Synthesis of the EFG-Ring System of Pectenotoxin-4

A thesis submitted to the Board of Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

in the

University of Oxford

by

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and

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Michaelmas 2017

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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.

Ahria Esphandiar Roushanbakhti

University of Oxford, Trinity Term 2017

Abstract

The EFG-ring system of pectenotoxin-4 was synthesised *via* a novel pathway which ultilised a cobalt-mediated oxidative cyclisation to access the *trans* F-ring, and an osmium-mediated oxidative cyclisation to form the *cis* E-ring.

Subsequent union of these fragments, under modified Julia-Kocienski olefination conditions, facilitated the synthesis of the EFG-ring system of pectenotoxin-4.

Introduction

This chapter reports the previous total syntheses of pectenotoxin molecules, along with completed syntheses of pectenotoxin fragments, including the Donohoe group's synthesis of the ABC-ring system of pectenotoxin-4.

Results and Discussion

The synthesis of the FG-ring system and subsequent coupling to the E-ring fragment are detailed in this chapter. The final steps from the Julia adduct to the EFG-ring system conclude this chapter.

Acknowledgements

First and foremost, I would like thank Professor Donohoe for having given me this extraordinary opportunity. It was a great privilege to have worked in your group, and the many great lessons I learnt helped turn parts of my youthful foolishness into wisdom. I wish Professor Donohoe and his research group every success for the future.

I would like to acknowledge all the members of the Donohoe group I had the pleasure of meeting and working alongside. I was fortunate enough to begin my PhD in the company of Leo Hardegger, Sandra Balcells Garcia, Simon Werrell, Johannes Walker, and Ekaterina Melikhov, and I am glad I could share this experience with you all. Thank you to Johannes Walker, Wasmin Akhtar, and Melodie Richardson for their patience and time in proofreading this thesis.

Lastly, thank you to my family for their unconditional love and support, without which none of this would be possible. I hope that one day I can produce a piece of work worthy enough to dedicate to my parents, but for now I can only say thank you, for everything.

'You are good when you walk to your firmly and with bold steps. Yet you are not evil when you go thither limping. Even those who limp go not backward.' K.Gibran

Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
AD	asymmetric dihydroxylation
Ar	aromatic
aq.	aqueous
Bn	benzyl
Bt	benzothiazole
Bu	butyl
ºC	degrees centigrade
cat.	catalytic
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DBB	4,4'-di-*tert*-butyl-1,1'-biphenyl
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQ	dihydroquinyl
DHQD	dihydroquinidyl
dd	doublet of doublets
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4 (dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide

dr	diastereomeric ratio
e^-	electron
ee	enantiomeric excess
equiv.	equivalents
ESI^+	electrospray ionisation
Et	ethyl
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution spectroscopy
Hz	Hertz
^{i}Pr	iso-propyl
Im	imidazole
Imd	imidate
IR	infrared
J	coupling constant
L	generic ligand
LDA	lithium diisopropylamide
LiDBB	lithium 4,4’-di-tert-butylbiphenylide
lut.	lutidine
m	multiplet
M	molar
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
mg	milligram(s)

MOM	methoxymethyl
m.p.	melting point
ms	molecular sieves
MS	mass spectroscopy
MTPA	methoxy(trifluoromethyl)phenylacetic acid
m/z	mass-to-charge ratio
NIS	N-iodosuccinimide
NME	N-methyl ephedrine
NMO	N-methyl morpholine-N-oxide
nOe	nuclear overhause effect
p	para
Ph	phenyl
PPTS	pyridinium *para*-toluenesulfonate
PMB	para-methoxybenzyl
PTX	pectenotoxin
Py	pyridine
ppm	parts per million
q	quatet
rt	room temperature
s	singlet
SA	seco acid
sat.	saturated
SEM	triethylsilylethoxymethyl
t	triplet
t	tert
^{t}Bu	tert-butyl
TAS-F	Tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	tert-butyl hydroperoxide
TBDPS	tert-butyldiphenylsilyl
TBODPS	*tert*-butoxide diphenylsilyl
TBS	tert-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	tosyl
X	generic halogen

Chapter 1

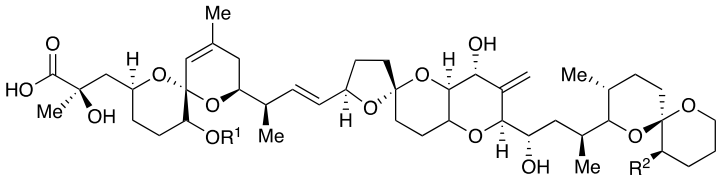
Introduction

1.1 The Pectenotoxin Family

1.1.1 Original Isolation and Characterisation

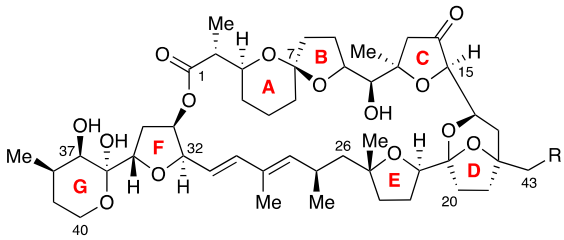
The pectenotoxin (PTX) family of natural products are a series of macrocyclic polyethers which boast intriguing structural complexity, and for certain members of the family, promising biological activity.

The first members of the family, PTX-1–5, were isolated by Yasumoto and co-workers off the northeastern coast of Japan, in 1985.[1] The folklore of this region described the frequent occurrence of gastroenteritis due to the ingestion of shellfish harvested in late spring to summer. This led Yasumoto and co-workers to examine the local scallops in the hope that the toxins causing this disease could be identified. Their investigations revealed that the digestive glands of the scallops contained PTX-1–5, along with the polyether fatty acids dinophysistoxin (DTX)-1 and -3 (***Figure 1***).[1]



DTX-1 (**1**): R^1 = H, R^2 = H

DTX-3 (**2**): R^1 = acyl, R^2 = CH_3



PTX-1 (**3**): R = OH

PTX-2 (**4**): R = H

Figure 1. *Structures of DPX and PTX molecules*

Yasumoto used a combination of nuclear magnetic resonance (NMR), mass spectrometry (MS), infrared (IR) spectroscopy and X-ray crystallography to identify the structure of PTX-1. PTX-2, based on its MS results, was assigned to C_{43}-deoxy PTX-1, while PTX-3, -4, and -5 were isolated in too small amounts to be fully characterised at this stage. The IR spectrum of PTX-1 indicated the presence hydroxyl, five-membered ring ketone, ester and conjugated diene

groups. The ^{13}C NMR spectrum revealed 47 carbons while MS gave an *m/z* 875 (M^+ + H), representing a molecular formula of $C_{47}H_{70}O_{15}$. The ^1H NMR spectrum exhibited 6 methyls and 3 olefinic protons of a *trans-trans* conjugated diene. Finally, X-ray crystallography confirmed the structure of PTX-1 and its relative stereochemistry (***Figure 2***).

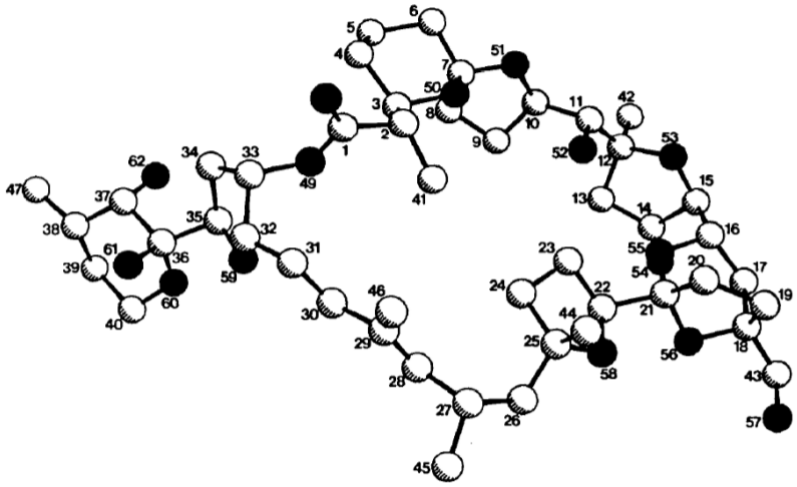


Figure 2. *X-ray model of PTX-1*[1]

It was not until 1997, however, that Yasumoto was able to determine the absolute stereochemistry of PTX-1 through further studies conducted on PTX-6.[2] Using chiral anisotropic shift reagents, the absolute stereochemistry of C_{18} in PTX-6 was identified as (*S*). Correlating the C_{18} stereochemistry to the data obtained from the X-ray crystallography of PTX-1, the absolute configurations of PTXs-1, -2, -3 and -6 were thus determined (***Figure 3***).[2]

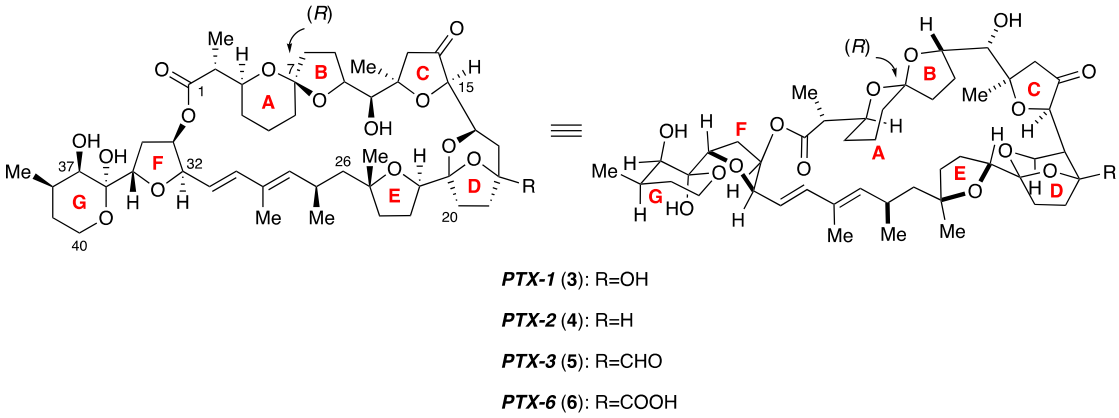


Figure 3. *Structure and absolute configuration of PTX-1, -2, -3 and -6*

The following year, Yasumoto showed through the acid-catalyzed interconversion of PTX-1 and -6, that PTX-4 and -7 were the C_7-*epi*-derivatives of PTX-1 and -6 respectively (***Figure***

4).[3] Treatment of PTX-1 and PTX-6 with an aqueous acetonitrile/TFA (0.1% v/v) solution resulted in their conversion to PTX-4 and PTX-7, along with the [6,6] spriroketal isomers PTX-8 and PTX-9, respectively. It had been suspected from the matching MS data of the PTX-1/4 and PTX-6/7 pairs that these congeners were isomeric. The NMR data obtained on PTX-4 and -7 confirmed this. It is thought that the biaxial arrangement of the C_7 C–O bonds in PTX-4 and -7 maximise the anomeric effect, thus rendering these as the more thermodynamically stable configurations compared to the biequatorial arrangements present in PTX-1 and -6.[3-4] PTX-8 and -9 were obtained as synthetiC Artifacts, unlike their [6,5] spriroketal counterparts, which were isolated naturally. It was suggested that their isomerizations to PTX-4 and -7 occur *via* enzyme catalysis in the digestive glands of the parent scallops.[3]

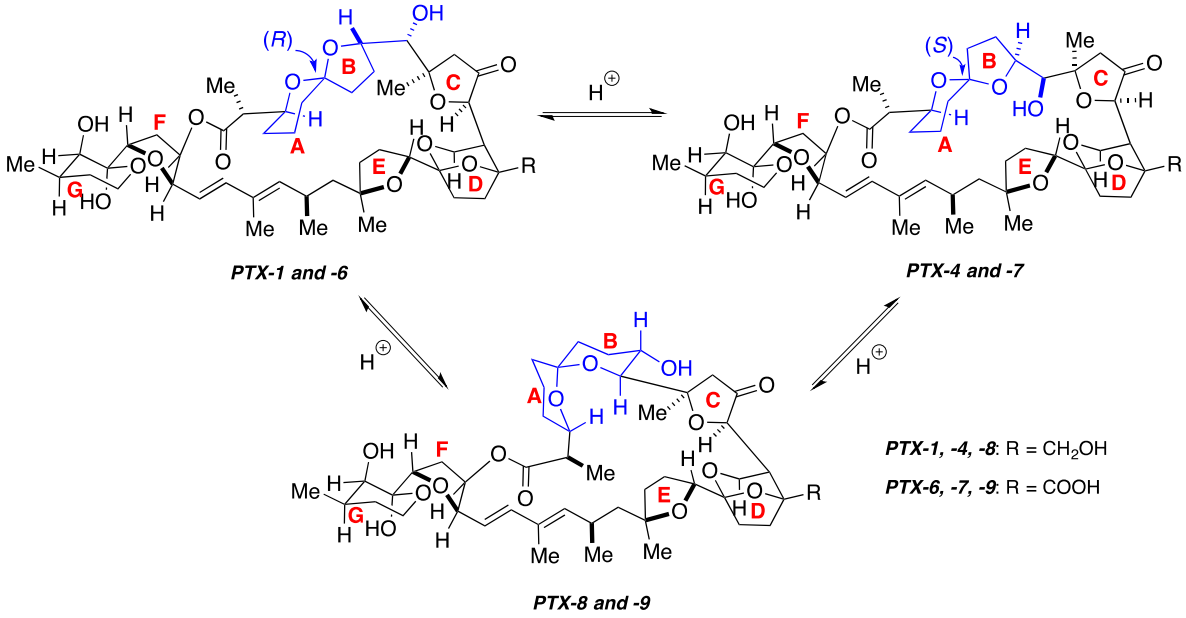


Figure 4. *Acid catalysed isomerisation at C7*

1.1.2 PTX-2, The Parent Toxin, and its Seco Acid Derivatives

It is known that edible fish can become toxic through accumulating the toxins of toxic organism on which they feed.[1] The scallops from which the aforementioned members of the PTX family were isolated, *Patinopecten yessoensis*, do not produce the PTX molecules themselves. Rather, they accumulate these toxins through ingesting toxigenic strains of the marine plankton, dinoflagellate known as *Dinophysis fortii*.[5]

Of all the aforementioned PTX-molecules, PTX-2 is the only one that has been found in *Dinophysis fortii*. This led to the proposal that PTX-2 is the parent toxin from which all other members of the PTX-family are derived. Evaluating the structures of PTX-1–4, -6 and -7, shows that they differ only in the oxidation state at C_{43} and in stereochemistry at C_7 (***Figure 5***). This structural diversity is thought to arise from the metabolism of PTX-2 in the digestive glands of *Patinopecten yessoensis*. Further evidence supporting the proposal of PTX-2 as the parent toxin comes from the toxicology data of the PTX molecules, PTX-2 demonstrating the greatest lethality to mice by intraperitoneal (i.p.) injection (LD_{50} = 219 μg/kg).[6]

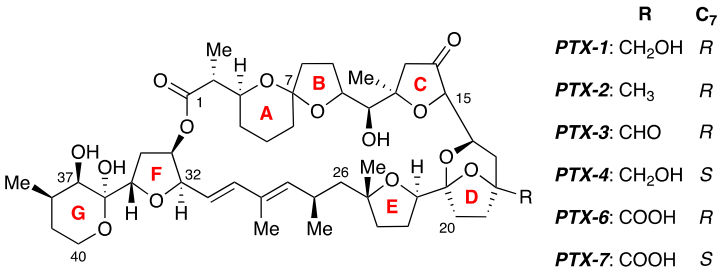


Figure 5. *Comparison of PTX structures*

In 1998, two new PTX analogues, PTX-2 seco acid (SA) and 7-*epi*-PTX-2 SA, were isolated in New Zealand from the mussels, *Perna canaliculus*, which were treated with the dinoflagellate, *Dinophysis acuta*.[7-8] Their acyclic structures arise from the enzymatic hydrolysis of PTX-2 to PTX-2 SA in the mussel tissues (***Figure 6***).[9] PTX-2 SA, in turn, undergoes progressive epimerization within the mussel tissue to the thermodynamically more stable, 7-*epi*-PTX-2 SA. Studies conducted by Suzuki and co-workers showed that PTX-2 was not converted to PTX-2 SA nor 7-*epi*-PTX-2 SA in phosphate buffers at pHs ranging from 4.1–9.1, indicating that the SA compounds are not artifacts of the isolation procedure.[9] Interestingly, neither PTX-2 SA nor 7-*epi*-PTX-2 SA showed cytotoxicity against KB cells at (1.8 μg/mL) dosage, while PTX-2 did at dosages of only 0.05 μg/mL. This indicates the imperative need of a cyclic macrolide structure for the cytotoxic potency to be exerted.[7]

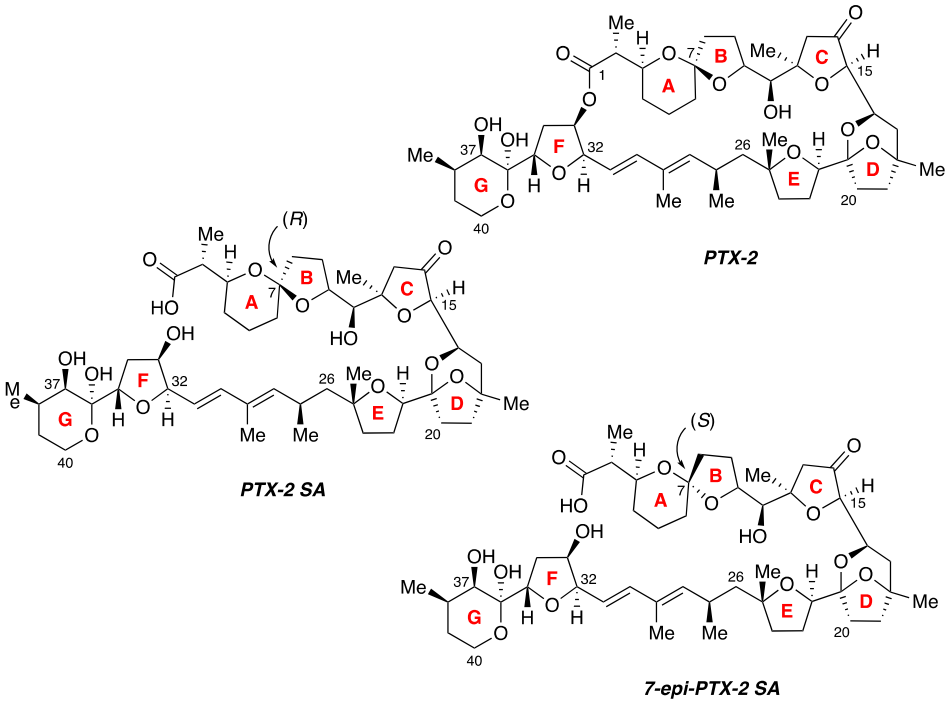


Figure 6. *PTX-2, PTX2 SA and 7-epi-PTX-2 SA*

1.1.3 PTX-2b and -2c, and PTX-11, -11b and -11c

In 2003, under the same conditions used by Yasumuto to convert PTX-1 (6) to PTX-4 (7), Suzuki and co-workers reported the acid-catalysed interconversion PTX-2 to PTX-2b and -2c *via* C_7-spiroketal isomerisation.[10] PTX-2b was assigned as the C_7-epimer of PTX-2, and PTX-2b was characterised as the [6,6] spiroketal analogue of PTX-2 (***Figure 7***).

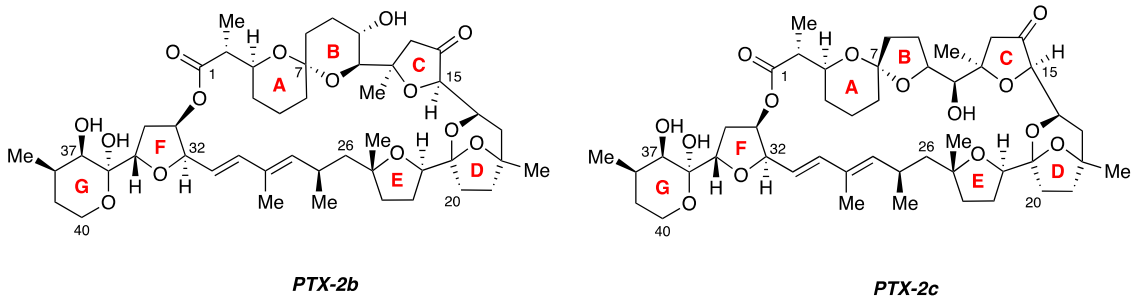


Figure 7. *Structures of PTX-2b and -2c*

In the same study, a novel isomer of PTX-1 was detected.[10] The structure of this new PTX isomer, named PTX-11, was later determined and shown to contain the same core structure as PTX-2. The two structures differ by an additional hydroxy group at C_{34} present only in PTX-11 (***Figure 8***). In addition to PTX-11, two novel compounds with almost identical

UV and MS spectra to PTX-11 were detected. These compounds were assigned as PTX-11b and -11c, the C_7-spiroketal isomers of PTX-11, and are thought to be produced from PTX-11 in analogous manner to which PTX-2b and -2C Are produced from PTX-2. However, the assignments of PTX-11b and -11c were tentative ones, as sufficient quantities for full characterisation were not obtained.[11]

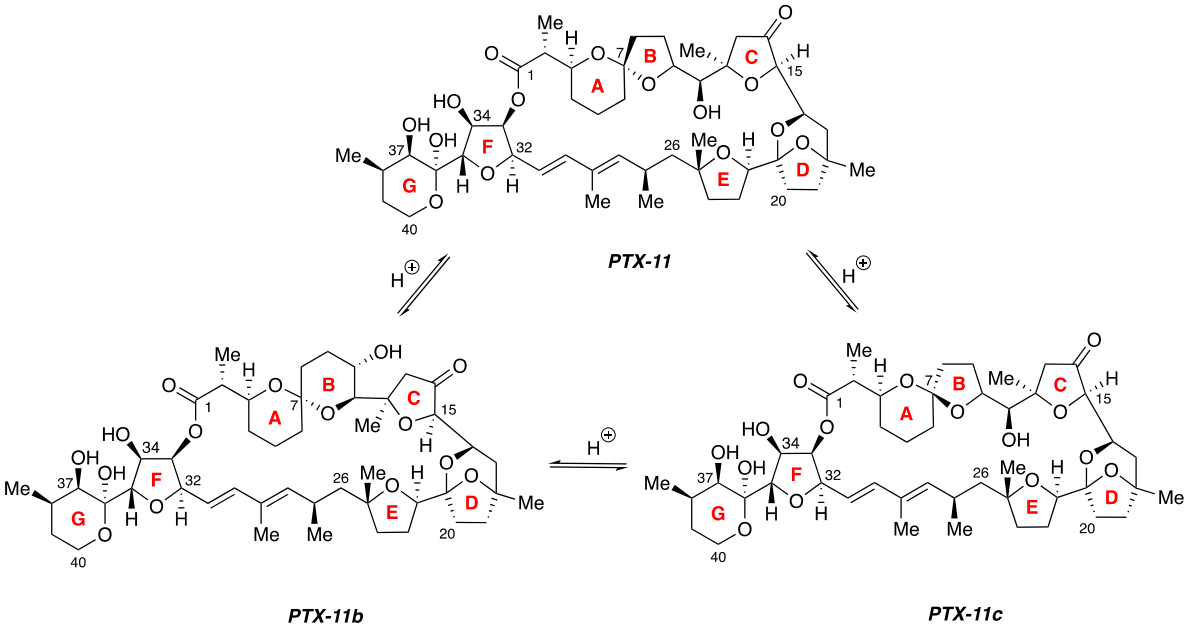


***Figure 8**. Structures of PTX-11, -11b and -11c*

Unlike PTX-2, PTX-11 does not undergo enzymatic hydrolysis in the mussel tissues to its corresponding seco acid derivatives.[11] It was postulated that due to the steric hindrance induced by the C_{34}-hydroxy group, and possibly the hydrogen bond between the C_{34}-hydroxy group and the C_1-carbonyl oxygen, PTX-11 is not a favoured substrate for enzyme(s) facilitating the hydrolysis of the lactone ring in PTX-2. Thus, given the lack of reactivity of PTX-11 towards enzymatic hydrolysis, it is thought to accumulate to a much greater extent that PTX-2 in mussels.[11-12] In terms of toxicity, however, PTX-11 showed similar levels of activity to PTX-2, with a LD_{50} by i.p. injection of 244 μg/kg (c.f. 219 μg/kg for PTX-2).[11]

1.1.4 PTX-12, -13 and -14

Shortly after the discovery of PTX-11 in 2003, PTX-12 was isolated from the flagellates, *Dinophysis acuminata* and *Dinophysis norvegica*, which were extracted from shellfish off the Norwegian coast.[12] PTX-12 was isolated as an equilibrating pair of C_{36}-epimers—$C_{36}S$-PTX-

11 and C_{36}*R*-PTX-11. A methylene group at C_{38} is present in these epimers, while a methyl group exists in this position of the parent toxin, PTX-2 (***Figure 9***).[12]

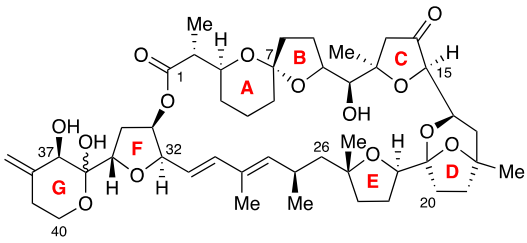


Figure 9*. Structure of PTX-12*

The latest discovery of a PTX molecule to date, is that of PTX-13 and -14, by Miles and co-workers, isolated together from extracts *Dinophysis acuta*, taken from the coast of New Zealand.[13] Both compounds are oxidized derivatives of PTX-2, identified by analysis of MS fragmentation patterns and comparison of their NMR spectra to those of previously reported PTX molecules.[13] PTX-13 contains an additional hydroxy group at C_{32}, relative to PTX-2, with (*R*) stereochemistry, while PTX-14 corresponds to the $C_{32,36}$-dehydration product of PTX-13, and may be an artifact (***Figure 10***).[13]

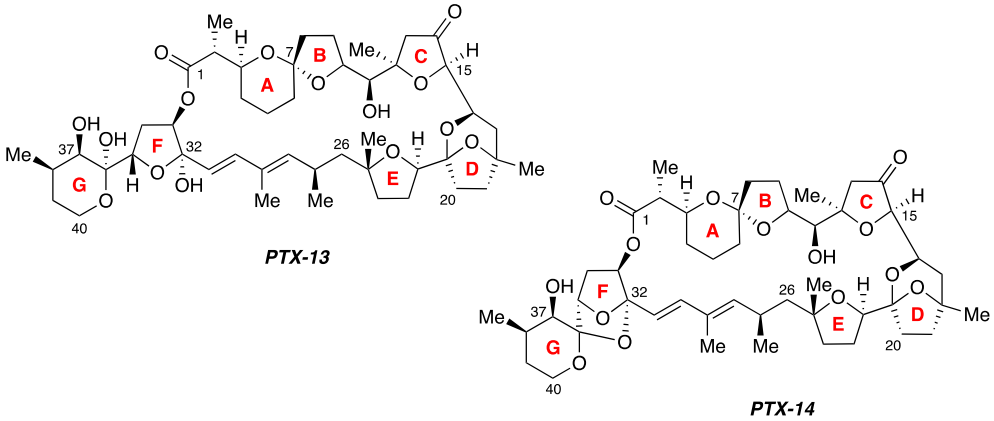


Figure 10*. Structures of PTX-13 and -14*

1.2 Previous Syntheses of the Pectenotoxin Family

1.2.1 Evan's Total Synthesis of PTX-4

In 2002, Evans and co-workers reported the first total syntheses of any PTX molecules—PTX-4 and PTX-8.[14-15] Evans chose these targets after evaluating the sensitivity of the AB-spiroketal to acid.[16] Yasumoto had showed that exposing PTX-1 to an aqueous MeCN/TFA (0.1% v/v) solution affords PTX-1, -4, and -8 in a 29:14:57 ratio (***Figure 11***).[7]

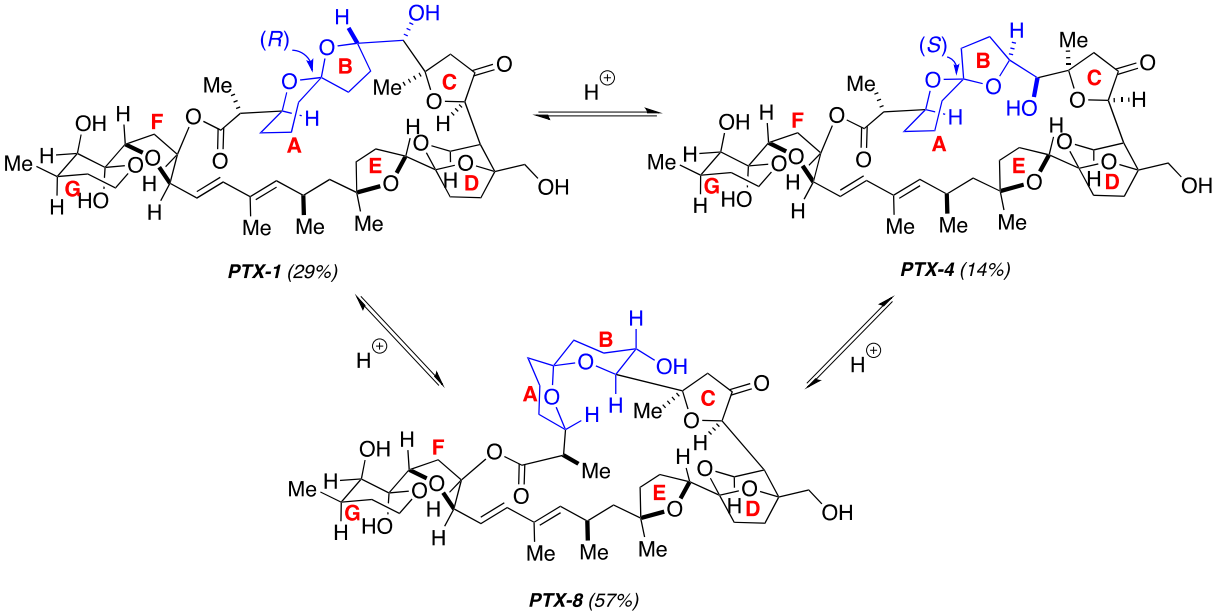
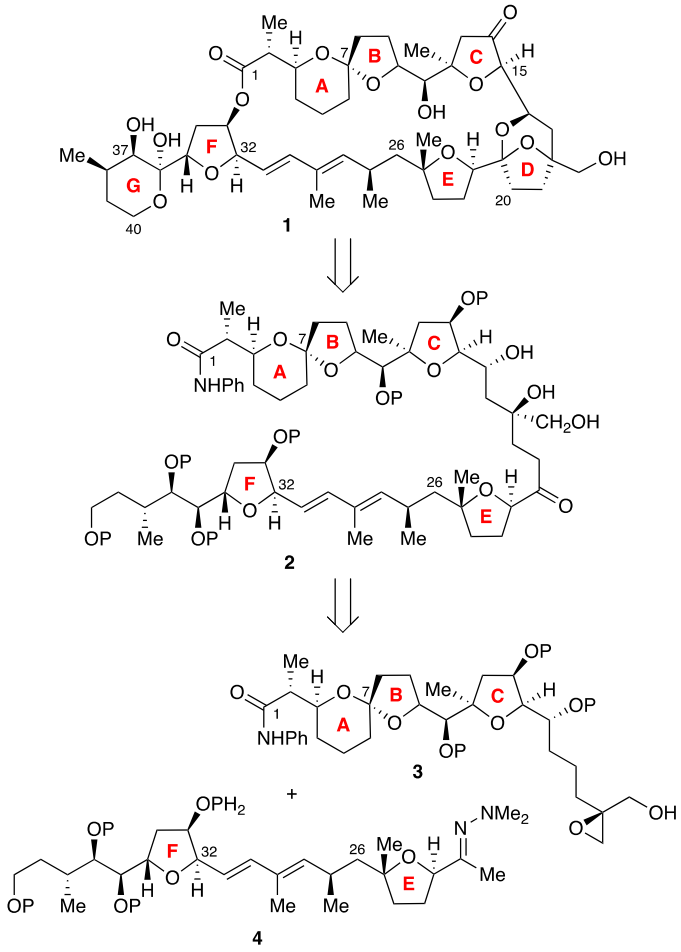


Figure 11. *Relative stability of C_7 in the closed macrolide*[16]

This suggests that the *R* configuration at C_7 is the most thermodynamically favoured isomer in the closed macrolide. In contrast, when extracted from mussel tissues, PTX-2 SA and 7-*epi*-PTX-2 SA were isolated (the [6,6] spriroketal of PTX-2 SA was not isolated) in a 1:1.9 ratio, indicating that the *S* configuration is thermodynamically more stable in the open chain form. Therefore, by synthesizing PTX-4 and carrying the *S* configuration at C_7 through the synthesis, the AB-spiroketal is less likely to undergo epimerization prior to cyclisation.

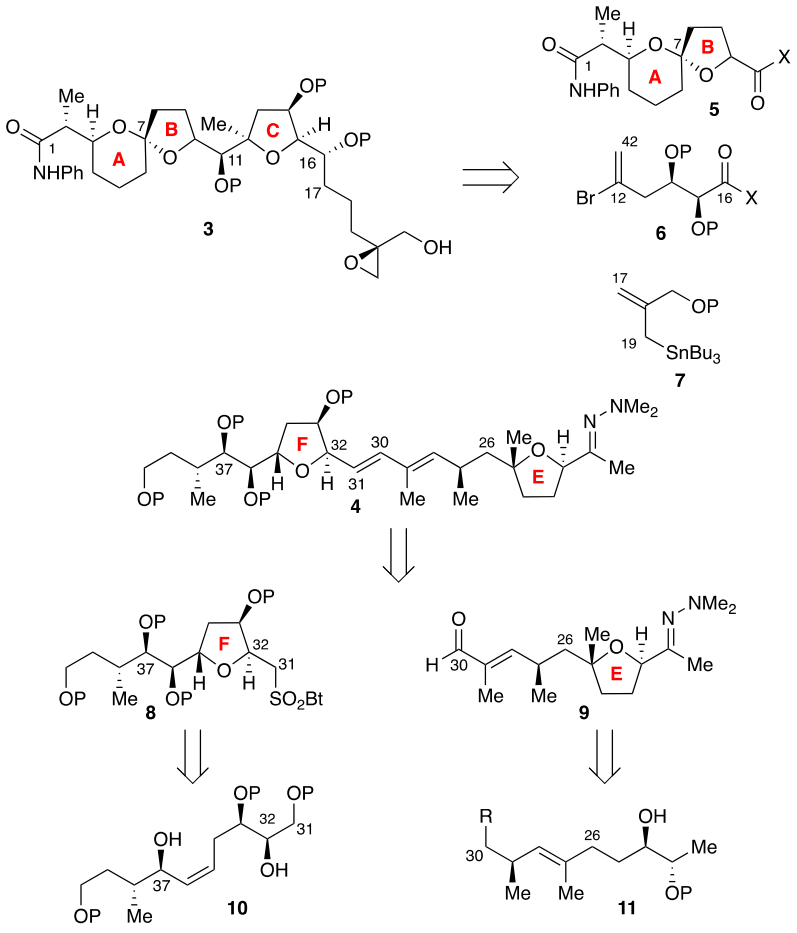
Evans' key disconnections, illustrated in ***Scheme 1***, yield a synthesis sub-goal, intermediate **2**, which could be assembled from two key fragments, **3** and **4**, by a metalloenamine-epoxide alkylation.[17-18] Ketones at C_{14} and C_{36} would need to be masked as protected alcohols, while protecting the C_1 carboxylate terminus as the *N*-phenylamide

derivative would enable the desired oxidation state to be preserved at this position, throughout the synthesis.



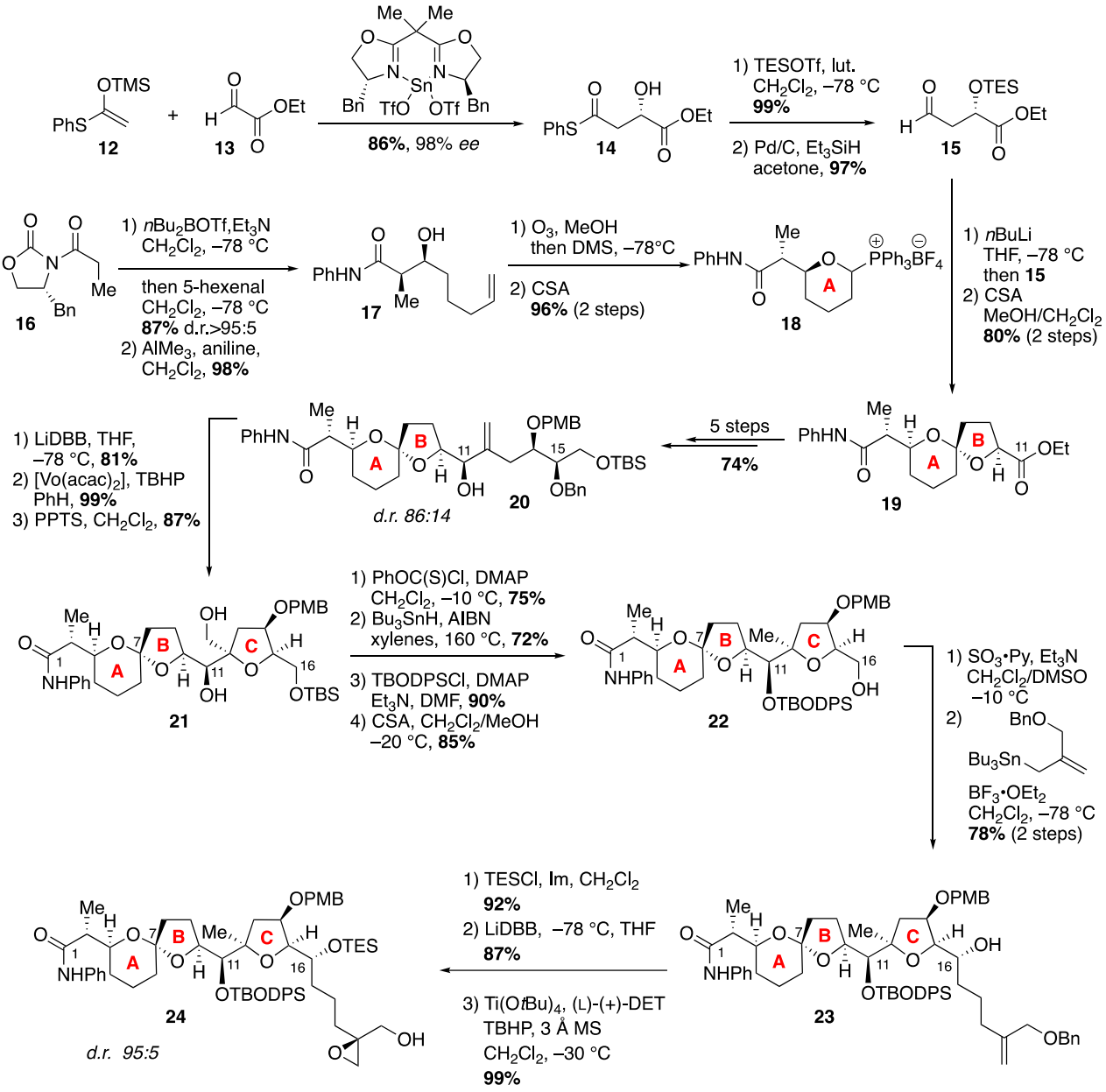
Scheme 1. *Evans' retrosynthesis of PTX-4*

The ABC fragment **3** was further simplified by disconnections made about the C_{16}-C_{17} and C_{11}-C_{12} bonds (***Scheme 2***). The C_{11} and C_{16} stereocentres were to be constructed by chelate-controlled ketone reductions, or by Felkin-controlled addition of an appropriate nucleophile to the corresponding aldehydes.[19] The EF-fragment **4** was simplified to E- and F-ring subunits, **8** and **9**, by disconnecting the C_{30}-C_{31} olefin bond. The *trans* F-ring THF **8** was to be constructed by a C_{37} hydroxy-directed epoxidation of the olefin **10** with a subsequent ring closure by the C_{32} hydroxy group. The *cis* E-ring THF **9**, on the other hand, could be accessed from an acyclic precursor **11** by an iodoetherification procedure.[20]



Scheme 2*. Evans' retrosynthesis of the ABC- and FG-fragments*

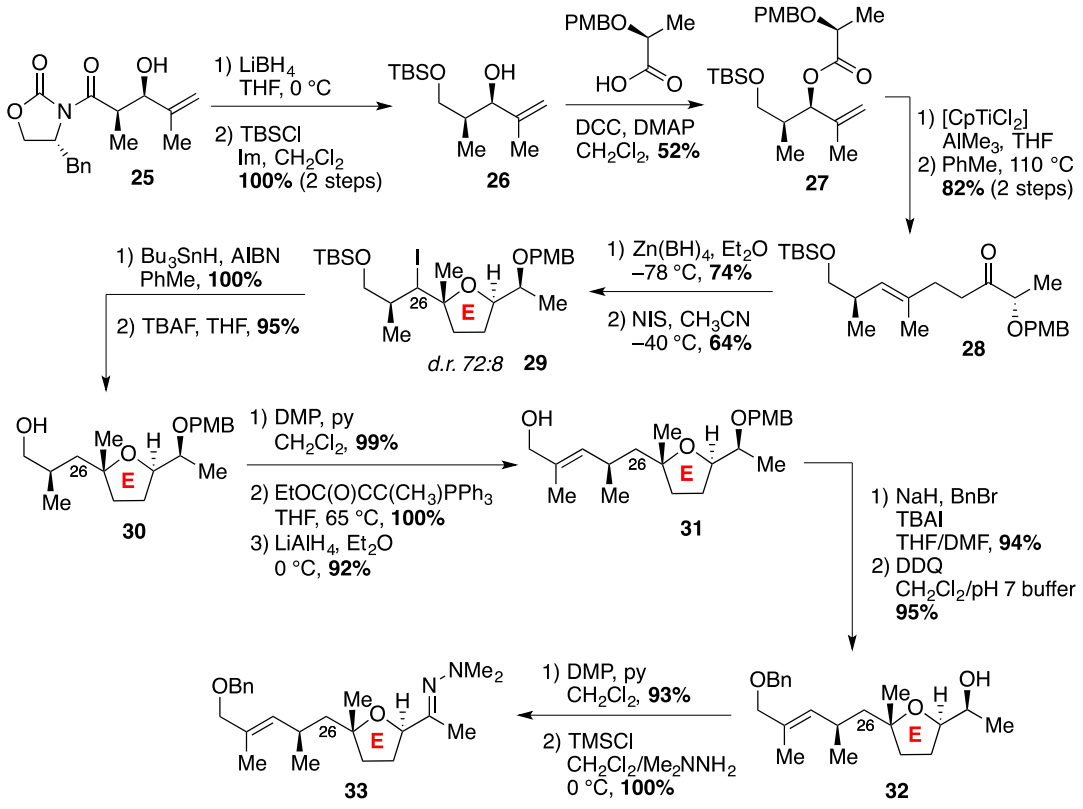
The synthesis of the ABC synthon **3** began with the addition of a boron enolate derived from **16** to 5-hexanal, affording a *syn*-aldol adduct (***Scheme 3***).[21] The A-ring lactol methyl ether was then formed by transamidation, olefin ozonolysis and *in situ* ether formation. Coupling the phosphonium salt **18**, of the A-ring methyl ether, with aldehyde **15**— accessed by protection of aldol adduct **14**, followed by chemoselective reduction of the *S*-phenyl thioester—under Wittig-type conditions afforded the corresponding enol ether, which was immediately subjected to CSA in MeOH to provide the AB-spiroketal **19** in high yield and excellent selectivity (80%, d.r.>95:5).[22]



***Scheme 3**. Evans' synthesis of the ABC-fragment*

A further five steps takes spiroketal **19** to hydroxy alkene **20**, from which selective deprotection of the benzyl ether group at C_{15} under reductive conditions, followed by C_{11} hydroxy-directed epoxidation with $[VO(acac)_2]$, yields a single diastereomer of an epoxide (not shown in ***Scheme 3***).[23] Cyclisation of this epoxide in mildly acidic conditions forms the primary alcohol **21** which was acylated with phenylthiono chloroformate, then deoxygentated under Barton conditions.[24] A protecting group manipulation, in which the *tert*-butoxydiphenylsilyl (TBODPS) ether is installed at C_{11} and the C_{16} *tert*-butyldimethylsilyl ether is cleaved, yields primary alcohol **22**. The C_{11} TBODPS ether, which was to be unmasked in the final global

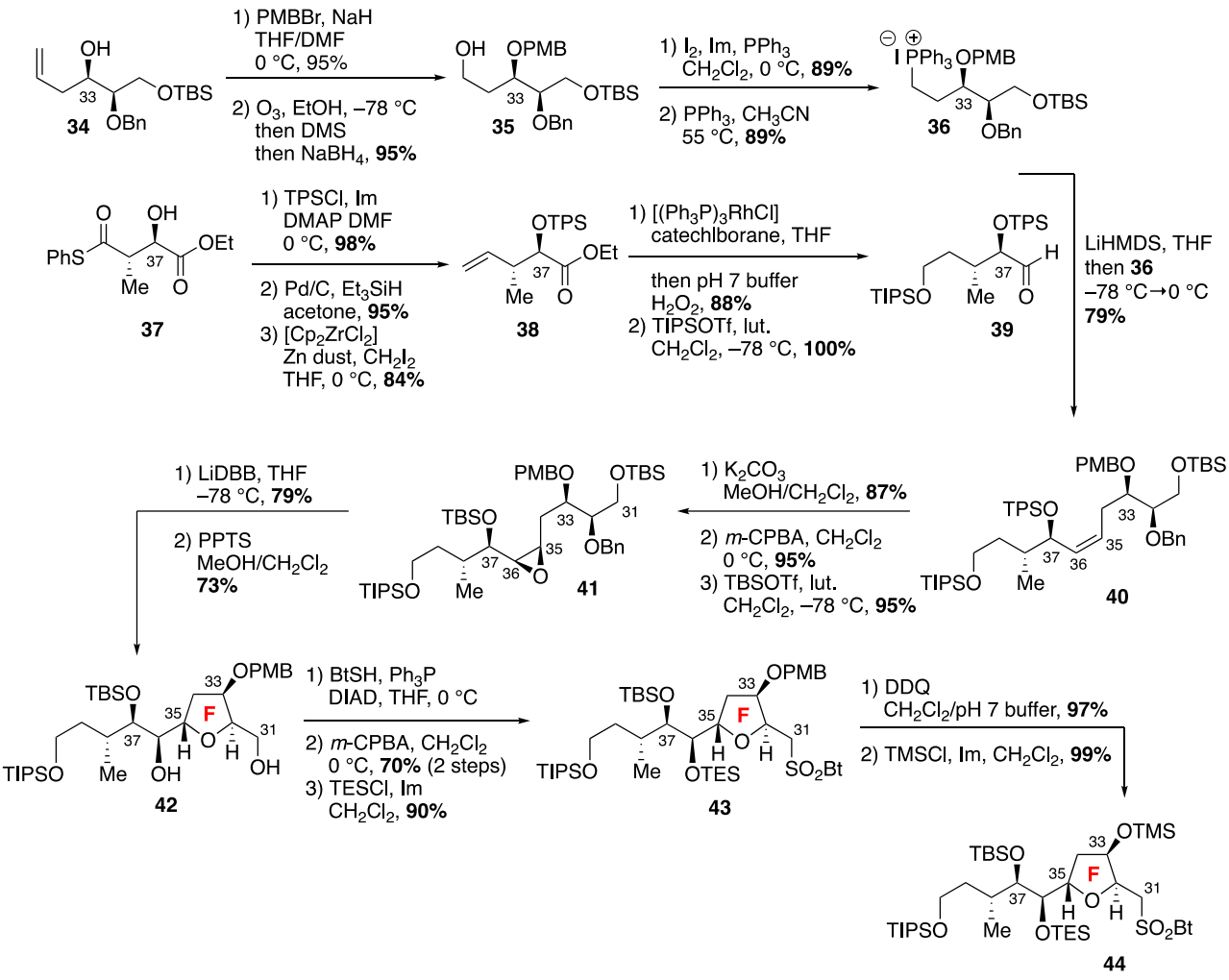
deprotection, was chosen for its stability to acid (greater than TES), but lability to fluoride. Oxidation of **22**, followed by allylation under Felkin-control, gave alkene **23** as a single diastereomer. The synthesis of the ABC synthon **3** was completed by a TES protection of the C_{15} hydroxy, reductive cleavage of the benzyl protecting group of the C_{16} hydroxy, and a Sharpless asymmetric epoxidation to yield the epoxide **24** in excellent selectivity (d.r. 95:5).[25]



Scheme 4*. Evan's Synthesis of the E-ring*

The synthesis of the E-ring synthon **32**, began with reduction of the aldol adduct **25**, followed by selective protection to give allyl alcohol **26** (***Scheme 4***).[15] Acylation of **26** with PMB-protected lactic acid afforded ester **27**, which underwent a subsequent Tebbe olefination and Claisen rearrangement to produce the γ,δ-unsaturated ketone **28**. Chelate-controlled reduction of **28** provided the precursor for the key iodoetherification reaction, which gave the desired *cis* E-ring THF **29** in modest selectivity and yield (64%, d.r. 72:28). Sequential radical dehalogenation and TBS ether-deprotection afforded alcohol **30**. DMP-mediated oxidation of **30**, followed by Wittig homologation and ester reduction, gave alcohol **31**, which contains the

complete carbon backbone of E-ring synthon **32**. A protecting group manipulation, oxidation, and hydrozone formation, then completed the synthesis of **32**.

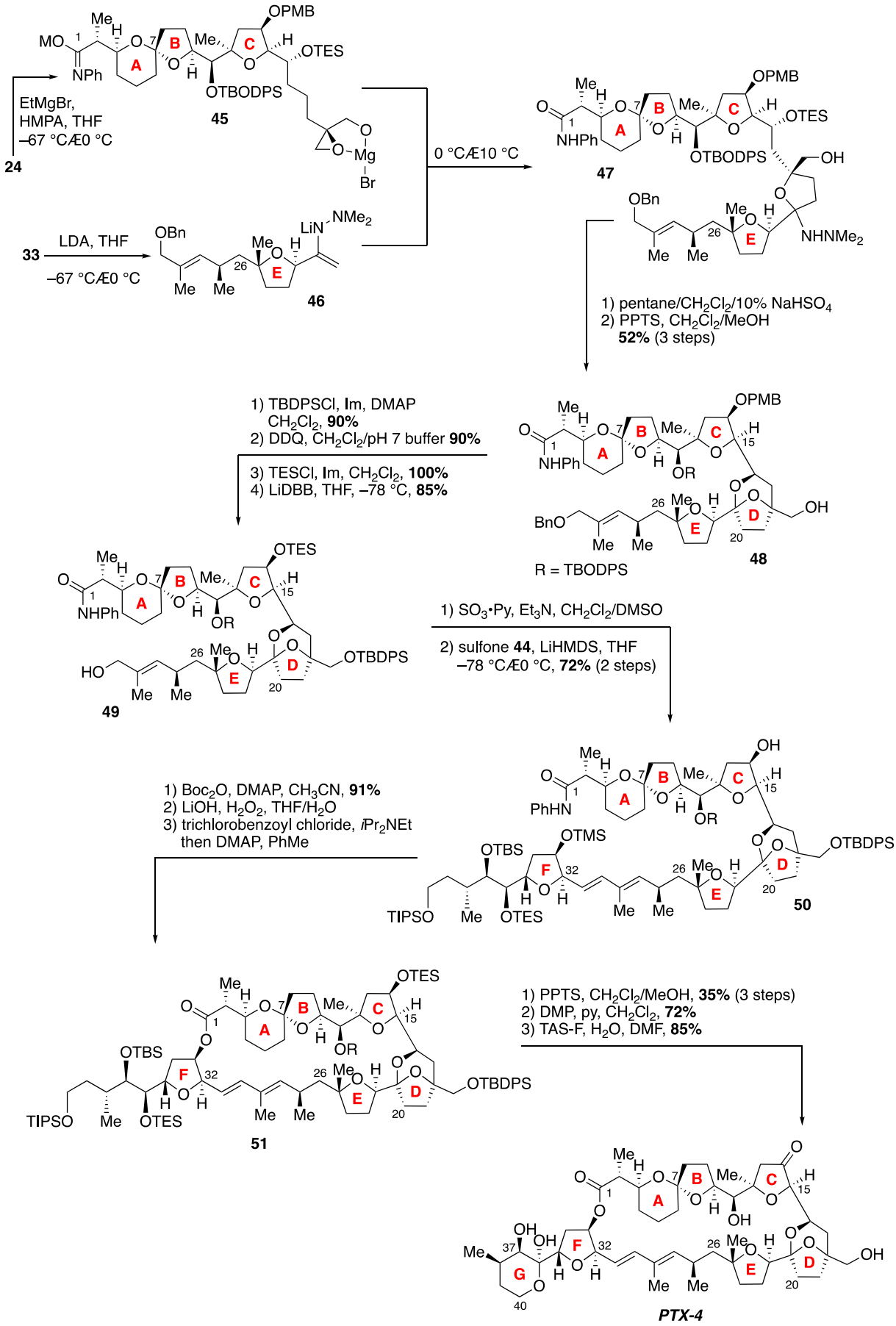


***Scheme 5**. Evan's synthesis of the F-ring*

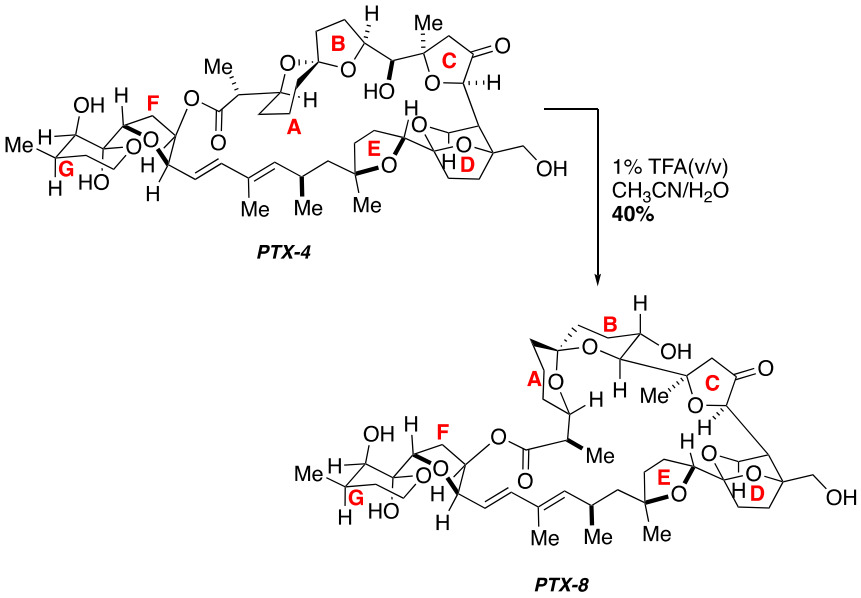
As outlined in ***Scheme 2***, the F-ring **8** can be simplified to the acyclic alkene synthon **10**, which was synthesized from the Wittig reaction of phosphonium salt **36** and aldehyde **39** (***Scheme 5***). Phosphonium salt **36** was accessed in four steps from the triol derivative **34**, beginning with protection of the C_{33} hydroxy group as the PMB ether, followed by reductive ozonolysis to give alcohol **35**, then successive iodination and nucleophilic displacement to afford **36**. Synthesis of the aldehyde partner **39**, began with protection of the C_{37} hydroxy group of aldol adduct **37**, from which selective reduction of the thioester and olefination of the resulting aldehyde under Lombardo conditions gave olefin **38**. Rhodium-catalysed hydroboration, TIPS protection of the resulting primary alcohol, and half reduction of the ethyl

ester completed the synthesis of aldehyde **39**. The Wittig olefination of **36** and **39** then proceeded smoothly to afford olefin **40**. Selective triphenylsilyl (TPS) deprotection of the C_{37} hydroxy group facilitated hydroxy directed epoxidation of the C_{35}-C_{36} olefin bond. A TBS protection of the resulting hydroxy group afforded epoxide **41** as a single diastereomer. Selective deprotection of the C_{32} benzyl ether and treatment of the resulting epoxy alcohol with PPTS, enabled cyclisation to form the F-ring and THF with simultaneous deprotection of the C_{31} TBS ether, to give diol **42**. Nucleophilic displacement of the primary alcohol and oxidation of the resulting benzthiaxole sulfide, installed the C_{31} sulfone. A subsequent protecting manipulation then completed the synthesis of the F-ring.

With the requisite fragments in hand, completion of Evans' synthesis began with the addition of epoxide complex **45**, activated by magnesium bromide, to the metalloenamine derivative **46** of **33** (***Scheme 6***).[26] Treatment of the resulting adduct **47** with aqueous acid hydrolysed the hydrazinyl lactol to the corresponding lactol, which upon treatment with PPTS in MeOH/CH_2Cl_2, underwent cleavage of the C_{16} TES ether and spontaneous cyclisation to form the bicyclic ketal **48**. Protection of the C_{18} hydroxy methyl moiety, followed by protecting group manipulation of the C_{14} hydroxy group, and cleavage of the C_{30} benzyl ether, afforded **49**. Oxidation of the C_{30} primary alcohol gave the corresponding aldehyde which was reacted with the sulfone of the F-ring fragment **44**, under conditions of the Julia olefination, to produce diene **50** in good yield and excellent selectivity (72% (2 over two steps, *E*:*Z*>95:5), and as a 88:12 mixture of C_{32} epimers, that result from E1cb elimination of the β-alkoxy sulfone moiety.[16, 27] Activation of the *N*-phenylamide to its *N*-boc imide, facilitated hydrolysis to the acid and concomitant deprotection of the C_{33}-OTMS.



***Scheme 6**. Completion of PTX-4 synthesis*

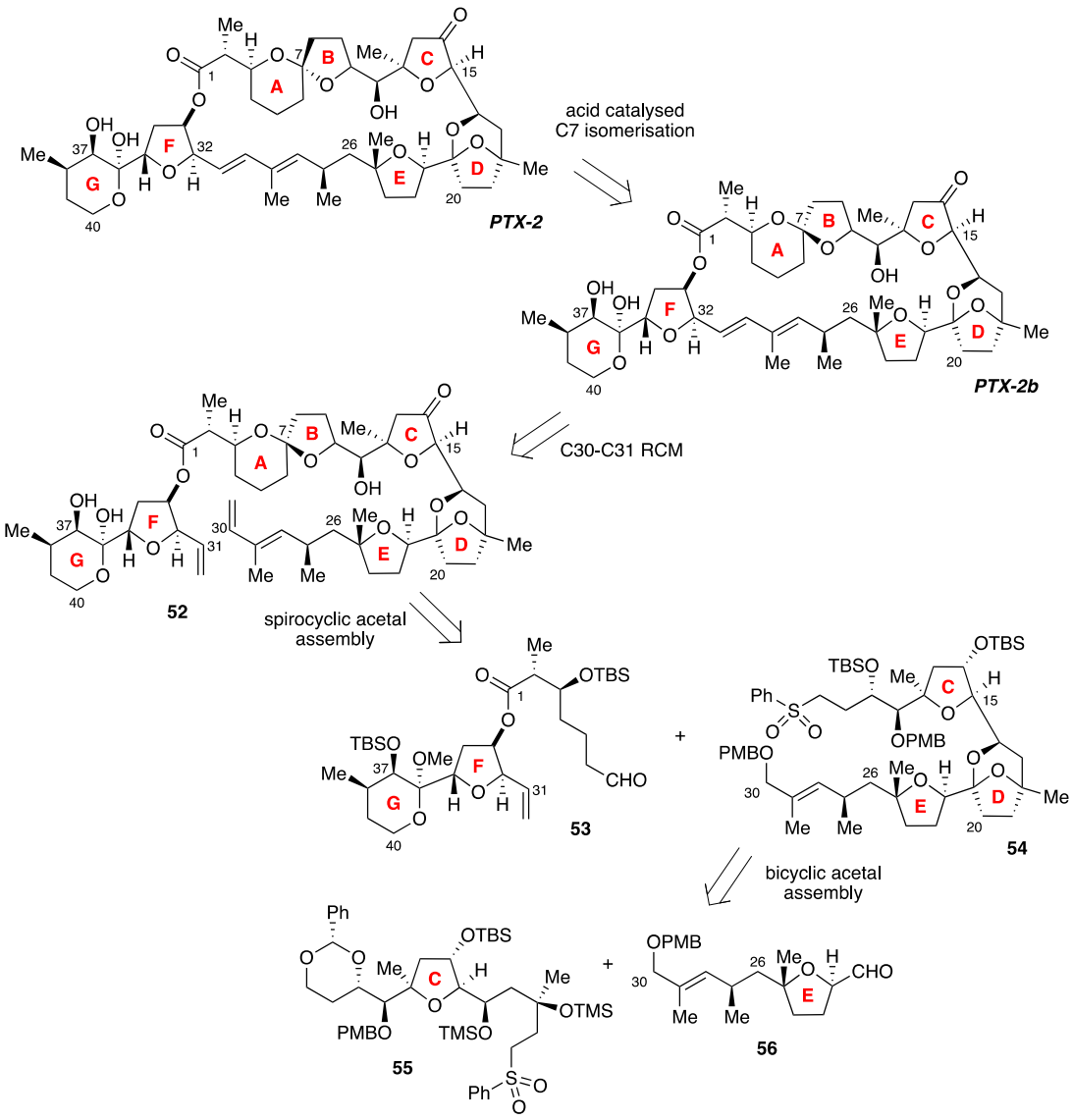


***Scheme 7**. Acid catalysed interconversion of PTX-4 to PTX-8*

Macrocyclisation under Yamagichi conditions afforded lactone **51**, which underwent selective deprotection of C_{14} and C_{36} OTES ethers upon treatment with PPTS.[28] Oxidation of the corresponding diol produced a diketone, followed by global deprotection and *in situ* cyclisation, afforded PTX-4 in 36 steps (longest linear sequence) and 0.3% overall yield. PTX-4 was then isomerized in by acid catalysis to PTX-8 in 40% yield (***Scheme 7***).

