1H, CH_AH_BCHOPMB), 2.03-1.86 (m, 4H, CH_AH_BCHOPMB and CHCH₃CHOTBS and SiOCH₂CH_AH_B and CH₂CH_AH_BCH), 1.86-1.77 (m, 3H, CH=CHCHCH₃ and CH₂CH_AH_BCH), 1.74-1.52 (m, 3H, CH_AH_BCH₂CH and CH_AH_BCH₂CH and CHCH₃CH_AH_B), 1.26 (s, 3H, CCH₃), 1.20-1.15 (m, 4H, CHCH₃CH₂ and SiOCH₂CH_AH_B), 1.11-1.03 (m, 21H, ((CH₃)₂CH)₃SiO), 1.03-0.86 (m, 31H, CHCH₃CH_AH_B, CHCH₃, OSi(CH₂CH₃)₃, OSi(CH₃)₂C(CH₃)₃ and OSi(CH₃)₂C(CH₃)₃), 0.69-0.56 (m, 6H, OSi(CH₂CH₃)₃), 0.13-0.01 (m, 12H, OSi(CH₃)₂C(CH₃)₃ and OSi(CH₃)₂C(CH₃)₃); δ_{C} (100 MHz, CDCl_3) 159.0 (ArC), 140.1 (CH₃C=CH), 137.4 (CH=CH), 130.7 (ArC), 129.0 (ArC), 129.1 (ArC), 123.4 (CH=CH), 113.7 (ArC), 113.6 (ArC), 83.5 (CH₃CO), 82.4 (CHCH=CH), 81.1 (CHCH₂OSi), 79.3 (CHOTBS), 78.8 (CHOPMB), 78.2 (CHOTES), 77.8 (CHOTESCH), 71.0 (CH₂OAr), 66.2 (CH₂OSi), 61.8 (SiOCH₂), 55.2 (OCH₃), 48.6

(CHCH₃CH₂), 37.5 (CH₂CH₂CH), 36.5 (SiOCH₂CH₂), 35.1 (CH₂CHOPMB), 32.6 (CHCH₃CHOTBS), 29.6 (CHCH₃CH₂), 28.4 (CH₂CH₂CH), 26.6 (CCH₃), 26.0 (OSi(CH₃)₂C(CH₃)₃), 25.9 (OSi(CH₃)₂C(CH₃)₃), 18.4 (OSi(CH₃)₂C(CH₃)₃), 18.2 OSi(CH₃)₂C(CH₃)₃, 18.1 ((CH₃)₂CH)₃SiO), 12.0 ((CH₃)₂CH)₃SiO), 7.1 (OSi(CH₂CH₃)₃), 5.3 (OSi(CH₂CH₃)₃), 1.0 (OSi(CH₃)₂C(CH₃)₃), -3.7 (OSi(CH₃)₂C(CH₃)₃), -4.5 (OSi(CH₃)₂C(CH₃)₃), -5.3 (OSi(CH₃)₂C(CH₃)₃); **HRMS** (ESI⁺) C₅₉H₁₁₂NaO₈Si₄ requires 1083.7326, found [M+Na]⁺ 1083.7328; **IR** ν_{max} (film)/cm⁻¹ 2955, 2929, 2864, 1614, 1514, 1462, 1388, 1249, 1099, 1006, 881, 835, 775, 740, 680.

Appendix

X-Ray Crystal Structure for ((2*R*, 3*R*, 5*S*)-2-hydroxymethyl)-5- phenyltetrahydrofuran-3-ol



Crystals of 0017aki09 were grown by Kirsty Davies from dichloromethane. A single crystal having dimensions approximately 0.2 x 0.32 x 0.4 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be *P n a 21*. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The hydrogen atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F^2 using the CRYSTALS program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogen atoms were refined with riding constraints.

A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.055$, $R_w = 0.105$.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is attached as supplementary data at the end, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning hydrogen atoms.

References:

1. Otwinowski, Z.; Minor, W., *Methods Enzymol.* **1997**, 276, 307-326.
2. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, M.; Burla, M.; Polidori, G.; Camalli, M., *J. Appl. Crystallogr.* **1994**, 27.
3. Betteridge, P.; Cooper, J.; Cooper, R.; Prout, K.; Watkin, D., *J. Appl. Crystallogr.* **2003**, 36, 1486.

