Towards the Total Synthesis of Pectenotoxin-4: Synthesis of the CDE and F rings



A thesis submitted to the Board of the 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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Trinity Term 2018

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source or a thesis.

Melodie See Won Richardson

University of Oxford, Trinity Term 2018

Abstract

Chapter 1: Introduction

This chapter outlines the isolation and structural identification of the pectenotoxin (PTX) family of natural products, as well as their reported biological activity. Finally, the chapter will be concluded with the completed total syntheses of members of the pectentoxin family by Evans and Fujiwara.

Chapter 2: Development of a Conjugate Addition-Cyclisation Approach towards the D ring

This chapter outlines previous approaches to forming the bicyclic D ring, our proposed approach using a rhodium-catalysed 1,4-addition as the key C–C bond-forming reaction to synthesis PTX-4, and model studies to test the feasibility of this disconnection.

Chapter 3: Synthesis of the desired E ring fragment

This chapter outlines our current synthesis of the E ring of PTX-4 and the elaborations on the E ring side chain to utilise the rhodium-catalysed 1,4-addition and dihydroxylation/cyclisation sequence as developed in **Chapter 2**.

Chapter 4: Synthesis of the desired F ring fragment

This chapter outlines the reoptimisation and scale-up of the F ring synthesis previously published, with modifications to the protecting group strategy employed in preparation for the Julia coupling with the ABCDE fragment in our total synthesis of PTX-4.

Chapter 5: Experimental

This chapter outlines all the experimental procedures for the reactions described in this thesis, as well as the characterisation data for the compounds synthesised.

Chapter 6: Appendices

This chapter contains the Mosher's ester analyses of compounds **282**, **331**, **463** and **539**; as well as nOe analysis of compounds **351**, **399**, **400**, **403**, **447**, **451** and **469** along with their ^{1}H and ^{13}C NMR spectra.

Chapter 7: References

This chapter contains the references cited within.

Acknowledgements

Firstly, I must thank my supervisor, Prof. Tim Donohoe, for his guidance and advice throughout my DPhil. It has been a great privilege working within your group and to be given the relative freedom to undertake my research at my own pace. I also must thank you for allowing (and trusting!) me to take on some tutorials for a brief period, as well as a Part II student alongside my research. I hope one day you will finally be able to say your group has synthesised this mammoth of a natural product! I can only hope my research has contributed in some way to the future of the synthesis.

I also must thank my industrial supervisors, Dr Chris Tame and Dr Darren Poole (GSK), for providing support, advice and new perspectives on problems I encountered during my time here. I thank the SBM (Prof. Darren Dixon, Prof. Martin Smith, Lara, Laura and Maitane) and the industrial partners, as well as Dr Michael Peagram, for giving me this opportunity to complete my DPhil. I also thank all the staff that help make the CRL run smoothly – particularly Ron (for fixing everything in sight), Dr Barbara O'Dell and Prof. Tim Claridge (for taking the time to help me with my lovely NMR spectra).

Thanks must also go to the many members – past and present – of the Donohoe group. I have thoroughly enjoyed spending time in F7, with my lab mates over the years helping pass the time with their crazy music choices and interesting conversations. Particular thanks must go to Waz and Sandy for being there when I was having a tough time, both inside and outside of the lab, as well as providing "bangers" and the occasional crazy dancing (again both inside and outside of the lab…). Many thanks go to James (the James modification, an appreciation for the art of distillation, and other chemistry advice), Harish, Roly and Hamish (for more great chemistry advice). Thanks also go to Johannes (for the sanity brews), Chris H (for continuing the brew tradition and cake shop cuttings), CB (for expert NMR advice), Henrique (for not so great life advice and always being up for a drink/BBQ), Anna (for taking over card angel duties – sorry!), Max (for cheering up the office with your plant collection), and Delaforce (for the lab sing-a-longs and epic pole dancing moves). Jess – I thank you for convincing me to join the group in the first place when you were a Part II, and for dragging me on trips away when I clearly needed one. I must also thank my proofreaders Anna, Max, Hamish, Roly and Lil Tim for taking the time to meticulously to go through chapter drafts and helping me finish on time!

Timmy and Oskar, my fellow Team Toxin members, thank you for cheering up the synthesis-side of F7. Oskar – it really wasn't me who put all those Byron cards everywhere, but I am sure you'll one day figure who did (possibly when you clear your desk). Lil Tim – good luck with the rest of the PTX-4 synthesis, you've been a pleasure to work with for the past couple of years! I truly believe you'll complete the synthesis and wield the legendary Sword of Results – just don't die from all the Byrons/Chutneys/Spice Lounges/Shoryu ramens/Rickety Press' angry wings.

Thank you to the previous members of Team PTX-4 for laying the foundation for my work, particularly the members I worked alongside: Xuezheng, Yifan, and Ahria.

Last but not least, I thank my parents, my little brother and sister and the rest of the family for being there when I needed them, for attempting to proofread this thesis, and not questioning why I haven't got a job yet. I will get one soon, promise!

I've finally finished a total of eight long years here among the dreamy spires of Oxford, and I can truly say I wouldn't ever change a thing.

Abbreviations

Ac	acetyl
acac	acetylacetonato
AD	asymmetric dihydroxylation
AIBN	2,2′-azobisisobutyronitrile
app.	apparent
aq.	aqueous
AQN	anthraquinone
Ar	aryl
AZA	azaspiracid
$BF_3{\cdot}OEt_2$	boron trifluoride diethyl ether complex
BINAP	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Boc	*tert*-butyloxycarbonyl
Bt	benzothiazole
BtSH	mercaptobenzothiazole
cat.	catalytic amount
cod	1,5-cyclooctadiene
cont.	continued
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N,N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	double doublet
ddd	double double doublet
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DET	diethyl tartrate
DHQ	dihydroquinine

DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	*N,N'*-diisopropylcarbodiimide
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
DSP	diarrhetic shellfish poisoning
dt	double triplet
DTX	dinophysistoxin
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
h	hour(s)
H_2O	water
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
HWE	Horner–Wadsworth–Emmons
i-Pr	isopropyl
J	coupling constant
LC_{50}	median lethal dose

LDA	lithium diisopropylamide
LiDBB	lithium di-*tert*-butyl diphenylide
LLS	longest linear sequence
LRMS	low resolution mass spectrometry
m	multiplet
m.p.	melting point
Mc	α-chloromesyl
Me	methyl
min	minute(s)
MLD	minimum lethal dose
MS	molecular sieves
MTPA	Mosher's acid/α-methoxy-α-trifluoromethylphenylacetic acid
MVK	methyl vinyl ketone
nbd	norbornadiene
NHK	Nozaki–Hiyama–Kishi
NIS	*N*-iodosuccinimide
NME	*N*-methylephedrine
NMO	*N*-methylmorpholine *N*-oxide
nmp	5,5-dimethyl-1-(4-methylpiperazin-1-yl)hexane-1,2,4-trione
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OA	okadaic acid
OTf	triflate
Ph	phenyl
PHAL	phthalazine
PhBr	bromobenzene
PhMe	toluene
pin	pinacolato
PMB	*para*-methoxybenzyl
PNO	pyridine *N*-oxide
PPTS	pyridinium *para*-toluenesulfonate

p-Tol	*para*-tolyl
PYR	pyrimidine
q	quartet
quant.	quantitative
RCM	ring-closing metathesis
R_f	retention factor
rt	room temperature
s	singlet
SAD	Sharpless asymmetric dihydroxylation
sat.	saturated
SO_3·py	sulfur trioxide pyridine complex
t	triplet
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBODPS	*tert*-butoxydiphenylsilyl
TBS	*tert*-butylsilyl
t-Bu	*tert*-butyl
td	triple doublet
tdd	triple double doublet
TES	triethylsilyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*, *N*, *N*′, *N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	tosyl
YTX	yessotoxin

Chapter 1

Chapter 1: Introduction

This chapter outlines the isolation and structural identification of the pectenotoxin (PTX) family of natural products, as well as their reported biological activity. Finally, the chapter will be concluded with the completed total syntheses of members of the pectentoxin family by Evans and Fujiwara.

1.1 The pectenotoxin family

1.1.1 Isolation and structure

The pectenotoxins (PTXs) are a family of polyether macrolides containing a spiroketal (AB ring), three substituted tetrahydrofurans (C, E and F rings) as well as 19 or more stereocentres decorating the 40-carbon chain (**Table 1-1**).[1] The first members of the family to be isolated were PTX-1 to PTX-5 by Yasumoto in 1985.[2] They were extracted from the digestive glands of the scallop *Patinopecten yessoensis* from which they were named. The relative configuration of PTX-1 was established by X-ray crystallography (**Figure 1-1**); however due to its structural complexity, it was not until 1997 that the absolute stereochemistry, along with that of PTX-6, was determined with NMR studies.[3]

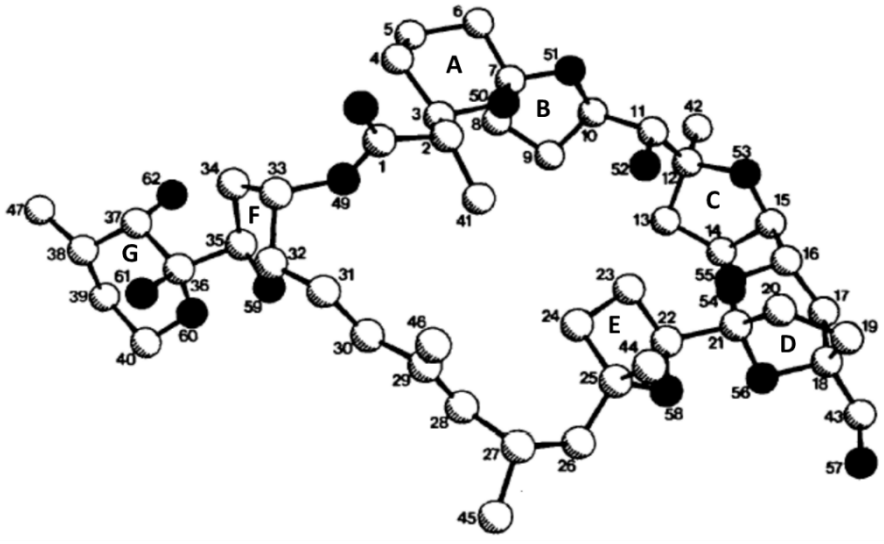
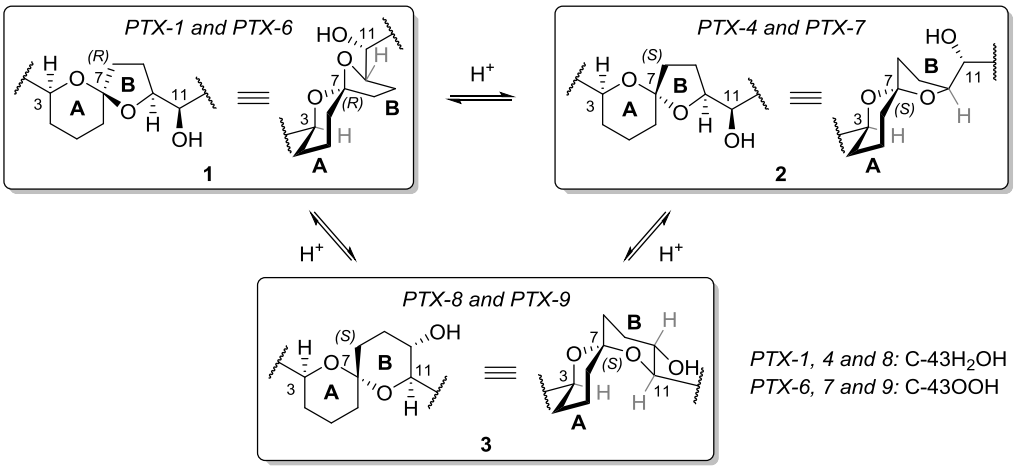


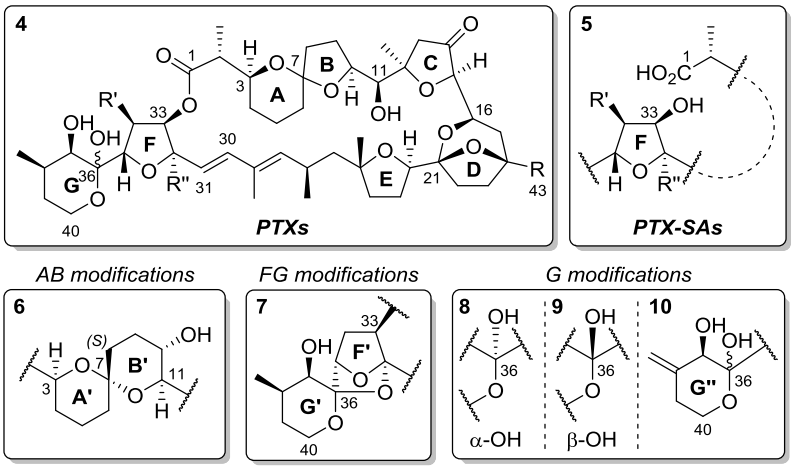
Figure 1-1: X-ray crystal structure of PTX-1 by Yasumoto modified from their paper.[2]

Yasumoto also discovered that PTX-4, as well as PTX-7, were C-7 epimers of PTX-1 and PTX-6.[4] This discovery led Yasumoto and co-workers to identify two more PTXs: PTX-8 and PTX-9, where the AB spiroketal is [6,6] as opposed to [6,5]. They found treatment of PTX-1 with TFA resulted in a 29:14:57 equilibrium mixture of PTX-1:PTX-4:PTX-8 (**Scheme 1-1**). Similarly, treatment of PTX-6 with TFA resulted in a 40:16:44 equilibrium mixture of PTX-6:PTX-7:PTX-9. As PTX-8 and 9 were not isolated from a natural source, they were thought to be synthetic artifacts unlike their [6,5]-spiroketal counterparts. It is thought the biaxial arrangement of the C–O bonds in the AB spiroketal in PTX-4 and PTX-7 are stabilised by the anomeric effect and are therefore the thermodynamically stable [6,5]-spiroketals. However, the apparent preference for the non-anomeric [6,5]-spiroketal in both cases (PTX-1 and PTX-6) was thought to be due to the steric constraint within the 40-carbon macrocycle. Similar interconversions were observed for PTX-2, PTX-2b and PTX-2c[5] as well as PTX-11, PTX-11b and PTX-11c.[6]



Scheme 1-1: Acid-catalysed equilibriation of the AB spiroketal of PTX-1, 4 and 8 and PTX-6, 7 and 9.

Since the initial isolation of PTX-1 to PTX-5 by Yasumoto, more than 20 PTXs and their seco acids (PTX-SA) have been identified (**Table 1-1**). The main differences between the family members are the stereochemistry at C-7 of the AB spiroketal and the oxidation level at C-43, though variation in the FG ring system has also been reported.[1]



Entry	PTX (SA)	Modification?	R	R'	R"	C-7	C-36
1	PTX-1[2]	-	CH_2OH	H	H	(*R*)	α-OH
2	PTX-2[2]	-	CH_3	H	H	(*R*)	α-OH
3	PTX-2b[5]	A'/B'	CH_3	H	H	(*S*)	α-OH
4	PTX-2c[5]	-	CH_3	H	H	(*S*)	α-OH
5	PTX-3[2, 7]	-	CHO	H	H	(*R*)	α-OH
6	**PTX-4[2]**	**-**	**CH_2OH**	**H**	**H**	**(*S*)**	**α-OH**
7	PTX-6[3]	-	CO_2H	H	H	(*R*)	α-OH
8	PTX-7[4]	-	CO_2H	H	H	(*S*)	α-OH
9	PTX-8[4]	A'/B'	CH_2OH	H	H	(*S*)	α-OH
10	PTX-9[4]	A'/B'	CO_2H	H	H	(*S*)	α-OH
11	PTX-11[6]	-	CH_3	OH	H	(*R*)	α-OH
12	PTX-11b[6]	-	CH_3	OH	H	(*S*)	α-OH
13	PTX-11c[6]	A'/B'	CH_3	OH	H	(*S*)	α-OH
14	36*S*-PTX-12[8]	G"	CH_3	H	H	(*R*)	α-OH
15	36*R*-PTX-12[8]	G"	CH_3	H	H	(*R*)	β-OH
16	PTX-13[9]	G"	CH_3	H	OH	(*R*)	α-OH
17	PTX-14[9]	F'/G'	CH_3	-*	-*	(*R*)	-*
18	PTX2-SA[10]	-	CH_3	H	H	(*R*)	α-OH
19	7-*epi*-PTX-2-SA[10]	-	CH_3	H	H	(*S*)	α-OH
20	PTX-12-SA[8]	G"	CH_3	H	H	(*R*)/(*S*)	α/β-OH

Table 1-1: Structures of the PTX family. PTX-5 and PTX-10 have not been fully characterised.
* Not determined.

Interestingly, it was found that the scallops (*Patinopecten yessoensis*) the PTXs were named after do not produce the toxins themselves. It was proposed that the scallops ingested toxic marine plankton, dinoflagellate known as *Dinophysis fortii*, and accumulated the toxins in their digestive system.[2, 11] However, only PTX-2 has been isolated from *Dinophysis fortii*.[12, 13] Therefore, it was hypothesised that PTX-2 is the parent toxin from which all other members of the PTX family are derived. Variations in oxidation state at C-43 were thought to occur *via* oxidation in the hepatopancreas of the scallops.[12] The epimerisation of the AB spiroketal was thought to occur in digestive glands of the scallop, possibly mediated by an enzyme as opposed to a non-specific acid-catalysed process. This hypothesis was supported by the lack of naturally-occurring PTX-8 and PTX-9 [6,6]-spiroketals within the scallop, which would be expected to form during non-specific acid-catalysed epimerisation.[4]

1.1.2 Biological activity

The PTXs were associated with diarrhetic shellfish poisoning (DSP), along with okadaic acid (OA, **11**), dinophysistoxins (DTXs, **12** and **13**), yessotoxins (YTXs, **14**), and azaspiracids (AZAs, **15** to **19**, **Figure 1-2**).[14] DSP is characterised by acute gastrointestinal disturbance, such as diarrhoea, nausea, vomiting and abdominal pain upon on consumption of contaminated shellfish. However, the causative effect of PTXs for DSP has been debated, as it has been reported that no diarrhetic effect was observed upon administering PTXs to mice.[6, 15, 16] The classification of causative agents for DSP likely arose from contamination during extraction of PTX with other DSP-causing toxins.[1]

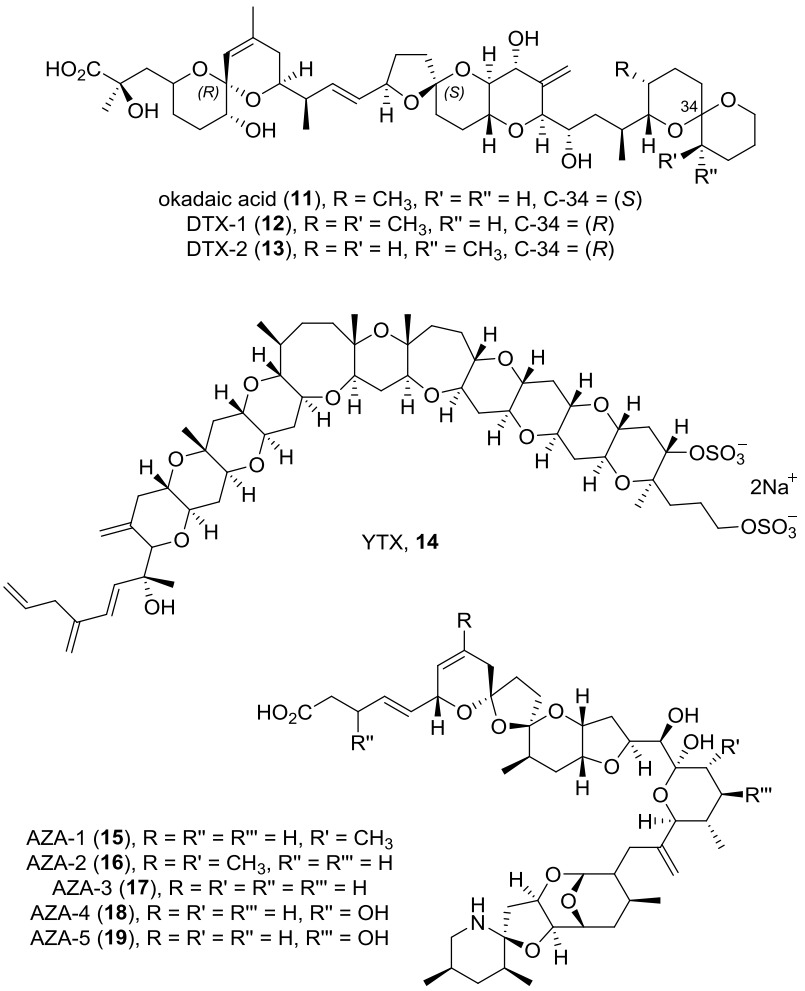


Figure 1-2: Other potential DSP-causing toxins.

Nevertheless, PTXs are reported to be hepatotoxic by causing apoptosis in rat and salmon hepatocytes.[17] PTX-2 is the most potent of the family, with a median lethal dose (LD_{50}) of 219 μg/kg through intraperitoneal injection in mice, with a minimum lethal dose (MLD) of 192 μg/kg.[16] However, no toxic effects were observed if orally dosed up to 5000 μg/kg, possibly due to poor gastrointestinal absorption or chemical detoxification through conversion into less toxic PTXs in the gut. Hydrolysis of the macrolactone ring to the corresponding seco acids resulted in lower toxicity, which may be a mechanism in the detoxification process.[16] Similarly, oxidation of the C-43 methyl group of PTX-2 to other PTXs also lowered toxicity, supporting the parental toxin hypothesis.[18]

The displayed cytotoxicity of PTXs led to investigation of their effect on tumours and cancer cell lines. PTX-2 exhibited very potent cytotoxicity against human lung, colon and breast cancer cell lines, as well as selective cytotoxicity against several cancer cell lines across ovarian, renal, CNS and melanoma.[11] The mode of action was shown to be inhibition of F-actin polymerisation, forming a complex with monomeric G-actin at a unique binding region not observed by other filament-destablising toxins (**Figure 1-3**).[19]

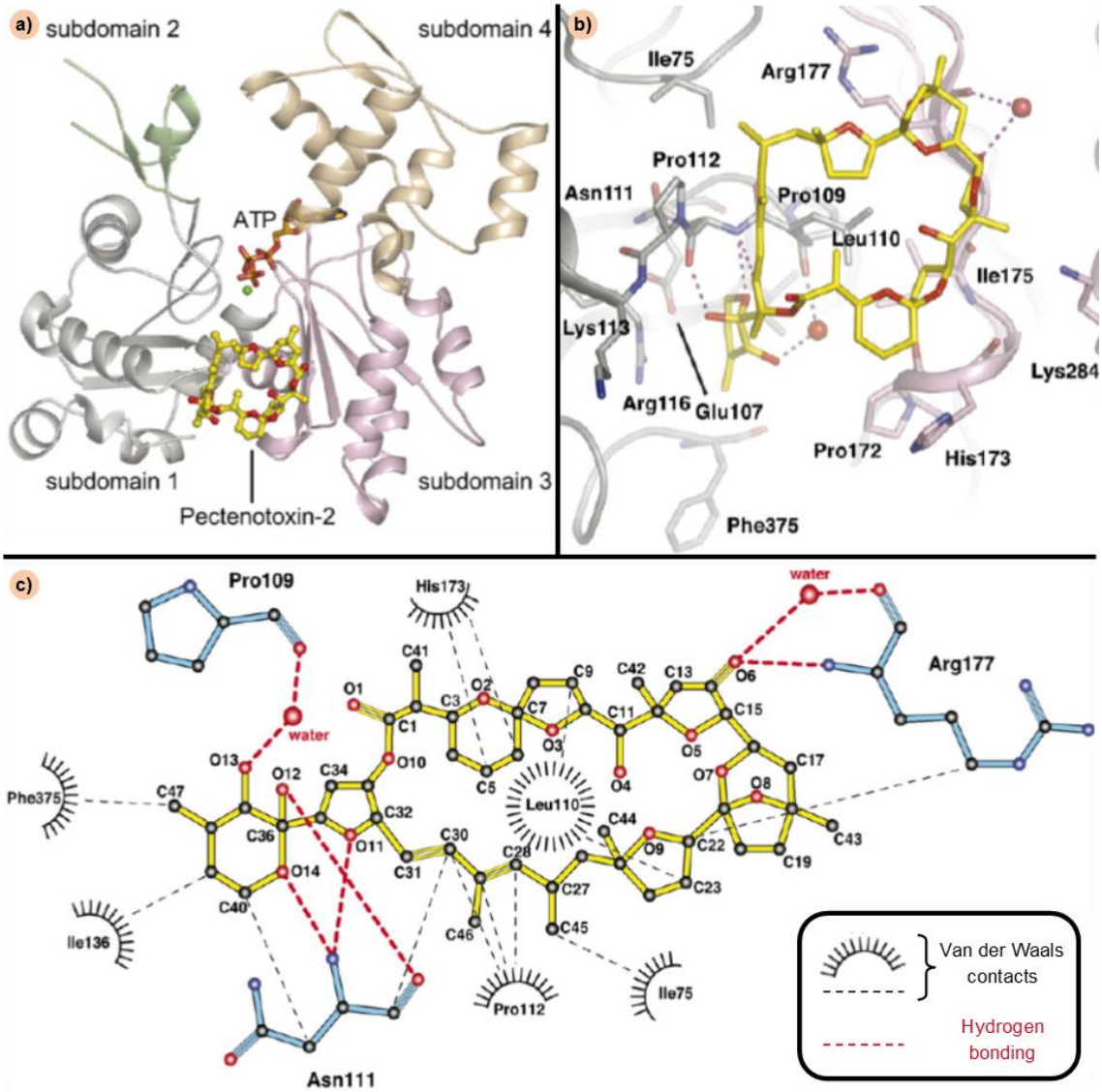


Figure 1-3: a) Crystal structure of PTX-2-actin complex. **b)** Stereoview of specific PTX-2-actin interactions with PTX-2 in yellow. **c)** Ligplot of the interactions between PTX-2 and actin, with PTX-2 in yellow. Van der Waals contacts are shown by black dotted lines, with the black spokes indicating the residues of actin involved. Hydrogen bonding is shown by red dotted lines, with the water molecules indicated by red spheres and the polar residues of actin involved coloured in cyan. Modified from Rayment's paper.[19]

PTX-2 binds between subdomains 1 and 3 (**Figure 1-3a**).[19] The ABCDE lactone motif (known as the "ring" portion) lies flat within the shallow groove between these domains, and predominantly interacts with actin in a hydrophobic manner (**Figure 1-3c**). The conformation of the non-anomeric AB [6,5]-spiroketal was crucial for hydrophobic binding between Leu110 and His173 and for maintaining the "ring" shape. The diene component between rings E and F was also thought to impose rigid conformational constraints to the "ring" shape to aid binding to actin. The lack of conformational freedom would decrease the entropic cost of binding within this hydrophobic pocket; therefore open-chain seco acids would exhibit poorer binding and lower toxicity as previously demonstrated.[10, 16, 20, 21] The FG motif (known as the "tail" portion) interacts predominantly with subdomain 1 of actin *via* hydrogen bonding. The G ring also participates in hydrophobic interactions within a narrow hole formed by Ile136, Phe375 and Asn111.