1.2.2 Fujiwara's Total Synthesis of PTX-2

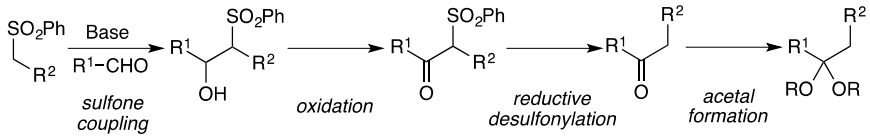
In 2014, Fujiwara and co-workers reported the total synthesis of PTX-2.[29] Their strategy was to access PTX-2 *via* a final stage acidic isomerisation of PTX-2b. Suzuki's 2003 study of the acid-catalysed interconversion between PTX-2, PTX-2b and -2c, showed that PTX-2 equilibrated rapidly with PTX-2b but much slower with PTX-2c.[10] Fujiwara thus proposed, that under the same acidic conditions, the isomerisation of PTX-2b would proceed to generate PTX-2, as the major product, so long as short reaction times were used.



***Scheme 8**. Fujiwara's retrosynthesis of PTX-2*

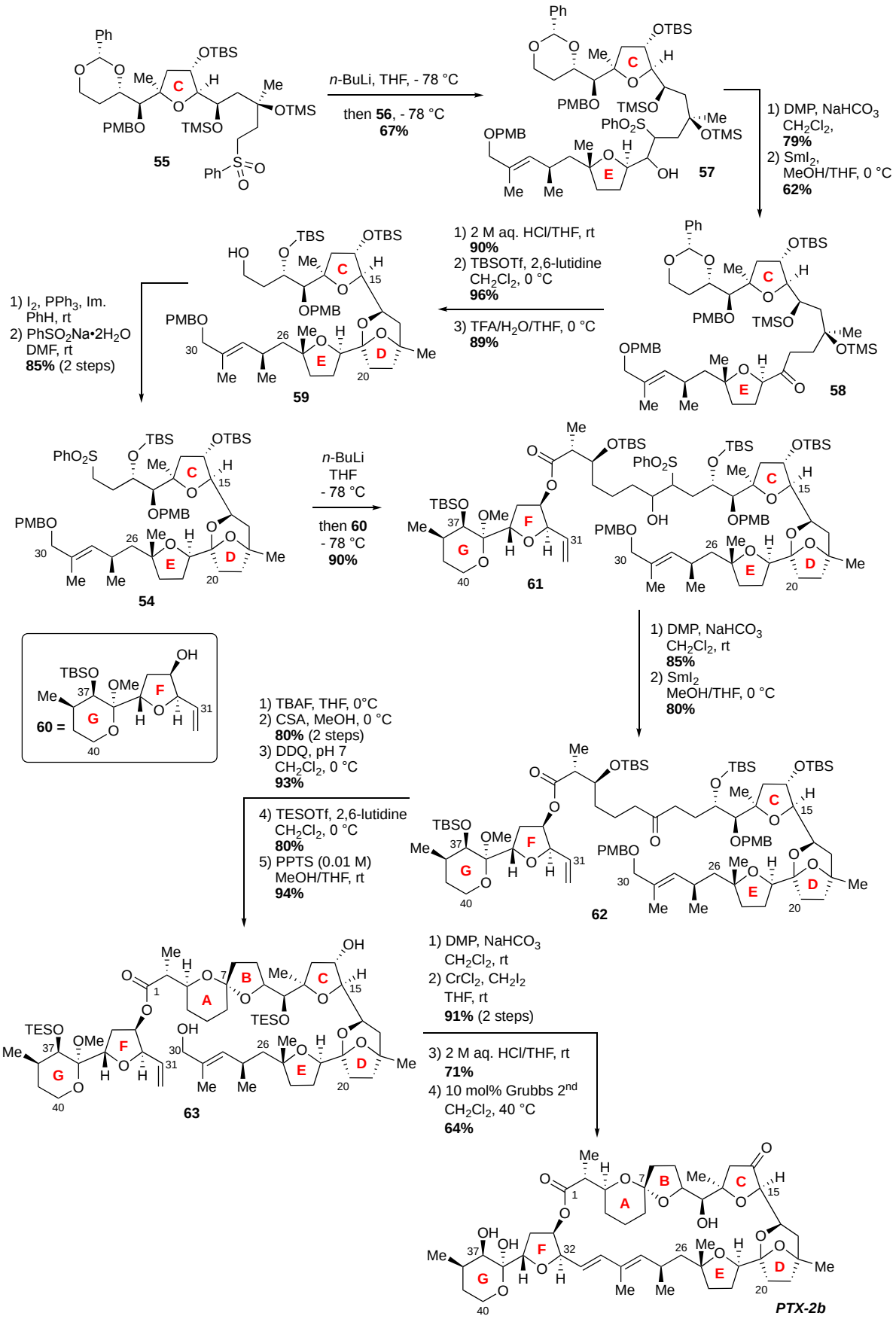
The synthesis of PTX-2b involved three major challenges: construction of the macrolactone ring, assembly of the anomeric spiroacetal of the AB-ring system, and formation of the bicyclic acetal of the D-ring (***Scheme 8***).

The macrolactone ring was to be prepared by a ring-closing metathesis (RCM) reaction between the C_{30} and C_{31} terminal olefins, while a common 3-step reaction sequence—involving a coupling reaction between sulfone and aldehyde fragments, oxidation of the resulting β-hydroxy sulfone to an α-sulfonylketone reductive desulfonylation—followed by spirocyclic (AB-ring system)/bicyclic ketal (D-ring) formation (***Scheme 9***), would be applied to solving both of the latter two challenges.

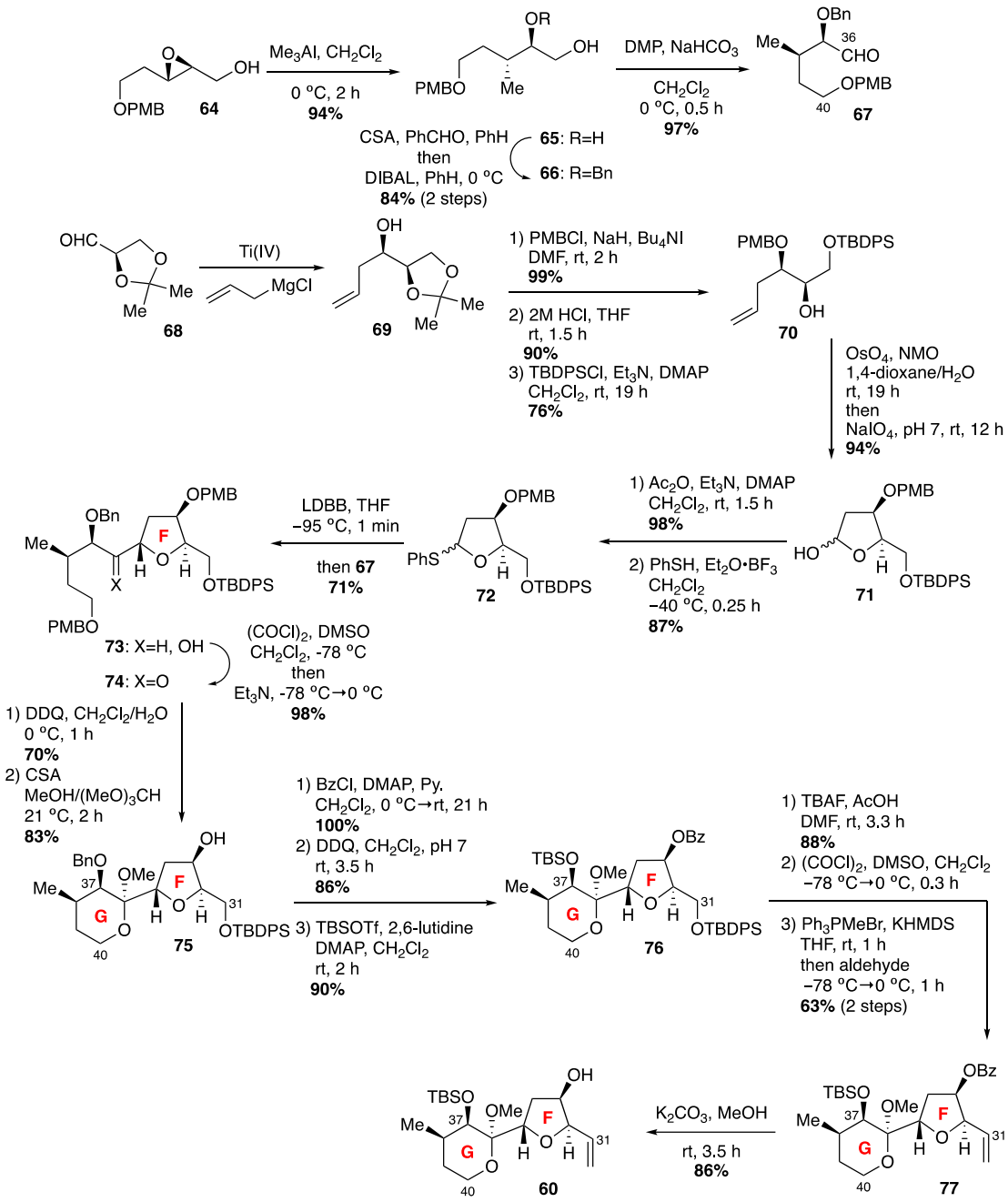


Scheme 9*. Key reaction sequence for assembly of AB-spiroketal and D-ring*

Synthesis of the D-ring bicyclic ketal was initiated by the coupling of the exocyclic aldehyde of E-ring compound **56** and the pendant sulfone of C-ring compound **55** to yield β-hydroxy sulfone **57** (***Scheme 10***). Note: the C-ring and E-ring were both accessed *via* an intramolecular 5-*exo*-epoxide cleavage strategy, previously developed by Brimble and co-workers.[30-31]



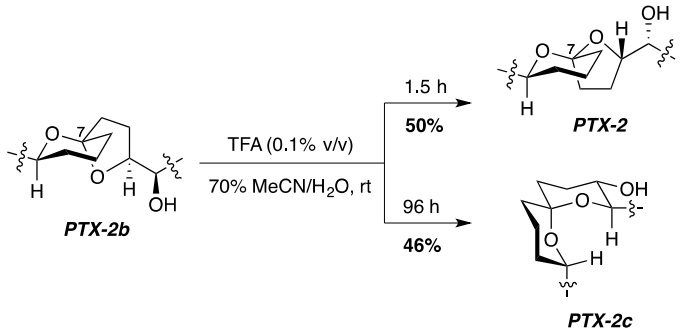
***Scheme 10**. Fujiwara's synthesis of PTX-2b*



Scheme 11. *Fujiwara's synthesis of the FG-fragment*

An oxidation/reductive desulfonylation then gave ketone **58**, which was converted to bicyclic ketal **59** in three further steps. Iodination of **59**, followed by nucleophilic displacement of the resulting iodide, gave sulfone **54** which was coupled with FG-fragment **60** using *n*-butyl lithium. (The F-ring of fragment **60** was accessed *via* hemiacetal formation and subsequent acetylation and treatment with thiophenol, while a Swern oxidation of alcohol **73** gave access to the G-ring (***Scheme 11***).[31]) Oxidation followed by reductive desulfonylation converted adduct **61** to ketone **62**, which was cyclised to the AB-ring spirocyclic ketal upon sequential treatment with TBAF and CSA. A protecting group manipulation afforded primary

alcohol **63** which was subsequently subjected to conditions of the DMP oxidation then Takai olefination. Global deprotection under acidic conditions, followed by a ring closing metathesis in the presence of Grubbs 2nd generation catalyst, formed the macrolactone, giving PTX-2b in 64% yield.

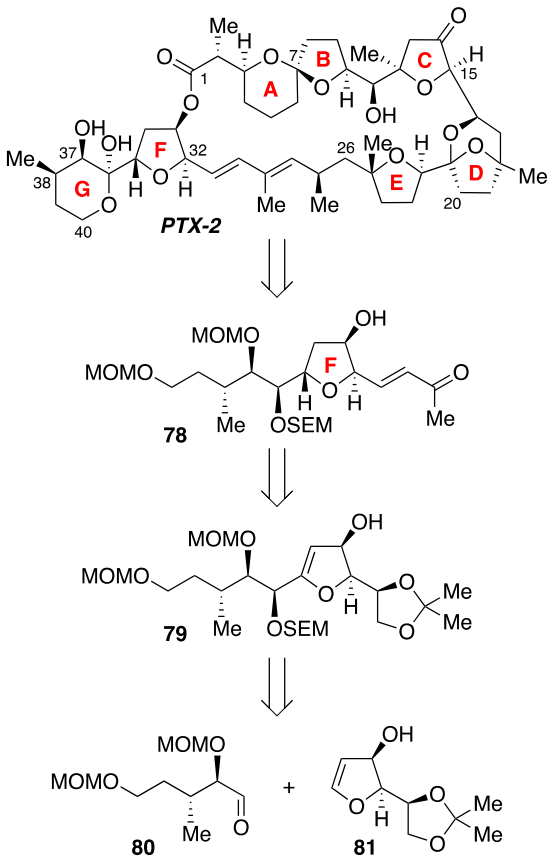


***Scheme 12**. Completion of PTX-2 synthesis*

The final step in this synthesis was the acid-catalysed isomerization of PTX-2b to PTX-2. Under conditions originally developed by Suzuki and co-workers, for a reaction time of 1.5 h, PTX-2 was formed as the major product in 50% yield. When longer reaction times of 96 h were used, PTX-2c was formed as the major product in 46% yield (***Scheme 12***).

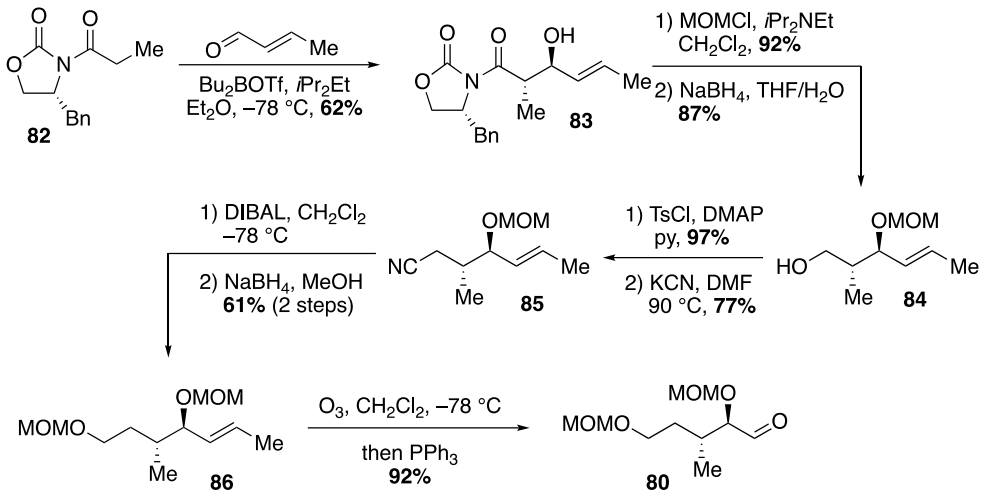
1.2.3 Paquette's Synthesis of the PTX-2 C_{29}-C_{40} fragment

In 2002, Paquette and co-workers reported the synthesis the C_{29}-C_{40} fragment of PTX-2, based on the retrosynthesis illustrated in ***Scheme 13***.[32] Synthon **78** was envisioned to constitute an advanced precursor to the F- and G-rings of PTX-2. The key step in forming the *trans* THF of the F-ring would be an alkoxide-directed hydrogenation of synthon **79**, which in turn, could be accessed from the coupling of aldehyde and dihydrofuran components, **80** and **81**.



***Scheme 13**. Paquette's retrosynthesis of the FG-portion*

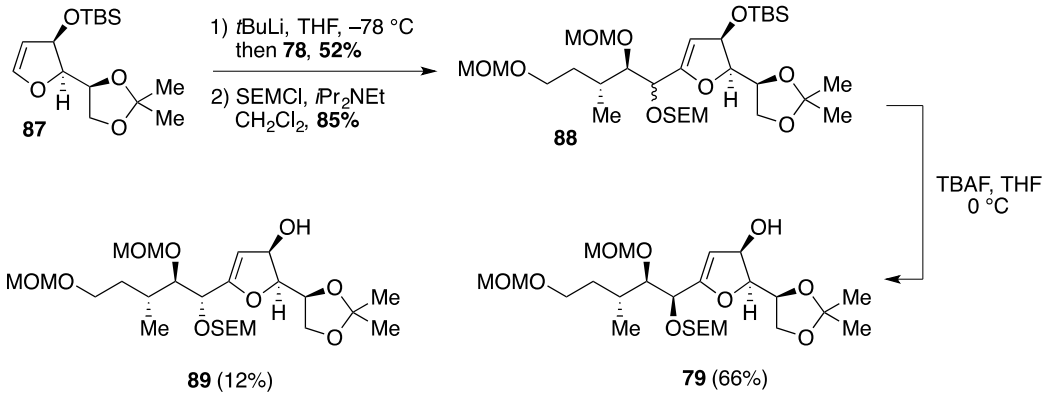
The synthesis of aldehyde **80** was achieved in 9 steps, starting with an *anti* aldol reaction between the *Z*-enolate of oxazolidinone **82** and crotonaldehyde to establish the stereochemical relationship between the C_{37}-hydroxy and C_{38}-methyl substituents (***Scheme 14*).** The resulting condensation product **82** was formed as the dominant or exclusive diastereomer, depending on the reaction scale. Protection of the C_{37} hydroxy as its MOM ether and subsequent reductive cleavage gave alcohol **83**, which following activation as the tosylate derivative, was displaced by cyanide to afford the homologated product **84**.



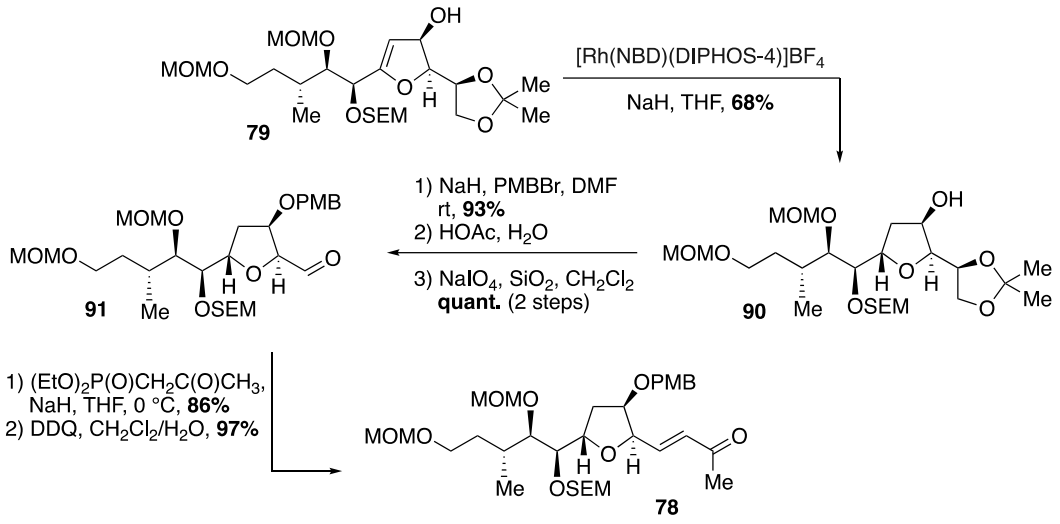
Scheme 14**. Synthesis of aldehyde **80

A two-stage reduction procedure produced a primary carbinol **85**, which was then protected as its MOM derivative **86** before being subjected to ozonolysis conditions and completing the synthesis of aldehyde **80**.

Concurrently, dihydrofuran **87**, readily available from D-mannose, was lithiated, and the resulting vinyl anion was coupled with **78** and the resulting adduct was immediately protected as the SEM ether **88**—isolated as an inseparable mixture of diastereomers (***Scheme 15***). A subsequent, chemoselective desilyation facilitated the separation of diastereomers **79** and **89**, isolated in a 5:1 ratio. Although the C_{36} configuration could not be ascertained, both diastereomers could be carried forward, as this centre would eventually be oxidised to a ketone for subsequent G-ring formation, and the major diastereomer **79** was arbitrarily assigned the β configuration and used for the remainder of the synthesis.



***Scheme 15**. Synthesis of FG-fragment carbon backbone*

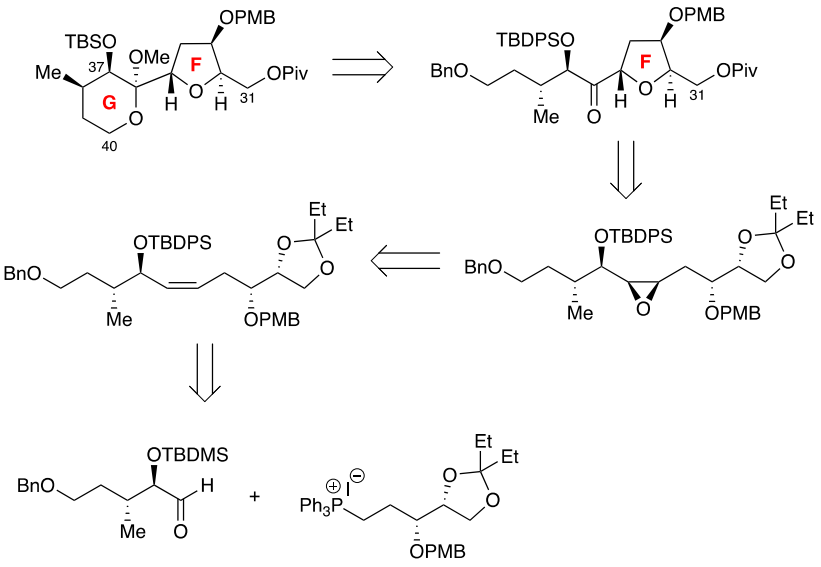


Scheme 16*. Completion of synthesis of C_{29}-C_{40} fragment*

The key hydroxy-directed hydrogentation proceeded to afford the F-ring THF **90** with the desired *trans* stereochemistry (***Scheme 16***). Ionic complexation between sodium salt of **79** and cationic rhodium catalyst was found to be crucial to achieve the desired stereochemistry at C_{35}, and the addition of NaH proved necessary to prevent undesired dehydration of the C_{33} hydroxy group. With **90** in hand, installation of the PMB ether at C_{33}, followed by hydrolysis of the pendant acetonide and oxidative cleavage of the resulting diol, provided aldehyde **91**. The synthesis of PTX-2 fragment **78** was completed by a Wittig homologation and subsequent DDQ-mediated C_{33}-PMB ether cleavage.

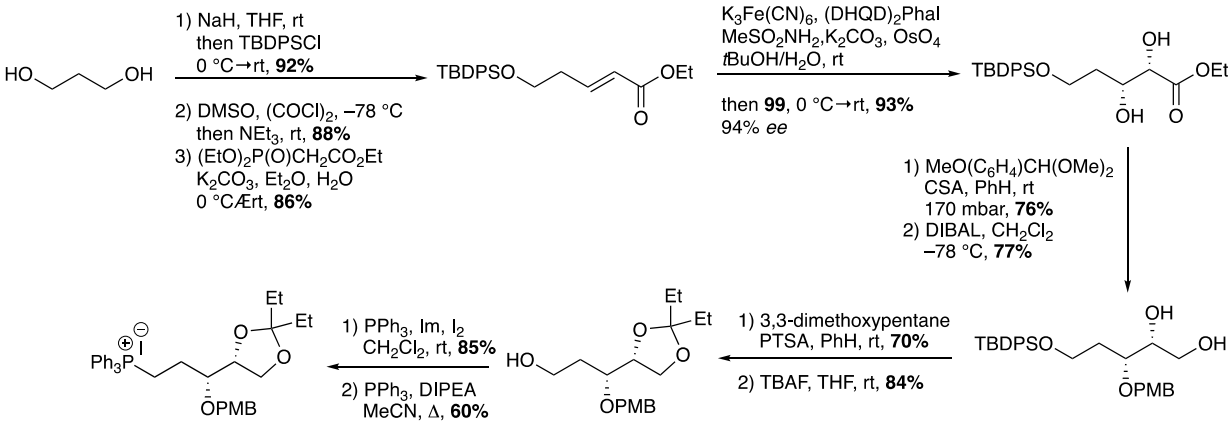
1.2.4 Brimble's Synthesis of the FG-Fragment

Brimble's synthesis of the FG-fragment, common to PTX molecules 1–9, was reported in 2010, and comprises a key 5-*exo*-tet and 6-*exo*-trig cyclisation to form the F- and G-ring, respectively.[4] Their retrosyntheses led to the aldehyde synthon **96** and phosphonium salt synthon **97** (***Scheme 17***). It was envisaged that a (*Z*)-selective Wittig coupling between these fragments would give access to alkene **95**, containing the carbon backbone of the FG-fragment, from which the synthesis could be complete *via* the two key cyclisations.

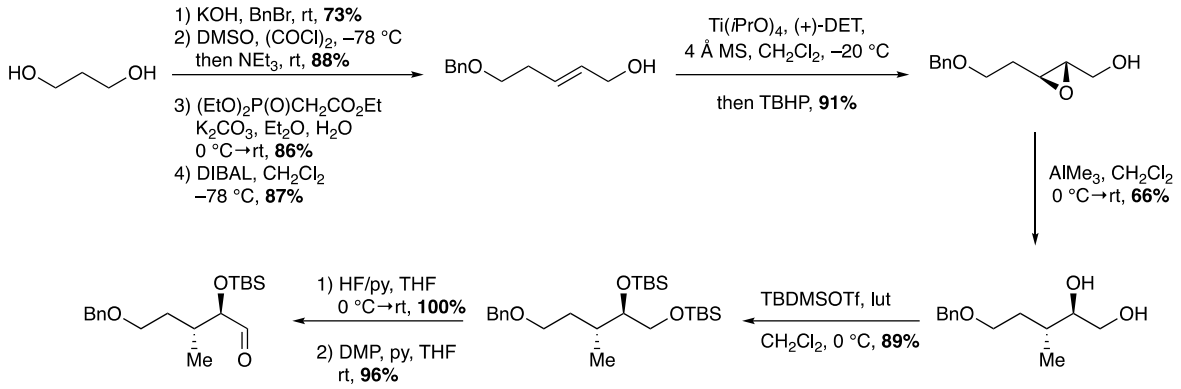


***Scheme 17**. Brimble's retrosynthesis of the FG-fragment*

Phosphonium salt **97** was accessed in 10 steps from diol **98** (***Scheme 18***), starting with a Swern oxidation of **98** and olefination of the resulting aldehyde under Horner–Wadsworth–Emmons conditions, to give *E*-olefin **99**. A Sharpless asymmetric dihydroxylation (SAD) of the olefin **99** formed *syn* diol **100**, installing the desired stereochemistry at the C_{32} and C_{33} centres. The C_{34}-PMB ether was installed by a two-step procedure that first converted diol **100** to the corresponding benzylidene acetal, which upon treatment with DIBAL, underwent regioselective (chelation controlled) reduction with concomitant reduction of the C_{31} ester to afford diol **101**. Protection of **101** as the 1,3-dioxolane was proceeded by desilylation to provide primary alcohol **102**. A subsequent iodination followed by displacement of the resulting iodide yielded phosphonium salt **97**.

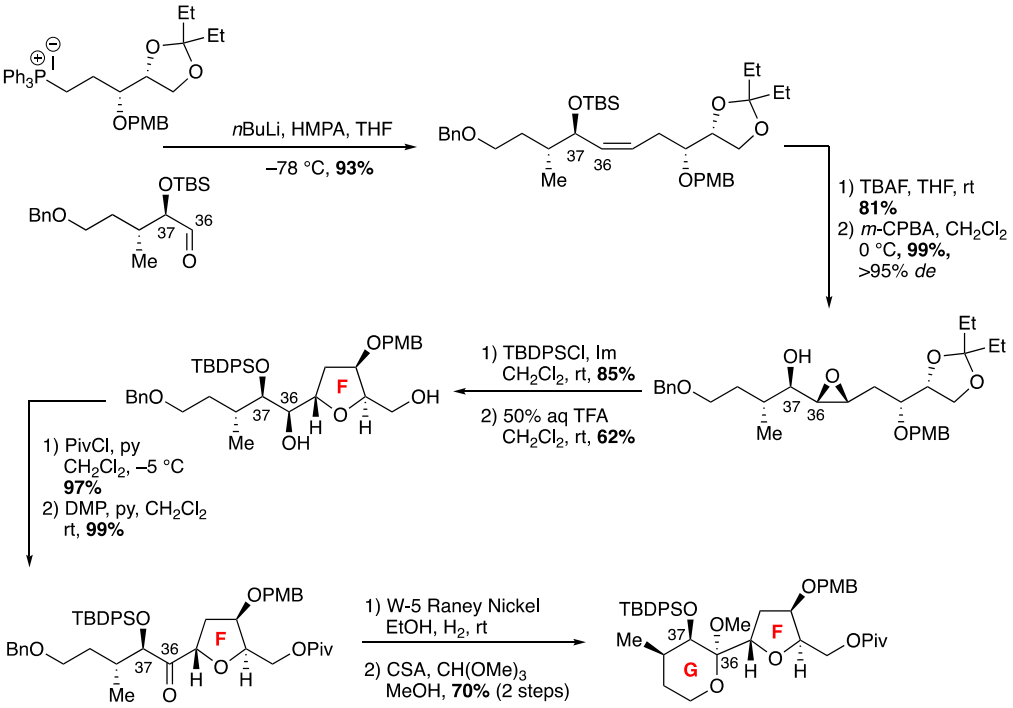


Scheme 18**. Synthesis of phosphonium salt **97



Scheme 19**. Synthesis of aldehyde **96

Synthesis of aldehyde **96** also began from diol **98** (***Scheme 19***). Four steps provided allyl alcohol **103** which underwent a Sharpless asymmetric expoxidation to afford epoxy-alcohol **104**. Regioselective epoxide opening using trimethylaluminium gave vicinal diol **105** which was subsequently protected as the bis-TBS ether compound **106**. Regioselective cleavage of the primary TBS ether and oxidation of the resulting alcohol completed the synthesis of aldehyde **96**.



***Scheme 20**. Completion of FG-fragment synthesis*

The Wittig coupling of aldehyde **96** and phosphonium salt **97** proceeded smoothly to afford the desired *Z*-olefin **95** (***Scheme 20***). Silyl deprotection was followed by epoxidation, directed by the C_{37}-hydroxy group, providing **107** as a single diastereomer. Reprotection of the C_{37}-hydroxy group gave a silyl ether as the precursor for the key 5-*exo*-tet cyclisation. Acid catalysis (50% aq. TFA) effected the *in situ* hydrolysis of dioxolane and cyclisation of the C_{32} hydroxy group onto the epoxide to afford the desired *trans* F-ring THF. Protection of the newly formed primary alcohol preceded oxidation of the C_{36}-hydroxy group to the corresponding ketone **109**. The synthesis of the FG-fragment **92** was then completed by reductive cleavage of the primary benzyl ether and concomitant ketalization, *via* the key 6-*exo*-trig cyclisaton, to give a lactol that was immediately subjected to acid-catalysed methylation, affording **92**.

1.2.5 Donohoe's Synthesis of the PTX-4 ABC-Fragment

In 2013, Donohoe and co-workers reported the synthesis of the ABC-fragment of PTX-4.[33] Their synthesis was designed around two key concepts: 1) a cascade oxidative cyclisation, catalysed by osmium(VI), to access the *cis* B- and C-ring THFs, and 2) a hydride shift-initiated-spiroketalization to form the AB-spiroketal (***Figure 12***).[34]

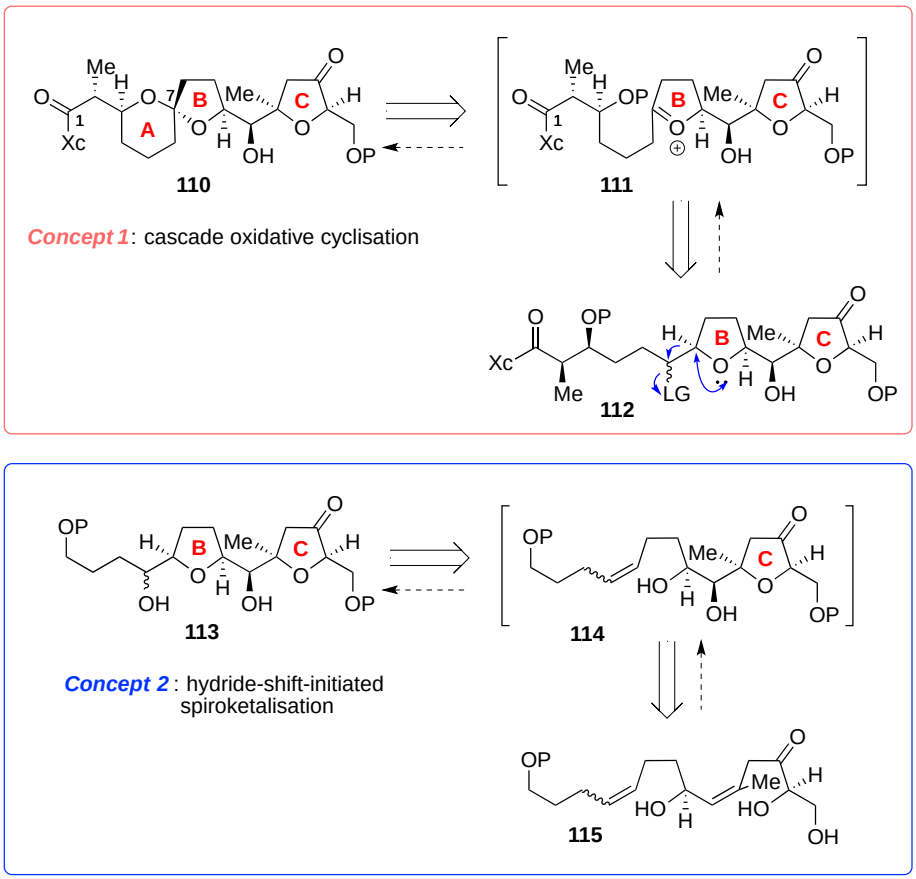
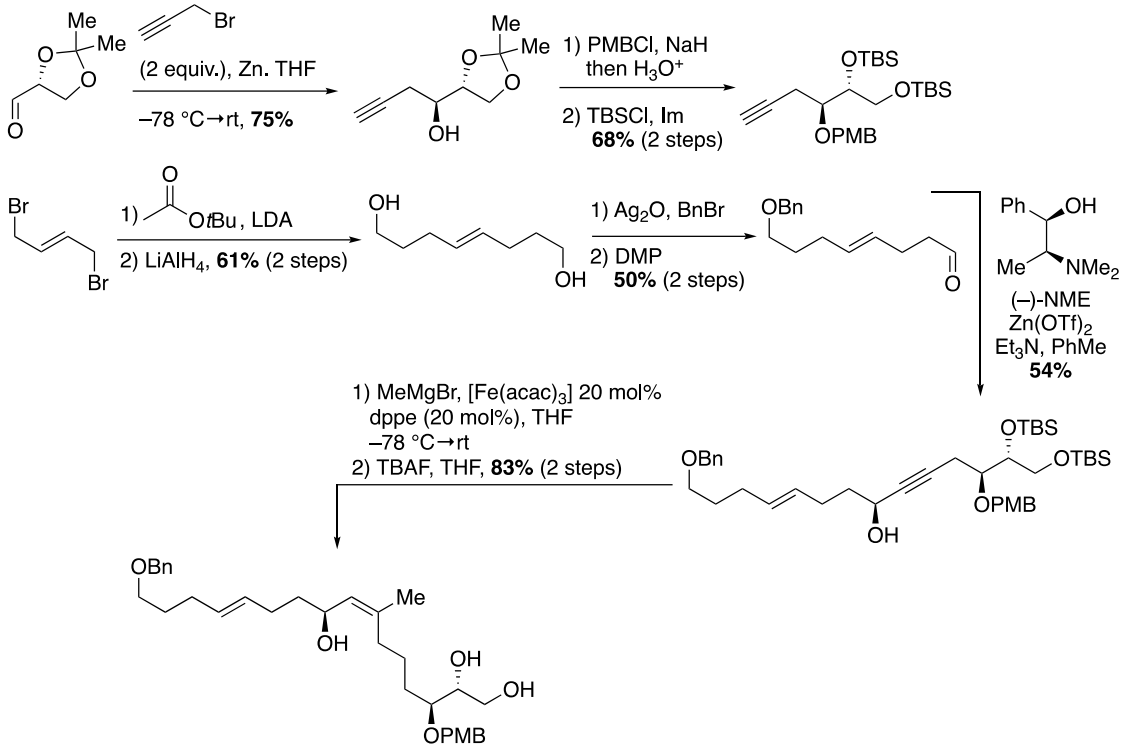


***Figure 12**. Donohoe's retrosynthesis of the ABC-fragment of PTX-4*[33]

Concept 1 assumes that a triol-containing linear diene, such as synthon **115**, would react with osmium(VI), such that the metal catalyst chelates between the vicinal diol unit, facilitating oxidative cyclisation onto the C_{11}-C_{12} trisubstituted alkene. The stereospecific, *syn* addition of the two oxygen atoms should ensure that the desired *cis* stereochemistry of the C-ring THF, and *S* configuration at C_{11} is achieved in the product. Translocation of the metal chelate onto the C_{10}-C_{11} vicinal diol could then initiate a second oxidative cyclisation onto the C_6-C_7 olefin, producing the B-ring THF in the same reaction pot.

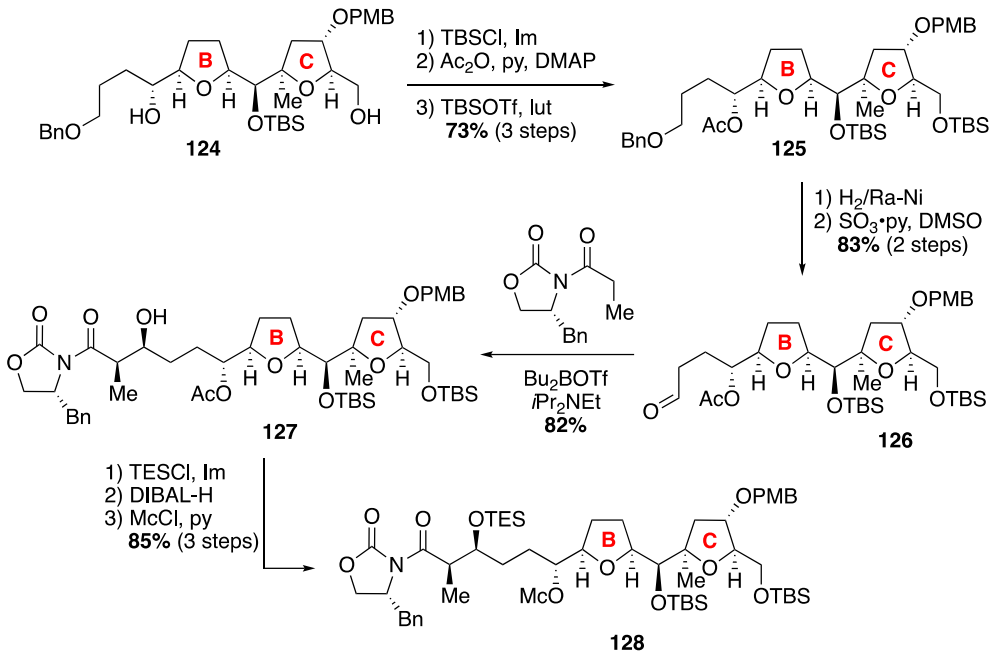
Concept 2 proceeds concept 1, and assumes that following the addition of an aldol-derived side chain, the exocyclic C_6 hydroxy group could be used as a leaving group to facilitate

a hydride shift from C_7. The C_3 hydroxy (or protected hydroxy group) could then trap the oxo-carbenium ion formed *in situ* to construct the AB-spiroketal.



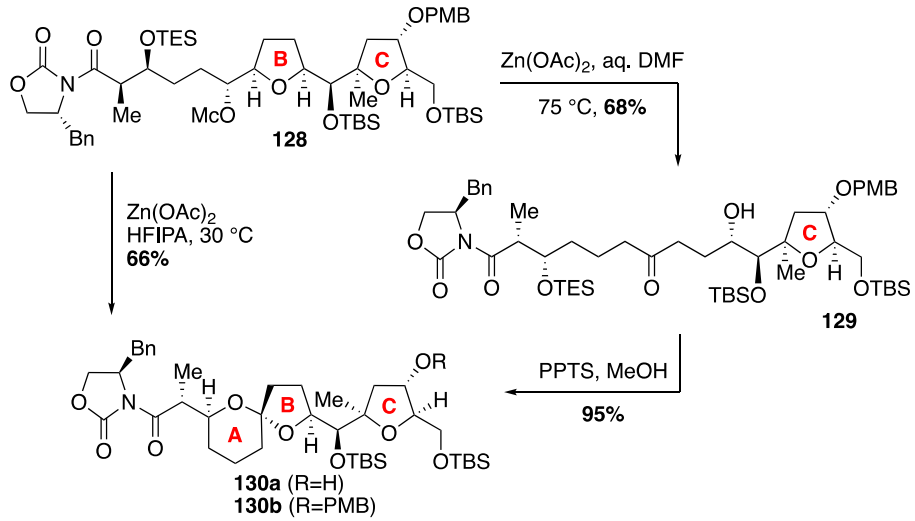
Scheme 21. *Synthesis of the BC-ring fragment* ***124***

A key Carreira reaction was to be used to access diene synthon **123**, required for the cascade oxidative cyclisation, and thus the forward synthesis began by preparing the alkyne and aldehyde partners for this reaction (***Scheme 22***). Alkyne **118** was prepared in three steps from known aldehyde **116**, while aldehyde **121** was prepared in four steps from dibromide **119**. The Carreira reaction proceeded with excellent stereoselectivity (dr 96:4), induced by the chiral ligand (–)-*N*-methylephedrine (NME) to afford alkyne **122**. A subsequent regio- and stereoselective methylation of **122**, provided alkene **123**, with the correct substitution pattern for cascade oxidative cyclisation. Subjecting **123** to the oxidative cyclisation conditions afforded the desired bis-THF **124**, in a reaction which generated four stereocentres and two THF rings.



***Scheme 22**. Installation of aldol derived side chain*

Installation of the aldol derived side chain began with a protecting group manipulation of the three hydroxy groups of product **124** (***Scheme 23***). A reductive cleavage of the primary benzyl ether was followed by an oxidation of the resulting alcohol to afford aldehyde **126**. An aldol reaction with Evans' oxazolidinone gave the desired *syn* adduct **127** as a single diastereomer. Protection of the newly formed C_3 hydroxy as the TES ether, followed by successive deprotection and activation of the C_6 hydroxy group as an α-chloromesylate derivative, gave the precursor **128** for the spiroketalization reaction.



***Scheme 23**. Completion of ABC-fragment synthesis*

The synthesis of the ABC-fragment was completed by the hydride-shift-initiated spiroketalisation reaction, which could be performed under two sets of conditions (***Scheme 24***). A one-step protocol, performed in hexafluoroisopropanol (HFIPA), effected spiroketalisation with the removal of the C_{14} PMB ether, to give **130a**. The two-step procedure, performed in aqueous DMF, cleaves the B-ring to afford the intermediate ketone **129**, which upon treatment with PPTS in MeOH, forms the AB-sprioketal unit to yield **130b**, with the C_{14} PMB ether intact.

1.3 Research Aim

The Donohoe group was drawn to the PTX-natural products by their intriguing structural complexity and promising biological activity. While PTX-2 is the most biologically active member of the PTX-family, PTX-4 was chosen as a synthetic target for the same reason that Evans decided to pursue its total synthesis: the *S* configuration at C_7 is the more thermodynamically favored isomer in the open chain form and thus is less likely to undergo epimerization prior to cyclisation.

We saw in section **1.2.5,** that the Donohoe group has already made significant progress towards the total synthesis of pectenotoxin-4 with the synthesis of the ABC-ring system; a route which utilized Donohoe's oxidative cyclisation methodology. The work described herein, however, focuses on a novel synthesis of the EFG-ring system of PTX-4 (***Figure 13)***, the synthesis of which is described herein.

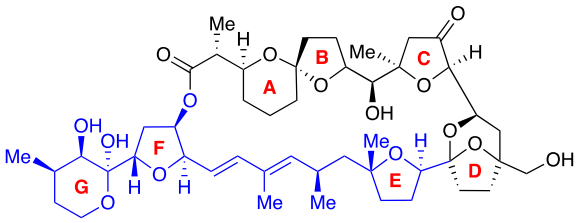


Figure 13*. The structure of PTX-4*

Chapter 2

Synthesis of the EFG-Fragment of Pectenotoxin-4

2.1 Synthesis Plan

2.1.1 Retrosynthetic Analysis of Pectenotoxin-4

Our retrosynthetic analysis of pectenotoxin-4 begins with a disconnection of the C_{36}–O bond, yielding the acyclic form of the G-ring, followed by cleavage of the C_1–O bond to give the open macrolide (***Figure 14***).

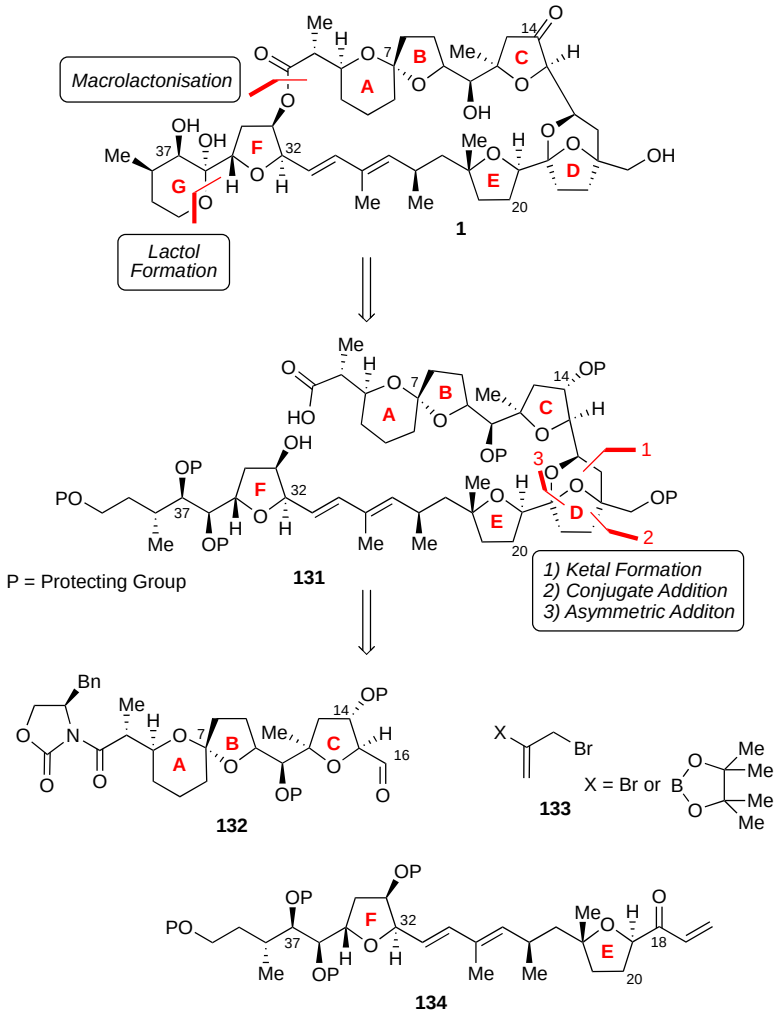


Figure 14*. Retrosynthetic analysis of pectenotoxin-4*

Precedent for late stage macrolactonisation exists in Evans' 2002 synthesis of pectenotoxin-4 in which it was shown that a room temperature macrocyclisation was possible under Yamaguchi conditions, while global deprotection followed by *in situ* lactol formation could be achieved with hydrated TASF.[16]

A three bond-disconnection sequence: asymmetric addition, under Felkin-Anh control, of nucleophile **133** to aldehyde **132**; conjugate addition of the resulting adduct to α,β-

unsaturated ketone **134**; followed by cyclisation onto the C_{20} ketone, simplifies the D-ring bicyclic ketal to alkene **133**, simultaneously separating the EFG-fragment from the ABC-ring system.

The ABC-ring system was synthesised by the Donohoe group in 2013 (Chapter 1, section 1.2.5), while synthetic studies towards the D-ring are currently underway within the group. Our retrosynthetic analysis and synthesis of the EFG-ring system is detailed in the remainder of this thesis.

2.1.2 The EFG-Ring System: Synthesis Plan

The first disconnection in our retrosynthesis of the EFG-ring system **135**, in analogy to that of the pectenotoxin-4, is of the C_{36}–O lactol bond to give ketone **136** (***Figure 15***).

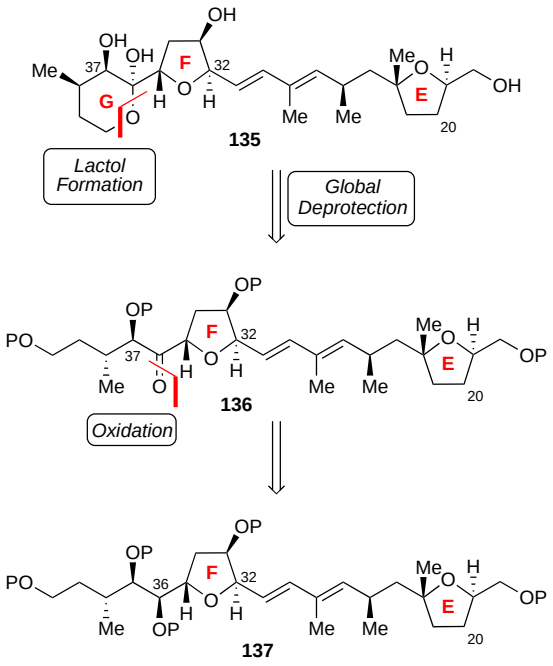


Figure 15*. Retrosynthetic analysis of the EFG-ring system* ***135***

It was envisaged that global deprotection could occur simultaneously to lactol formation, under conditions developed by Evans and co-workers, to yield the thermodynamically favoured stereochmistry of the G-ring, in which the C_{36}-hydroxy group occupies an axial position. The desired ketone **136** could then be accessed *via* a selective deprotection of C_{36}-alcohol followed by an oxidation.

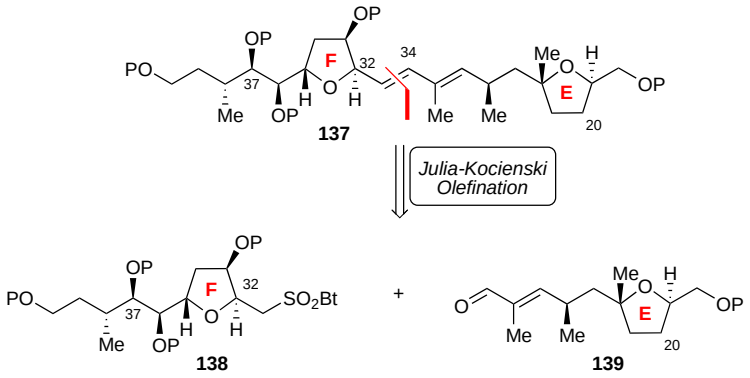
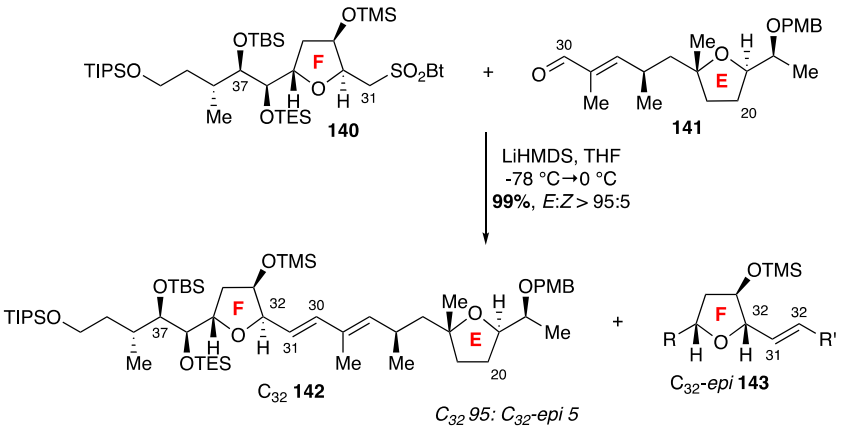


***Figure 16**. Disconnection of the C33-C34 olefin bond*

Disconnecting the C_{33}–C_{34} double bond simplifies compound **137** to the FG-ring system **138** and E-ring **139** (***Figure 16***). Evans and co-workers showed that reacting a C_{31} sulfone **140** with a pendant C_{30} aldehyde **141**, under modified Julia-Kocienski conditions,[27] enables C_{31}–C_{32} olefinic bond formation in 99% yield and an *E:Z* selectivity of greater than 95:5 (***Scheme 24***).[14-15]



***Scheme 24**. Evans' use of the Julia-Kocienski olefination*[16]

A C_{32}-epimer (C_{32}-*epi*) **143** of product **142** was also isolated in this reaction. Its formation is thought to arise from a ring opening of the F-ring THF following deprotonation alpha to the sulfone. This mechanism will be discussed in more detail later in this chapter. Given the high C_{32} **142** to C_{32}-epimer **143** ratio, and the excellent yield and *E:Z* selectivity, we decided to utilise this reactivity in our synthesis.

Aldehyde **141** of the Julia-Kocienski olefination could be accessed by a two-step reduction/oxidation procedure from ester **144**. This ester can be formed from the Wittig

olefination of the corresponding aldehyde **145** (***Figure 17***).

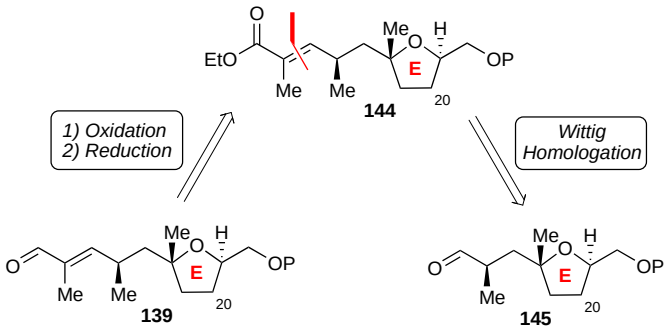
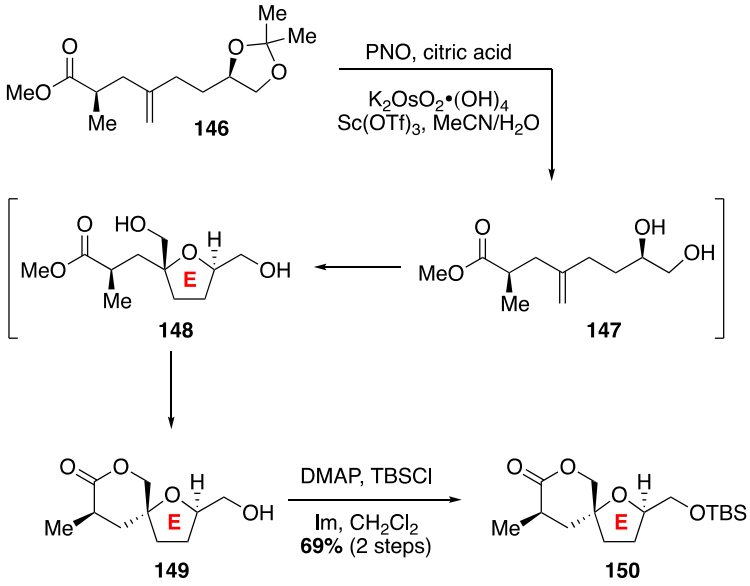


Figure 17*. Retrosynthesis of aldehyde* ***139*** *to aldehyde* ***145***

Dr P. Winship and Dr Y. Liu of the Donohoe group had previously developed a synthetic route towards aldehyde **145**, shown in ***Scheme 25***, that featured an osmium-mediated oxidative cyclisation, methodology developed within the Donohoe group, to form the *cis*-THF of the E-ring.[34] This route will be discussed in more detail later in this chapter.[35-36]



Scheme 25*. Donohoe group synthesis of the E-ring*

The masked triol **138** of the FG-fragement could be accessed from the SAD reaction of alkene **151**, which in turn could be the product of a cross metathesis reaction between F-ring alkene **152** and hydroxy alkene **153**, the latter of which contains the carbon atoms of the G-ring (***Figure 18***).[37]

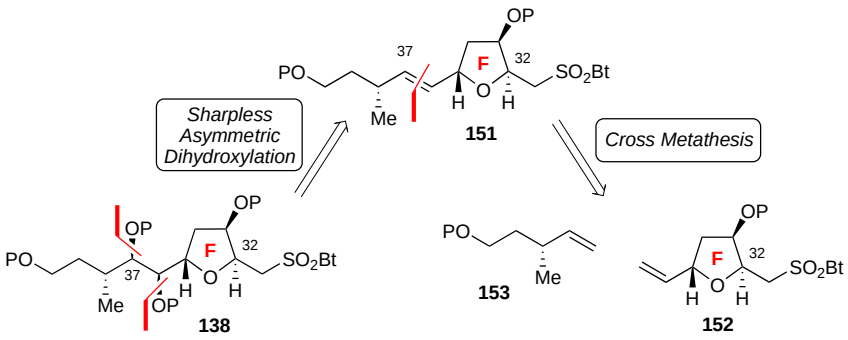
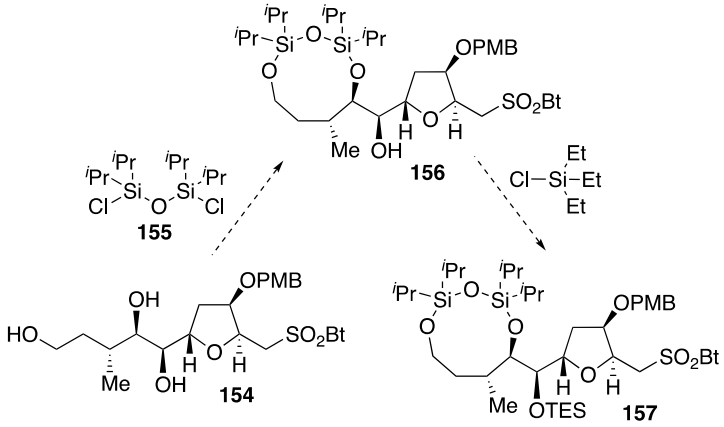


***Figure 18**. Retrosynthesis of the FG-ring system*

A key aspect of this synthesis would be the protection of the C_{40}-, C_{37}-, C_{36}-, and C_{33}-hydroxy groups. Specifically, these four hydroxy groups would have to be protected in a manner which could facilitate the selective deprotection of the C_{36}-hydroxy group later in the synthesis; this would then allow for the selective oxidation of the C_{36}-hydroxy group. As the C_{33}-hydroxy group could be protected before the SAD, we anticipated that our main challenge would be the selective protection of the C_{40}-, C_{37}-, and C_{36}-hydroxy groups. We envisaged that this could be achieved by first tethering the C_{40}- and C_{37}-hydroxy groups of triol **154** with the Markeweicz reagent **155**,[38] which has been widely used in nucleic acid chemistry,[39-40] then protecting the free C_{36}-hydroxy of alcohol **156** as a more labile silyl ether **157**, in analogy to Evan's synthesis (***Scheme 26***).



***Scheme 26**. Proposed protection strategy*

Given that the C_{40}-, C_{37}-, and C_{36}-hydroxy groups were to be protected as silyl ethers, we decided to protect the C_{33}-hydroxy group as a PMB ether as this group is unlikely to be reactive towards conditions typical for silyl ether cleavage.

Thus, our retrosynthetic analysis of the EFG-ring system leads to three key compounds: F-ring sulfone **152**, 1,5-hydroxy alkene **153**, and E-ring aldehyde **139**. The syntheses of these compounds, and the subsequent chemistry that leads to the synthesis of the EFG-ring system, are described herein.