X-Ray Crystal Structure for ((2*R*, 3*R*, 5*S*)-2-hydroxymethyl)-5-phenyltetrahydrofuran-3-ol

Kirsty Davies

(017aki09)

Crystal data

$C_{11}H_{14}O_3$	$F(000) = 416$
$M_r = 194.23$	$D_x = 1.326 \text{ Mg m}^{-3}$
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
Hall symbol: $-P 2_1 n$	Cell parameters from 1638 reflections
$a = 5.7198 (2) \text{ \AA}$	$\theta = 5\text{--}27^\circ$
$b = 29.2922 (11) \text{ \AA}$	$\mu = 0.10 \text{ mm}^{-1}$
$c = 5.9087 (3) \text{ \AA}$	$T = 150 \text{ K}$
$\beta = 100.7583 (17)^\circ$	Plate, colourless
$V = 972.58 (7) \text{ \AA}^3$	$0.20 \times 0.20 \times 0.10 \text{ mm}$
$Z = 4$	

Data collection

Area diffractometer	1212 reflections with $I > 2.0\sigma(I)$
graphite	$R_{\text{int}} = 0.000$
ω scans	$\theta_{\text{max}} = 27.5^\circ$, $\theta_{\text{min}} = 5.3^\circ$
Absorption correction: multi-scan DENZO/SCALEPACK (Otwinowski & Minor, 1997)	$h = -7 \rightarrow 7$
$T_{\text{min}} = 0.99$, $T_{\text{max}} = 1$	$k = -31 \rightarrow 38$
6511 measured reflections	$l = -7 \rightarrow 7$
2079 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.045$	H-atom parameters constrained
$wR(F^2) = 0.105$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.03P)^2 + 0.89P]$, where $P = (\max(F_o^2, 0) + 2F_c^2)/3$
$S = 1.03$	$(\Delta/\sigma)_{\text{max}} = 0.001$
1421 reflections	$\Delta\rho_{\text{max}} = 0.23 \text{ e \AA}^{-3}$
127 parameters	$\Delta\rho_{\text{min}} = -0.24 \text{ e \AA}^{-3}$

0 restraints

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.8924 (3)	0.53384 (5)	1.2118 (2)	0.0318
C2	0.8772 (4)	0.57702 (8)	1.0966 (4)	0.0288
C3	0.6372 (4)	0.58048 (7)	0.9375 (4)	0.0271
O4	0.6150 (3)	0.62418 (5)	0.8266 (2)	0.0306
C5	0.5108 (4)	0.61873 (7)	0.5846 (3)	0.0265
C6	0.3255 (4)	0.65470 (7)	0.5063 (3)	0.0253
C7	0.3171 (4)	0.67656 (8)	0.2959 (4)	0.0302
C8	0.1348 (4)	0.70709 (8)	0.2155 (4)	0.0339
C9	−0.0385 (4)	0.71634 (8)	0.3437 (4)	0.0347
C10	−0.0298 (4)	0.69506 (8)	0.5542 (4)	0.0328
C11	0.1509 (4)	0.66428 (8)	0.6341 (4)	0.0290
C12	0.4137 (4)	0.56999 (7)	0.5668 (4)	0.0280
C13	0.5920 (4)	0.54487 (8)	0.7454 (3)	0.0258
O14	0.8002 (3)	0.53632 (5)	0.6501 (2)	0.0312
H21	0.8974	0.6031	1.2075	0.0338*
H22	1.0031	0.5782	1.0022	0.0326*
H31	0.5103	0.5771	1.0300	0.0307*
H51	0.6393	0.6216	0.4932	0.0306*
H71	0.4363	0.6709	0.2058	0.0372*
H81	0.1303	0.7214	0.0703	0.0391*
H91	−0.1634	0.7378	0.2887	0.0416*
H101	−0.1486	0.7016	0.6449	0.0398*
H111	0.1584	0.6498	0.7767	0.0341*
H122	0.2561	0.5690	0.6080	0.0323*
H121	0.4032	0.5572	0.4113	0.0324*
H131	0.5283	0.5166	0.7959	0.0297*
H11	0.8440	0.5359	1.3378	0.0483*
H141	0.8809	0.5134	0.7196	0.0491*