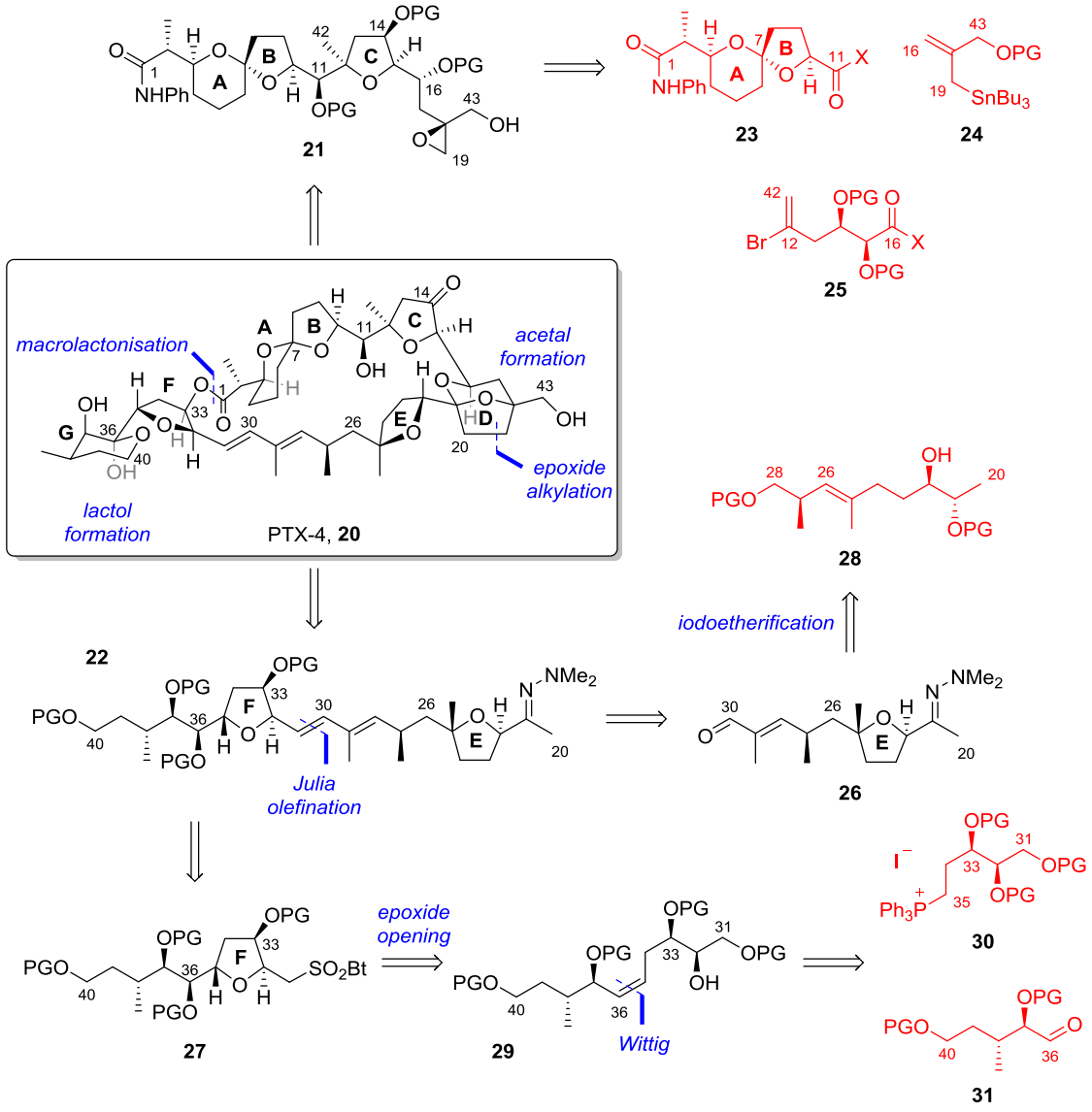
As a consequence of their interesting and challenging structures, promising biological activity and the mode of action of the PTXs, many groups have sought to synthesise these natural products.[1] However, to date, only two total syntheses have been reported: Evans' synthesis of PTX-4 in 2002,[22, 23] and, more recently, Fujiwara's synthesis of PTX-2 in 2014.[24] These will be discussed in the following section.

1.2 Previous total syntheses

1.2.1 Evans' total synthesis of PTX-4

Evans and co-workers chose PTX-4 (**20**) as their initial target, possibly because the anomeric AB spiroketal is the thermodynamically most stable [6,5]-spiroketal when not constrained within the macrolactone ring. Their retrosynthesis consists of a macrolactonisation disconnection between C-33 hydroxyl group and C-1 carbonyl group,

and an epoxide alkylation between C-19 and C-20 to split the complex molecule **20** into two equal-sized fragments ABC **21** and EF **22** (**Scheme 1-2**).[22, 23] This route requires C-14 and C-36 ketones to be masked as protected alcohols until late into the synthesis. The C-1 terminus was kept at the correct oxidation state throughout the synthesis and masked as a *N*-phenylamide. ABC fragment **21** can be disconnected further into **23**, **24** and **25**. The stereochemistry at C-11 and C-16 was envisioned to be installed *via* chelation-controlled reduction of the corresponding ketone, or originate from Felkin–Ahn controlled addition of the desired nucleophile to the respective aldehydes.[22]

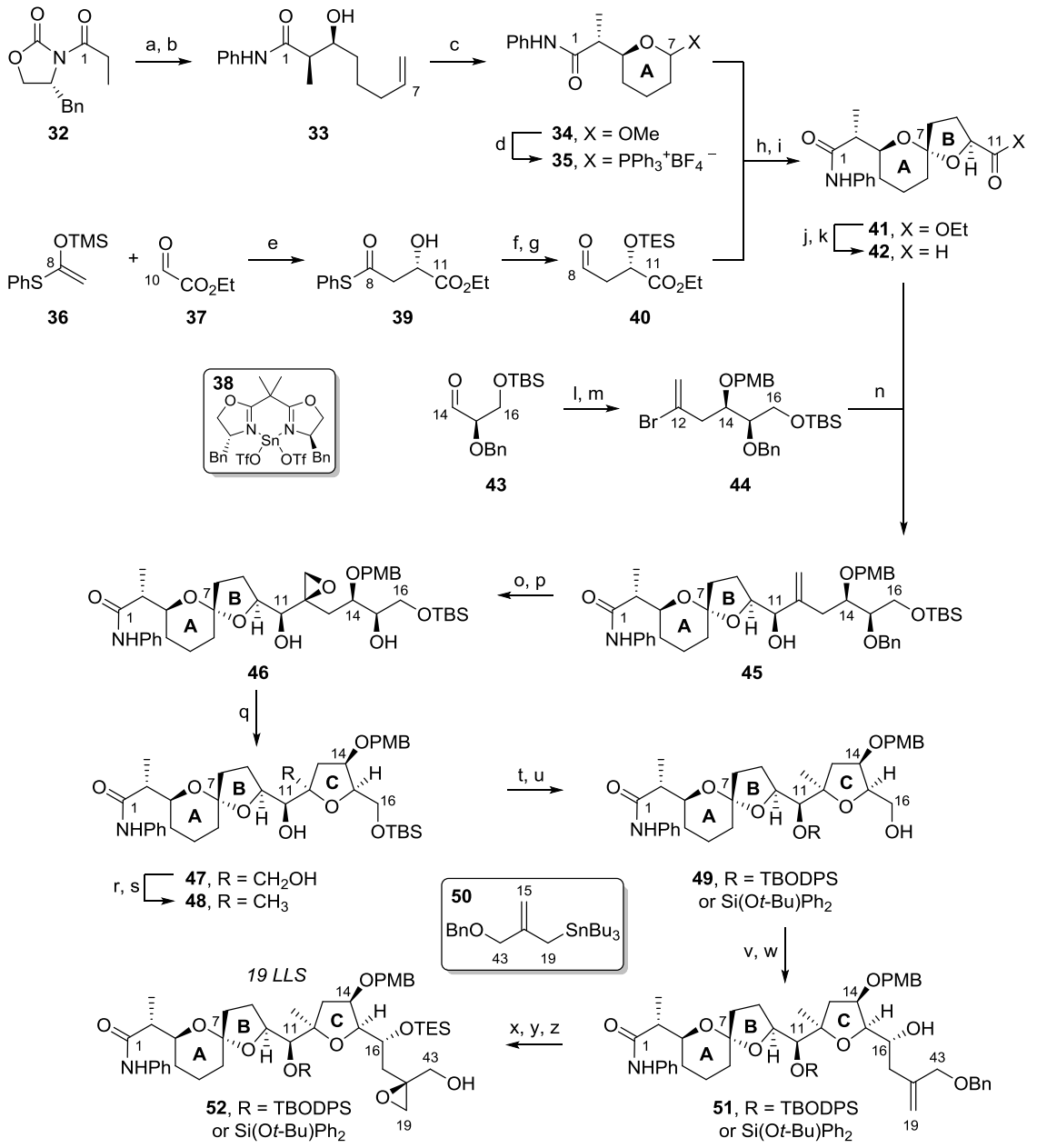


Scheme 1-2: Evans's retrosynthesis of PTX-4.

The EF fragment, with the side chain C-36 to C-40 protected to allow formation of the lactol at a late-stage, can be disconnected further to the E fragment **26** and F fragment **27** *via* a Julia olefination between C-30 and C-31 (**Scheme 1-2**).[23] The E fragment **26** was to be prepared from linear precursor **28** through a proposed iodoetherification. The *trans*-tetrahydrofuran of F fragment **27** originated from an epoxide opening, where the epoxide was derived from (*Z*)-alkene linear precursor **29**. The (*Z*)-alkene was proposed to come from a Wittig reaction between phosphonium salt **30** and aldehyde **31**.

The ABC fragment synthesis began with an asymmetric aldol using Evans' auxillary derivative **32** with 5-hexenal *via* the boron enolate, and subsequent transamidation with aniline produced the *syn*-aldol adduct **33** in 85% yield over two steps in >95:5 dr (**Scheme 1-3**).[22] Ozonolysis of olefin **33** followed by *in situ* ether formation with CSA gave A ring methyl acetal **34** in 96% yield. Simultaneously, the C-8 to C-11 fragment **40** was synthesised in three steps *via* a tin-mediated enantioselective aldol reaction between **36** and **37**, TES-protection of the subsequent hydroxyl at C-10 and finally a reduction of the thioester to access aldehyde **40** in 83% overall yield.[25] The methyl acetal **41** was converted into phosphonium salt **35**[26] in preparation for a Wittig-based fragment coupling to aldehyde **40** followed by treatment with CSA to obtain AB anomeric [6,5]-spiroketal **41** in 80% over three steps.

The C-12 to C-16 carbon backbone of the C ring was attached to the AB ring *via* a Felkin–Ahn controlled addition of the lithiated fragment **44** (two steps from **43**) to aldehyde **42** of the AB ring, setting the stereochemistry at C-11. The benzyl ether at C-15 of **45** was removed with LiDBB, before the alkene was subjected to hydroxyl-directed epoxidation[27] to afford a single diasteromer of epoxide **46** in 70% overall yield. This was subjected to mildly acidic conditions to form the C ring giving **47** in 87% yield.



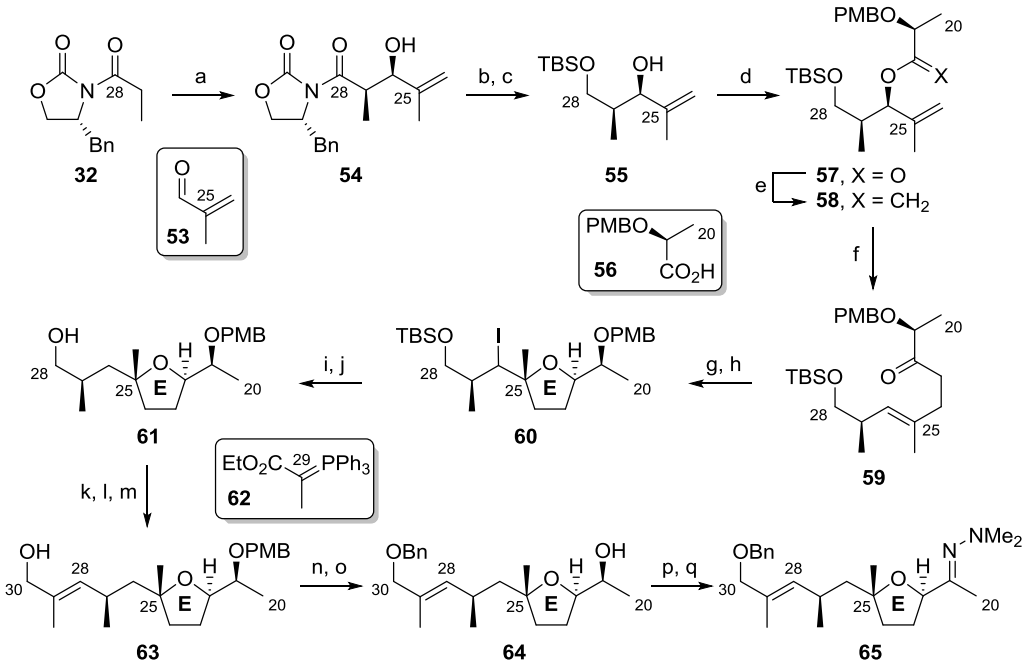
Scheme 1-3: Evans' synthesis of ABC fragment **52**.

Reagents and conditions: a) *n*-Bu_2BOTf, Et_3N, DCM then 5-hexanal, DCM, –78 °C, 87%; b) $AlMe_3$, $PhNH_2$, DCM, 98%; c) O_3, Me_2S then CSA, MeOH, –78 °C, 96%; d) $PPh_3{\cdot}HBF_4$, MeCN, 60 °C; e) **38** (10 mol%), DCM, –78 °C, 86%, 98% ee; f) TESOTf, 2,6-lutidine, DCM, –78 °C, 86%; g) Pd/C, Et_3SiH, acetone, 97%; h) **35**, *n*-BuLi then **40**, THF, –78 °C; i) CSA, DCM/MeOH (1:1), 80% over three steps, >95:5 dr; j) $LiBH_4$, THF, –10 °C, 93%; k) $SO_3{\cdot}py$, Et_3N, DMSO/DCM (1:1), 91%; l) Ti(O*i*-Pr)Cl_3, 2-bromoallyltrimethylsilane, DCM, –78 °C, 87%, >95:5 dr; m) PMB-trichloroacetimidate, TfOH, Et_2O, 20 °C to 0 °C, 79%; n) **44**, *t*-BuLi then $MgBr_2$, **42**, Et_2O, –78 °C, 68%, 86:14 dr; o) LiDBB, THF, –78 °C, 81%; p) $VO(acac)_2$, *t*-BuOOH, benzene, 99%, >95:5 dr; q) PPTS, DCM, 87%; r) PhOC(=S)Cl, DMAP, DCM, –10 °C, 75%; s) Bu_3SnH, AIBN, xylenes, 160 °C, 72%; t) TBODPSCl, DMAP, Et_3N, DMF, 90%; u) CSA, DCM/MeOH (1:1), –20 °C, 85%; v) $SO_3{\cdot}py$, Et_3N, DMSO/DCM (1:1), –10 °C; w) **50**, $BF_3{\cdot}OEt_2$, DCM, –78 °C, 78% over two steps, >95:5 dr; x) TESCl, imidazole, DCM, 92%; y) LiDBB, THF, –78 °C, 87%; z) Ti(O*t*-Bu)$_4$, (L)-(+)-DET, *t*-BuOOH, 3 Å MS, DCM, –30 °C, 99%, 95:5 dr.

Standard Barton conditions[28] were used to deoxygenate the C-12 hydroxymethyl group to give **48** in 54% over two steps (**Scheme 1-3**). After protecting the C-11 hydroxyl with TBODPS and removing the C-16 TBS group, ABC fragment **49** was oxidised using a Parikh–Doering[29] reaction and the resulting aldehyde was subjected to allylation with vinyl stannane **50** to obtain **51** in 78% overall yield. Finally, TES-protection of the C-16 hydroxyl group, benzyl-deprotection of the C-43 benzyl ether and a Sharpless asymmetric epoxidation of the C-18 to C-19 alkene afforded the desired ABC epoxide **52** in 80% yield over three steps. The ABC epoxide **52** was synthesised in 5.5% overall yield over 19 steps LLS from Evans' auxiliary derivative **32**.

The synthesis of the E ring fragment began with an asymmetric aldol reaction between Evans' auxiliary derivative **32** and aldehyde **53** to deliver *syn*-aldol adduct **54** in 86% yield (**Scheme 1-4**).[30] After removal of the auxiliary and TBS-protection of the resulting primary alcohol to give **55**, the secondary hydroxyl was acylated with PMB-protected lactic acid **56** in 58% yield to give **57**.[23] Methylenation of the ester carbonyl group with Tebbe reagent produced **58**, which upon heating underwent a Claisen rearrangement afforded **59** in 82% yield over two steps. Chelation-controlled reduction of the C-22 ketone with $Zn(BH_4)_2$ followed by iodoetherification provided the desired E ring **60** in 68% yield. Radical dehalogenation and subsequent TBS-protection gave alcohol **61** in 95% yield over two steps. Oxidation of the primary alcohol, Wittig reaction with ylide **62** and reduction of the corresponding ethyl ester provided the desired alcohol **63** in 91% yield over three steps. Benzyl-protection of the primary alcohol with benzylbromide followed by PMB-deprotection of the C-21 PMB-ether afforded alcohol **64** in 89% yield. Finally, oxidation of the C-21 alcohol wth DMP to the corresponding ketone and

hydrazone formation obtained the desired E ring fragment **65** in 93% yield. Overall, synthesis of the E ring fragment **65** was achieved in 14% yield over 17 steps.

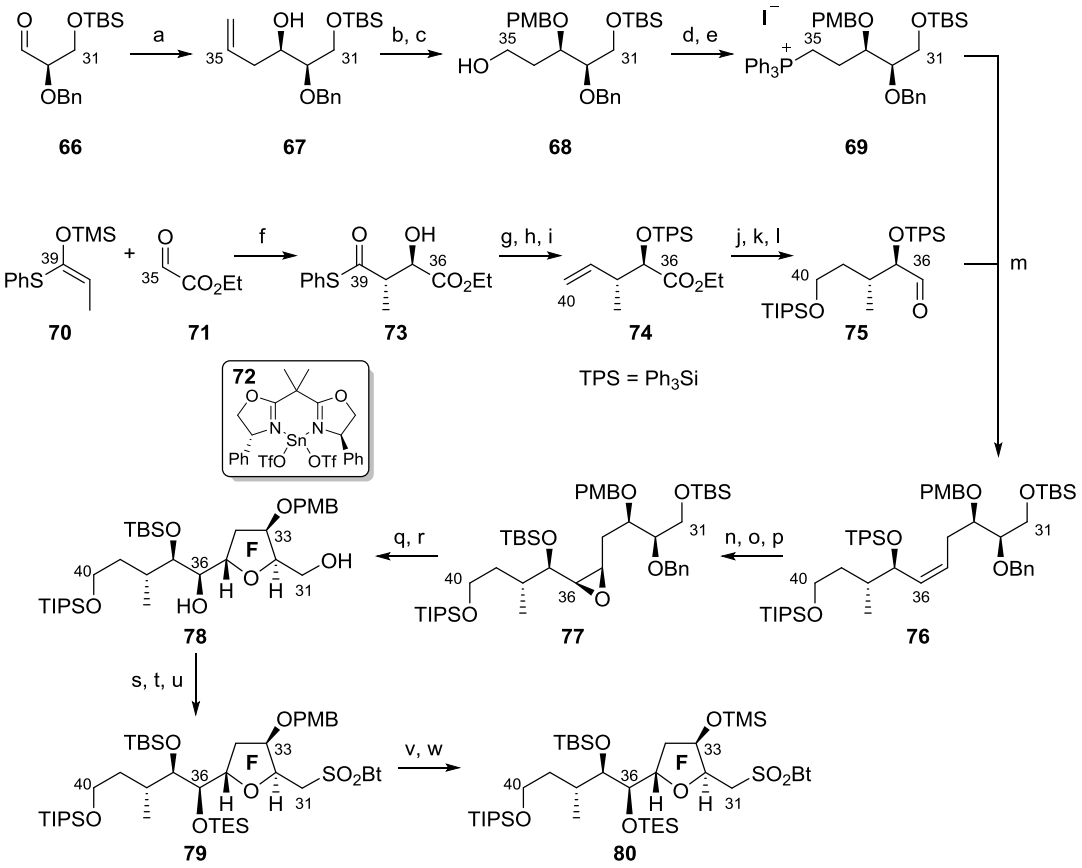


Scheme 1-4: Evans' synthesis of the E ring fragment **65**.
Reagents and conditions: a) *n*-Bu_2BOTf, *i*-Pr_2NEt, DCM then **53**, DCM, –78 °C, 86%; b) $LiBH_4$, THF, 0 °C; c) TBSCl, imidazole, DCM, 100% over two steps; d) **56**, DCC, DMAP, DCM, 58%; e) Cp_2TiCl_2, $AlMe_3$, THF then **57**; f) PhMe, 100 °C, 82% over two steps; g) $Zn(BH_4)_2$, Et_2O, –78 °C, 74%; h) NIS, MeCN, –40 °C, 64%, 72:28 dr; i) Bu_3SnH, AIBN, PhMe, 100%; j) TBAF, THF, 95%; k) DMP, pyridine, DCM, 99%; l) **62**, THF, 65 °C, 100%; m) $LiAlH_4$, Et_2O, 0 °C, 92%; n) NaH, BnBr, TBAI, THF/DMF (3:1), 94%; o) DDQ, DCM/pH 7 buffer (8:1), 95%; p) DMP, pyridine, DCM, 93%; q) TMSCl, DCM/H_2NNH_2 (1:1), 0 °C, 100%.

The synthesis of the F ring fragment began with a tin chloride mediated allylsilane addition into aldehyde **66** to obtain *syn*-adduct **67** in 83% to set the stereochemistry at C-33 (**Scheme 1-5**).[31] PMB-protection of the C-33 hydroxyl followed by ozonolysis with a reductive work-up afforded **68** in 90% yield over two steps. Conversion of the primary alcohol into phosphonium salt **69** was achieved in two steps *via* the iodide obtained from an Appel reaction followed by displacement with triphenylphosphine.

Concurrently, an asymmetric aldol reaction between **70** and **71** catalysed by tin complex **72** afforded *anti*-adduct **73** in 95% yield and 96:4 dr (**Scheme 1-5**). Protection of C-36 with a base-sensitive triphenylsilane (TPS) group, reduction of the C-39 thioester to the

aldehyde with Et_3SiH and olefination under modified Lombardo conditions[32, 33] afforded olefin **74** in 78% yield over three steps. Aldehyde **75** was accessed in a further three steps *via* rhodium-catalysed hydroboration, TIPS-protection of the C-40 hydroxyl group and DIBAL-H reduction of the ethyl ester.



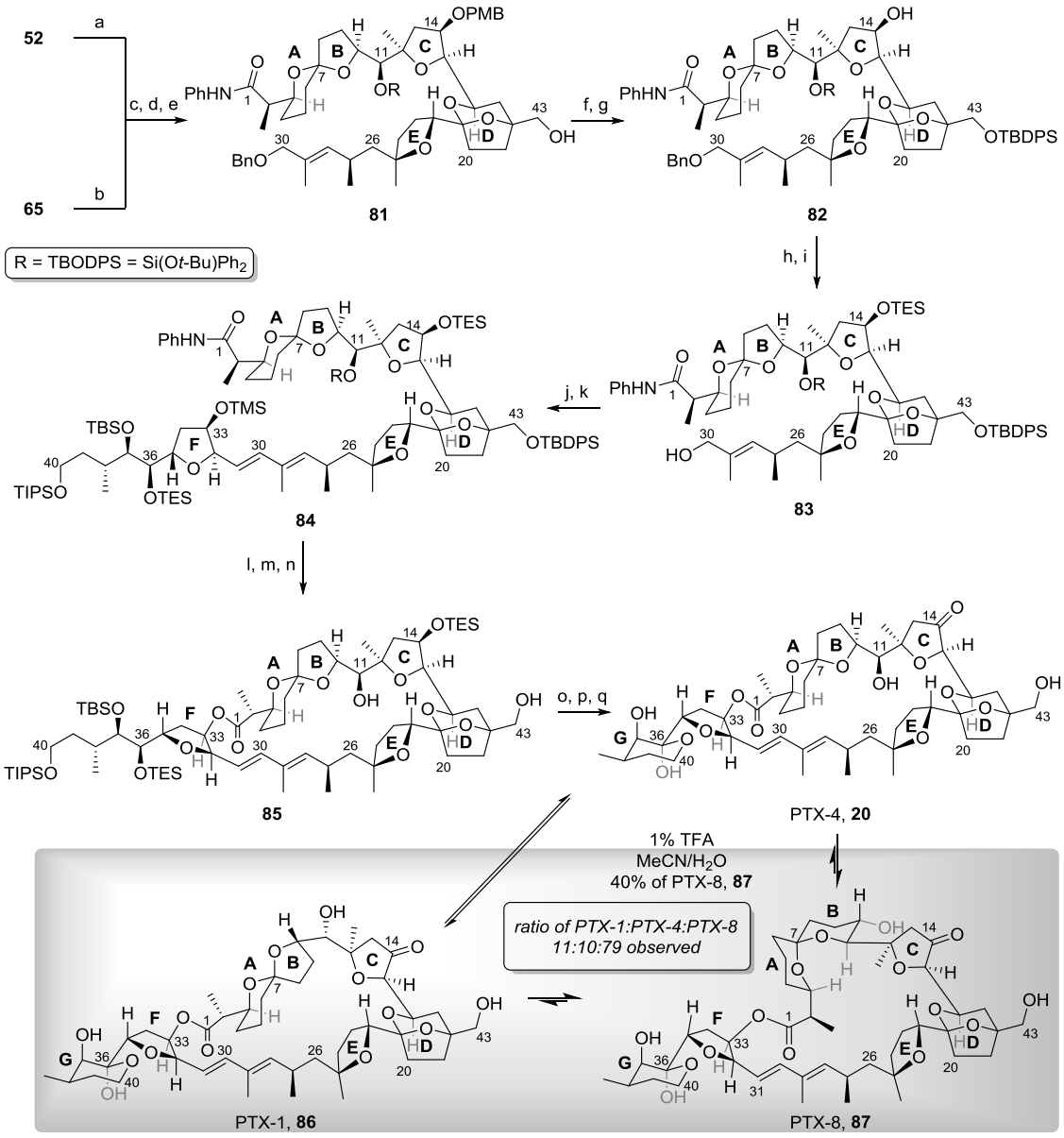
Scheme 1-5: Evans' synthesis of the F ring fragment **80**.
Reagents and conditions: a) $SnCl_4$, allyltrimethylsilane, DCM, –78 °C, 83%; b) PMBBr, NaH, THF/DMF (3:1), 0 °C, 95%; c) O_3, then Me_2S, $NaBH_4$, EtOH, –78 °C, 95%; d) I_2, imidazole, PPh_3, DCM, 0 °C, 89%; e) PPh_3, MeCN, 55 °C, 89%; f) **72**, DCM, –78 °C, 95%, 96:4 dr; g) TPSCl, imidazole, DMAP, DMF, 0 °C, 98%; h) Pd/C, Et_3SiH, acetone, 95%; i) Cp_2ZrCl_2, Zn dust, CH_2I_2, THF, 0 °C, 84%; j) $(Ph_3P)_3RhCl$, catecholborane, THF then pH 7 buffer, H_2O_2, 88%; k) TIPSOTf, 2,6-lutidine, DCM, –78 °C, 100%; l) DIBAL-H, PhMe, –78 °C, 89%; m) LiHMDS, THF, then **75**, –78 °C to 0 °C, 79%; n) K_2CO_3, MeOH/DCM (2:1), 87%; o) *m*-CPBA, DCM, 0 °C, 95%; p) TBSOTf, 2,6-lutidine, DCM, –78 °C, 95%; q) LiDBB, THF, –78 °C, 79%; r) PPTS, MeOH/DCM (1:1), 73%; s) BtSH, PPh_3, DIAD, THF, 0 °C; t) *m*-CPBA, DCM, 0 °C, 70% over two steps; u) TESCl, imidazole, DCM, 90%; v) DDQ, DCM/pH 7 buffer (10:1), 97%; w) TMSCl, imidazole, DCM, 99%.