2.2 Synthesis of the F-ring

2.2.1 Previous Work

Co-workers in the Donohoe group had previously attempted to synthesise the *trans*-THF of the F-ring *via* a novel strategy that utilised a Sharpless Asymmetric Epoxidation (SAE) to desymmetrise *meso*-diol **158** (***Figure 19***).[41-43] It was thought that by using the appropriate tartrate-derived enantiomer ((–)-DIP in the case of the F-ring), the two enantiotopic allylic alkenes, and their diastereotopic faces, could be differentiated. A 5-*exo*-tet ring opening, induced either by subsequent protonation of the epoxide or *in situ* activation by the oxaphilic titanium(IV) species, of the resultant *anti* epoxy alcohol, could then give access to a *trans*-THF.[44-46]

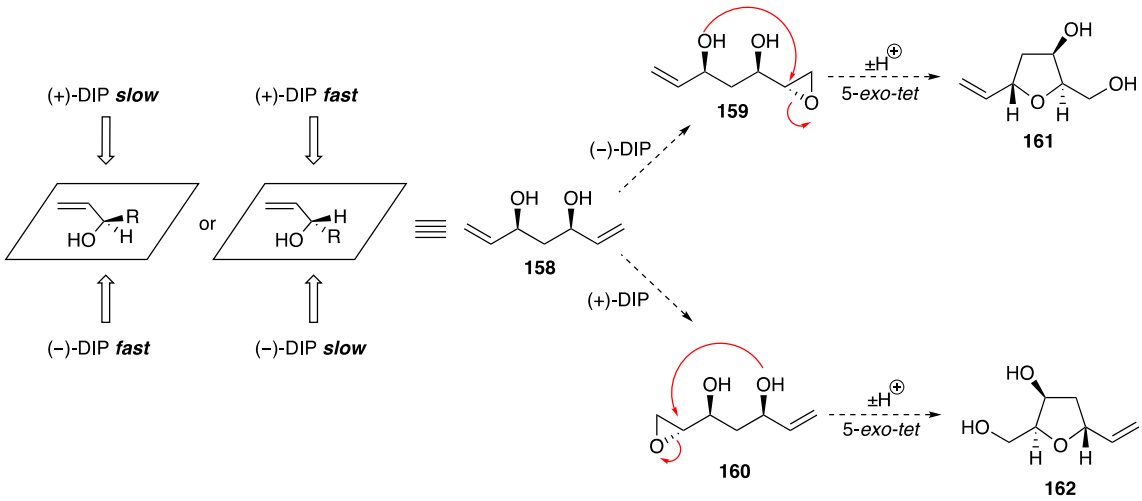
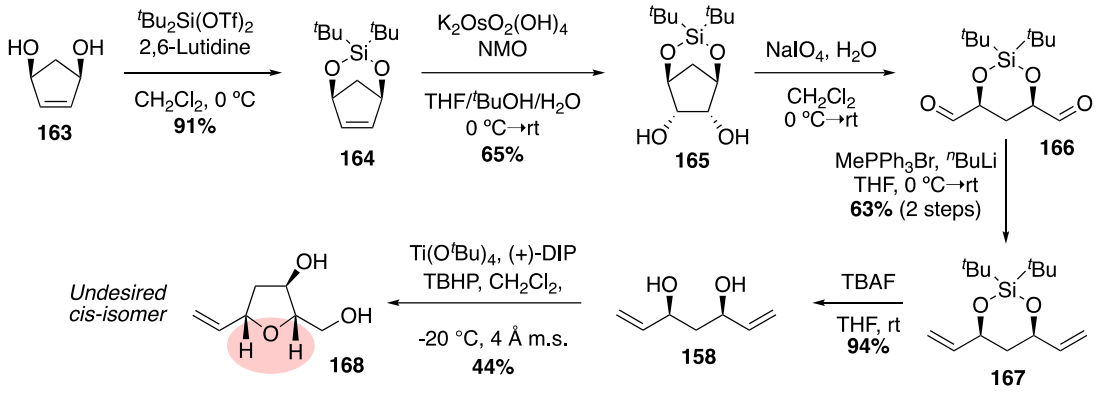


***Figure 19**. SAE strategy*

Unfortunately, however, it was found that the *undesired cis*-THF **168** was formed in this reaction sequence (***Scheme 27***). For this to occur, the *syn*-epoxy alcohol must have been formed upon epoxidation rather than the desired *anti*-isomer. The reason for this result remains

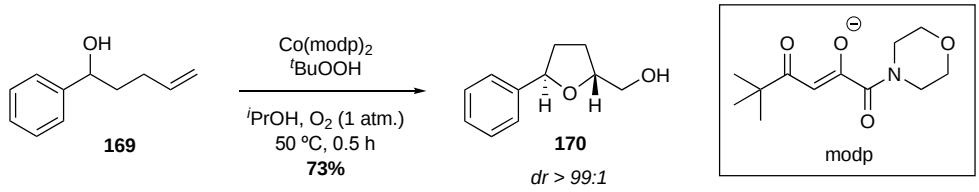
unknown and therefore meant that a new strategy towards the *trans*-THF of the F-ring was required.



***Scheme 27**. Attempted synthesis of the F-ring using the SAE strategy (Dr. M. Tucker).*[43]

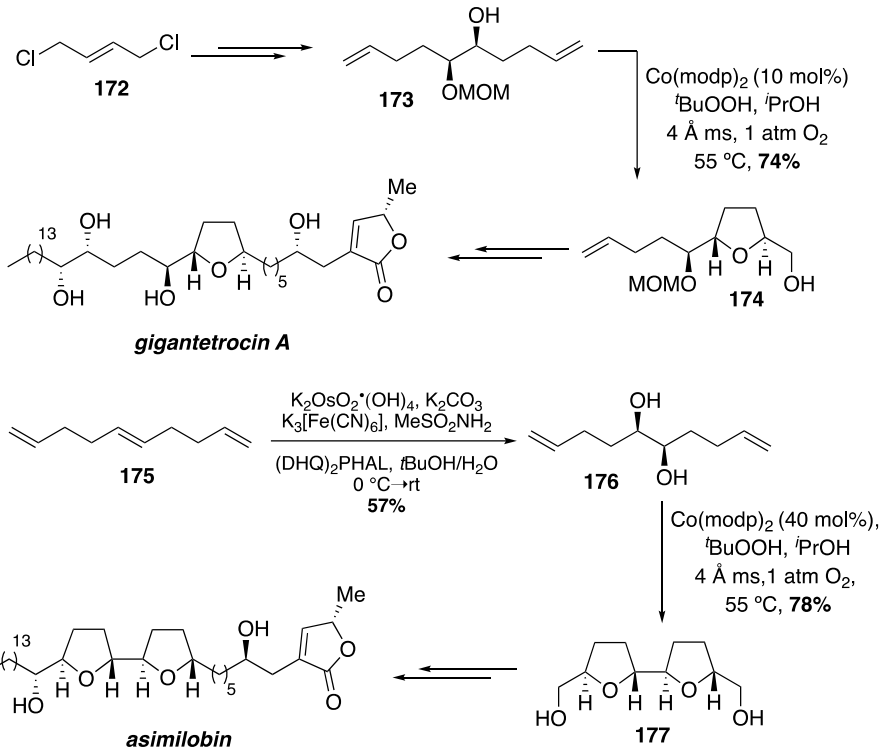
2.2.2 Mukaiyama's Oxidative Cyclisation

In 1989, Mukaiyama and co-workers showed that the oxidative cyclisation of 1,5-hydroxy alkenes to 2,5-disubstituted *trans*-THFs could be achieved in excellent yields and diastereoselectivities (>99:1) using complexes of cobalt(II) (***Scheme 28***).[47]



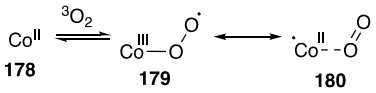
***Scheme 28**. Mukaiyama's oxidative cyclisation*

Since its discovery, the Mukaiyama oxidative cyclisation has proven to be a powerful tool in total synthesis, with Shi and co-workers applying this reactivity in their total syntheses of gigantetrocin A and asimilobin (***Scheme 29***).[48-49]



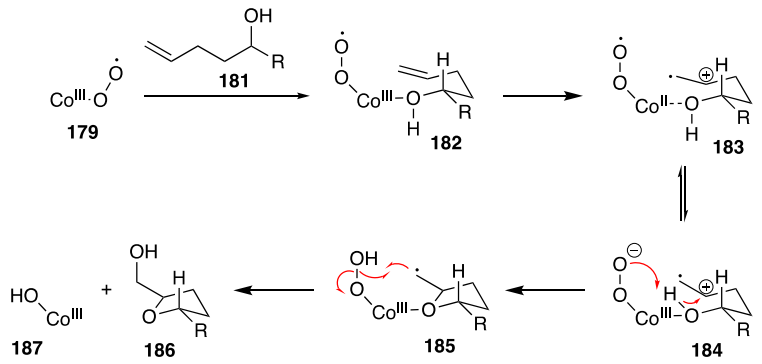
***Scheme 29**. Shi's total syntheses of gigantetrocin A and asimilobin.*

The mechanism of Mukaiyama's oxidative cyclisation has been extensively studied. In 2008, Hartung proposed a radical mediated pathway for the mechanism of this reaction which explained the stereoselectivity observed and preference for 5-*exo*-ring closure.[50] Firstly, activation of triplet oxygen is said to occur through a superoxo-mode of binding to the paramagnetic cobalt(II) species **178** (***Scheme 30***). The resultant cobalt(III) species **179** is considered a strong Lewis acid and a metal based oxidant.



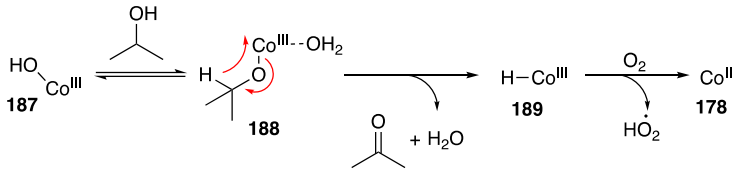
***Scheme 30**. Activation of cobalt(II)*

The Lewis acidic nature of complex **178** is thought to facilitate its coordination to 1,5-hydroxy alkene **181** which reacts *via* a chair like confirmation, in which its substituents occupy pseudo-equatorial positions to minimize diaxial strain (***Scheme 31***).



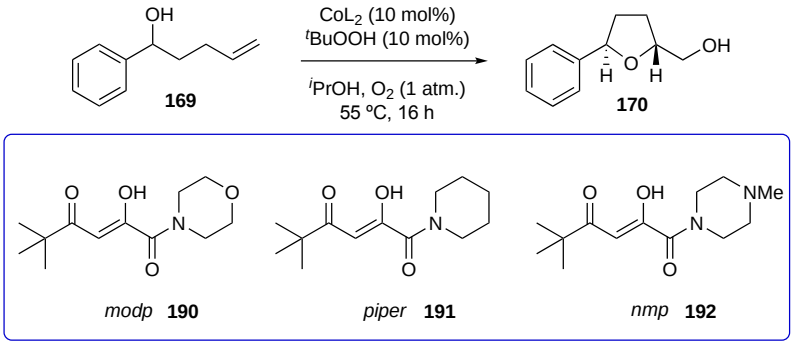
Scheme 31. *A radical mediated pathway to ring closure*

The powerful oxidising capability of cobalt(III) (E^{θ} = +1.84 V) then effects the conversion of alkenic intermediate **182** into the radical cation **183**, simultaneously regenerating cobalt(II). The oxidised π-bond undergoes a subsequent 5-*exo*-ring closure of the hydroxy-oxygen atom to the form *trans*-THF **186** and the hydroperoxide cobalt(III) species **187**. The O–O single bond of this hydroperoxide species is weak, and thus readily cleaved to give the product *trans*-THF **186**. Regeneration of Co(II) is said to occur *via* a hydride shift from a coordinated solvent molecule to give acetone, H_2O and a hydridocobalt(III) complex **189** which decomposes, in the presence of molecular oxygen, to cobalt(II) **178** and a hydroperoxyl radical (***Scheme 32***).



Scheme 32. *Regeneration of cobalt(II)*

One limitation of this powerful methodology is the difficulty faced in removing catalyst residues from the reaction product due to the latter's polar nature. Pagenkopf and co-workers were able to solve this problem by modifying the modp ligand **190** (***Figure 23***).[48]

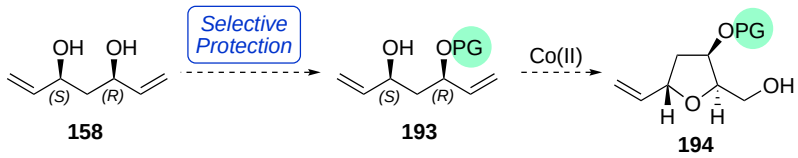


yield (%)			
		nmp	
modp	piper	MeI	buffer
47	54	**91**	45

***Figure 20**. Pagenkopf's development of the nmp ligand*

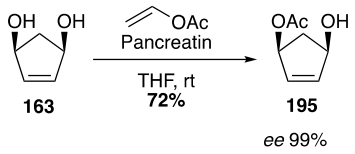
They found that by replacing the neutral morpholine subunit of this ligand with basic *N*-methyl piperazine, the resulting ligand, nmp **192**, could facilitate the removal of cobalt residues from the reaction mixture—either by straightforward acidic extraction or after treatment with MeI. The latter work-up procedure, which gave superior results, produces a quaternary ammonium salt, the salts of which are highly water soluble and can thus be readily removed by neutral aqueous extraction. For all substrates tested by Pagenkopf, the second-generation $Co(nmp)_2$ catalyst gave superior yields to those achieved with the first-generation $Co(modp)_2$ catalyst.

In studying this reaction, we noticed that *meso*-diol **158**, the key substrate in the SAE methodology, effectively consists of two 1,5-hydroxy alkenes, the substrates used in the Mukaiyama oxidative cyclisation. This led us to postulate that if the *S* hydroxy group of diol **158** could be selectively protected, then Mukiayama's oxidative cyclisation could be used to access to the *trans* THF of the F-ring **194** (***Scheme 33***).



***Scheme 33**. Proposed use of the Mukiayama oxidative cyclisation*

The monoacetylation of diol **163** under enzymatic resolution has been well documented in the literature.[51-53] Tietze and co-workers, for example, have shown that *meso* diol **163** can be asymmetrically acetylated with vinyl acetate in the presence of the enzyme pancreatin (***Scheme 34***).[54] This diol is the starting material used in the Donohoe group's previous attempt to synthesis the F-ring (SAE route, ***Scheme 27***). This reaction thus, provides a potential starting point for a novel synthesis of the F-ring. Analogous reactions to those in the SAE route could be used to access a monoprotected derivative of *meso*-diol **158**, and therefore, by utilising the monoacetylation of diol **163** and Mukaiyama's oxidative cyclisation as a key step, a new synthetic route towards the F-ring could be developed.

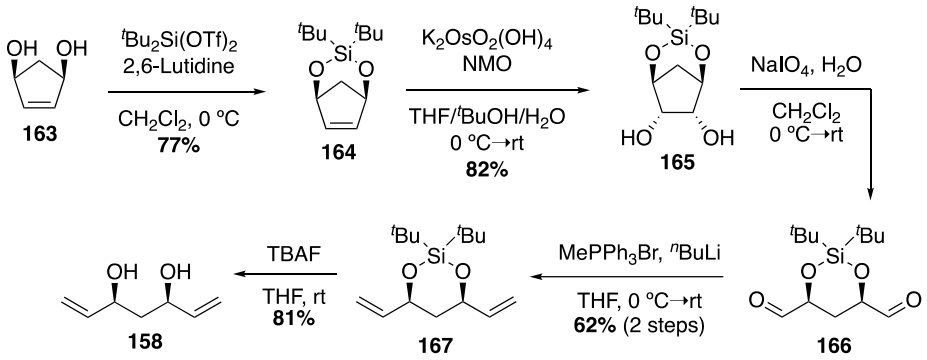


Scheme 34*. Tietze's monoacetylation of diol* ***163***

Before pursuing an asymmetric route towards the F-ring based on this strategy, however, we decided to synthesise *meso*-diol **158**, using the route previously developed by the Donohoe group, to test whether it was compatible in Mukaiyama's oxidative cyclisation and if it would yield a THF with the desired *trans* stereochemistry.

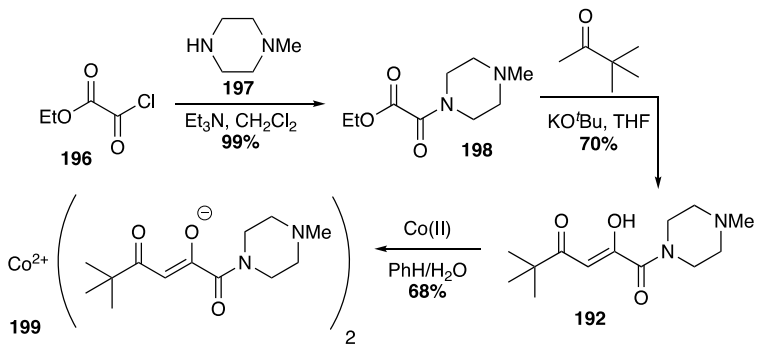
2.2.3. Synthesis of *Meso* Diol 158 and the F-ring

The first step in our synthesis of *meso*-diol **158** was a tethering of the two hydroxy groups of *meso*-diol **163** with di-*tert*-butylsilyl bis(trifluoromethanesulfonate), which reaction gave the bicyclic alkene **164** in 77% yield (***Scheme 35***).



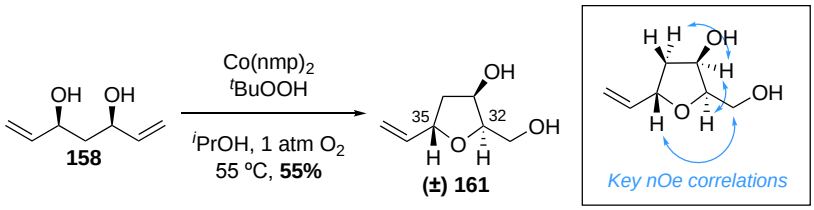
Scheme 35*. Synthetic steps towards the F-ring*

Dihydroxlation of **164** in the presence of potassium osmate, gave diol **165** in 82% yield. The formation of the product was inferred from the disappearance of the multiplet corresponding to the two olefinic protons at δ_H 6.48 – 6.44 ppm (2H) in the ^{1}H NMR spectrum. Sodium periodate-mediated cleavage of diol **165** gave dialdehyde **166**, which was identified by the appearance of a chemical shift at δ_H 9.66 ppm (2H, d) in the ^{1}H NMR spectrum of the crude material. Given the risk of epimerisation at the α-stereocentres of the aldehydes, dialdehyde **166** was carried forward without further purification. Subjecting the crude material to Wittig olefination conditions gave the di-methylenated product **167** in 62% yield over two steps. Interestingly, the cyclic *meso* nature of the product results in two sets of *tert*-butyl methyl protons which appear as separate singlets, δ_H 1.05 ppm (9H) and δ_H 1.02 ppm (9H), in the ^{1}H NMR spectrum. A subsequent TBAF-mediated cleavage of the tethering silyl group of dialkene **167** then gave *meso*-diol **158** in 81% yield. The symmetric nature of **158** was confirmed from the presence of only 4 resonance signals in the ^{13}C NMR. With **158** in hand, the key Mukaiyama oxidative cyclisation could be attempted.



***Scheme 36**. Synthesis of Co(nmp)₂.*

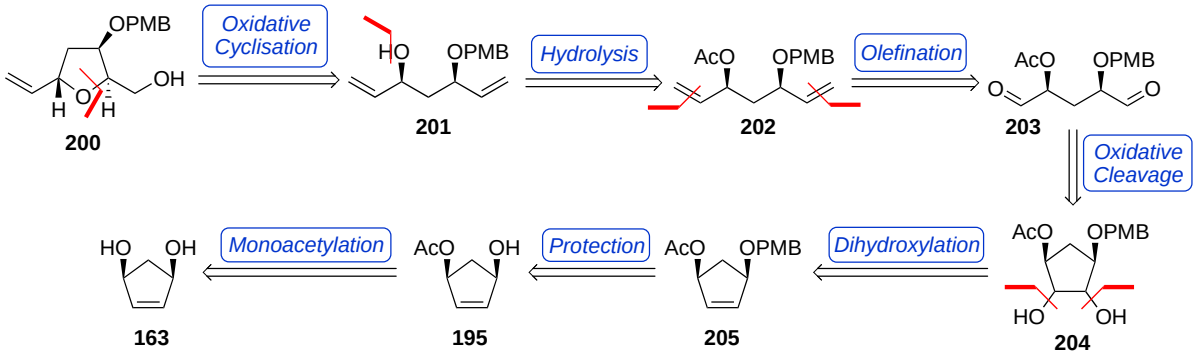
Using Pagenkopf's second generation Co(nmp)$_2$ catalyst **199** (synthesized in three steps and 47% overall yield from *N*-methyl piperazine **197**—***Scheme 36***) *meso*-diol **158** was reacted to afford *trans*-THF **161** as a racemic mixture in 55% yield (***Scheme 37***).[55] The formation THF **(±)-161** was confirmed from the appearance of a multiplet at δ_H 4.05 – 3.90 in the ^{1}H NMR spectrum which corresponds to the C*H*CH$_2$OH protons. The *trans* nature of the THF was confirmed by nOe analysis, the key correlations of which are shown in ***Scheme 37***. Critically, no correlation between the protons of C$_{32}$ and C$_{35}$ existed, while there were strong correlations between the protons of C$_{32}$ and C$_{33}$, C$_{33}$ and C$_{34}$, and C$_{31}$ and C$_{35}$. Thus, having shown that Mukaiyama's oxidative cyclisation could be successfully applied to synthesising the F-ring as a racemic mixture, we set out to develop an asymmetric route towards THF **161**.



***Scheme 37**. Synthesis of the F-ring as a racemate and key nOe correlations.*

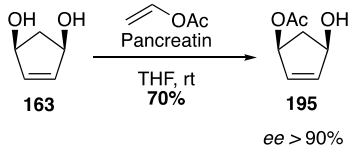
2.2.4. Asymmetric Synthesis of the F-ring

Our retrosynthetic analysis of the F-ring **200**, outlined in ***Scheme 38***, begins with a disconnection of the C_{32}-O bond, which leads to the mono-protected alcohol **201**. This alcohol, which is the substrate for the key Mukaiyama oxidative cyclisation, can be accessed from hydrolysis of the corresponding acetate **202**. In analogy to our synthesis of F-ring **(±)-161**, acetate **202** can be formed from the dimethylenation of dialdehyde **203** under Wittig olefination conditions. This dialdehyde could be the product of a sodium periodate-mediated cleavage of diol **204** which, in turn, can be synthesised from the dihydroxlation of alkene **205**. Protection of alcohol **195**, with PMB-chloride under basic conditions, or with PMB-imidate under acidic conditions, could then facilate the formation of PMB-ether **205**. As mentioned in ***section 2.2.3***, we intended to access alcohol **195** from *meso* diol **163** using a well established enzyme-mediated protocol.



Scheme 38. *Retrosynthesis of the F-ring **200***

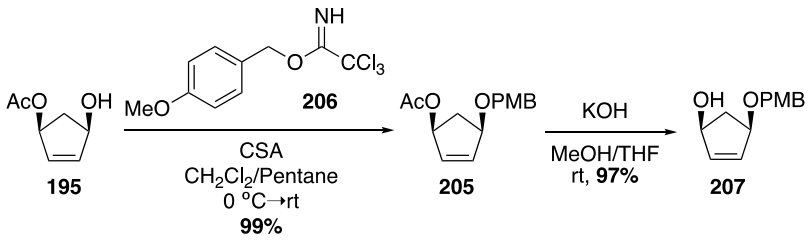
Proceeding with the forward synthesis, the reaction of diol **163** and vinyl acetate in the presence of pancreatin gave the monoacetyated product **195** in 72% yield (***Scheme 39***). The specific rotation of monoacetate **195** was in agreement with values reported in the literature,[54] however, further analysis would be required to confirm the absolute stereochemistry of the product and to determine the *ee* of the reaction.



Scheme 39. *Asymmetric monoacetylation of diol **163***

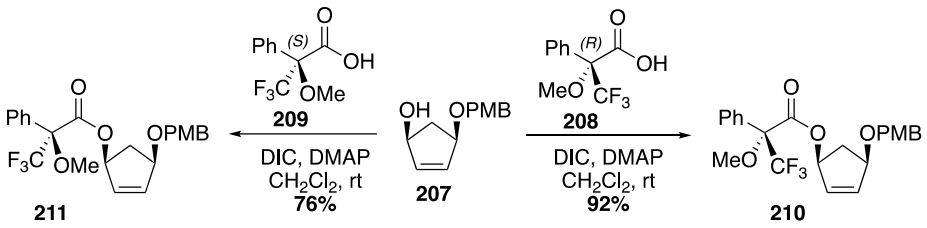
We decided to carry out Mosher's esters analysis, but not directly using monoacetate **195** because acetate migration could occur during the preparation of the Mosher's esters. Instead, we decided to synthesise the PMB-ether of monoacetate **195**, in line with our route to the F-ring, then hydrolyse the acetate group and prepare the Moshers esters from the corresponding alcohol **207**. This would provide us with an indirect method to determine the absolute stereochemistry of monoacetate **195** and the *ee* of the monoacetylation.

Reacting monoacetate **195** with PMB-imidate **206** (synthesised in one step from PMB-alcohol) and camphor sulfonic acid in dichloromethane/pentane, afforded the desired PMB-ether **205** in 99% yield (***Scheme 40***).[56] The appearance of chemcial shifts at δ_H 7.32 – 7.19 ppm (2H, dd) and 6.95 – 6.78 ppm (2H, m) in the ^{1}H NMR spectrum are indicative of PMB phenyl protons. Hydrolysis of **205**, in a basic solution of methanol, gave alcohol **207** in 97% yield.



Scheme 40. *Mosher's ester substrate preparation*

Reacting alcohol **207**, separately with (*R*)-Mosher's acid **208** and (*S*)-Mosher's acid **209**, under Hoye's conditions, gave the corresponding Mosher's esters, **210** and **211**, in yields of 92% and 76% respectively (***Scheme 41***).[57] The ^{19}F NMR spectra of **210** and **211** showed singlets at δ_F -71.7 ppm and -71.9 ppm, respectively, indicating that the Mosher's esters had been successfully formed.

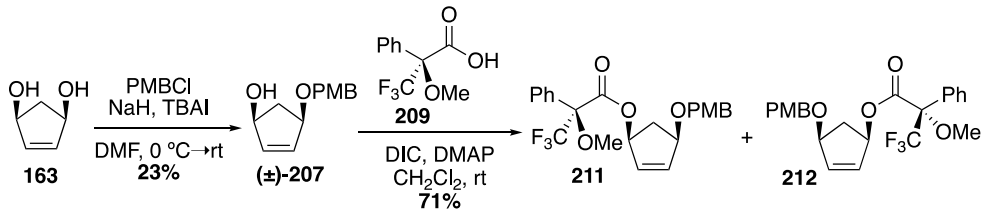


Scheme 41. *Synthesis of Mosher's esters **210** and **211***

With **210** and **211** in hand, the absolute stereochemistry of C_{35} was determined to be

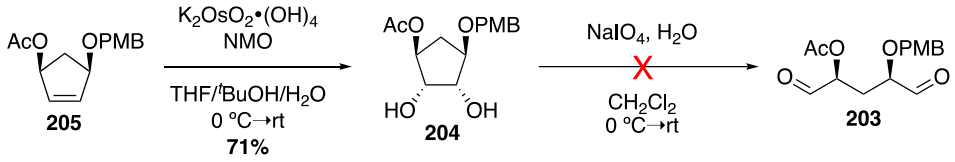
the desired *S* configuration, thus confirming the stereochemistry of monoacetate **195** to be the desired *S* at C_{35}-OAc and *R* at C_{32}-OH.

In order to determine the *ee* of the monoacetylation, a racemic mixture of alcohol **207** needed to be made. Either *R* or *S* Mosher's acid could the be reacted with the resulting racemate. Evaluting the ^{1}H NMR spectrum of the resulting diastereomers against that of the corresponding Mosher's ester would then enable us to calculate the *ee.* Thus, taking *meso*-diol **163,** and reacting it with PMB-imidate under conditions analogous to those used for monoacetate **195**, alcohol **207** was formed as a racemic mixture in 23% yield.[56] Treatment of **(±)-207** with *S* Mosher's acid— chosen over (*R*)-Mosher's acid as it gave a higher yield when reacted with enantiomeric **207** (***Scheme 42***)—afforded the target Mosher's ester **211** and **212** as an inseparable 1:1.3 mixture of diastereomers in 71% yield.[57] With the ^{1}H and ^{19}F NMR spectra of this mixture in hand, we were able to integrate the signals corresponding to the desired Mosher's ester **211** against that of its diastereomer **212**, in both the ^{1}H NMR and ^{19}F NMR spectrum of **211**, to give an *ee* > 90%.



Scheme 42*. Synthesis of diastereomers **211** and **212***

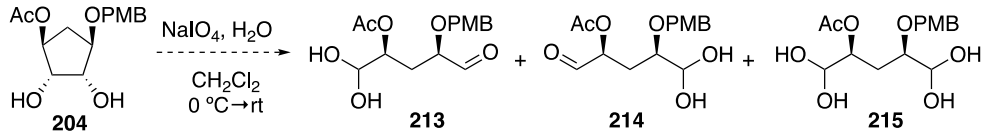
Our synthesis towards the F-ring continued with the dihydroxlation of PMB-ether **205** with potassium osmate to give diol **204** in 71% yield (***Scheme 43***). However, subjecting this diol to the periodate cleavage conditions, however, did not yield the desired dialdehyde **203**.



Scheme 43*. Attempted synthesis of aldehyde **203***

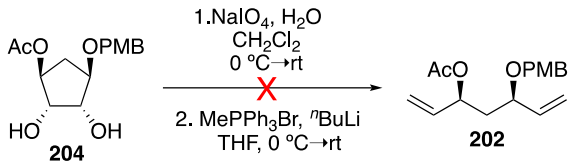
Analysis of the ^{1}H NMR spectrum of the crude material suggested that the two monohydrate compounds, **213** and **214**, and dihydrate compound **215**, none of the desired

dialdehyde **203** had been formed (***Scheme 44***).



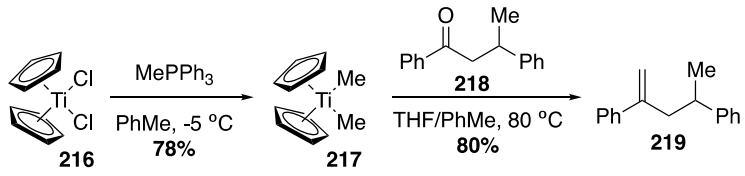
Scheme 44*. Proposed hydrate formation*

It was thought that if these hydrates were indeed formed, then subjecting the crude material from the periodate-cleavage to the Wittig olefination conditons could form dialdehyde **203** *in situ* which would subsequently be methylenated. Unfortunately, this attempt failed to yield the desired product, as did the use of 4 Å molecular sieves (***Scheme 45***).



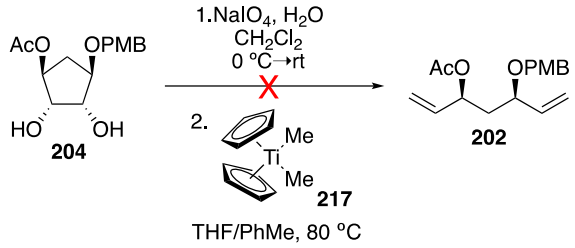
Scheme 45*. Attempted synthesis of alkene **202***

Using the same logic, we postulated that the high temperatures required for the Tebbe-Petasis olefination could form dialdehyde **203** *in situ*.[58-59] Thus, firstly we decided to synthesise the Petasis reagent **217** which was formed in 78% yield in one step from titanocene dichloride **216**, using the conditions developed by Payack and co-workers (***Scheme 46***).[60] We decided to test our conditions for the Tebbe-Petatsis olefination on aryl ketone **218** which underwent reaction in a THF/toluene solvent mixture to give alkene **219** in 80% yield.[61]



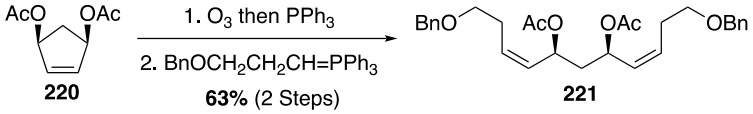
Scheme 46*. Synthesis of alkene **219***

Confident that our conditions for the Tebbe-Petathesis olefination were reliable, we next attempted the sodium periodate mediated cleavage of diol **204** and the subsequent olefination of the resulting crude material, under Tebbe-Petathesis conditions (***Scheme 47***). Unfortunately, however, this reaction sequence resulted only in what seeemed to be decomposition of the starting materials. At this stage we decided to pursue an alternative method for the oxidation of diol **204**.



Scheme 47**. Attempted oxidation/Tebbe-Petasis olefination of diol **204

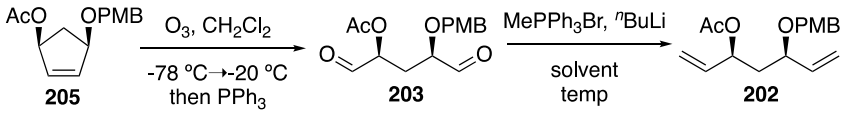
Arneson and co-workers showed that the ozonolysis of diacetate **220** and Horner-Wadsworth-Emmons olefination of the resulting aldehyde could be achieved in 63% yield over two steps (***Scheme 48***).[62] We envisaged that dialdehyde **203** could be formed by applying these ozonolysis conditions to alkene **205**. A subsequent Wittig olefination could then give access to dialkene **202**.



Scheme 48**. Arneson's synthesis of alkene **221

Alkene **205** was dissolved in dichloromethane and subjected to a stream of ozone gas followed by triphenylphosphine (***Figure 21***). A 0.05 mL aliqout of the reaction mixture was taken and concentred *in vacuo*. The existence of dialdehyde **203** in the reaction mixture was confirmed by the presence of two signals at δ_H 9.69 and 9.64 ppm in the ^{1}H NMR spectrum. The Wittig olefination was then attempted, adding the phosphonium ylide as a solution in THF to the ozonlysis reaction mixture at –78 °C then warming to room temperature. The ^{1}H NMR spectrum of the crude material showed that the product did not exist in the reaction mixture. The reaction was attempted again, this time warming to –20 °C from –78 °C, after the addition of the ylide, and then to room temperature. Under these conditions, the desired dialkene **202** was obtained in 17% yield. We believed that the result of this reaction was being determined by the stability of the phosphonium ylide in dichloromethane. We postulated whether higher yields could be achieved if the Wittig reaction was carried out in THF instead. Thus, once the ozonolysis reaction had gone to completion, dichloromethane was removed *in vacuo* and the reaction mixture was redissolved in THF. Pleasingly, the subsequent Wittig olefination gave

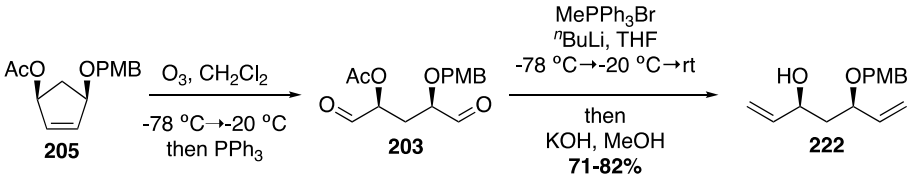
the desired dialkene **202** in a high yield of 72%.



entry	temperature (°C)	solvent	yield (%)
1	-78 → 25	CH_2Cl_2	0%
2	-78 → -20 → 25	CH_2Cl_2	17%
3	-78 → -20 → 25	THF	72%

Figure 21**. Optimising the conditions for the synthesis of dialkene **202

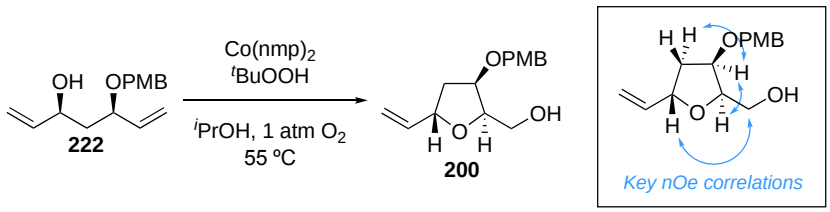
When repeating this reaction it was found that extended reaction times led to the partial cleavage of the acetate group of the product alkene. We believed, therefore, that it may possible to fully cleave the acetate group in the same pot as the ozonolysis-Wittig reaction. Taking an aliquot of the Wittig-ozonolysis reaction and acquiring a ^{1}H NMR spectrum of the corresponding crude material, allowed us to determine when the reaction had gone to completion. At this point, a 0.2 M solution of potassium hydroxide in methanol was added, and after further stirring and subsequent purification, the desired alcohol **222** was obtained in yields of 71%-82% (***Scheme 49***). A broad absorption peak at 3438 cm^{-1}, characteristic of a hydroxy group, confirmed the formation of the product.



***Scheme 49**. One-pot Wittig olefination and acetate cleavage*

The key Mukaiyama oxidative cyclisation was then carried out on alcohol **222** to give THF **200** in 48% yield (entry 1, ***Figure 22***). The *trans* nature of the product was confirmed by nOe experiments, the key correlations of which are summarised in ***Figure 22*.** We began our optimisation efforts by changing the work-up procedure to the use of an aqueous buffer instead of MeI. The result was a 10% decrease in yield but an 11% increase in the amount of recovered

starting material (entry 2, ***Figure 22***). Although a greater amount of starting material was recovered using the aqueous buffer, we decided to conintue our optimisation efforts with the MeI work-up porcedure as it gave higher yields. Increasing the catalyst loading to 15 mol% (entry 3, ***Figure 22***) resulted in a small decrease in yield, and a slight increase in the amount of recovered starting material. Increasing the catalyst loading further to 30 mol% (entry 4, ***Figure 22***) gave a small increase in product yield, with a small decrease in the amount of recovered starting material. Using 10 molar equivalents of MeI, compared to 1.0 in entries 1,3 and 4, resulted in a 1% decrease in the reaction yield; however, a significant decrease in the amount of recovered starting material from 6% (entry 5, ***Figure 22***) to less than 1% was observed.



entry[a]	catalyst loading (mol%)	workup procedure	yield **200** (%)	RSM (%)
1	10	MeI	48	11
2	10	buffer	38	22
3	15	MeI	44	14
4	30	MeI	51	6
5[b]	**30**	**MeI**	**50**	**<1**

[a]All reactions carried out on a 50 mg scale.

[b]THF **200** was also synthesised in 50% yield on a 1.05g scale under the conditions shown in entry 5.

Figure 22*. Attempts to optimise the Mukaiyama oxidative cyclisation*

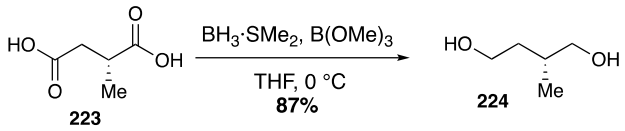
It is difficult to understand the exact reasons for the low yield of this reaction. We see a negligible increase in yield upon doubling the catalyst loading, while the amount of recovered starting material almost halves, suggesting that the catalyst may degrade the starting material or complicate its isolation from the reaction mixture. The exact role of *tert*-butyl hydroperoxide (TBHP) in the reaction mechanism remains unclear.[50] Mukaiyama and co-workers note in their

original report that the addition of an equimolar amount of TBHP increased yields and decreased reaction times, without influencing the stereoselectivity of the reaction.[47] In Pagenkopf's studies, 0.1 molar equivalents of TBHP were used, yet excellent yields were consistently obtained.[55] Therefore, we did not believe that varying the molar equivalents of TBHP would have any effect on the reaction yield. Furthermore, Hartung and co-workers showed that the addition of 4 Å molecular sieves had no effect on the reaction yield.[50] It was unlikely, therefore, that the presence of water in the reaction mixture was detrimental.

We decided to conclude our optimisation efforts at this point and continue with the forward synthesis of the EFG-fragment, the next stage of which was to synthesise the G-ring precursor—1,5-hydroxy alkene **153**.

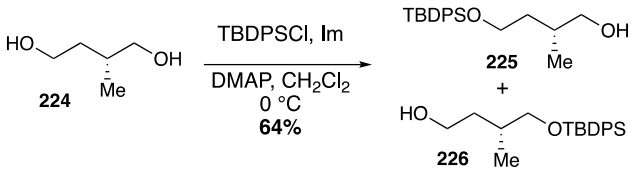
2.3 Synthesis of 1,5-Hydroxy Alkene 232

Using a route that was previosuly developed within the Donohoe group, hydroxy alkene **232** was synthesised in 5 steps from (*R*)-methyl succinic acid **223**.[43] The first step was a borane dimethyl sulfide mediated reduction which gave diol **224** in 87% yield (***Scheme 50***). The lack of any resonance at δ_H 11-12 ppm in the ^{1}H NMR spectrum, along with the presence of methylene proton shifts at δ_H 3.77-3.43 ppm, proved the formation of the diol.



Scheme 50**. Synthesis of diol **224

To access the desired 1,5-relationship between the alkene and hydroxy group of the target molecule, diol **224** needed to be selectively monoprotected at the less hindered alcohol. It was thought that this could be achieved by using a bulky silyl protecting group. Diol **224**, therefore, was reacted with TBDPS-Cl under basic conditions to give a mixture of regioisomers **225** and **226** in 64% overall yield (***Scheme 51***).



Scheme 51**. Monosilylation of diol **224

The ratio of these regiosomers could not be determined at this point due to the overlapping of their shifts in the ^{1}H NMR spectrum. The bis-protected product **227** was also formed in this reaction (***Figure 23***) and was identified from the lack of an O-H stretch in its I.R. spectrum and from the integrals of the aromatic shifts in its ^{1}H NMR spectrum.

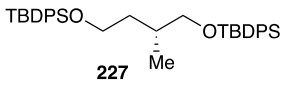
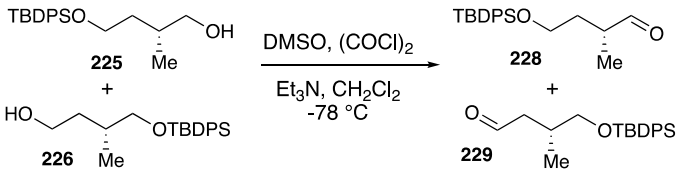


Figure 23**. Bis-protected diol **227

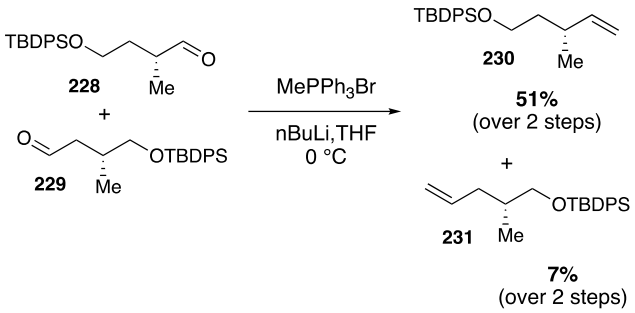
Subjecting the mixture of mono-silylated alcohols **225** and **226** to Swern oxidation conditions afforded the corresponding aldehydes **228** and **229** which, due to the risk of epimerisation of the stereogenic centre α to the aldehyde, were used without further purification (***Scheme 52*)**. We were now able to determine the ratio of the two regisomers by analysis of the ^{1}H NMR spectrum of the crude mixture: integrating the doublet at δ_H 9.66, corresponding to aldehyde **228**, against the triplet at δ_H 9.78, corresponding to aldehyde **229**, revealed the ratio of aldehyde **228** to **229** to be 1:2.9.



Scheme 52**. Oxidation of alcohols **225** and **226

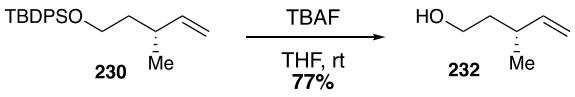
This mixture was then treated with methyltriphosphonium bromide under Wittig olefination conditions, to give alkenes **230** and **231** (***Scheme 53***). At this point, the two regioisomers could be separated by flash coloumn chromotography. After examining the COSY spectra of both isomers, alkene **230** was confirmed to be the major isomer, isolated in 51% yield (over two steps), with **231** the minor isomer, isolated in 7% yield (over two steps). The COSY spectrum of major isomer **230** revealed a coupling between the allylic C*H*CH$_3$

proton and the vinylic C*H*$_2$=CH protons. Conversely, in the COSY spectrum of minor isomer **231**, the C*H*CH$_3$ proton couples to two sets of methylenic protons instead.



Scheme 53*. Synthesis of alkenes **230** and **231***

The final step in this sequence, removal of the TBDPS-protecting group, was performed with TBAF in THF, rendering alcohol **232** in 77% (***Scheme 54***). The spectroscopic data of this compound matched those that were reported in the literature.[43] The yield, which was lower than anticipated, could be attributed to the volatilty of alkene **232** and the consequent difficulty in removing the reaction solvent *in vacuo* without reducing the product yield.



Scheme 54*. Synthesis of hydroxy-alkene **232***

With hydroxy-alkene **232** and F-ring **200** in hand, the key cross metathesis reaction between these two compounds could now be attmepted.

2.4 Cross Metathesis of Hydroxy-Alkene 232 and Sulfone 240

In 2002, Grubbs and co-workers developed a general model for selectivity (summarised in ***Table 1***, with selected olefins) in olefin cross metathesis which categorises alkenes into four types, based on their structures, and also identifies which metathesis catalyst is suitbale for each type (different catalyst types are shown in ***Figure 24***).[63-67]

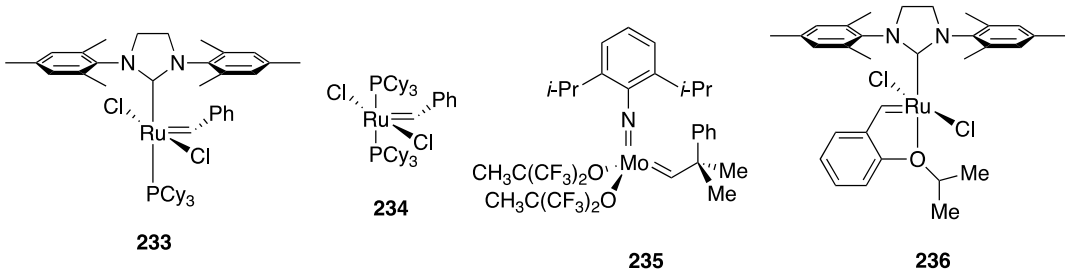


***Figure 24**. Metathesis catalysts*

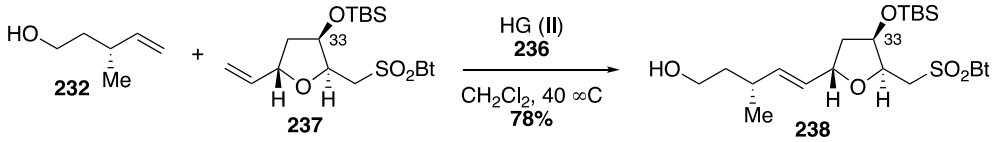
Catalyst **233**, Grubbs 2nd generation catalyst, is said to be more active than **234**, Grubbs 1st generation catalyst. Although catalyst **236**, Hoveya-Grubbs 2nd generation catalyst, is not included in this model, it is a widely used catalyst in olefin metathesis as it is known as a more stable initiator than **233** under air and moisture due to chelation of its *iso*-propoxy ligand. This renders catalyst **236** more bench-stable and thus practially more easy to handle. It is worth noting, though, that the stability of the 16 e^- pre-catalyst species differs from that of the active 14 e^- species.

	Catalyst		
Olefin Type	**223**	**234**	**235**
Type I (fast homodimerisation)	*terminal olefins*, 1° allylic alcohols, esters, ally halides, styrenes, ally sulfides, allyl phosphonates, allyl silanes	*terminal olefins*, 1° allylic alcohols, esters, ally halides, styrenes, allyl silanes	allyl silanes, terminal olefines
Type II (slow homodimerisation)	styrenes, acrylates, vinyl ketones, allylic alcohols, 2° allylic alcohols, unprotected 3° allylic alcohols	stryrene, 2° allylic alcohols	styrene, allyl stannan
Type III (no homodimerisation)	1,1-disubstituted olefins, protected 3° allyl alcohols, 4° allylic carbons	vinyl siloxanes	3° allyl amines, acrylonitrile
Type IV (spectators to CM)	protected trisubsituted allyl alcohols	1,1-disubstituted olefins, 4° allylic carbon-containing olefins	1,1-disubstituted olefins

***Table 1**. Grubbs' model for olefin selectivity in the cross-metathesis reaction*

Previous work in the Donohoe group includes the cross metathesis of sulfone **237** and alkene **232**, using catalyst **236**, which gave alkene **238** in 78% yield (***Scheme 55***).[43] Here it was assumed that both **237** and **232** were type 1 olefins and thus by Grubbs' model, catalyst **233** or **234** would have been suitable for this reaction. The use of catalyst **236** was favoured

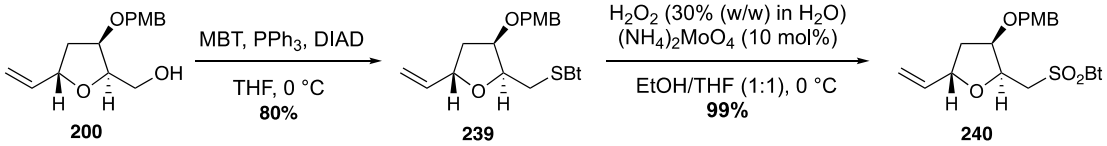
for its superior bench-stability. It was thought that the use of excess alkene **232** in the reaction would discourage the homodimerisation of the more valuable sulfone **237**, favouring formation of the desired product **238**.[43] Due to the volatility of alkene **232**, it was found that performing this reaction in a sealed tube, as opposed to a flask with a reflux condenser attached, resulted in higher yields. The only difference between the reagents used in this reaction and those in our synthesis, is the presence of a PMB-ether at C_{33} in **200** instead of a silyl-ether in **237**. We envisaged that by applying the conditions used for the cross-methasis of **232** and **237** to our synthesis the desired alkene **241** could be obtained in high yields.



entry	temperature (°C)	yield (%)
1	40 °C	53%
2	40 °C	78%

Scheme 55*. Previous use of the cross-metathesis reaction by the Donohoe group*

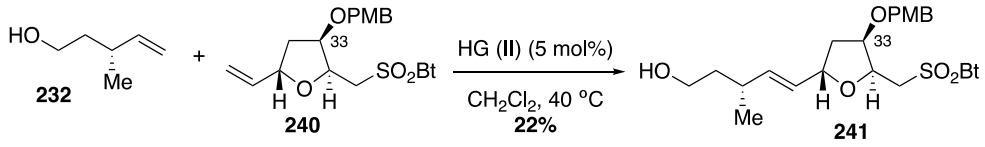
The sequence began with the synthesis of sulfide **239**. Starting from alcohol **200,** this was achieved in 80% yield (two steps) v*ia* a Mitsunobu reaction followed by an oxidation of the resultant sulfide (***Scheme 56***).[68] The structure of the sulfone was confirmed from abosrption bands at 1326 cm^{-1} and 1146 cm^{-1} which are typical for sulfone functional groups.



Scheme 56*. Synthesis of sulfone **240***

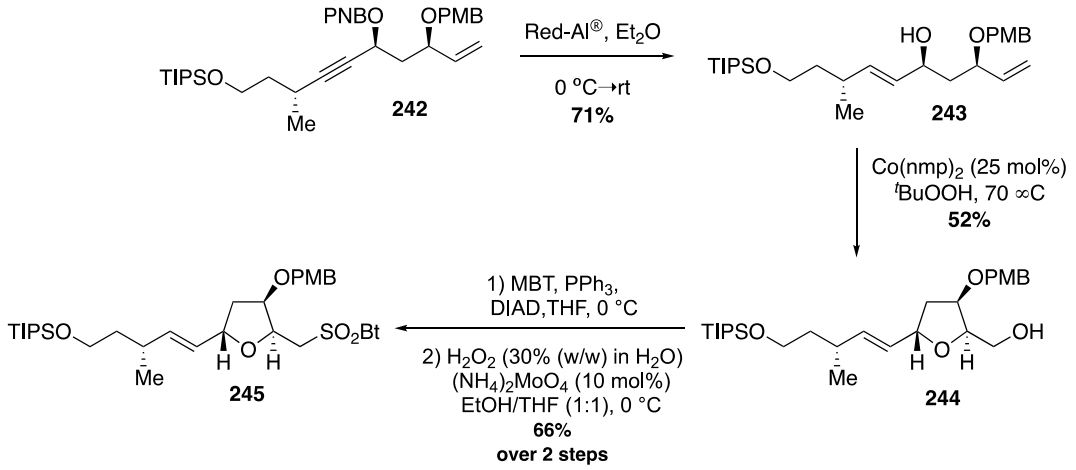
Cross metathesis of sulfone **240** and alkene **232** rendered the desired alkene **241** in 22% yield (***Scheme 57***). The formation of the alkene was inferred from the lack of terminal olefin peaks in the ^1H NMR spectrum. Interestingly, signals of the C_{36}-C_{37} olefinic protons

overlapped in the ^{1}H NMR spectrum. The stereochemistry of the newly formed C_{36}-C_{37} olefin bond could not be determined at this point as the magnitude of the coupling constant across this bond could not be measured.



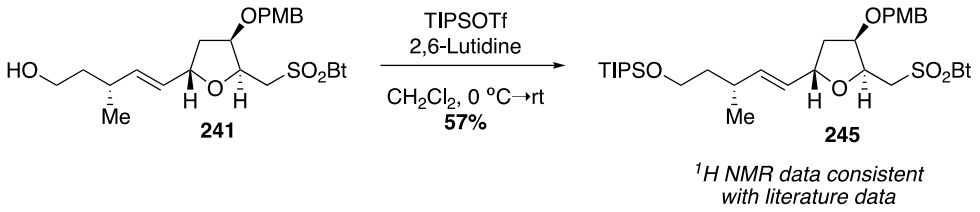
***Scheme 57**. Synthesis of alkene **241** via cross-metathesis*

Alkene **245** had previously been synthesised by the Donohoe group *via* an *E* selective alkyne reduction of **242**.[68] The *trans* nature of alkene **243** was confirmed by a coupling constant of J = 15.5 Hz across the olefinic bond. A Mukaiyama oxidative cyclisation followed by a Mitsunobu reaction and oxidation were then performed to give alkene **245** (***Scheme 58***).[68]



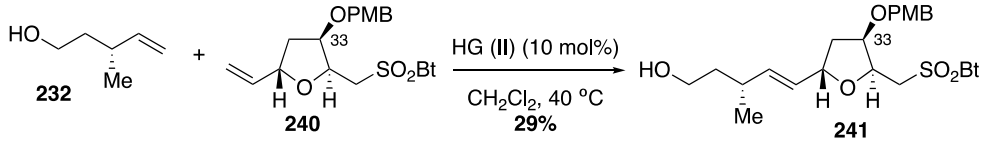
***Scheme 58**. Previous work in the Donohoe group to access the FG-ring system*

It was thought that by synthesising **245**, which could be accesed in one step from alcohol **241**, then the stereochemistry of the C_{36}-C_{37} double bond could be determined. Thus, alkene **241** was treated with TIPS-OTf under basic conditions, which gave alkene **245** in 57% yield. The spectroscopic data matched that which was previosuly reported by the Donohoe group, and the coupling constant across the C_{36}-C_{37} olefinic bond was measured to be J = 15.4 Hz, thus confirming its *trans* stereochemistry and also that of alkene **241**.[68] Our attentiom turned to optimising the cross-metathesis reaction of **232** and **240**.



Scheme 59**. Synthesis of alkene **245

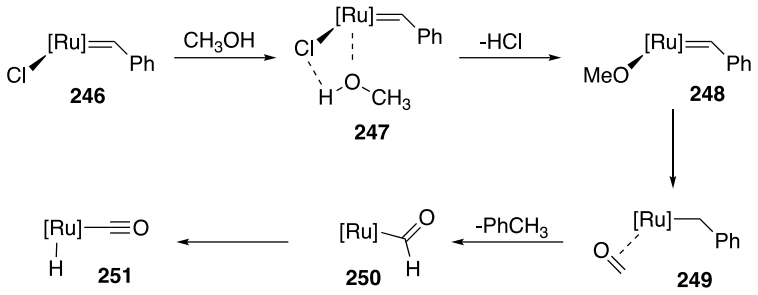
Our efforts began by doubling the catalyst loading to 10 mol% which resulted in a 7% increase in product yield (***Scheme 60***). It was evident from this small increase in yield that it would not be feasible to continue increasing the catalyst loading to try to achieve better results.



Scheme 60**. Attempted optimisation of the cross metathesis between **232** and **240

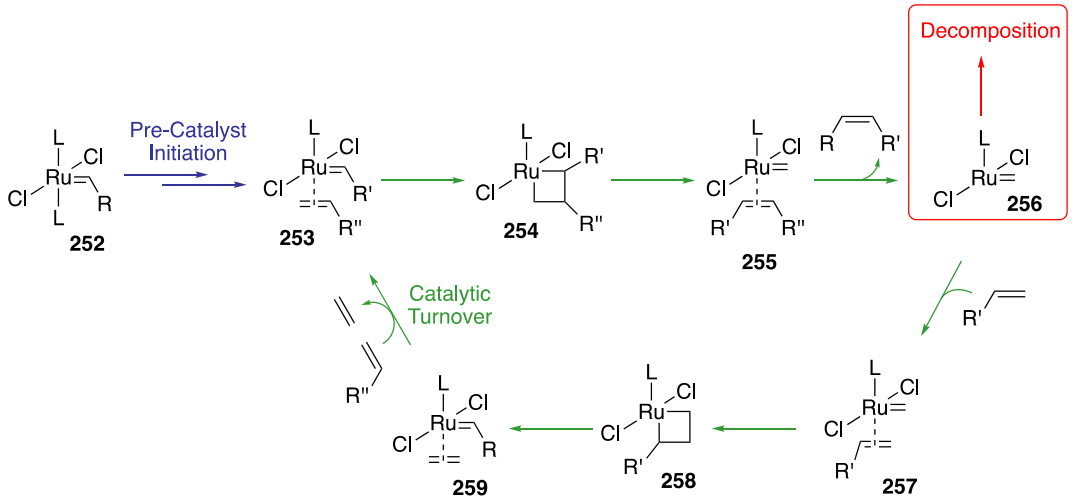
We postulated that the main reason for the low yields was the decomposition of the ruthenium catalyst which could occur *via* two predominant pathways, both of which include the generation of ruthenium-hydride species.

The first of these decomposition pathways is thought to occur by alcoholysis, induced by the substrate alcohol **232**. The degradation of the Grubbs 1st generation catalyst with primary alcohols has been reported by Mol and co-workers.[69-71] This process is said to occur *via* alcoholysis of the metathesis pre-catalyst which leads to a ruthenium-hydride decomposition product. A mechanism for this process was proposed by Mol *et al.* and later studied by Percy, Hillier and Tuttle using DFT calculations (***Scheme 61***).[72-73] The generation of the ruthenium-hydride species **251** is thought to occur by alcohol dehydrogenation followed by decarbonylation. It is possible, therefore, that hydroxy-alkene **232** induces decomposition of the metathesis catalyst, which could proceed *via* a similar pathway to that shown in ***Scheme 61***.[71]



***Scheme 61**. Proposed mechanism for ruthenium-hydride formation*[71]

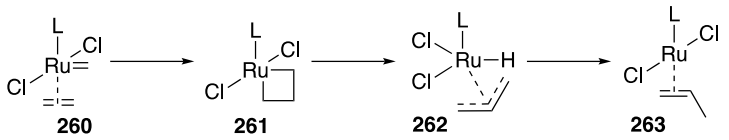
The second decompostion pathway is thought to arise from the inefficient removal of ethylene from the reaction mixture. To elucidate this hypothesis, the key stages of the metathesis reaction of terminal alkenes must be be considered. Pre-catalyst iniaiton renders the active 14e$^-$ ruthenium species **253** from the stable 16e$^-$ pre-catalyst **252** (***Scheme 62***).[73] In the propagating steps that follow, the 14e$^-$ methylidene species **256** formed from catalyst turnover is thought to be one of the most fragile species in the metathesis reaction, and is thus prone to rapid decomposition.



***Scheme 62**. Proposed mechanism for catalyst decomposition in the cross-metathesis reaction*[73]

Van Rensburg and co-workers have shown that the decomposition of methylidene complexes can occur in the presence of ethylene (***Scheme 63***).[74] Using DFT calculations that were subsequently supported by experimental findings, they proposed that the decomposition pathway proceeds *via* β-hydride transfer from a ruthenacyclobutane **261** to give a η^3-allyl

complex **262**.

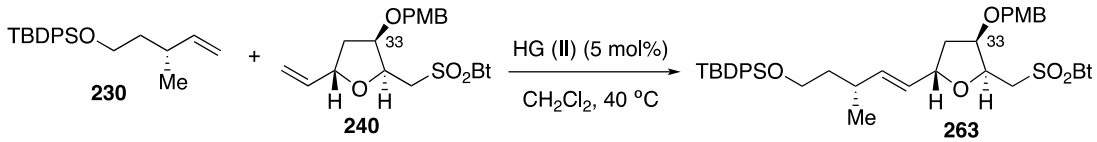


***Scheme 63**. Decomposition of a ruthenium-methylidene complex*[74]

The use of a sealed tube in our metathesis reaction is likely to prevent the loss of ethylene from the reaction. If the ethylene concentration of the reaction mixture is high, then the methylidene complex is prone to decompostion *via* the β-hydride transfer pathway. Due to the volatility of alcohol **232**, a sealed system is necessary, especially as the reaction is heated to 40 °C.

Our solution to the hypothesised problem was to use silyl-ether **230** in place of alcohol **232**. Due to the bulky nature of the TBDPS group in silyl-ether in **230**, substrate volatility would not be an issue. This would allow us to use a reflux condenser in place of a sealed tube which we envisaged would facilitate ethylene gas removal. Furthermore, the use of silyl-ether **230** eliminates the potential decompositon of the metathesis catatlyst *via* alcoholysis. Following the cross metathesis of silyl-ether **230** and sulfone **240**, cleavage of the TBDPS-ether from the product could then afford the desired alkene **241**.