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0339 (9)	0.0392 (10)	0.0217 (8)	0.0078 (7)	0.0038 (6)	0.0031 (7)
C2	0.0278 (12)	0.0352 (13)	0.0224 (12)	0.0012 (10)	0.0020 (9)	0.0024 (9)
C3	0.0264 (12)	0.0315 (12)	0.0229 (12)	0.0022 (10)	0.0031 (9)	0.0023 (9)
O4	0.0345 (9)	0.0307 (9)	0.0229 (8)	0.0006 (7)	−0.0044 (6)	0.0002 (6)
C5	0.0251 (12)	0.0361 (13)	0.0175 (11)	−0.0006 (10)	0.0022 (9)	0.0000 (9)
C6	0.0241 (11)	0.0276 (12)	0.0221 (11)	−0.0020 (9)	−0.0011 (9)	−0.0001 (9)
C7	0.0271 (12)	0.0368 (13)	0.0261 (12)	−0.0018 (10)	0.0037 (9)	0.0020 (10)
C8	0.0391 (14)	0.0332 (13)	0.0267 (13)	0.0000 (11)	−0.0010 (10)	0.0066 (10)
C9	0.0301 (13)	0.0317 (13)	0.0389 (14)	0.0043 (10)	−0.0026 (10)	0.0021 (11)
C10	0.0248 (12)	0.0373 (14)	0.0366 (14)	0.0004 (11)	0.0065 (10)	−0.0034 (11)
C11	0.0297 (13)	0.0315 (12)	0.0245 (12)	−0.0010 (10)	0.0016 (9)	0.0014 (9)

C12	0.0278 (12)	0.0316 (13)	0.0227 (11)	0.0013 (10)	−0.0001 (9)	−0.0013 (9)
C13	0.0243 (11)	0.0291 (12)	0.0242 (11)	−0.0001 (9)	0.0049 (9)	0.0027 (9)
O14	0.0337 (9)	0.0356 (9)	0.0246 (8)	0.0103 (7)	0.0064 (6)	0.0037 (7)

Geometric parameters (Å, °)

O1—C2	1.431 (3)	C7—H71	0.954
O1—H11	0.844	C8—C9	1.382 (3)
C2—C3	1.515 (3)	C8—H81	0.951
C2—H21	0.999	C9—C10	1.384 (3)
C2—H22	0.990	C9—H91	0.962
C3—O4	1.433 (3)	C10—C11	1.386 (3)
C3—C13	1.528 (3)	C10—H101	0.960
C3—H31	0.992	C11—H111	0.938
O4—C5	1.451 (2)	C12—C13	1.514 (3)
C5—C6	1.505 (3)	C12—H122	0.977
C5—C12	1.528 (3)	C12—H121	0.984
C5—H51	0.993	C13—O14	1.432 (2)
C6—C7	1.391 (3)	C13—H131	0.975
C6—C11	1.389 (3)	O14—H141	0.872
C7—C8	1.388 (3)		
C2—O1—H11	110.8	C7—C8—C9	120.5 (2)
O1—C2—C3	108.78 (17)	C7—C8—H81	119.0
O1—C2—H21	112.0	C9—C8—H81	120.4
C3—C2—H21	109.7	C8—C9—C10	119.7 (2)
O1—C2—H22	108.3	C8—C9—H91	120.4
C3—C2—H22	108.6	C10—C9—H91	119.9
H21—C2—H22	109.6	C9—C10—C11	119.9 (2)
C2—C3—O4	109.66 (17)	C9—C10—H101	120.0
C2—C3—C13	115.05 (18)	C11—C10—H101	120.1
O4—C3—C13	106.36 (16)	C6—C11—C10	120.8 (2)
C2—C3—H31	108.9	C6—C11—H111	118.7
O4—C3—H31	109.2	C10—C11—H111	120.5
C13—C3—H31	107.5	C5—C12—C13	102.54 (17)
C3—O4—C5	109.73 (15)	C5—C12—H122	110.5
O4—C5—C6	111.22 (17)	C13—C12—H122	110.2
O4—C5—C12	104.34 (16)	C5—C12—H121	112.3
C6—C5—C12	114.02 (17)	C13—C12—H121	112.4
O4—C5—H51	108.5	H122—C12—H121	108.9
C6—C5—H51	108.9	C3—C13—C12	100.66 (17)
C12—C5—H51	109.7	C3—C13—O14	111.96 (17)
C5—C6—C7	120.14 (19)	C12—C13—O14	108.18 (16)
C5—C6—C11	120.73 (19)	C3—C13—H131	112.0
C7—C6—C11	119.0 (2)	C12—C13—H131	112.6
C6—C7—C8	120.1 (2)	O14—C13—H131	110.9
C6—C7—H71	120.6	C13—O14—H141	110.8
C8—C7—H71	119.3		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
O1—H11 $\cdots$ O14 ⁱ	0.84	1.91	2.739 (3)	168
O14—H141 $\cdots$ O1 ⁱⁱ	0.87	1.89	2.728 (3)	161