The Wittig reaction between unstabilised phosphonium **69** and aldehyde **75** provided the desired (*Z*)-alkene **76** in 79% yield (**Scheme 1-5**). Removal of the TPS group revealed the C-37 hydroxyl group to allow for hydroxyl-directed epoxidation of the (*Z*)-alkene

with *m*-CPBA. Reprotection of the C-37 hydroxyl with TBSCl afforded epoxide **77** in 79% yield across the three steps. Benzyl deprotection with LiDBB allowed for the cyclisation of the F ring when the epoxide was treated with PPTS. This afforded the desired *trans*-geometry across the C-32 and C-35 tetrahydrofuran junction in 58% yield of **78** over two steps. A Mitsunobu reaction with mercaptobenzothiazole and oxidation of the sulfide provided the desired sulfone moiety **79** required for the Julia coupling to the E ring fragment. Finally, as PMB group removal was difficult in the presence of the 1,3-diene after the Julia coupling of the E and F rings,[23] a few protecting group manipulations afforded F ring fragment **80** in 13% overall yield (18 LLS) from 7**0** and **71**.

The final steps in the synthesis of PTX-4 (**20**) are shown in **Scheme 1-6**. The synthesis of D ring **81** *via* metal-mediated ABC epoxide opening using a metalloenamine of the E ring will be described in more detail in **Chapter 2.1.1**. Protection of the C-43 primary hydroxyl with TBDPSCl, replacement of the C-14 PMB group with a TES group as well as removal of the C-30 benzyl-group prior to the Julia coupling of the F ring, afforded **83** in 69% yield over four steps. A Parikh–Doering oxidation followed by Julia olefination with F ring fragment **80** furnished **84** in 72% yield, with the desired (*E*)-alkene between C-30 and C-31. Hydrolysis of the phenylamide and removal of the TMS group at C-33 paved the way for the Yamaguchi macrolactonisation to form **85**.[34] Finally, removal of the C-36 TES group, DMP oxidation and global deprotection with subsequent lactol formation of the G ring afforded PTX-4 (**20**) in 19% yield from **85**. The total synthesis of PTX-4 (**20**) was completed in an overall yield of 0.3% with 36 steps LLS from Evans auxiliary derivative **32**. The data for the synthetic material matched the spectroscopic data obtained from the natural sample.[23]

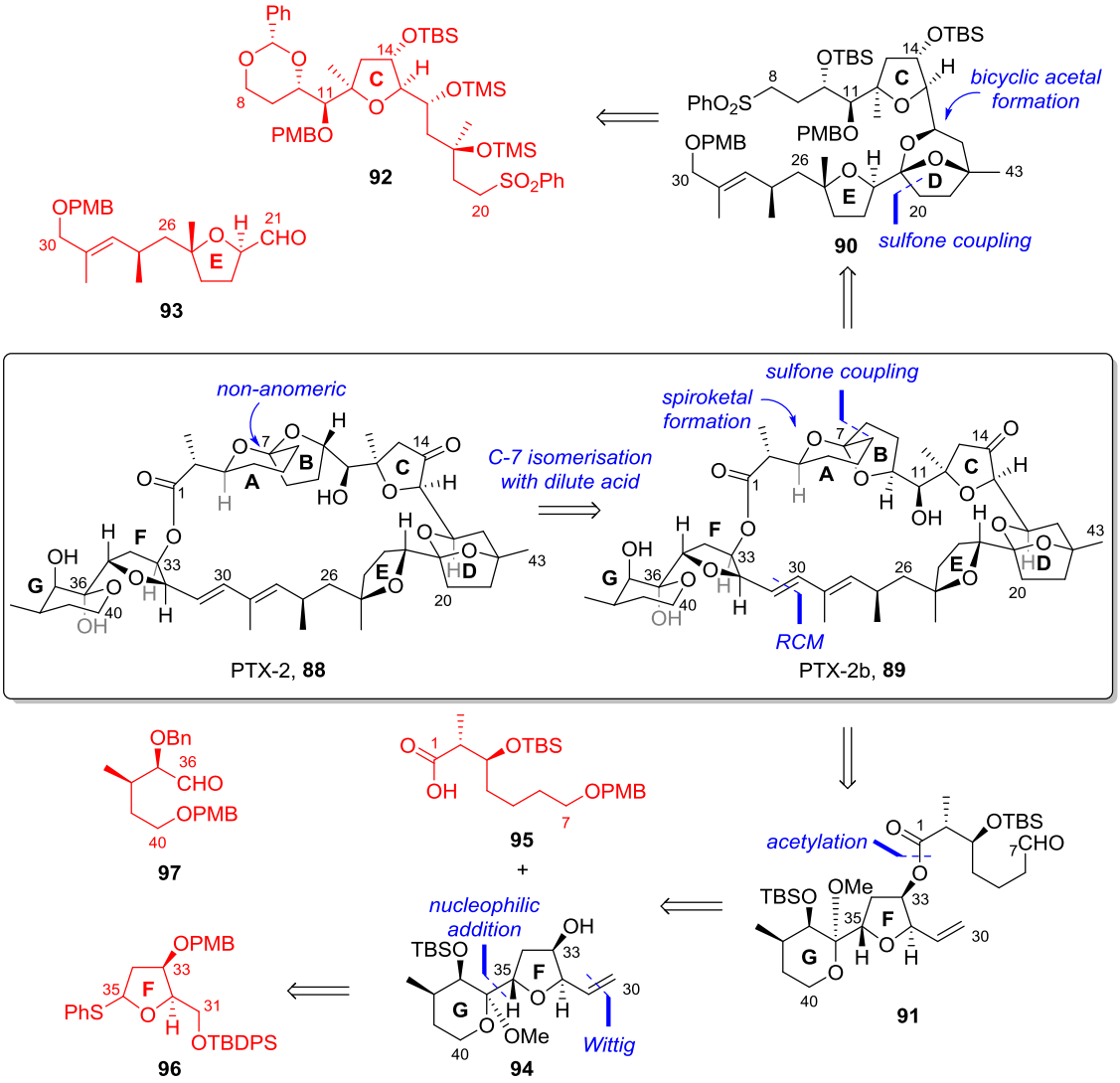
As further proof of structure, Evans subjected PTX-4 (**20**) to C-7 isomerisation conditions[4] and observed conversion to predominantly the [6,6]-spiroacetal of PTX-8 (**87**) to maximise the anomeric effect (**Scheme 1-6** in the greyed box). The observed ratio of PTX-1:PTX-4:PTX-8 ratio was 11:10:79.[23]



Scheme 1-6: Final steps in Evans' synthesis of PTX-4, **20**.
Reagents and conditions: a) EtMgBr, HMPA, THF, –67 °C to 0 °C; b) LDA, THF, , –67 °C to 0 °C; c) add **52**-$MgBr_2$ to **65**-Li, 10 °C; d) pentane/DCM/10% $NaHSO_4$ (4.5:1.5:4); e) PPTS, DCM/MeOH (1:1), 52% over 3 steps; f) TBSDPSCl, imidazole, DMAP, DCM, 90%; g) DDQ, DCM/pH 7 buffer (6:1), 90%; h) TESCl, imidazole, DCM, 100%; i) LiDBB, THF, –78 °C, 85%; j) SO_3·py, Et_3N, DCM/DMSO (1:1); k) F ring fragment **80**, LiHMDS, THF, –78 °C to 0 °C, 72% over two steps; l) Boc_2O, DMAP, MeCN, 91%; m) LiOH, H_2O_2, THF/H_2O (3:1); n) trichlorobenzoyl chloride, *i*-Pr_2NEt, then DMAP, PhMe; o) PPTS, DCM/MeOH (1:1), 35% over three steps; p) DMP, pyridine, DCM, 72%; q) TASF, H_2O, DMF, 85%.

1.2.2 *Fujiwara's total synthesis of PTX-2*

Fujiwara's synthesis of the PTX-2 (**88**) used the dilute acid C-7 isomerisation conditions[5] to favour the non-anomeric AB [6,5]-spiroketal when the macrocyclic lactone is formed (**Scheme 1-7**).[24] These conditions allow for the anomeric AB [6,5]-spiroketal (*via* PTX-2b, **89**) to be initially formed, which is thermodynamically more stable than its non-anomeric counterpart. The key disconnections were a ring-closing metathesis (RCM) for the C-30 to C-31 double bond, and a sulfone coupling followed by AB spiroketal formation to split the molecule into the CDE fragment **90** and FG fragment **91**.



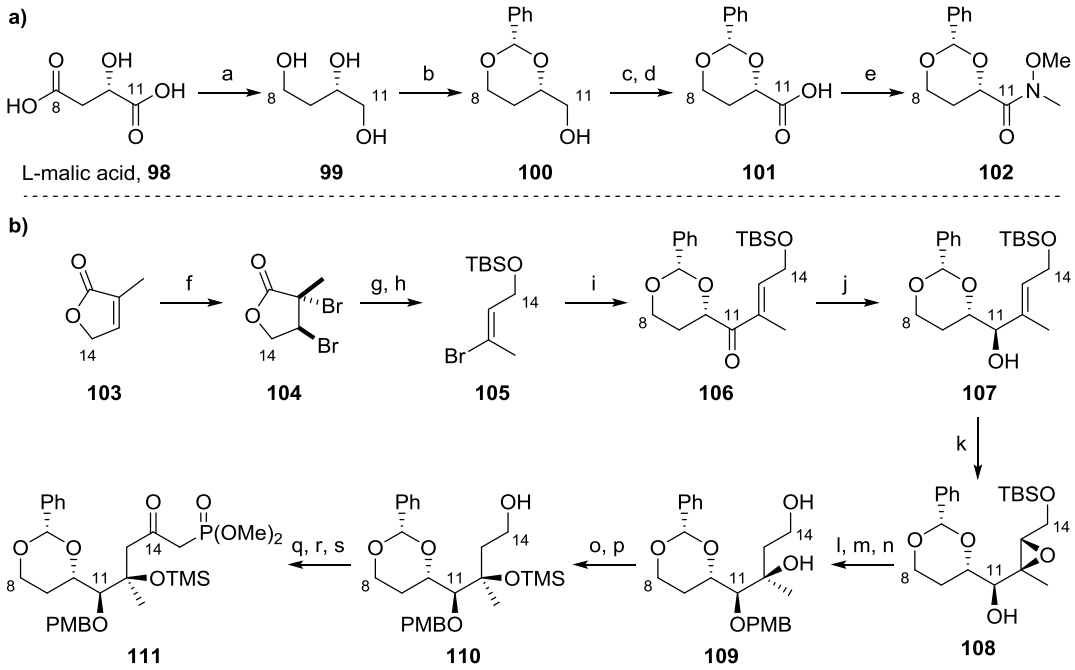
Scheme 1-7: Fujiwara's retrosynthesis of PTX-2, **88**.

The CDE fragment **90** was disconnected further *via* another sulfone coupling and bicyclic acetal formation to C ring fragment **92**[35] and E ring fragment **93**[36] (**Scheme 1-7**). The FG fragment **91** originated from deacylated FG fragment **94** and acid **95**.[37] The deacylated FG fragment **94** was further disconnected to fragments **96** and **97** *via* a reductive lithiation of F fragment **96** and nucleophilic addition into aldehyde **97**.

The synthesis of the C-8 to C-20 C fragment started with L-malic acid **98** (**Scheme 1-8a**).[35] Reduction of both carboxylic acid groups followed by protection of the 1,3-diol motif with benzaldehyde afforded **100** in 96% yield over two steps. Oxidation of the C-11 alcohol to the carboxylic acid using a Swern oxidation reaction followed by a Pinnick oxidation reaction accessed acid **101**. Amide formation using EDCI and *N*,*O*-dimethylhydroxylamine hydrochloride afforded Weinreb amide **102** in 79% over three steps.

Vinyl bromide **105** was synthesised in three steps from lactone **103** *via* a decarboxylation-debromination sequence of dibromide **104** (**Scheme 1-8b**).[38] Lithiation of vinyl bromide **105** and nucleophilic addition to Weinreb amide **102** afforded **106** in 87% yield. Diastereoselective reduction of the C-11 ketone to alcohol **107** was achieved with $Zn(BH_4)_2$ in 94% yield in 16:1 dr. Hydroxyl-directed epoxidation using the newly furnished C-11 hydroxyl afforded epoxide **108** in 95% yield. Protection of the C-11 hydroxyl group with PMBBr, cleavage of the C-14 TBS ether and reductive ring opening of the epoxide at C-13 with $LiAlH_4$ afforded **109** in quantitative yield. Protection of both primary C-14 and secondary C-12 hydroxyl groups was achieved with TMSOTf, before selective deprotection of the primary C-14 hydroxyl group delivered **110** in 91% yield. Alkylation at C-14 to access phosphonate **111** was accomplished by oxidation of the primary hydroxyl with DMP, nucleophilic addition to the aldehyde with the anion of

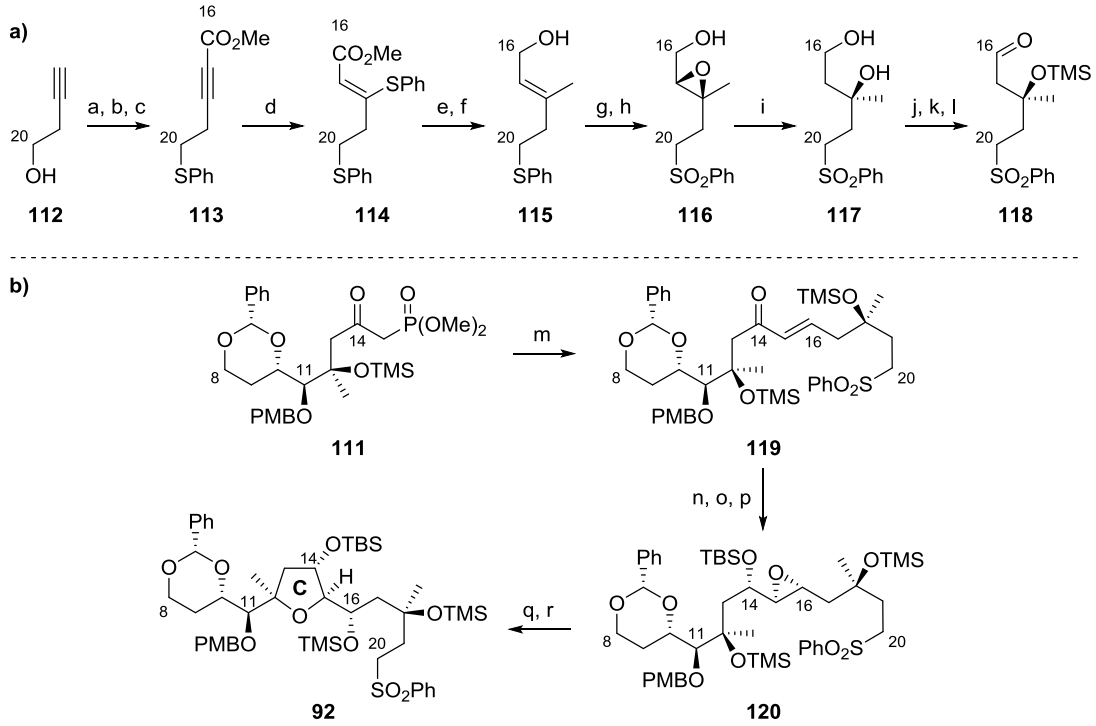
dimethyl methylphosphonate, and a further oxidation of the resulting hydroxyl group to the ketone with DMP.



Scheme 1-8: Fujiwara's synthesis of the C ring fragment **92**.
Reagents and conditions: a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF; b) benzaldehyde dimethyl acetal, CSA, DCM, 96% over two steps; c) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, 0 °C to rt; e) MeNHOMe·HCl, EDCI, DMAP, DCM, 79% over three steps; f) Br_2, DCM, –10 °C, 93%; g) LiOH, DMF/H_2O (4:1), 59%; h) TBDPSCl, Et_3N, DMAP, DCM, 100%; i) *t*-BuLi then **102**, THF, 87%; j) $Zn(BH_4)_2$, Et_2O, –78 °C to –30 °C, 94%, 16:1 dr; k) $VO(acac)_2$, *t*-BuOOH, DCM, 0 °C to rt, 95%; l) PMBBr, NaH, TBAI, THF, 0 °C to rt, 100%; m) TBAF, THF, 100%; n) $LiAlH_4$, THF, –15 °C, 100%; o) TMSOTf, 2,6-lutidine, DCM, –40 °C; p) K_2CO_3, MeOH, –15 °C, 91% over two steps; q) DMP, $NaHCO_3$, DCM; r) $MePO(OMe)_2$, *n*-BuLi, THF, –78 °C, 87% over two steps; s) DMP, $NaHCO_3$, DCM, 92%.

The aldehyde coupling partner for the Horner–Wadsworth–Emmons (HWE) reaction was synthesised in 12 steps from 3-butyn-1-ol **112** (**Scheme 1-9a**).[35] Displacement of the hydroxyl group with a thiophenolate anion *via* the tosylate, and alkylation of the terminal alkyne with methyl chloroformate gave **113** in 89% yield. Conjugate addition of another thiophenolate anion provided (*Z*)-alkene **114** in 89% in 8:1 *Z*/*E* geometry. Addition of methylcuprate followed by elimination of the thiophenolate and reduction of the ethyl ester afforded **115** in 98% yield. Sulfide oxidation and hydroxyl-directed epoxidation of the C-17 to C-18 olefin afforded **116** in 90% yield. Reductive epoxide opening at the least

hindered epoxide site with $LiAlH_4$ afforded diol **117** in 99% yield. Protection of the C-18 hydroxyl with the two-step TMS-protection procedure used previously, followed by DMP oxidation of the unprotected C-16 alcohol afforded aldehyde **118** in 70% yield.

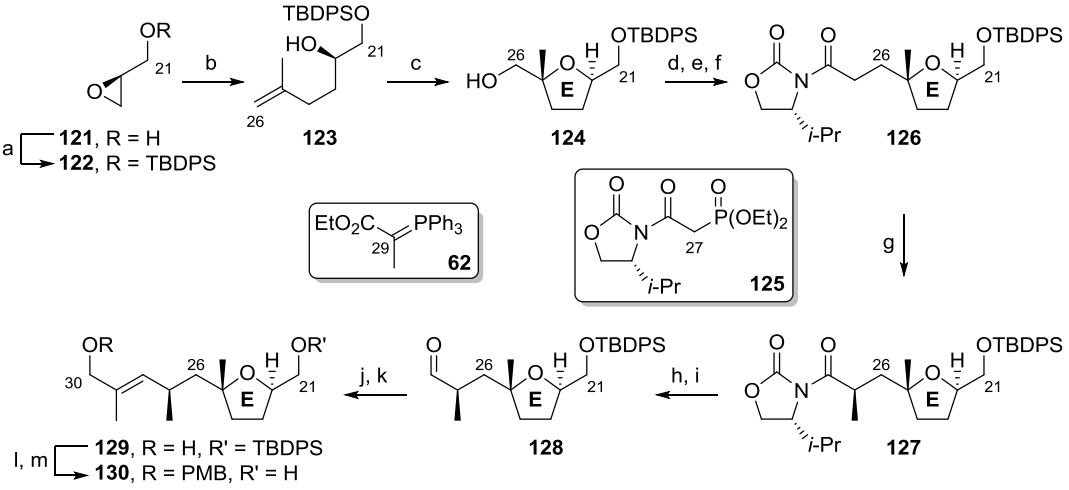


Scheme 1-9: Fujiwara's synthesis of the C ring fragment **92** (cont.).
Reagents and conditions: a) TsCl, pyridine, DCM, 100%; b) PhSH, *n*-BuLi, THF, 100%; c) *n*-BuLi, MeOCOCl, THF, –78 °C, 89%; d) PhSH, PhSNa, MeOH, 89% of *Z*, *Z*/*E* = 8:1; e) MeMgBr, CuI, THF –78 °C, 98%; f) DIBAL-H, DCM, 0 °C, 100%; g) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, –15 °C, 100%; h) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, DCM, –40 °C, 90%; i) $LiAlH_4$, THF, 99%; j) TMSOTf, 2,6-lutidine, DCM, –40 °C; k) K_2CO_3, MeOH, –15 °C, 72% over two steps; l) DMP, $NaHCO_3$, DCM, 97%; m) NaH, then **118**, 0 °C, benzene/THF (1:3), 91%; n) DIBAL-H, DCM, –104 °C, 99%, 9.4:1 dr; o) *m*-CPBA, $NaHCO_3$, DCM, 0 °C, 68%, 3.7:1 dr; p) TBSOTf, 2,6-lutidine, DCM, K_2CO_3, MeOH, –20 °C, 81%; q) CSA, DCM, 0 °C, 76%; r) TMSOTf, 2,6-lutidine, DCM, 0 °C, 100%.

The assembly of **119** *via* a HWE reaction of phosphonate **111** with aldehyde **118** was undertaken in 91% yield (**Scheme 1-9b**).[35] Reduction of the C-14 ketone with DIBAL-H, followed by hydroxyl-directed epoxidation and TBS-protection of the C-14 hydroxyl group afforded **120** in 55% yield, with a 3.7:1 dr for the epoxide formation. Cleavage of the C-12 TMS ether allowed for the spontaneous 5-*exo* cyclisation of the C ring *via* epoxide opening in 76% yield. Final protection of the resulting C-16 hydroxyl with TMSOTf afforded the desired C ring fragment **92** in quantitative yield. Overall, synthesis

of the C ring fragment **92** was achieved in a total of 22 steps LLS from L-malic acid **98** in 16% overall yield.

The E ring fragment originated from (*S*)-glycidol **121** (**Scheme 1-10**).[36] Protection of the primary alcohol followed by epoxide opening with the Grignard reagent generated from 3-chloro-2-methylpropene gave **123** in quantitative yield. Cyclisation to assemble the E ring was achieved by hydroxyl-directed epoxidation with $VO(acac)_2$ to give **124** in 57% yield, in addition to its diastereomer (18% yield) and recovered starting material **123** (11% yield). The attachment of the Evans auxiliary was achieved in three steps: oxidation of the C-26 alcohol, followed by a HWE reaction using the anion of **125** and hydrogenation of the resulting double bond gives **126**. Diastereoselective methylation produced **127** in 93% yield, with removal of the auxiliary and elaboration to access the desired aldehyde **128** in 97% yield. Finally, a Wittig reaction with ylide **62**, reduction of the ethyl ester with DIBAL-H and protecting group manipulation afforded the desired E ring fragment **130**, which was assembled in 13 steps from **121** in an overall yield of 40%.

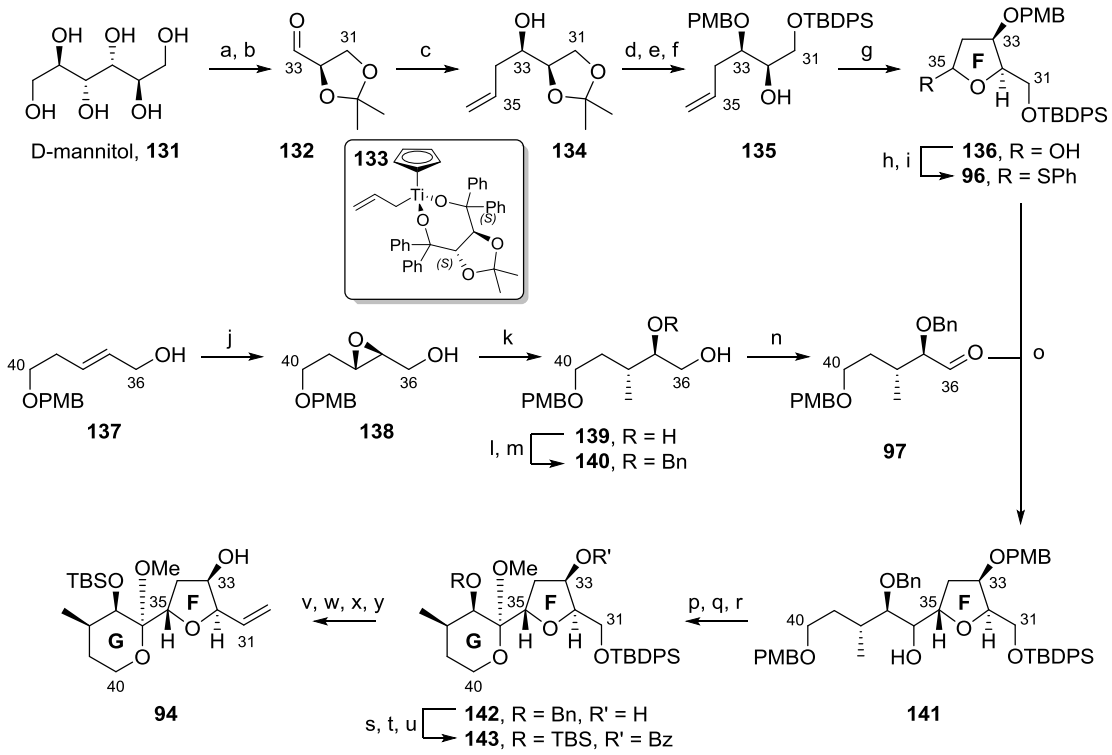


Scheme 1-10: Fujiwara's synthesis of the E ring fragment **130**.
Reagents and conditions: a) TBDPSCl, imidazole, DMF, 100%; b) 3-chloro-2-methylpropene, Mg, THF, –40 °C, 100%; c) $VO(acac)_2$, *t*-BuOOH, benzene, 55 °C, then CSA, 57%; d) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C, 96%; e) **125**, NaH, THF, 93%; f) H_2, Pd/C, EtOH, 100%; g) NaHMDS, the MeI, THF, –78 °C, 93%; h) $NaBH_4$, THF/H_2O (3:1), 100%; i) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C, 97%; j) **62**, benzene, Δ; k) DIBAL-H, DCM, –78 °C, 92% over two steps; l) NaH, PMBBr, TBAI, THF, 96%; m) TBAF, THF, 100%.