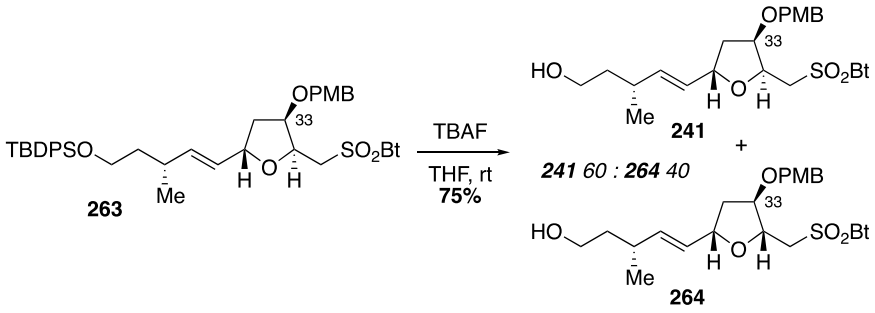
Conducting the reaction of **230** and **240** in a round bottom flask with a reflux condenser attached, under a stationary argon atmosphere with 5 mol% of HG (II) and 4 molar equivalents of silyl-ether **230** gave alkene **263** in 66% yield, with 16% of recovered starting material (***Figure 25***). The *trans*-nature of the C_{36}-C_{37} double bond was confirmed by the magnitude of the coupling constant across it, measured to be J = 15.5 Hz. In our second metathesis attempt, the reaction parameters were kept the same, but now a stream of nitrogen gas was passed over the surface of the reaction mixture. Simon Werrel, a co-worker in the Donohoe group, has shown that this technique can lead to increased yields for the cross metathesis of terminal alcohols.[75] Under these conditions, alkene **263** was obtained in 92% yield and in a > 95:5 ratio of of *E:Z* isomers (***Figure 25***).



entry	yield (%)	RSM (%)
1	66	16
2	**92**	**0**

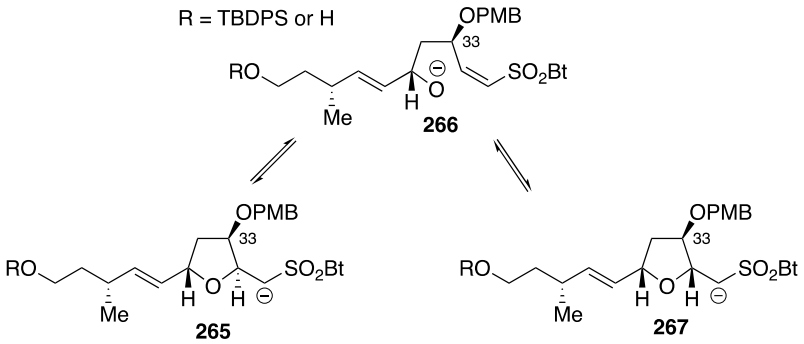
Figure 25*. Optimisation of cross-metathesis*

With yields of the cross metathesis optimised, conditions for the removal of the TBDPS-protecting group of the metathesis product **263** needed to be developed. Using TBAF in THF appeared to give an inseparable mixture of *trans*- and *cis*-THF products, **241** and **264**, in a 60:40 ratio, as judged from the ^{1}H NMR spectrum (***Scheme 64***).



Scheme 64*. TBAF-mediated deprotection of silyl ether **263***

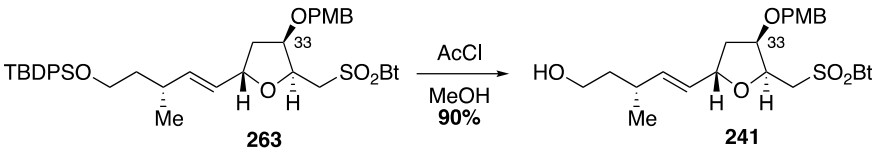
We postulated that TBAF could deprotonate α to the sulfone and the resulting anion **265** could then effect a ring opening of the THF ring. Upon subsequent ring closure *via* 1,4 additon, the thermodynamically more stable *cis*-THF ring **267** could be formed over its *trans*-counterpart (***Scheme 65***).



Scheme 65*. Proposed mechanism for THF-epimerisation*

To overcome this problem, we decided to use acidic conditions for the removal of the

TBDPS-protecting group.[76] Thus, reacting **263** with a 0.1 M solution of acetyl chloride in methanol, gave the desired alcohol **241** in excellent yields of 90% with no epimerisation of the C_{32} stereocentre. Pleasingly, the spectroscopic data of the product obtained from this reaction matched that from the cross-metathesis of alcohol **232** and sulfone **240** (***Scheme 57***).



Scheme 66*. Synthesis of alcohol **241***

2.5 Asymmetric Dihydroxylation of the C_{36}-C_{37} double bond

The next key step in our synthesis of the pectenotoxin-4 EFG-ring system was the Sharpless asymmetric dihydroxylation of the C_{36}-C_{37} double bond of **241**. This reaction would allow us to obtain the desired stereochemistry at C_{37}.

According to the mnemonic developed by Sharpless (***Figure 26***), the quinidine-based ligand $(DHQD)_2PHAL$ would give rise to the desired (*R*)-stereochemistry at C_{37} by directing the dihydroxylation to the top face of the C_{36}-C_{37} double bond.

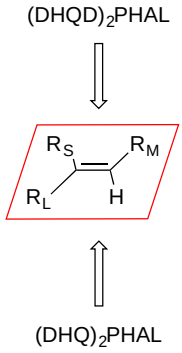
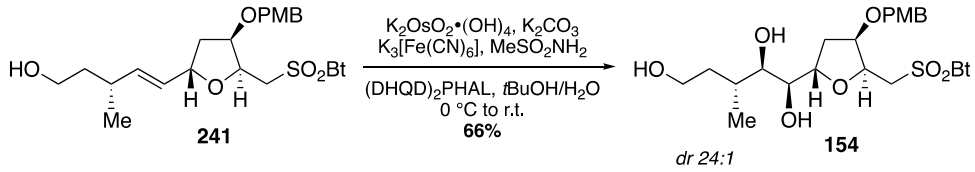


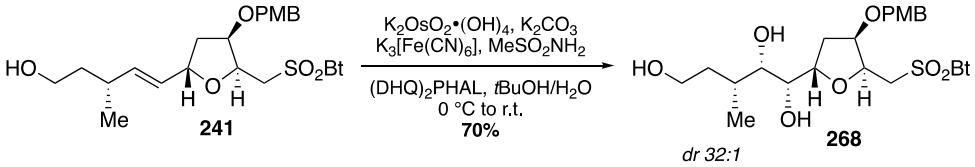
Figure 26*. Sharpless mnemonic for asymmetric dihydroxylation*

Reacting alkene **241** under the Sharpless dihydroxylation conditions with $(DHQD)_2PHAL$ gave diol **154** in 66% yield (***Scheme 67***). The formation of the *syn* diol was inferred from the lack of olefinic shifts in the region δ_H 5.34 – 5.17 ppm of the ^1H NMR spectrum.



Scheme 67**. Synthesis of triol **154

To ensure that the desired diastereomer of **154** had been formed as the major product, we also synthesised diastereomer **268** using $(DHQ)_2PHAL$. Under analagous dihydroxylation conditions, diastereomer **268** was obtained in 70% yield (***Scheme 68***).



Scheme 68**. Synthesis of triol **268

Superimposing the ^1H NMR spectra of the two diastereomers **154** and **268** confirmed that each dihydroxylation reaction produced a separate diastereomer (***Figure 27***).

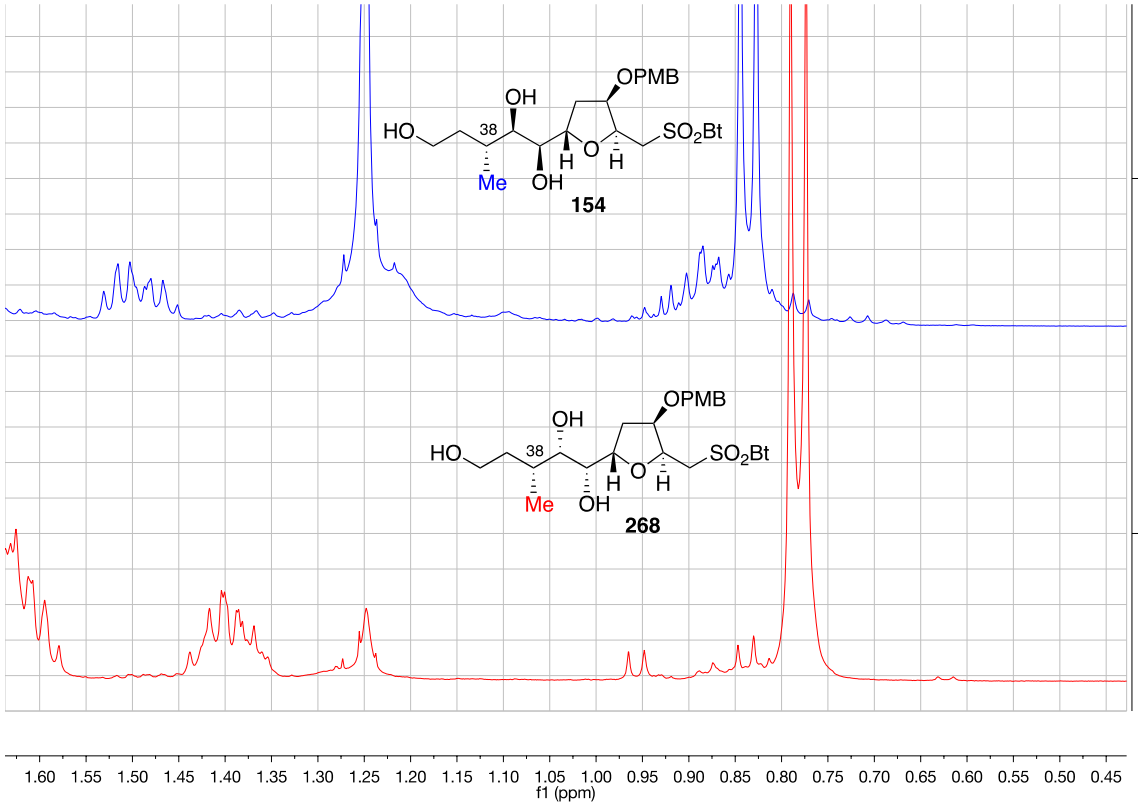


Figure 27**. Superimposed ^1H NMR spectra of diastereomers **154** and **268

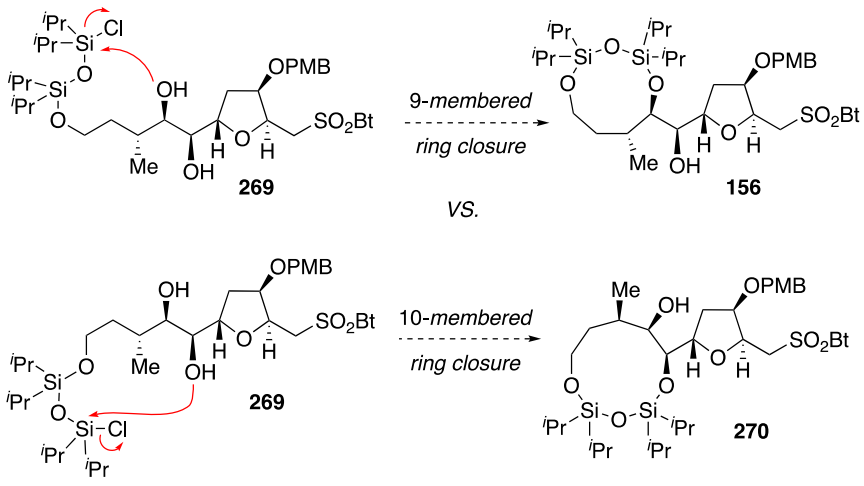
While the majority of the diastereomers' peaks overlapped, the desired triol **154** could be

distinguished from the diastereomer **268** by its $C_{38}CH_3$ methyl signal, which appeared at δ_H 0.84 (d, 3H) compared to δ_H 0.78 (d, 3H) for the undesired **268**. Integration of the major $C_{38}CH_3$ methyl signal against the minor $C_{38}CH_3$ signal in the ^{1}H NMR spectrum for each diastereomer revelaed that $(DHQD)_2PHAL$ afforded **154** and **268** as a 24:1 diastereomeric mixture, while $(DHQ)_2PHAL$ gave **154** and **268** as a 1:32 diastereomeric mixture. In each case, we assume that the sense of selectivity of the asymmetric dihydroxlation follows the Sharpless mnemonic.

2.6 Selective Protection of C_{40}-, C_{37}- and C_{36}-Hydroxy Groups

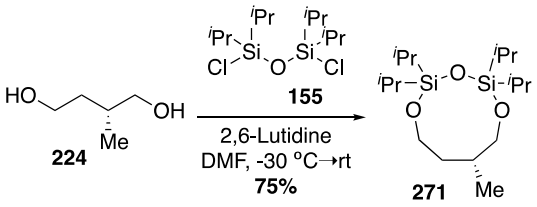
The key Julia-Koecienski olefination reaction between the E-ring aldehyde and F-ring sulfone fragments requires the use of strong base. Therefore, protecting groups that are able to withstand these strong basic conditions needed to be installed on the C_{40}-, C_{37}- and C_{36}-hydroxy groups of triol **154**. Furthermore, our protecting group strategy needed to facilitate the subsequent, selective deprotection of the C_{36}-hydroxy group.

We planned to use the Markiewicz reagent to tether the C_{40}-alcohol with the C_{37}-alcohol, exclusively, in favour of the C_{36}-alcohol (***Scheme 69***). It is thought that diol **269** would form as an intermediate in this reaction as the less sterically hindered primary C_{40}-alcohol would react first with the Markiewicz reagent. Diol **269** can then undergo either a 9-membered ring closure to give alcohol **156**, or a 10-membered ring closure to give alcohol **270**. Presuming that formation of the 9-membered ring is favoured at lower temperatures, under kinetic control, a TES-ether could then be installed on the C_{36}-hydroxy group in analogy to Evan's synthesis. Given the difference in steric bulk between these protecting groups, we envisaged that the TES-ether could be selectively cleaved after the Julia-Kocienski reaction.



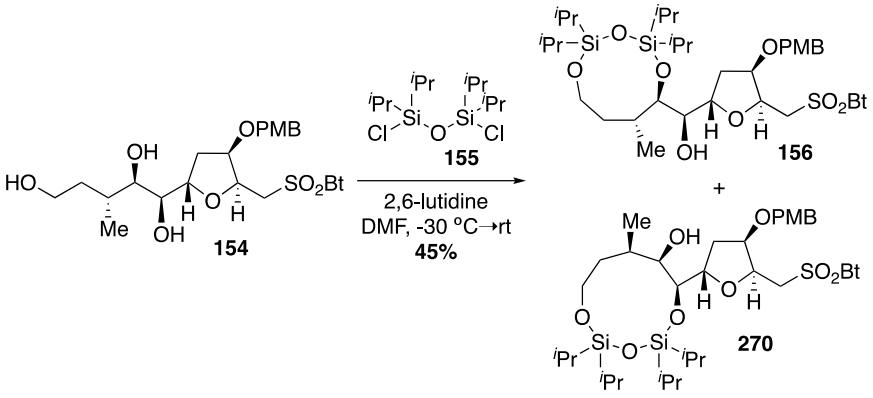
Scheme 69**. Proposed selective protection of triol **154

Before attempting the reaction with triol **154**, we thought it be prudent to test the reaction conditions on a model system. Alcohol **224**, used in the synthesis of 1,5-hydroxy alkene **232**, was chosen as the substrate for our model studies. Reacting **224** with the Markiewicz reagent **155** and 2,6-lutidune in DMF gave silyl ether **271** in 75% yield (***Scheme 70***). The lack of a broad signal in the 3550 – 3200 cm^{-1} region of the I.R. spectrum verified the formation of the product.



Scheme 70**. Synthesis of silyl ether **271

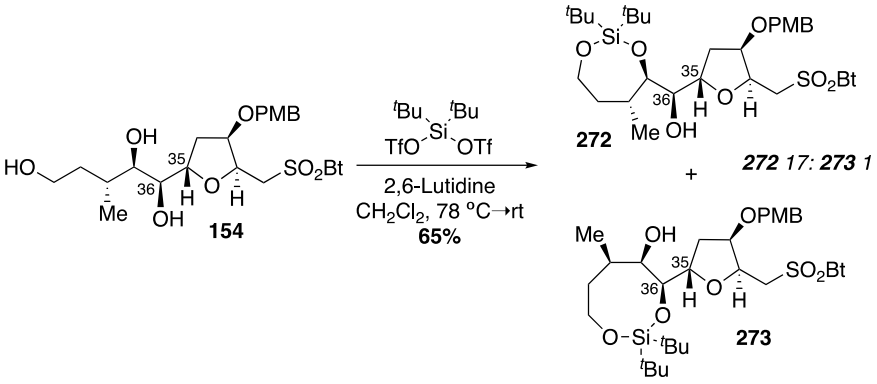
Applying these conditions to triol **154** gave an inseparable 2:1 mixture of what we assumed to be regioisomers **156** and **270,** in 65% yield (***Scheme 71***). At this stage, it was not possible to determine which of the regiosomers was formed as the major product. It was thought that the reaction temperature of -30 °C may not have been low enough to favour selective formation of the desired 9-membered heterocyclic ring **156** over its 10-membered isomer **270**. Therefore, we decided to pursue an alternative protecting group reagent.



***Scheme 71**. Silylation of triol **154** with the MC Arkeweicz reagent*

In our synthesis of (±)-F-ring, di-*tert*-butylsilyl ditriflate was used to tether 1,3-*meso*-diol **163** in forming the bicyclic [7,5] compound **164**. The use of this reagent for the selective tethering of the C_{40}- and C_{37}-alcohols would allow for the reaction to be run in dichloromethane and thus cooled to -78 °C, as opposed to -30 °C when using the Markiewicz reagent **155**. We postulated that at lower temperatures of -78 °C, kinetic control may be great enough to favour the formation of a 7-membered (rather than an 8-membered) heterocyclic ring and thus decided to pursue the selective tethering reaction with di-*tert*-butylsilyl ditriflate.

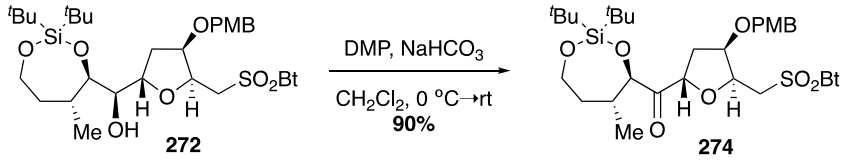
Pleasingly, the reaction of triol **154** with di-*tert*-butylsilyl ditriflate gave alcohol **272** and **273** as a 17:1 mixture of regioisomers in 65% yield (***Scheme 72***). Analysis of the ^1H and COSY NMR spectra suggested that the major isomer contained a 7-membered ring tether. The C_{36}-proton was identified as a peak at δ_H 3.39 ppm (td, 1H) from its coupling to the C_{35}-proton in the COSY spectrum. The C_{36}-proton also showed a strong coupling to a proton of the multiplet at δ_H 2.29 – 2.17 ppm (2H) which was assigned to the C_{36}-hydroxy group (the other proton of this multiplet belongs to $C_{34}H$).



Scheme 72**. Selective silylation of triol **154

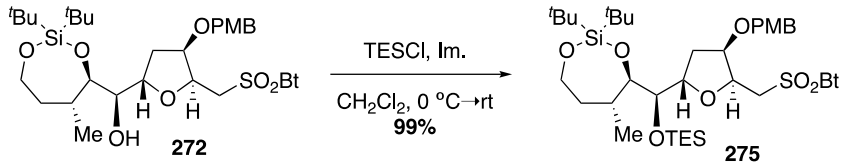
Interestingly, no coupling between the protons of C_{36} and C_{37} was observed in the COSY spectrum; and the chemical shift for C_{37}-H, a dd at δ_H 3.53 ppm (1H), has a strong coupling to C_{38}-H (J=9.2 Hz) and a much weaker one to C_{35}-H (J=1.3 Hz). According to the Karplus equation, this suggests that the dihedral angle between C_{37}-H and C_{36}-H is ~90°

In order to gain further evidence that the 7-membered ring was formed in the major isomer **272**, we oxidized the C_{36}-alcohol to ketone **274** then evaluated the ^{1}H NMR spectrum of this product against that of alcohol **272** (***Scheme 73***). The chemical shift of C_{35}-H appears as a ddd at δ_H 4.23 ppm (1H) in the ^{1}H NMR spectrum of alcohol **272**, but as a dd at δ_H 4.84 ppm (1H) in that of ketone **274**. Furthermore, the chemical shift of C_{37}-H moves downfield from δ_H 3.53 ppm (dd, 1H) in in the ^{1}H NMR spectrum of alcohol **272** to overlap with other signals in a multiplet at δ_H 4.00 – 3.77 ppm (5H) in that of ketone **274**. These findings thus give strong evidence that alcohol **272** was the major regisomer in the reaction of triol **154** with di-*tert*-butylsilyl ditriflate.



Scheme 73**. Synthesis of ketone **274

The installation of a silyl ether on the C_{36}-alcohol could now be attempted. This would be necessary for the key Julia-Kocienski Olefination. Alcohol **272** was thus reacted with TES-chloride and imidazole to give silyl ether **275** in an excellent yield of 95% (***Scheme 74***).

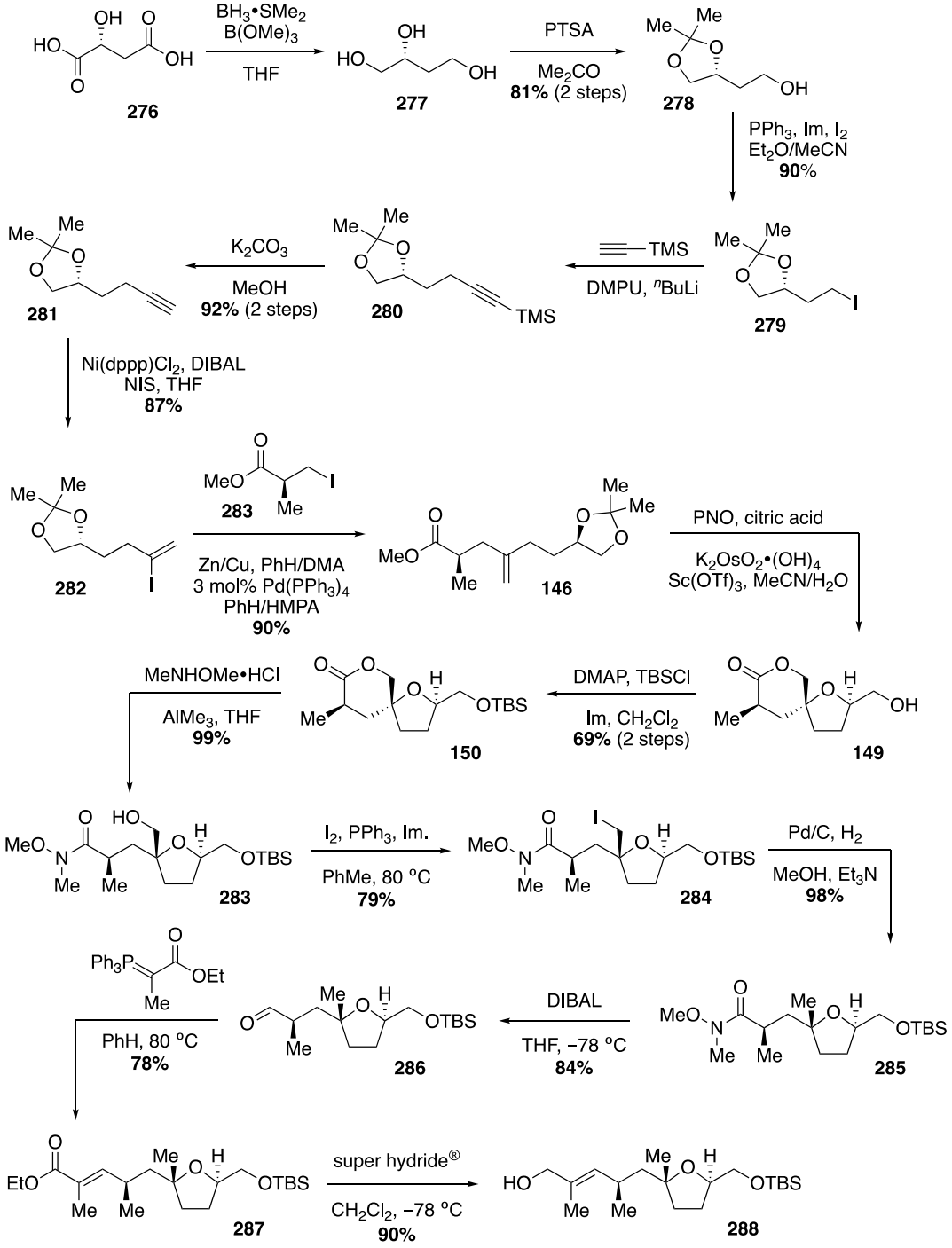


Scheme 74**. Silylation of alcohol **272

The formation of the silyl ether was inferred from the lack of an O-H stretch in the I.R. spectrum. With a successful route to sulfone **275** in hand, our attention turned to synthesizing the E-ring fragment aldehyde for the key Julia-Kocienski coupling.

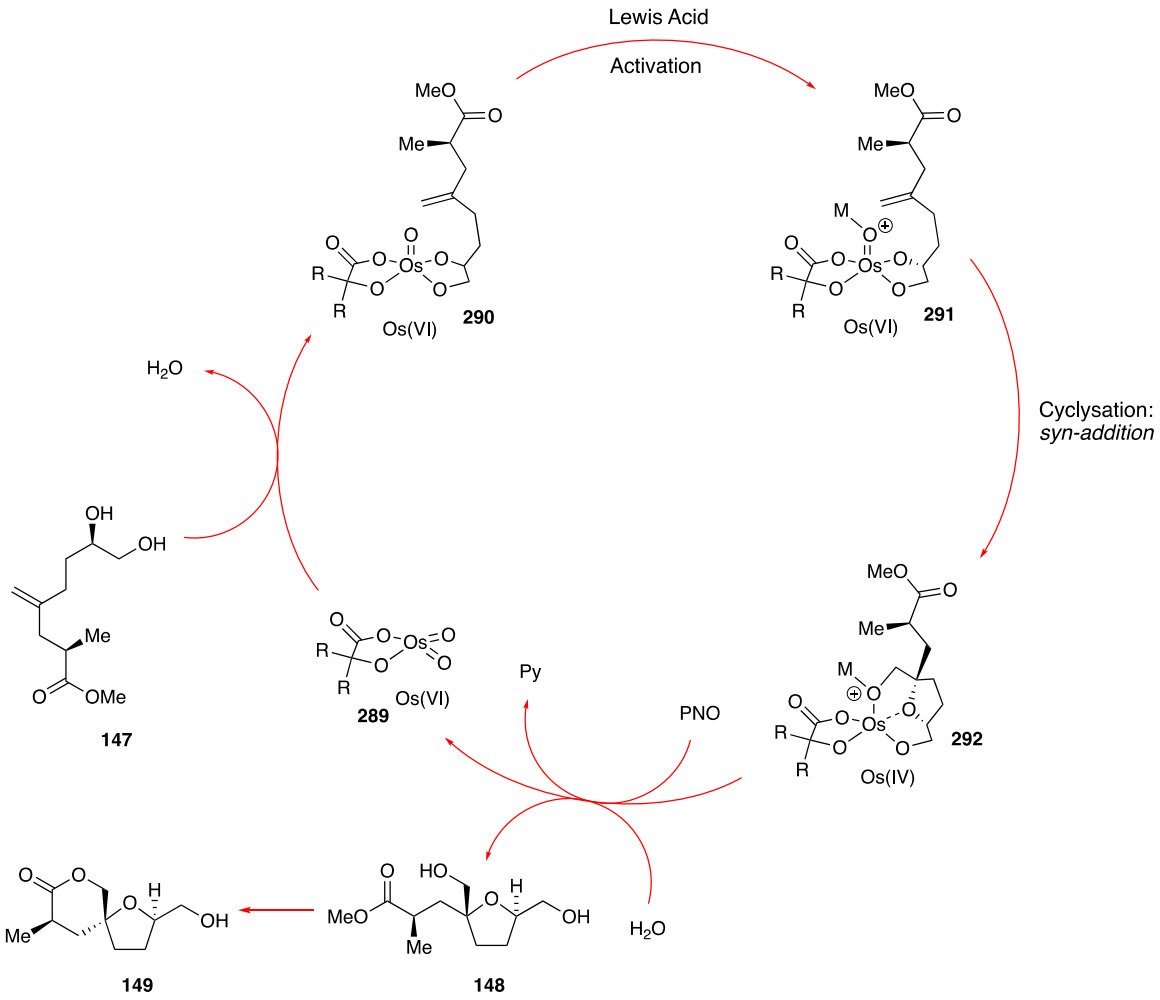
2.7 Synthesis of Aldehyde 289

Dr Paul Winship and Dr Yifan Liu, co-workers in the Donohoe group, had previously accomplished the synthesis of alcohol **288** in 16 steps from D-(+)-Malic acid (***Scheme 75***).[35-36]



Scheme 75. *Previous synthesis of the E-ring by the Donohoe group*

This route utilized a key osmium-mediated oxidative cyclisation—methodology developed by the Donohoe group—to form the *cis*-THF of the E-ring. The mechanism for this reaction is shown in ***Scheme 76***.[34]

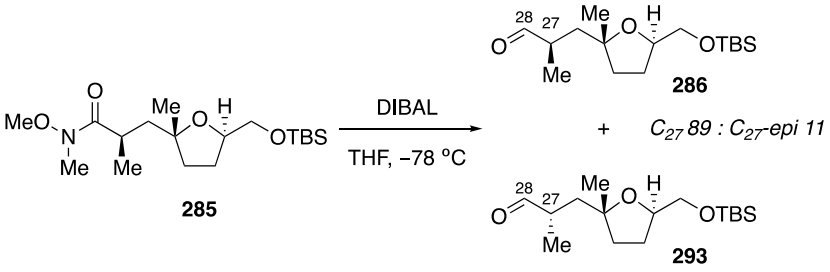


***Scheme 76**. Mechanism of the osmium-mediated oxidative cyclisation*[35]

The Lewis acid, $Sc(OTf)_3$, induces *in situ* cleavage of acetonide **146** to diol **147**, which chelates to potassium osmate to form the osmium(VI) complex **290**. Activation by $Sc(OTf)_3$ facilitates oxidative cyclisation of **291**, which proceeds in a *syn* fashion, to generate the osmium(IV) complex **290**. Hydrolysis of complex **292** gives alcohol **148**, which, in the presence of $Sc(OTf)_3$, undergoes lactonisation *in situ* to form the spiro-lactone **149**. The reoxidant species PNO regenerates osmium (VI) to complete the catalytic cycle. It is thought that citric acid accelerates the rate of hydrolysis of complex **292** to alcohol **148** through neighboring group participation—in which the pendant carboxylic acid group of citric acid forms a hydrophilic region in the vicinity of the vacant coordination site of the osmium(VI) species.

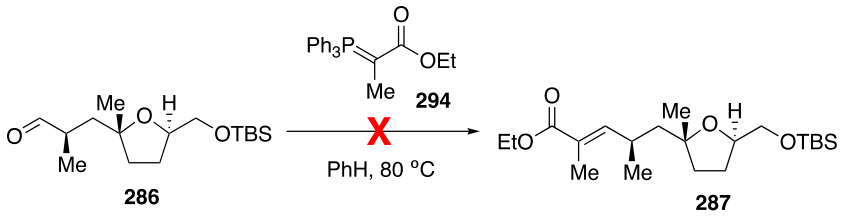
Our synthesis of aldehyde **289** started from Weinreb amide **285** (provided by Dr. Yifan Liu) from which four steps were required. The first was a reduction of Weinreb amide **285** by DIBAL to give aldehyde **286** which was isolated along with its C_{27}-epimer **293** as an 89:11

mixture (***Scheme 77***). It was found that temperature control and avoiding the use of column chromatography in the work-up procedure were essential in preventing epimerisation from occurring at the aldehyde α stereocentre. The two epimers were distinguishable in the ^{1}H NMR spectrum by their C_{28}-aldehylic resonances (δ_H 9.41 ppm for **286** and 9.61 ppm for C_{27}-*epi* **293**).



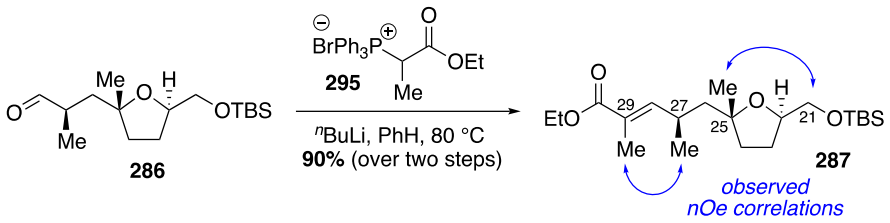
Scheme 77*. Synthesis of aldehyde* ***286***

Using the conditions taken from the synthetic route shown in ***Scheme 75***, the Wittig olefination between aldehyde **293** and (carbethoxyethylidene)triphenylphosphorane **294** gave only recovered starting material (***Scheme 78***). It was thought that the nucleophilicity of (carbethoxyethylidene)triphenylphosphorane **293** was too weak to induce a reaction.



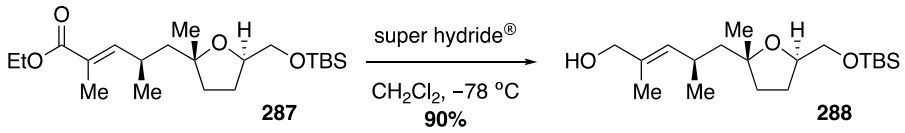
Scheme 78*. Attempted Wittig homologation of aldehyde* ***286***

Therefore, we decided to use (ethoxycarbonyl)ethyl)triphenylphosphonium bromide **295** and ^{n}BuLi to form what we assumed to be the more reactive ylide *in situ*. Under these conditions, ester **287** was isolated as a > 95:5 mixture of C_{27}:C_{27}-*epi* isomers in 90% yield over two steps (***Scheme 79***). The disappearance of a chemical shift at δ_H 9.41 ppm (1H, d) in the ^{1}H NMR spectrum, along with the appearance of the ethyl protons of the ester at δ_H 4.27 – 4.11 ppm (2H, m) and 1.28 ppm (3H, t), confirmed formation of the alkene, while key nOe correlations between the C_{29}-C*H*$_3$ and C_{27}-C*H*$_3$ protons evidenced the alkene's *trans* geometry. In addition, nOe correlations between the C_{25}-C*H*$_3$ and C_{21}*H*$_2$ provided evidence for the *cis* stereochemistry of the E-ring (Scheme 46).



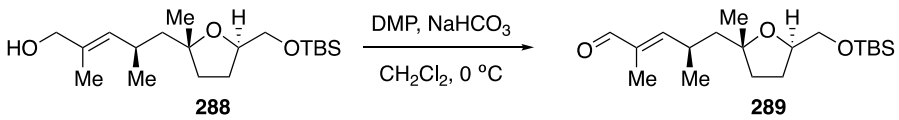
***Scheme 79**. Wittig homologation of aldehyde via forming ylide in-situ*

The next step was a super hydride reduction of ester **287** which gave alcohol **288** (> 95:5 C_{27}:C_{27}-*epi*) in 90% yield (***Scheme 80***). It was found that unless the starting material was thoroughly dried by azeotrope formation, the reaction would only result in recovered starting material. The presence of the alcohol was inferred from a broad signal at 3370 cm^{-1} in the I.R. spectrum.



Scheme 80**. Synthesis of alcohol **288

The final step required to access aldehyde **289** was an oxidation of alcohol **288**. It was essential to prevent epimerization at C_{27} from occurring in this reaction. Therefore, it was desirable to avoid the use of column chromatography; however, aldehyde **289** needed to be of high purity for the key Julia-Kocienski olefination. We thought that this could be best achieved using DMP as oxidant in the presence of $NaHCO_3$, since the workup procedure requires only a simple filtration. Thus, under these conditions, aldehyde **289** was obtained as a single epimer in >95% purity as determined from its ^1H NMR spectrum. The chemical shift of the aldehyde proton was evident at δ_H 9.38 ppm (1H, s).

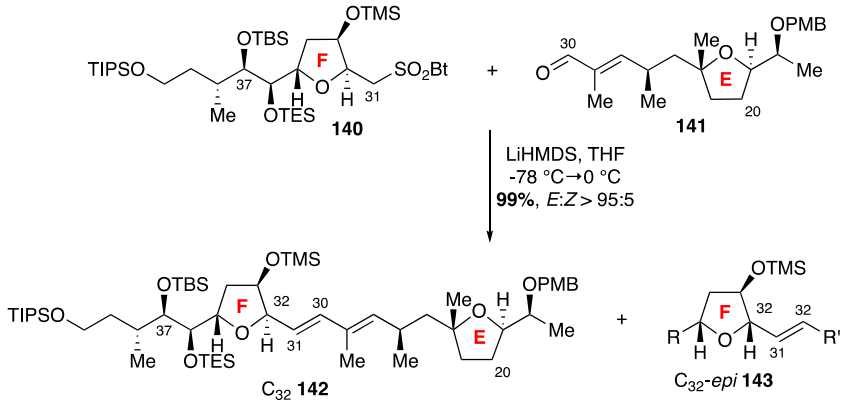


Scheme 81**. Synthesis of aldehyde **289

With aldehyde **289** and sulfone **275** in hand, the key Julia-Kocienski coupling of these fragments could now be attempted.

2.8 Julia-Kocienski Olefination of Aldehyde 289 and Sulfone 275

Evans' synthesis of pectenotoxin-4 utilized a Julia-Kocienski olefination as a key step to couple the F-ring with the carbon atoms of the G-ring (***Scheme 82***).[16] It was found that the counterion of the base had a significant effect on both the reaction yield and the rate of epimersation at C_{32}. The optimal base for the reaction was identified to be LiHMDS, which provided the desired coupling product **142** in quantitative yield with minimal C_{32} epimerisation. In contrast, KHMDS gave modest yields with the undesired C_{32}-epimer formed as the major product.



M	**142 : 143**	yield (%)
Li	**95:5**	**100**
Na	29:71	54

Scheme 82**. Evans' Julia-Kocienski olefination of sulfone **140** and aldehyde **141

The proposed rationale for this observation was based on the relative association abilities of the two cations, K^+ and Li^+. The lithium cation, more associative than the potassium cation, is thought to stabilize the sulfone anion **297** to the extent that addition to the aldehyde **298** is faster than β-elimination ($k_3 >> k_2$) (***Figure 28***). The potassium cation on the other hand, leads to rapid β-elimination, which results in the ring-opening of the F-ring and slow addition to the aldehyde ($k_3 >> k_2$). Upon warming, the 1,4-additon of the oxy-anion to the vinyl anion **296** favours the thermodynamically more stable *cis*-THF, which gives a 29:71 mixture of the desired alkene **142** and C_{32}-epimer **143**. Evans and co-workers also found that adding the base to a premixed solution of the sulfone and aldehyde at -78°C was crucial in minimizing

decomposition of the sulfone through β-elimination. When excess sulfone **142** was used, an identical 30:70 ratio, which mirrors the product distribution with KHMDS, of C_{32} epimers was obtained with either base thus further supporting Evans' hypothesis.

The silicon protecting groups present in Evan's substrates were stable to the conditions of the Julia-Kocienski olefination. This gave us confidence that the $C_{40}O$-$C_{37}O$ silicon tether and the $C_{36}O$-TES group of our substrate would be stable to these conditions too.

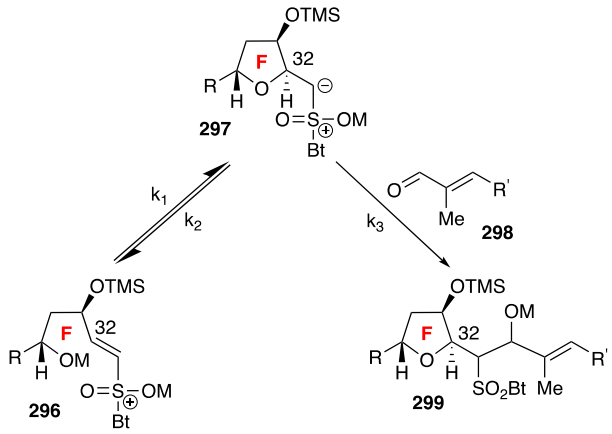
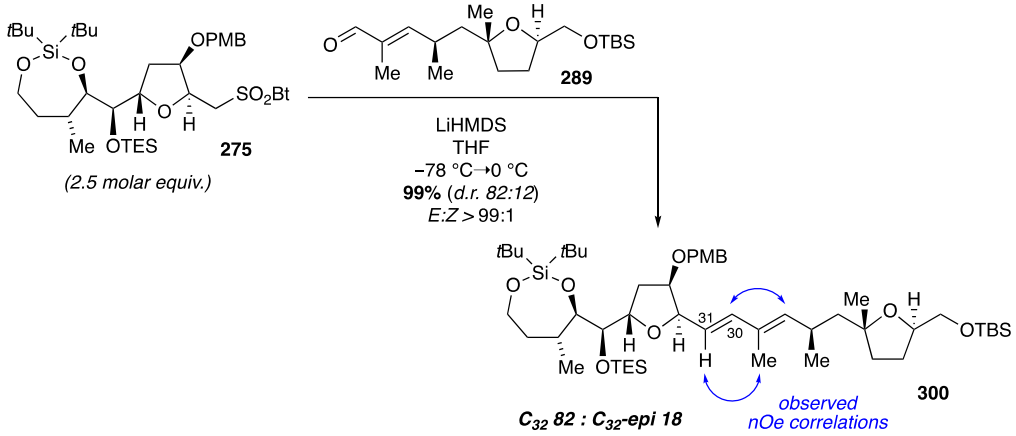


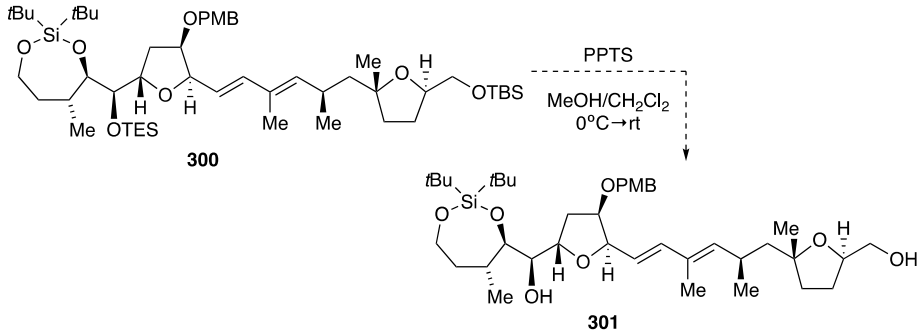
***Figure 28**. Proposed mechanism for C32 epimerisation*[16]

Using Evans' conditions, sulfone **275** was reacted with an excess of aldehyde **289** (2.5 molar equivalents) to give alkene **300** in quantitative yield (***Scheme 84***). The *trans*-nature of the newly formed olefin bond was confirmed from magnitude of the coupling constant (J = 15.7 Hz) across the C_{31}-C_{30} olefin bond and by key nOe correlations that are shown in ***Scheme 84***. The ^{1}H NMR spectrum of the product, however, contained a doublet of doublets (dd) at δ_H 5.77 ppm and one at δ_H 5.21 ppm in an 82:18 ratio. The ^{1}H NMR spectrum of Evans' product from the Julia-Kocienski olefination was reported to contain a dd at δ_H 5.66 ppm (1H), corresponding to the C_{32}-proton of the *trans*-THF.



Scheme 83**. Julia-Kocienski olefination of TES-ether **275** and aldehyde **289

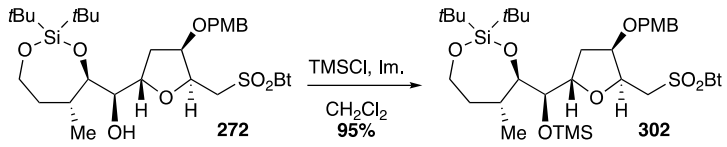
We assumed, therefore, that the dd at δ_H 5.77 ppm in our spectrum belonged to the C_{32}-proton of the desired product **300**, whereas that at δ_H 5.21 ppm corresponded to the same proton of the *cis* C_{32}-epimer. Integrating these signals allowed us to determine a desired product **300** to C_{32}-epimer ratio of 82:18. The formation of the undesired C_{32}-epimer was thought to occur *via* the mechanism of β-elimination of the sulfone and 1,4-additon to the resulting vinyl sulfone, as outlined in ***Figure 28***.



Scheme 84**. Double desilylation of Julia-Kocienski adduct **300

The next step in our synthesis was the deprotection of the secondary TES-ether group at C_{36}. Evans showed that the use of PPTS in dichloromethane could facilitate the removal of this group without affecting silyl ethers at C_{37} and C_{40}.[15] Using these conditions, however, the desired product could not be obtained. Instead, as suggested from the lack of TES and TBS signals in the ^{1}H NMR spectrum of the crude material, it appeared that the C_{36} TES-ether group could not be cleaved without simultaneously removing the primary TBS-ether at C_{21}.

This result prompted us to alter the alcohol protecting group at C_{36} from a TES-ether to a more labile TMS-ether. Thus, treating alcohol **272** with TMS-chloride and imidazole in dichloromethane gave the desired TMS-ether **302** in 95% yield (***Scheme 86***).



Scheme 85. *Protection of alcohol **272** as the TMS ether **302***

The appearance of a singlet at δ_H 0.01 ppm (9H) indicated that the desired product had been formed. Pleasingly, an X-ray crystal structure of silyl ether **302** could be obtained (***Figure 29***). From this data, a number of key structural issues can be proved with some confidence. Firstly, it can be concluded that the Mukaiyama oxidative cyclisation gave the desired the *trans* THF stereochemistry. Secondly, the diastereoselectivity of the Sharpless Asymmetric Dihydroxylation was correct, judging from the relative stereochemistry of C_{38}-CH_3, C_{37}-OSi and C_{36}-OSi. And finally, the correct regioselectivity in the protection of triol **154** with di-*tert*-butylsilyl ditriflate was obtained.

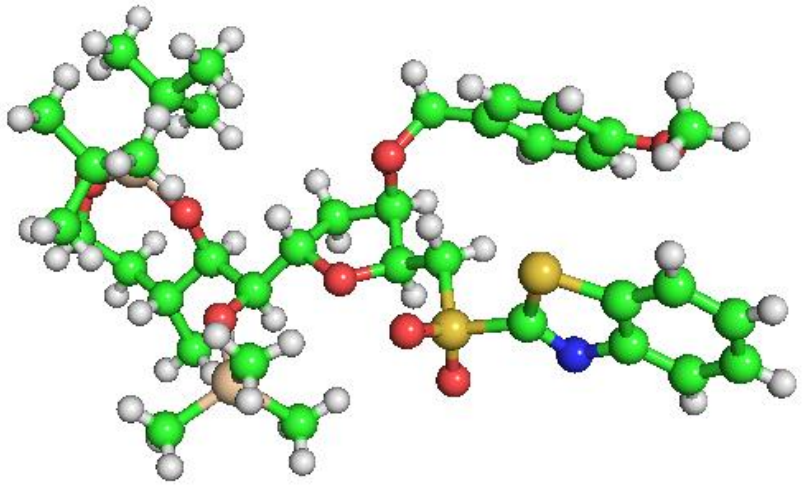
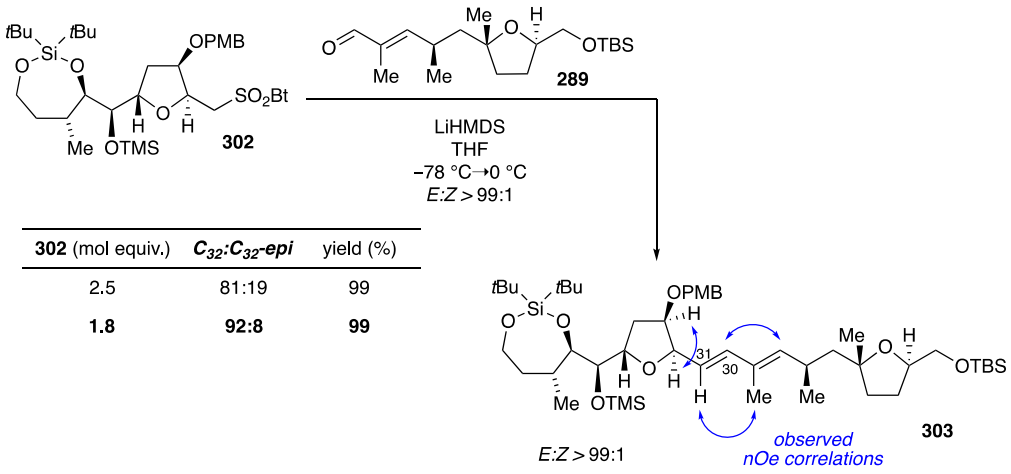


Figure 29. *Crystal structure of TMS-ether **302***

Our first attempt at the Julia-Kocienski olefination between TMS-ether **302** and aldehyde **289**, used analogous conditions to those for the coupling of TES-ether **300** and **289** (2.5 molar equivalents of the sulfone partner), and afforded the desired *trans* alkene **303** in quantitative yield with a C_{32}:C_{32}-*epi* ratio of 81:19 (***Scheme 86***). Both the *trans* nature of the

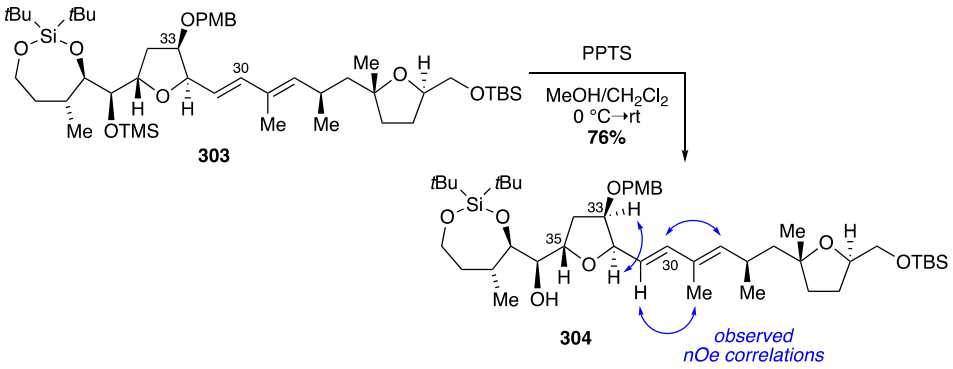
C_{30}–C_{31} double bond and the F-ring THF were confirmed by nOe experiments, the key correlations of which are shown in ***Scheme 86***. Furthermore, the magnitude of the coupling constant across the C_{30}–C_{31} double bond (J = 15.8 Hz) gives strong evidence for the bond's *trans* stereochemistry.

Although the yield and C_{32}:C_{32}-*epi* ratio were similar to those accomplished for TES-ether **300**, we wished to lower the number of molar equivalents of TMS-ether **302** used in this reaction, due the compound's valuable nature. Our second attempt at the Julia-Kocienski olefination used 1.8 molar equivalents of TMS-ether **302** alkene and afforded *trans* alkene **303** in quantitative yield and an improved C_{32}:C_{32}-*epi* ratio of 92:8. While the C_{32}:C_{32}-*epi* ratio improved with a lower number of molecular equivalents of sulfone **302**, we found that this ratio would vary from 78:22 – 92:8 for each reaction attempt. It was postulated that due to the scale that these reactions were performed on (the smallest scale was ~1 mg of aldehyde **289** and 6 mg of sulfone **302**), a consistent C_{32}:C_{32}-*epi* ratio could not be obtained. It should be noted that while quantitative yields were reported, these reactions, due to the small scale that they were performed on, are more prone to systematic error and product yields may be superficially elevated by minor impurities in the product.



Scheme 86*. Julia-Kocienski olefination of TMS ether **302** and aldehyde **289***

With silyl ether **303** in hand, the PPTS-mediated cleavage could be re-attempted. Under the same conditions as previously used, alcohol **304** was obtained in 76% yield with no observation of C_{21}-TBS-ether deprotection (***Scheme 88***).



Scheme 87**. Desilylation of Julia-Koecienski adduct **303

A byproduct **305**, believed to be the C_{32}-epimer of alcohol **304**, was also obtained from this reaction. Epimerisation was thought to occur in the Julia-Kocienski olefination, but now the two epimers could be separated by flash column chromatography. The stereochemistry of the F-ring THF and the C_{31}-C_{30} and C_{29}-C_{28} double bonds, in both alcohol **304** and epimer **305**, were confirmed by results of nOe experiments (***Figure 30***). The *trans* stereochemistry of the alcohol **304** F-ring was proven by a correlation between the $C_{32}H$ and $C_{33}H$ protons, and the absence of a correlation between $C_{35}H$ and $C_{32}H$. In the C_{32}-epimer **305**, however, a strong correlation was observed between the $C_{35}H$ and $C_{32}H$ protons, thus confirming the *cis* nature of the THF.

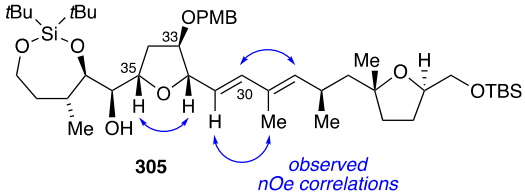
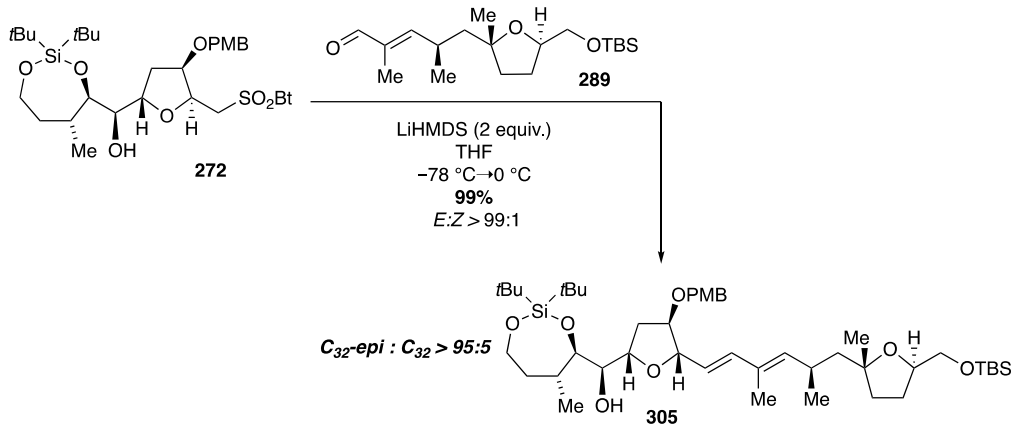


Figure 30**. C32 epimer **305

For both *cis* and *trans* compounds, key C_{30}H–C_{28}-H and $C_{29}(CH_3)$–C_{27}H nOe correlations verified the respective *E* and *Z* stereochemistries of the C_{31}-C_{30} and C_{29}-C_{28} olefin bonds. Furthermore, the appearance of the C_{31}-H dd at δ_H 5.79 ppm in the ^{1}H NMR of the desired product, and at δ_H 5.49 in that of the C_{32}-epimer, provides strong evidence for the existence of a *trans* C_{31}-C_{30} double bond in compound **300**, formed from TES-ether **275**.

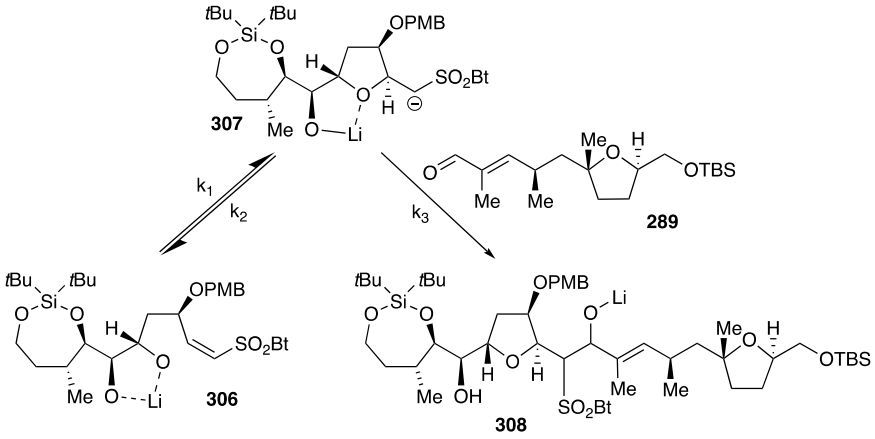
Although alcohol **304** could be formed in high yields from the cleavage of TMS-ether, we decided to perform the key Julia-Kocienski olefination using alcohol **272** instead of TMS-ether **302**. If successful, this reaction would shorten our synthetic route by two steps. Due to

the additional hydroxy group at C_{36} in alcohol **272**, it was thought that by using 2 molar equivalents of LiHMDS, the Julia-Kocienski coupling reaction of **272** and aldehyde **289** could successfully yield alcohol **304**.



Scheme 88**. Julia-Koecinski olefination of alcohol **272** and aldehyde **289

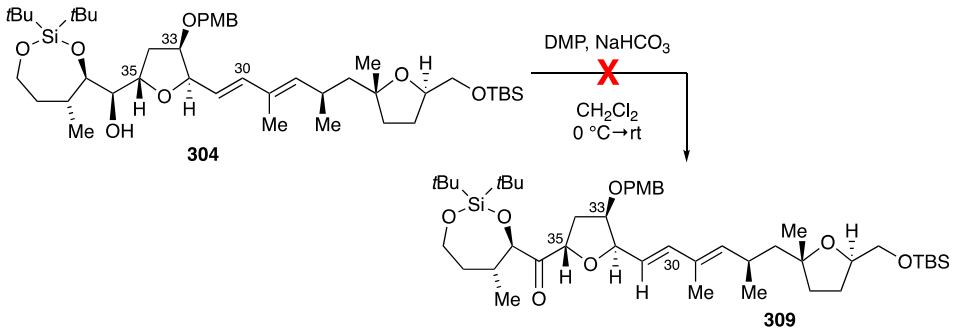
Interestingly, however, this reaction gave the C_{32}-epimer, *cis*-THF **305** as the major product (*cis* C_{32}-epimer: *trans* C_{32} > 95:5). LiHMDS was reported to minimize epimerization due to the greater association ability of Li^+ compared to K^+, however, this may be the reason for the observed selectivity in the case of alcohol **272** and aldehyde **305**. We postulated that a 5-membered chelate could form between the alcohol of the THF-ring and a C_{36}-oxy-anion, which may promote β-elimination over addition of the sulfone anion **307** to the aldehyde such that $k_3 >> k_2$ (***Scheme 90***). Upon subsequent 1,4-additon to the vinyl sulfone **306**, the thermodynamically more stable *cis*-THF could be formed in favour of the desired *trans*-isomer.



Scheme 89**. Proposed mechanism for formation of cis THF **305

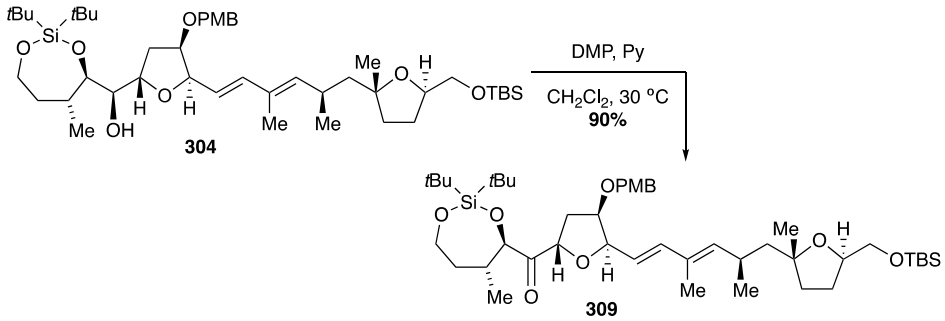
2.9 Completion of the EFG-Ring System Synthesis

The remaining steps in our synthesis of the EFG-ring system of pectenotoxin-4 were an oxidation of the C_{36}-alcohol, and a global deprotection with *in situ* hemiacetal formation as the final step. It was thought that for the oxidation reaction, conditions could be adopted from our synthesis of ketone **274,** which was produced in an excellent yield of 90% from alcohol **272**. Subjecting alcohol **304** to DMP and $NaHCO_3$ in dichloromethane, gave only retention of starting material (***Scheme 91***).



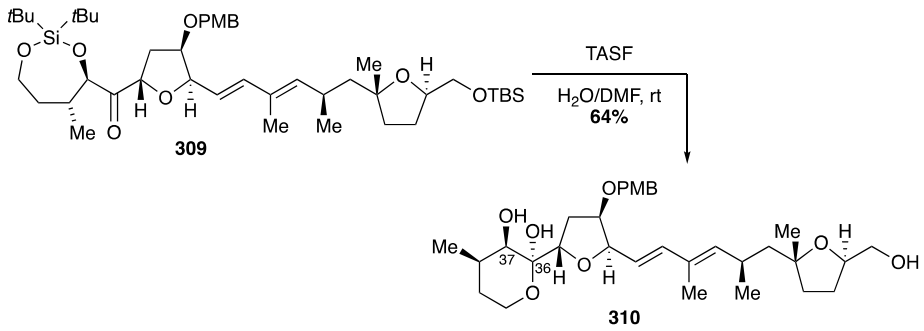
Scheme 90. *Failed DMP-mediated oxidation of alcohol* ***304***

Extended reaction times and the addition of extra molar equivalents of DMP (and $NaHCO_3$) gave only the slightest indication of product formation by TLC, but again only starting material was recovered. It was found that using pyridine instead of $NaHCO_3$, gratifyingly, gave the desired ketone **309** in excellent yields of 92% (***Scheme 92***). The formation of the ketone was confirmed by the downfield movement of the $C_{35}H$ signal (which overlaps with the OCH_2Ar, $C_{32}H$ signals) from δ_H 4.53 – 4.38 ppm (4H, m) in the ^1H NMR spectrum of alcohol **304** to δ_H 5.14 ppm (1H, dd) in that of ketone **309**. In addition, the I.R. spectrum of ketone **309** contained an absorption band at 1734 cm^{-1}, characteristic of a ketone carbonyl stretch.



Scheme 91. *Synthesis of ketone* ***307***

With ketone **307** in hand the final step in our synthesis could be attempted. Using TASF in DMF/H_2O ketone **309** was globally deprotected and cyclized in the same pot, to give the EFG-ring system **310** of pectenotoxin-4 in 64% yield (***Scheme 93***).