Symmetry codes: (i) $x, y, z+1$; (ii) $-x+2, -y+1, -z+2$.

References

1. Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J., *Tetrahedron* **1985**, *41* (6), 1019-1025.
2. Sasaki, K.; Satake, M.; Yasumoto, T., *Biosci., Biotechnol., Biochem.* **1997**, *61* (10), 1783-1785.
3. Yasumoto, T.; Murata, M., *Chem. Rev.* **1993**, *93* (5), 1897-1909.
4. Sasaki, K.; Wright, J. L. C.; Yasumoto, T., *J. Org. Chem.* **1998**, *63* (8), 2475-2480.
5. Halim, R.; Brimble, M. A., *Org. Biomol. Chem.* **2006**, *4* (22), 4048-4058.
6. Jung, J. H.; Sim, C. J.; Lee, C. O., *J. Nat. Prod.* **1995**, *58* (11), 1722-1726.
7. Miles, C. O.; Wilkins, A. L.; Munday, R.; Dines, M. H.; Hawkes, A. D.; Briggs, L. R.; Sandvik, M.; Jensen, D. J.; Cooney, J. M.; Holland, P. T.; Quilliam, M. A.; MacKenzie, A. L.; Beuzenberg, V.; Towers, N. R., *Toxicon* **2004**, *43* (1), 1-9.
8. Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; MacKenzie, L.; Naoki, H.; Yasumoto, T., *Chem. Lett.* **1998**, (7), 653-654.
9. James, K. J.; Bishop, A. G.; Draisci, R.; Palleschi, L.; Marchiafava, C.; Ferretti, E.; Satake, M.; Yasumoto, T., *J. Chromatogr., A* **1999**, *844* (1-2), 53-65.
10. Suzuki, T.; Mackenzie, L.; Stirling, D.; Adamson, J., *Toxicon* **2001**, *39* (4), 507-514.
11. Suzuki, T.; Beuzenberg, V.; Mackenzie, L.; Quilliam, M. A., *J. Chromatogr., A* **2003**, *992* (1-2), 141-150.
12. Suzuki, T.; Walter, J. A.; LeBlanc, P.; MacKinnon, S.; Miles, C. O.; Wilkins, A. L.; Munday, R.; Beuzenberg, V.; MacKenzie, A. L.; Jensen, D. J.; Cooney, J. M.; Quilliam, M. A., *Chem. Res. Toxicol.* **2006**, *19* (2), 310-318.