The FG ring fragment **91** was synthesised from D-mannitol (**131**, **Scheme 1-11**).[37] Conversion of **131** into aldehyde **132** was achieved in two steps in 45% yield.[39] Aldehyde **132** was allylated with chiral titanium allylating reagent **133** in 71% yield.[40] The C-33 hydroxyl groupwas PMB-protected, the acetonide was hydrolysed and the revealed primary hydroxyl group at C-31 was protected with TBDPSCl to give **135**. The F ring cyclisation was initiated by dihydroxylation of the alkene with OsO_4 and NMO to afford F ring alcohol **136** in 94% yield, which was converted to the thioether **96** in a further two steps in preparation for reductive lithiation.

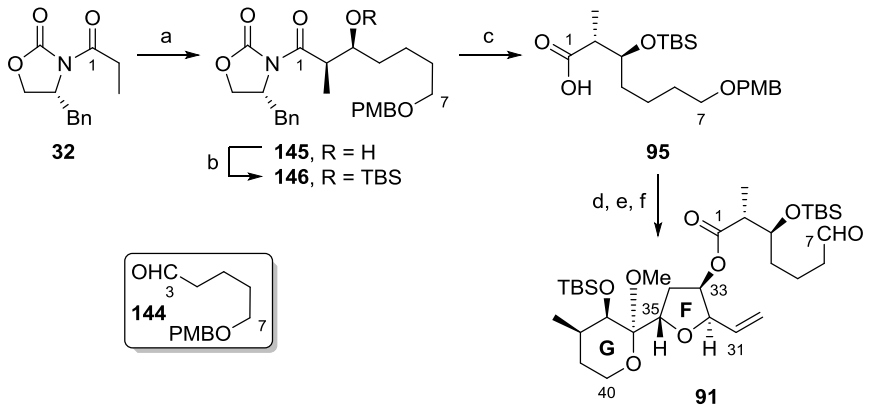
The aldehyde **97** required for the synthesis was accessed from **137** (**Scheme 1-11**). Sharpless asymmetric epoxidation of **137** afforded epoxide **138** in 94% yield.[41] Ring opening of the epoxide was achieved with $AlMe_3$ to provide the desired alcohol **139** in 94%. Benzyl protection of the newly-created hydroxyl group delivered **140** in 70% over two steps, and subsequent DMP oxidation provided the desired aldehyde **97** in 97% yield.

The key reductive lithiation of F ring **96** followed by nuclophilic addition to aldehyde **97** was accomplished in 71% yield, providing the desired *trans*-geometry across C-32 and C-35 of the F ring **141** (**Scheme 1-11**). The hydroxyl group at C-36 was oxidised using Swern conditions, and after PMB removal of the C-40 hydroxyl, the G ring lactol was formed upon treatment with CSA and trapped as methylated hemiacetal **142**. After a series of protecting group manipulations giving **143**, the primary TBDPS group was removed with TBAF and the resulting alcohol was oxidised to the aldehyde under Swern conditions. A Wittig reaction to form the terminal C-30 to C-31 olefin followed by hydrolysis of the C-33 benzoate ester produced FG fragment **94**.



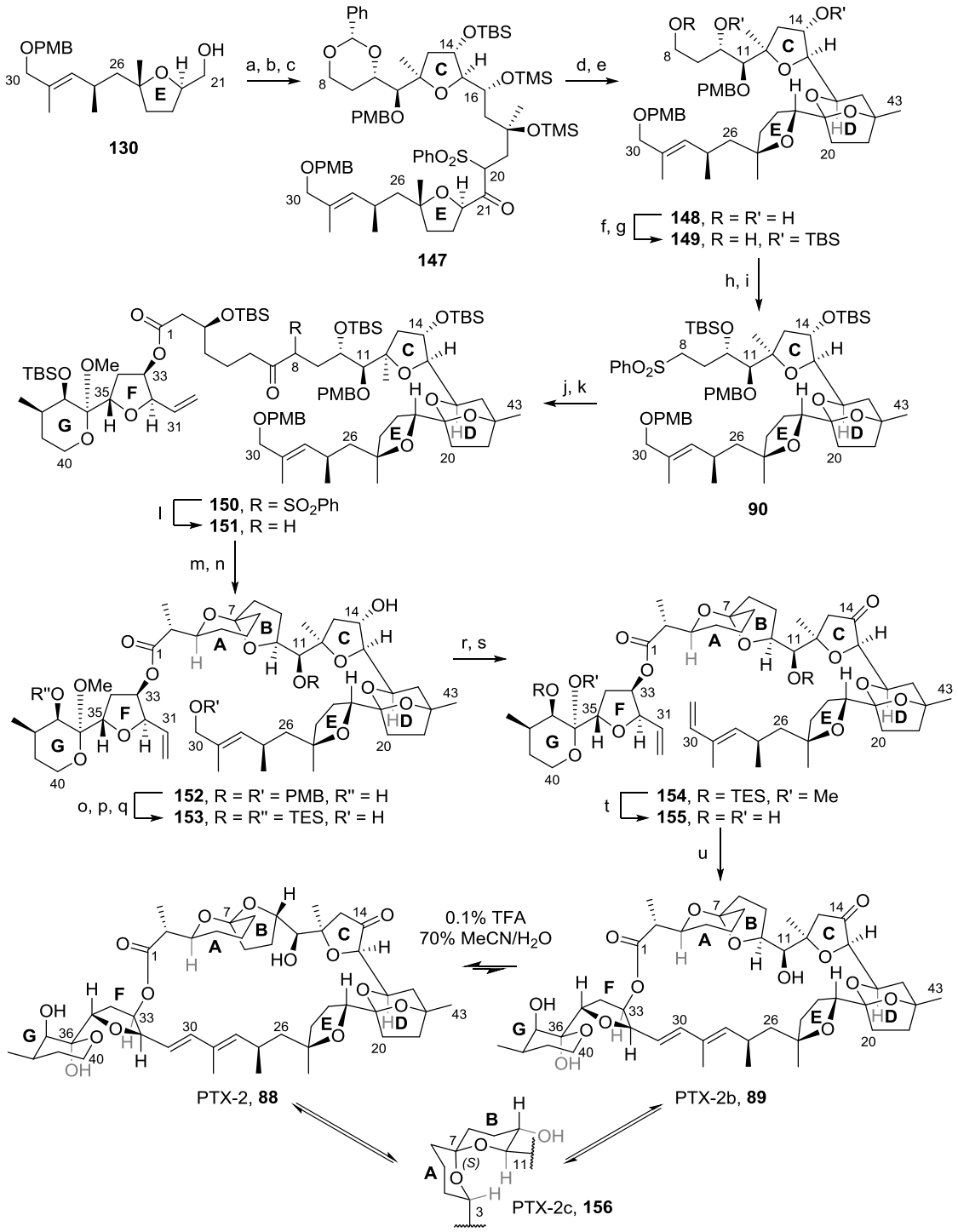
Scheme 1-11: Fujiwara's synthesis of the FG ring fragment **91**.
Reagents and conditions: a) 2,2-dimethoxypropane, $SnCl_4$, Δ; b) $NaIO_4$, $NaHCO_3$, DCM, 45% over two steps; c) **133**, Et_2O, –74 °C, 71%, 98:2 dr; d) PMBCl, NaH, TBAI, DMF, 99%; e) 2 M HCl (aq.)/THF (2:1), 90%; f) TBDPSCl, Et_3N, DMAP, DCM, 76%; g) OsO_4, NMO, 1,4-dioxane/H_2O (3:1) then $NaIO_4$, pH 7 buffer, 94%; h) Ac_2O, Et_3N, DMAP, DCM, 98%; i) PhSH, $BF_3{\cdot}OEt_2$, DCM, –40 °C, 87%; j) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, DCM, –20 °C, 94%; k) $AlMe_3$, DCM, 0 °C, 94%; l) CSA, PhCHO, benzene, Δ, 94%; m) DIBAL-H, benzene, 0 °C, 74%; n) DMP, $NaHCO_3$, DCM, 0 °C, 97%; o) LiDBB, THF, –95 °C, then **97**, –78 °C, 71%; p) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C, 98%; q) DDQ, DCM/pH 7 buffer (1:1), 86%; r) CSA, MeOH/$(MeO)_3CH$ (1:1), 83%; s) BzCl, DMAP, pyridine, DCM, 0 °C to rt, 100%; t) DDQ, DCM/pH 7 buffer (1:1), 90%; u) TBSOTf, 2,6-lutidine, DMAP, DCM, 90%; v) TBAF, AcOH, DMF, 88%; w) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C; x) Ph_3PCH_3Br, NaHMDS, THF, –78 °C to 0 °C, 63% over two steps; y) K_2CO_3, MeOH, 86%.

Preparation of acid **95** used to acylate the C-33 hydroxyl group of the FG ring **94** was accomplished in three steps using an Evans asymmetric aldol reaction with propionyl oxazolidinone **32** (**Scheme 1-12**).[37] Esterification of **95** with FG fragment **94**, followed by PMB group removal and oxidation to the C-7 aldehyde afforded the completed FG fragment **91** in 35% yield over three steps. In summary, FG fragment **91** was assembled in 23 steps LLS from D-mannitol **131** in 14% overall yield.



Scheme 1-12: Fujiwara's synthesis of the FG ring fragment **91** (cont.).
Reagents and conditions: a) *n*-Bu_2BOTf, Et_3N, DCM then **144**, DCM, –78 °C, 100%; b) TBSOTf, 2,6-lutidine, 0 °C, 98%; c) LiOH, H_2O_2, THF/H_2O, 94%; d) **94**, DCC, DMAP, DCM, 82%; e) DDQ, DCM/H_2O (10:1), 0 °C, 82%; f) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C, 52%.

With all the fragments in hand, the final steps of the total synthesis described by Fujiwara are shown in **Scheme 1-13**.[24] The assembly of the D ring *via* the sulfone coupling of the C and E ring fragments **92** and **130** afforded CDE fragment **148** over five steps, which will be discussed **Chapter 2.1.2**. A two-step procedure to access the TBS-protected C-10 and C-14 hydroxyl groups whilst deprotecting the C-8 primary hydroxyl group gave **149** in 85% yield from **148**. Nucleophilic substitution of the C-8 hydroxyl group of **149** to give sulfone **90** *via* the iodide was accomplished in 85% yield. Sulfone coupling to attach the F ring fragment aldehyde **91** followed by oxidation of the resulting C-7 hydroxyl group afforded **150** in 77% yield over two steps. Reductive removal of the sulfone using SmI_2 gave **151** in 80% yield. Deprotection of the TBS silyl ethers at C-3, C-10, C-14 and C-37, along with treatment with CSA allowed for the cyclisation of the AB anomeric [6,5]-spiroketal **152** in 80% yield. Removal of both PMB groups revealed the C-11 and C-30 hydroxyl groups, followed by global TES-protection and then selective removal of the TES group on C-30 accessed **153** in 70% yield. A Takai olefination reaction was performed on the aldehyde derived from C-30 alcohol **153** to access the terminal olefin **154** in 91% yield. Global deprotection with HCl furnished **155**, which was subjected to Grubbs second generation catalyst to deliver PTX-2b (**89**) in 45% yield from **154**.



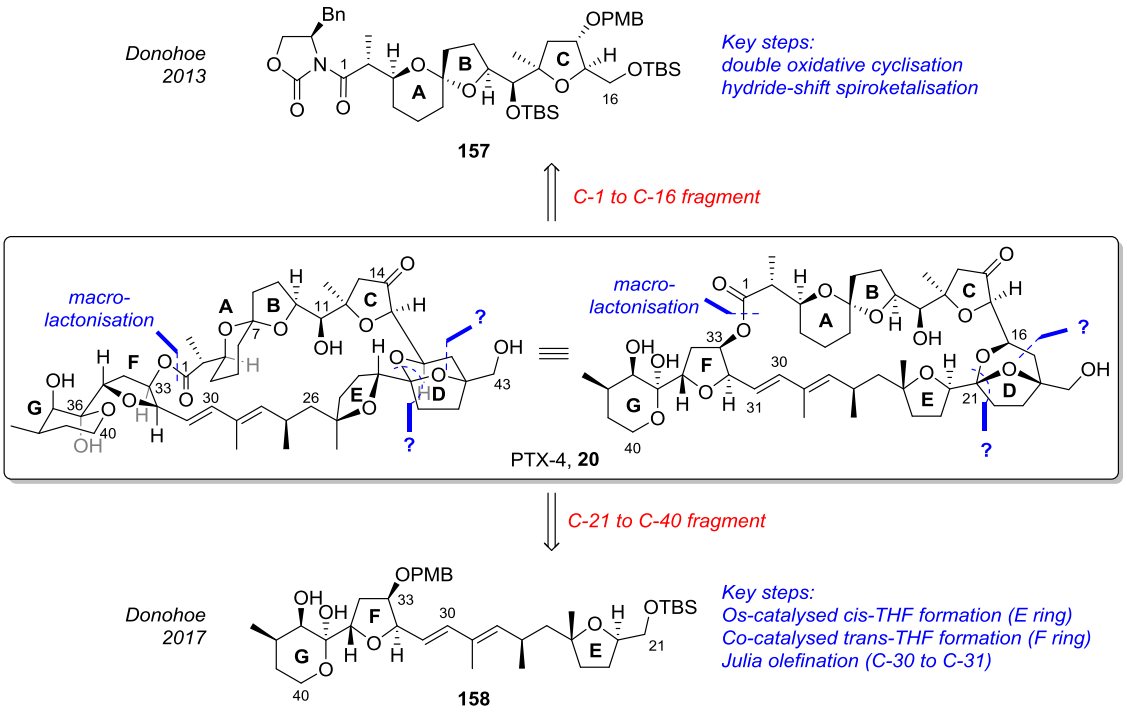
Scheme 1-13: Final steps in Fujiwara's synthesis of PTX-2, **88**.
Reagents and conditions: a) $(COCl)_2$, DMSO, DCM then Et_3N, –78 °C to 0 °C, 95%; b) C ring fragment **92**, *n*-BuLi, THF, –78 °C, 67%; c) DMP, $NaHCO_3$, DCM, 0 °C, 79%; d) SmI_2, THF/MeOH (1:1), 0 °C, 62%; e) 2 M HCl (aq.)/THF (1:4), 90%; f) TBSOTf, 2,6-lutidine, DCM, 0 °C, 96%; g) TFA/THF/H_2O (1:10:5), 0 °C, 89%; h) I_2, PPh_3, imidazole, benzene; i) $PhSO_2Na{\cdot}2H_2O$, DMF, 85% over two steps; j) *n*-BuLi, F ring fragment **91**, THF, –78 °C, 90%; k) DMP, $NaHCO_3$, DCM, 0 °C, 85%; l) SmI_2, THF/MeOH (1:1), 0 °C, 80%; m) TBAF, THF, 0 °C; n) CSA, MeOH, 0 °C, 80% over two steps; o) DDQ, pH 7 buffer, DCM, 0 °C, 93%; p) TESOTf, 2,6-lutidine, DCM, 0 °C, 80%; q) PPTS, MeOH/THF (1:1), 94%; r) DMP, $NaHCO_3$, DCM, 0 °C; s) $CrCl_2$, CH_2I_2, THF, 91% over two steps; t) 2 M HCl (aq.)/THF (1:4), 71%; u) Grubbs second generation catalyst, DCM, 40 °C, 64%.

PTX-2b (**89**) was isomerised at C-7 with careful use of TFA over 1.5 hours,[5] to give PTX-2 (**88**) in 50% yield (**Scheme 1-13**).[24] Fujiwara noted that PTX-2b (**89**) and PTX-2c (**156**) were also present, and isolated in yields of 18% and 11% respectively. The isomerisation was also allowed to run for 96 hours, and in this case the [6,6]-spiroketal PTX-2c (**156**) was isolated in 46% yield, along with PTX-2 (**88**) and PTX-2b (**89**) in yields of 22% and 18% respectively. The total synthesis of PTX-2 (**88**) was accomplished in 43 steps LLS from L-malic acid **98** and in 0.2% overall yield.

1.3 Donohoe's approach to PTX-4

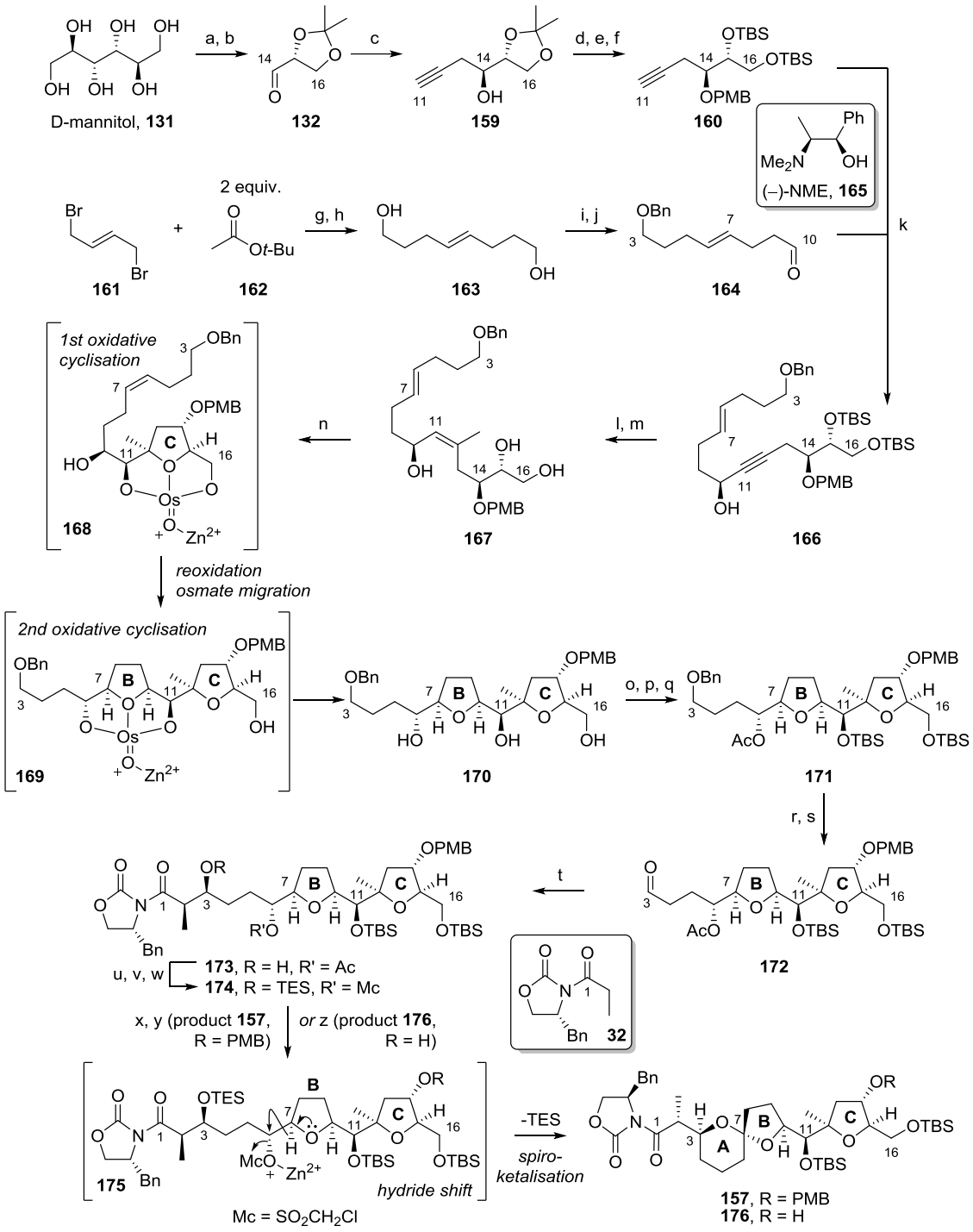
The Donohoe group has been interested in accomplishing the total synthesis of the PTXs because of their structural complexity and promising biological activity described previously in **Chapter 1.1**. Our target is PTX-4 (**20**) due to its anomeric AB [6,5]-spiroketal, which is thought to be thermodynamically favoured relative to its non-anomeric counterpart,[4] as described in **Chapter 1.1.1**. Significant progress in synthesising fragments of the molecule have been disclosed, with completion of the ABC fragment **157** reported in 2013[42] and more recently the construction of the EFG fragment **158** in 2017 (**Scheme 1-14**).[43] The elusive bicyclic acetal, known as the D ring between C-16 and C-21 of the C and E rings respectively, remains the only ring system yet to be synthesised by the Donohoe group. Our efforts to synthesise this ring system will be described in **Chapter 2**, and further elaborated in **Chapter 3** using the E ring fragment previously disclosed.

As **Chapters 3.1** and **4** will cover the synthesis of the E and F ring fragments, including the key Julia olefination reaction and final steps to give EFG fragment **158** in **Chapter 4.1**, as described in the 2017 paper,[43] this will not be discussed here. However, the route to the ABC fragment **157** will be covered briefly herein.



Scheme 1-14: Fragments of PTX-4 (**20**) synthesised previously by the Donohoe group.

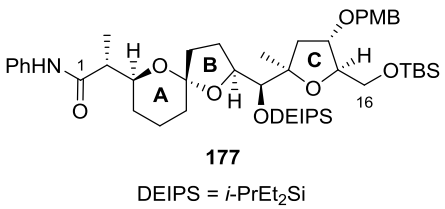
Donohoe's synthesis of the ABC fragment **157** is shown in **Scheme 1-15**,[42] and was conducted by Dr Radosław Lipiński.[44] The alkyne **160** required for the Carriera reaction was derived in six steps from D-mannitol **131**, whilst the aldehyde **164** was derived from dibromide **161** in four steps. The Carriera reaction mediated by (–)-NME **165** installed the C-10 stereocentre with excellent stereoselectivity (96:4 dr) and delivered **166** in 54% yield. Methylation of alkyne **166** was achieved regio- and stereoselectively by the reaction with $Fe(acac)_3$ and methyl magnesium bromide in 88% yield. After TBS-deprotection, the osmium-catalysed double oxidative cyclisation cascade[45, 46] was accomplished in 69% yield to afford BC fragment **170**. Protecting group manipulations and oxidation of the C-3 hydroxyl group afforded aldehyde **172**, which was subjected to an Evans asymmetric aldol reaction with **32** to install the desired *syn*-geometry at C-2 and C-3. Further protecting group manipulations and installation of the α-chloromesylate at C-6 hydroxyl group, allowed the hydride-shift spiroketalisation cascade to be attempted.



Scheme 1-15: Donohoe's synthesis of the ABC fragment.
Reagents and conditions: a) 2,2-dimethoxypropane, TsOH, DMSO, 55%; b) $NaIO_4$, $NaHCO_3$, DCM, 75%; c) propargyl bromide, Zn, THF, –78 °C to rt, 75%; d) PMBCl, NaH, TBAI, THF, 0 °C to 60 °C; e) H_3O^+, 82% over two steps; f) TBSCl, imidazole, DMF, 83%; g) LDA, THF, –78 °C to rt, 62%; h) $LiAlH_4$, THF, 0 °C, 94%; i) Ag_2O, BnBr, Et_2O, 55%; j) DMP, DCM, 91%; k) **165**, $Zn(OTf)_2$, Et_3N, PhMe, 54%, 96:4 dr; l) MeMgBr, $Fe(acac)_3$ (20 mol%), dppe (20 mol%), THF, –78 °C to 0 °C, 88%; m) TBAF, THF, 94%; n) $K_2OsO_2(OH)_4$, (5 mol%), $Zn(OTf)_2$, citric acid, PNO, MeCN/pH 6.5 buffer (3:2), 69%; o) TBSCl, imidazole, DCM, 94%; p) Ac_2O, pyridine, DMAP, DCM, 0 °C, 80%; q) TBSOTf, 2,6-lutidine, DCM, –78 °C, 97%; r) H_2, Raney-Ni, EtOAc, 84%; s) SO_3·py, *i*-Pr_2NEt, DMSO, DCM, –10 °C, 98%; t) **32**, *n*-Bu_2BOTf, *i*-Pr_2NEt, DCM, –78 °C, 82%; u) TESCl, imidazole, DCM, 0 °C, 99%; v) DIBAL-H, THF, –78 °C, 87%; w) McCl, pyridine, 0 °C, 99%; x) $Zn(OAc)_2$, aq. DMF, 75 °C, 68%; y) PPTS, MeOH, 98% of **157** (R = PMB); z) $Zn(OAc)_2$, HFIP, 30 °C, 68% of **176** (R = H).

The two-step procedure used $Zn(OAc)_2$ in aqueous DMF followed by PPTS which gave ABC fragment **157** in 65% yield over the two steps (**Scheme 1-15**).[42] The hydride shift results in the formation of an oxocarbenium ion at C-7 (**175**), which then participates in a cyclisation with the C-3 hydroxyl group to form the [6,5]-spiroketal. Alternatively, using HFIP as the solvent with $Zn(OAc)_2$ afforded the ABC fragment **176** directly, without the PMB group attached at C-14. Although unexpected, *in situ* removal of the PMB group could be beneficial because the C-14 hydroxyl group would have to be oxidised to the ketone for the completion of the total synthesis. The ABC fragment was assembled in 20 (**157**) or 21 (**176**) steps, and in 2.3% overall yield in both cases.

This route has since been repeated and reoptimised by Dr Xuezheng Yang,[47] and more recently co-worker Timothy Kwok.[48] It was noted by Dr Xuezheng Yang that when the Evans auxiliary is used as a protecting group after installation of the C-2 and C-3 stereocentres it cannot be removed at the end of the synthesis, and therefore must be removed earlier on, preferably immediately following installation (step t, **Scheme 1-15**). Dr Xuezheng Yang also optimised the route to produce an intermediate that possesses a diethylisopropylsilyl (DEIPS) group at the C-11 hydroxyl instead of a TBS group. Co-worker Timothy Kwok has since successfully removed the Evans auxiliary and has synthesised the new ABC fragment **177** (**Figure 1-4**); he continues work towards the total synthesis of PTX-4.



177

DEIPS = *i*-$PrEt_2Si$

Figure 1-4: New ABC ring fragment **177** synthesised by co-worker Timothy Kwok based upon work accomplished by Dr Xuezheng Yang.

The following chapters will detail the work undertaken towards a route to the bicyclic acetal D ring, using model studies (**Chapter 2**) and the real E ring fragment (**Chapter 3**). The chapters will also outline the synthesis and scale-up of the F ring fragment (**Chapter 4**) in preparation for the Julia coupling with the proposed ABCDE fragment of PTX-4.

Chapter 2

Chapter 2: Development of a Conjugate Addition-Cyclisation Approach towards the D ring

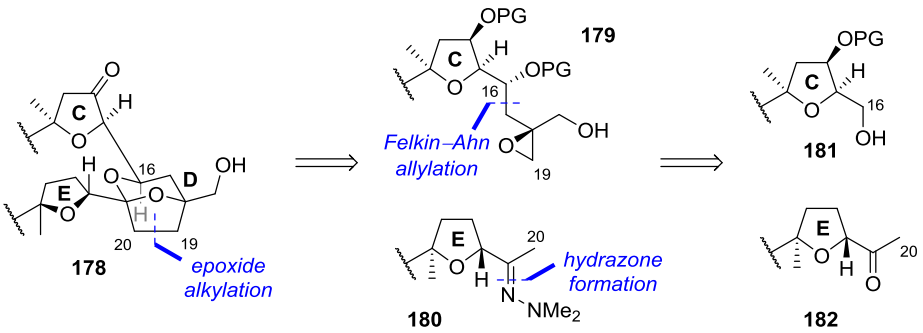
As outlined in **Chapter 1.3**, the final ring system of PTX-4 to be synthesised by the Donohoe group is the D ring. This chapter outlines previous approaches to forming the bicyclic D ring, our proposed approach using a rhodium-catalysed 1,4-addition as the key C–C bond-forming reaction, and model studies to test the feasibility of this disconnection.