Scheme 92*. Synthesis of the EFG-ring system* ***310***

The formation of the C_{36} quaternary centre was evidenced from the appearance of a signal at δ_C 96.9 ppm in the ^{13}C NMR spectrum, and a singlet at δ_H 3.24 ppm (1H) in the ^1H NMR spectrum corresponding to the C_{36}-hydroxy group. A key nOe correlation was observed between $C_{37}H$ and $C_{38}H$ protons, providing evidence for the thermodynamically more stable configuration of the G-ring, in which the $C_{37}H$ and $C_{38}H$ protons have an equatorial–axial relationship, as found in the natural product and reported by Evans and Fujiwara (***Figure 31***). It was presumed that due to the anomeric effect and significant difference in steric bulk between the *exo*-cyclic substituents of C_{36}, the hydroxy group occupies an axial position with the C_{36}–C_{35} bond adopting the equatorial position. Furthermore, the magnitude of the coupling constant between the $C_{37}H$ and $C_{38}H$ protons was found to be unusually small: $C_{37}H$ appears at δ_H ($CDCl_3$) 3.25 ppm as a dd (J = 10.6, 2.2 Hz), with $C_{37}OH$ appearing as a doublet (J = 10.6 Hz) at δ_H ($CDCl_3$) 1.67 ppm, thus confirming that the J = 2.2 Hz value arises from the coupling of $C_{37}H$ and $C_{38}H$. The PTX molecules share common stereochemistry of the FG-ring, and thus our observation of a small $C_{37}H$–$C_{38}H$ coupling is consistent with what is reported in the literature: Fujiwara reports $C_{37}H$ in pectenotoxin-2b as a dd (J = 7.5, 2.2 Hz), δ_H (acetone-D_6) 3.31 ppm, and a dd (J = 9.1, 2.5 Hz), δ_H (acetone-D_6) 3.28 ppm, in PTX-2c.[29] Evans on the other hand, reports $C_{37}H$ as a singlet, δ_H (C_6D_6) 4.16 ppm, in PTX-8 and a doublet (J = 8.3 Hz), δ_H (C_5H_5N) 3.83 ppm.

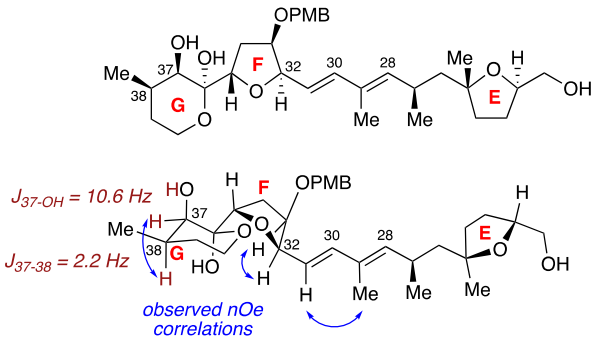


Figure 31. *Evidence for the stereochemistry of the EFG-ring system using nOe experiments*

2.10 An Alternative Route to the F-ring

In 2012, Roulland and co-workers reported the diastereoselective synthesis of *trans* 2,5-disubstituted 3-hydroxy-THFs *via* counterion-directed catalysis in the Tsuji-Trost reaction (***Figure 32***).[77] Using DFT calculations and chemical experiments they proposed a mechanism which involves the formation of π-allyl/Pd(II) intermediate. It is thought that noncovalent interactions between the carboxylate counterion and cationic π-allyl/Pd complex play a key role in the observed diastereoselectivity. Specifically, an additional noncovalent bond between the counterion and allyic hydrogen existing in transition state **314**, which cannot be formed in

transition state **317** due to geometric constraints. Transition state **317** thus lies higher in free energy ($\Delta G^{\neq}$ = 2.1 kcal mol^{-1}) resulting in the formation of *trans* THF **312** as the major product.

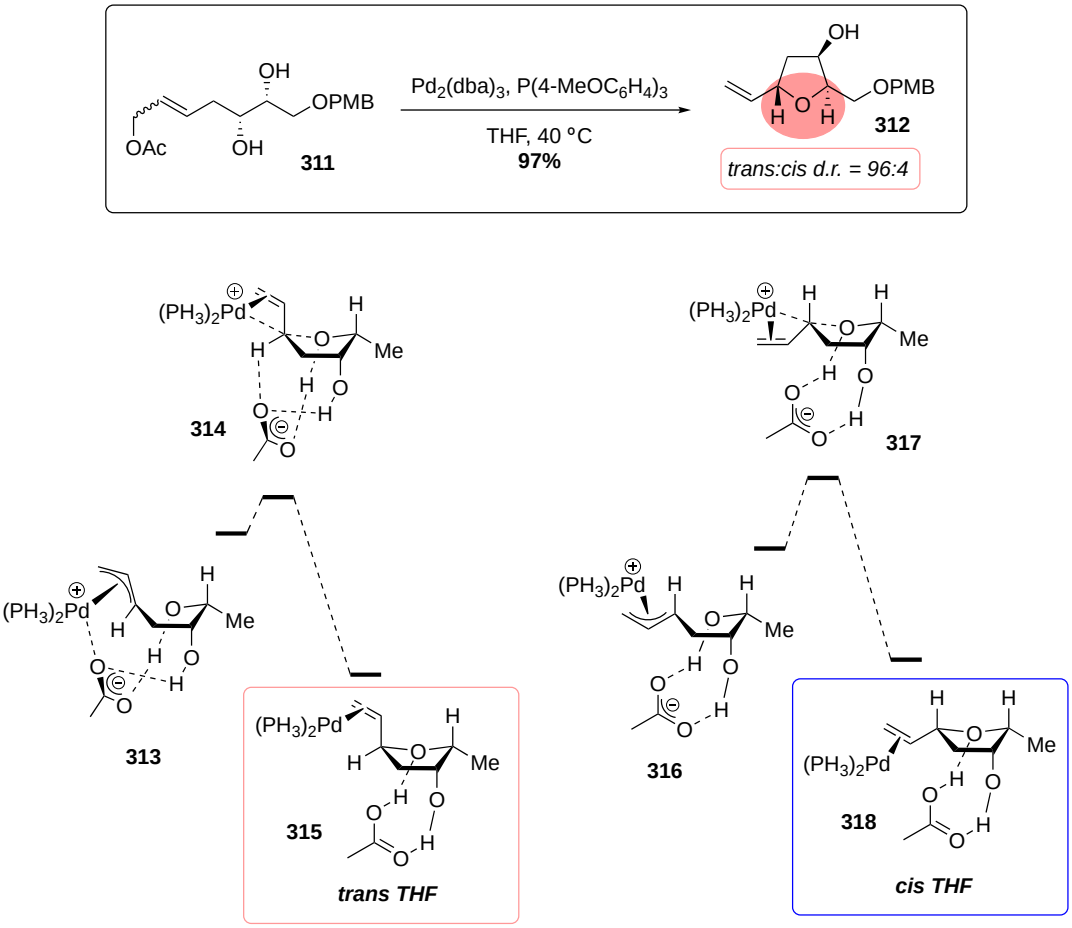
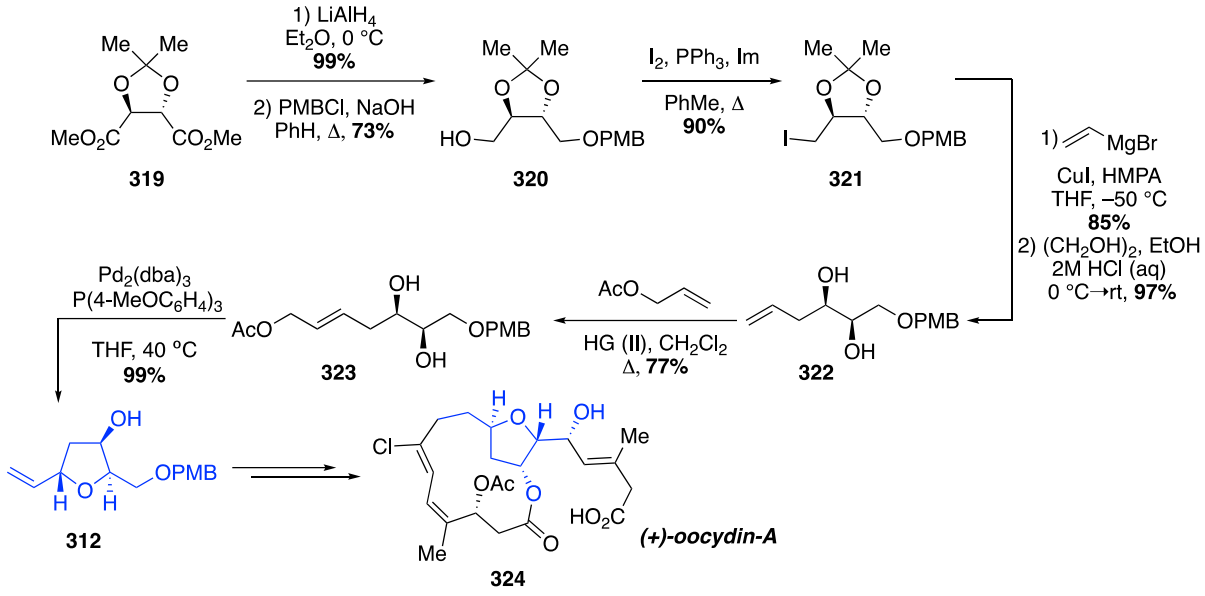


***Figure 32**. Roulland's use of the Tsuji-Trost reaction to access 2,5-disubstituted trans THFs*[77]

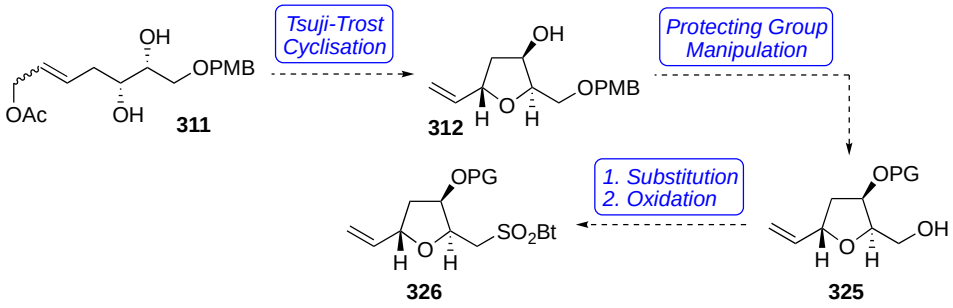
Roulland also discovered that *anti* 1,2-diols could be cyclised under the same reaction conditions to predominantly give *cis* THFs. For both *syn* and *anti* 1,2-diols, the vinyl group of the product is always installed *trans* to the β-hydroxy group, which does not cyclise, while the stereogenic γ-hydroxy group, which does cyclise, bears no effect on the observed stereoselectivity. Therefore, *syn* 1,2-diols react to give *trans* THFs whereas *anti* 1,2-diols react to give the *cis* isomers.

Roulland utilized this methodology to prepare *trans* THF **312**, an intermediate in his total synthesis of (+)-oocydin A (***Scheme 95***).[78]



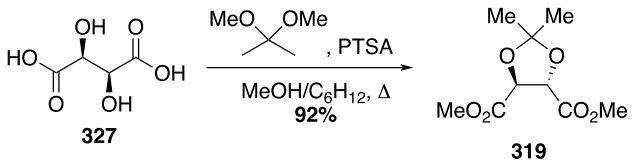
Scheme 93**. Roulland's total synthesis of (+)-oocydin-A **325

Earlier in this thesis it was shown that we had difficulty forming the substrate for the key Mukaiyama oxidative cyclisation, which we aimed to use to access the F-ring (***Scheme 38***). While we were investigating solutions to this problem, we deemed it prudent to replicate Roulland's synthesis of *trans* THF **312** in order to access the F-ring of pectenotoxin and advance our forward synthesis. If implemented successfully, Roulland's method would bring us to THF **312**, from which a protecting group interchange could render a free alcohol on C_{31} (***Scheme 84***). Two additional steps—a Mitsonubu reaction and subsequent oxidation—could then yield sulfone **326** of the Julia-Kocienski olefination.



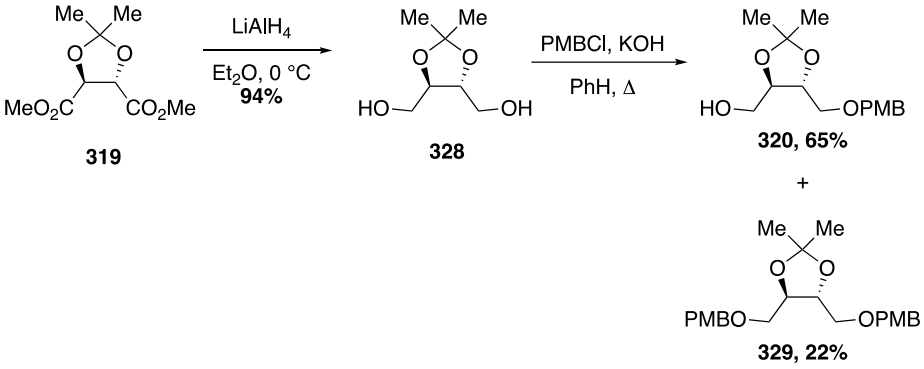
***Scheme 94**. Proposed application of Roulland's methodology to EFG-ring system synthesis*

The first step was the synthesis of diester **319** from D-(–)-tartaric acid **327**, which was accomplished under acidic conditions and in 88% yield (***Scheme 95***). The existence of the diester was inferred from the appearance of a methyl singlet at δ_H 1.49 ppm (6H) in the ^{1}H HMR spectrum of the product.



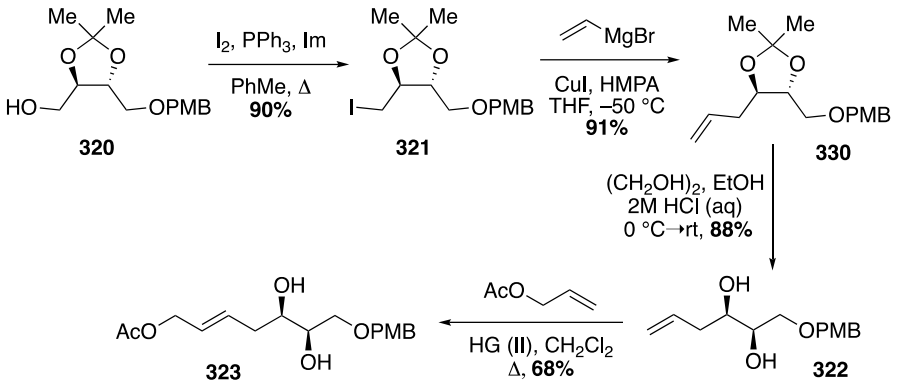
Scheme 95*. Synthesis of acetonide **319***

Diester **319** was then reduced with $LiAlH_4$ to diol **328** in 94% yield (***Scheme 96***). Treatment of diol **328** with PMB-Cl and anhydrous potassium hydroxide then gave the mono-protected product **320** in 65% yield. A byproduct from this reaction, identified from the magnitude of the integrals of the PMB-ether signals in the ^{1}H NMR spectrum as the bis-protected compound **329**, was also obtained.



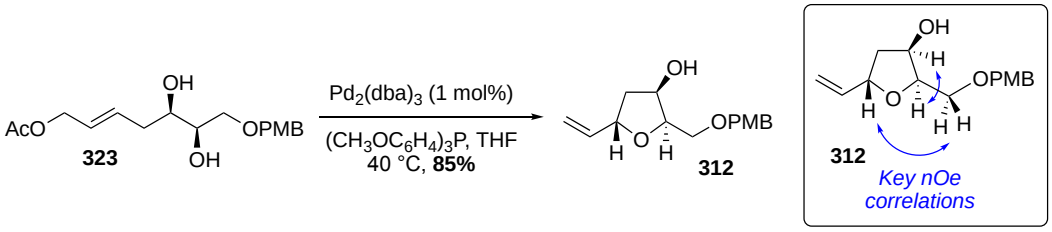
Scheme 96*. Synthesis of alcohol **328***

Iodination of the mono-protected product gave iodide **321** in excellent yields of 90% (***Scheme 97***). The lack of a broad absorption band in the region 3550 – 3200 cm^{-1} in the IR spectrum confirmed the formation of **321**. A subsequent alkylation with vinylmagnesium bromide gave alkene **330** in 91% yield. The existence of alkene **330** was evidenced from the appearance of terminal olefin peaks in the ^{1}H NMR spectrum. Hydrolysis of the acetonide motif of **330** then gave diol **322**, from which a cross metathesis with allyl acetate afforded acetate **323**—the substrate for the key Tsuji-Trost reaction. The acetate was identified from the lack of terminal olefin peaks and the acetate methyl singlet at δ_H 2.06 ppm (3H) in the ^{1}H NMR spectrum.



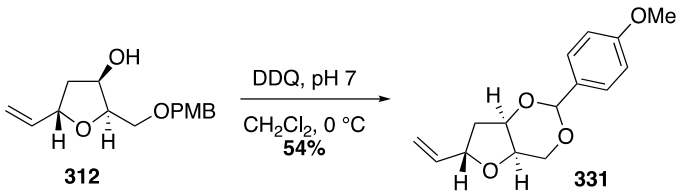
Scheme 97**. Synthesis of Tsuji-Trost precursor **323

Under the conditions reported by Roulland, acetate **323** was cyclized to give THF **312** in a high yield of 85% and a 96:4 mixture of *trans*:*cis* THF isomers (***Scheme 98***). The lack of a carbonyl peak in the ^{13}C NMR, along with the appearance of terminal olefin peaks in the δ_H 5.27 – 4.63 ppm region of the ^{1}H NMR, confirmed the formaton of the THF. The *trans* stereochemistry of the THF was elucidated by nOe experiments, the key correlations from which are shown in ***Scheme 98***. Importantly, no correlation was observed between the C_{32} and C_{35} protons, while strong correlations were observed between the C_{35} and the C_{31} protons. The diastereoselectivity of this reaction was determined from the ^{1}H NMR spectrum by comparing the integrals of $C_{36}H$ chemical shifts for both isomers. It should also be noted that the spectroscopic data for all of the compounds previously synthesised by Roulland, presented here, matched those of Roulland.[78]



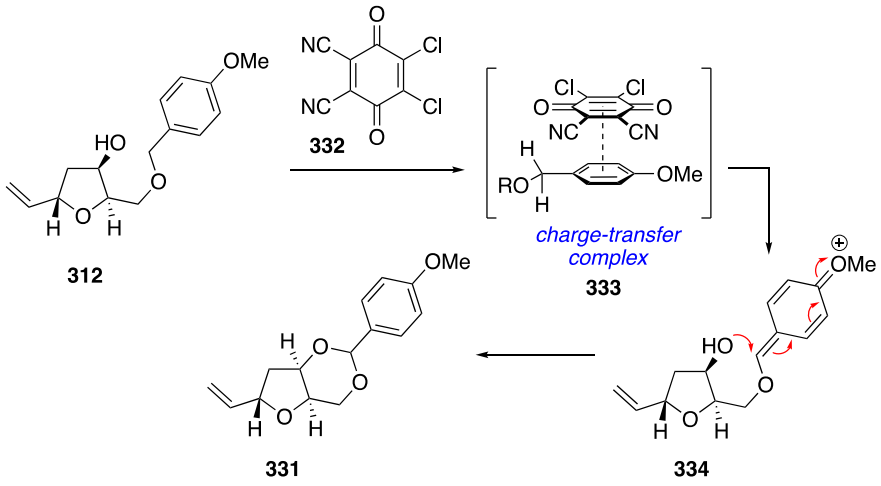
Scheme 98**. Tsuji-Trost cyclisation to give trans THF **312

In order to gain further evidence that cyclisation occurred to give the desired *trans* stereochemistry in the product, THF **312** was treated with DDQ and water to form THF **200**, which we had previously synthesized *via* the Mukiayama oxidative cyclisation. If the spectroscopic data of the independently formed THFs matched, then we could conclude that the Tsuji-Trost reaction gave the desired *trans* stereochemistry in the product.



Scheme 99**. Unexpected formation of acetal **331

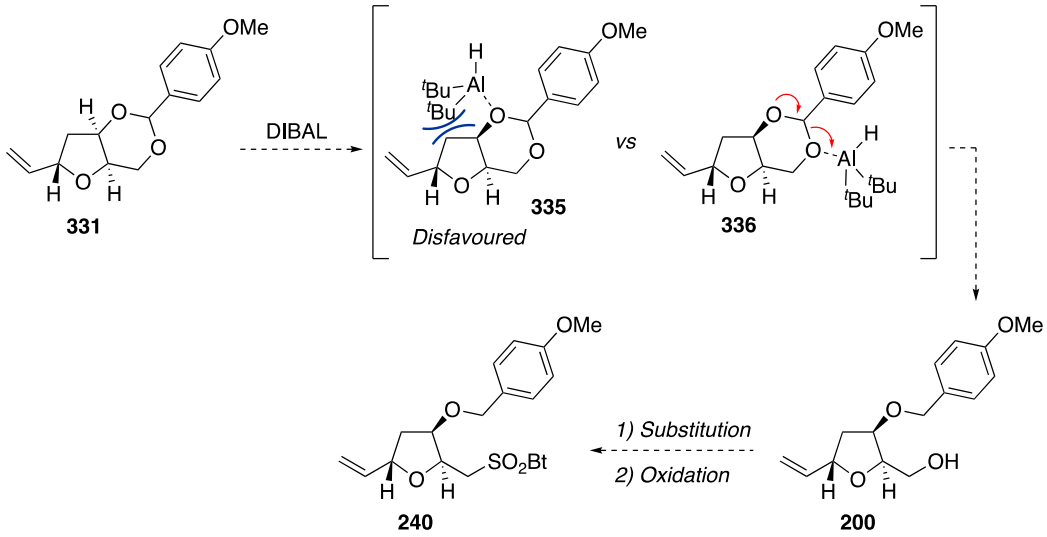
Interestingly, however, acetal **331** was obtained from the attempted cleavage of the PMB-ether (***Scheme 99***). The formation of **331** was evidenced from the appearance of a singlet at δ_H 5.42 ppm (1H) in the ^{1}H NMR spectrum. Oikawa and co-workers had previously reported similar results under analogous conditions.[79] We postulated that under the oxidative conditions used to cleave the PMB ether, an intramolecular attack of the C_{33}-hydroxy group onto the cationic intermediate **334** proceeded faster than the intermolecular attack of a water molecule (***Scheme 100***).



Scheme 100**. Proposed mechanism for the formation of acetal **331

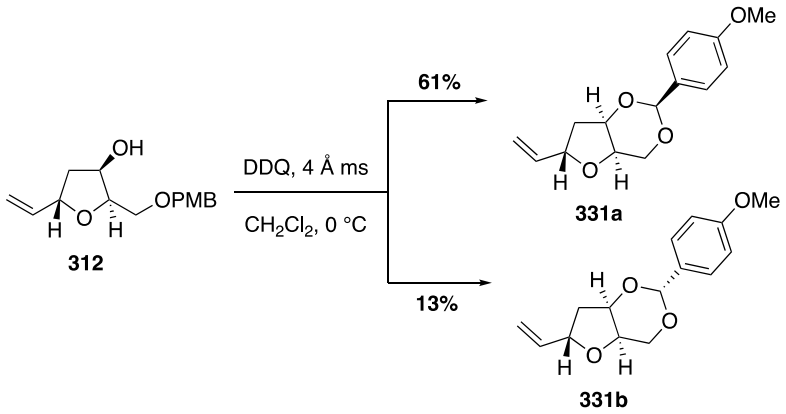
Although acetal **331** was not the desired product of this reaction, we believed that it could be applied effectively to our synthesis of the EFG-ring system. The key cross-metathesis reaction between the F-ring hydroxy-alkene **232** was thought to require protection of the C_{33}-alcohol, while the formation of the C_{31}-sulfone, which would be reacted in the key Julia-Kocienski coupling, required a protecting group shift from the C_{31}-alcohol to the C_{33}-alcohol. Both of these objectives could be achieved utilizing acetal **331**: the first by formation of acetal **331**, and the second by subsequent reductive cleavage of acetal **331**. It has been shown that in the reaction of a benzylidene acetals with DIBAL, the aluminium species coordinates to the

less sterically hindered oxygen of the acetal, promoting ring opening in a direction which ultimately renders the PMB group on the more sterically hindered oxygen of the acetal.[80-81] This would leave the C_{31}-alcohol free, which could then react to give the desired sulfone **240** *via* a two-step procedure (***Scheme 101***).



Scheme 101. *Proposed route for formation of sulfone **240***

Before subjecting acetal **331** to conditions of the forward synthesis, however, we wished to improve the yield of the DDQ oxidation from which it is formed. We envisaged that by using 4 Å molecular sieves, potential competing pathways involving the intermolecular attack of water could be minimized. Under these conditions, acetal **331** was obtained as the separable epimers **331a** and **331b** (***Scheme 102***). The major epimer **331a** was obtained in 61% yield while the minor epimer **331b** was formed in 12% yield.



Scheme 102. *DDQ oxidation of PMB ether **312***

Key correlations from nOe experiments showed that the exocyclic phenyl group and F-ring lie *trans* to each other in major isomer **331a** and *cis* in the minor isomer **331b** (***Figure 33***).

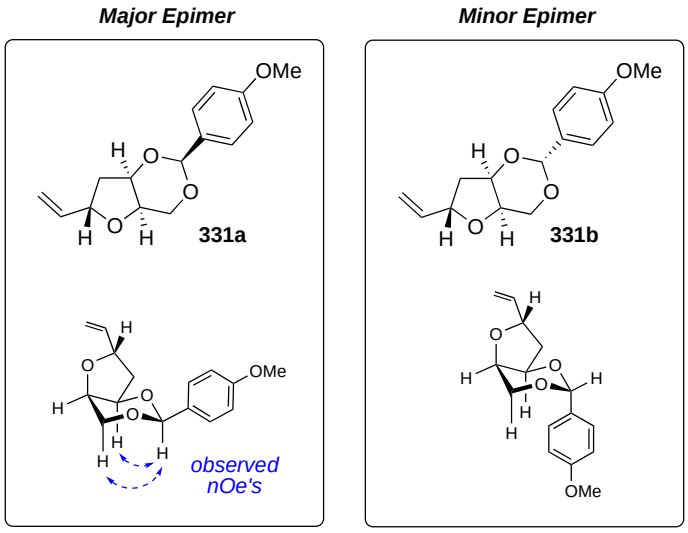
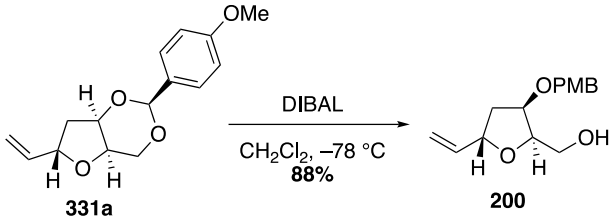


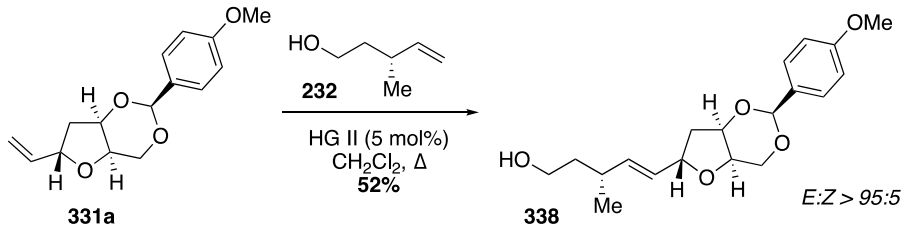
Figure 33**. The structures of epimers **331a** and **331b

Before carrying out the cross-metathesis reaction of alcohol **232** and acetal **331a**, the DIBAL mediated reduction of acetal **331a** was tested. Treating acetal **331a** with DIBAL in CH_2Cl_2 afforded alcohol **200** in 88% yield (***Scheme 103***). The appearance of the C_{31} protons as a multiplet at δ_H 3.91 – 3.76 ppm (2H) in the ^{1}H NMR spectrum, compared to a doublet at δ_H 3.77 ppm (2H) in the spectrum of secondary alcohol **200**, confirmed the formation of the primary alcohol. In addition, the ^{1}H and ^{13}C NMR data, and α_D value, for **200** matched those which were obtained *via* the oxidative cyclisation pathway.



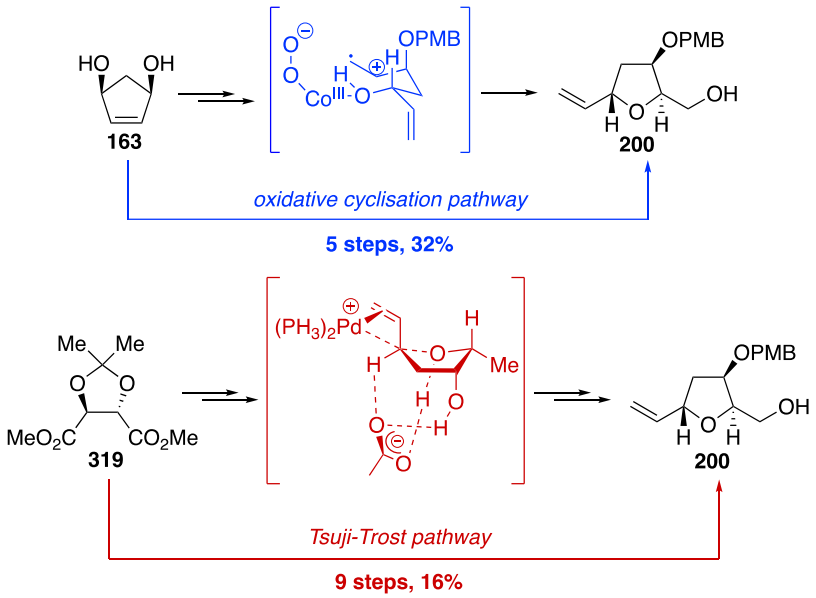
Scheme 103**. Regioselective Reduction of acetal **331a

With a suitable set of conditions for the reduction of the C_{32}–C_{33} acetal in hand, the cross metathesis of acetal **331a** and alcohol **232** was attempted next. In the presence of the Hoveyda-Grubbs 2nd generation catalyst, acetal **331a** and alcohol **232** reacted to give alkene **338** in 52% yield.



Scheme 104**. Cross-metathesis between alcohol **232** and acetal **331a

At this point in our studies, the oxidative cyclisation pathway to THF **200** was proving successful and more efficient than that which involved Roulland's methodology and the formation of acetal **331**. THF **200** was synthesized in 5 linear steps and 32% overall yield from diol **163** *via* the oxidative cyclisation pathway, compared to 9 linear steps and 16% overall yield from diester **319** *via* Tsuji-Trost pathway (***Scheme 105***). Therefore, our forward synthesis continued using THF **200** which we synthesized *via* the oxidative cyclisation pathway, and acetal **331** was no longer used in our synthesis.

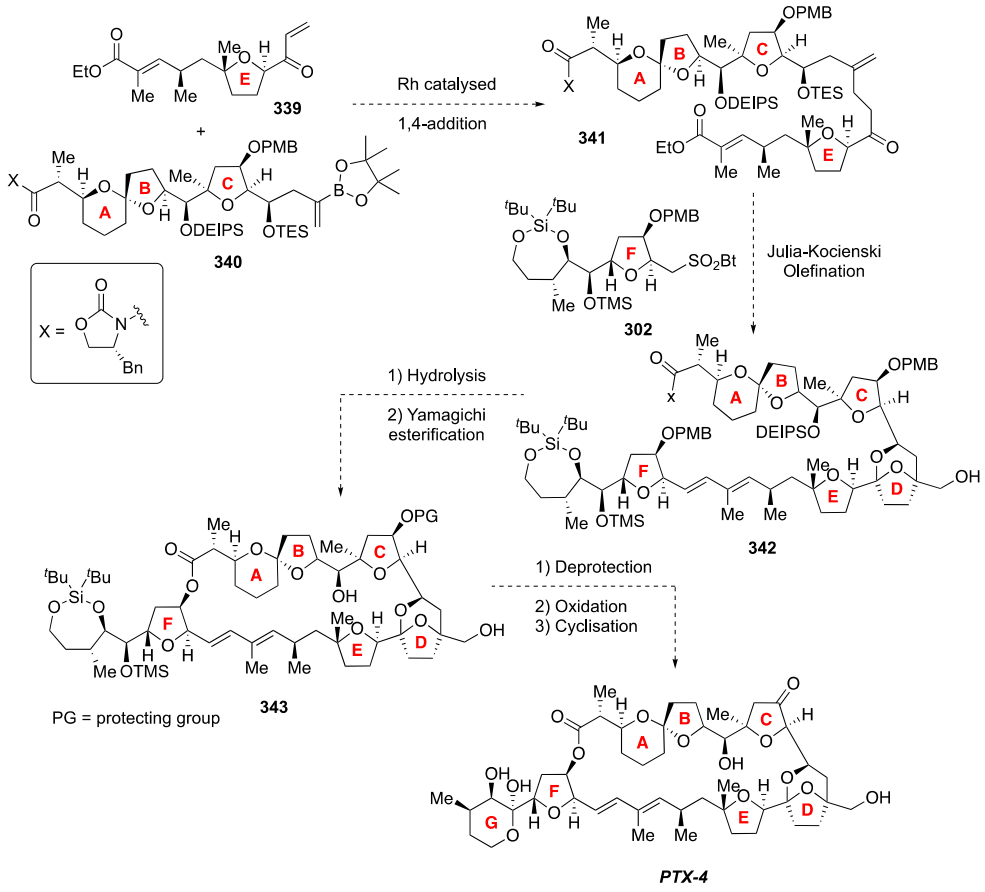


Scheme 105**. A comparison between the two routes used to access THF **200

2.11 Conclusion and Future Work

In summary, the EFG-ring system of pectenotoxin-4 was successfully synthesised with control of *trans* selectivity in the formation of the THF F-ring formation, and a key Julia-Kocienski coupling of the FG- and E-ring fragments. A selective 7-membered ring formation facilitated formation of the G-ring and the completion of the EFG-ring system synthesis.

With a successful synthetic route to the EFG-ring system in place, the final ring of pectenotoxin-4 left to be synthesised is the bicyclic D-ring. Work is currently underway within the Donohoe on a D-ring synthesis which aims to ultilise a key rhodium catalysed conjugate addition of a boron derived nucleophile to an α,β-unsaturated ketone (***Scheme 106***) to enable D-ring formation and union of the ABC- and E-ring fragments.



Scheme 106. *Proposed D-ring formation and end-game strategy*

A subsequent coupling to the FG-fragment, under modified Julia-Kocienski conditions, could render the open chain macrolide of pectenotoxin-4. Finally, a Yamaguchi macrolactonisation, followed by global deprotection and *in situ* lactol formation could complete the synthesis of the pectenotoxin-4.

Chapter 3

Experimental Information

General Experimental Techniques

^{1}H, ^{13}C and ^{19}F NMR were recorded on Bruker Advance Spectrometers—DPX200 (^{1}H 200 MHz, ^{13}C 50 MHz), AVB400 (^{1}H 400 MHz, ^{13}C 101 MHz), AVF400 (^{1}H 400 MHz, ^{13}C 101 MHz), AVB500 (^{1}H 500 MHz, ^{13}C 126 MHz) and AVC500 (^{1}H 500 MHz, ^{13}C 126 MHz) — at room temperature, in $CDCl_3$ or C_6D_6, and referenced to residual solvent peaks. Chemical shifts are quoted in ppm and signal splittings are recorded as singlet (s), doublet (d), triplet (t), quatet (q), septet (spt) and multiplet (m). Coupling constants, *J*, are measured in Hz and quoted to the nearest 0.1 Hz. Assignments were based on DEPT, COSY, HSQC, HMBC, NOESY and TOCSY experiments.

Infrared spectra were recorded as thin films of neat samples between NaCl plates on a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima are quoted in wavenumbers (cm^{-1}).

Accurate mass spectra (HRMS) were recorded on a Bruker Micro ToF spectrometer under conditions of electrospray ionisation (ESI) unless otherwise stated. Calibration was performed *via* a lock-mass of tetraoctyl ammonium bromide in the positive ion mode and sodium dodecyl sulfate in the negative ion mode. Values are reported as a ratio of mass to charge in Daltons and to four decimal places.

Melting points were determined using a Leica VMTG heated-stage apparatus and are uncorrected.

Specific optical rotations were measured on a Perkin Elmer 241 polarimeter at the sodium D line (589.3) in CH_2Cl_2, MeOH, or $CHCl_3$. Optical rotations are quoted measured units of 10^{-1} deg cm^2 g^{-1}. Solutions concentrations are quoted in units of 10^{-2} g mL^{-1}.

Flash column chromatography was performed using silica gel 60 (0.033-0.070 mm, BDH) using head pressure by means of head bellows, employing the method the method of Still *et al.* TLC analyses were performed on Merck Kiesegel 60 F254 0.25 mm precoated aluminium-backed plates. Product spots were visualised under UV light (λ_{max}=254nm) and/or by staining with a potassium permanganate or vanillin solution.

Preparative thin layer chromatography was performed on silica gel (20 x 20 cm, 500 microns, Z51303-2, UNIPLATE^{TM}) Spots were visualised under UV light (λ_{max}=254nm).

Reagents obtained from Acros, Alpha Aesar, Fluorochem, Sigma Aldrich and TCI fine chemicals suppliers were used directly as supplied unless otherwise stated.

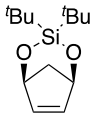
Anhydrous reactions were carried out under an inert atmosphere of argon. Flasks were dried in a flame then cooled under a stream of nitrogen or argon.

Toluene, dichloromethane, diethyl ether, tetrahydrofuran, methanol, pentane and benzene were dried by filtration through two activated alumina, purification columns. Brine refers to a saturated aqueous solution of sodium chloride.

All compounds which relate to PTX-4 are numbered according to their position in the natural product. Compounds are otherwise numbered according to a ***Scheme*** and ***Figure*** which may differ from IUPAC recommendations.

Experimental Data

(1*R*,5*S*)-3,3-Di-*tert*-butyl-2,4-dioxa-3-silabicyclo[3.2.1]oct-6-ene, 164



164

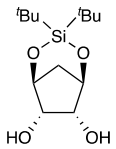
A solution of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.93 mL, 2.9 mmol) in CH_2Cl_2 (5 mL) was added dropwise, over a period of 15 minutes, to a solution of *cis*-4-cyclopentene-1,3-diol **163** (260 mg, 2.60 mmol) and 2,6–lutidine (0.91 mL, 7.8 mmol) in CH_2Cl_2 (26 mL) at 0 °C. After stirring for 20 minutes at room temperature the reaction was concentrated *in vacuo.* Flash column chromatography (1:4 CH_2Cl_2/pentane) yielded the title compound **164** as a colourless oil (479 mg, 77%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.48 – 6.44 (2H, m, C*H*=C*H*), 4.83 – 4.76 (2H, m, 2 x C*H*OSi), 2.53 – 2.45 (1H, m, CH_AH$_B$), 1.80 (1H, dt, *J* = 12.4, 3.2 Hz, CH$_A$*H*$_B$), 1.03 (9H, s, SiC(C*H*$_3$)$_3$), 0.96 (9H, s, SiC(C*H*$_3$)$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 140.2 (*C*=*C*), 76.3 (*C*HOSi), 44.7 (*C*H$_2$), 28.9 (SiC(*C*H$_3$)$_3$), 28.1 (SiC(*C*H$_3$)$_3$), 21.4 (Si*C*(CH$_3$)$_3$), 20.9 (Si*C*(CH$_3$)$_3$).

The spectral data were consistent with those in the literature.[43]

(1*R*,5*S*,6*S*,7*R*)-3,3-Di-*tert*-butyl-2,4-dioxa-3-silabicyclo[3.2.1]octane-6,7-diol, 165



165

A solution of potassium osmate dihydrate (38.3 mg, 0.100 mmol) in H_2O (1 mL) was added to a solution of alkene **164** (500 mg, 2.08 mmol) and *N*-methylmorpholine *N*-oxide (292 mg, 2.50 mmol) in a 10:9:1 mixture of THF (10.0 mL), ^{t}BuOH (9.00 mL) and H_2O (1.00 mL) at room temperature. The reaction was left to stir at room temperature for 16 h before being diluted with H_2O (10 mL) then quenched with sodium sulfite (500 mg). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane) yielded title compound **165** as a single diastereomer and white solid (466 mg, 82%).

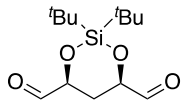
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.50 – 4.43 (2H, m, 2 x C*H*OH), 4.32 – 4.26 (2H, dd, *J* = 3.2, 0.9 Hz, 2 x C*H*OSi), 2.88 (2H, s, 2 x O*H*), 2.34 – 2.25 (1H, m, CH_AH$_B$), 1.83 (1H, dt, *J* = 14.3, 3.2 Hz, CH$_A$$H_B$), 1.04 (9H, s, SiC(C$H_3$)$_3$), 1.00 (9H, s, SiC(C$H_3$)$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 80.2 (*C*HOH), 75.7 (*C*HOSi), 34.9 (*C*H$_2$), 28.5 (SiC(*C*H$_3$)$_3$), 27.8 (SiC(*C*H$_3$)$_3$), 20.9 (Si*C*(CH$_3$)$_3$), 20.7 (Si*C*(CH$_3$)$_3$).

m.p. 90 – 94°C.

The spectral data were consistent with those in the literature.[43]

(4*R*,6*S*)-2,2-Di-*tert*-butyl-1,3,2-dioxasilinane-4,6-dicarbaldehyde, 166



166

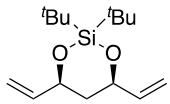
Sodium periodate (902 mg, 11.1 mmol) was added to a mixture of diol **165** and H_2O (0.32 mL) in CH_2Cl_2 (15 mL) at room temperature. The reaction was stirred for 2 h before a second portion of sodium periodate (902 mg, 11.1 mmol) was added at room temperature. After stirring for a further 2 h, the reaction was filtered, diluted with PhMe (10 mL) and concentrated *in vacuo*. The title compound **166** was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.66 (2H, d, *J* = 0.8 Hz, 2 x C*H*O), 4.49 (2H, ddd, *J* = 11.9, 2.7, 0.9 Hz, 2 x *C*HOSi), 2.18 (1H, dt, *J* = 14.2, 2.7 Hz, CH_AH_B), 1.64 (1H, dd, *J* = 14.2, 11.9 Hz, CH_AH_B), 1.08 (9H, s, SiC(CH_3)$_3$), 1.05 (9H, s, SiC(CH_3)$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 201.8 (*C*HO), 76.7 (*C*HOSi), 30.7 (*C*H_2), 27.0 (SiC(*C*H_3)$_3$), 26.7 (SiC(*C*H_3)$_3$), 22.6 (Si*C*(CH$_3$)$_3$), 19.7 (Si*C*(CH$_3$)$_3$).

The spectral data were consistent with those in the literature.[43]

(4*R*,6*S*)-2,2-Di-*tert*-butyl-4,6-divinyl-1,3,2-dioxasilinane, 167



167

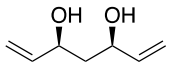
*n*Butyllithium (2.5 M in hexanes, 5.57 mL, 13.9 mmol) was added dropwise to a solution of triphenylphosphonium bromide (5.19 g, 14.6 mmol) in THF (34 mL) at 0 °C. After 15 minutes, a solution of dialdehyde **166** (900 mg, 3.31 mmol) in THF (6 mL) was added dropwise at 0 °C and the reaction was left to stir at room temperature. After 16 h the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (1:19 CH_2Cl_2/pentane) yielded the title compound **167** as a colourless oil (543 mg, 62%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.84 (2H, ddd, J = 17.0, 10.4, 4.6 Hz, 2 x C*H*=CH_2), 5.32 (2H, dt, J = 17.1, 1.8 Hz, 2 x CH=C$H_A$$H_B$), 5.07 (2H, dt, J = 10.5, 1.7 Hz, 2 x CH=C$H_A$$H_B$), 4.66 – 4.56 (2H, m, 2 x C*H*OSi), 1.75 (1H, dt, J = 14.2, 2.3 Hz, C$H_A$$H_B$), 1.52 (1H, dt, J = 14.1, 11.5 Hz, C$H_A$$H_B$), 1.05 (9H, s, SiC(C$H_3$)$_3$), 1.02 (9H, s, SiC(C$H_3$)$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 140.7 (CH=*C*H_2), 113.4 (*C*H=CH_2), 74.1 (*C*HOSi), 42.3 (*C*H_2), 27.6 (SiC(*C*H_3)$_3$), 27.4 (SiC(*C*H_3)$_3$), 22.9 (Si*C*(CH$_3$)$_3$), 20.1 (Si*C*(CH$_3$)$_3$).

The spectral data were consistent with those in the literature.[43]

(3*R*,5*S*)-Hepta-1,6-diene-3,5-diol, 158



158

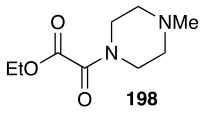
Tetrabutylammonium fluoride solution (1.0 M in THF, 4.16 mL, 4.16 mmol) was added to a solution of compound **167** (280 mg, 1.04 mmol) in THF (1 mL) at room temperature and the reaction was heated to reflux for 16 h. The reaction was cooled to room temperature and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:1 EtOAc/pentane) yielded the title compound **158** as a colourless oil (109 mg, 81%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.89 (2H, ddd, *J* = 16.8, 10.4, 6.0 Hz, 2 x C*H*=CH_2), 5.27 (2H, dt, *J* = 17.3, 1.5 Hz, 2 x CH=C*H*$_A$H$_B$), 5.12 (2H, dt, *J* = 10.4, 1.4 Hz, 2 x CH=CH$_A$*H*$_B$), 4.46 – 4.35 (2H, m, 2 x C*H*OH), 2.87 (2H, s, 2 x O*H*), 1.78 – 1.63 (2H, m, C*H*$_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 140.6 (CH=*C*H_2), 114.8 (*C*H=CH_2), 73.3 (*C*HOH), 43.1 (*C*H_2).

The spectral data were consistent with those in the literature.[43]

Ethyl 2-(4-methylpiperazin-1-yl)-2-oxoacetate, 198



198

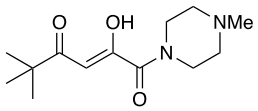
To a solution of *N*-methylpiperazine **197** (1.10 mL, 9.92 mmol) and triethylamine (1.40 ml, 0.726 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added ethyl oxalyl chloride **196** (1.12 mL, 1.22 mmol). The reaction was allowed to warm to room temperature then stirred for 16 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The title compound **198** was obtained as a yellow oil (2.08 g, 99%) and used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.28 (2H, q, *J* = 7.1 Hz, CH_3CH_2), 3.61 (2H, t, *J* = 5.0 Hz, 2 x NCH_AH_B), 3.40 (2H, m, 2 x NCH_AH_B), 2.44 – 2.36 (4H, m, 2 x NCH_2), 2.28 (3H, s, NCH_3), 1.32 (3H, t, *J* = 7.2 Hz, CH_3CH_2).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 162.7 (*C*=O), 160.1 (*C*=O), 62.2 (CH_3CH_2), 54.8 (NCH_2), 54.8 (NCH_2), 46.0 (NCH_2), 46.0 (NCH_3), 41.2 (NCH_2), 14.0 (CH_3CH_2).

The spectral data were consistent with those in the literature.[55]

(*Z*)-2-Hydroxy-5,5-dimethyl-1-(4-methylpiperazin-1-yl)hex-2-ene-1,4-dione, 192



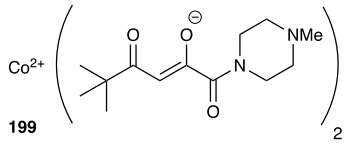
192

To a solution of sublimation-grade potassium *tert*-butoxide (561mg, 5.00 mmol) in THF (12 mL) was added to a solution of compound **198** (500 mg, 2.50 mmol) and pinacolone (0.31 mL, 2.50 mmol) in THF (3.0 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature then stirred for 16 h. Freshly prepared acetic acid (1.0 M in CH_2Cl_2, 5.0 mL) was added and the mixture stirred for 30 minutes before being filtered through Celite® and concentrated *in vacuo* to afford the title compound **192** as an orange syrup (443 mg, 70%). The product was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) (1:9.8 mixture of keto:enol tautomers) (*denotes minor keto tautomer peak): 5.98 (1H, s, C*H*=C(OH)), 4.04* (2H, s, C*H*$_2$C=O) 3.71 – 3.56 (4H, m, 2 x NC*H*$_2$), 2.49 – 2.37 (4H, m, 2 x C*H*$_2$N), 2.32 (3H, s, NC*H*$_3$), 1.20 (9H, s, C(CH$_3$)$_3$), 1.17 (s, 2H).

The spectral data were consistent with those in the literature.[55]

Co(nmp)$_2$, 199



199

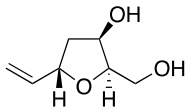
To a solution of nmp **192** (443 mg, 1.72 mmol) in benzene (8 mL) was added cobalt(II) ethylhexanoate (65 wt% in mineral spirits, 0.44 mL, 0.88 mmol) at room temperature. After stirring for 10 minutes, water (50 μL, 3.8 mmol) was added and the reaction mixture was stirred for 16 h. Hexane (35 mL) was then added and the solids were separated by centrifugation. The solvent was decanted and the catalyst was triturated with hexane. The remaining solvent was removed *in vacuo* to afford the Co(nmp)$_2$ catalyst **199** as a beige solid (561 mg, 99%).

IR (ν_{max}/cm^{-1}): 2955, 2790, 1644, 1581, 1521, 1430, 1362, 1295, 1257, 1145.

HRMS (ESI$^+$, *m/z*): Calculated 588.2329 ($C_{26}H_{42}CoN_4NaO_6$), Found 588.2331 (Δ +0.34 ppm)

The spectral data were consistent with those in the literature.[55]

(2*R*,3*R*,5*S*)-2-(Hydroxymethyl)-5-vinyltetrahydrofuran-3-ol, (±)-161



(±) 161

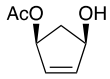
A solution of diol **158** (50.0 mg, 0.390 mmol) in ^{i}PrOH (4 mL) was added to Co(nmp)$_2$ (45.0 mg, 0.0800 mmol) under a stationary oxygen atmosphere (balloon) followed by *tert*-butyl hydroperoxide (5.5 M in decane, 7µL, 0.04 mmol). The reaction was stirred for 16 h at 55 °C under oxygen then allowed to cool to room temperature. Once cooled, the reaction was purged of oxygen with argon and methyl iodide (0.13 mL, 2.0 mmol) was added. After 16 h of stirring at room temperature, the reaction was concentrated *in vacuo* then treated with 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 layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:1 EtOAc/pentane to EtOAc) yielded a racemic mixture of the title compound **161** as a brown oil (28.0 mg, 50%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.84 (1H, ddd, *J* = 17.0, 10.2, 6.7 Hz, C*H*=CH$_2$), 5.29 (1H, dt, *J* = 17.1, 1.4 Hz, CH=C*H*$_A$H$_B$), 5.14 (1H, dt, *J* = 10.2, 1.3 Hz, CH=CH$_A$*H*$_B$), 4.77 – 4.66 (1H, m, C*H*CH=CH$_2$), 4.58 – 4.53 (1H, s, C*H*OH), 4.05 – 3.90 (3H, m, C*H*$_2$OH and C*H*CH$_2$OH), 3.62 – 3.57 (1H, m, O*H*), 2.82 (1H, s, O*H*), 2.17 (1H, ddd, *J* = 13.2, 5.9, 1.6 Hz, C*H*$_A$H$_B$CHOH), 1.86 (1H, ddd, *J* = 13.2, 9.6, 4.7 Hz, CH$_A$*H*$_B$CHOH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 138.5 (CH=*C*H$_2$), 116.2 (*C*H=CH$_2$), 80.9 (*C*HCH$_2$OH), 79.5 (*C*HCH=CH$_2$), 74.5 (*C*HOH), 62.0 (*C*H$_2$OH), 42.6 (*C*H$_2$CHOH).

The spectral data were consistent with those in the literature.[43]

(1*S*,4*R*)-4-Hydroxycyclopent-2-en-1-yl acetate, 195



195

Pancreatin (9.38 g) and *meso*-diol **163** (2.50 g, 25.0 mmol) were suspended in THF (50 mL). Vinyl acetate (16.0 mL, 175 mmol) and triethylamine (2.40 mL, 17.5 mmol) were then added and the reaction mixture was shaken in an incubator at room temperature until the starting material was completely consumed, as indicated by thin layer chromatography. Once complete, the reaction was filtered through Celite® and the solvent removed *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane) yielded diacetate **345** first, as a by-product, then the title compound **195** as white crystals (2.49 g, 70%).

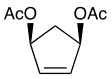
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.11 (1H, ddd, *J* = 5.6, 2.1, 1.2 Hz, CH=C*H*CHOAc), 5.98 (1H, ddd, *J* = 5.5, 2.1, 1.1 Hz, CH=C*H*CHOH), 5.53 – 5.45 (1H, m, C*H*OAc), 4.76 – 4.68 (1H, m, C*H*OH), 2.80 (1H, dt, *J* = 14.7, 7.4 Hz, CHCH_AH$_B$CH), 2.05 (s, 3H, OCOCH_3), 1.65 (1H, dt, *J* = 14.6, 3.8 Hz, CHCH$_A$$H_B$CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 170.9 (*C*=O), 138.6 (CH=*C*HCHOAc), 132.7 (CH=*C*HCHOH), 77.2 (*C*HOAc), 75.0 (*C*HOH), 40.6 (*C*H_2), 21.4 (OCO*C*H_3).

$[\alpha]_D^{25}$ –64.4 (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[54]

(1*R*,3*S*)-Cyclopent-4-ene-1,3-diyl diacetate, 345



345

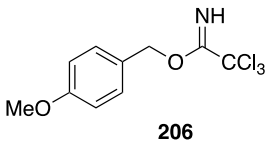
Compound **345** was isolated as a by-product in the synthesis of alcohol **195**.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.08 (2H, s, C*H*=C*H*), 5.53 (2H, dd, *J* = 7.5, 3.8 Hz, 2 x C*H*OAc), 2.91-2.82 (1H, m, C$H_A$$H_B$), 2.05 (6H, s, 2 x C$H_3$CO), 1.73 (1H, dt, *J* = 14.8, 3.7 Hz, C$H_A$$H_B$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 170.6 (2 x quat. *C*=O), 134.5 (*C*H=*C*H), 76.5 (2 x *C*HOAc), 37.0 (*C*H_2), 21.0 (2 x *C*H_3).

The spectral data were consistent with those in the literature.[54]

4-Methoxybenzyl-2,2,2-trichloroacetimidate, 206



206

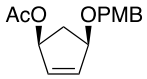
Sodium hydride (64.4 mg, 1.61 mmol) was washed with pentane (3 x 2 mL) before being treated with a solution of 4-mehtoxybenzyl alcohol (1.80 mL, 16.1 mmol) in Et_2O (5 mL) at room temperature. After 30 minutes of stirring at room temperature, the reaction was cooled to 0°C then trichloroacetonitrile (1.77 mL, 17.6 mmol) was added dropwise. After stirring for 1 h at 0 °C the reaction was allowed to warm to room temperature then concentrated *in vacuo*. The reaction mixture was diluted with a mixture of pentane and MeOH (275:1 pentane/MeOH, 17 mL) and left to stir for 30 minutes at room temperature. Filtration through celite followed by concentration *in vacuo* yielded the crude material **206** as an orange oil which was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.37 (1H, s, N*H*), 7.42 – 7.33 (2H, m, Ar*H*), 6.97 – 6.87 (2H, m, Ar*H*), 5.28 (2H, s, CH_2), 3.82 (3H, s, ArOCH_3).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 162.7 (*C*=NH), 159.8 (quat. *C* Ar), 129.8 (*C* Ar), 127.6 (quat. *C* Ar), 114.0 (*C* Ar), 70.8 (*C*H_2), 55.4 (ArO*C*H_3).

The spectral data were consistent with those in the literature.[82]

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl acetate, 205



205

Trichloroacetimidate (1.54 mL, 7.70 mmol) was added to a solution of alcohol **195** (2.18 g, 10.9 mmol) and camphorsulfonic acid (254 mg, 1.09 mmol) in a 4:1 mixture of CH_2Cl_2/pentane (54 mL) at 0 °C. After 1 h of stirring at room temperature, the reaction was cooled to 0 °C and a second portion of trichloroacetimidate **206** (1.54 mL, 7.70 mmol) was added. After stirring for 16 h at room temperature, the reaction was cooled to 0 °C and a third portion of trichloroacetimidate **206** (1.54 mL, 7.70 mmol) was added. After stirring for a further 16 h at room temperature, the reaction was quenched with a saturated solution of $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:15 EtOAc/pentane) yielded the title compound **205** as white crystals (4.02 g, 99%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.32 – 7.19 (2H, m, *ArH*), 6.95 – 6.78 (2H, m, Ar*H*), 6.11 (1H, ddd, *J* = 5.6, 1.9, 1.3 Hz, CH=C*H*CHOAc), 5.98 (1H, ddd, *J* = 5.6, 2.0, 1.3 Hz, CH=C*H*CHOPMB) 5.50 (1H, dddt, *J* = 6.5, 4.4, 2.0, 1.0 Hz, C*H*OAc), 4.52 (1H, d, *J* = 11.4 Hz, OC*H*$_A$H$_B$Ar), 4.47 (1H, d, *J* = 11.4 Hz, OCH$_A$*H*$_B$Ar), 4.49 – 4.46 (1H, m, C*H*OPMB) 3.80 (3H, s, ArOC*H*$_3$), 2.76 (1H, dt, *J* = 14.2, 7.4 Hz, CHC*H*$_A$H$_B$CH), 2.05 (s, 3H, C*H*$_3$CO$_2$), 1.74 (1H, dt, *J* = 14.2, 4.4 Hz, CHCH$_A$*H*$_B$CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 171.1 (quat. *C*=O), 159.4 (quat. *C* Ar) 136.3 (CH=*C*HCHOAc), 132.9 (CH=*C*HCHOPMB), 130.5 (quat. *C* Ar), 129.6 (*C* Ar), 114.5 (*C* Ar) 81.0 (*C*HOPMB), 77.0 (*C*HOAc), 70.9 (O*C*H$_2$Ar), 55.4 (ArO*C*H$_3$), 37.7 (CH*C*H$_2$CH), 21.3 (*C*H$_3$CO$_2$).

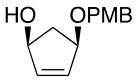
IR (ν_{max}/cm^{-1}): 1733, 1613, 1514, 1365, 1244, 1174, 1033, 821.

HRMS (ESI$^+$, *m/z*): Calculated 285.1092 ($C_{15}H_{18}NaO_4$), Found 285.1093 (Δ –1.46 ppm).

m.p. 30 – 35°C.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ –5.6 (*c* 1.0, $CHCl_3$).

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-ol, 207



207

KOH (17 mg, 0.31 mmol) was dissolved in a 4:1 mixture of MeOH/THF (1 mL) then added to acetate **205** (20 mg, 0.076 mmol). The reaction mixture was stirred for 16 h at room temperature before being quenched at 0 °C with a saturated solution of NH_4Cl (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:1 EtOAc/pentane) yielded the title compound **207** as a colourless oil (32 mg, 23%).

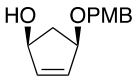
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.30 – 7.23 (2H, m, Ar*H*), 6.91 – 6.84 (2H, m, Ar*H*), 6.06 – 6.00 (2H, m, C*H*=C*H*), 4.65 – 4.60 (1H, m, C*H*OH), 4.55 – 4.38 (3H, m, OCH_2Ar and C*H*OPMB), 3.80 (3H, s, ArOCH_3), 2.71 – 2.59 (1H, m, CHCH_AH$_B$CH), 1.81 (1H, d, J = 7.6 Hz, O*H*), 1.70 – 1.60 (1H, m, CHCH_AH$_B$CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.4 (quat. *C* Ar), 137.2 (*C*H=CH), 134.5(CH=*C*H), 130.5 (quat. *C* Ar), 129.6 (*C* Ar), 114.0 (C Ar), 81.3 (*C*HOPMB), 75.2 (*C*HOH), 70.9 (O*C*H_2Ar), 55.4 (ArO*C*H_3), 41.2 (CH*C*H_2CH).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +17.2 (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[83]

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-ol, (±)-207



(±) 207

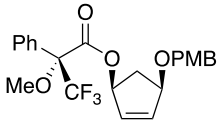
Diol **163** (64 mg, 0.64 mmol) was dissolved in DMF (6 mL) and cooled to 0 °C. TBAI (24 mg, 0.064 mmol) and NaH (13 mg, 0.32 mmol, 60% dispersion in mineral oil) were to the reaction mixture, followed by PMB-Cl (50mg, 0.32 mmol). The reaction mixture was allowed to warm to room temperature then quenched with H_2O (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:3 EtOAc/pentane) yielded the title compound **207** as a colourless oil (16 mg, 97%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.31 – 7.24 (2H, m, Ar*H*), 6.91 – 6.84 (2H, m, Ar*H*), 6.09 – 5.96 (2H, m, C*H*=C*H*), 4.67 – 4.58 (1H, m, C*H*OH), 4.55 – 4.37 (3H, m, OCH_2Ar and C*H*OPMB), 3.80 (3H, s, ArOCH_3), 2.65 (1H, dt, *J* = 14.1, 7.1 Hz, CHCH_AH$_B$CH), 1.87 (1H, d, *J* = 7.7 Hz, O*H*), 1.65 (1H, dt, *J* = 14.0, 4.1 Hz, CHCH$_A$$H_B$CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.4 (quat. *C* Ar), 137.2 (*C*H=CH), 134.4 (CH=C*H*), 130.5 (quat. *C* Ar), 129.6 (*C* Ar), 114.0 (*C* Ar), 81.3 (*C*HOPMB), 75.2 (*C*HOH), 70.9 (O*C*H_2Ar), 55.4 (ArO*C*H_3), 41.2 (CH*C*H_2CH).