-
13. Miles, C. O.; Wilkins, A. L.; Samdal, I.; Sandvik, M.; Petersen, D.; Quilliam, M. A.; Naustvoll, L. J.; Rundberget, T.; Torgersen, T.; Hovgaard, P.; Jensen, D. J.; Cooney, J. M., *Chem. Res. Toxicol.* **2004**, *17* (11), 1423-1433.
 14. Miles, C. O.; Wilkins, A. L.; Hawkes, A. D.; Jensen, D. J.; Selwood, A. I.; Beuzenberg, V.; MacKenzie, A. L.; Cooney, J. M.; Holland, P. T., *Toxicon* **2006**, *48* (2), 152-159.
 15. Leira, F.; Cabado, A. G.; Vieytes, M. R.; Roman, Y.; Alfonso, A.; Botana, L. M.; Yasumoto, T.; Malaguti, C.; Rossini, G. P., *Biochem. Pharmacol.* **2002**, *63* (11), 1979-1988.
 16. Terao, K.; Ito, E.; Yanagi, T.; Yasumoto, T., *Toxicon* **1986**, *24* (11-12), 1141-1151.
 17. Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. R., *Microsc. Res. Tech.* **1999**, *47* (1), 18-37.
 18. Allingham, J. S.; Miles, C. O.; Rayment, E., *J. Mol. Biol.* **2007**, *371* (4), 959-970.
 19. Kim, G. Y.; Kim, W. J.; Choi, Y. H., *Mar. Drugs* **2011**, *9* (11), 2176-2187.
 20. Evans, D. A.; Rajapakse, H. A.; Stenkamp, D., *Angew. Chem., Int. Ed.* **2002**, *41* (23), 4569-4573.
 21. Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D., *Angew. Chem., Int. Ed.* **2002**, *41* (23), 4573-4576.
 22. Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B., *Tetrahedron Lett.* **1979**, (49), 4733-4736.
 23. Reetz, M. T.; Kessler, K., *J. Org. Chem.* **1985**, *50* (25), 5434-5436.
 24. Evans, D. A.; MacMillan, D. W. C.; Campos, K. R., *J. Am. Chem. Soc.* **1997**, *119* (44), 10859-10860.
 25. Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Reul, O., *Bull. Soc. Chim. Fr.* **1993**, *130* (6), 856-878.

-
26. Rajapakse, H. A. Asymmetric Syntheses of Pectenotoxins-4 and -8. Harvard University, Cambridge, Massachusetts, **2002**.
27. Parikh, J. R.; Doering, W. V. E., *J. Am. Chem. Soc.* **1967**, 89 (21), 5505-5507.
28. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M., *Bull. Chem. Soc. Jpn.* **1979**, 52 (7), 1989-1993.
29. Amano, S.; Fujiwara, K.; Murai, A., *Synlett* **1997**, (11), 1300-1302.
30. Fujiwara, K.; Kobayashi, M.; Yamamoto, F.; Aki, Y.; Kawamura, M.; Awakura, D.; Amano, S.; Okano, A.; Murai, A.; Kawai, H.; Suzuki, T., *Tetrahedron Lett.* **2005**, 46 (30), 5067-5069.
31. Amano, S.; Fujiwara, K.; Murai, A., *Chem. Lett.* **1998**, (5), 409-410.
32. Schmid, C. R.; Bryant, J. D., *Org. Synth., Vol 72* **1995**, 72, 6-13.
33. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothestreit, P.; Schwarzenbach, F., *J. Am. Chem. Soc.* **1992**, 114 (7), 2321-2336.
34. Oka, T.; Murai, A., *Chem. Lett.* **1994**, (9), 1611-1614.
35. Freeman, P. K.; Hutchinson, L. L., *J. Org. Chem.* **1980**, 45 (10), 1924-1930.
36. Mancuso, A. J.; Huang, S. L.; Swern, D., *J. Org. Chem.* **1978**, 43 (12), 2480-2482.
37. Paquette, L. A.; Peng, X. W.; Bondar, D., *Org. Lett.* **2002**, 4 (6), 937-940.
38. Gage, J. R.; Evans, D. A., *Org. Synth.* **1990**, 68, 77-82.
39. Gage, J. R.; Evans, D. A., *Org. Synth.* **1990**, 68, 83-91.
40. Danda, H.; Hansen, M. M.; Heathcock, C. H., *J. Org. Chem.* **1990**, 55 (1), 173-181.
41. Ghosh, A. K.; Mckee, S. P.; Thompson, W. J., *J. Org. Chem.* **1991**, 56 (23), 6500-6503.
42. Lipshutz, B. H.; Pegram, J. J., *Tetrahedron Lett.* **1980**, 21 (35), 3343-3346.
43. Evans, D. A.; Morrissey, M. M., *J. Am. Chem. Soc.* **1984**, 106 (13), 3866-3868.
44. Brown, J. M.; Naik, R. G., *J. Chem. Soc., Chem. Commun.* **1982**, (6), 348-350.