2.1 Introduction: Previous methods of synthesising the D ring

The following section describes the previous approaches that have been used to synthesise the D ring of various PTXs. The approaches from the total syntheses by Evans and Fujiwara are described in **Chapters 2.1.1** and **2.1.2**, whilst other approaches to the D ring fragment are described in **Chapter 2.1.3**.

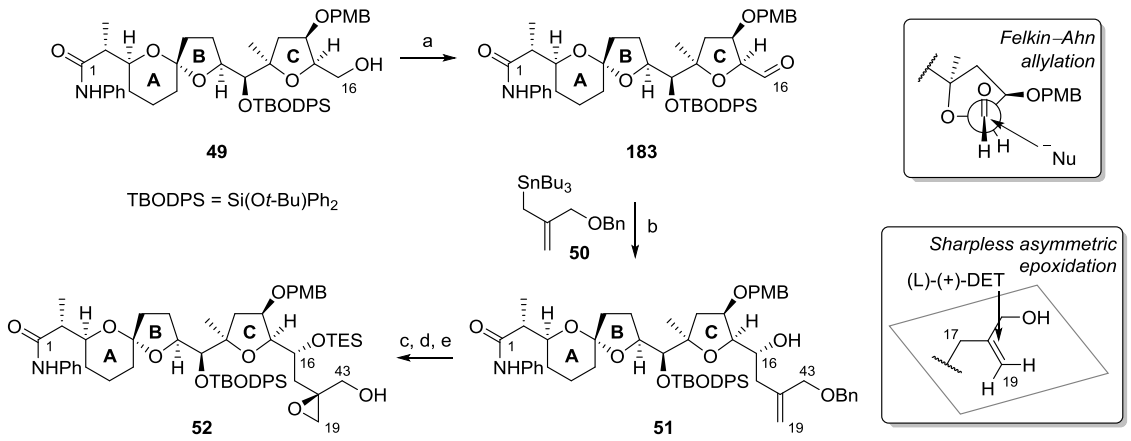
2.1.1 Evans

The key C–C bond-forming reaction used in Evans' synthesis of PTX-4 involves a Lewis acid-assisted epoxide opening by a metallo-enamine between the C and E rings (**Scheme 2-1**).[22, 23] The C-16 to C-19 chain that forms the majority of the carbon skeleton of the D ring is attached to the C ring *via* a Felkin–Ahn controlled allylation reaction. The AB ring system is pre-attached to the C ring, whereas the E ring is attached to the C-26 to C-30 side chain in preparation for the Julia olefination to introduce the F ring.



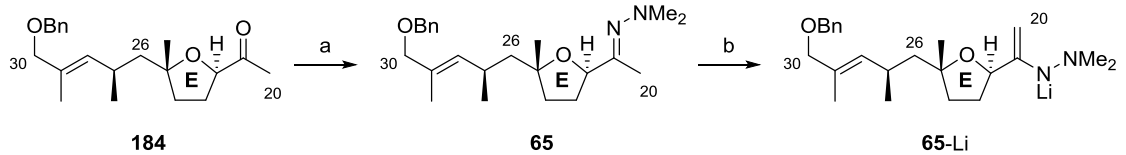
Scheme 2-1: Retrosynthetic analysis of Evans' approach to the D ring of PTX-4.

In the forward synthesis from the primary alcohol of the C ring (compound **49**), a Parikh–Doering oxidation reaction[29] was used to access the unstable C-16 aldehyde **183** (**Scheme 2-2**). Felkin–Ahn controlled allylation of aldehyde **183** in the presence of 2-(benzyloxymethyl)allyltributylstannane **50** and $BF_3{\cdot}OEt_2$ provided the desired homoallylic alcohol **51** in 78% yield over two steps and in 95:5 dr. In order to access epoxide **52** required for alkylation with the E ring, the C-16 alcohol was TES-protected with chlorotriethylsilane and the C-43 hydroxyl group was deprotected using LiDBB. Finally, a Sharpless asymmetric epoxidation was employed to access the desired epoxide in 79% yield over three steps from **51**.[22]



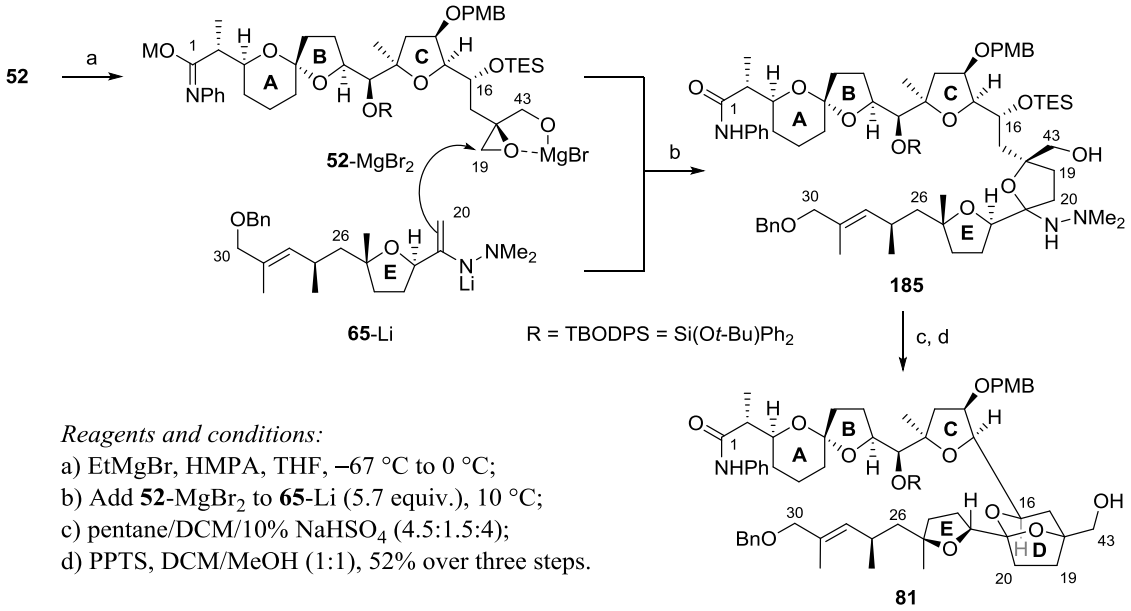
Scheme 2-2: Forward synthesis of Evan's ABC fragment **52** for the synthesis of the D ring in PTX-4. *Reagents and conditions:* a) $SO_3{\cdot}$py, Et_3N, DCM/DMSO (1:1), –10 °C; b) **50**, $BF_3{\cdot}OEt_2$, DCM, –78 °C, 78% over two steps; c) TESCl, imidazole, DCM, 92%; d) LiDBB, THF, –78 °C, 87%; d) Ti(O*t*-Bu)$_4$, (L)-(+)-DET; *t*-BuOOH, 3 Å MS, DCM, –30 °C, 99%.

Hydrazone **65** was prepared by the reaction of ketone **184** with *N*,*N*-dimethylhydrazine in quantitative yield (**Scheme 2-3**). Subsequent lithiation using LDA led to the formation metallo-enamine **65**-Li in preparation for the nucleophilic opening of the epoxide.[23]



Scheme 2-3: Forward synthesis of Evans' E ring fragment **65**-Li for the synthesis of the D ring in PTX-4. *Reagents and conditions:* a) TMSCl, DCM/H_2NNMe_2 (1:1), 100%; b) LDA, THF, –67 °C to 0 °C.

The ABC epoxide fragment **52** was activated towards nucleophilic attack by formation of the $MgBr_2$ salt, generated by deprotonation of the C-43 hydroxyl group with EtMgBr (**Scheme 2-4**). Addition of the activated $MgBr_2$ salt **52**-$MgBr_2$ to metallo-enamine **65**-Li furnished the unstable hydrazinyl lactol **185**. This intermediate was treated under biphasic conditions (pentane/DCM/10% $NaHSO_4$) to give the corresponding lactol, which was then subsequently treated with PPTS to deprotect the C-16 alcohol. Spontaneous cyclisation was then observed and the D ring **81** was formed in 52% over three steps.

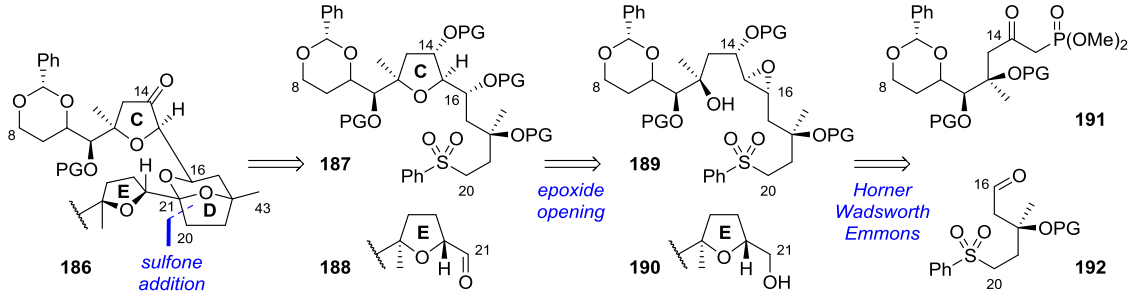


Scheme 2-4: Final steps in Evans' synthesis of the D ring of PTX-4.

The key C–C bond-forming step requires an excess (5.7 equivalents) of the metallo-enamine **65**-Li compared to the epoxide ABC fragment **52**-$MgBr_2$. Although 48% of unreacted hydrazone **65** was recovered after coupling with ABC fragment **52**-$MgBr_2$,[49] the requirement of a large excess of the E ring fragment is a significant limitation, because a 17 step synthesis is required in order to access hydrazone **65** from commercial starting materials.[23, 30]

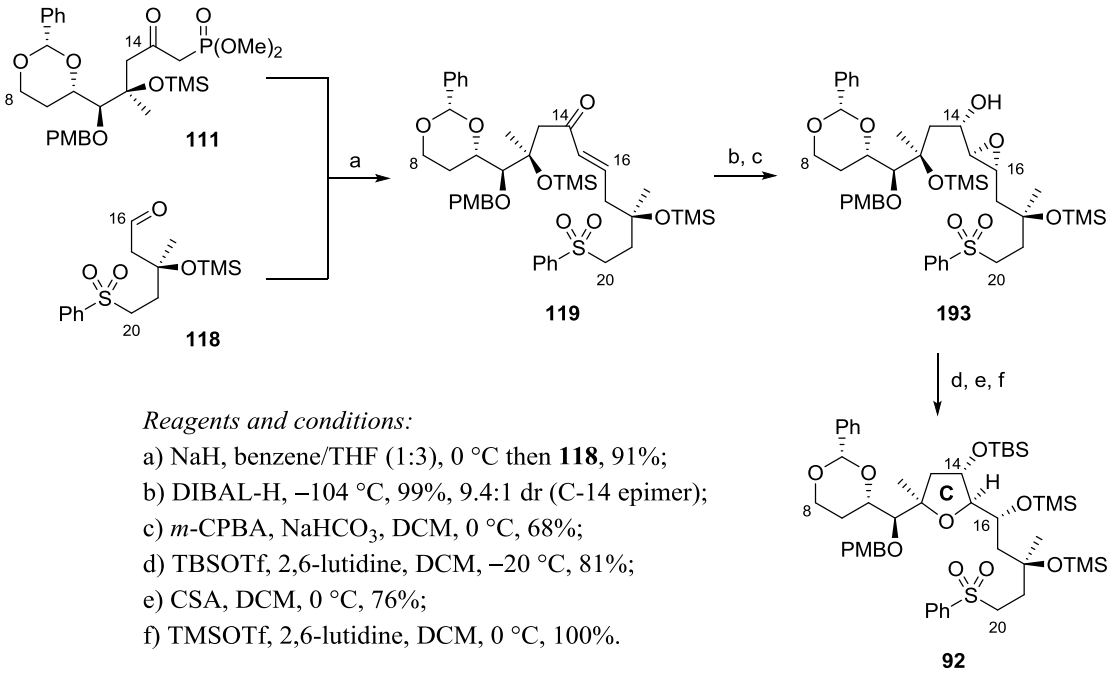
2.1.2 Fujiwara

Fujiwara's approach to the D ring in PTX-2 employs a sulfone addition to an aldehyde to form the key C–C bond (**Scheme 2-5**).[24] It should be noted that PTX-2 is not oxygenated at C-43 of the D ring, unlike PTX-4. The AB ring is incomplete, in contrast with Evans' synthesis of PTX-4, because the spirocyclic ketal is non-anomeric in PTX-2 and is constructed at a later stage. However, the E ring side chain bears a similar C-26 to C-30 carbon framework for coupling to the F ring.



Scheme 2-5: Retrosynthetic analysis of Fujiwara's approach to the D ring of PTX-2.

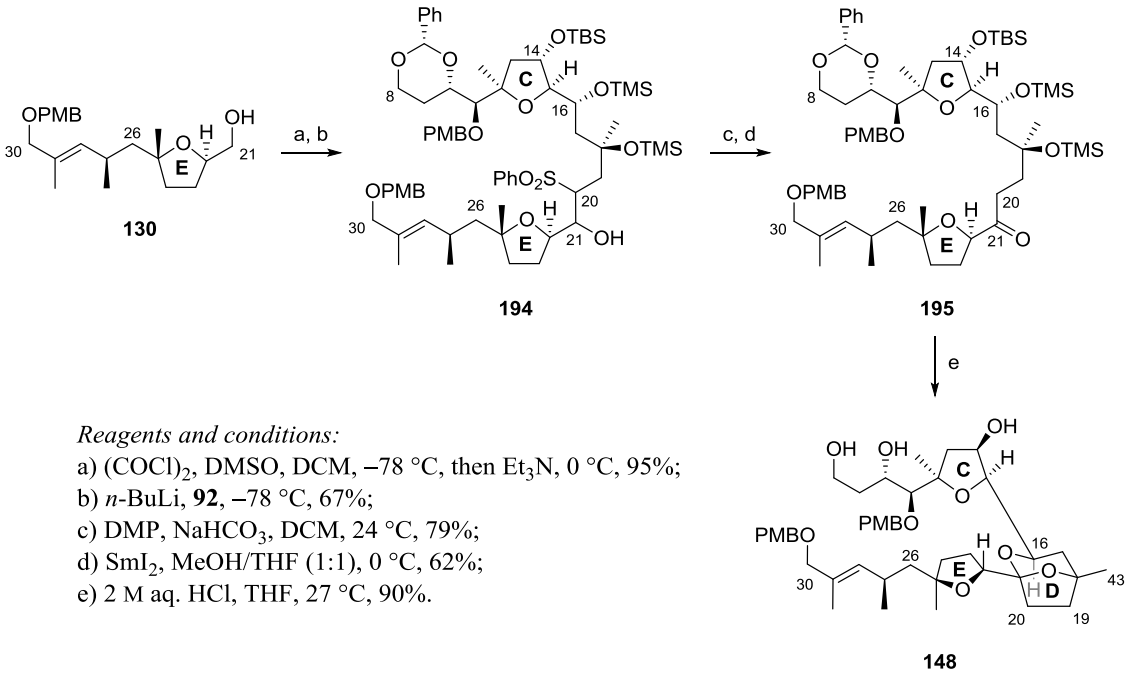
The C ring, along with the carbon backbone of the D ring, was assembled by using a HWE reaction with C-8 to C-15 fragment **111** and C-16 to C-20 fragment **118**, followed by a reduction of the C-14 ketone with DIBAL-H and double bond epoxidation to form **193**.[35] The secondary C-14 alcohol was then protected using TBSOTf in 81% yield. Subsequent treatment with CSA removed the TMS protecting groups and activated the epoxide towards nucleophilic attack, forming the C ring in 76% yield. The remaining C-16 and C-18 secondary alcohols were protected with TMSOTf in preparation for coupling to the E ring (**Scheme 2-6**).



Reagents and conditions:
a) NaH, benzene/THF (1:3), 0 °C then **118**, 91%;
b) DIBAL-H, −104 °C, 99%, 9.4:1 dr (C-14 epimer);
c) *m*-CPBA, $NaHCO_3$, DCM, 0 °C, 68%;
d) TBSOTf, 2,6-lutidine, DCM, −20 °C, 81%;
e) CSA, DCM, 0 °C, 76%;
f) TMSOTf, 2,6-lutidine, DCM, 0 °C, 100%.

Scheme 2-6: Forward synthesis of Fujiwara's C ring fragment **92** for the synthesis of the D ring in PTX-2.

The E ring **130** was oxidised at the primary alcohol at C-21 using Swern conditions to the corresponding aldehyde (**Scheme 2-7**). Deprotonation of C ring sulfone **92** with *n*-BuLi, followed by the addition of the E ring aldehyde afforded adduct **194** in 67% yield. Oxidation of the C-21 alcohol with DMP and subsequent SmI_2-mediated reduction of the sulfone at C-20 completed the synthesis of the carbon backbone of the D ring. Deprotection of the hydroxyl groups at C-14, C-16 and C-18 by the treatment of **195** with 2 M aq. HCl allowed for spontaneous cyclisation to form the bicyclic D ring **148** of PTX-2 in 90% yield (**Scheme 2-7**).



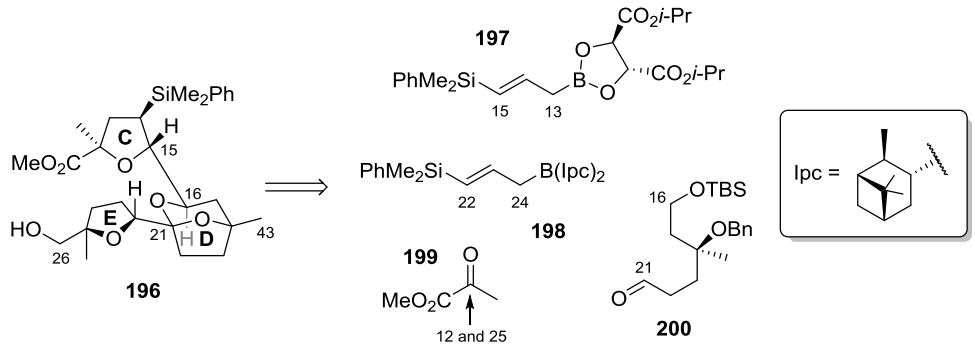
Scheme 2-7: Final steps in Fujiwara's synthesis of the D ring of PTX-2.

2.1.3 Other approaches to the D ring fragment

Several other groups that have published alternative methods of synthesising the D ring fragment of the PTXs. Synthetic routes to access the C-16 to C-20 backbone of the D ring have been published. For example, Paquette used a Julia reaction to couple the AB fragment with the E fragment.[50, 51] This section will focus on the completion of both the carbon backbone and the cyclisation to form the bicyclic D ring of the PTXs.

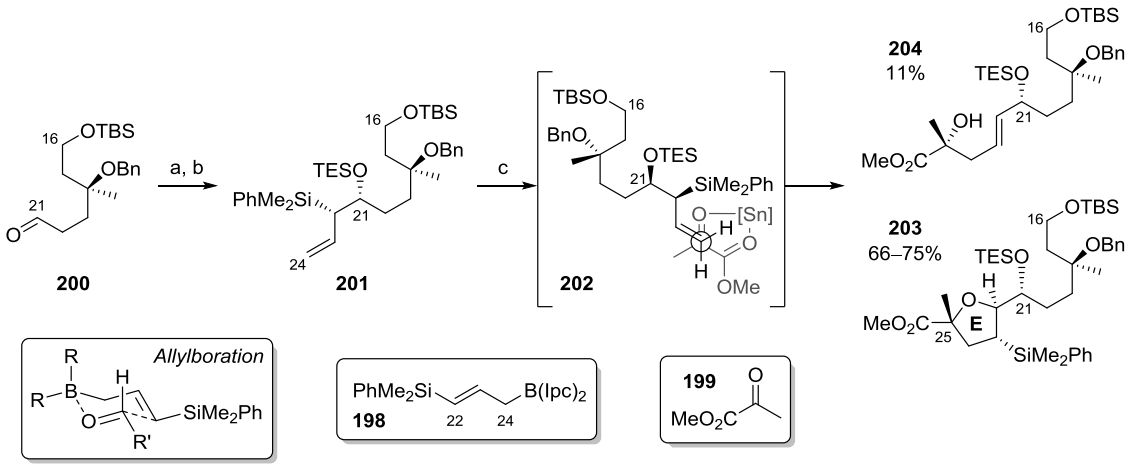
2.1.3.1 Roush

Roush and co-workers published the first successful approach to the D ring fragment of PTX-2 in 2001.[52] Their approach focussed on a convergent three-component coupling sequence for tetrahydrofuran synthesis *via* a chiral vinyl silane intermediate (**Scheme 2-8**). The stereochemistry at C-15 is epimeric when compared to PTX-2, however it was proposed that the desired isomer could be obtained *via* base-promoted epimerisation at a later stage.



Scheme 2-8: Retrosynthetic analysis of Roush's approach to the D ring of PTX-2.

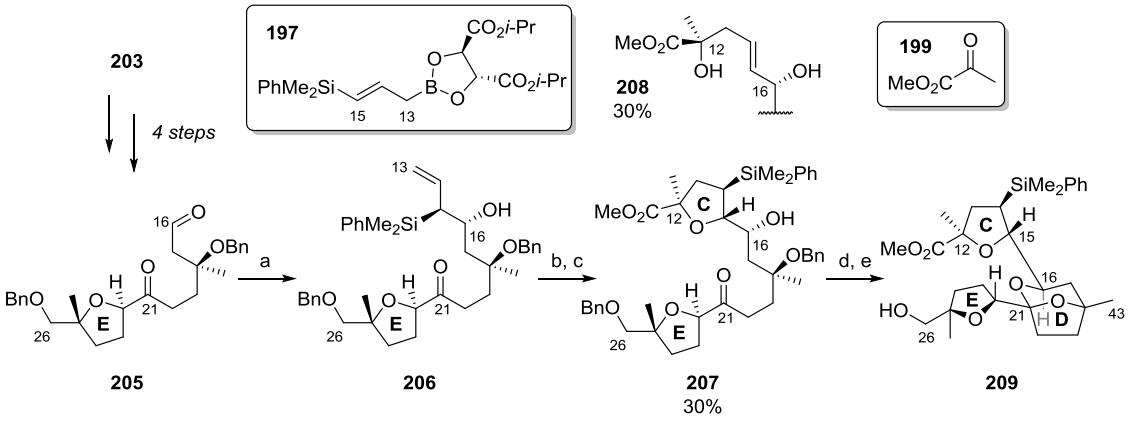
Starting from aldehyde **200**,[52] allylboration using chiral silylallylborane **198**[53] furnished the desired *anti*-β-hydroxyallylsilane in 77% yield and 9–14:1 dr (**Scheme 2-9**). Subsequent protection with chlorotriethylsilane afforded **201** in 93% yield. Next, a $SnCl_4$-promoted [3+2] annulation of methyl pyruvate **199** afforded the tetra-substituted tetrahydrofuran **203** in 66–75% yield, along with 11% of the allylation product **204** (**Scheme 2-9**). The [3+2] annulation proceeds through a *syn*-synclinal transition state **202**, with methyl pyruvate **199** approaching from the opposite face to the -$SiMe_2Ph$ group at C-22 in order to minimise steric interactions.



Scheme 2-9: Forward synthesis of Roush's approach to the D ring of PTX-2.
Reagents and conditions: a) **198**, THF, –78 °C to 23 °C, 77%, 9–14:1 dr; b) TESCl, Et_3N, DMAP, DCM, 93%; c) **199**, $SnCl_4$, DCM, –78 °C, 66–75% of **203**, 11% of **204**.

Tetrahydrofuran **203** was converted in four steps to aldehyde **205** in preparation for a second key allylboration reaction (**Scheme 2-10**).[52] However, in this instance the

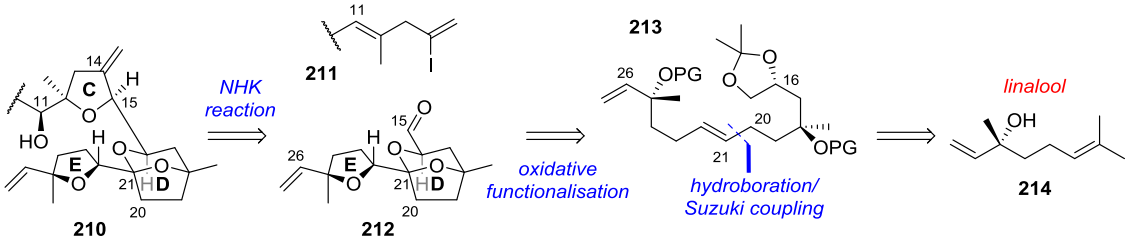
modified chiral silylallylborane **197**[54] was used to prepare *anti*-β-hydroxyallylsilane **206** in 80% yield. Protection of the alcohol with chlorotriethylsilane followed by a further [3+2] annulation of methyl pyruvate **199** afforded a 1:1 mixture of the desired cyclised C ring **207** and the allylated product **208**. The final cyclisation was achieved by treatment of **207** with PPTS followed by palladium-catalysed benzyl deprotection to afford the CDE fragment **209** in 63% yield from **207**.



Scheme 2-10: Forward synthesis of Roush's approach to the D ring of PTX-2 (cont.).
Reagents and conditions: a) **197**, PhMe, 4 Å MS, –78 °C, 84%; b) TESCl, DMF, 88%; c) **199**, $SnCl_4$, DCM, –78 °C, 30% of **207**, 30% of **208**; d) PPTS, MeOH, 77%; e) $Pd(OH)_2$, H_2, MeOH, 82%.

2.1.3.2 Micalizio

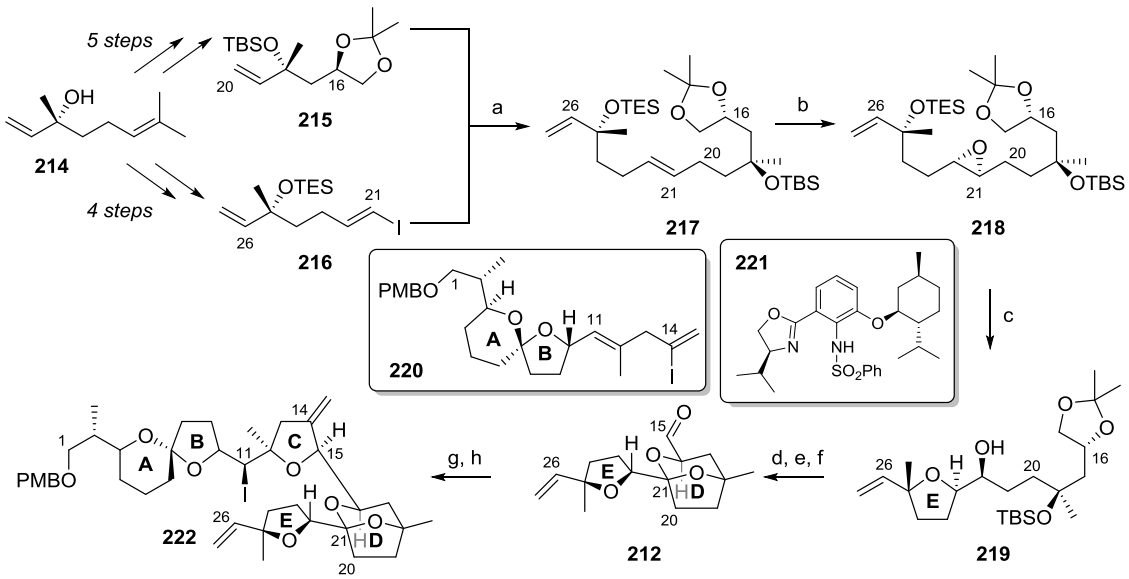
Micalizio's approach to the D ring of PTX-2 involved a key Nozaki–Hiyama–Kishi (NHK) reaction of AB ring vinyl iodide **211** with DE fragment aldehyde **212** (**Scheme 2-11**). The D and E rings themselves were to be accessed by an oxidative functionalisation of linear precursor **213**, itself derived from a head-to-tail dimerisation of two derivatives of linalool **214** *via* a hydroboration/Suzuki coupling reaction.[55, 56]



Scheme 2-11: Retrosynthetic analysis of Micalizio's approach to the D ring of PTX-2.