The spectral data were consistent with those in the literature.[83]

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 210



210

To a solution of alcohol **207** (6.0 mg, 0.027 mmol) and *R*-Mosher acid (2R, *R*-(+)-MTPA-OH) (7.5 mg, 0.032 mmol) in CH_2Cl_2 (0.5 mL) were added DIC (4.0 mg, 0.032 mmol) and DMAP (1.7 mg, 0.014 mmol) at room temperature. After 16 h of stirring at room temperature, the reaction mixture was purified by preparatory thin layer chromatography (1:8 EtOAc/cyclohexane) to yield the title compound **210** as a colourless oil (11 mg, 92%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.57 – 7.49 (2H, m, Ar*H*), 7.44 – 7.33 (3H, m, Ar*H*), 7.27 – 7.19 (2H, m, Ar*H*), 6.91 – 6.82 (2H, m, Ar*H*), 6.16 (1H, ddd, *J* = 5.7, 1.9, 1.2 Hz, CH=C*H*CHOPMB), 5.98 (1H, ddd, *J* = 5.7, 2.1, 1.3 Hz, C*H*=CHCHOPMB), 5.75 – 5.67 (1H, m, C*H*OC=O), 4.57 – 4.50 (1H, m, C*H*OPMB), 4.50 – 4.40 (2H, m, OCH_2Ar), 3.80 (3H, s, ArOCH_3), 3.54 (3H, q, *J* = 1.2 Hz, CH_3OC(CF_3)), 2.85 (1H, dt, *J* = 14.5, 7.3 Hz, CHC$H_A$$H_B$CH), 1.85 (1H, dt, *J* = 14.2, 4.5 Hz, CHC$H_A$$H_B$CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 137.5 (CH=*C*HCHOPMB), 131.5 (*C*H=CHCHOPMB), 129.6 (*C* Ar), 129.4 (*C* Ar), 128.4 (quat. *C* Ar), 127.3 (*C* Ar), 113.8 (*C* Ar), 80.7 (*C*HOPMB), 79.2 (*C*HOC=O), 70.6 (O*C*H_2Ar), 55.4 (*C*H_3OC(Ph)(CF_3)CO_2), 55.3 (ArO*C*H_3), 37.4 (CH*C*H_2CH).

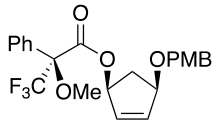
^{19}F NMR δ_F (100 MHz, $CDCl_3$): -71.9 (C*F*$_3$).

IR (ν_{max}/cm^{-1}): 2920, 2850, 2358, 1744, 1613, 1514, 1464, 1250, 1171, 1019.

HRMS (ESI$^+$, *m/z*): Calculated 459.1390 ($C_{23}F_3H_{23}NaO_5$); Found 459.1388 (Δ -0.40 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +2.66 (*c* 0.6, $CHCl_3$).

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 211



211

To a solution of alcohol **207** (6.0 mg, 0.027 mmol) and *S*-Mosher acid (2S, *S*-(+)-MTPA-OH) (7.5 mg, 0.032 mmol) in CH_2Cl_2 (0.5 mL) were added DIC (4.0 mg, 0.032 mmol) and DMAP (1.7 mg, 0.014 mmol) at room temperature. After 16 h of stirring at room temperature, the reaction mixture was purified by preparatory thin layer chromatography (1:8 EtOAc/cyclohexane) to yield the title compound **211** as a colourless oil (9 mg, 76%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.57 – 7.49 (2H, m, Ar*H*), 7.45 – 7.33 (3H, m, Ar*H*), 7.25 – 7.18 (2H, m, Ar*H*), 6.90 – 6.82 (2H, m, Ar*H*), 6.18 (1H, ddd, *J* = 5.7, 2.0, 1.2 Hz, CH=C*H*CHOPMB), 6.05 (1H, ddd, *J* = 5.7, 2.0, 1.3 Hz, C*H*=CHCHOPMB), 5.77 – 5.68 (1H, m, C*H*OC=O), 4.55 – 4.49 (1H, m, C*H*OPMB), 4.46 (1H, d, *J* = 11.3 Hz, OCH_AH_BAr), 4.41 (1H, d, *J* = 11.3 Hz, OCH_AH_BAr), 3.80 (3H, s, ArOCH_3), 3.55 (3H, q, *J* = 1.2 Hz, CH_3OC(CF_3)), 2.80 (1H, dt, *J* = 14.5, 7.4 Hz, CHCH_AH_BCH), 1.78 (1H, dt, *J* = 14.2, 4.5 Hz, CHCH_AH_BCH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.5 (*C*=O), 159.4 (quat. *C* Ar), 137.8 (CH=*C*HCHOPMB), 131.6 (*C*H=CHCHOPMB), 130.32 (quat. *C* Ar), 129.7 (*C* Ar), 129.5 (*C* Ar), 128.6 (quat. *C* Ar), 127.4 (*C* Ar), 114.0 (*C* Ar), 100.1 (Ph*C*(CF_3)(OMe)CO_2), 80.8 (*C*HOPMB), 79.3 (*C*HOC=O), 70.7 (O*C*H_2Ar), 55.6 (*C*H_3OC(Ph)(CF_3)CO_2), 55.4 (ArO*C*H_3), 37.2 (CH*C*H_2CH).

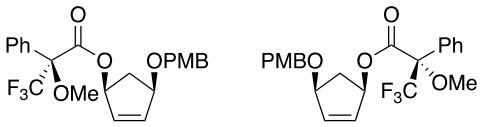
^{19}F NMR δ_F (100 MHz, $CDCl_3$): -71.7 (C*F*$_3$).

IR (ν_{max}/cm^{-1}): 2920, 2850, 1744, 1613, 1514, 1453, 1251, 1171, 1019.

HRMS (ESI$^+$, *m/z*): Calculated 459. 1390 ($C_{23}F_3H_{23}NaO_5$); Found 459.1382 (Δ -0.75 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -54.8 (*c* 0.9, $CHCl_3$).

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 211 and (1*R*,4*S*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 212



211 **212**

To a solution of alcohol (±)-**207** (10 mg, 0.045 mmol) and *S*-Mosher acid (2S, *S*-(+)-MTPA-OH) (30 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) were added DIC (16 mg, 0.13 mmol) and DMAP (3.0 mg, 0.025 mmol) at room temperature. After 16 h of stirring at room temperature, the reaction mixture was purified by preparatory thin layer chromatography (1:8 EtOAc/cyclohexane) to yield an inseparable mixture of the title compounds **211** and **212** as a colourless oil (14 mg, 71%).

^{1}H NMR δ_H (400 MHz, C_6D_6): 7.77 – 7.68 (4H, m, Ar*H*), 7.17 – 6.90 (10H, m, Ar*H*), 6.83 – 6.73 (m, 4H), 5.89 – 5.82 (2H, m, C*H*=C*H*), 5.82 – 5.78 (2H, m, C*H*=C*H*), 5.68 – 5.64 (1H, m, C*H*OC=O), 5.55 – 5.46 (1H, m, C*H*OC=O), 4.26 – 4.11 (4H, m, 2 x OCH_2Ar), 4.10 – 4.04 (2H, m, 2 x C*H*OPMB), 3.45 – 3.38 (6H, m, 2 x CH_3OC(CF_3)), 3.33 – 3.27 (6H, m, 2 x ArOCH_3), 2.43 (1H, dt, *J* = 14.3, 7.3 Hz, CHCH_AH$_B$CH), 2.31 (1H, dt, *J* = 14.4, 7.3 Hz, CHCH_AH$_B$CH), 1.85 (1H, dt, *J* = 14.2, 4.3 Hz, CHCH$_A$$H_B$CH), 1.76 (1H, dt, *J* = 14.2, 4.3 Hz, CHCH$_A$$H_B$CH).

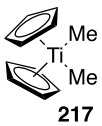
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.4 (2 x quat. *C* Ar), 137.8 (CH=*C*HCHOPMB), 137.6 (CH=*C*HCHOPMB), 131.7 (*C*H=CHCHOPMB), 131.6 (*C*H=CHCHOPMB), 130.3 (2 x quat. *C* Ar), 129.7 (2 x *C* Ar), 129.5 (2 x *C* Ar), 128.6 (2 x quat. *C* Ar), 127.4 (2 x *C* Ar), 114.0 (2 x *C* Ar), 80.8 (*C*HOPMB), 80.8 (*C*HOPMB), 79.3 (2 x *C*HOC=O), 70.8 (O*C*H_2Ar), 70.7 (O*C*H_2Ar), 55.6 (2 x *C*H_3OC(Ph)(CF_3)CO_2), 55.4 (2 x ArO*C*H_3), 37.5 (CH*C*H_2CH), 37.1 (CH*C*H_2CH).

^{19}F NMR δ_F (100 MHz, C_6D_6): -71.6 (C*F*$_3$), -71.6 (C*F*$_3$).

IR (ν_{max}/cm^{-1}): 2920, 2850, 2356, 1744, 1613, 1514, 1464, 1250, 1171, 1018.

HRMS (ESI$^+$, *m/z*): Calculated 459. 1390 ($C_{23}F_3H_{23}NaO_5$); Found 459.1388 (Δ -0.44 ppm).

Bis(cyclopentadienyl)dimethyltitanium, 217



217

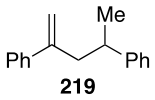
Methylmagnesium bromide solution (3M in tetrahydrofuran, 25.3 mL, 76.0 mmol) was added dropwise over a period of 15 minutes to a mixture of titanocene dichloride **216** (8.30 g, 33.4 mmol) in toluene (90 mL) at -5 °C while maintaining an internal temperature below 8 °C. The resulting slurry was stirred for two hours at an internal temperature between 0° C and 5°C and the reaction is assayed by ^{1}H NMR. Once complete, the reaction was quenched by addition into a 6% aqueous ammonium chloride solution (23.4 mL) at 0 °C over a period of 30 minutes while maintaining an internal temperature between 0 °C and 5 °C in both the reaction vessel and the work up vessel. The layers were separated and the organic layer was washed with cold water (3 x 40 mL) then brine (40 mL). The organic layer was dried over magnesium sulfate, filtered and carefully concentrated *in vacuo* to yield the title compound **217** as an orange solution in toluene/THF (17 wt%, 5.36 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.11 (10H, s, $(C_5\mathit{H}_5)_2TiMe_2$), -0.04 (6H, s, $Cp_2Ti(C\mathit{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 113.2 (($\mathit{C}_5H_5)_2TiMe_2$), 45.7 ($Cp_2Ti(\mathit{C}H_3)_2$).

The spectral data were consistent with those in the literature.[60]

Pent-1-ene-2,4-diyldibenzene, 219



219

Ketone **218** (100 mg, 0.446 mol) was added to a solution titanium bis(η5-2,4-cyclopentadien-1-yl)dimethyl in toluene/THF (3.2 wt%, 0.19 mL, 0.890 mmol) and the resulting solution was heated to 80 °C. After 16 hours of stirring the reaction was allowed to cool to room temperature and concentrated over silica *in vacuo.* Flash column chromatography (20:1 pentane/EtOAc) yielded the title compound **219** as a colourless oil (40.0 mg, 80%).

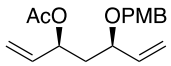
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.42-7.26 (7H, m, Ar*H*), 7.22-7.14 (3H, m, Ar*H*), 5.15 (1H, d, *J* = 1.7 Hz, H_AH_BC=C), 4.90 (1H, s, H_AH_BC=C), 2.92-2.77 (2H, m, CH_2), 2.71-2.65 (1H, m, CHCH_3), 1.14 (3H, d, *J* = 6.8 Hz, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 147.2 (*C*H=CH_2), 128.4 (*C* Ar), 128.3 (*C* Ar), 128.3 (*C* Ar), 128.1 (*C* Ar), 127.8 (*C* Ar), 127.3 (*C* Ar), 126.9 (*C* Ar), 126.4 (*C* Ar), 114.3 (CH=*C*H_2), 44.6 (*C*H), 37.8 (*C*H_2), 21.2 (*C*H_3).

IR (υ_{max}/cm^{-1}): 3027, 2962, 2927, 1601, 1494, 1453, 1017, 897, 777, 762, 699, 610.

HRMS (ESI^+, *m/z*): Calculated 222.3310 ($C_{17}H_{18}$), Found 222.1414 (Δ -4.16 ppm).

(3*S*,5*R*)-5-((4-Methoxybenzyl)oxy)hepta-1,6-dien-3-yl acetate, 202



202

Alkene **205** (100 mg, 0.382 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to -78 °C. The reaction mixture was subjected to a stream of ozone gas until the solution turned blue at which point ozone was removed and nitrogen gas was passed through the solution until the blue colour disappeared. Triphenylphospine (200 mg, 0.764 mmol) was added and the reaction was allowed to warm to -20 °C. After 2 hours the reaction was allowed to warm to room temperature and the solvent was removed *in vacuo* to yield the crude aldehyde **203**. In a separate flask, KHMDS (0.5 M in PhMe, 4.58 mL, 2.29 mmol) was added dropwise at 0 °C to a suspension of triphenylmethylphosphonium bromide (818 mg, 2.29 mmol) in THF (5 mL). After 15 minutes, the suspension was cooled to –78 °C and the crude aldehyde **203** was added dropwise as a solution in THF (2 mL). The reaction was allowed to warm to room temperature and stirred for 16 h then quenched by the addition of a saturated solution of NH_4Cl (5 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:30 EtOAc/pentane) yielded the title compound **202** as a colourless oil (76.0 mg, 72% over two steps).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.28 – 7.21 (2H, m, Ar*H*), 6.97 – 6.81 (2H, m, Ar*H*), 5.81 – 5.66 (2H, m, 2 x CH_2=C*H*), 5.42 – 5.30 (1H, m, C*H*OAc), 5.35 – 5.10 (4H, m, 2 x CH_2=CH), 4.50 (1H, d, *J* = 11.2 Hz, 1 x OCH_2Ar), 4.23 (1H, d, *J* = 11.2 Hz, 1 x OCH_2Ar), 3.80 (3H, s, ArOCH_3), 3.89 – 3.74 (1H, m, C*H*OPMB), 2.06 (1H, dt, *J* = 14.0, 7.6 Hz, 1 x CHCH_2CH), 2.00 (3H, s, CH_3CO_2), 1.72 (1H, dt, *J* = 14.0, 6.1 Hz, 1 x CHCH_2CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 169.9 (quat. *C*=O), 158.9 (quat. *C* Ar), 138.0 (CH_2=*C*H), 136.0 (CH_2=*C*H), 129.3 (*C* Ar), 130.3 (quat. *C* Ar), 117.8 (*C*H_2=CH), 116.9 (*C*H_2=CH), 113.6

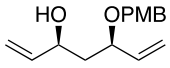
(C Ar), 77.0 (ArO*C*H$_3$), 72.0 (*C*HOAc), 69.6 (O*C*H$_2$Ar), 55.1 (*C*HOPMB), 39.8 (CH*C*H$_2$CH), 29.5 (*C*H$_3$CO$_2$).

IR (ν_{max}/cm^{-1}): 3080, 2922, 2849, 1738, 1613, 1514, 1244, 1034.

HRMS (ESI$^+$, *m/z*): Calculated 313.1410 ($C_{17}H_{22}NaO_4$), Found 313.1417 (Δ +2.24 ppm)□□□

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +23.1 (*c* 1.0, $CHCl_3$).

(3*S*,5*R*)-5-((4-Methoxybenzyl)oxy)hepta-1,6-dien-3-ol, 201



201

Procedure A:

K_2CO_3 (71 mg, 0.52 mmol) was added to a solution of alkene **202** (75 mg, 0.26 mmol) in a 1:1 mixture of MeOH/H_2O (2.5 mL) at room temperature. The reaction was heated to 50 °C and stirred for 16 h. The reaction was then cooled to 0 °C quenched by the addition of a saturated solution of NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:6 EtOAc/pentane to 1:4 EtOAc/pentane) yielded the title compound **201** as a colourless oil (65 mg, 99%).

Procedure B:

Alkene **202** (1.07 g, 4.08 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78 °C. The reaction mixture was subjected to a stream of ozone gas until the solution turned blue, at which point ozone was removed and nitrogen gas was passed through the solution until the blue colour disappeared. Triphenylphospine (2.14 g, 8.16 mmol) was added and the reaction was allowed to warm to -20 °C. After 2 hours the reaction was allowed to warm to room temperature and the solvent was removed *in vacuo* to yield the crude aldehyde **203**. In a separate flask, KHMDS (0.5 M in PhMe, 29.0 mL, 14.5 mmol) was added dropwise at 0 °C to a suspension of triphenylmethylphosphonium bromide (6.24 g, 17.5 mmol) in THF (40 mL). After 15 minutes, the suspension was cooled to –78 °C and the crude aldehyde **203** was added dropwise as a solution in THF (10 mL). The reaction was allowed to warm to room temperature and stirred for 16 h then quenched by the addition of a solution of KOH (282 mg, 5.05 mmol) in MeOH (30 mL) at 0 °C. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (1:9 EtOAc/pentane to 1:6 EtOAc/pentane) to yield the title compound **201** as a colourless oil (717 mg, 71% over three steps).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.29 – 7.20 (2H, m, Ar*H*), 6.92 – 6.83 (2H, m, Ar*H*), 5.89 – 5.69 (2H, m, 2 x CH_2=C*H*), 5.32 – 5.18 (3H, m, C*H*$_A$H$_B$=CH, C*H*$_{A'}$*H*$_{B'}$=CH), 5.06 (1H, dt, *J* = 10.4, 1.5 Hz, CH$_A$*H*$_B$=CH), 4.57 (1H, d, *J* = 11.2 Hz, OC*H*$_A$H$_B$Ar), 4.35 – 4.24 (m, 2H, OCH$_A$*H*$_B$Ar, C*H*OH), 4.13 – 3.98 (1H, m, C*H*OPMB), 3.80 (3H, s, ArOC*H*$_3$), 3.47 (1H, d, *J* = 1.8 Hz, O*H*), 1.83 (1H, dt, *J* = 14.5, 9.6 Hz, CHC*H*$_A$H$_B$CH), 1.66 (1H, ddd, *J* = 14.5, 3.8, 3.0 Hz, CHCH$_A$*H*$_B$CH).

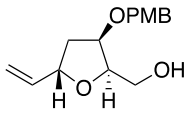
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.4 (quat. *C* Ar), 140.6 (CH$_A$H$_B$=*C*H), 138.2 (CH$_{A'}$H$_{B'}$=*C*H), 130.0 (quat. *C* Ar), 129.8 (*C* Ar), 117.9 (*C*H$_{A'}$H$_{B'}$=CH), 114.4 (*C*H$_A$H$_B$=CH), 114.1 (C Ar), 80.6 (*C*HOPMB) 72.27 (*C*HOH), 70.0 (O*C*H$_2$Ar), 55.4 (ArO*C*H$_3$), 42.7 (CH*C*H$_2$CH).

IR (ν_{max}/cm^{-1}): 3438, 3077, 3007, 2917, 2837, 1644, 1514, 1248, 1067, 926, 822.

HRMS (ESI$^+$, *m/z*):□□□

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +70.7 (*c* 1.0, $CHCl_3$).

((2*R*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methanol, 200



200

*Mukaiyama Oxidative Cyclisation of Alcohol **201**:*

$Co(nmp)_2$ (723 mg, 1.27 mmol) was dissolved in ^{i}PrOH (30 mL) and placed under a stationary oxygen atmosphere (balloon). Alcohol **201** (1.05 g, 4.23 mmol) was added as a solution in ^{i}PrOH (10 mL) followed by *tert*-butyl hydroperoxide (5.5 M in decane, 0.230 mL, 1.27 mmol). The reaction was heated to 55 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature then purged of oxygen with argon. Methyl iodide (0.260 mL, 4.23 mmol) was added and the reaction was left to stir at room temperature for 16 h. The solvent was removed *in vacuo* and the crude product was redissolved in EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:3 EtOAc/pentane to 1:1 EtOAc/pentane) yielded the title compound as a colourless oil **200** (533 mg, 50%).

*DIBAL-Mediated Cleavage of Acetal **338:***

DIBAL (1.23 M in PhMe, 26.3 mL, 32.5 mmol) was added dropwise to a solution of compound **338** (1.70 g, 6.49 mmol) in CH_2Cl_2 (65 mL) at -78 °C and the reaction was allowed to warm to room temperature. After stirring for 16 h the reaction was quenched with EtOAc (10 mL) at -78 °C then warmed to 0 °C and a saturated solution of NH_4Cl (50 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane to 1:3 EtOAc/pentane) yielded the title compound **200** as a colourless oil (1.52 g, 88%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.24 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.92 – 6.85 (2H, m, Ar*H*), 5.84 (1H, ddd, *J* = 17.0, 10.3, 6.6 Hz, CH_AH_B=C*H*), 5.28 (1H, dt, *J* = 17.1, 1.4 Hz, C*H*$_A$H$_B$=CH),

5.13 (1H, dt, *J* = 10.3, 1.3 Hz, CH_AH_B=CH), 4.70 – 4.55 (2H, m, C*H*CH=CH_2 and OCH_AH_BAr), 4.37 (1H, d, *J* = 11.5 Hz, OCH_AH_BAr), 4.28 (1H, td, *J* = 5.1, 2.0 Hz, C*H*OPMB), 4.13 (1H, q, *J* = 5.0 Hz, C*H*CH_2OH), 3.91 – 3.76 (2H, m, CH_2OH), 3.81 (3H, s, ArOCH_3), 2.28 (1H, ddd, *J* = 13.2, 5.9, 2.1 Hz, 1 x CHCH_2CH), 1.78 (1H, ddd, *J* = 13.2, 9.1, 5.2 Hz, 1 x CHCH_2CH).

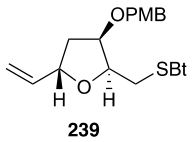
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.5 (quat. *C* Ar), 138.4 (CH_2=*C*H), 129.8 (quat. *C* Ar), 129.3 (*C* Ar), 116.3 (*C*H_2=CH), 114.1 (*C* Ar), 81.2 (*C*HCH_2OH), 80.4 (*C*HOPMB), 79.0 (CH_2=CH*C*H), 71.5 (O*C*H_2Ar), 62.4 (*C*H_2OH), 55.4 (ArO*C*H_3), 38.4 (CH*C*H_2CH).

IR (ν_{max}/cm^{-1}): 3428, 2934, 1612, 1513, 1247, 1034.

HRMS (ESI^+, *m/z*): Calculated 287.125 ($C_{15}H_{20}NaO_4$), Found 287.1255 (Δ +0.27 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -46.5 (*c* 1.0, $CHCl_3$).

1-((((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)thio)-1*H*-benzo[*d*][1,2,3]triazole, 239



239

DIAD (0.820 mL, 4.15 mmol) was added dropwise to a solution of alcohol **200** (440 mg, 1.66 mmol), 2-mercaptobenzothiazole (694 mg, 4.15 mmol) and triphenylphosphine (1.09 g, 4.15 mmol) in THF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature then stirred for 16 h before being concentrated over silica gel *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane) yielded the title compound **239** as a white solid (560 mg, 81%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.85 (1H, dt, *J* = 8.1, 0.9 Hz, Ar*H*), 7.78 – 7.71 (1H, m, Ar*H*), 7.40 (1H, ddd, *J* = 8.3, 7.3, 1.3 Hz, Ar*H*), 7.36 – 7.22 (3H, m, Ar*H*), 6.93 – 6.85 (2H, m, Ar*H*), 5.84 (1H, ddd, *J* = 17.1, 10.2, 6.9 Hz, CH_AH_B=C*H*), 5.28 (1H, dt, *J* = 17.1, 1.4 Hz, C*H*$_A$H$_B$=CH), 5.13 (1H, ddd, *J* = 10.2, 1.6, 1.0 Hz, CH$_A$*H*$_B$=CH), 4.66 (1H, dt, *J* = 9.8, 6.4 Hz, CH$_A$H$_B$=CHC*H*), 4.59 (1H, d, *J* = 11.2 Hz, 1 x OC*H*$_2$Ar), 4.51 – 4.42 (2H, m, 1 x OC*H*$_2$Ar, C*H*CH$_2$SBt), 4.25 (1H, td, *J* = 4.4, 1.5 Hz, C*H*OPMB), 3.81 (3H, s, ArOC*H*$_3$), 3.70 (1H, dd, *J* = 13.3, 6.3 Hz, 1 x C*H*$_2$SBt), 3.59 (1H, dd, *J* = 13.4, 8.0 Hz, 1 x C*H*$_2$SBt), 2.31 (1H, ddd, *J* = 13.3, 5.7, 1.5 Hz, C*H*$_2$SBt), 1.75 (1H, ddd, *J* = 13.3, 9.8, 4.6 Hz, 1 x CHC*H*$_2$CH), 1.49 (1H, d, *J* = 6.5 Hz, 1 x CHC*H*$_2$CH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 167.2 (quat. *C* Ar), 159.4 (quat. *C* Ar), 153.4 (quat. *C* Ar), 138.4 (CH$_2$=*C*H), 135.5 (quat. *C* Ar), 130.1 (quat. *C* Ar), 129.5 (*C* Ar), 126.1 (*C* Ar), 124.3 (*C* Ar), 121.7 (*C* Ar), 121.1 (*C* Ar), 116.4 (*C*H$_2$=CH), 114.0 (*C* Ar), 80.5 (*C*HCH$_2$SBt), 79.4 (*C*HCH=CH$_2$), 79.3 (*C*HOPMB), 71.6 (O*C*H$_2$Ar), 55.4 (ArO*C*H$_3$), 38.2 (CH*C*H$_2$CH), 32.6 (*C*H$_2$SBt).

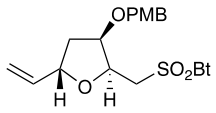
IR (ν_{max}/cm^{-1}): 3061, 1613, 1514, 1459, 1428, 1247.

HRMS (ESI$^+$, *m/z*): Calculated 414.1192 ($C_{22}H_{24}NO_3S_2$), Found 414.1182 (Δ –2.31 ppm).

m.p. 84 – 86 °C.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -105 (*c* 1.0, $CHCl_3$).

1-((((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)sulfonyl)-1*H*-benzo[*d*][1,2,3]triazole, 240



240

Sulfide **239** (560 mg, 1.35 mmol) was dissolved in a 4:1 mixture of EtOH/THF (8 mL) and the resulting solution was cooled to 0 °C. In a separate flask, ammonium molybdate (157 mg, 0.135 mmol) was added to H_2O_2 (30 wt%/H_2O, 1.68 mL, 16.6 mmol) at 0 °C. The resulting solution was added dropwise to the sulfide solution at 0 °C. The reaction mixture was stirred for 16 h at room temperature then quenched by the addition of a saturated solution of $NaHCO_3$ (4 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 8 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane) yielded the title compound **240** as a white solid (478 mg, 79%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.24 – 8.17 (1H, m, Ar*H*), 8.03 – 7.95 (1H, m, Ar*H*), 7.67 – 7.53 (2H, m, Ar*H*), 7.27 – 7.19 (2H, m, Ar*H*), 6.92 – 6.83 (2H, m, Ar*H*), 5.65 (1H, ddd, *J* = 16.9, 10.3, 6.4 Hz, CH_2=C*H*), 5.07 – 4.92 (2H, m, C*H*$_2$=CH), 4.65 (1H, ddd, *J* = 6.7, 5.6, 4.3 Hz, C*H*CH_2SO_2Bt), 4.51 (1H, d, *J* = 11.1 Hz, OC*H*$_A$H$_B$Ar), 4.47 – 4.38 (1H, m, CH_2=CHC*H*), 4.35 (1H, d, *J* = 11.1 Hz, OCH$_A$*H*$_B$Ar), 4.29 – 4.21 (1H, m, C*H*OPMB), 3.97 (1H, dd, *J* = 14.9, 6.8 Hz, C*H*$_A$H$_B$$SO_2Bt$), 3.89 (1H, dd, *J* = 14.9, 5.7 Hz, CH$_A$*H*$_B$$SO_2Bt$), 3.81 (3H, s, ArOC*H*$_3$), 2.23 (1H, ddd, *J* = 13.4, 6.0, 1.6 Hz, C*H*$_A$H$_B$CHOPMB), 1.70 (1H, ddd, *J* = 13.3, 9.6, 4.8 Hz, CH$_A$*H*$_B$CHOPMB).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.5 (quat. *C* Ar), 159.5 (quat. *C* Ar), 152.8 (quat. *C* Ar), 137.6 (CH_2=*C*H), 137.1 (quat. *C* Ar), 129.7 (quat. *C* Ar), 129.5 (*C* Ar), 128.0 (*C* Ar), 127.6 (*C* Ar), 125.6 (*C* Ar), 122.4 (*C* Ar), 116.1 (*C*H_2=CH), 114.0 (*C* Ar), 79.3 (*C*HOPMB), 78.7 (CH_2=CH*C*H), 75.7 (*C*HCH_2SO_2Bt), 71.5 (O*C*H_2Ar), 55.4 (ArO*C*H_3), 55.2 (*C*H_2SO_2Bt), 37.9 (CH*C*H_2CH).

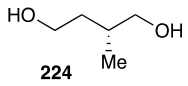
IR (ν_{max}/cm^{-1}): 2932, 1613, 1514, 1472, 1326, 1248, 1146.

HRMS (ESI^+, *m/z*): Calculated 446.1090 ($C_{22}H_{24}NO_3S_2$); Found 446.1091 (Δ +0.13 ppm).

m.p. 84 – 86 °C.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -11.1 (*c* 1.0, $CHCl_3$).

(*R*)-2-Methylbutane-1,4-diol, 224



224

A solution of (*R*)-2-methylsuccinic acid **223** (1.00 g, 7.57 mmol) in THF (5 mL) was added dropwise to a solution of borane dimethylsulfide complex (2.85 mL, 30.0 mmol) and trimethyl borate (3.25 mL, 29.2 mmol) in THF (10 mL) at 0 °C. The reaction was stirred for 16 h at room temperature then quenched by the careful dropwise addition of MeOH (15 mL) at 0 °C. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (1:1 EtOAc/pentane to 3:1 EtOAc/pentane) to yield the title compound **224** as a colourless oil (685 mg, 87%).

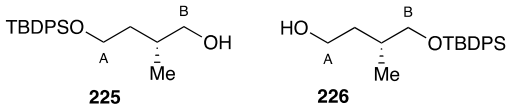
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 3.77 (1H, dt, *J* = 10.9, 5.4 Hz, $CH_2CH_AH_BOH$), 3.65 (1H, m, $CH_2CH_AH_BOH$), 3.56 (1H, dd, *J* = 10.7, 4.6 Hz, $CHCH_AH_BOH$), 3.43 (1H, ddd, *J* = 10.8, 7.3, 1.3 Hz, $CHCH_AH_BOH$), 2.79 (2H, s, 2 x O*H*), 1.89 – 1.73 (1H, m, $CHCH_3$), 1.68 – 1.50 (2H, m, CH_2CH_2OH), 0.93 (3H, d, *J* = 6.9 Hz, $CHCH_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 68.4 (CH_2OH), 61.2 (CH_2OH), 37.7 (CH_2CH_2OH), 34.3 ($CHCH_3$), 17.5 ($CHCH_3$).

$[\alpha]_D^{25}$ + 24.0 (*c* = 1.0, CH_2Cl_2).

The spectral data were consistent with those in the literature.[84]

(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbutan-1-ol, 225 and (*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbutan-1-ol, 226



225 **226**

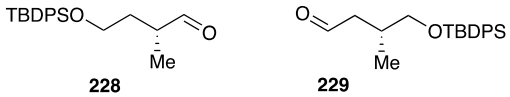
tert-Butyl(chloro)diphenylsilane (1.87 mL, 7.18 mmol) was added dropwise to a solution of diol **224** (680 mg, 6.53 mmol), imidazole (488 mg, 7.18 mmol) and 4-dimethylaminopyridine (80.0 mg, 0.650 mmol) in CH_2Cl_2 (65 mL) at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched with a saturated solution of NH_4Cl (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:30 EtOAc/pentane to 1:10 EtOAc/pentane) yielded the title compounds **225** and **226** as an inseparable mixture of colourless oils, in an unknown ratio (1.43 g, 64%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.67 (8H, m, Ar*H*), 7.49 – 7.34 (12H, m, Ar*H*), 3.81 – 3.62 (4H, m, 2 x C_AH_2O), 3.58 – 3.43 (4H, m, 2 x C_BH_2O), 1.92 – 1.78 (2H, m, 2 x C*H*CH_3) 1.75 – 1.43 (4H, m, 2 x C*H*$_2$CHCH_3), 1.06 (18H, m, 2 x SiC(C*H*$_3$)$_3$), 0.90 (6H, m, 2 x CHC*H*$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 135.7 (quat. *C* Ar), 133.5 (quat. *C* Ar), 129.9 (*C* Ar), 127.9 (*C* Ar), 68.4 (*C*H_2OSi), 62.7 (*C*H_2OSi), 36.9 (*C*H_2CH_2OH), 34.1 (*C*HCH_3), 27.0 (SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 17.3 (CH*C*H$_3$).

The spectral data were consistent with those in the literature.[84]

(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbutanal, 228 and(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbutanal, 229



228 **229**

DMSO (0.90 mL, 13 mmol) was added dropwise to a solution of oxalyl chloride (0.54 mL, 6.3 mmol) in CH_2Cl_2 (86 mL) at -78 °C. After 30 minutes, a solution of alcohols **225** and **226** (1.43 g, 4.17 mmol) in CH_2Cl_2 (29 mL) was added dropwise to the reaction at -78 °C. After 30 minutes, triethylamine (2.90 mL, 20.9 mmol) was added dropwise to the reaction at -78 °C. After an additional 30 minutes, the reaction was allowed to warm to 0 °C then quenched with a saturated solution of NH_4Cl (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over magnesium $MgSO_4$, filtered, and concentrated *in vacuo* to yield a 2.9:1 crude mixture of the title compounds **228** and **229** respectively. The crude aldehydes **225** and **226** were used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.66 (1H, d, *J* = 1.6 Hz, OC*H*), 7.63 (4H, m, Ar*H*), 7.47 – 7.32 (6H, m, Ar*H*), 3.76 – 3.62 (2H, m, SiOCH_2), 2.65 – 2.50 (1H, m, C*H*CH_3), 2.06 – 1.92 (1H, m, C$H_A$$H_B$$CHCH_3$), 1.67 – 1.54 (1H, m, $CH_A$$H_B$$CHCH_3$), 1.07 (3H, d, *J* = 7.1 Hz, $CHCH_3$), 1.02 (9H, s, $SiC(CH_3)_3$).

The spectral data were consistent with those in the literature.[43]

(*R*)-*tert*-Butyl((3-methylpent-4-en-1-yl)oxy)diphenylsilane, 230 and (*R*)-*tert*-Butyl((2-methylpent-4-en-1-yl)oxy)diphenylsilane, 231

230 **231**

*n*Butyllithium (2.5 M in hexanes, 3.34 mL, 8.35 mmol) was added dropwise to a suspension of triphenylphosphonium bromide (3.29 g, 9.20 mmol) in THF (30 mL) at 0 °C. After 15 minutes, a solution of aldehydes **228** and **229** (2.8:1 mixture, 1.42 g, 4.17 mmol) in THF (10 mL) was added dropwise to the reaction at 0 °C. The reaction was stirred for 16 h at room temperature then quenched with a saturated solution of NH_4Cl (40 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:15 CH_2Cl_2/pentane) yielded firstly alkene **230** as a colourless oil (722 mg, 51%) then alkene **231** as a colourless oil (101 mg, 7%).

*Alkene **230**:*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.71 – 7.63 (4H, m, Ar*H*), 7.48 – 7.33 (7H, m, Ar*H*), 5.66 (1H, ddd, *J* = 17.5, 10.3, 7.5 Hz, C*H*=CH_2), 4.99 – 4.84 (2H, m, CH=C*H*$_2$), 3.67 (2H, t, *J* = 6.6 Hz, SiOC*H*$_2$), 2.44 – 2.28 (1H, m, C*H*CH_3), 1.58 – 1.52 (2H, m, C*H*$_2$CHCH_3) 1.04 (9H, s, SiC(C*H*$_3$)$_3$), 0.97 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 144.5 (*C*H=CH_2), 135.7 (C Ar), 134.2 (quat. C Ar), 129.6 (C Ar), 127.7 (C Ar), 112.8 (CH=*C*H$_2$), 62.1 (SiO*C*H$_2$), 39.4 (*C*H$_2$CHCH_3), 34.3 (*C*HCH_3), 27.0 (C(*C*H$_3$)), 20.3 (CH*C*H$_3$), 19.4 (*C*(CH_3)).

HRMS (ESI$^+$, *m/z*): Calculated 339.2139 ($C_{15}H_{18}NaO_4$), Found 339.2139 (Δ +0.18 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +4.4 (*c* 1.0, $CHCl_3$).

*Alkene **231**:*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.71-7.59 (4H, m, Ar*H*), 7.43-7.33 (6H, m, Ar*H*), 5.75 (1H, ddt, *J* = 17.1, 10.0, 7.1, 7.1 Hz, C*H*=CH_2), 5.03-4.92 (2H, m, CH=C*H*$_2$), 3.48 (2H, dd, *J* = 6.0,

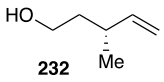
2.1 Hz, SiOCH_2), 2.29-2.15 (1H, m, CHCH$_3$), 1.97-1.80 (1H, m, CH_AH$_B$CHCH$_3$), 1.79-1.68 (1H, m, CH$_A$$H_B$CHCH$_3$), 1.03 (9H, s, SiC(C$H_3$)$_3$), 0.92 (3H, d, J = 6.6 Hz, CHCH_3).

^{13}C NMR δ_C (100 MHz, CDCl$_3$): 137.3 (*C* Ar), 135.5 (*C*H=CH$_2$), 134.0 (quat. *C* Ar), 129.4 (*C* Ar), 127.7 (*C* Ar), 115.7 (CH=*C*H$_2$), 68.4 (OSi*C*H$_2$), 37.7 (*C*H$_2$CHCH$_3$), 26.9 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 16.5 (CH*C*H$_3$)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +6.9 (*c* 1.0, CHCl$_3$).

The spectral data were consistent with those in the literature.

(*R*)-3-Methylpent-4-en-1-ol, 232



232

Tetrabutylammonium fluoride solution (1.0 M in THF, 4.14 mL, 4.14 mmol) was added to a solution of alkene **230** (700 mg, 2.07 mmol) in THF (4 mL) at room temperature. The reaction mixture was stirred for 16 h at room temperature then quenched with a saturated solution of NH_4Cl (4 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Flash column chromatography (1:3 Et_2O/pentane) yielded the title compound **232** as a colourless oil (162 mg, 78%).

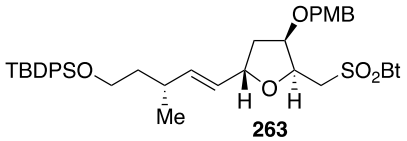
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.72 (1H, ddd, *J* = 17.2, 10.3, 7.9 Hz, C*H*=CH_2), 5.06 – 4.91 (2H, m, CH=C*H*$_2$), 3.72 – 3.61 (2H, m, OHC*H*$_2$), 2.37 – 2.24 (1H, m, C*H*CH_3), 1.66 – 1.49 (2H, m, $OHCH_2CH_2$), 1.35 (1H, s, O*H*), 1.02 (3H, d, *J* = 6.8 Hz, $CHCH_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 144.4 (*C*H=CH_2), 113.3 (CH=*C*H_2), 61.4 (OH*C*H_2), 39.5 ($OHCH_2CH_2$), 35.1 (*C*HCH_3), 20.6 ($CHCH_3$).

$[\alpha]_D^{25}$ -32.7 (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[85]

2-((((2*S*,3*R*,5*S*)-5-((*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpent-1-en-1-yl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[*d*]thiazole, 263



263

Hoveyda-Grubbs second generation catalyst (4.7 mg, 0.0075 mmol) was added to a solution of alkene **232** (220 mg, 0.650 mmol) and sulfone **237** (67.0 mg, 0.150 mmol) in CH_2Cl_2 (15 mL) at room temperature. The reaction was heated to reflux and stirred for 16 h under a stream of N_2. The reaction was cooled to room temperature then concentrated over silica gel *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane to 1:4 EtOAc/pentane) yielded the title compound **263** as a colourless oil (105 mg, 92%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.22 – 8.14 (1H, m, Ar*H*), 7.90 (1H, ddd, *J* = 8.1, 1.3, 0.7 Hz, Ar*H*), 7.69 – 7.61 (4H, m, Ar*H*), 7.57 (1H, ddd, *J* = 8.4, 7.2, 1.3 Hz, Ar*H*), 7.50 (1H, ddd, *J* = 8.3, 7.2, 1.3 Hz, Ar*H*), 7.45 – 7.33 (6H, m, Ar*H*), 7.27 – 7.18 (2H, m, Ar*H*), 6.92 – 6.79 (2H, m, Ar*H*), 5.22 (1H, dd, *J* = 15.4, 6.7 Hz, CH_3CHCH=CH), 5.15 (1H, dd, *J* = 15.5, 6.5 Hz, CH_3CHCH=C*H*), 4.63 (1H, ddd, *J* = 6.9, 5.7, 4.6 Hz, C*H*CH_2SO_2Bt), 4.49 (1H, d, *J* = 11.1 Hz, 1 x OCH_2Ar), 4.34 (1H, d, *J* = 11.1 Hz, 1 x OCH_2Ar), 4.28 (1H, dt, *J* = 9.7, 6.1 Hz, C*H*CH=CH), 4.23 (1H, td, *J* = 4.8, 1.7 Hz, C*H*OPMB), 3.99 (1H, dd, *J* = 14.9, 6.9 Hz, 1 x CH_2SO_2Bt), 3.86 (1H, dd, *J* = 14.9, 5.7 Hz, 1 x CH_2SO_2Bt), 3.82 (3H, s, ArOCH_3), 3.61 – 3.46 (2H, m, OTBDPSCH_2), 2.28 – 2.08 (2H, m, 1 x CHCH_2CH, C*H*CH_3), 1.60 (1H, ddd, *J* = 13.3, 9.7, 5.0 Hz, 1 x CHCH_2CH), 1.38 (2H, q, *J* = 6.6 Hz, OTBDPSCH_2CH_2), 1.02 (9H, s, SiC(CH_3)$_3$), 0.82 (3H, d, *J* = 6.8 Hz, CHCH_3).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.8 (quat. *C* Ar), 159.5 (quat. *C* Ar), 152.8 (quat. *C* Ar), 139.0 (1 x CH=CH), 137.1 (*C* Ar), 135.7 (*C* Ar), 134.1 (*C* Ar), 134.1 (quat. *C* Ar), 129.7 (quat. *C* Ar), 129.4 (quat. *C* Ar), 127.8 (*C* Ar), 127.5 (1 x CH=CH), 125.5 (*C* Ar), 122.4 (*C* Ar), 114.0 (*C* Ar), 79.4 (*C*HOPMB), 78.6 (CH=CH*C*H), 75.5 (*C*HCH_2SO_2Bt), 71.5 (OCH_2Ar), 61.8

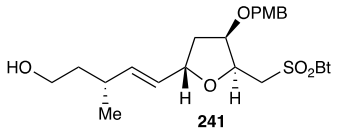
(OTBDPSCH$_2$), 55.4 (ArOCH$_3$), 55.0 (CHCH$_2$SO$_2$Bt), 39.2 (OHCH$_2$CH$_2$), 38.3 (CHCH$_2$CH), 32.5 (CHCH$_3$), 27.0 (SiC(CH$_3$)$_3$), 20.0 (CHCH$_3$), 19.3 (SiC(CH$_3$)$_3$).

IR (ν_{max}/cm^{-1}): 2932, 1613, 1514, 1472, 1326, 1248, 1146.

HRMS (ESI$^+$, *m/z*): Calculated 756.2843 ($C_{42}H_{49}NO_6S_2Si$); Found 756.2843 (Δ -0.13ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -10.7 (*c* 1.0, $CHCl_3$).

(*R*,*E*)-5-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methylpent-4-en-1-ol, 241



241

*Cross Metathesis of Alcohol **232** and Sulfone **237**:*

Hoveyda-Grubbs second generation catalyst (3.5 mg, 0.0056 mmol) was added to a solution of alcohol **232** (45.0 mg, 0.449 mmol) and sulfone **237** (50.0 mg, 0.112) in CH_2Cl_2 (12 mL). The reaction mixture was sealed and heated to 40 °C. After stirring for 16 h the reaction mixture was cooled to room temperature then concentrated over silica gel *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane to 1:4 EtOAc/pentane to 1:1 EtOAc/pentane) yielded the title compound **238** as a colourless oil (18 mg, 30%).

*Cleavage of Silyl Ether **263**:*

Compound **263** (93 mg, 0.12 mmol) was dissolved in a 0.1 M solution of AcCl in MeOH (0.2 mL, 0.02 mmol). After stirring for 6 h at room temperature the reaction mixture was diluted with EtOAC (2 mL), cooled to 0 °C then quenched with a saturated solution of $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Flash column chromatography (2:1 EtOAc /pentane) yielded the title compound **238** as a colourless oil (57 mg, 90%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.20 (1H, dd, *J* = 8.0, 1.4 Hz, Ar*H*), 7.99 (1H, dd, *J* = 7.9, 1.4 Hz, Ar*H*), 7.67 – 7.52 (2H, m, Ar*H*), 7.27 – 7.17 (2H, m, Ar*H*), 6.92 – 6.83 (2H, m, Ar*H*), 5.34 – 5.17 (2H, m, C*H*=C*H*), 4.65 (1H, dt, *J* = 7.1, 5.2 Hz, C*H*CH_2SO_2Bt), 4.50 (1H, d, *J* = 11.1 Hz, 1 x OCH_2Ar), 4.39 – 4.29 (2H, m, 1 x OCH_2Ar, C*H*CH=CH), 4.24 (1H, td, *J* = 4.8, 1.6 Hz, C*H*OPMB), 3.99 (1H, dd, *J* = 14.9, 7.0 Hz, 1 x CH_2SO_2Bt), 3.90 – 3.76 (1H, m, 1 x CH_2SO_2Bt), 3.81 (3H, s, ArOCH_3), 3.59 – 3.42 (2H, m, OHCH_2), 2.17 (2H, m, CHC$H_A$$H_B$CH and C*H*$CH_3$),

1.66 (1H, ddd, *J* = 13.3, 9.7, 4.9 Hz, CHCH$_A$*H*$_B$CH), 1.46 (1H, m, 1 x OHCH$_2$C*H*$_2$), 1.36 (1H, m, 1 x OHCH$_2$C*H*$_2$), 0.88 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$).

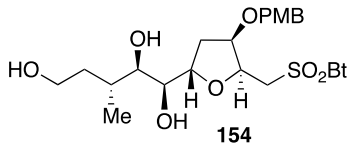
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.7 (quat. *C* Ar), 159.5 (quat. *C* Ar), 152.8 (quat. *C* Ar), 138.9 (1 x CH=CH), 137.1 (quat. *C* Ar), 129.7 (quat. *C* Ar), 129.5 (quat. *C* Ar), 128.2 (1 x CH=CH), 127.9 (2 x *C* Ar), 127.6 (*C* Ar), 125.6 (*C* Ar), 122.5 (*C* Ar), 114.0 (2 x *C* Ar), 79.4 (*C*HOPMB), 78.5 (CH=CH*C*H), 75.6 (*C*HCH$_2$SO$_2$Bt), 71.5 (O*C*H$_2$Ar), 61.0 (OH*C*H$_2$), 55.4 (ArO*C*H$_3$), 55.1 (CH*C*H$_2$SO$_2$Bt), 39.3 (OHCH$_2$*C*H$_2$), 38.3 (CH*C*H$_2$CH), 33.2 (*C*HCH$_3$), 20.5 (CH*C*H$_3$).

IR (ν_{max}/cm^{-1}): 3429, 1722, 1514, 1468, 1323, 1248, 1146, 1038.

HRMS (ESI$^+$, *m/z*): Calculated 540.1485 ($C_{26}H_{31}NNaO_6S_2$); Found 540.1484 (Δ -0.23ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -16.9 (*c* 1.0, $CHCl_3$).

(1*S*,2*R*,3*R*)-1-((2*S*,4*R*,5*S*)-5-(((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)sulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methylpentane-1,2,5-triol, 154



154

Potassium ferricyanide (220 mg, 0.668 mmol), K_2CO_3 (91.0 mg, 0.668 mmol), methanesulfonamide (21.5 mg, 0.226 mmol), and $(DHQD)_2PHAL$ (13.8 mg, 0.0177 mmol) were added to a solution of alkene **238** (116 mg, 0.224 mmol) in ^{t}BuOH (1.0 mL) and H_2O (1.0 mL) at room temperature. The reaction was cooled to 0 °C and a solution of potassium osmate (4.3 mg, 0.012 mmol) in H_2O (0.2 mL) was added. After 16 h of stirring at room temperature the reaction was quenched with sodium sulfite (35 mg), diluted with H_2O (4 mL), warmed to room temperature and stirred vigorously. EtOAc (4 mL) was added, the layers separated and the aqueous layer was extracted with ethyl EtOAc (3 × 8 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:1 EtOAc/pentane to EtOAc) yielded the title compound **154** as a colourless oil (81 mg, 66%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.27 – 8.17 (1H, m, Ar*H*), 8.05 – 7.96 (1H, m, Ar*H*), 7.69 – 7.55 (2H, m, Ar*H*), 7.24 – 7.16 (2H, m, Ar*H*), 6.90 – 6.82 (2H, m, Ar*H*), 4.63 (1H, dt, *J* = 8.7, 3.6 Hz, C*H*CH_2SO_2Bt), 4.52 (1H, d, *J* = 11.3 Hz, OC*H*$_A$H$_B$Ar), 4.33 (1H, d, *J* = 11.3 Hz, OCH$_A$*H*$_B$Ar), 4.23 – 4.10 (2H, m, C*H*OPMB and OC*H*CHOH), 3.93 (1H, dd, *J* = 15.1, 8.8 Hz, C*H*$_A$CH$_B$$SO_2Bt$), 3.80 (3H, s, ArOC*H*$_3$), 3.76 – 3.65 (2H, m, CH$_A$C*H*$_B$$SO_2Bt$ and OHC*H*$_A$CH$_B$), 3.61 – 3.52 (1H, m, OHCH$_A$C*H*$_B$), 3.45 – 3.38 (1H, m, OCHC*H*OH), 3.16 (1H, dd, *J* = 7.9, 1.4 Hz, OHC*H*$CHCH_3$), 2.25 – 2.06 (2H, m, 2 x CHC*H*$_2$CH), 1.84 – 1.63 (2H, m, C*H*CH_3 and $OHCH_2$C*H*$_A$H$_B$), 1.56 – 1.43 (1H, m, $OHCH_2$CH$_A$*H*$_B$) 0.84 (3H, d, CHC*H*$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.3 (quat. *C* Ar), 159.6 (quat. *C* Ar), 152.8 (quat. *C* Ar), 137.0 (quat. *C* Ar), 129.5 (quat. *C* Ar), 129.5 (quat. *C* Ar), 128.3 (*C* Ar), 127.9 (*C* Ar), 125.6 (*C* Ar), 122.6 (*C* Ar), 114.1 (*C* Ar), 82.1 (O*C*HCHOH), 79.3 (*C*HOPMB), 77.3

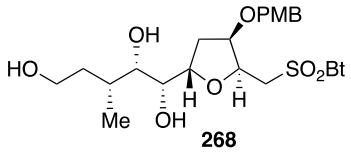
(OH*C*HCHCH$_3$), 76.7 (*C*HCH$_2$SO$_2$Bt), 71.3 (O*C*H$_2$Ar), 70.8 (OCH*C*HOH), 60.9 (OH*C*H$_2$), 55.8 (*C*H$_2$SO$_2$Bt), 55.4 (ArO*C*H$_3$), 36.5 (OHCH$_2$*C*H$_2$), 33.7 (*C*HCH$_3$), 33.0 (CH*C*H$_2$CH), 17.2 (CH*C*H$_3$).

IR (ν_{max}/cm^{-1}): 3449, 1613, 1514, 1470, 1324, 1248, 1146, 1061, 1034.

HRMS (ESI$^+$, *m/z*): Calculated 574.1540 ($C_{26}H_{33}NNaO_8S_2$); Found 574.1534 (Δ -0.40 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +1.4 (*c* 1.0, $CHCl_3$).

(1*R*,2*S*,3*R*)-1-((2*S*,4*R*,5*S*)-5-(((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)sulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methylpentane-1,2,5-triol, 268



268

Potassium ferricyanide (220 mg, 0.248 mmol), K_2CO_3 (33.7 mg, 0.248 mmol), methanesulfonamide (8.0 mg, 0.083 mmol), and $(DHQ)_2PHAL$ (5.1 mg, 0.0066 mmol) were added to a solution of alkene **238** (43 mg, 0.083 mmol) in ^tBuOH (0.5 mL) and H_2O (0.5 mL) at room temperature. The reaction was cooled to 0 °C and a solution of potassium osmate (1.6 mg, 0.0044 mmol) in H_2O (0.16 mL) was added. After 16 h of stirring at room temperature the reaction was quenched with sodium sulfite (13 mg), diluted with H_2O (2 mL), warmed to room temperature and stirred vigorously. EtOAc (4 mL) was added, the layers separated and the aqueous layer was extracted with ethyl EtOAc (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:1 EtOAc/pentane to EtOAc to 5:95 MeOH/$CHCl_3$) yielded the title compound **268** as a colourless oil (32 mg, 70%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.24 – 8.16 (1H, m, Ar*H*), 8.05 – 7.97 (1H, m, Ar*H*), 7.68 – 7.54 (2H, m, Ar*H*), 7.24 – 7.17 (2H, m, Ar*H*), 6.90 – 6.83 (2H, m, Ar*H*), 4.67 – 4.58 (1H, m, C*H*CH_2SO_2Bt), 4.50 (1H, d, *J* = 11.3 Hz, OC*H*$_A$H$_B$Ar), 4.32 (1H, d, *J* = 11.3 Hz, OCH$_A$*H*$_B$Ar), 4.23 – 4.16 (1H, m, C*H*OPMB), 4.01 (1H, ddd, *J* = 10.2, 5.8, 4.6 Hz, OC*H*CHOH) 3.95 (1H, dd, *J* = 15.0, 8.3 Hz, C*H*$_A$CH$_B$$SO_2Bt$), 3.80 (3H, s, ArOC*H*$_3$), 3.75 (1H, dd, *J* = 15.0, 3.9 Hz, CH$_A$C*H*$_B$$SO_2Bt$), 3.71 – 3.65 (1H, m, OHC*H*$_A$CH$_B$), 3.65 – 3.53 (1H, m, OHCH$_A$C*H*$_B$), 3.48 (1H, br. s, OCHC*H*OH), 3.21 (1H, t, *J* = 4.2 Hz, OHC*H*$CHCH_3$), 2.16 – 2.02 (1H, m, CHC*H*$_A$H$_B$CH), 1.94 (1H, ddd, *J* = 13.5, 9.6, 4.8 Hz, CHCH$_A$*H*$_B$CH), 1.72 – 1.55 (2H, m, C*H*CH_3 and $OHCH_2$C*H*$_A$H$_B$), 1.46 – 1.33 (1H, m, $OHCH_2$CH$_A$*H*$_B$), 0.78 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$).

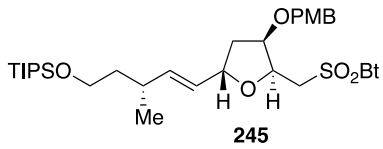
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.5 (quat. *C* Ar), 159.5 (quat. *C* Ar), 152.8 (quat. *C* Ar), 137.0 (quat. *C* Ar), 129.6 (quat. *C* Ar), 129.5 (quat. *C* Ar), 128.2 (*C* Ar), 127.8 (*C* Ar), 125.6 (*C* Ar), 122.5 (*C* Ar), 114.0 (*C* Ar), 79.5 (*C*HOPMB), 79.2 (O*C*HCHOH), 75.9 (*C*HCH$_2$SO$_2$Bt), 73.4 (OHC*H*CHCH$_3$), 72.3 (OCH*C*HOH), 71.3 (O*C*H$_2$Ar), 60.4 (OH*C*H$_2$), 55.8 (*C*H$_2$SO$_2$Bt), 55.4 (ArO*C*H$_3$), 36.4 (OHCH$_2$*C*H$_2$), 33.1 (*C*HCH$_3$), 32.1 (CH*C*H$_2$CH), 14.4 (CH*C*H$_3$).

IR (ν_{max}/cm^{-1}): 3451, 1613, 1516, 1470, 1322, 1248, 1146, 1061, 1034.

HRMS (ESI$^+$, *m/z*): Calculated 574.1540 ($C_{26}H_{33}NNaO_8S_2$); Found 574.1539 (-0.17 Δppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -2.6 (*c* 1.0, $CHCl_3$).

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)sulfonyl)benzo[*d*]thiazole, 245

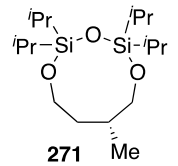


245

2,6-Lutidine (0.01 mL, 0.097 mmol) was added dropwise to a solution of alkene **238** (5.0 mg, 0.0097 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture was cooled to -78 °C and TIPSOTf (0.013 mL, 0.048 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and left to stir for 16 h. The reaction mixture was then quenched with a saturated solution of $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:15 EtOAc/pentane) yielded the title compound **272** as a colourless oil (3.5 mg, 57%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.24 – 8.17 (1H, m, Ar*H*), 8.03 – 7.94 (1H, m, Ar*H*), 7.66 – 7.52 (2H, m, Ar*H*), 7.26 – 7.14 (2H, m, Ar*H*), 6.91 – 6.81 (2H, m, Ar*H*), 5.30 (1H, dd, *J* = 15.4, 7.1 Hz, C*H*=CH), 5.20 (1H, dd, *J* = 15.4, 6.8 Hz, CH=C*H*), 4.64 (1H, q, *J* = 6.0 Hz, C*H*CH_2SO_2Bt), 4.50 (1H, d, *J* = 11.1 Hz, OCH_AH_BAr), 4.39 – 4.31 (2H, m, OCH_AH_BAr and CH=CHC*H*), 4.29 – 4.20 (1H, m, C*H*OPMB), 4.03 – 3.83 (2H, m, CH_2SO_2Bt), 3.81 (3H, s, ArOCH_3), 3.70 – 3.52 (2H, m, TIPSOCH_2), 2.24 – 2.13 (2H, m, CHCH_AH_BCH and C*H*CH_3), 1.67 (1H, ddd, *J* = 13.9, 9.8, 5.0 Hz, CHCH_AH_BCH), 1.47 – 1.29 (2H, m, *J* = 6.8 Hz, SiOCH_2CH_2), 1.13 – 1.03 (21H, m, OSi(C*H*(CH_3)$_2$)$_3$) , 0.87 (3H, d, *J* = 6.8 Hz, CHCH_3).

(*R*)-2,2,4,4-Tetraisopropyl-7-methyl-1,3,5,2,4-trioxadisilonane, 271



271

Diol **224** (50.0 mg, 0.480 mmol) and imidazole (229 mg, 3.36 mmol) were dissolved in DMF (4.8 mL) and cooled to 0 °C. TIPDSiCl_2 (0.17 mL, 0.53 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. After stirring for 4 h, the reaction was quenched with MeOH (0.5 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:400 EtOAc /pentane) yielded the title compound **271** as a colourless oil (122 mg, 73%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.13 (1H, ddd, *J* = 11.5, 7.4, 4.2 Hz, OC*H*$_A$H$_B$CH_2), 3.92 (1H, dd, *J* = 10.7, 3.4 Hz, OC*H*$_A$H$_B$CH(CH_3)), 3.88 – 3.75 (1H, m, OCH$_A$*H*$_B$CH_2), 3.62 (1H, dd, *J* = 10.8, 8.2 Hz, OCH$_A$*H*$_B$CH(CH_3)), 2.05 – 1.93 (1H, m, C*H*(CH_3)), 1.71 – 1.59 (2H, m, OCH_2C*H*$_2$), 1.11 – 1.00 (24H, m, 4 x C(C*H*$_3$)$_2$), 0.88 (3H, d, *J* = 7.0 Hz, CH(C*H*$_3$)).

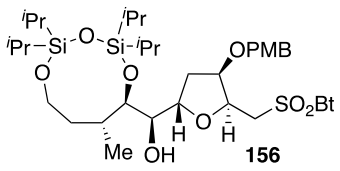
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 68.9 (O*C*H_2CH(CH_3)), 62.2 (O*C*H_2CH_2), 36.6 (OCH_2*C*H_2), 33.4 (*C*H(CH_3)), 17.9 (CH(*C*H_3)), 17.7 (C(*C*H_3)$_2$), 17. 7 (C(*C*H_3)$_2$), 17.6 (C(*C*H_3)$_2$), 17.6 (C(*C*H_3)$_2$), 13.5 (*C*(CH_3)$_2$), 13.5 (*C*(CH_3)$_2$), 13.2 (*C*(CH_3)$_2$), 13.2 (*C*(CH_3)$_2$).

IR (ν_{max}/cm^{-1}): 1514, 1464, 1330, 1249, 1115.

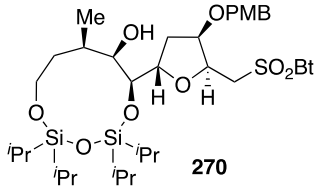
HRMS (ESI$^+$, *m/z*): Calculated 369.2252 ($C_{17}H_{38}NaO_3Si_2$); Found 369.2259 (+1.90 Δppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +11.4 (*c* 1.0, $CHCl_3$).

(*R*)-((2*S*,4*R*,5*S*)-5-(((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)sulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((6*R*,7*R*)-2,2,4,4-tetraisopropyl-7-methyl-1,3,5,2,4-trioxadisilonan-6-yl)methanol, 156 and (6*S*,7*R*,8*R*)-6-((2*S*,4*R*,5*S*)-5-(((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)sulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-2,2,4,4-tetraisopropyl-8-methyl-1,3,5,2,4-trioxadisilecan-7-ol, 270



156



270

$TIPDSiCl_2$ (0.1M in DMF, 0.38 mL, 0.038 mmol) was added dropwise to a solution of triol **154** (20 mg, 0.036 mmol) and imidazole (26 mg, 0.38 mmol) in DMF (3.6 mL) at -30 °C. The reaction mixture was allowed to warm to room temperature. After 16 h the reaction mixture was cooled to 0 °C and quenched with a solution of MeOH:H_2O (3:20, 1.9 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Flash column chromatography (1:20 EtOAc /pentane) yielded an inseparable 2:1 mixture of **156** and **270** (major component not determined) as a colourless oil (19 mg, 65%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.27 – 8.16 (2H, m, Ar*H*), 8.05 – 7.96 (2H, m, Ar*H*), 7.69 – 7.52 (4H, m, Ar*H*), 7.28 – 7.12 (4H, m, Ar*H*), 6.91 – 6.82 (4H, m, Ar*H*), 4.67 – 4.56 (2H, m, 2 x C*H*CH_2SO_2Bt), 4.56 – 4.43 (2H, m, 2 x OCH_AH_BAr), 4.36 – 4.09 (6H, m, 2 x OCH_AH_BAr, 2 x C*H*OPMB and 2 x $C_{35}H$), 3.99 – 3.67 (m, 14H, 2 x CH_2SO_2Bt, 2 x SiOCH_2CH_2 and 2 x ArOCH_3), 3.49 – 3.36 (2H, m, 2 x C*H*OH), 3.16 – 3.06 (2H, m, 2 x C*H*OSi), 2.18 – 1.99 (2H, m, 2 x $C_{34}H_AH_B$), 1.88 – 1.71 (3H, m, 2 x $C_{38}H$ and 1 x $C_{34}H_AH_B$), 1.42 – 1.23 (5H, m, 1 x $C_{34}H_AH_B$, 2 x $C_{39}H_2$), 1.07 – 0.94 (56H, m, CH(CH_3)$_2$, C*H*(CH_3)$_2$), 0.99 – 0.83 (4H, m, 2 x CH_2), 0.86 – 0.78 (6H, m, 2 x C_{38}HCH_3).