-
45. Heapy, A. M.; Brimble, M. A., *Tetrahedron* **2010**, 66 (29), 5424-5431.
46. Villieras, J.; Rambaud, M., *Synthesis* **1983**, (4), 300-303.
47. Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B., *Chem. Rev.* **1994**, 94 (8), 2483-2547.
48. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B., *J. Am. Chem. Soc.* **1987**, 109 (19), 5765-5780.
49. Adkins, H.; Billica, H. R., *J. Am. Chem. Soc.* **1948**, 70 (2), 695-698.
50. Alali, F. Q.; Liu, X. X.; McLaughlin, J. L., *J. Nat. Prod.* **1999**, 62 (3), 504-540.
51. Tang, S. H.; Kennedy, R. M., *Tetrahedron Lett.* **1992**, 33 (37), 5299-5302.
52. Inoki, S.; Mukaiyama, T., *Chem. Lett.* **1990**, (1), 67-70.
53. Motoyama, T.; Yabunaka, H.; Miyoshi, H., *Bioorganic & Medicinal Chem. Lett.* **2002**, 12 (16), 2089-2092.
54. Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S., *J. Org. Chem.* **1995**, 60 (14), 4419-4427.
55. Li, K. Q.; Vig, S.; Uckun, F. M., *Tetrahedron Lett.* **1998**, 39 (15), 2063-2066.
56. Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Keinan, E., *J. Am. Chem. Soc.* **1998**, 120 (44), 11279-11284.
57. Schaus, S. E.; Branalt, J.; Jacobsen, E. N., *J. Org. Chem.* **1998**, 63 (15), 4876-4877.
58. Crimmins, M. T.; Zhang, Y.; Diaz, F. A., *Org. Lett.* **2006**, 8 (11), 2369-2372.
59. Emde, U.; Koert, U., *European J. Org. Chem.* **2000**, (10), 1889-1904.
60. Yu, Q.; Wu, Y. K.; Ding, H.; Wu, Y. L., *J. Chem. Soc., Perkin Trans. 1* **1999**, (9), 1183-1188.
61. Inoki, S.; Kayo, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T., *Chem. Lett.* **1989**, (3), 515-518.

-
62. Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T., *Chem. Lett.* **1989**, (3), 449-452.
63. Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S., *Bull. Chem. Soc. Jpn.* **1990**, 63 (1), 179-186.
64. Wang, Z. M.; Tian, S. K.; Shi, M., *Tetrahedron: Asymmetry* **1999**, 10 (4), 667-670.
65. Tian, S. K.; Wang, Z. M.; Jiang, J. K.; Shi, M., *Tetrahedron: Asymmetry* **1999**, 10 (13), 2551-2562.
66. Wang, Z. M.; Tian, S. K.; Shi, M., *Tetrahedron Lett.* **1999**, 40 (5), 977-980.
67. Perez, B. M.; Schuch, D.; Hartung, J., *Org. Biomol. Chem.* **2008**, 6 (19), 3532-3541.
68. Hartung, J.; Greb, M., *J. Organomet. Chem.* **2002**, 661 (1-2), 67-84.
69. Tang, R.; Kochi, J. K., *Journal of Inorganic & Nuclear Chemistry* **1973**, 35 (11), 3845-3856.
70. Hiatt, R.; Irwin, K. C.; Gould, C. W., *J. Org. Chem.* **1968**, 33 (4), 1430-1435.
71. Wang, J.; Morra, N. A.; Zhao, H.; Gorman, J. S. T.; Lynch, V.; McDonald, R.; Reichwein, J.; Pagenkopf, B. L., *Can. J. Chem.* **2009**, 87 (1), 328-334.
72. Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B. P.; Machin, B.; Pagenkopf, B. L., *Org. Lett.* **2009**, 11 (24), 5614-5617.
73. Morra, N. A.; Pagenkopf, B. L., *Org. Lett.* **2011**, 13 (4), 572-575.
74. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N., *Science* **1997**, 277 (5328), 936-938.
75. Donohoe, T. J.; Butterworth, S., *Angew. Chem., Int. Ed.* **2003**, 42 (8), 948-951.
76. Mitsunobu, O.; Yamada, M.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1967**, 40 (4), 935-939.