Compounds **215** and **216** were synthesised from the divergent derivatisation of linalool **214** in five and four steps respectively (**Scheme 2-12**).[55] The hydroboration/Suzuki coupling of fragments **215** and **216** was achieved in 81% yield to form the key C-20/C-21 bond. Shi epoxidation of adduct **217**, followed by TBAF deprotection and acid treatment afforded the E ring **219** in 51% yield over two steps.

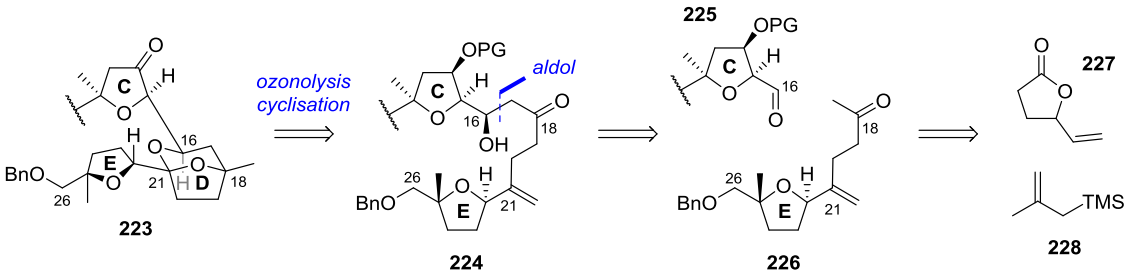
Parikh–Doering oxidation[29] of the C-22 alcohol followed by deprotection of the acetal and TBS groups allowed for cyclisation to form the bicyclic D ring. Subjection of this compound to Swern oxidation conditions formed aldehyde **212** in 66% yield in preparation for the NHK reaction with the AB fragment.[55] Coupling DE fragment **212** with AB fragment **220** under NHK conditions using chiral sulfonamide ligand **221** formed the ABDE fragment in 79% yield. However, attempted epoxidation with cyclisation using *m*-CPBA or Shi conditions both failed to afford the desired C ring product. Nevertheless, an iodoetherification reaction was employed to close the C ring, resulting in the formation of an iodide at C-11 as opposed to the desired alcohol.[56]



Scheme 2-12: Forward synthesis of Micalizio's approach to the D ring of PTX-2.
Reagents and conditions: a) **215**, 9-BBN, THF then **216**, $Pd(dppf)Cl_2$, Tl_2CO_3, THF/H_2O (8:1), 81%; b) Shi epoxidation, 59%, dr ≥ 20:1; c) TBAF, THF, 3 Å MS then HCl, $CHCl_3$, 86%; d) SO_3·py, DMSO, DCM, 77%; e) CSA, MeOH, 59%; f) $(COCl)_2$, DMSO, DCM then Et_3N, 66%; g) **220**, $CrCl_2$, LiCl, Mn, $NiCl_2$, Cp_2ZrCl_2, MeCN, Ligand **221**, 54%; h) NIS, DCM, –78 °C, 87%, 12:1 dr.

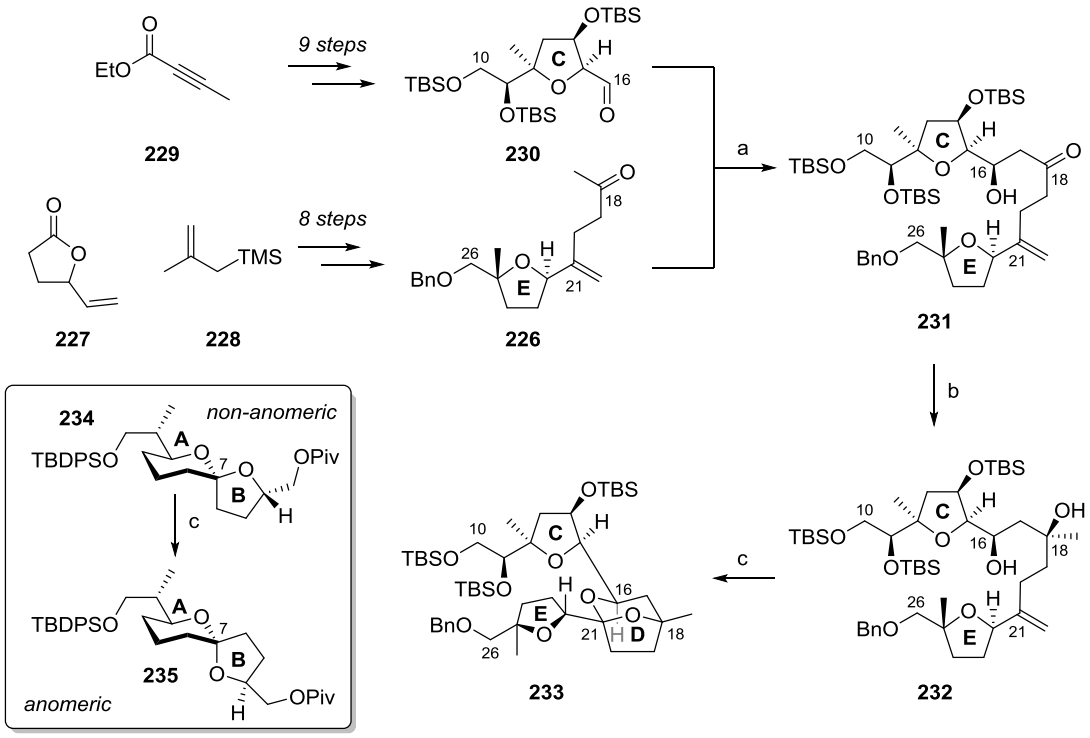
2.1.3.3 Pihko

Pihko's retrosynthesis of the D ring of PTX-2 focussed on using a late-stage ozonolysis of the C-21 olefin leading to cyclisation of the bicyclic acetal (**Scheme 2-13**). An aldol reaction between E ring methyl ketone **226** and C ring aldehyde **225** was proposed to form the carbon backbone between the C and E rings. As the structure of PTX-2 features a non-anomeric AB spiroketal, this was planned to be installed at a later stage.



Scheme 2-13: Retrosynthetic analysis of Pihko's approach to the D ring of PTX-2.

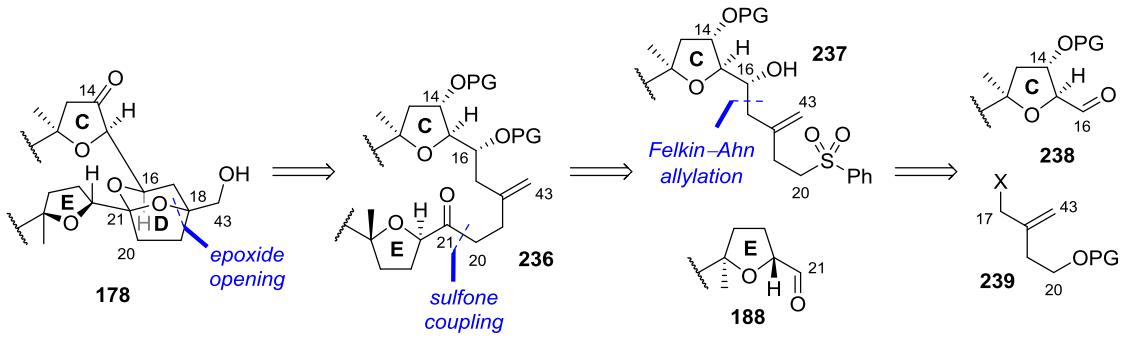
The C ring aldehyde **230** was accessed in 9 steps from ethyl 2-butynoate **229** (**Scheme 2-14**).[57, 58] The E ring ketone **226** was synthesised in 8 steps from γ-vinyl butyrolactone **227** and methallylsilane **228**.[59] With these two fragments in hand, an aldol reaction using LDA afforded adduct **231** in 74% yield and 10:1 dr. A stereoselective hydroxyl-directed methyltitanation at the C-18 ketone was achieved in 81% yield with an acceptable 3:1 dr. Finally, treatment of **232** with ozone allowed for the spontaneous ring-closure of the D ring **233** in 63% yield.[59] The author noted that the non-anomeric AB ring system, required for the synthesis of PTX-2, underwent complete isomerisation under the conditions described for the cyclisation of the D ring (box in **Scheme 2-14**). As a consequence of this, the AB ring system would have to be installed after completion of the D ring.



Scheme 2-14: Forward synthesis of Pihko's approach to the D ring of PTX-2. The AB non-anomeric spiroketal underwent isomerisation to the anomeric form under cyclisation conditions.
Reagents and conditions: a) **226**, LDA, THF, –78 °C then **230**, 74%, 10:1 dr; b) $MeTi(O\textit{i}\text{-}Pr)_3$, THF, 80%, 3:1 dr; c) Sudan Red 7B indicator, O_3, DCM then Me_2S, 63%.

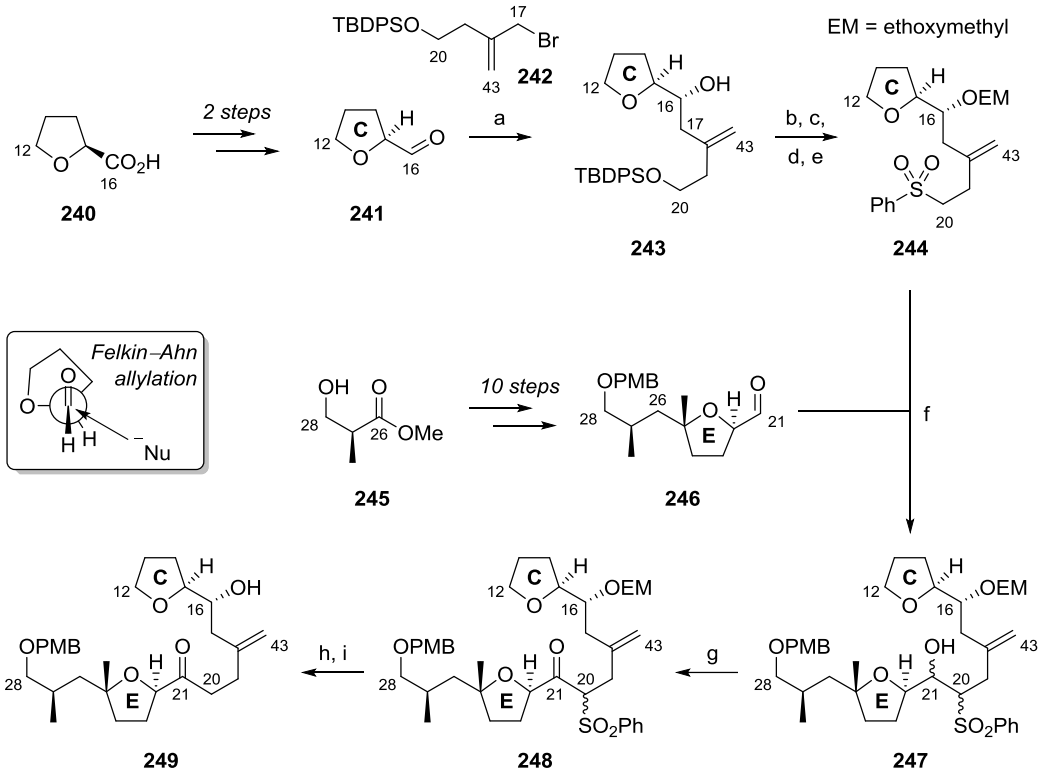
2.1.3.4 Brimble

Brimble has previously synthesised both the ABC[60] and FG[61] rings of PTX-4. Accordingly, their strategy focussed on the synthesis of a highly functionalised DE fragment that could be connected to the ABC and FG ring systems made previously. The D ring was proposed to form from an epoxide opening using the C-21 hydroxyl group to attack at C-18 (**Scheme 2-15**).[62] The key C–C bond-forming reaction involved the addition of C ring sulfone **237** to E ring aldehyde **188**, in common with Fujiwara's approach towards PTX-2 (as discussed in **Chapter 2.1.2**).[24] The sulfone side chain of the C ring is derived from a Felkin–Ahn controlled allylation of the C ring aldehyde.



Scheme 2-15: Retrosynthetic analysis of Brimble's approach to the D ring of PTX-4.

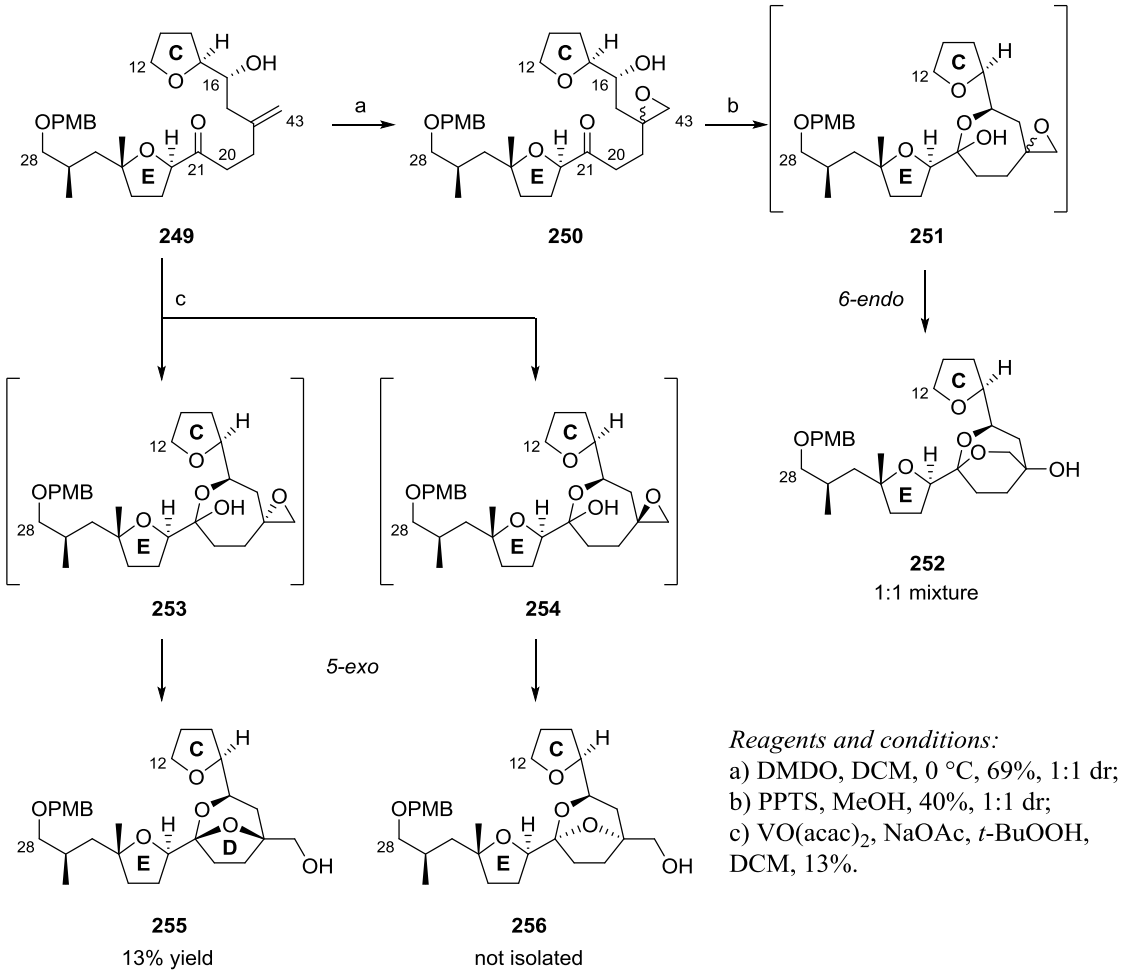
The E ring aldehyde **246** was synthesised in 10 steps from Roche ester **245** (**Scheme 2-16**).[62] The model C ring was synthesised from (*S*)-(−)-tetrahydro-2-furoic acid **240**. The acid **240** was converted into the corresponding aldehyde **241** in two steps, which underwent a Felkin–Ahn allylation with moderate selectivity (1.5:1 dr) using the organoindium species of **242**. The diastereomers could be separated upon protection of the secondary alcohol as a chloromethyl ethyl ether. The TBDPS-protected alcohol was converted into the desired sulfone **244** in four steps. The sulfone coupling of C ring fragment **244** and E ring aldehyde **246** initially formed an equal mixture of four diastereomeric hydroxy sulfones **247** in 91% yield, which were oxidised using DMP to afford two diastereomeric keto sulfones **248**. The phenylsulfonyl group was removed using sodium amalgam and cleavage of the ethoxymethyl ether affording **249** in 53% yield over two steps.



Scheme 2-16: Forward synthesis of Brimble's approach to the D ring carbon framework of PTX-4. *Reagents and conditions:* a) In, aq. DMF, 99%, 1.5:1 dr; b) *i*-Pr_2NEt, $MeOCH_2Cl$, DCM; c) TBAF, THF, 71% over two steps; d) Et_3N, MsCl then PhSH, THF, 77%; e) oxone®, wet alumina, $CHCl_3$, 80%; f) **244**, *n*-BuLi then **246**, THF, –78 °C, 91%; g) DMP, pyridine, DCM, 71%; h) 5% Na/Hg, Na_2HPO_4, MeOH, 70%; i) $NaHSO_4{\cdot}SiO_2$, DCM, 75%.

Initial attempts to oxidise the C-18 olefin to the corresponding epoxide with *m*-CPBA led to decomposition. The use of DMDO as the oxidant afforded a 1:1 mixture of diastereoisomers that, upon treatment with PPTS, gave a 1:1 mixture of the undesired 6-*endo* cyclisation product **252** (**Scheme 2-17**). However, it was found that vanadium-catalysed epoxidation afforded a mixture of the diastereomeric epoxides, which appeared to cyclise to form only the desired bicyclic acetal corresponding to the D ring **255** in 13% yield.

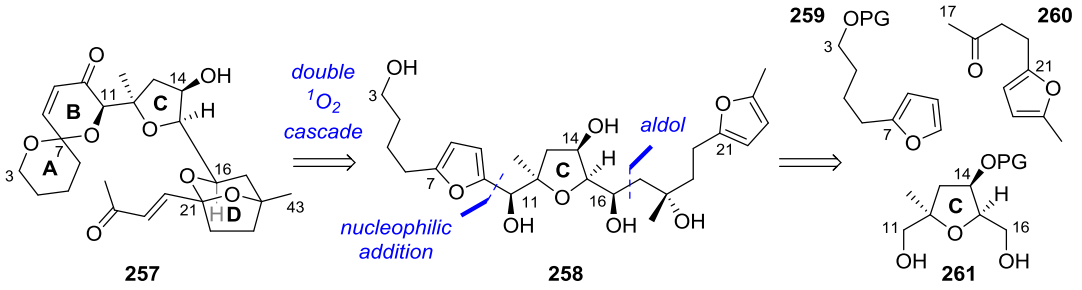
Although the NMR analysis of the crude product indicated the presence of two diastereomers, other bicyclic acetals, including diastereomer **256**, were not isolated. It was proposed that steric strain prevented other bicyclic acetals from forming, and isomer **256** may have degraded upon purification.[62]



Scheme 2-17: Epoxidation of the olefin of **249** to form the D ring of PTX-4.

2.1.3.5 *Vassilikogiannakis*

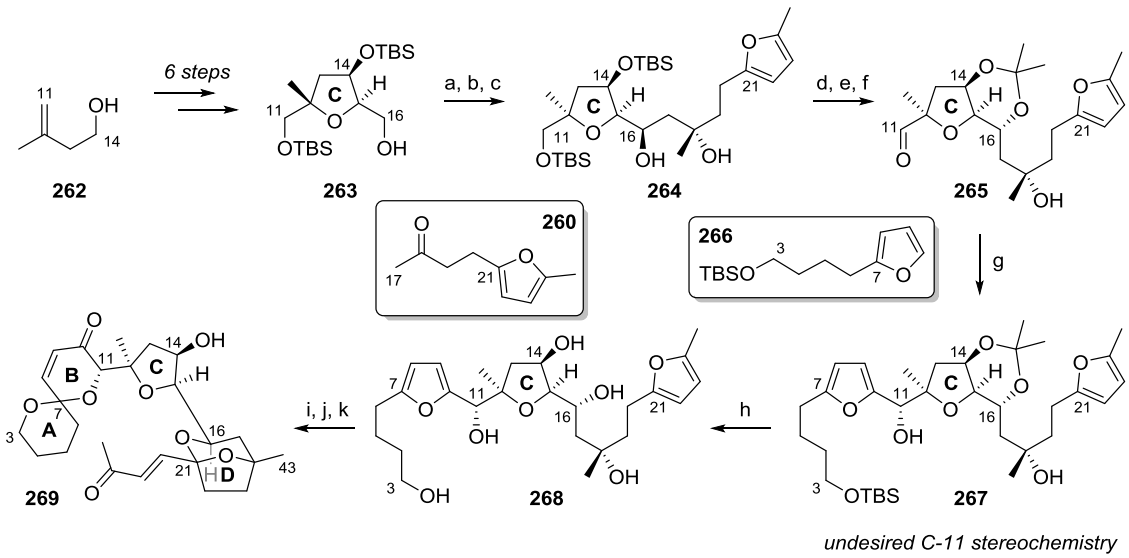
Vassilikogiannakis' novel approach to the D ring employed a singlet oxygen initiated double cascade reaction.[63] This methodology was initially extended to synthesise the C ring,[64] and further extended to synthesise the AB spiroketal of various PTXs (2c, 8, 9, 11c) simultaneously (**Scheme 2-18**).[65]



Scheme 2-18: Retrosynthetic analysis of Vassilikogiannakis' approach to the D ring of PTX-2c and 11c.

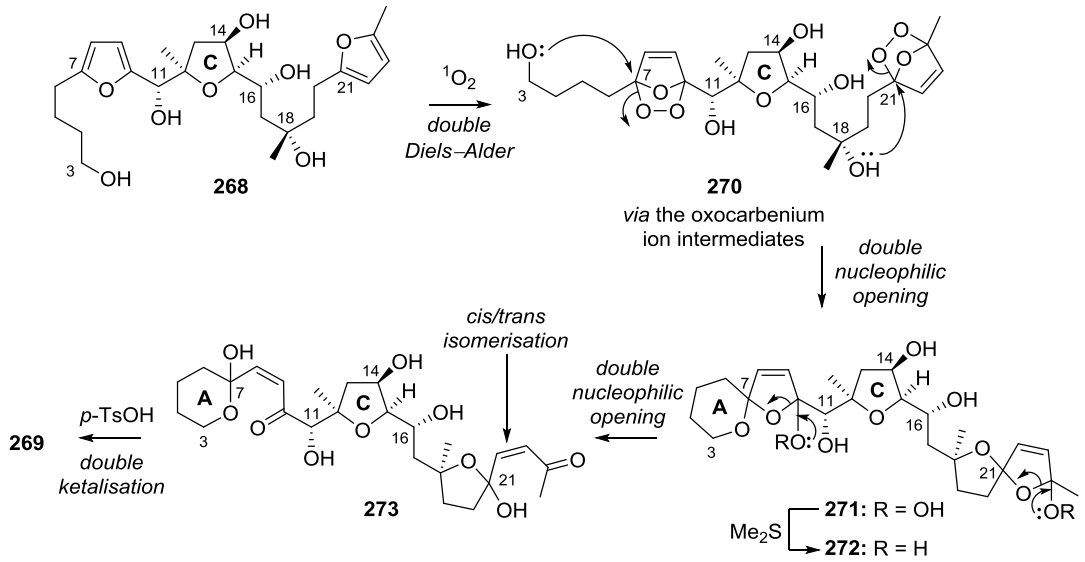
The C ring **263** was synthesised from 3-methylbut-3-en-1-ol **262** in six steps (**Scheme 2-19**).[64] The C-17 to C-21 carbon framework was attached by an aldol reaction of methyl ketone **260** to the aldehyde of **263**, followed by a stereoselective methyltitanation at C-18 ketone with 4:1 dr to afford **264**. The TBS protecting groups were removed with TBAF, and the C-14 and C-16 hydroxyl groups were protected as an acetal with 2,2-dimethoxypropane before the remaining primary hydroxyl group at C-11 was oxidised to give aldehyde **265**.

Unfortunately, nucleophilic addition of furan **266** to aldehyde **265** resulted in a 3.5:1 mixture of diastereomers in favour of the undesired diastereomer at C-11. Attempts to invert the configuration at C-11 were unsuccessful due to steric hindrance. Nevertheless, it was decided to proceed with this diastereomer to test the singlet oxygen cascade reaction. To avoid decomposition, the TBS group and acetal of **267** were removed with iodine to afford **268** in 55% yield. The singlet-oxygen-mediated cascade was employed on **268** to furnish the ABCD fragment **269** in 54% yield over 3 steps (5:7 dr at C-7).[65]



Scheme 2-19: Forward synthesis of Vassilikogiannakis' approach to the D ring of PTX-2c and 11c. *Reagents and conditions:* a) IBX, DMSO, 98%; b) **260**, LDA, THF, 70%, 10:1 dr; c) MeTi(O*i*-Pr)$_3$, Et$_2$O, 83%, 4:1 dr; d) TBAF, THF, 96%; e) 2,2-dimethoxypropane, *p*-TsOH, acetone, 96%; f) IBX, DMF, 88%; g) **266**, *n*-BuLi then **265**, THF, 0 °C, 77%, 3.5:1 dr; h) I_2, MeOH, 55%; i) O_2, rose Bengal, MeOH, hυ, –78 °C; j) Me_2S, –78 °C; k) *p*-TsOH, rt, 54% over three steps, 5:1 dr.