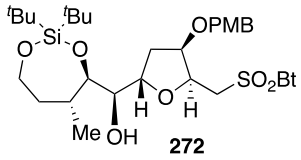
^{13}C NMR δ_C (100 MHz, $CDCl_3$): ^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ 166.4 (2 x quat. *C* Ar), 159.5 (2 x quat. *C* Ar), 152.8 (2 x quat. *C* Ar), 137.0 (2 x quat. *C* Ar), 129.5 (2 x quat. *C* Ar),

128.2 (2 x *C* Ar), 127.8 (2 x *C* Ar), 125.6 (2 x *C* Ar), 122.5 (2 x *C* Ar), 114.1 (2 x *C* Ar), 81.6 (2 x SiO*C*H), 79.4 (2 x C_{35}H), 79.3 (2 x *C*HOPMB) 76.8 (2 x C_{32}H), 76.5 (2 x *C*HOH), 71.3 (2 x O*C*H_2Ar), 61.2 (2 x SiO*C*$H_2C H_2$), 55.7 (2 x ArO*C*H_3), 55.4 (2 x *C*H_2SO_2Bt), 35.4 (*C*H_2), 33.0 (2 x *C*HCH$_3$, *C*H_2), 17.5 (CH(*C*H_3)$_2$), 17.4 (CH(*C*H_3)$_2$), 17.4 (CH(*C*H_3)$_2$), 13.4 (*C*H(CH$_3$)$_2$), 13.1 (*C*H(CH$_3$)$_2$), 13.0 (*C*H(CH$_3$)$_2$).

IR (ν_{max}/cm^{-1}): 2912, 2848, 1514, 1465, 1332, 1249, 1115.

HRMS (ESI$^+$, *m/z*): Calculated 794.3243 ($C_{38}H_{60}NO_9S_2Si_2$); Found 794.3246 (Δ +0.50 ppm).

(*R*)-((2*S*,4*R*,5*S*)-5-(((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)sulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanol, 272



272

Alcohol **154** (65.0 mg, 0.118 mmol) was dissolved in CH_2Cl_2 (12 mL) over 4 Å molecular sieves. 2,6-Lutidine (0.07 mL, 0.6 mmol) was added at room temperature and the reaction was stirred for 15 minutes then cooled to -78 ºC. Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.1 M in CH_2Cl_2, 1.32 mL, 0.132 mmol) was added dropwise and the reaction was allowed to warm to room temperature. After 16 h of stirring, the reaction was filtered then quenched with a saturated solution of $NaHCO_3$ (6 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 12 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:6 EtOAc/pentane) yielded the title compound **272** as a colourless oil (53 mg, 65%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.24 – 8.15 (1H, m, Ar*H*), 8.06 – 7.96 (1H, m, Ar*H*), 7.68 – 7.54 (2H, m, Ar*H*), 7.24 – 7.17 (2H, m, Ar*H*), 6.89 – 6.82 (2H, m, Ar*H*), 4.59 (1H, ddd, *J* = 6.7, 5.6, 3.9 Hz, C*H*CH_2SO_2Bt), 4.50 (1H, d, *J* = 10.9 Hz, OC*H*$_A$H$_B$Ar), 4.34 (1H, d, *J* = 11.0 Hz, OCH$_A$*H*$_B$Ar), 4.29 (1H, t, *J* = 4.2 Hz, C*H*OPMB), 4.23 (1H, ddd, *J* = 9.6, 7.3, 5.9 Hz, OC*H*CHOH), 4.05 – 3.84 (4H, m, C*H*$_2SO_2$Bt and SiOC*H*$_2CH_2$), 3.81 (3H, s, ArOC*H*$_3$), 3.53 (1H, dd, *J* = 9.2, 1.3 Hz, SiOC*H*CHOH), 3.39 (1H, td, *J* = 7.3, 1.2 Hz, C*H*OH), 2.29 – 2.17 (2H, m, CHC*H*$_A$H$_B$CH and O*H*), 1.95 – 1.83 (1H, m, C*H*CH_3), 1.75 – 1.67 (2H, m, CHCH$_A$*H*$_B$CH and OSiCH$_2$C*H*$_A$H$_B$), 1.62 – 1.56 (1H, m, OSiCH$_2$CH$_A$*H*$_B$), 0.98 (9H, s, Si(C(C*H*$_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$), 0.95 (9H, s, Si(C(CH$_3$)$_3$)$_A$(C(C*H*$_3$)$_3$)$_B$), 0.88 (3H, d, *J* = 6.9 Hz,CHC*H*$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 166.3 (quat. *C* Ar), 159.5 (quat. *C* Ar), 152.8 (quat. *C* Ar), 137.0 (quat. *C* Ar), 129.7 (quat. *C* Ar), 129.6 (quat. *C* Ar), 128.2 (*C* Ar), 127.8 (*C* Ar), 125.7

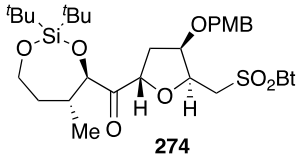
(*C* Ar), 122.5 (*C* Ar), 114.0 (*C* Ar), 80.7 (SiO*C*HCHOH), 80.0 (O*C*HCHOH), 79.1(*C*HOPMB), 75.9 (*C*HCH$_2$SO$_2$Bt), 75.0 (*C*HOH), 71.5 (O*C*H$_2$Ar), 65.9 (SiO*C*H$_2$CH$_2$), 55.4 (ArO*C*H$_3$), 54.7 (*C*H$_2$SO$_2$Bt), 42.3 (SiOCH$_2$*C*H$_2$), 38.7 (*C*HCH$_3$), 34.5 (CH*C*H$_2$CH), 28.2 (Si(C(*C*H$_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$), 28.1 (Si(C(CH$_3$)$_3$)$_A$(C(*C*H$_3$)$_3$)$_B$), 21.9 ((Si(*C*(*C*H$_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$), 21.6 (Si(C(CH$_3$)$_3$)$_A$(*C*(CH$_3$)$_3$)$_B$), 19.4 (CH*C*H$_3$).

IR (ν_{max}/cm^{-1}): 2919, 2851, 1514, 1465, 1330, 1249, 1115.

HRMS (ESI$^+$, *m/z*): Calculated 714.2561 (C$_{34}$H$_{49}$NNaO$_8$S$_2$Si); Found 714.2557 (Δ -0.60 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -14.1 (*c* 0.93, CHCl$_3$).

((2*S*,4*R*,5*S*)-5-(((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)sulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanone, 274



274

Dess–Martin periodinane (68.7 mg, 0.162 mmol) was suspended in CH_2Cl_2 (0.2 mL) and cooled to 0 ºC before $NaHCO_3$ (20.0 mg, 0.243 mmol) was added. After 30 minutes of stirring, alcohol **272** (10.0 mg, 0.0162 mmol) was added to the reaction as a solution in CH_2Cl_2 (0.1 mL). After 16 h of stirring at room temperature the reaction mixture was diluted with Et_2O (2 mL) and poured into a saturated solution of $Na_2S_2O_3$ (2 mL). The mixture was stirred vigorously until all solids dissolved. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (12 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane) yielded the title compound **274** as a white solid (9.0 mg, 93%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.24 – 8.14 (1H, m, Ar*H*), 8.05 – 7.94 (1H, m, Ar*H*), 7.67 – 7.52 (2H, m, Ar*H*), 7.27 – 7.16 (2H, m, Ar*H*), 6.92 – 6.80 (2H, m, Ar*H*), 4.84 (1H, dd, *J* = 8.8, 6.9 Hz, CH_2CHC=O), 4.77 – 4.72 (1H, m, C*H*CH_2SO_2Bt), 4.50 (1H, d, *J* = 11.0 Hz, OC*H*$_A$H$_B$Ar), 4.39 (1H, d, *J* = 10.9 Hz, OCH$_A$*H*$_B$Ar), 4.35 – 4.30 (1H, m, C*H*OPMB), 4.03 – 3.77 (5H, m, C*H*$_2$SO$_2$Bt, SiOC*H*$_2$ and SiOC*H*), 3.82 (3H, s, ArOC*H*$_3$), 2.44 (1H, ddd, *J* = 13.5, 7.0, 2.2 Hz, CHC*H*$_A$H$_B$CH), 1.96 (ddd, *J* = 13.6, 8.8, 4.8 Hz, CHCH$_A$*H*$_B$CH), 1.70 – 1.46 (3H, m, SiOCH$_2$C*H*$_2$ and C*H*CH$_3$), 1.03 (9H, s, SiC(C*H*$_3$)$_3$) 0.95 (9H, s, SiC(C*H*$_3$)$_3$), 0.45 (3H, d, *J* = 6.2 Hz, CHC*H*$_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 209.2 (*C*=O), 159.6 (quat. *C* Ar), 152.9 (quat. *C* Ar), 137.2 (quat. *C* Ar), 129.7 (quat. *C* Ar), 129.5 (quat. *C* Ar), 128.0 (*C* Ar), 127.6 (*C* Ar), 125.7 (*C* Ar),

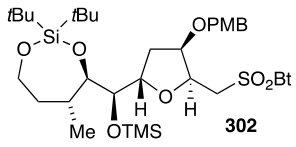
122.4 (*C* Ar), 114.1 (*C* Ar), 85.4 (SiO*C*HC=O), 78.9 (*C*HOPMB), 77.1 (*C*HCH$_2$SO$_2$Bt), 76.6 (CH$_2$*C*HC=O), 71.8 (OCH$_2$Ar), 65.3 (SiO*C*H$_2$CH$_2$), 55.4 (ArO*C*H), 54.9 (*C*H$_2$SO$_2$Bt), 42.4 (SiOCH$_2$*C*H$_2$), 39.5 (*C*HCH$_3$), 36.3 (CH*C*H$_2$CH), 28.3 (SiC(*C*H$_3$)$_3$), 28.2 (SiC(*C*H$_3$)$_3$), 21.5 (Si*C*(CH$_3$)$_3$), 21.2 (Si*C*(CH$_3$)$_3$), 17.4 (CHC*H*$_3$).

IR (ν_{max}/cm^{-1}): 2919, 2851, 1733, 1514, 1464, 1330, 1249, 1115.

HRMS (ESI$^+$, *m/z*): Calculated 712.2405 (C$_{34}$H$_{47}$NNaO$_8$S$_2$Si); Found 712.2402 (Δ -0.40 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -2.61 (*c* 1.0, CHCl$_3$).

1-((((2*S*,3*R*,5*S*)-5-((*R*)-((4*R*,5*R*)-2,2-Di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)((trimethylsilyl)oxy)methyl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)-1*H*-benzo[*d*][1,2,3]triazole, 302



302

Alcohol **272** (48.0 mg, 0.0694 mmol) and imidazole (71.0 mg, 1.04 mmol) were dissolved in CH_2Cl_2 (0.7 mL) and stirred for 10 minutes at room temperature. The reaction was cooled to 0 ºC and trimethylsilyl chloride (0.06 mL, 0.5 mmol) was added dropwise. After stirring for 16 h at room temperature, the reaction was diluted with CH_2Cl_2 (2 mL) then quenched with a saturated solution of $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Flash column chromatography (1:10 EtOAc/pentane to 1:8 EtOAc/pentane) yielded the title compound **302** as a white crystalline solid (48 mg, 91%).

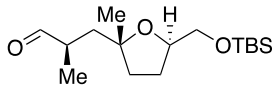
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.22 – 8.18 (1H, m, Ar*H*), 8.04 – 7.96 (1H, m, Ar*H*), 7.68 – 7.54 (2H, m, Ar*H*), 7.26 – 7.12 (2H, m, Ar*H*), 6.88 – 6.79 (2H, m, Ar*H*), 4.55 (1H, dt, *J* = 7.8, 4.1 Hz, C*H*CH_2SO_2Bt), 4.48 (1H, d, *J* = 10.8 Hz, OC*H*$_A$H$_B$Ar), 4.40 – 4.34 (1H, m, OC*H*CHOTMS), 4.32 (1H, d, *J* = 10.9 Hz, OCH$_A$*H*$_B$Ar), 4.24 (1H, t, *J* = 4.0 Hz, C*H*OPMB), 4.16 (1H, dd, *J* = 14.7, 7.4 Hz, C*H*$_A$H$_B$$SO_2Bt$), 3.96 (1H, dt, *J* = 11.6, 3.6 Hz, OSi(^{t}Bu)$_2$C*H*$_A$H$_B$), 3.90 – 3.77 (1H, m, OSi(^{t}Bu)$_2$CH$_A$*H*$_B$), 3.80 (3H, s, ArOC*H*$_3$), 3.52 – 3.39 (2H, m, C*H*OTMS and C*H*OSi(^{t}Bu)$_2$), 2.37 – 2.24 (1H, m, C*H*$_A$H$_B$CHOPMB), 1.88 – 1.83 (1H, m, C*H*CH_3), 1.65 – 1.57 (3H, m, C*H*$_2$$CHCH_3$ and CH$_A$*H*$_B$CHOPMB), 0.98 (9H, s, SiC(C*H*$_3$)$_3$), 0.97 (9H, s, SiC(C*H*$_3$)$_3$), 0.83 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 0.01 (9H, s, Si(C*H*$_3$)$_3$).

IR (ν_{max}/cm^{-1}): 1614, 1515, 1464, 1330, 1249, 1147, 1114.

HRMS (ESI$^+$, *m/z*): Calculated 786.2951 ($C_{37}H_{57}NNaO_8S_2Si_2$); Found 786.2956 (Δ -0.75 ppm).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -4.45 (*c* 0.70, $CHCl_3$)

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2-methylpropanal, 286



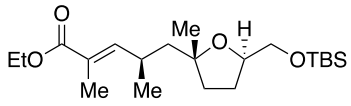
286

Weinreb amide **285** (20 mg, 0.055 mmol) was dissolved in THF (0.5 mL) and cooled to -78 ºC. DIBAL (1.0 M in PhMe, 0.11 mL, 0.11 mmol) was added dropwise and the reaction was left to stir for 3 h. The reaction was quenched at -78 ºC with EtOAc (1.0 mL), warmed to 0 ºC, then treated with a saturated solution of NH_4Cl (1.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2.0 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product **286** (20 mg) which was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.41 (1H, d, *J* = 4.1 Hz, O=C*H*), 3.84 – 3.72 (1H, m, C*H*CH_2OTBS), 3.55 (2H, t, *J* = 4.4 Hz, CH_2OTBS), 2.52 – 2.37 (1H, m, C*H*CH_3), 2.14 – 2.01 (1H, m, C$H_A$$H_B$C($CH_3$)O), 1.93 – 1.64 (4H, m, CH_2CH_2CHCH_2OTBS), 1.55 (1H, dd, *J* = 14.5, 3.9 Hz, C$H_A$$H_B$C($CH_3$)O), 1.20 (3H, s, C(C$H_3$)O), 1.09 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$).

The spectral data were consistent with those in the literature.[36]

ethyl (*R*,*E*)-5-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate, 287



287

*n*Butyllithium (2.5 M in hexanes, 0.050 mL, 0.12 mmol) was added to a suspension of (carbethoxyethylidene)triphenylphosphorane (58.0 mg, 0.131 mmol) in PhH (1 mL) at room temperature. After 30 minutes of stirring, crude aldehyde **286** (15 mg, 0.044 mmol) was added as a solution in PhH (0.5 mL) to the yellow reaction mixture which was then heated to 80 ºC. After 16 h of stirring the reaction was cooled to 0 ºC and quenched with a saturated solution of NH_4Cl (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2.0 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:12 EtOAc/pentane) yielded the title compound **287** as a colourless oil (15 mg, 90%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.67 – 6.59 (1H, m, C=C*H*), 4.27 – 4.11 (2H, m, CH_3CH_2O), 3.97 – 3.84 (1H, m, OC*H*), 3.61 (1H, dd, *J* = 10.3, 4.3 Hz, CH_AH_BOTBS), 3.58 – 3.46 (1H, m, CH_AH_BOTBS), 2.76 – 2.63 (1H, m, $CHCH_3$), 2.00 – 1.86 (1H, m, $C(CH_3)CH_AH_BCH_2$), 1.85 (3H, d, *J* = 1.5 Hz, CH_3C=CH), 1.83 – 1.74 (1H, m, $C(CH_3)CH_AH_BCH_2$) 1.72 – 1.51 (4H, m, $CH_2C(CH_3)O$ and CH_2CHO), 1.28 (3H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.15 (3H, s, $C(CH_3)O$), 1.02 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 168.7 (*C*=O), 149.1 (C=*C*H), 125.0 (*C*=CH), 83.2 ($C(CH_3)O$), 79.2 (O*C*H), 66.3 (CH_2OTBS) , 60.5 (CH_3CH_2O), 48.1 ($CHCH_3$), 37.7 (CH_2CHO), 30.2 ($CH_2C(CH_3)O$), 28.5 (CH_3C=CH), 27.0 (CH_3CHCH_2), 26.1 ($SiC(CH_3)_3$), 21.6 ($C(CH_3)O$), 18.5 ($SiC(CH_3)_3$), 14.5 ($CHCH_3$), 12.5 (CH_3CH_2O), -5.1 ($SiCH_3$) , -5.2 ($SiCH_3$).

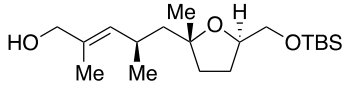
IR (ν_{max}/cm^{-1}): 1711, 1649, 1462, 1366, 1251, 1126, 1099.

HRMS (ESI$^+$, *m/z*): Calculated 385.2769 ($C_{21}H_{41}O_4Si$); Found 385.2769 (Δ -1.84 ppm).

$[\alpha]_D^{25}$ -7.46 (*c* 1.0, CH_2Cl_2).

The spectral data were consistent with those in the literature.[36]

(*R*,*E*)-5-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-en-1-ol, 288



288

Freshly azeotroped ester **287** (15 mg, 0.039 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to -78 ºC. Super-hydride® (1.0 M in THF, 0.16 mL) was added dropwise and the reaction was left to warm to room temperature. After stirring for 16 h, the reaction mixture was cooled to -78 ºC and quenched with EtOAc (1 mL) then warmed to 0 ºC. A saturated solution of NH_4Cl (1 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 2 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:5 EtOAc/pentane) yielded the title compound **288** as a colourless oil (12 mg, 90%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.31 – 5.22 (1H, m, C=C*H*), 3.97 (2H, s, OHCH_2), 3.95 – 3.88 (1H, m, OC*H*), 3.61 (1H, dd, *J* = 10.4, 4.7 Hz, CH_AH$_B$OTBS), 3.53 (1H, dd, *J* = 10.4, 5.4 Hz, CH$_A$$H_B$OTBS), 2.63 – 2.51 (1H, m, C*H*CH_3), 1.97 – 1.84 (1H, m, CH_AH$_B$CHCH$_2$OTBS), 1.83 – 1.70 (2H, m, CH$_A$$H_B$CHCH$_2$OTBS and C($CH_3$)C$H_AH_B$$CH_2$), 1.68 (3H, d, *J* = 1.4 Hz, CH_3C=CH), 1.64 – 1.55 (2H, m, C(CH_3)CH$_A$$H_B$$CH_2$ and CH_AH$_B$C(CH_3)O), 1.51 (1H, dd, *J* = 13.9, 8.3 Hz, CH$_A$$H_B$C($CH_3$)O), 1.17 (3H, s, C(C$H_3$)O), 0.97 (3H, d, *J* = 6.7 Hz, CHCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$).

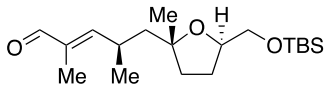
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 134.2 (C=*C*H), 131.4 (*C*=CH), 83.5 (*C*(CH_3)O), 79.1 (O*C*H), 69.3 (*C*H_2OH), 66.6 (*C*H_2OTBS), 48.6 (*C*HCH_3), 37.4 (*C*H_2CHO), 29.1 (*C*H_2C(CH_3)O), 28.6 (*C*H_3C=CH), 27.3 (CH_3CH*C*H_2), 26.1 (SiC(*C*H_3)$_3$), 22.8 (C(*C*H_3)O), 18.6 (Si*C*(CH_3)$_3$), 13.9 (CH*C*H_3), -5.1 (Si*C*H_3), -5.1 (Si*C*H_3).

IR (ν_{max}/cm^{-1}): 3370, 1461, 1361, 1254, 1098, 1008.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ 0.9 (*c* 1.0, CH_2Cl_2).

The spectral data were consistent with those in the literature.[36]

(*R*,*E*)-5-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enal, 289

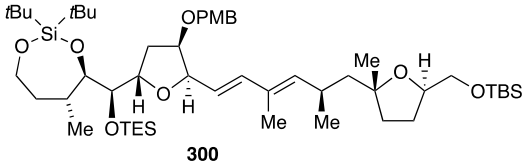


289

Dess–Martin periodinane (30 mg, 0.070 mmol) was suspended in CH_2Cl_2 (0.2 mL) and cooled to 0 ºC before $NaHCO_3$ (9.0 mg, 0.11 mmol) was added. After 30 minutes of stirring, alcohol **288** (6.0 mg, 0.018 mmol) was added to the reaction as a solution in CH_2Cl_2 (0.1 mL). After 16 h of stirring the reaction was diluted with Et_2O (2 mL) and poured into a saturated solution of $Na_2S_2O_3$ (2 mL). The mixture was stirred vigorously until all solids dissolved and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (12 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aldehyde **289** (3.7 mg) was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.38 (1H, s, O=C*H*), 6.45 – 6.34 (1H, m, C=C*H*), 3.90 – 3.79 (1H, m, OC*H*), 3.63 – 3.47 (2H, m, CH_2OTBS), 2.99 – 2.81 (1H, m, C*H*CH_3), 1.98 – 1.79 (2H, m, CH_2CHCH_2OTBS), 1.78 – 1.74 (3H, m, CH_3C=CH), 1.73 – 1.60 (4H, m, C(CH_3)C$H_2$$CH_2$ and CH_2C(CH_3)O), 1.16 (3H, s, C(CH_3)O), 1.08 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.89 – 0.87 (9H, m, SiC(CH_3)$_3$), 0.18 (3H, s, SiCH_3), 0.05 – 0.02 (6H, m, Si(CH_3)$_2$).

(4*R*,5*R*)-2,2-Di-*tert*-butyl-4-((*R*)-((2*S*,4*R*,5*R*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((triethylsilyl)oxy)methyl)-5-methyl-1,3,2-dioxasilepane, 300

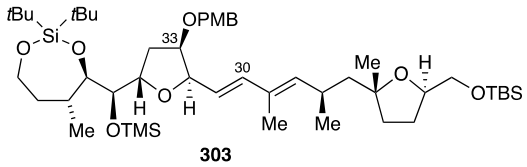


300

Freshly azeotroped aldehyde **289** (0.60 mg, 0.0018 mmol) and freshly azeotroped sulfone **275** (3.5 mg, 0.0043 mmol) were dissolved in THF (0.05 mL) and cooled to -78 ºC. LiHMDS (1.0 M in PhMe, 0.028 mL, 0.028 mmol) was added dropwise and after 20 minutes of stirring at -78 ºC the reaction was warmed to 0 ºC and stirred for a further 15 minutes. The reaction was diluted with EtOAc (2 mL) then quenched with a saturated solution of $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Preparative thin layer chromatography (1:25 EtOAc/cyclohexane) yielded the title compound **300** (2.2 mg, 99% over two steps) as a white amorphous solid.

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.23 (2H, dd, *J* = 8.5, 3.8 Hz, Ar*H*), 6.90 – 6.81 (2H, m, Ar*H*), 6.24 (1H, d, *J* = 15.8 Hz, Ar*H*), 5.77 (1H, dd, *J* = 15.7, 7.3 Hz, $C_{31}H$), 5.38 – 5.26 (1H, m, $C_{28}H$), 4.55 – 4.37 (3H, m, OCH_2Ar and $C_{35}H$), 4.36 – 4.26 (1H, m, $C_{32}H$), 4.01 – 3.89 (3H, m, $C_{40}H_2$, $C_{33}H$ and $C_{22}H$), 3.80 (3H, s, $ArOCH_3$), 3.62 (1H, dd, *J* = 10.3, 4.3 Hz, $C_{21}H_AH_B$), 3.56 – 3.47 (3H, m, $C_{37}H$, $C_{36}H$ and $C_{21}H_AH_B$), 2.71 – 2.66 (1H, m, $C_{27}H$), 2.27 (1H, dd, *J* = 13.0, 6.7 Hz, $C_{34}H_AH_B$), 2.15−1.84 (2H, m, $C_{38}H$ and $C_{23}H_AH_B$), 1.83 – 1.54 (10 H, m, $C_{39}H_2$, $C_{34}H_AH_B$, CH_3C_{29}, $C_{26}H_AH_B$, $C_{24}H_2$ and $C_{23}H_AH_B$), 1.54 – 1.48 (1H, m, $C_{26}H_AH_B$), 1.17 (3H, s, CH_3C_{25}), 1.05 – 0.94 (21H, m, $Si(C(CH_3)_3)_2$ and CH_3C_{27}), 0.98 – 0.84 (12 H, m, $SiCH_2(CH_3)_3$ and CH_3C_{38}), 0.77 – 0.50 (6H, m, $Si(CH_2CH_3)_3$), 0.10 – 0.02 (15H, m, $Si(CH_3)_3$ and $Si(CH_3)_2$).

(4*R*,5*R*)-2,2-Di-*tert*-butyl-4-((*R*)-((2*S*,4*R*,5*R*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((trimethylsilyl)oxy)methyl)-5-methyl-1,3,2-dioxasilepane, 303



303

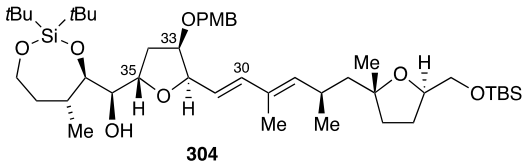
Freshly azeotroped aldehyde **289** (3.10 mg, 0.00910 mmol) and freshly azeotroped sulfone **302** (12.5 mg, 0.0141 mmol) were dissolved in THF (0.07 mL) and cooled to -78 ºC. LiHMDS (1.0 M in PhMe, 0.025 mL, 0.025 mmol) was added dropwise and after 20 minutes of stirring at -78 ºC the reaction was warmed to 0 ºC and stirred for a further 15 minutes. The reaction was diluted with EtOAc (2 mL) then quenched with a saturated solution of $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Preparative thin layer chromatography (1:25 EtOAc/cyclohexane) yielded the title compound **303** (9.1 mg, 99% over two steps) as a white amorphous solid.

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.26 – 7.19 (2H, m, Ar*H*), 6.89 – 6.81 (2H, m, Ar*H*), 6.24 (1H, d, *J* = 15.8 Hz, $C_{30}H$), 5.78 (1H, dd, *J* = 15.7, 7.4 Hz, $C_{31}H$), 5.31 (1H, d, *J* = 9.7 Hz, $C_{28}H$), 4.51 (1H, d, *J* = 11.9 Hz, OCH_AH_BAr), 4.49 – 4.44 (1H, m, $C_{35}H$), 4.41 (1H, d, *J* = 11.9 Hz, OCH_AH_BAr), 4.28 (1H, dd, *J* = 7.5, 3.3 Hz, $C_{32}H$), 4.03 – 3.87 (4H, m, $C_{40}H_2$, $C_{33}H$, and $C_{22}H$), 3.80 (3H, s, $ArOCH_3$), 3.61 (1H, dd, *J* = 10.3, 4.3 Hz, $C_{21}H_AH_B$), 3.56 – 3.44 (3H, m, $C_{37}H$, $C_{36}H$ and $C_{21}H_AH_B$), 2.71 – 2.64 (1H, m, $C_{27}H$), 2.25 (1H, ddd, *J* = 13.2, 6.7, 1.5 Hz, $C_{34}H_AH_B$), 2.02 – 1.86 (2H, m, $C_{38}H$ and $C_{23}H_AH_B$), 1.85 – 1.56 (10H, m, $C_{39}H_2$, $C_{34}H_AH_B$, CH_3C_{29}, $C_{26}H_AH_B$, $C_{24}H_2$ and $C_{23}H_AH_B$), 1.52 (1H, dd, *J* = 13.9, 8.5 Hz, $C_{26}H_AH_B$), 1.19 – 1.14 (3H, m, CH_3C_{25}), 1.05 – 0.97 (21H, m, $Si(C(CH_3)_3)_2$ and CH_3C_{27}), 0.92 – 0.85 (12H, m, $SiC(CH_3)_3$ and CH_3C_{38}), 0.12 – 0.08 (9H, m, $Si(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.2 (quat. *C* Ar), 140.5 (C_{28}), 137.8 (C_{30}), 130.8 (C_{29}), 130.7 (quat. *C* Ar), 129.2 (*C* Ar), 123.1 (C_{31}), 113.8 (*C* Ar), 83.6 (C_{25}), 82.5 (C_{32}), 81.8 (C_{37}), 81.3 (C_{33}), 79.3 (C_{35}), 79.1 (C_{22}), 77.3 (C_{36}), 71.1 (OCH_2Ar), 66.4 (C_{21}), 66.3 (C_{40}), 55.4 ($ArOCH_3$), 48.7 (C_{26}), 42.3 (C_{39}), 38.6 (C_{38}), 37.6 (C_{24}), 34.9 (C_{34}), 29.6 (C_{27}), 28.5 (C_{23}), 28.0 ($Si(C(CH_3)_3$), 28.0 ($Si(C(CH_3)_3$), 27.0 (CH_3C_{25}), 26.1 ($Si(C(CH_3)_3$), 22.8 (CH_3C_{27}), 22.2 ($Si(C(CH_3)_3$), 21.6 ($Si(C(CH_3)_3$), 19.5 (CH_3C_{38}), 18.6 ($Si(C(CH_3)_3$), 12.8 (CH_3C_{29}), -5.1 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_3$).

HRMS (ESI^+, *m/z*): Calculated 839.5284 ($C_{46}H_{80}NaO_8Si_2$); Found 839.5279 (Δ -0.60 ppm).

(*R*)-((2*S*,4*R*,5*R*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanol, 304



304

To a solution of TMS ether **303** (6.5 mg, 0.0073 mmol) in a 1:1 mixture of MeOH/CH_2Cl_2 (0.2 mL) at 0 °C was added a spatula tip of PPTS. After 20 minutes of stirring the reaction was diluted with EtOAc (2 mL) and quenched with a saturated solution of $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:5 EtOAc/pentane) yielded the title compound **304** (4.4 mg, 76%) as a white amorphous solid.

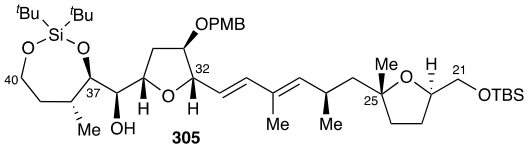
^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.26 – 7.19 (2H, m, Ar*H*), 6.88 – 6.82 (2H, m, Ar*H*), 6.24 (1H, d, *J* = 15.6 Hz, $C_{30}H$), 5.79 (1H, dd, *J* = 15.7, 8.3 Hz, $C_{31}H$), 5.31 (1H, d, *J* = 10.0 Hz, $C_{28}H$), 4.53 – 4.38 (4H, m, OCH_2Ar, $C_{35}H$ and $C_{32}H$), 4.06 – 3.90 (4H, m, $C_{40}H_2$, $C_{33}H$ and $C_{22}H$), 3.80 (3H, s, $ArOCH_3$), 3.65 – 3.58 (2H, m, $C_{37}H$ and $C_{21}H_AH_B$), 3.52 (1H, dd, *J* = 10.4, 5.5 Hz, $C_{21}H_AH_B$), 3.47 (1H, t, *J* = 7.4 Hz, $C_{36}H$), 2.74 – 2.62 (1H, m, $C_{27}H$), 2.48 (1H, d, *J* = 7.8 Hz, OHC_{36}), 2.30 – 2.22 (1H, m, $C_{34}H_AH_B$), 2.03 – 1.85 (2H, m, $C_{38}H$ and $C_{23}H_AH_B$), 1.82 – 1.56 (10H, m, $C_{39}H_2$, $C_{34}H_AH_B$, CH_3C_{29}, $C_{26}H_AH_B$, $C_{24}H_2$ and $C_{23}H_AH_B$) 1.51 (dd, *J* = 13.8, 8.9 Hz, $C_{26}H_AH_B$), 1.15 (3H, s, CH_3C_{25}), 1.04 – 1.00 (18H, m, $Si(C(CH_3)_3)_2$), 0.99 (3H, d, *J* = 6.7 Hz, CH_3C_{27}), 0.94 (3H, d, *J* = 6.9 Hz, CH_3C_{38}), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 – 0.04 (6H, m, $Si(CH_3)_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.2 (quat. *C* Ar), 141.0 (C_{28}), 138.9 (C_{30}), 130.8 (C_{29}), 130.6 (quat. *C* Ar), 129.1 (*C* Ar), 122.6 (C_{31}), 113.8 (*C* Ar), 83.7 (C_{32}), 83.6 (C_{25}), 81.2 (C_{33}), 80.9 (C_{37}), 79.5 (C_{35}), 79.0 (C_{22}), 75.1 (C_{36}), 71.4 (OCH_2Ar), 66.4 (C_{21}), 65.9 (C_{40}), 55.4

(ArO*C*H$_3$), 48.9 (*C*$_{26}$), 42.5 (*C*$_{39}$), 38.9 (*C*$_{38}$), 37.7 (*C*$_{24}$), 35.6 (*C*$_{34}$), 29.9 (*C*$_{27}$), 28.6 (*C*$_{23}$), 28.3 (SiC(*C*H$_3$)$_3$), 28.1 (SiC(*C*H$_3$)$_3$), 26.8 (*C*H$_3$C$_{25}$), 26.1 (SiC(*C*H$_3$)$_3$), 22.9 (*C*H$_3$C$_{27}$), 21.9 (Si*C*(CH$_3$)$_3$), 21.7 (Si*C*(CH$_3$)$_3$), 19.5 (*C*H$_3$C$_{38}$), 18.6 (Si*C*(CH$_3$)$_3$), 12.8 (*C*H$_3$C$_{29}$), -5.1 (Si*C*H$_3$), -5.1 (Si*C*H$_3$).

HRMS (ESI$^+$, *m/z*): Calculated 839.5284 (C$_{46}$H$_{80}$NaO$_8$Si$_2$); Found 839.5279 (Δ -0.60 ppm).

(*R*)-((2*S*,4*R*,5*S*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanol, 305



Julia Olefination:

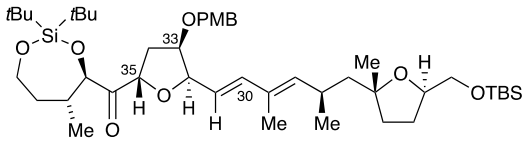
Freshly azeotroped aldehyde **289** (1.00 mg, 0.0029 mmol) and freshly azeotroped sulfone **272** (5.1 mg, 0.0074 mmol) were dissolved in THF (0.03 mL) and cooled to -78 ºC. LiHMDS (1.0 M in PhMe, 0.019 mL, 0.019 mmol) was added dropwise and after 20 minutes of stirring at -78 ºC the reaction was warmed to 0 ºC and stirred for a further 15 minutes. The reaction was diluted with EtOAc (2 mL) then quenched with a saturated solution of $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Preparative thin layer chromatography (1:20 EtOAc/cyclohexane) yielded the title compound **305** (1.9 mg, 79% over two steps) as a white amorphous solid. Compound **305** was also isolated as a by-product from the deprotection of silyl ether **303**.

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.23 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.90 – 6.83 (2H, m, Ar*H*), 6.28 (1H, d, *J* = 15.6 Hz, $C_{30}H$), 5.49 (1H, dd, *J* = 15.6, 6.9 Hz, $C_{31}H$), 5.32 (1H, d, *J* = 9.9 Hz, $C_{28}H$), 4.51 – 4.44 (2H, m, OCH_2Ar), 4.40 (1H, dd, *J* = 6.9, 3.5 Hz, $C_{32}H$), 4.33 – 4.24 (1H, m, $C_{35}H$), 4.10 – 3.90 (3H, m, $C_{40}H_2$ and $C_{22}H$), 3.90 – 3.85 (1H, m, $C_{33}H$), 3.80 (3H, s, $ArOCH_3$), 3.67 – 3.58 (2H, m, $C_{37}H$ and $C_{21}H_AH_B$), 3.57 – 3.48 (2H, m, $C_{36}H$ and $C_{21}H_AH_B$), 2.71 – 2.61 (1H, m, $C_{27}H$), 2.46 (1H, d, *J* = 8.3 Hz, O*H*), 2.12 – 2.06 (1H, m, $C_{34}H_AH_B$), 2.01 – 1.95 (1H, m, $C_{38}H$), 2.01 – 1.85 (1H, m, $C_{23}H_AH_B$), 1.84 – 1.55 (10H, m, $C_{39}H_2$, $C_{34}H_AH_B$, CH_3C_{29}, $C_{26}H_AH_B$, $C_{24}H_2$ and $C_{23}H_AH_B$), 1.50 (1H, dd, *J* = 13.9, 8.4 Hz, $C_{26}H_AH_B$), 1.16 (3H, s,

C*H*$_3$C$_{25}$), 1.05 – 1.00 (18H, m, 18H, m, Si(C(C*H*$_3$)$_3$)$_2$), 1.00 – 0.92 (6H, m, C*H*$_3$C$_{38}$ and C*H*$_3$C$_{27}$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.05 –0.03 (m, 6H, Si(C*H*$_3$)$_2$).

HRMS (ESI$^+$, *m/z*): Calculated 817.5470 ($C_{47}H_{80}O_8Si_2$); Found 817.5483 (Δ +1.6 ppm).

((2*S*,4*R*,5*R*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanone, 309



309

Pyridine (0.026 mL, 0.32 mmol) and Dess-Martin periodinane (16 mg, 0.037 mmol) were added sequentially to a solution of alcohol **304** (2.0 mg, 0.0024 mmol) in CH_2Cl_2 (0.2 mL). The reaction was heated to 30 ºC and stirred for 1.5 h. The reaction was then diluted with CH_2Cl_2 (2 mL) and poured into a saturated solution of $Na_2S_2O_3$ (2 mL). The mixture was stirred vigorously until all solids dissolved and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (12 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane) yielded the title compound **309** (1.9 mg, 95%) as white amorphous solid.

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.27 – 7.19 (2H, m, Ar*H*), 6.89 – 6.82 (2H, m, Ar*H*), 6.31 (1H, d, *J* = 15.8 Hz, $C_{30}H$), 5.76 (1H, dd, *J* = 15.7, 8.3 Hz, $C_{31}H$), 5.35 (1H, d, *J* = 9.7 Hz, $C_{28}H$), 5.14 (1H, dd, *J* = 8.5, 7.3 Hz, $C_{35}H$), 4.62 (1H, dd, *J* = 8.3, 3.5 Hz, $C_{32}H$), 4.51 (1H, d, *J* = 11.7 Hz, OCH_AH$_B$Ar), 4.44 (1H, d, *J* = 11.6 Hz, OCH_AH$_B$Ar), 4.13 (1H, d, *J* = 9.2 Hz, $C_{37}H$), 4.09 – 4.05 (1H, m, $C_{33}H$), 4.04 – 3.99 (2H, m, $C_{40}H_2$), 3.99 – 3.88 (1H, m, $C_{22}H$), 3.80 (3H, s, ArOCH_3), 3.62 (1H, dd, *J* = 10.4, 4.4 Hz, $C_{21}H_AH_B$), 3.52 (1H, dd, *J* = 10.4, 5.6 Hz, $C_{21}H_AH_B$), 2.75 – 2.62 (1H, m, $C_{27}H$), 2.58 – 2.50 (1H, m, $C_{34}H_AH_B$), 2.05 (1H, ddd, *J* = 13.4, 8.6, 4.8 Hz, $C_{34}H_AH_B$), 1.97 – 1.84 (2H, m, $C_{38}H$ and $C_{23}H_AH_B$), 1.84 – 1.72 (5H, m, $C_{39}H_AH_B$, CH_3C_{29} and $C_{23}H_AH_B$), 1.71 – 1.56 (4H, m, $C_{39}H_AH_B$, $C_{26}H_AH_B$ and $C_{24}H_2$), 1.51 (1H, dd, *J* = 13.8, 8.7 Hz, $C_{26}H_AH_B$), 1.15 (3H, s, CH_3C_{25}), 1.08 (9H, s, SiC(CH_3)$_3$), 1.03 – 0.97 (12H, s,

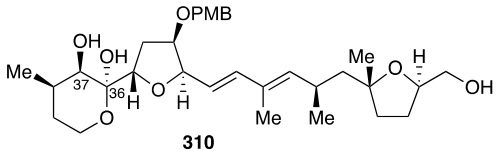
C*H*$_3$C$_{27}$ and SiC(C*H*$_3$)$_3$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.85 (3H, d, *J* = 6.9 Hz, C*H*$_3$C$_{38}$), 0.05 (s, 6H).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 210.9 (*C*$_{38}$), 159.3 (quat. *C* Ar), 141.52 (*C*$_{28}$), 139.6 (*C*$_{30}$), 130.6 (*C*$_{29}$), 130.4 (quat. *C* Ar), 129.2 (*C* Ar), 121.7 (*C*$_{31}$), 113.9 (quat. *C* Ar), 85.5 (*C*$_{37}$), 85.4 (*C*$_{32}$), 83.6 (*C*$_{25}$), 80.8 (*C*$_{33}$), 79.0 (*C*$_{22}$), 77.4 (*C*$_{35}$), 71.5 (O*C*H$_2$Ar), 66.4 (*C*$_{21}$), 65.4 (*C*$_{40}$), 55.4 (ArO*C*H$_3$), 48.8 (*C*$_{26}$), 42.6 (*C*$_{39}$), 39.7 (*C*$_{38}$), 37.8 (C$_{24}$), 37.7 (*C*$_{34}$), 29.9 (*C*$_{27}$), 28.6 (*C*$_{23}$), 28.3 (SiC(*C*H$_3$)$_3$), 28.3 (SiC(*C*H$_3$)$_3$), 26.8 (*C*H$_3$C$_{25}$), 26.1 (SiC(*C*H$_3$)$_3$), 22.9 (*C*H$_3$C$_{27}$), 21.6 (Si*C*(CH$_3$)$_3$), 21.2 (Si*C*(CH$_3$)$_3$), 18.6 (Si*C*(CH$_3$)$_3$), 18.0 (*C*H$_3$C$_{38}$), 12.8 (*C*H$_3$C$_{29}$), -5.1 (Si*C*H$_3$), -5.1 (Si*C*H$_3$).

IR (ν_{max}/cm^{-1}): 1734, 1515, 1473, 1458, 1250, 1107.

HRMS (ESI$^+$, *m/z*): Calculated 814.5235 ($C_{46}H_{78}O_8Si_2$); Found 814.5250 (Δ +1.50 ppm).

(2*S*,3*R*,4*R*)-2-((2*S*,4*R*,5*R*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(Hydroxymethyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-4-methyltetrahydro-2*H*-pyran-2,3-diol, 310



310

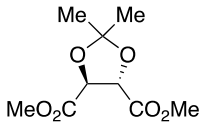
TAS-F (1.0 M solution in DMF, 0.010 mL, 0.0069 mmol) was added to a solution of ketone **309** (1.6 mg, 0.0020 mmol) in H_2O/DMF (1.5 M solution of H_2O in DMF, 0.020 mL, 0.014 mmol) at room temperature. After stirring for 16 h the reaction was washed through a plug of silica gel with EtOAc and subsequently purified by preparative thin layer chromatography (1:2 EtOAc/cyclohexane) to yield the title compound **310** as a white amorphous solid (0.6 mg, 64%).

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.23 (2H, d, J = 8.6 Hz, Ar*H*), 6.89 – 6.81 (2H, m, Ar*H*), 6.22 (1H, d, J = 15.7 Hz, $C_{30}H$), 5.80 (1H, dd, J = 15.7, 8.4 Hz, $C_{31}H$), 5.33 (1H, d, J = 9.9 Hz, $C_{28}H$), 4.56 – 4.40 (4H, m, OCH_2Ar, $C_{35}H$ and $C_{32}H$,), 4.03 (1H, t, J = 4.0 Hz, $C_{33}H$), 3.98 (2H, m, $C_{22}H$ and $C_{21}H_AH_B$), 3.80 (3H, s, ArOCH_3), 3.73 – 3.61 (2H, m, $C_{40}H_AH_B$ and $C_{21}H_AH_B$), 3.45 (1H, dt, J = 11.6, 6.0 Hz, $C_{40}H_AH_B$), 3.35 (1H, dd, J = 10.6, 2.2 Hz, $C_{37}H$), 3.24 (1H, s, $C_{36}OH$), 2.73 – 2.63 (1H, m, $C_{27}H$), 2.34 (1H, dd, J = 13.1, 5.7 Hz, $C_{34}H_AH_B$), 2.15 (1H, m, $C_{38}H$), 1.94 – 1.81 (2H, m, $C_{39}H_AH_B$ and $C_{34}H_AH_B$), 1.80 – 1.71 (5H, m, $C_{39}H_AH_B$, CH_3C_{29} and $C_{24}H_AH_B$), 1.67 (1H, d, J = 10.6 Hz, $C_{37}OH$), 1.65 – 1.43 (3H, m, $C_{26}H_2$ and $C_{24}H_AH_B$), 1.35 – 1.20 (2H, m, $C_{23}H_2$), 1.17 (3H, s, CH_3C_{25}), 1.04 – 0.93 (6H, m, CH_3C_{38} and CH_3C_{27}).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.0 (quat. *C* Ar), 140.7 (C_{28}), 138.6 (C_{30}), 130.5 (C_{29}), 130.3 (quat. *C* Ar), 128.7 (*C* Ar), 122.4 (C_{31}), 113.6 (*C* Ar), 96.9 (C_{36}), 85.2 (C_{32}), 83.6 (C_{25}), 81.1 (C_{35}), 80.5 (C_{33}), 78.5 (C_{22}), 71.0 (OCH_2Ar), 71.0 (C_{37}), 65.2 (C_{40}), 60.6 (C_{21}), 55.2 (ArOCH_3), 48.4 (C_{26}), 37.7 (C_{24}), 33.0 (C_{34}), 29.6 (C_{27}), 29.3 (C_{38}), 27.5 (C_{39}), 27.0 (C_{23}), 22.6 (CH_3C_{27}), 17.3 (CH_3C_{38}), 12.6 (CH_3C_{29}).

HRMS (ESI^+, *m/z*): Calculated 583.3241 ($C_{32}H_{48}NaO_8$); Found 583.3237 (Δ -0.81 ppm).

Dimethyl (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate, 319



319

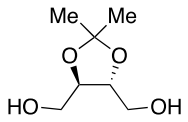
D-(-)-Tartaric acid **327** (40.0 g, 267 mmol) and PTSA (460 mg, 2.67 mmol) were dissolved in a mixture of 2,2-dimethoxypropane (114 mL, 927 mmol) and MeOH (17.8 mL, 440 mmol) and the resulting solution was heated to reflux. After stirring for 2 h cyclohexane (193 mL) and a further portion of 2,2-dimethoxypropane (37.0 mL, 301 mmol) were added at room temperature and the reaction vessel was fitted with a vigreux column. The reaction was heated to 70 °C and left to stir for 16 h while MeOH and H_2O were azeotropically removed. Additional 2,2-dimethoxypropane (37.0 mL, 301 mmol) and cyclohexane (270 mL) were added at room temperature and the reaction was heated to 70 °C with MeOH and H_2O being removed azeotropically. After 16 h of stirring the reaction was quenched with anhydrous K_2CO_3 (2.00 g, 14.5 mmol) at room temperature then concentrated *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane to 1:5 EtOAc/pentane) yielded the title compound **319** as a yellow oil (53.2 g, 92%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.81 (2H, s, 2 x C*H*), 3.82 (6H, s, 2 x CH_3O), 1.49 (6H, s, C(CH_3)$_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 170.2 (2 x CH_3OCO), 114.0 (*C*$(CH_3)_2$), 77.1 (2 x *C*H), 53.0 (2 x *C*H_3O), 26.4 (C(*C*H_3)$_2$).

The spectral data were consistent with those in the literature.[78]

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol, 328



328

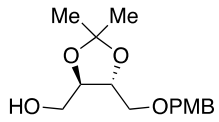
Diester **319** (36.0 g, 165 mmol) was dissolved in Et_2O (900 mL) and the resulting solution was cooled to 0 °C. $LiAlH_4$ (30.0 g, 791 mmol) was added portionwise with caution over a period of 40 minutes. After stirring for 3 h at room temperature, the reaction was cooled to 0 °C and quenched carefully with the dropwise addition of H_2O (30 mL) followed by a 3M aqueous solution of NaOH (30 mL) and then a further portion of H_2O (94 mL). The resulting mixture was concentrated over silica gel *in vacuo* and flash column chromatography (1:2 Et_2O/pentane to 1:1 Et_2O/pentane) yielded the title compound **328** as a colourless oil (25.2 g, 94%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.05 – 3.94 (2H, m, 2 x C*H*), 3.84 – 3.76 (2H, m, CH_2), 3.73 – 3.66 (2H, m, CH_2), 2.48 – 2.24 (1H, m, O*H*), 1.45 – 1.40 (6H, m, C(CH_3)$_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 109.4 (*C*(CH$_3$)$_2$), 78.1 (*C*H), 78.1 (*C*H), 62.1 (*C*H$_2$), 27.2 (C(*C*H$_3$)$_2$).

The spectral data were consistent with those in the literature.[78]

((4*R*,5*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol, 320



320

4-Methoxybenzyl chloride (16.6 mL, 122 mmol) was added to a mixture of diol **328** (20.8 g, 129 mmol) and anhydrous KOH (6.85 g, 122 mmol) in PhH (250 mL) at room temperature and the reaction was heated to reflux. After stirring under reflux for 16 h the reaction was cooled to room temperature, filtered, and concentrated *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane to 1:1 EtOAc/pentane) yielded the bis PMB-ether **329** first, as a by-product, then the title compound **320** as a colourless oil (22.6 g, 65%).

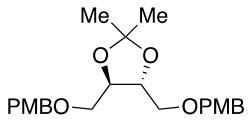
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.33 – 7.20 (2H, m, Ar*H*), 6.93 – 6.83 (2H, m, Ar*H*), 4.57 – 4.46 (2H, m, OC*H*$_2$Ar), 4.02 (1H, ddd, *J* = 8.3, 6.0, 5.0 Hz, C*H*CH$_2$OPMB), 3.96 – 3.87 (1H, m, OHCH$_2$C*H*), 3.80 (3H, s, ArOC*H*$_3$), 3.75 (1H, dd, *J* = 11.7, 4.6 Hz, OHC*H*$_A$H$_B$), 3.71 – 3.62 (2H, m, OHCH$_A$*H*$_B$ and C*H*$_A$H$_B$OPMB), 3.51 (1H, dd, *J* = 9.8, 6.0 Hz, CH$_A$*H*$_B$OPMB), 2.32 (1H, s, O*H*), 1.42 – 1.39 (6H, m, C(C*H*$_3$)$_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.5 (quat. *C* Ar), 130.0 (quat. *C* Ar), 129.6 (*C* Ar), 114.0 (*C* Ar), 109.4 (*C*(CH$_3$)$_2$), 79.9 (OHCH$_2$*C*H), 76.9 (*C*HCH$_2$OPMB) 73.5 (O*C*H$_2$Ar), 70.1 (*C*H$_2$OPMB), 62.6 (OH*C*H$_2$), 55.4 (ArO*C*H$_3$), 27.1 (C(*C*H$_3$)$_2$).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ –13.1 (*c* 1.08, $CHCl_3$).

The spectral data were consistent with those in the literature.[78]

(4*R*,5*R*)-4,5-Bis(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane, 329



329

Compound **329** was isolated as a byproduct in the synthesis of alcohol **320**.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.28 – 7.24 (4H, m, Ar*H*), 6.91 – 6.87 (4H, m, Ar*H*), 4.53 (4H, dd, *J* = 16.2, 11.7 Hz, 2 x OC*H*$_2$Ar), 4.09 – 3.97 (2H, m, 2 x C*H*), 3.83 (6H, s, 2 x ArOC*H*$_3$), 3.65 – 3.53 (4H, m, 2 x C*H*$_2$CHO), 1.45 (6H, s, C(C*H*$_3$)$_2$).

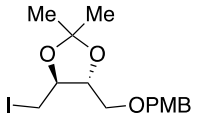
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.1 (quat. *C* Ar), 130.0 (quat. *C* Ar), 129.1 (*C* Ar), 113.7 (*C* Ar), 109.6 (*C*(CH$_3$)$_2$), 77.5 (*C*HCH$_2$OPMB) 73.1 (OCH$_2$Ar), 70.3 (*C*H$_2$OPMB), 55.2 (ArOCH$_3$), 27.0 (C(*C*H$_3$)$_2$).

IR (ν_{max}/cm^{-1}): 2862, 1612, 1513, 1463, 1369, 1302, 1246, 1172, 1083, 1034, 819.

HRMS (ESI$^+$, *m/z*): Calculated 425.1929 ($C_{23}H_{30}NaO_6$), Found 425.1935 (Δ -1.82 ppm).

The spectral data were consistent with those in the literature.[78]

(4*S*,5*R*)-4-(Iodomethyl)-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane, 321



321

Alcohol **320** (21.0 g, 74.4 mmol), triphenylphosphine (23.4 g, 89.3 mmol) and imidazole (15.2 g, 223 mmol) were dissolved in PhMe (460 mL) and the resulting solution was heated to reflux then cooled to room temperature. Iodine (24.4 g, 96.1 mmol) was added portionwise and the reaction was heated to reflux for 1 h. The reaction was quenched with MeOH (300 mL) at room temperature then concentrated *in vacuo.* Flash column chromatography (1:8 EtOAc/pentane) yielded the title compound **321** as a colourless oil (26.2 g, 90%).

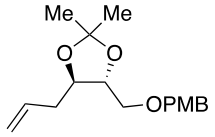
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.30 – 7.22 (2H, m, Ar*H*), 6.93 – 6.84 (2H, m, Ar*H*), 4.52 (2H, s, OC*H*$_2$Ar), 4.01 – 3.90 (1H, m, C*H*CH$_2$OPMB), 3.87 – 3.82 (1H, m, ICH$_2$C*H*), 3.81 (3H, s, ArOC*H*$_3$), 3.67 – 3.55 (2H, m, C*H*$_2$OPMB), 3.34 (1H, dd, *J* = 10.6, 5.0 Hz, IC*H*$_A$H$_B$), 3.26 (1H, dd, *J* = 10.6, 5.4 Hz, ICH$_A$*H*$_B$), 1.46 (3H, s, C(C*H*$_3$)), 1.41 (3H, s, C(C*H*$_3$)).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.4 (quat. *C* Ar), 130.0 (quat. *C* Ar), 129.5 (*C* Ar), 114.0 (*C* Ar), 109.9 (*C*(CH$_3$)$_2$), 80.2 (I*C*H$_2$), 77.9 (*C*HCH$_2$OPMB), 73.4 (O*C*H$_2$Ar), 70.3 (*C*H$_2$OPMB), 55.4 (ArO*C*H$_3$), 27.5 (C(*C*H$_3$)), 27.4 (C(*C*H$_3$)).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +10.7 (*c* 1.8, $CHCl_3$).

The spectral data were consistent with those in the literature.[78]

(4*R*,5*R*)-4-Allyl-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane, 330



330

Iodide **321 (**20.0 g, 51.0 mmol) was added to a suspension of HMPA (35.5 mL, 204 mmol) and copper iodide (917 mg, 5.10 mmol) in THF (100 mL) at room temperature. The resulting mixture was cooled to -50 °C and vinylmagnesium bromide (1M in THF, 102 mL, 102 mmol) was added dropwise over a period of 30 minutes. After stirring for 1 h the reaction was allowed to warm to room temperature and quenched with a saturated solution of $NaHCO_3$ (200 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Flash column chromatography (1:15 EtOAc/pentane to 1:10 EtOAc/pentane) yielded the title compound **320** as a colourless oil (13.6 g, 91%).

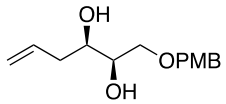
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.29 – 7.22 (2H, m, Ar*H*), 6.92 – 6.84 (2H, m, Ar*H*), 5.81 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, CH_2=C*H*), 5.17 – 5.03 (2H, m, CH_2=CH), 4.57 – 4.46 (2H, m, OCH_2Ar), 3.90 – 3.81 (2H, m, CH_2=CHCH_2C*H* and C*H*CH_2OPMB), 3.81 (3H, s, ArOCH_3), 3.56 – 3.50 (2H, m, CH_2OPMB), 2.41 – 2.32 (2H, m, CH_2=CHCH_2), 1.41 (3H, s, C(CH_3)), 1.40 (3H, s, C(CH_3)).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.3 (quat. *C* Ar), 133.9 (CH_2=*C*H), 130.2 (quat. *C* Ar), 129.4 (*C* Ar), 117.7 (*C*H_2=CH), 113.9 (*C* Ar), 109.0 (*C*$(CH_3)_2$), 79.7 (CH_2=CHCH_2*C*H), 77.5 (*C*HCH_2OPMB), 73.3 (OCH_2Ar), 70.2 (*C*H_2OPMB), 55.4 (ArOCH_3), 37.5 (CH_2=CH*C*H_2), 27.4 (C(*C*H_3)), 27.2 (C(*C*H_3)).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +14.9 (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[78]

(2*R*,3*R*)-1-((4-Methoxybenzyl)oxy)hex-5-ene-2,3-diol, 322



322

Alkene **320** (12.0 g, 41.0 mmol) was dissolved in a solution of EtOH (100 mL) and ethylene glycol (80 mL) at room temperature. The resulting solution was cooled to 0 °C and a 2 M aqueous solution of HCl (180 mL) was added portionwise. The reaction was allowed to stir for 16 h at room temperature before being quenched with a 2 M aqueous solution of NaOH. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (EtOAc/pentane 1:1) yielded the title compound **322** as a colourless solid (9.11 g, 88%).

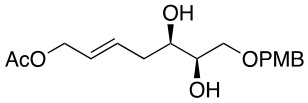
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.30 – 7.20 (2H, m, Ar*H*), 6.93 – 6.84 (2H, m, Ar*H*), 5.84 (1H, ddt, *J* = 17.2, 10.2, 7.1 Hz, CH_2=C*H*), 5.18 – 5.06 (2H, m, C*H*$_2$=CH), 4.55 – 4.42 (2H, m, OC*H*$_2$Ar), 3.81 (3H, s, ArOC*H*$_3$), 3.80 – 3.59 (3H, m, 2 x C*H*OH and C*H*$_A$H$_B$OPMB), 3.55 (1H, dd, *J* = 9.6, 5.7 Hz, CH$_A$*H*$_B$OPMB), 2.61 – 2.52 (2H, m, 2 x O*H*), 2.37 – 2.21 (2H, m, CH_2=CHC*H*$_2$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.6 (quat. *C* Ar), 134.6 (CH_2=*C*H), 129.8 (quat. *C* Ar), 129.6 (*C* Ar), 118.0 (*C*H_2=CH), 114.0 (*C* Ar), 73.5 (O*C*H_2Ar), 72.5 (*C*H_2OPMB), 71.7 (*C*HOH), 71.7 (*C*HOH), 55.4 (ArO*C*H_3), 38.3 (CH_2=CH*C*H_2).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +17.9 (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[78]

(5*R*,6*R*,*E*)-5,6-Dihydroxy-7-((4-methoxybenzyl)oxy)hept-2-en-1-yl acetate, 323



323

Compound **322** (119 mg, 0.470 mmol) and allyl acetate (0.30 mL, 2.8 mmol) were added to a suspension of Hoveyda-Grubbs second generation catalyst (14.0 mg, 0.0230 mmol) in CH_2Cl_2 (10 mL) and the resulting solution was heated to reflux for 16 h. Once cooled to room temperature, silica gel was added to the reaction mixture and the solvent was removed *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane to 4:1 EtOAc/pentane) yielded the title compound **323** as a faint brown oil (93.0 mg, 68%).