-
77. Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L., *J. Am. Chem. Soc.* **1994**, *116* (20), 9361-9362.
78. Vrielynck, S.; Vandewalle, M.; Garcia, A. M.; Mascarenas, J. L.; Mourino, A., *Tetrahedron Lett.* **1995**, *36* (49), 9023-9026.
79. Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A., *J. Am. Chem. Soc.* **2000**, *122* (46), 11348-11357.
80. Enschede, C.; Hesse, M., *Helv. Chim. Acta* **2003**, *86* (1), 233-246.
81. Watanabe, S.; Suga, K.; Fujita, T.; Saito, N., *Aust. J. Chem.* **1977**, *30* (2), 427-431.
82. Kiyooka, S.; Kuroda, H.; Shimasaki, Y., *Tetrahedron Lett.* **1986**, *27* (26), 3009-3012.
83. Rychnovsky, S. D.; Rogers, B.; Yang, G., *J. Org. Chem.* **1993**, *58* (13), 3511-3515.
84. Winstein, S.; Holness, N. J., *J. Am. Chem. Soc.* **1955**, *77* (21), 5562-5578.
85. Wohlrab, A.; Lamer, R.; VanNieuwenhze, M. S., *J. Am. Chem. Soc.* **2007**, *129* (14), 4175-4177.
86. Dale, J. A.; Dull, D. L.; Mosher, H. S., *J. Org. Chem.* **1969**, *34* (9), 2543-2547.
87. Patterson, J.; Sigurdsson, S. T., *J. Chem. Educ.* **2005**, *82* (7), 1049-1050.
88. Dale, J.A.; Mosher, H.A., *Journal of the American Chemical Society* **1973**, *95* (2), 512-519.
89. Seiser, T.; Kamena, F.; Cramer, N., *Angew. Chem., Int. Ed.* **2008**, *47* (34), 6483-6485.
90. Nasveschuk, C. G.; Ungermannova, D.; Liu, X. D.; Phillips, A. J., *Org. Lett.* **2008**, *10* (16), 3595-3598.
91. Zurwerra, D.; Gertsch, J.; Altmann, K. H., *Org. Lett.* **2010**, *12* (10), 2302-2305.
92. Wolf, C.; Liu, S. L., *J. Am. Chem. Soc.* **2006**, *128* (34), 10996-10997.

-
93. Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M., *J. Am. Chem. Soc.* **2005**, *127* (40), 13760-13761.
94. Boyall, D.; Frantz, D. E.; Carreira, E. M., *Org. Lett.* **2002**, *4* (15), 2605-2606.
95. Furstner, A.; Bouchez, L. C.; Morency, L.; Funel, J. A.; Liepins, V.; Poree, F. H.; Gilmour, R.; Laurich, D.; Beaufils, F.; Tamiya, M., *Chem.-Eur. J.* **2009**, *15* (16), 3983-4010.
96. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L., *J. Am. Chem. Soc.* **1997**, *119* (28), 6496-6511.
97. Myers, A. G.; Yang, B. H.; Kopecky, D. J., *Tetrahedron Lett.* **1996**, *37* (21), 3623-3626.
98. Gilbert, J. C.; Weerasooriya, U., *J. Org. Chem.* **1982**, *47* (10), 1837-1845.
99. Seyferth, D.; Marmor, R. S.; Hilbert, P., *J. Org. Chem.* **1971**, *36* (10), 1379-1385.
100. Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J., *Synlett* **1996**, (6), 521-522.
101. Trost, B. M.; Ball, Z. T.; Joge, T., *J. Am. Chem. Soc.* **2002**, *124* (27), 7922-7923.
102. Chan, K. K.; Cohen, N.; Denoble, J. P.; Specian, A. C.; Saucy, G., *J. Org. Chem.* **1976**, *41* (22), 3497-3505.
103. Yamazaki, T.; Mizutani, K.; Kitazume, T., *J. Org. Chem.* **1995**, *60* (19), 6046-6056.
104. Meta, C. T.; Koide, K., *Org. Lett.* **2004**, *6* (11), 1785-1787.
105. Denmark, S. E.; Jones, T. K., *J. Org. Chem.* **1982**, *47* (23), 4595-4597.
106. Charette, A. B.; Berthelette, C.; St-Martin, D., *Tetrahedron Lett.* **2001**, *42* (31), 5149-5153.
107. Trost, B. M.; Masuyama, Y., *Isr. J. Chem.* **1984**, *24* (2), 134-143.
108. Vanrheenen, V.; Kelly, R. C.; Cha, D. Y., *Tetrahedron Lett.* **1976**, (23), 1973-1976.