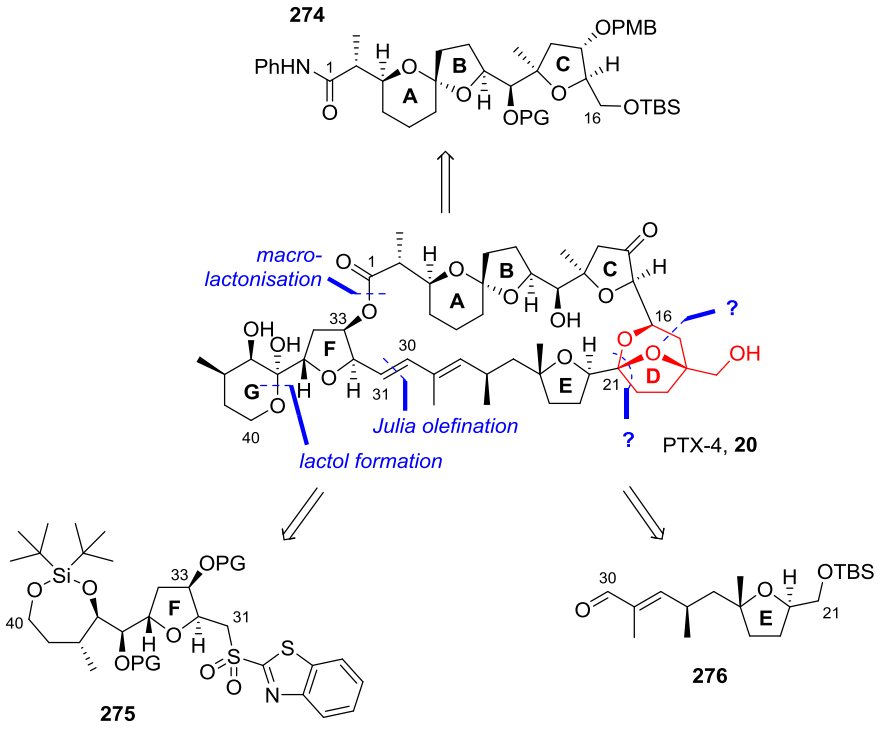
The proposed mechanism for the singlet-oxygen-mediated cascade is outlined in **Scheme 2-20**. Singlet oxygen initially undergoes two [4+2] cycloaddition reactions with both furans in **268** to form the bis-ozonide **270**. The pendant alcohols at C-3 and C-18 open the ozonides *via* nucleophilic attack at C-7 and C-21 respectively, forming the [6,5] and [5,5]-spirocyclic hydroperoxides, which are reduced to the corresponding hemiacetals by dimethyl sulfide. Bis-hemiacetal **272** opens to form **273**, which undergoes double ketalisation under acidic conditions to form the desired ABCD structure **269**.



Scheme 2-20: Proposed mechanism for singlet-oxygen-mediated cascade reaction in the D ring synthesis by Vassilikogiannakis and co-workers.

2.2 Donohoe's approach to the D ring

As described in **Chapter 1.3**, the Donohoe group have already synthesised the ABC[42] and the EFG[43] ring fragments of PTX-4. Our approach to the natural product was to combine the ABC fragment with the E ring fragment to cyclise and form the bicyclic acetal D ring system, before final coupling of the F ring (**Scheme 2-21**). The 1,3-diene formed after the Julia coupling[66] of the E ring to the F ring was unlikely to survive the conditions required to synthesise the D ring, therefore this step was planned to take place after D ring formation.

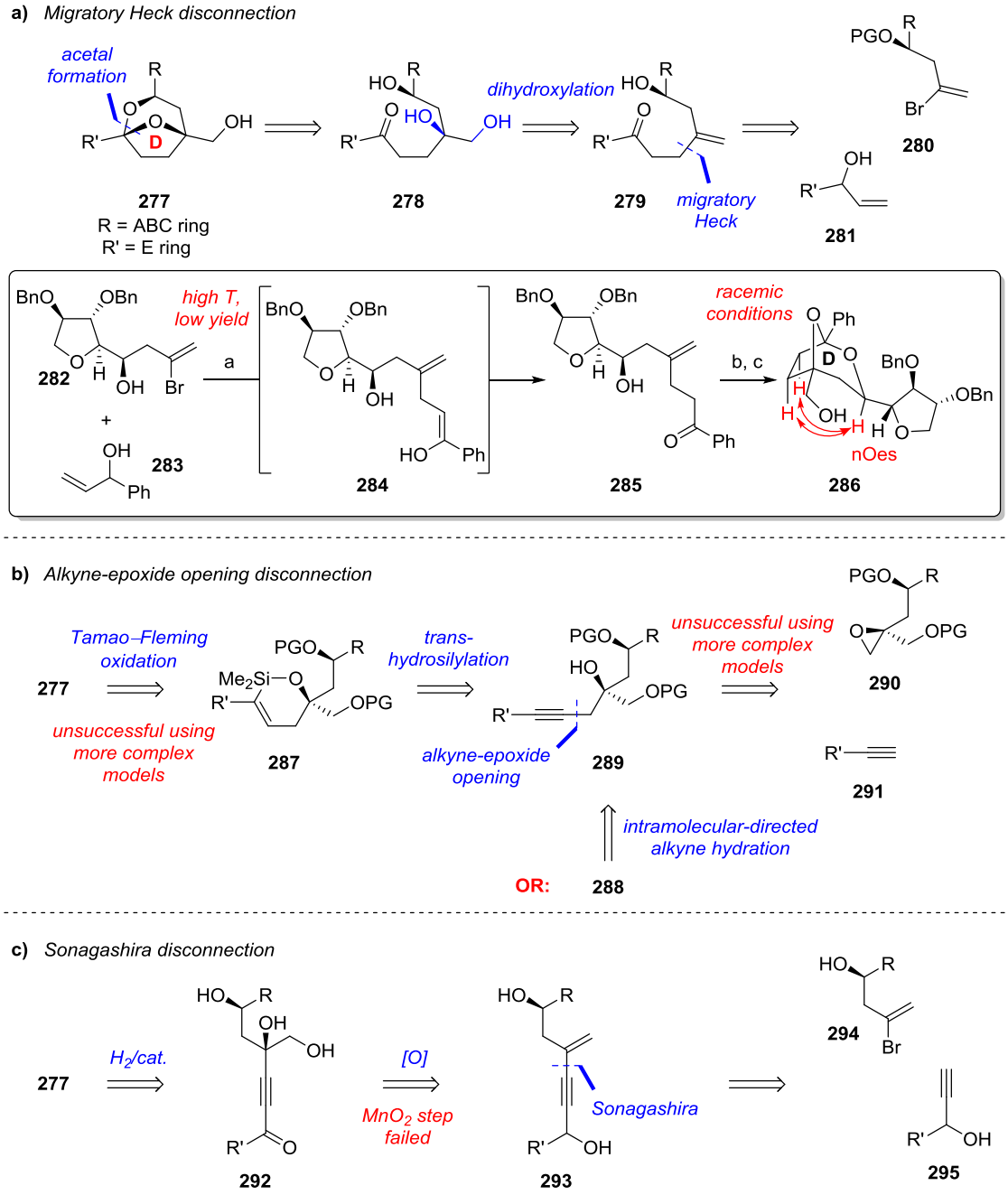


Scheme 2-21: Retrosynthesis of PTX-4 for the major fragments ABC, E and F fragments.

2.2.1 Previous approaches

In previous work, the group had investigated approaches to the D ring *via* a migratory Heck reaction (**a**)),[67] an alkyne-epoxide opening (**b**)),[68, 69] and a Sonagashira reaction (**c**))[68] as the key C–C bond forming steps (**Scheme 2-22**). However, most of these strategies failed when applied to more complex models which resembled the ring systems (C and E) of PTX-4.

The most advanced methodology that successfully assembled the D ring model was based on the migratory Heck disconnection (**Scheme 2-22a** in the box).[67] However, the migratory Heck reaction required high temperatures of 100 °C and was low yielding at 35% yield. Additionally, the dihydroxylation conditions used were not stereoselective and therefore the maximum possible yield was limited. This strategy relies solely on substrate bias for stereoselective induction to form the correct diol leading to the D ring structure **286**.

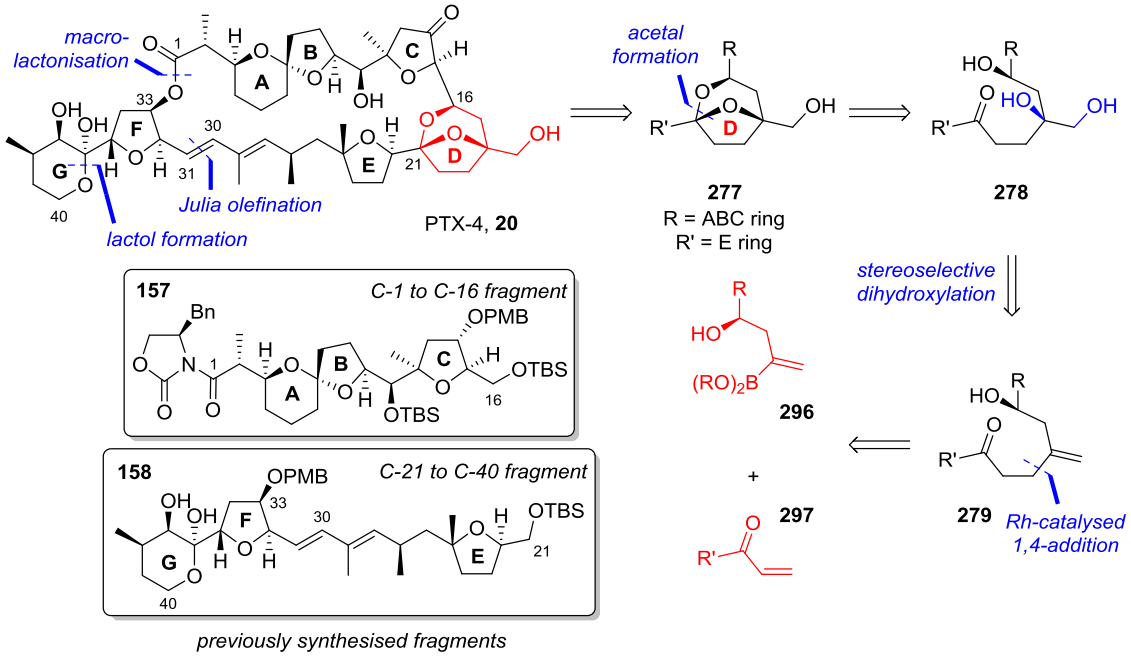


Scheme 2-22: Previous Donohoe group approaches to the D ring.
Reagents and conditions: a) $Pd(OAc)_2$, PPh_3, piperidine, DMF, 100 °C, 35%; b) $K_2OsO_2(OH)_4$ (10 mol%), NMO, acetone/H_2O (4:1); c) 4 M HCl, THF, 32% over two steps. Note non-stereoselective step b), so maximum yield is 50% assuming no substrate bias.

2.2.2 *Our proposed approach*

In light of this work, our retrosynthetic analysis shows the attachment of the FG ring system *via* a Julia olefination reaction[66] at C-30 and C-31 to the E ring, and a Yamaguchi macrolactonisation reaction[34] of the C-33 hydroxyl group to join to the ABC ring system

(**Scheme 2-23**). The bicyclic acetal of the D ring **277** can be disconnected to give the corresponding triol **278**. The 1,2-diol highlighted can be accessed *via* a Sharpless asymmetric dihydroxylation of the *exo*-olefin **279**. Our key C–C bond disconnection is a rhodium-catalysed 1,4-addition of the vinyl boronate of the ABC ring **296** with the enone of the E ring **297**.



Scheme 2-23: Our retrosynthetic analysis of the D ring of PTX-4.

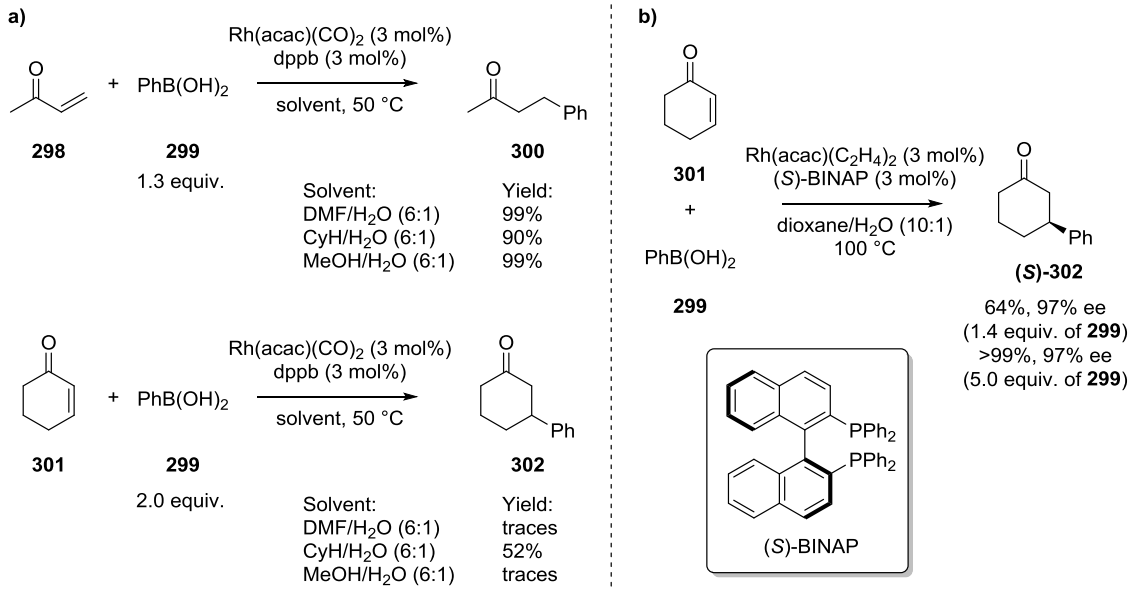
To determine whether this approach was feasible, model substrates were synthesised and tested. These models will be discussed in the following chapters.

2.3 *Introduction: The rhodium-catalysed 1,4-addition disconnection*

Conjugate addition reactions to enones are powerful reactions for the formation of C–C bonds.[70] The traditional route to achieve this is through organocuprate chemistry, with the one of the first reports by Kharasch in 1941. The reaction of methylmagnesium bromide was attenuated with 1 mol% copper(I) chloride to affect the 1,4- over the 1,2-addition to isophorone.[71] Other metals have been reported to catalyse conjugate addition

reactions, including Ni,[72] Co,[73] Pd[74, 75] and Rh[75, 76] with a variety of carbon nucleophiles.[70, 77, 78]

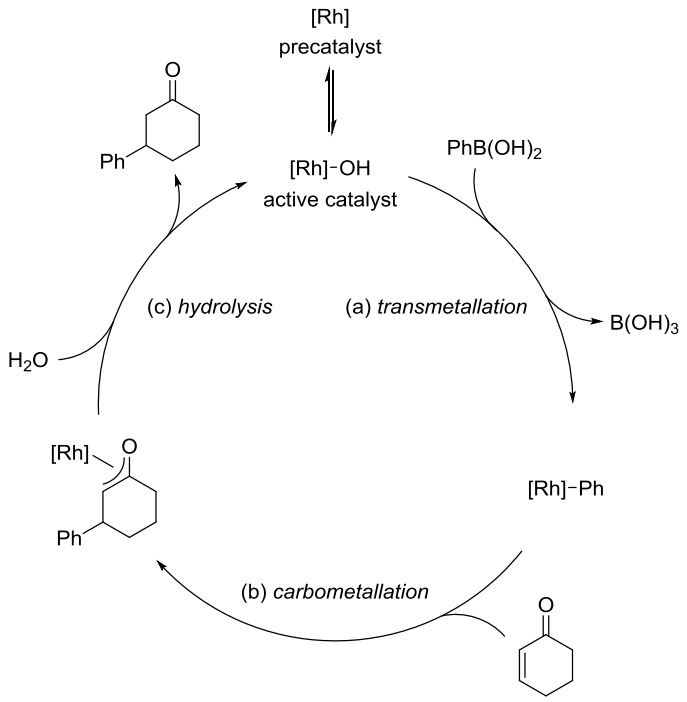
Rhodium-catalysed 1,4-additions have been studied extensively over the years.[70, 75, 77-81] A seminal report by Miyaura in 1997 described the use of a $Rh(acac)(CO)_2$ catalyst and dppb as a ligand in aqueous solvents to perform efficient conjugate addition of aryl boronic acids to both linear enones, such as methyl vinyl ketone (MVK) **298**, as well as cyclic enones such as 2-cyclohexen-1-one **301** (**Scheme 2-24a**).[76] The reaction involves the conversion of an sp^2 carbon to an sp^3 carbon, and so efforts were made to render the reaction enantioselective. This objective was achieved by Hayashi and Miyaura in 1998, using $Rh(acac)(C_2H_4)_2$ and (*S*)-BINAP at 3 mol% loading to produce the desired **(*S*)-302** in 64% yield and with an ee of 97% (**Scheme 2-24b**).[82]



Scheme 2-24: Seminal work by Miyaura on rhodium-catalysed 1,4-addition and an enantioselective variant by Hayashi and Miyaura.

The mechanism for the reaction was established by Hayashi in 2002.[83] The catalytic cycle is proposed to involve (a) transmetallation of the boron reagent to rhodium; (b) carbometallation of enone with the aryl-rhodium intermediate to form a rhodium enolate; and (c) the hydrolysis of the rhodium enolate to release the 1,4-addition product and the

hydroxorhodium species, considered to be the active catalyst (**Scheme 2-25**). Further mechanistic work determined that under simple conditions, the transmetallation step is rate-determining.[84] Throughout the catalytic cycle, rhodium remains in the +1 oxidation state. The species identified were confirmed and observed by NMR spectroscopic studies.[83]

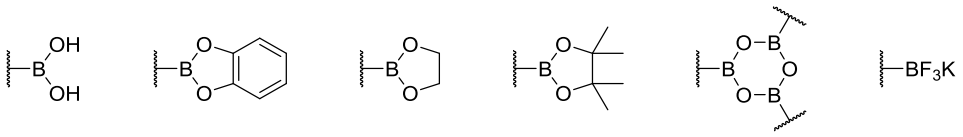


Scheme 2-25: Proposed mechanism of the rhodium-catalysed 1,4-addition by Hayashi.

This reaction has garnered significant interest because there is no competitive 1,2-addition to the ketone, functional group tolerance is high and the reaction conditions are mild.[75, 85] Additionally, this reaction is performed in aq. solvent, and so has advantages over other organometallic reactions as these often require rigorously anhydrous conditions to avoid quenching the Grignard or organolithium reagent before transmetallation.[82, 85]

With many advantages over traditional organometallic routes to conjugate additions, the rhodium-catalysed 1,4-addition reaction is an attractive option to access the desired

carbon backbone for our synthesis of the D ring. However, despite the reaction being studied extensively, there are fewer examples of alkenyl (as opposed to aryl) boronates undergoing the reaction, especially with such highly complex molecules as our disconnection proposes.[76, 82, 86] In addition, boronic acids, especially alkenyl boronic acids, are not particularly stable and often protodeborate or polymerise.[75, 87] Other more stable variants of boronic acid derivatives that have been utilised include esters derived from catechol (**304**),[88] ethylene glycol (**305**),[89] pinacol (**306**),[86, 89, 90] boroxines (**307**)[91] and potassium trifluoroborates (**308**, **Figure 2-1**).[92, 93]



303 **304** **305** **306** **307** **308**

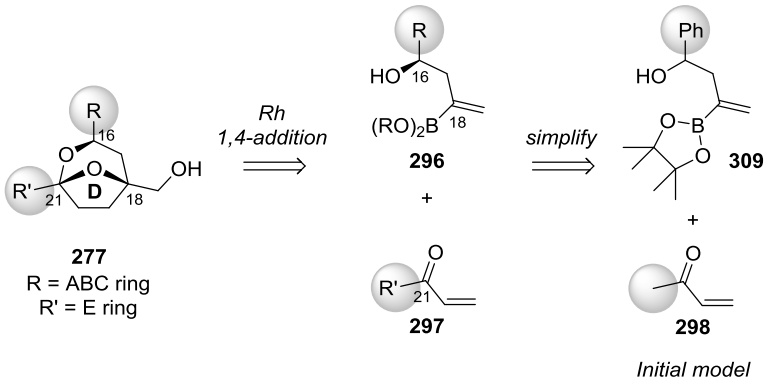
Figure 2-1: A selection of boron species competent at the rhodium-catalysed 1,4-addition reaction.

With these factors in mind, we chose to employ a vinyl pinacol boronate due to its increased stability over boronic acids and its ease of synthesis.[94]

2.4 Results & Discussion: Model studies on the synthesis of the D ring

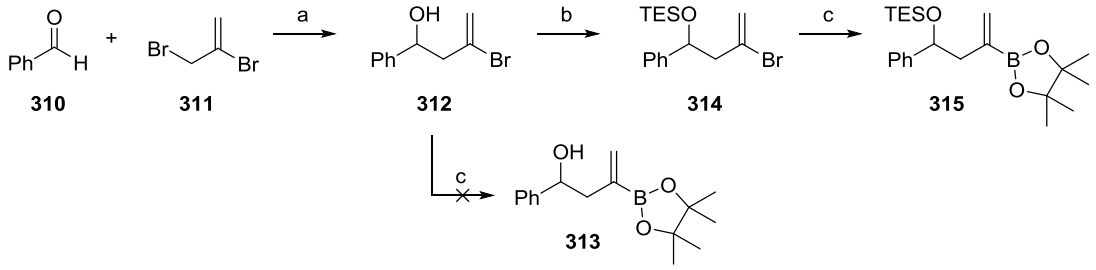
2.4.1 Initial model study

To test the rhodium-catalysed 1,4-addition reaction, we first chose to attempt the reaction with simple substitutes for the C and E rings respectively. Firstly, we chose to replace the C ring with a phenyl ring, and the E ring as a methyl group (**Scheme 2-26**).



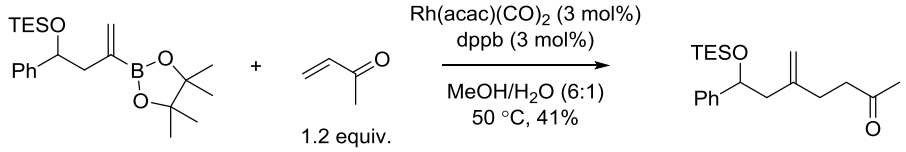
Scheme 2-26: Our proposed retrosynthesis and our first initial test substrates.

MVK **298** is commercially available, but racemic boronate **309** had to be synthesised. This was achieved easily in 3 steps from benzaldehyde **310** (**Scheme 2-27**). A tin-mediated Barbier[95] reaction of 2,3-dibromopropene **311** with benzaldehyde **310** furnished vinyl bromide **312** in 99% yield. An attempt was made to convert vinyl bromide **312** directly into the corresponding vinyl boronate **313** through a Pd-catalysed borylation, but the reaction failed. TES-protection of the hydroxyl group allowed for the Miyaura borylation to occur which gave the desired boronate **315** in 74% yield.[94]



Scheme 2-27: Three-step synthesis of boronate **315** substrate.
Reagents and conditions: a) Sn powder, conc. HBr, Et_2O/H_2O (1:1), 99%; b) TESOTf, imidazole, DCM, 99%; c) $(B(pin))_2$, $PdCl_2(PPh_3)_2$, PPh_3, KOPh, PhMe, 50 °C, 74%.

Boronate **315** was then subjected to rhodium-catalysed 1,4-addition reaction conditions with MVK **298**.[76, 86] Pleasingly, this initial reaction was successful and the desired adduct **316** was obtained in 41% yield (**Scheme 2-28**). As MVK is relatively volatile (b.p. 81.4 °C) and prone to polymerisation,[96] this could account for lower yields than expected.



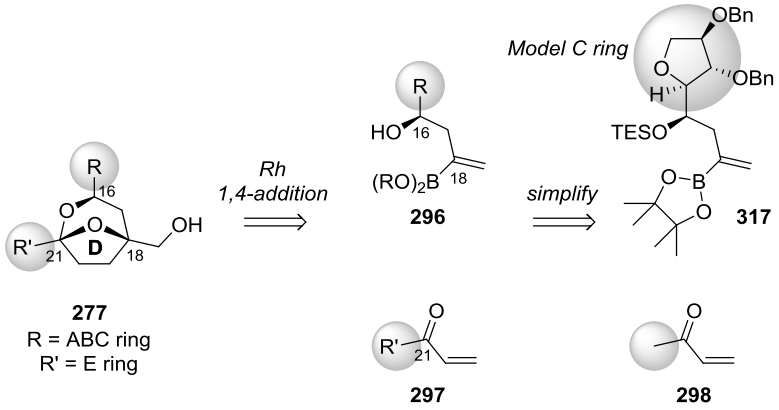
Scheme 2-28: Rhodium-catalysed 1,4-addition of boronate **315** with MVK **298**.

With this result in hand, the substrates used in further rhodium-catalysed 1,4-addition reactions were increased in complexity to mimic the tetrahydrofuran C and E rings respectively.

2.4.2 The model C ring boronate

2.4.2.1 Synthesis of model C ring boronate

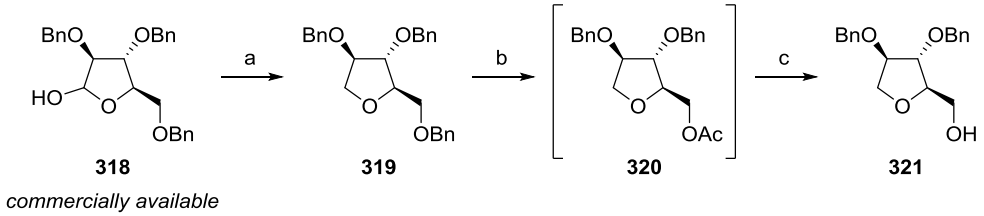
It was decided to replace the phenyl group first with a closer mimic of the C ring, as this substrate must allow for the synthesis of the desired boronate. The substrate chosen was based upon a furanose used previously in the group by Dr Yifan Liu and Matthew Reeves (**Scheme 2-29**).[67, 68]



Scheme 2-29: Our proposed retrosynthesis and our model C ring substrate.

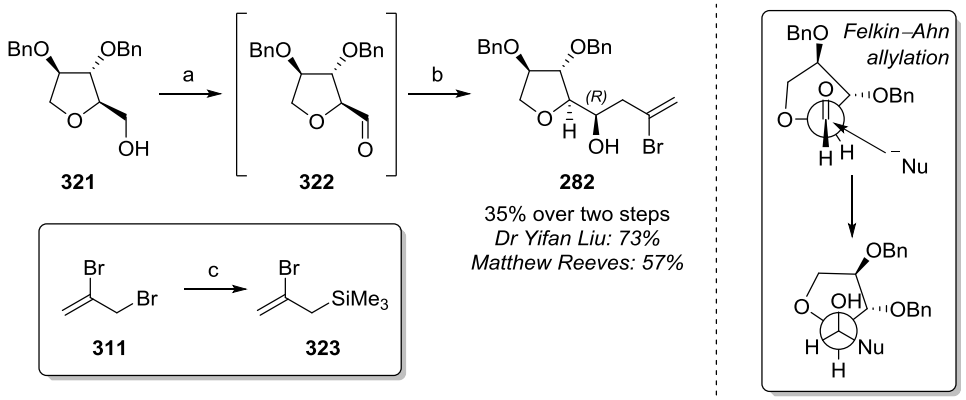
Model C ring boronate **317** was synthesised in 7 steps from the commercially available furanose **318**. Furanose **318** was reduced to **319** using triethylsilane in the presence of boron trifluoride etherate in 95% yield. The benzyl-protected primary alcohol was

substituted for an acetate group before hydrolysis under basic conditions to afford alcohol **321** in 89% yield over two steps (**Scheme 2-30**).