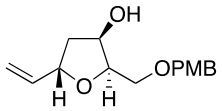
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.28 – 7.20 (2H, m, Ar*H*), 6.93 – 6.84 (2H, m, Ar*H*), 5.86 – 5.59 (2H, m, C*H*=C*H*), 4.55 – 4.42 (4H, m, AcOCH_2 and OCH_2Ar), 3.81 (3H, s, ArOCH_3), 3.76 – 3.67 (1H, m, CH=CHCH$_2$C*H*OH), 3.67 – 3.51 (2H, m, CH_2OPMB and C*H*(OH)CH$_2$OPMB), 2.63 (1H, d, *J* = 4.3 Hz, CH=CHCH$_2$CHO*H*), 2.60 (1H, d, *J* = 6.0 Hz, CH(O*H*)CH$_2$OPMB), 2.42 – 2.27 (2H, m, CH=CHCH_2CHOH), 2.06 (3H, s, CH_3COO).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 171.0 (*C*=O), 159.6 (quat. *C* Ar), 131.7 (AcOCH$_2$*C*H=CH), 129.7 (quat. *C* Ar), 129.6 (*C* Ar), 127.2 (CH=*C*HCH$_2$CHOH), 114.1 (*C* Ar), 73.5 (O*C*H$_2$Ar), 72.5 (*C*H$_2$OPMB), 71.8 (CH=CHCH$_2$*C*HOH), 65.0 (AcO*C*H$_2$), 55.4 (ArO*C*H$_3$), 36.7 (CH=CH*C*H$_2$CHOH), 21.2 (*C*H$_3$COO).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **+16.9** (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[78]

(2*R*,3*R*,5*S*)-2-(((4-Methoxybenzyl)oxy)methyl)-5-vinyltetrahydrofuran-3-ol, 312



312

A solution of $Pd_2(dba)_3$ (2.30 mg, 0.00300 mmol) and tris(*p*-methoxyphenyl)phosphine (3.50 mg, 0.0100 mmol) in THF (0.90 mL) was heated to reflux for 2 minutes. Once cooled to room temperature the solution was added to a solution of diol **323** (80.0 mg, 0.247 mmol) in THF (2 mL) and the resulting solution was heated to 40 °C. After 2 h of stirring the reaction mixture was cooled to room temperature concentrated over silica gel *in vacuo*. Flash column chromatography (1:10 EtOAc/pentane to 2:3 EtOAc/pentane) yielded the title compound **312** as a colourless oil (56.0 mg, 85%).

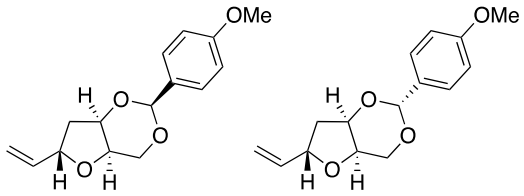
^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.30 – 7.22 (2H, m, Ar*H*), 6.92 – 6.85 (2H, m, Ar*H*), 5.83 (1H, ddd, *J* = 17.1, 10.3, 6.7 Hz, CH_2=C*H*), 5.27 (1H, dt, *J* = 17.1, 1.4 Hz, C$H_A$$H_B$=CH), 5.11 (1H, ddd, *J* = 10.3, 1.6, 1.0 Hz, C$H_A$$H_B$=CH), 4.74 – 4.63 (1H, m, CH_2=CHC*H*), 4.57 – 4.41 (3H, m, OCH_2Ar and C*H*OH), 4.11 (1H, td, *J* = 5.2, 3.9 Hz, C*H*CH_2OPMB), 3.80 (3H, s, ArOCH_3), 3.77 (2H, d, *J* = 5.2 Hz, CH_2OPMB), 3.06 (1H, d, *J* = 3.9 Hz, O*H*), 2.14 (1H, ddd, *J* = 13.1, 5.8, 1.5 Hz, C$H_A$$H_B$CHOH), 1.83 (1H, ddd, *J* = 13.2, 9.7, 4.9 Hz, C$H_A$$H_B$CHOH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 159.6 (quat. *C* Ar), 138.7 (CH_2=*C*H), 129.7 (quat. *C* Ar and *C* Ar), 116.0 (*C*H_2=CH), 114.1 (*C* Ar), 80.2 (CH_2=CH*C*H), 79.3 (*C*HOH), 73.9 (*C*HCH_2OPMB), 73.7 (O*C*H_2Ar), 68.9 (*C*H_2OPMB), 55.4 (ArO*C*H_3), 42.1 (*C*H_2CHOH).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -14.9 (*c* 1.0, $CHCl_3$).

The spectral data were consistent with those in the literature.[78]

(2*S*,4a*R*,6*S*,7a*R*)-2-(4-Methoxyphenyl)-6-vinyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxine, 331a and (2*R*,4a*R*,6*S*,7a*R*)-2-(4-Methoxyphenyl)-6-vinyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxine, 331b



331a **331b**

THF **312** (100 mg, 0.378 mmol) was dissolved in CH_2Cl_2 (4 mL) over 4 Å molecular sieves. The reaction was cooled to 0 °C and DDQ (94.0 mg, 0.416 mmol) was added. After stirring for 16 h at room temperature, the reaction was filtered then quenched with a pH 7 buffer (4 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane) yielded firstly major isomer **331a** (60 mg, 61%) then the minor isomer **331b** (13mg, 12%).

Major Isomer **331a**:

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.48 – 7.39 (2H, m, Ar*H*), 6.94 – 6.85 (2H, m, Ar*H*), 5.89 (1H, ddd, *J* = 17.2, 10.2, 7.0 Hz, CH_2=C*H*), 5.42 (1H, s, C*H*(O)$_2$Ar), 5.31 (1H, dt, *J* = 17.1, 1.4 Hz, CH_AH_B=CH), 5.15 (1H, ddd, *J* = 10.2, 1.6, 1.0 Hz, CH$_A$*H*$_B$=CH), 4.96 – 4.85 (1H, m, CH_2=CHC*H*), 4.58 – 4.52 (1H, m, CH_2C*H*O), 4.45 – 4.36 (1H, m, CHCH_AH_BO), 4.07 (1H, dd, *J* = 13.0, 2.1 Hz, CHCH$_A$*H*$_B$O), 3.92 – 3.85 (1H, m, C*H*CH_2O), 3.80 (3H, s, ArOC*H*$_3$), 2.39 – 2.29 (1H, m, CH_AH_BCHO), 1.92 – 1.80 (1H, m, CH$_A$*H*$_B$CHO).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 160.2 (quat. *C* Ar), 138.8 (CH_2=*C*H), 130.8 (quat. *C* Ar), 127.6 (*C* Ar), 116.3 (*C*H_2=CH), 113.8 (*C* Ar), 99.5 (*C*H(O)$_2$Ar), 80.6 (CH_2=CH*C*H), 77.4 (CH_2*C*HO), 74.1 (*C*HCH_2O), 68.2 (CH*C*H_2O), 55.4 (ArO*C*H), 40.7 (*C*H_2CHO).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -37.5 (*c* 1.0, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2936, 1613, 1513, 1247, 1244, 1033.

HRMS (ESI$^+$, *m/z*): Calculated 263.1278 ($C_{15}H_{19}O_4$), Found 263.1279 (Δ +0.43 ppm).

m.p. 62 – 65 °C.

Minor Isomer **331b**:

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.48 – 7.37 (2H, m, Ar*H*), 7.05 – 6.85 (2H, m, Ar*H*), 5.96 – 5.79 (1H, m, CH_2=C*H*), 5.43 (1H, s, C*H*$(O)_2$Ar), 5.37 – 5.27 (1H, m, CH_AH_B=CH), 5.19 – 5.11 (1H, m, CH_AH_B=CH), 4.96 – 4.81 (1H, m, CH_2=CHC*H*), 4.56 (1H, t, *J* = 3.1 Hz, CH_2C*H*O), 4.49 – 4.37 (1H, m, CHCH_AH_BO), 4.15 – 4.02 (1H, m, CHCH_AH_BO), 3.98 – 3.86 (1H, m, C*H*CH_2O), 3.80 (3H, s, ArOCH_3), 2.40 – 2.27 (1H, m, CH_AH_BCHO), 1.92 – 1.75 (1H, m, CH_AH_BCHO).

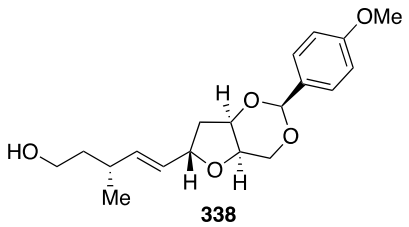
^{13}C NMR δ_C (100 MHz, $CDCl_3$): 160.2 (quat. *C* Ar), 138.5 (CH_2=*C*H), 130.8 (quat. *C* Ar), 128.2 (*C* Ar), 116.4 (*C*H_2=CH), 114.1 (*C* Ar), 99.5 (*C*H$(O)_2$Ar), 79.9 (CH_2=CH*C*H), 77.5 (CH_2*C*HO), 74.8 (*C*HCH_2O), 68.2 (CH*C*H_2O), 55.5 (ArO*C*H_3), 40.7 (*C*H_2CHO).

IR (ν_{max}/cm^{-1}): 2934, 1612, 1513, 1247, 1244, 1033.

HRMS (ESI$^+$, *m/z*): Calculated 285.1097 ($C_{15}H_{18}NaO_4$), Found 285.1098 (Δ +0.25 ppm).

m.p. 58 – 64°C.

(*R*,*E*)-5-((2*S*,4a*R*,6*S*,7a*R*)-2-(4-Methoxyphenyl)tetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)-3-methylpent-4-en-1-ol, 338



338

Hoveyda-Grubbs second generation catalyst (5.0 mg, 0.008 mmol) was dissolved in CH_2Cl_2 and added dropwise to a solution of actetal **337** (45 mg, 0.16 mmol) and alcohol **232** (64 mg, 0.641 mmol) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture then heated to 40 °C and stirred for 16 h. The reaction was allowed to cool to room temperature then concentrated over silica gel *in vacuo*. Flash column chromatography (1:4 EtOAc/pentane) yielded the title compound **339** as a colourless oil (30 mg, 52%).

^{1}H NMR δ_H (400 MHz, C_6D_6): 7.64 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.86 (2H, d, *J* = 8.7 Hz, Ar*H*), 5.55 – 5.35 (2H, m, C*H*=C*H*), 5.23 (1H, s, C*H*O_2), 5.03 – 4.93 (1H, m, CH=CHC*H*O), 4.35 (1H, d, *J* = 12.8 Hz, CH_AH_BOCHAr), 3.95 (1H, t, *J* = 3.1 Hz, C*H*OCHAr), 3.57 (1H, dd, *J* = 12.7, 2.2 Hz, CH_AH_BOCHAr), 3.47 (2H, t, *J* = 6.5 Hz, OHCH_2), 3.41– 3.36 (1H, m, OC*H*CH_2O), 3.26 (3H, s, ArOCH_3), 2.33 – 2.21 (1H, m, C*H*CH_3), 2.13 (1H, dd, *J* = 13.0, 5.5 Hz, CH_AH_BCHO), 1.51 – 1.27 (3H, m, CH_AH_BCHO and OHCH_2CH_2), 0.90 (3H, d, *J* = 6.8 Hz, C*H*CH_3).

^{13}C NMR δ_C (100 MHz, C_6D_6): 160.5 (quat. *C* Ar), 138.4 (*C*H=CH), 131.9 (quat. *C* Ar), 130.2 (CH=*C*H), 127.9 (*C* Ar), 113.8 (*C* Ar), 99.3 (*C*H$(O)_2$Ar), 80.4 (CH=CH*C*HO), 77.4 (*C*HOCHAr), 74.1 (O*C*HCH_2O), 68.2 (*C*H_2OCHAr), 60.7 (OH*C*H_2), 54.8 (ArO*C*H_3), 41.3 (*C*H_2CHO), 39.9 (OHCH_2*C*H_2), 33.7 (*C*HCH_3), 20.9 (CH*C*H_3).

IR (ν_{max}/cm^{-1}): 3428, 1514, 1468, 1323, 1248, 1146, 1038.

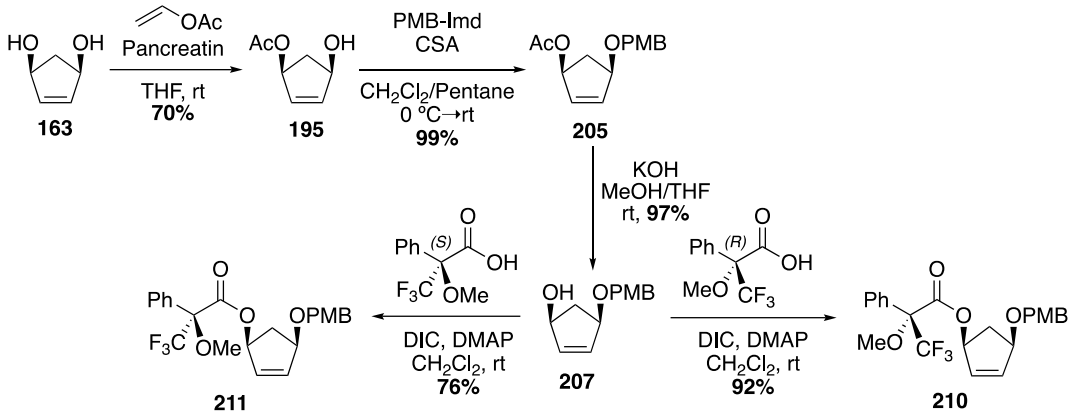
HRMS (ESI$^+$, *m/z*): Calculated 357.1672 ($C_{19}H_{26}NaO_5$), Found 357.1677 (Δ +1.40 ppm).

Appendix 1

Mosher's Ester Data

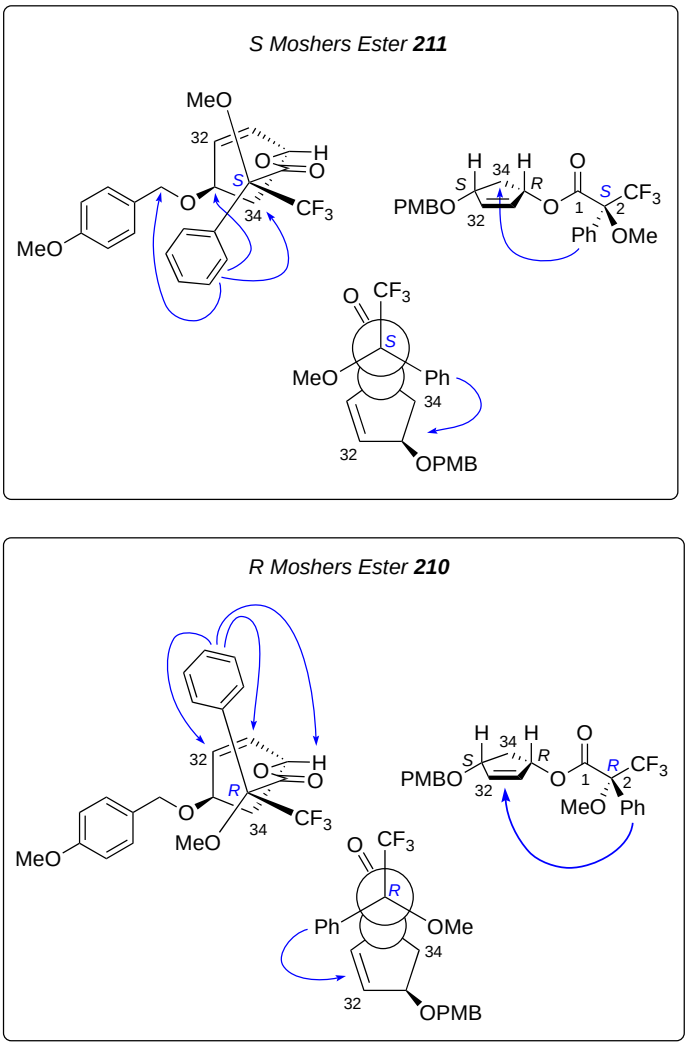
A 1.1 Absolute Configuration of Acetate 195

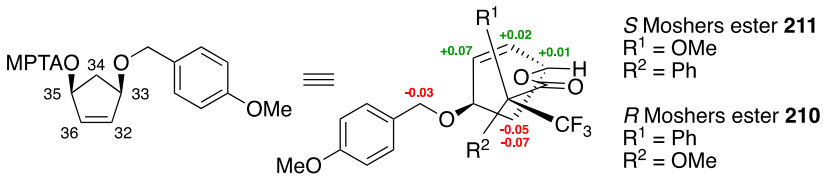
In order to determine the absolute configuration of acetate **195** (specifically the stereochemistry of C_{35}) formed from the asymmetric monoacetylation of *meso* diol **163** (***Scheme 107***), its *R* and *S* Mosher's Ester derivatives, **210** and **211**, were synthesised.



Scheme 107*. Synthesis of R and S Mosher's Esters **210** and **211***

The phenyl ring of the Mosher's Ester motif imposes an anisotropic, magnetic shielding effect on spatially proximal protons that lie above or below the plane of the phenyl ring. The affected protons thus display a more upfield chemical shift in the ^{1}H NMR spectrum. Assuming that C_{35} and $OC_1(O)C_2$ adopt a coplanar configuration in both Mosher's Esters **210** and **212**, we would expect that for **211** (*S* Mosher's ester), the $C_{33}H$, $C_{34}H$, and CH_2Ar protons of the PMB group will experience a greater anisotropic effect from the Mosher's ester phenyl group than the $C_{32}H$, $C_{35}H$ and $C_{36}H$ protons, while the opposite can be expected to occur in **210** (*R* Mosher's ester). Therefore, $\Delta\delta^{SR}$ ($\Delta\delta^{SR}=\delta^S - \delta^R$, the difference in chemical shift between equivalent protons of *R* and *S* Mosher's ester) should be positive for $C_{32}H$, $C_{35}H$ and $C_{36}H$ and negative for $C_{33}H$, $C_{34}H$ and CH_2Ar.





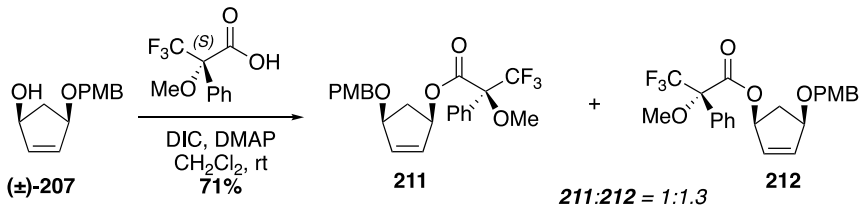
Proton number	δ^S (ppm)	δ^R (ppm)	$\Delta\delta^{SR}$ (ppm)
$C_{35}H$	5.71	5.72	+0.01
$C_{36}H$	6.16	6.18	+0.02
$C_{32}H$	5.98	6.05	+0.07
$C_{33}H$	4.53	4.52	-0.01
$C_{34}H_A$	2.85	2.8	-0.05
$C_{34}H_A$	1.85	1.78	-0.07
CH_2Ar	4.45	4.42	-0.03

Figure 34**. Model conformations used for the analysis of diastereomeric esters **210** and **211

The results from our Mosher's Ester analysis are summarised in ***Figure 34***. We can see that $\Delta\delta^{SR}$ is positive for $C_{32}H$, $C_{35}H$ and $C_{36}H$ and negative for $C_{33}H$, $C_{34}H$ and CH_2Ar, giving strong evidence for the formation of the desired *R* stereochemistry was formed at C_{35} from the monoacetylation of diol **163**.

A 1.2 Enantiomeric Excess of Acetate 195

Moshers ester analysis was also used to determine the *ee* of the monoacetylation of diol **163**. A racemic sample of alcohol **207** was treated with *S* Mosher's acid to give Mosher's esters **211** and **212** as an inseparable 1:1.3 mixture of diastereomers in 71% yield. (***Scheme 108***).



Scheme 108*. Synthesis of diastereomeric Mosher's esters **211** and **212***

Evaluation of the ^{19}F NMR and ^{1}H NMR of the **211** and **212** mixture, against that of **211**, derived from the desired acetate **195**, revealed an *ee* > 90%.

^{1}H NMR (400 MHz $CDCl_3$):

1:1.3 mixture of diastereomers **211** and **212**

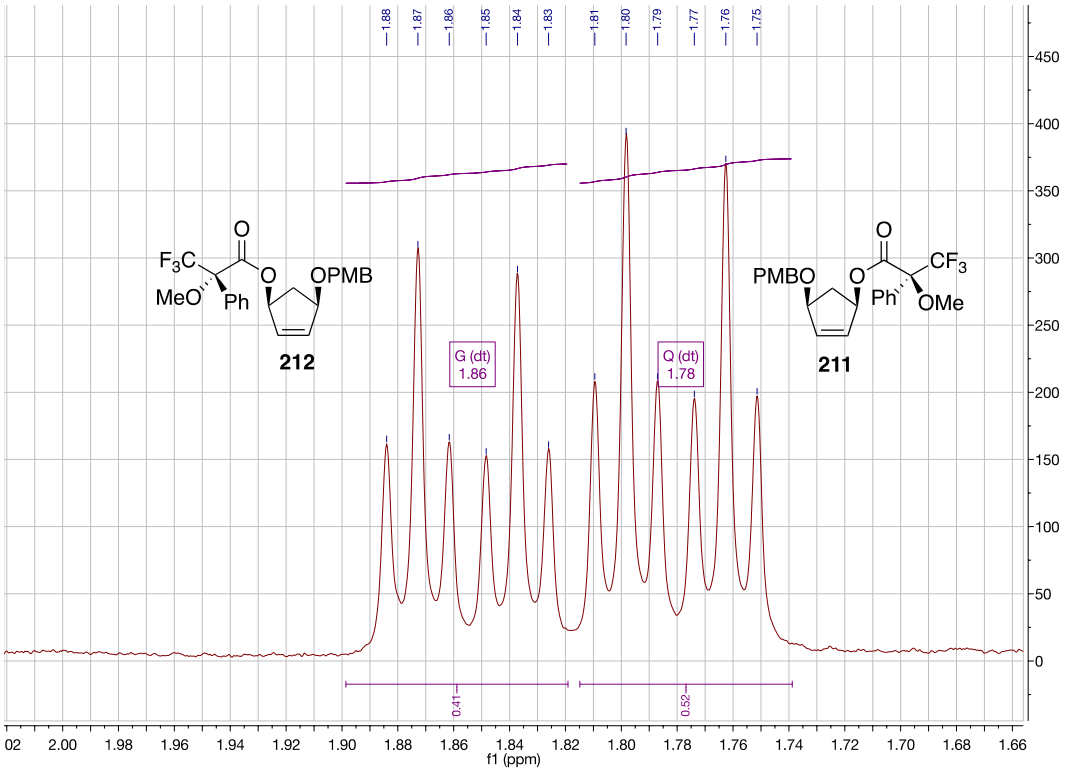


***Figure 34**. ^{1}H NMR of 1:1.3 **211/212** mixture*

>95:5 mixture of diastereomers **211** and **212**

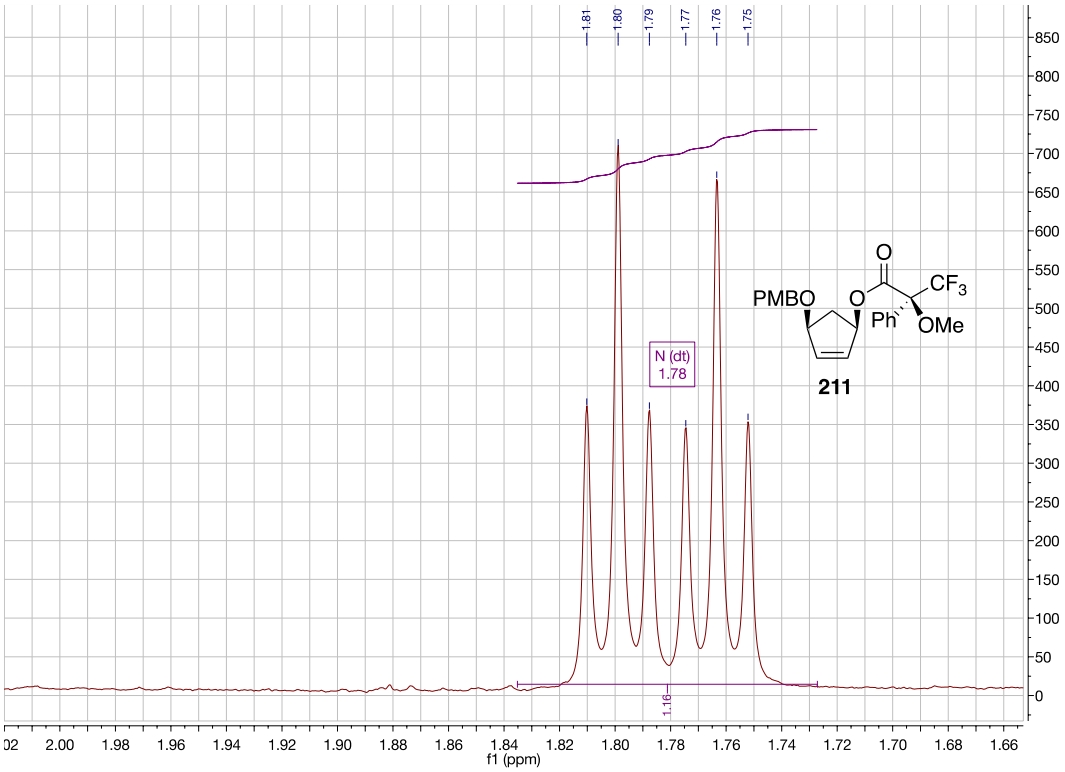
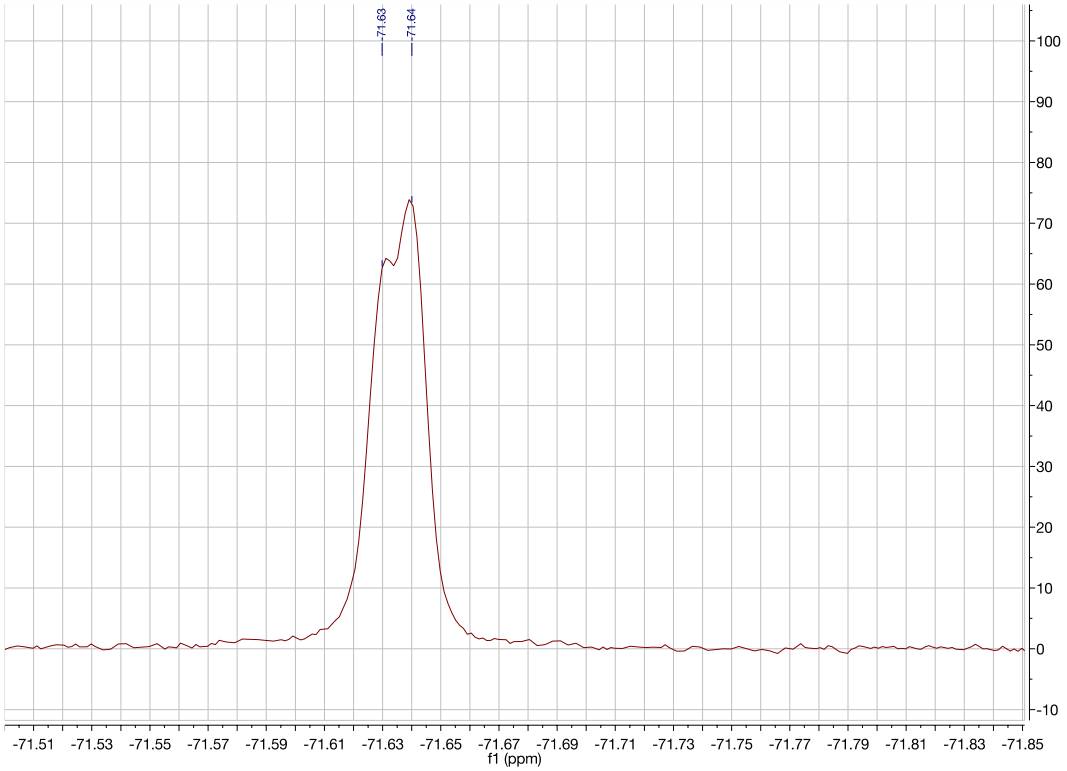


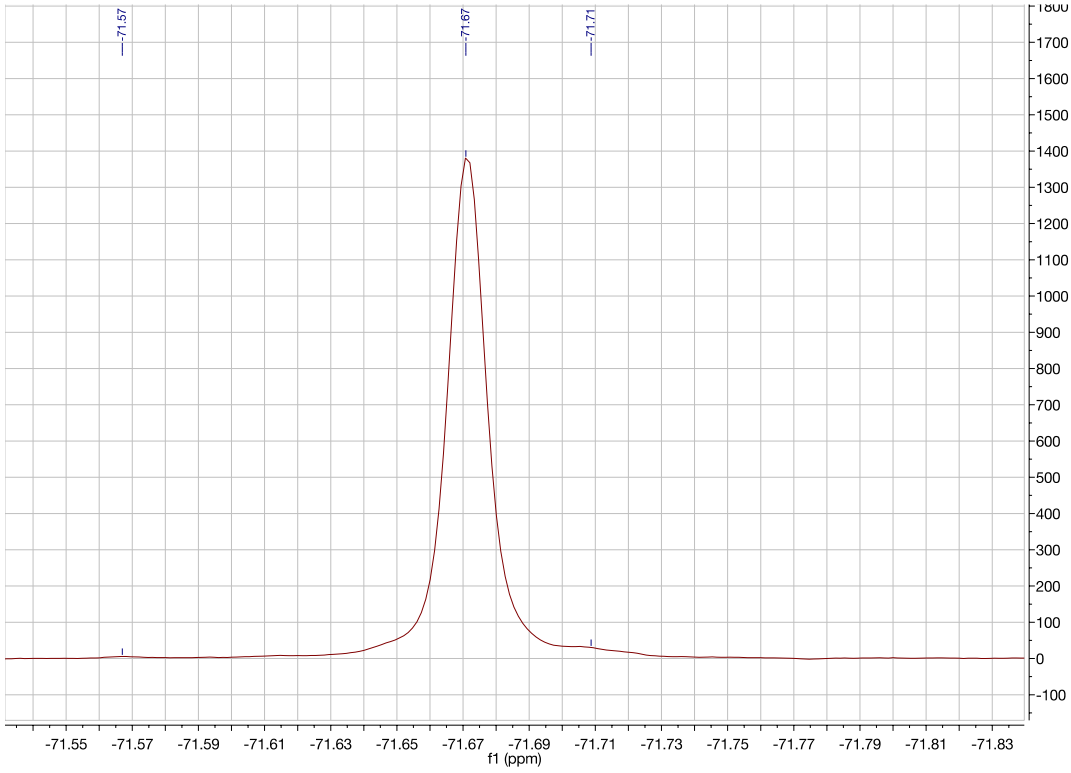
***Figure 35**. 1H NMR of > 95:5 **211/212** mixture*

^{19}F NMR (400 MHz $CDCl_3$):

1:1.3 mixture of diastereomers **211** and **212**



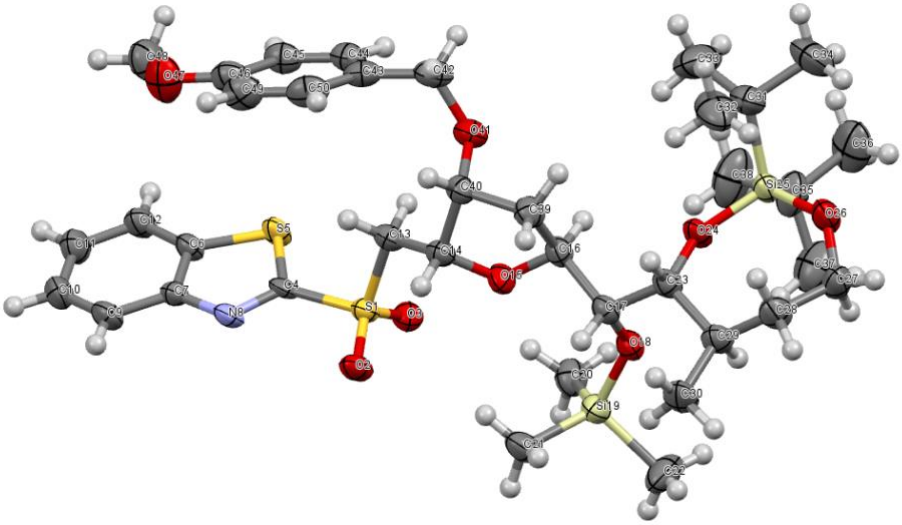
>95:5 mixture of diastereomers **211** and **212**

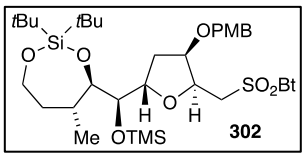


Appendix 2

Single X-ray Diffraction Data

A 2.1 Single-Crystal X-ray Diffraction Report for TMS-Ether 302





Crystals of **302** were grown by Ahria Roushanbakhti from benzene and run by Wasim Akthar. A single crystal having dimensions approximately ***0.01 x 0.06 x 0.14 mm*** was mounted on was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 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.

Examination of the systematic absences of the intensity data showed the space group to be **P 1 2/1 1.** The structure was solved in this space group using the direct-methods program SIR92, which located all non-hydrogen atoms. The H 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. Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms,

and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.063, wR = 0.139.**

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

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
S1	0.34485(11)	0.84093(11)	0.08101(4)	0.0320	1.0000
O2	-0.2934(4)	0.9664(3)	0.09250(14)	0.0417	1.0000
O3	-0.4477(3)	0.7877(3)	0.11879(13)	0.0400	1.0000
C4	-0.4405(4)	0.8354(3)	0.00421(18)	0.0304	1.0000
S5	0.54961(12)	0.70748(11)	0.02090(5)	0.0378	1.0000
C6	-0.6026(5)	0.7862(4)	0.09032(19)	0.0356	1.0000
C7	-0.5305(5)	0.9028(4)	0.08753(18)	0.0323	1.0000
N8	-0.4382(4)	0.9280(3)	0.03368(16)	0.0343	1.0000
C9	-0.5634(6)	0.9843(4)	-0.1376(2)	0.0444	1.0000
C10	-0.6657(6)	0.9499(4)	-0.1866(2)	0.0481	1.0000
C11	-0.7353(6)	0.8336(5)	-0.1882(2)	0.0507	1.0000
C12	-0.7039(5)	0.7504(4)	-0.1405(2)	0.0435	1.0000
H121	-0.7501(5)	0.6746(4)	-0.1423(2)	0.0529	1.0000
H111	-0.8045(6)	0.8109(5)	-0.2224(2)	0.0619	1.0000
H101	-0.6903(6)	1.0024(4)	-0.2205(2)	0.0588	1.0000
H91	-0.5151(6)	1.0599(4)	-0.1375(2)	0.0546	1.0000
C13	-0.1866(5)	0.7402(4)	0.0780(2)	0.0376	1.0000
C14	-0.0570(5)	0.7671(4)	0.12775(18)	0.0363	1.0000
O15	-0.1016(3)	0.7522(3)	0.18762(13)	0.0392	1.0000
C16	0.0207(5)	0.6958(4)	0.22840(18)	0.0377	1.0000
C17	0.0538(5)	0.7732(4)	0.28729(18)	0.0343	1.0000
O18	-0.0730(4)	0.7794(3)	0.31905(13)	0.0413	1.0000
Si19	0.21850(15)	0.87575(13)	0.31044(6)	0.0417	1.0000
C20	-0.3888(5)	0.7874(5)	0.2783(2)	0.0494	1.0000
H202	-0.4792(5)	0.8349(5)	0.2808(2)	0.0769	1.0000
H203	-0.3830(5)	0.7710(5)	0.2343(2)	0.0768	1.0000
H201	-0.3952(5)	0.7130(5)	0.3009(2)	0.0769	1.0000
C21	-0.1805(6)	1.0122(4)	0.2615(3)	0.0539	1.0000

H211	-0.2619(6)	1.0699(4)	0.2630(3)	0.0830	1.0000
H213	-0.1767(6)	0.9858(4)	0.2186(3)	0.0831	1.0000
H212	-0.0872(6)	1.0479(4)	0.2777(3)	0.0830	1.0000
C22	-0.2438(8)	0.9314(7)	0.3893(2)	0.0732	1.0000
H221	-0.3300(8)	0.9824(7)	0.3871(2)	0.1131	1.0000
H222	-0.2561(8)	0.8631(7)	0.4155(2)	0.1127	1.0000
H223	-0.1565(8)	0.9771(7)	0.4062(2)	0.1127	1.0000
C23	0.1862(5)	0.7186(4)	0.33163(19)	0.0362	1.0000
O24	0.1460(4)	0.5931(3)	0.34062(14)	0.0413	1.0000
Si25	0.19954(14)	0.47470(12)	0.38414(5)	0.0384	1.0000
O26	0.3160(4)	0.5141(3)	0.44482(15)	0.0510	1.0000
C27	0.3363(7)	0.6302(5)	0.4758(2)	0.0524	1.0000
C28	0.3589(6)	0.7390(4)	0.4341(2)	0.0484	1.0000
C29	0.2181(5)	0.7889(4)	0.3925(2)	0.0408	1.0000
C30	0.2439(7)	0.9279(4)	0.3805(2)	0.0560	1.0000
H302	0.2764(7)	0.9700(4)	0.4191(2)	0.0877	1.0000
H303	0.1502(7)	0.9642(4)	0.3607(2)	0.0876	1.0000
H301	0.3199(7)	0.9369(4)	0.3529(2)	0.0877	1.0000
H291	0.1287(5)	0.7800(4)	0.4155(2)	0.0489	1.0000
H282	0.4343(6)	0.7156(4)	0.4071(2)	0.0590	1.0000
H281	0.4008(6)	0.8054(4)	0.4606(2)	0.0592	1.0000
H272	0.2452(7)	0.6448(5)	0.4959(2)	0.0652	1.0000
H271	0.4238(7)	0.6237(5)	0.5073(2)	0.0645	1.0000
C31	0.3172(7)	0.3682(5)	0.3401(3)	0.0582	1.0000
C32	0.4391(8)	0.4485(7)	0.3170(3)	0.0809	1.0000
H322	0.5007(8)	0.4827(7)	0.3528(3)	0.1248	1.0000
H323	0.5017(8)	0.4002(7)	0.2932(3)	0.1250	1.0000
H321	0.3926(8)	0.5142(7)	0.2910(3)	0.1250	1.0000
C33	0.2221(11)	0.3095(8)	0.2845(4)	0.1068	1.0000
H332	0.1639(11)	0.2435(8)	0.2987(4)	0.1619	1.0000
H331	0.2872(11)	0.2785(8)	0.2561(4)	0.1617	1.0000
H333	0.1556(11)	0.3699(8)	0.2636(4)	0.1619	1.0000
C34	0.3959(10)	0.2656(6)	0.3815(4)	0.0930	1.0000
H341	0.3206(10)	0.2185(6)	0.3992(4)	0.1387	1.0000
H342	0.4509(10)	0.2138(6)	0.3570(4)	0.1389	1.0000
H343	0.4634(10)	0.3019(6)	0.4143(4)	0.1387	1.0000
C35	0.0188(7)	0.4110(6)	0.4074(2)	0.0623	1.0000
C36	0.0438(10)	0.2871(6)	0.4429(3)	0.0880	1.0000
H361	-0.0486(10)	0.2623(6)	0.4580(3)	0.1381	1.0000
H363	0.0727(10)	0.2256(6)	0.4139(3)	0.1380	1.0000

H362	0.1234(10)	0.2967(6)	0.4767(3)	0.1378	1.0000
C37	-0.0432(8)	0.5046(8)	0.4501(3)	0.0824	1.0000
H372	-0.1408(8)	0.4802(8)	0.4589(3)	0.1220	1.0000
H371	-0.0524(8)	0.5838(8)	0.4305(3)	0.1220	1.0000
H373	0.0245(8)	0.5121(8)	0.4881(3)	0.1215	1.0000
C38	-0.1016(8)	0.3922(9)	0.3509(3)	0.0925	1.0000
H382	-0.1973(8)	0.3704(9)	0.3639(3)	0.1378	1.0000
H381	-0.0703(8)	0.3274(9)	0.3249(3)	0.1379	1.0000
H383	-0.1132(8)	0.4670(9)	0.3269(3)	0.1378	1.0000
H231	0.2785(5)	0.7209(4)	0.31017(19)	0.0452	1.0000
H171	0.0830(5)	0.8567(4)	0.27663(18)	0.0410	1.0000
C39	0.1530(5)	0.6884(4)	0.1909(2)	0.0419	1.0000
C40	0.0757(5)	0.6781(4)	0.12454(19)	0.0360	1.0000
O41	0.0215(4)	0.5534(3)	0.11422(15)	0.0421	1.0000
C42	0.0776(6)	0.4922(4)	0.0632(2)	0.0510	1.0000
C43	-0.0154(5)	0.5196(4)	0.0024(2)	0.0428	1.0000
C44	-0.1512(5)	0.4600(4)	-0.0158(2)	0.0444	1.0000
C45	-0.2400(5)	0.4851(4)	-0.0712(2)	0.0436	1.0000
C46	-0.1913(6)	0.5747(4)	-0.1106(2)	0.0479	1.0000
O47	-0.2665(5)	0.6064(4)	0.16597(19)	0.0665	1.0000
C48	-0.4037(7)	0.5447(5)	-0.1870(3)	0.0626	1.0000
H481	-0.4389(7)	0.5713(5)	-0.2288(3)	0.0948	1.0000
H482	-0.3885(7)	0.4571(5)	-0.1868(3)	0.0948	1.0000
H483	-0.4776(7)	0.5653(5)	-0.1595(3)	0.0946	1.0000
C49	-0.0556(6)	0.6340(5)	-0.0934(3)	0.0554	1.0000
C50	0.0307(6)	0.6074(4)	-0.0380(2)	0.0500	1.0000
H501	0.1235(6)	0.6472(4)	-0.0266(2)	0.0630	1.0000
H491	-0.0201(6)	0.6902(5)	-0.1204(3)	0.0678	1.0000
H451	-0.3320(5)	0.4445(4)	-0.0820(2)	0.0515	1.0000
H441	-0.1856(5)	0.4034(4)	0.0115(2)	0.0544	1.0000
H421	0.0741(6)	0.4049(4)	0.0707(2)	0.0633	1.0000
H422	0.1830(6)	0.5172(4)	0.0611(2)	0.0629	1.0000
H401	0.1419(5)	0.7026(4)	0.09327(19)	0.0434	1.0000
H392	0.2150(5)	0.6163(4)	0.2026(2)	0.0509	1.0000
H391	0.2155(5)	0.7607(4)	0.1965(2)	0.0510	1.0000
H161	-0.0096(5)	0.6130(4)	0.23821(18)	0.0462	1.0000
H141	-0.0232(5)	0.8519(4)	0.12211(18)	0.0440	1.0000
H131	-0.1524(5)	0.7507(4)	0.0376(2)	0.0471	1.0000
H132	-0.2185(5)	0.6557(4)	0.0819(2)	0.0472	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	0.0344(4)	0.0250(4)	0.0352(4)	-0.0021(4)	-0.0007(4)	0.0034(4)
O2	0.0466(17)	0.0256(13)	0.0496(16)	-0.0057(12)	-0.0061(13)	0.0023(13)
O3	0.0407(16)	0.0410(15)	0.0390(15)	0.0013(12)	0.0071(12)	0.0066(13)
C4	0.0294(17)	0.0175(15)	0.0430(19)	0.0006(15)	0.0000(15)	0.0086(15)
S5	0.0458(5)	0.0223(4)	0.0423(5)	0.0035(4)	-0.0056(4)	-0.0049(4)
C6	0.040(2)	0.0242(18)	0.042(2)	0.0049(16)	0.0018(17)	0.0029(17)
C7	0.037(2)	0.0235(17)	0.0361(19)	-0.0007(15)	0.0024(16)	0.0031(15)
N8	0.0375(18)	0.0200(14)	0.0446(18)	0.0010(13)	0.0019(15)	0.0057(13)
C9	0.059(3)	0.0262(19)	0.048(2)	0.0056(18)	0.007(2)	0.0030(19)
C10	0.063(3)	0.040(2)	0.040(2)	0.0089(18)	0.000(2)	0.007(2)
C11	0.058(3)	0.046(3)	0.043(2)	0.002(2)	-0.011(2)	0.005(2)
C12	0.050(3)	0.031(2)	0.046(2)	-0.0023(18)	-0.008(2)	-0.0014(19)
C13	0.041(2)	0.0287(19)	0.043(2)	0.0015(16)	0.0042(17)	0.0090(17)
C14	0.043(2)	0.0267(19)	0.039(2)	0.0005(16)	0.0025(17)	0.0019(17)
O15	0.0367(15)	0.0443(16)	0.0357(14)	0.0050(12)	0.0013(12)	0.0120(13)
C16	0.039(2)	0.035(2)	0.037(2)	0.0061(17)	-0.0026(16)	0.0014(18)
C17	0.036(2)	0.0278(19)	0.039(2)	0.0041(15)	0.0035(16)	-0.0010(16)
O18	0.0475(17)	0.0374(16)	0.0393(15)	0.0091(12)	0.0067(13)	0.0079(13)
Si19	0.0449(6)	0.0399(6)	0.0391(6)	-0.0021(5)	0.0006(5)	0.0090(5)
C20	0.041(2)	0.059(3)	0.048(2)	0.006(2)	0.0037(19)	0.002(2)
C21	0.056(3)	0.034(2)	0.069(3)	0.003(2)	-0.005(2)	0.008(2)
C22	0.077(4)	0.098(5)	0.043(3)	-0.018(3)	0.003(3)	0.023(4)
C23	0.037(2)	0.0302(19)	0.040(2)	0.0008(16)	-0.0003(16)	-0.0016(17)
O24	0.0538(19)	0.0233(13)	0.0424(15)	0.0017(11)	-0.0109(14)	-0.0015(13)
Si25	0.0492(7)	0.0302(5)	0.0333(5)	0.0029(4)	-0.0040(5)	-0.0017(5)
O26	0.069(2)	0.0343(16)	0.0443(17)	0.0058(13)	-0.0126(16)	-0.0016(15)
C27	0.077(4)	0.041(2)	0.036(2)	-0.0033(19)	-0.008(2)	-0.005(2)
C28	0.055(3)	0.036(2)	0.049(3)	-0.0049(19)	-0.012(2)	-0.007(2)
C29	0.047(2)	0.0296(19)	0.044(2)	-0.0033(17)	-0.0005(18)	-0.0029(18)
C30	0.081(4)	0.028(2)	0.055(3)	-0.001(2)	-0.005(3)	-0.006(2)
C31	0.076(4)	0.041(3)	0.056(3)	-0.003(2)	0.002(2)	0.019(2)
C32	0.080(4)	0.086(5)	0.083(4)	0.019(4)	0.035(3)	0.039(4)
C33	0.138(8)	0.092(6)	0.082(5)	-0.042(4)	-0.016(5)	0.045(5)
C34	0.120(7)	0.049(3)	0.105(5)	0.013(4)	-0.003(5)	0.029(4)
C35	0.066(4)	0.074(4)	0.046(3)	0.007(3)	0.005(2)	-0.020(3)
C36	0.119(6)	0.073(4)	0.072(4)	0.016(3)	0.014(4)	-0.044(4)
C37	0.070(4)	0.118(6)	0.063(4)	-0.001(4)	0.022(3)	-0.012(4)
C38	0.075(5)	0.138(7)	0.061(4)	-0.003(4)	-0.006(3)	-0.040(5)

C39	0.039(2)	0.042(2)	0.043(2)	0.0007(18)	0.0024(17)	0.0032(19)
C40	0.036(2)	0.033(2)	0.040(2)	0.0015(16)	0.0060(16)	0.0040(16)
O41	0.0436(17)	0.0325(15)	0.0501(17)	-0.0008(13)	0.0062(14)	0.0047(13)
C42	0.046(3)	0.040(3)	0.065(3)	-0.009(2)	0.003(2)	0.012(2)
C43	0.043(2)	0.033(2)	0.054(3)	-0.0118(19)	0.0114(19)	0.0000(19)
C44	0.046(2)	0.035(2)	0.055(3)	-0.0013(19)	0.014(2)	0.003(2)
C45	0.040(2)	0.034(2)	0.058(3)	-0.0024(19)	0.0112(19)	-0.0100(19)
C46	0.054(3)	0.036(2)	0.054(3)	-0.004(2)	0.011(2)	-0.007(2)
O47	0.068(3)	0.063(2)	0.066(2)	0.0143(19)	-0.0004(19)	-0.026(2)
C48	0.058(3)	0.059(3)	0.066(3)	0.005(3)	-0.007(3)	-0.004(3)
C49	0.061(3)	0.043(3)	0.064(3)	-0.004(2)	0.014(3)	-0.018(2)
C50	0.044(3)	0.040(2)	0.067(3)	-0.013(2)	0.012(2)	-0.016(2)

Distances

S1	O2	1.440(3)Å		S1	O3	1.430(3)Å
S1	C4	1.778(4)Å		S1	C13	1.789(4)Å
C4	S5	1.735(4)Å		C4	N8	1.297(5)Å
S5	C6	1.745(4)Å		C6	C7	1.410(5)Å
C6	C12	1.380(6)Å		C7	N8	1.371(5)Å
C7	C9	1.401(6)Å		C9	C10	1.365(7)Å
C9	H91	0.922Å		C10	C11	1.397(7)Å
C10	H101	0.933Å		C11	C12	1.375(6)Å
C11	H111	0.936Å		C12	H121	0.914Å
C13	C14	1.508(6)Å		C13	H131	0.974Å
C13	H132	0.961Å		C14	O15	1.421(5)Å
C14	C40	1.532(6)Å		C14	H141	0.975Å
O15	C16	1.449(5)Å		C16	C17	1.527(6)Å
C16	C39	1.523(6)Å		C16	H161	0.965Å
C17	O18	1.402(5)Å		C17	C23	1.543(5)Å
C17	H171	0.973Å		O18	Si19	1.654(3)Å
Si19	C20	1.853(5)Å		Si19	C21	1.873(5)Å
Si19	C22	1.861(5)Å		C20	H202	0.963Å
C20	H203	0.981Å		C20	H201	0.947Å
C21	H211	0.961Å		C21	H213	0.982Å
C21	H212	0.944Å		C22	H221	0.942Å
C22	H222	0.947Å		C22	H223	0.955Å
C23	O24	1.420(5)Å		C23	C29	1.522(6)Å
C23	H231	0.999Å		O24	Si25	1.625(3)Å
Si25	O26	1.628(3)Å		Si25	C31	1.898(5)Å
Si25	C35	1.881(6)Å		O26	C27	1.422(6)Å

C27	C28	1.514(7)Å		C27	H272	0.985Å
C27	H271	0.973Å		C28	C29	1.547(6)Å
C28	H282	0.982Å		C28	H281	0.964Å
C29	C30	1.543(6)Å		C29	H291	1.000Å
C30	H302	0.967Å		C30	H303	0.972Å
C30	H301	0.967Å		C31	C32	1.526(9)Å
C31	C33	1.524(9)Å		C31	C34	1.538(8)Å
C32	H322	0.969Å		C32	H323	0.963Å
C32	H321	0.965Å		C33	H332	0.956Å
C33	H331	0.961Å		C33	H333	0.955Å
C34	H341	0.961Å		C34	H342	0.951Å
C34	H343	0.956Å		C35	C36	1.544(8)Å
C35	C37	1.525(9)Å		C35	C38	1.539(8)Å
C36	H361	0.966Å		C36	H363	0.973Å
C36	H362	0.961Å		C37	H372	0.953Å
C37	H371	0.953Å		C37	H373	0.962Å
C38	H382	0.964Å		C38	H381	0.962Å
C38	H383	0.959Å		C39	C40	1.523(6)Å
C39	H392	0.968Å		C39	H391	0.957Å
C40	O41	1.436(5)Å		C40	H401	0.994Å
O41	C42	1.437(6)Å		C42	C43	1.499(7)Å
C42	H421	0.956Å		C42	H422	0.985Å
C43	C44	1.384(7)Å		C43	C50	1.390(7)Å
C44	C45	1.381(7)Å		C44	H441	0.931Å
C45	C46	1.398(6)Å		C45	H451	0.934Å
C46	O47	1.347(6)Å		C46	C49	1.378(7)Å
O47	C48	1.416(6)Å		C48	H481	0.968Å
C48	H482	0.954Å		C48	H483	0.973Å
C49	C50	1.376(8)Å		C49	H491	0.928Å
C50	H501	0.937Å				

Angles

O2	S1	O3	119.39(19)°		O2	S1	C4	107.36(18)°
O3	S1	C4	105.22(18)°		O2	S1	C13	109.9(2)°
O3	S1	C13	110.26(19)°		C4	S1	C13	103.29(18)°
S1	C4	S5	120.3(2)°		S1	C4	N8	121.9(3)°
S5	C4	N8	117.7(3)°		C4	S5	C6	87.99(19)°
S5	C6	C7	109.0(3)°		S5	C6	C12	128.8(3)°
C7	C6	C12	122.1(4)°		C6	C7	N8	115.7(4)°
C6	C7	C9	118.5(4)°		N8	C7	C9	125.7(4)°

C4	N8	C7	109.5(3)°		C7	C9	C10	119.4(4)°
C7	C9	H91	120.124°		C10	C9	H91	120.485°
C9	C10	C11	120.9(4)°		C9	C10	H101	121.255°
C11	C10	H101	117.827°		C10	C11	C12	121.3(4)°
C10	C11	H111	119.990°		C12	C11	H111	118.709°
C6	C12	C11	117.8(4)°		C6	C12	H121	121.971°
C11	C12	H121	120.239°		S1	C13	C14	113.1(3)°
S1	C13	H131	107.680°		C14	C13	H131	109.004°
S1	C13	H132	109.126°		C14	C13	H132	109.063°
H131	C13	H132	108.792°		C13	C14	O15	111.0(3)°
C13	C14	C40	111.8(3)°		O15	C14	C40	106.3(3)°
C13	C14	H141	108.115°		O15	C14	H141	110.448°
C40	C14	H141	109.108°		C14	O15	C16	109.4(3)°
O15	C16	C17	109.5(3)°		O15	C16	C39	105.5(3)°
C17	C16	C39	113.6(4)°		O15	C16	H161	108.264°
C17	C16	H161	110.400°		C39	C16	H161	109.256°
C16	C17	O18	111.1(3)°		C16	C17	C23	111.5(3)°
O18	C17	C23	108.1(3)°		C16	C17	H171	109.479°
O18	C17	H171	109.378°		C23	C17	H171	107.146°
C17	O18	Si19	130.2(3)°		O18	Si19	C20	108.3(2)°
O18	Si19	C21	111.1(2)°		C20	Si19	C21	112.9(2)°
O18	Si19	C22	106.6(2)°		C20	Si19	C22	108.9(3)°
C21	Si19	C22	109.0(3)°		Si19	C20	H202	110.896°
Si19	C20	H203	108.474°		H202	C20	H203	107.600°
Si19	C20	H201	109.863°		H202	C20	H201	108.292°
H203	C20	H201	111.707°		Si19	C21	H211	107.234°
Si19	C21	H213	110.213°		H211	C21	H213	109.865°
Si19	C21	H212	108.885°		H211	C21	H212	110.941°
H213	C21	H212	109.669°		Si19	C22	H221	109.658°
Si19	C22	H222	110.088°		H221	C22	H222	109.147°
Si19	C22	H223	109.385°		H221	C22	H223	109.850°
H222	C22	H223	108.696°		C17	C23	O24	105.2(3)°
C17	C23	C29	113.4(4)°		O24	C23	C29	112.1(3)°
C17	C23	H231	107.990°		O24	C23	H231	109.054°
C29	C23	H231	108.852°		C23	O24	Si25	140.2(3)°
O24	Si25	O26	112.17(16)°		O24	Si25	C31	108.7(2)°
O26	Si25	C31	103.4(2)°		O24	Si25	C35	104.3(2)°
O26	Si25	C35	110.9(2)°		C31	Si25	C35	117.7(3)°
Si25	O26	C27	130.1(3)°		O26	C27	C28	114.5(4)°
O26	C27	H272	106.829°		C28	C27	H272	108.961°

O26	C27	H271	108.294°		C28	C27	H271	108.811°
H272	C27	H271	109.315°		C27	C28	C29	117.4(4)°
C27	C28	H282	108.373°		C29	C28	H282	107.853°
C27	C28	H281	106.605°		C29	C28	H281	108.391°
H282	C28	H281	107.883°		C23	C29	C28	112.5(4)°
C23	C29	C30	110.5(4)°		C28	C29	C30	108.0(4)°
C23	C29	H291	108.556°		C28	C29	H291	108.218°
C30	C29	H291	108.968°		C29	C30	H302	110.003°
C29	C30	H303	109.110°		H302	C30	H303	109.917°
C29	C30	H301	109.602°		H302	C30	H301	109.707°
H303	C30	H301	108.477°		Si25	C31	C32	106.8(4)°
Si25	C31	C33	111.5(5)°		C32	C31	C33	108.7(6)°
Si25	C31	C34	112.2(5)°		C32	C31	C34	108.1(6)°
C33	C31	C34	109.5(6)°		C31	C32	H322	107.730°
C31	C32	H323	111.044°		H322	C32	H323	109.360°
C31	C32	H321	109.817°		H322	C32	H321	110.436°
H323	C32	H321	108.456°		C31	C33	H332	108.756°
C31	C33	H331	109.609°		H332	C33	H331	110.419°
C31	C33	H333	110.023°		H332	C33	H333	109.240°
H331	C33	H333	108.784°		C31	C34	H341	108.949°
C31	C34	H342	108.774°		H341	C34	H342	110.665°
C31	C34	H343	109.834°		H341	C34	H343	108.881°
H342	C34	H343	109.725°		Si25	C35	C36	112.1(5)°
Si25	C35	C37	108.3(4)°		C36	C35	C37	107.8(5)°
Si25	C35	C38	111.5(4)°		C36	C35	C38	109.1(6)°
C37	C35	C38	107.8(6)°		C35	C36	H361	109.691°
C35	C36	H363	107.306°		H361	C36	H363	110.055°
C35	C36	H362	109.633°		H361	C36	H362	110.208°
H363	C36	H362	109.900°		C35	C37	H372	110.742°
C35	C37	H371	109.641°		H372	C37	H371	107.966°
C35	C37	H373	110.121°		H372	C37	H373	109.785°
H371	C37	H373	108.529°		C35	C38	H382	110.542°
C35	C38	H381	109.850°		H382	C38	H381	109.363°
C35	C38	H383	109.883°		H382	C38	H383	109.129°
H381	C38	H383	108.029°		C16	C39	C40	103.0(3)°
C16	C39	H392	110.906°		C40	C39	H392	111.395°
C16	C39	H391	111.622°		C40	C39	H391	111.389°
H392	C39	H391	108.468°		C14	C40	C39	99.7(3)°
C14	C40	O41	110.3(3)°		C39	C40	O41	108.6(3)°
C14	C40	H401	113.390°		C39	C40	H401	113.242°

O41	C40	H401	111.037°		C40	O41	C42	114.0(4)°
O41	C42	C43	112.6(4)°		O41	C42	H421	107.365°
C43	C42	H421	108.515°		O41	C42	H422	109.913°
C43	C42	H422	109.141°		H421	C42	H422	109.272°
C42	C43	C44	121.8(5)°		C42	C43	C50	121.2(5)°
C44	C43	C50	117.0(5)°		C43	C44	C45	122.8(4)°
C43	C44	H441	118.004°		C45	C44	H441	119.132°
C44	C45	C46	118.9(4)°		C44	C45	H451	121.019°
C46	C45	H451	120.098°		C45	C46	O47	124.5(4)°
C45	C46	C49	119.1(5)°		O47	C46	C49	116.4(5)°
C46	O47	C48	118.8(4)°		O47	C48	H481	109.121°
O47	C48	H482	110.303°		H481	C48	H482	109.151°
O47	C48	H483	108.650°		H481	C48	H483	110.361°
H482	C48	H483	109.248°		C46	C49	C50	121.0(5)°
C46	C49	H491	119.386°		C50	C49	H491	119.597°
C43	C50	C49	121.3(5)°		C43	C50	H501	117.969°
C49	C50	H501	120.757°					

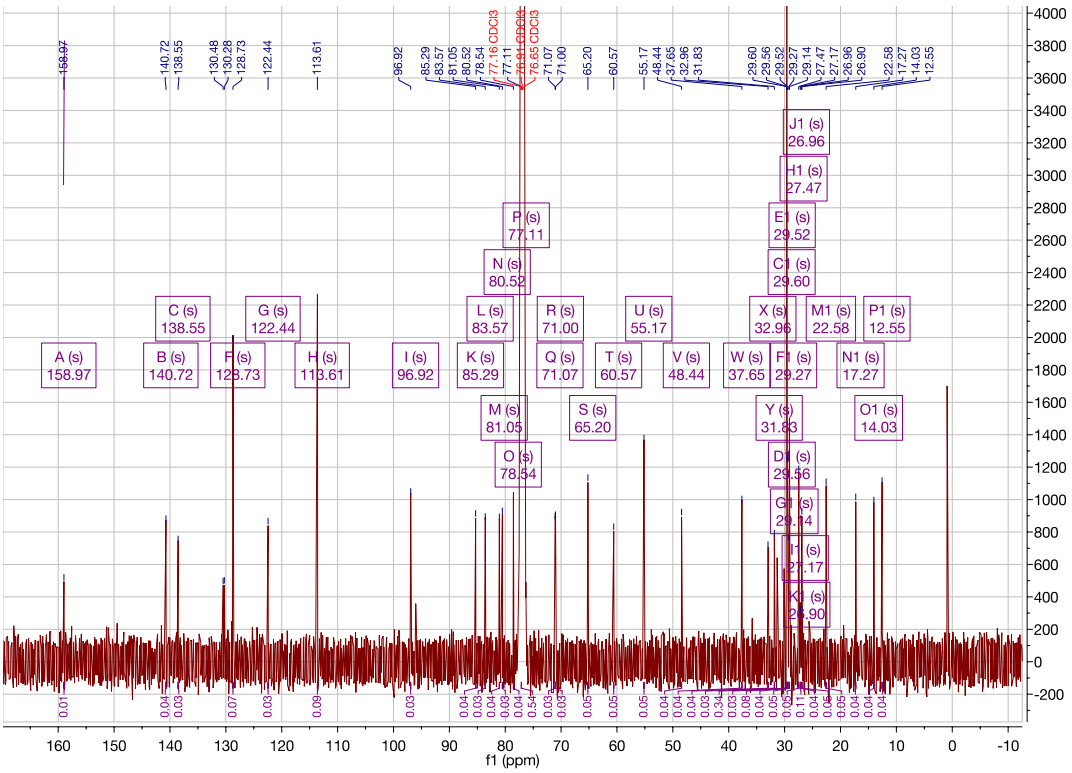
Appendix 3

Pectenotoxin-4 EFG-Ring System NMR Data

A 3.1 EFG-Ring System of Pectenotoxin 4

^{1}H NMR (500 MHz $CDCl_3$):

^{13}C NMR (500 MHz $CDCl_3$):



Appendix 4

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A 4.1 References

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