-
109. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D. Q.; Zhang, X. L., *J. Org. Chem.* **1992**, 57 (10), 2768-2771.
110. Takasu, M.; Naruse, Y.; Yamamoto, H., *Tetrahedron Lett.* **1988**, 29 (16), 1947-1950.
111. Ishihara, K.; Mori, A.; Yamamoto, H., *Tetrahedron* **1990**, 46 (13-14), 4595-4612.
112. Winship, P. C., The Development and Applications of the Lewis Acid-Mediated Osmium-Catalysed Oxidative Cyclisation. University of Oxford, **2011**.
113. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., *Tetrahedron Lett.* **1991**, 32 (9), 1175-1178.
114. Blakemore, P. R., *J. Chem. Soc., Perkin Trans. 1* **2002**, (23), 2563-2585.
115. Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978**, 43 (14), 2923-2925.
116. Amarego, W.; Chai, C., *Purification of Laboratory Chemicals*. 5th ed.; Butterworth-Heinemann: Oxford, **2003**.
117. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996**, 15 (5), 1518-1520.
118. Fukuzawa, S.; Sakai, S., *Bull. Chem. Soc. Jpn.* **1992**, 65 (12), 3308-3314.
119. Heinisch, L.; Kuchler, C.; Kuchler, W., *Arzneim. Forsch.* **1968**, 18 (10), 1324-1328.
120. Smith, S. M.; Uteuliyev, M.; Takacs, J. M., *Chem. Commun.* **2011**, 47 (27), 7812-7814.
121. Tamaru, Y.; Hojo, M.; Kawamura, S. I.; Sawada, S.; Yoshida, Z. I., *J. Org. Chem.* **1987**, 52 (18), 4062-4072.
122. Adam, W.; Saha-Moller, C.; Schmid, K., *J. Org. Chem.* **2000**, 65 (5), 1431-1433.
123. Feldman, K. S.; Simpson, R. E., *J. Am. Chem. Soc.* **1989**, 111 (13), 4878-4886.

-
124. Zhong, Y. L.; Shing, T. K. M., *J. Org. Chem.* **1997**, 62 (8), 2622-2624.
125. Almendros, P.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. 1* **1997**, (17), 2561-2568.
126. Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S., *J. Org. Chem.* **2002**, 67 (7), 1982-1992.
127. Sharma, G. V. M.; Mahalingam, A. K., *J. Org. Chem.* **1999**, 64 (24), 8943-8944.
128. Nagaiah, K.; Sreenu, D.; Purnima, K. V.; Rao, R. S.; Yadav, J. S., *Synthesis* **2009**, (8), 1386-1392.
129. Bauer, M.; Maier, M. E., *Org. Lett.* **2002**, 4 (13), 2205-2208.
130. Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T., *Chem.-Asian J.* **2011**, 6 (2), 560-572.
131. Fieser, L. F.; Fieser, M., *Reagents for Organic Synthesis*. Wiley-Interscience, New York: **1967**.
132. Muranaka, K.; Sano, A.; Ichikawa, S.; Matsuda, A., *Bioorg. Med. Chem.* **2008**, 16 (11), 5862-5870.
133. Corey, E. J.; Cimprich, K. A., *J. Am. Chem. Soc.* **1994**, 116 (7), 3151-3152.
134. Kim, S.; Kim, B.; In, J., *Synthesis* **2009**, (12), 1963-1968.
135. Petri, A. F.; Schneekloth, J. S.; Mandal, A. K.; Crews, C. M., *Org. Lett.* **2007**, 9 (16), 3001-3004.
136. Jessen, H. J.; Barbaras, D.; Hamburger, M.; Gademann, K., *Org. Lett.* **2009**, 11 (15), 3446-3449.