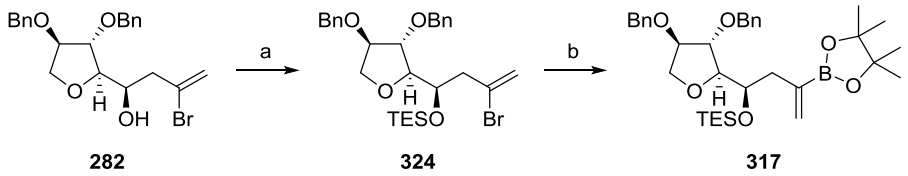
Scheme 2-30: Part I of the synthesis of C ring boronate **317**.
Reagents and conditions: a) Et_3SiH, $BF_3{\cdot}OEt_2$, MeCN, 95%; b) Ac_2O, TFA; c) NaOMe, MeOH, 89% over two steps.

To install the desired stereochemistry at C-16 of PTX-4, we proposed a Felkin–Ahn controlled addition of an allylic silane. This transformation bears resemblance to a step Evans' synthesis, as described in **Chapter 2.1.1**.[22] Previously, this reaction has been accomplished by Dr Yifan Liu and Matthew Reeves in 73% and 57% yields respectively,[67, 68] but the procedure proved to be unreliable. The Hosomi–Sakurai[97] reaction consistently produced only 35% yield of vinyl bromide **282** in my hands (**Scheme 2-31**). Nevertheless, only one diastereomer was isolated (>20:1 dr) and the stereochemistry was confirmed as (*R*) by Mosher's ester analysis (see **Appendix 6.1.1**).[98-100] Methodology on how this step was improved will be discussed in **Chapter 2.4.2.3**.



Scheme 2-31: Part II of the synthesis of C ring boronate **317**. Attempts to repeat procedure of synthesising vinyl bromide **282** by Dr Yifan Liu and Matthew Reeves.
Reagents and conditions: a) DMSO, $SO_3{\cdot}$py, *i*-Pr_2NH, DCM, 0 °C; b) **323**, TMSOTf, MeCN, –10 °C, 35% over two steps, >20:1 dr; c) Cl_3SiH, CuCl, Et_3N, Δ then MeMgBr, Et_2O, 0 °C, 38%.

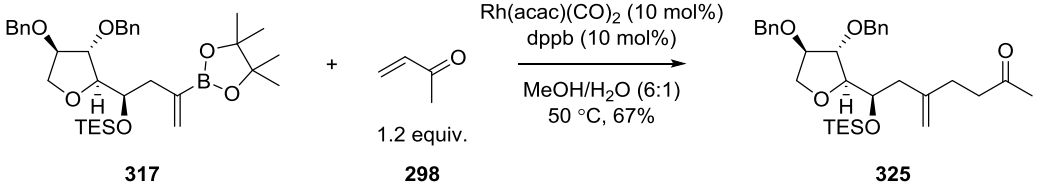
With vinyl bromide **282** in hand, the final steps in the synthesis of the desired boronate were undertaken. The alcohol was TES-protected in high yield (85%) before the Miyaura borylation of vinyl bromide **282** was accomplished in 79% yield (**Scheme 2-32**).[94]



Scheme 2-32: Part III of the synthesis of C ring boronate **317**.
Reagents and conditions: a) TESOTf, imidazole, DCM, 85%; b) $(B(pin))_2$, $PdCl_2(PPh_3)_2$ (3 mol%), PPh_3 (6 mol%), KOPh, PhMe, 50 °C, 79%.

2.4.2.2 Rhodium-catalysed 1,4 addition with MVK

The rhodium-catalysed 1,4-addition reaction was attempted with the model C ring boronate **317** and MVK **298** as previously shown. However, due to the considerable increase in complexity of the boronate, the catalyst and ligand loading was increased to 10 mol%. Pleasingly, the reaction proceeded in a 67% yield to afford adduct **325** (**Scheme 2-33**).



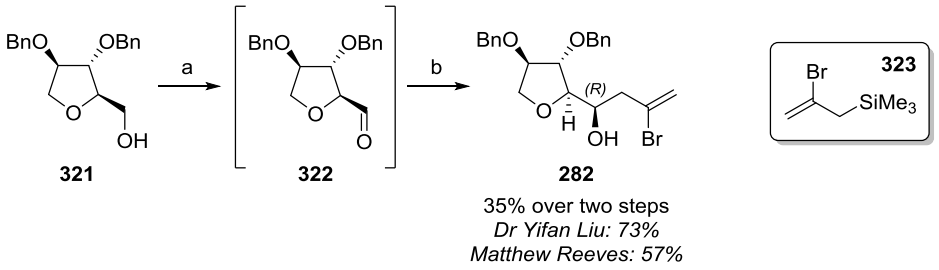
Scheme 2-33: Rhodium-catalysed 1,4-addition of model C ring boronate **317** with MVK **298**.

As stated in **Chapter 2.4.1**, MVK **298** is not an ideal enone substrate.[96] It should be noted that older bottles of MVK **298** afforded lower yields (17–26%) of **325**. The next challenge was to increase the complexity of E ring model from a methyl group to a substituent that resembles the desired E ring fragment, which would eliminate the use of MVK **298**. This will be discussed in **Chapter 2.4.3**.

However, the optimisation of the synthesis of the model C ring boronate **317** will be discussed first, because the Sakurai allylation was low-yielding and unoptimised.

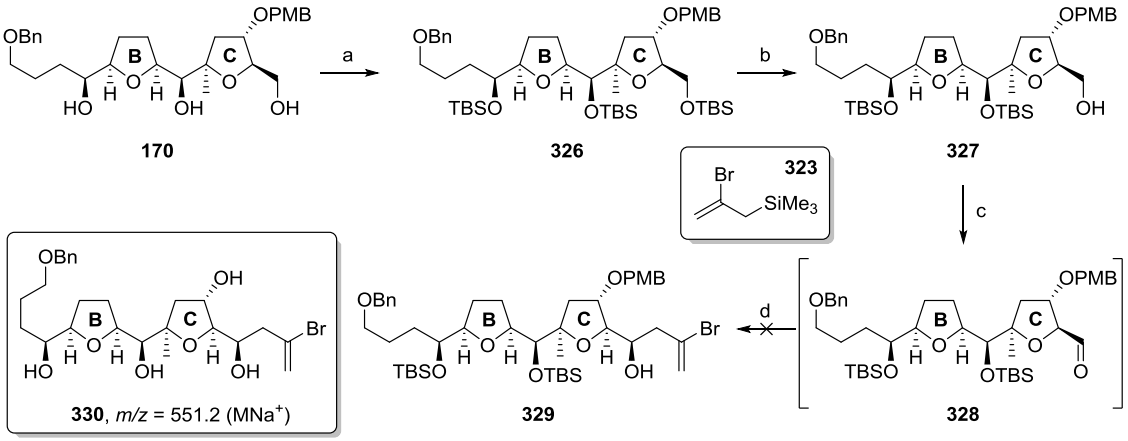
2.4.2.3 Optimising the synthesis of the vinyl boronate

As described in **Chapter 2.4.2.1**, the Sakurai reaction of allyl silane **323** and aldehyde **322** derived from alcohol **321** only afforded a 35% yield of desired vinyl bromide **282** (**Scheme 2-34**).



Scheme 2-34: Synthesis of vinyl bromide **282** described in **Chapter 2.4.2.1**.
Reagents and conditions: a) DMSO, SO_3·py, *i*-Pr_2NH, DCM, 0 °C; b) **323**, TMSOTf, MeCN, –10 °C, 35% over two steps, >20:1 dr.

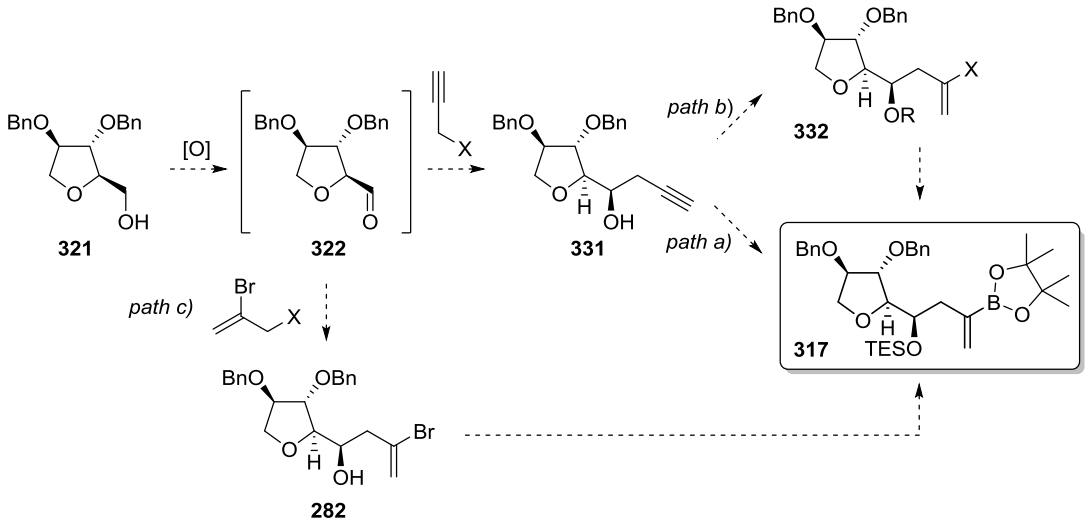
To discover if the Sakurai allylation reaction was feasible on the real ABC ring system, and whether the reaction was worth optimising or an alternative route should be investigated, an advanced intermediate in the route to the real ABC fragment was utilised. Fragment **170**, generously donated by co-worker Timothy Kwok,[48] was chosen as the advanced test substrate (**Scheme 2-35**). The triol **170** was triply TBS-protected to afford **326**, and the primary hydroxyl group was deprotected by treatment with TBAF to access **327**. However, Parikh–Doering oxidation[29] followed by the reaction of the aldehyde under the original Sakurai allylation conditions did not provide **329**. Analysis of the complex reaction mixture by mass spectrometry showed a peak for *m/z* = 551.2 which would correspond to MNa^+ of **330**, where all the protecting groups (except for the benzyl group) have fallen off. Apparently, adventitious triflic acid was acidic enough to deprotect the TBS and PMB groups. The protecting groups, in particular the PMB group, are designed to stay on for the majority of the synthesis and are installed early in the synthesis, so these Sakurai conditions cannot be used in our synthesis of PTX-4.



Scheme 2-35: Advanced BC fragment in the original Sakurai allylation conditions. *Reagents and conditions:* a) TBSOTf, 2,6-lutidine, DCM, –78 °C, 67%; b) TBAF, THF, 0 °C, 89%; c) DMSO, SO_3·py, *i*-Pr_2NH, DCM, 0 °C; d) **323**, TMSOTf, MeCN, –10 °C.

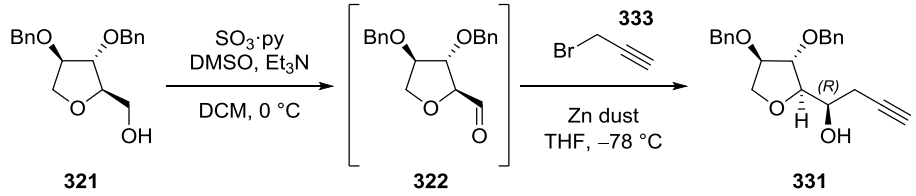
To both improve the transformation of alcohol **321** and avoid the accidental removal of important protecting groups in the real system, alternative routes were investigated to either access either vinyl bromide **282** or the vinyl boronate **317** directly.

An alternative route would involve a synthesis of the terminal alkyne **331** instead of vinyl bromide **282**. There would be two potential routes to the vinyl boronate: either *via path a*) where the alkyne is directly converted into the vinyl boronate; or *via path b*) where the alkyne is converted into a vinyl halide first before converting into the vinyl boronate (**Scheme 2-36**). Alongside the alternative alkyne route, other metals and allyl substrates were investigated *via* the original *path c*).



Scheme 2-36: Alternative routes to vinyl boronate **317**.

Propargylation followed by either *path a*) or *path b*) will be discussed first. Alcohol **321** was oxidised to the aldehyde under Parikh–Doering conditions[101] and the propargylation was carried out with various equivalents of propargyl bromide **333** and Zn dust (**Table 2-1**).[102] Increasing the number of equivalents of propargyl bromide **333** and Zn to 7 and 5 respectively, afforded the best yield of 52% (comparing **entries 1** and **2**), whilst increasing the number of equivalents further did not improve the yield (**entry 3**).

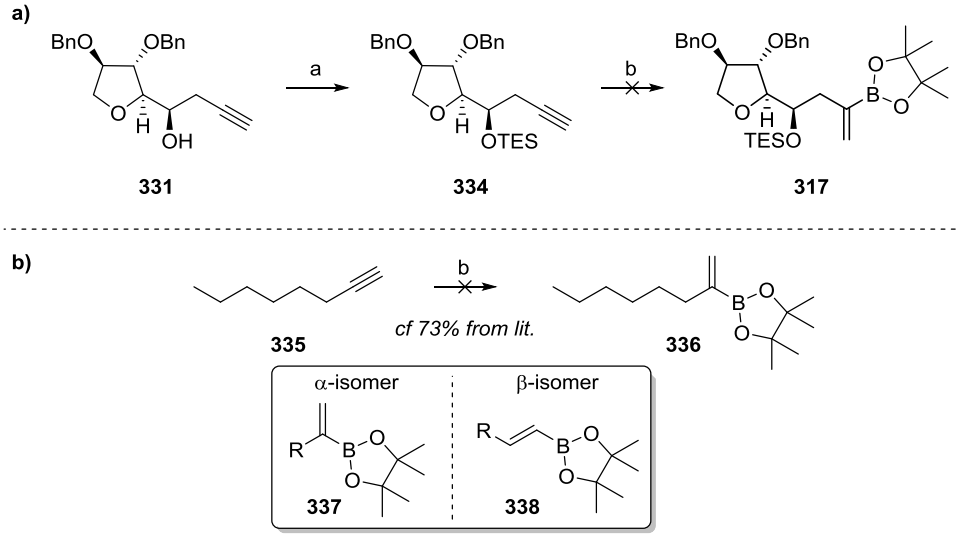


Entry	Equiv. of **333**	Equiv. of Zn	Yield
1	2	3	28%
2	**7**	**5**	**52%**
3	14	10	50%

Table 2-1: Optimisation of propargylation of **321**. >20:1 dr for all entries.

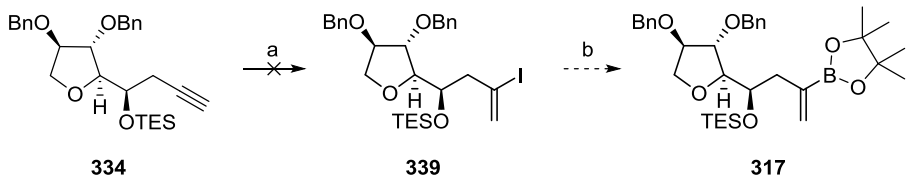
The stereochemistry was confirmed by Mosher's ester analysis as (*R*) (see **Appendix 6.1.2**).[98, 99] With propargylic alcohol **331** in hand, attempts were made to convert the alkyne into the desired vinyl boronate. Direct conversion (*via* path a), **Scheme 2-36**) of

terminal alkynes have been described by Prabhu, by utilising $[Pd(OAc)_2]_3$ and tricyclohexylphosphine with bis(pinacolato)diboron to access the α-vinyl boronate **337** instead of the β-isomer **338**.[103] However, after the TES-protection of the secondary alcohol, the reaction of **334** under the conditions described did not afford the desired boronate **317** and produced a complex mixture of products (**Scheme 2-37a**). To check if the issue was the substrate, an attempt was made to repeat one of the literature examples. However, this reaction could not be reproduced either and a complex mixture of compounds was obtained (**Scheme 2-37b**).



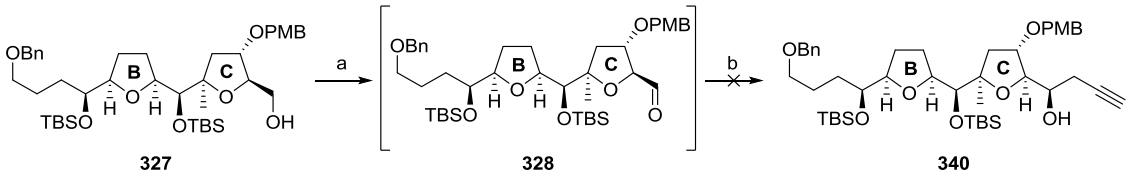
Scheme 2-37: Attempt to directly convert terminal alkyne **334** into vinyl boronate **317**.
Reagents and conditions: a) TESOTf, imidazole, DCM, quant.; b) $(B(pin))_2$, $[Pd(OAc)_2]_3$ (5 mol%), PCy_3 (10 mol%), PhBr, TFE,[104] PhMe, 80 °C.

To convert alkyne **334** into vinyl boronate **317** indirectly (*via path b*), **Scheme 2-36**), the alkyne can be converted into vinyl iodide **339** by a method described by Hoveyda.[105] This reaction has already been applied in the group to the synthesis of the E ring.[43, 68] The vinyl iodide could then be converted using the conditions used for converting the vinyl bromide **282** into the vinyl boronate **217**. However, using these conditions on alkyne **334** did not react to give the desired vinyl iodide **339** and unreacted alkyne **334** along with a complex mixture of products was obtained (**Scheme 2-38**).



Scheme 2-38: Attempt to indirectly convert terminal alkyne **334** into vinyl boronate **317**.
Reagents and conditions: a) DIBAL-H, NIS, $Ni(dppp)Cl_2$ (3 mol%), THF, 0 °C; b) $(B(pin))_2$, $PdCl_2(PPh_3)_2$ (3 mol%), PPh_3 (6 mol%), KOPh, PhMe, 50 °C.

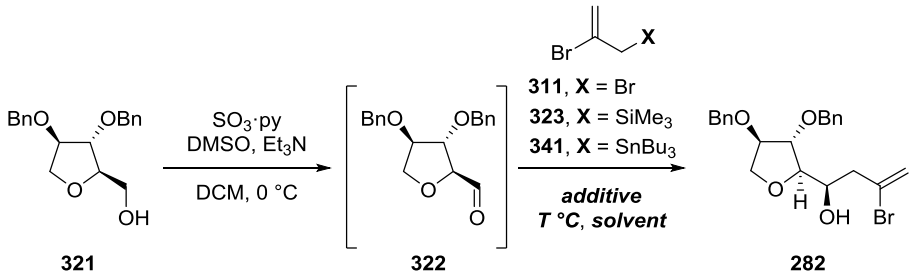
Despite the difficulties of converting the terminal alkyne to the vinyl boronate, propargylation of the advanced BC fragment was attempted. Unfortunately, this reaction was not successful either and resulted in decomposition of the starting material (**Scheme 2-39**).



Scheme 2-39: Attempted propargylation of advanced BC fragment.
Reagents and conditions: a) DMSO, SO_3·py, Et_3N, DCM, 0 °C; b) propargyl bromide **333**, Zn dust, THF, –78 °C.

Alongside this investigation, alternative allylating reagents were tested to access vinyl bromide **282** (*via path c*), **Scheme 2-36**). The results of these reactions are summarised in **Table 2-2**. **Entry 1** describes the original conditions and the yield achieved when repeating the procedure outlined by Dr Yifan Liu and Matthew Reeves.[67, 68] Using Ti(O*i*-Pr)$_4$ as the Lewis acid with allylsilane **323** resulted in no product **282** formation (**entry 2**).[106] The use of $TiCl_4$ slightly improved the yield from the original conditions in **entry 1** to 39% when allylsilane **323** was dried azeotropically (**entry 3**).[106] However, use of BF_3·OEt_2 resulted in a significant increase in yield to 56% (**entry 4**).[22, 49] These conditions could not be improved upon by use of the alternative allylating agent 2,3-dibromopropene **311** with either Sn or In as the metal for the Barbier reactions (**entries 5** and **6**).[107, 108] An

attempt was made to form the stannylated allylating agent **341**,[109] but this reagent was difficult to prepare and proved impractical for scale-up.

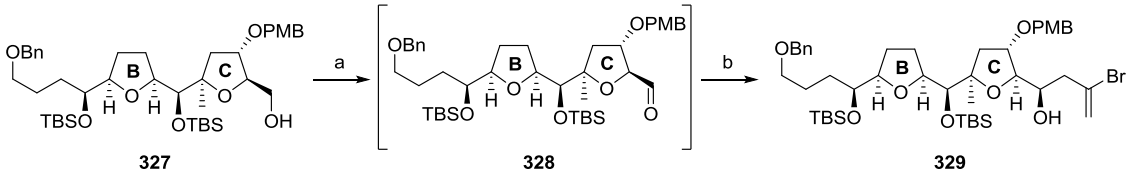


321 **322** **282**

Entry	**X** substituent	Additive	T °C	Solvent	Yield
1	$SiMe_3$	TMSOTf	–10 °C	MeCN	35% [a]
2	$SiMe_3$	Ti(O*i*-Pr)$_4$	–78 °C	DCM	0%
3	$SiMe_3$	$TiCl_4$	–78 °C	DCM	39% [b]
4	**$SiMe_3$**	**$BF_3{\cdot}OEt_2$**	**–78 °C**	**DCM**	**56%**
5	Br	Sn, conc. HBr	rt	Et_2O/H_2O (1:1)	17%
6	Br	In	–20 °C	DMF/H_2O (1:1)	11%

Table 2-2: Optimisation of allylation of **321**. >20:1 dr for all entries. [a] Oxidation of alcohol **321** to aldehyde **322** conditions: DMSO, $SO_3{\cdot}$py, *i*-Pr_2NH, DCM, 0 °C; [b] 0% yield if allylating reagent was not dried azeotropically in benzene.

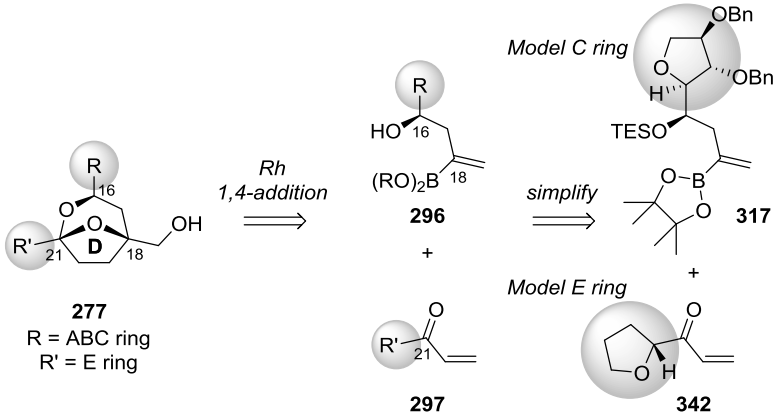
Using the best conditions outlined in **entry 4** of **Table 2-2**, another Sakurai allylation was attempted on the advanced BC fragment. This attempt was successful and the desired vinyl bromide **329** was obtained in an albeit low yield of 22% (**Scheme 2-40**). It was noted that the original Parikh–Doering conditions[101] were not working reliably, and so Swern conditions were used alternatively. However, this experiment is a proof of concept to demonstrate that the allylation reaction can be performed on the advanced intermediate, and further optimisation should improve the yield. Due to the lack of precious BC fragment, further optimisation was not explored on this substrate, nor was the Miyaura borylation investigated. Suggestions to improve the yield would be to use Rochelle's salt in the workup to avoid the boron species coordinating and sequestering **329** into the aqueous phase.



Scheme 2-40: Attempted Sakurai allylation with new conditions on advanced BC fragment. *Reagents and conditions:* a) DMSO, $(COCl)_2$, Et_3N, DCM, –78 °C; b) **323**, $BF_3{\cdot}OEt_2$, DCM, –78 °C, 22% over two steps, >20:1 dr.

2.4.3 The model E ring enone

As stated in **Chapter 2.4.2.2**, the next challenge was to increase the complexity of E ring model from a methyl group to a substituent that resembles the desired E ring to eliminate the use of MVK **298**. It was decided to use another tetrahydrofuran scaffold as the E ring mimic (**Scheme 2-41**).



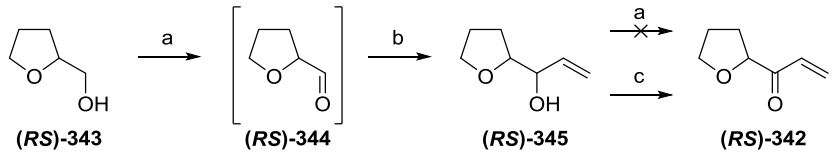
Scheme 2-41: Our proposed retrosynthesis and our models for C and E ring substrates.

As the corresponding enantiopure (*R*)-alcohol that is required for the synthesis of the model E ring is more expensive in comparison to the racemic alcohol, preparation of the racemic model E ring was attempted first.

2.4.3.1 Racemic E ring enone

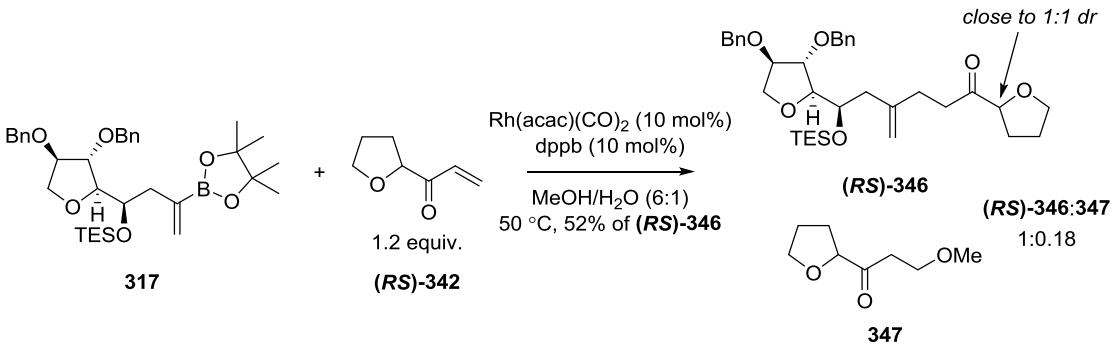
Racemic alcohol **(*RS*)-343** was oxidised to the corresponding aldehyde **(*RS*)-344** using Swern conditions.[110] Vinyl magnesium bromide was added to aldehyde **(*RS*)-344** to form secondary alcohol **(*RS*)-345** in 23% yield over two steps with 1.15:1 dr at the hydroxyl group. The final oxidation to give the enone was unsuccessful using Swern conditions,

but oxidation of the allylic alcohol with Dess–Martin periodinane (DMP) afforded enone **(*RS*)-342** in 65% yield (**Scheme 2-42**). It should be noted that all these compounds are volatile and cannot be removed from $CDCl_3$, which also explains the relatively low yields.



Scheme 2-42: Synthesis of the racemic E ring model **(*RS*)-342**.
Reagents and conditions: a) DMSO, $(COCl)_2$, Et_3N, DCM, –78 °C; b) vinyl magnesium bromide, Et_2O, –78 °C, 22% over two steps, 1.15:1 dr; c) DMP, $NaHCO_3$, DCM, 65%.

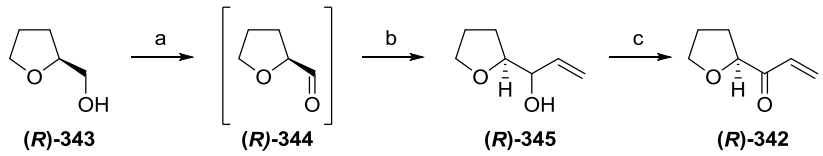
E ring model enone **(*RS*)-342** was then subjected to the rhodium-catalysed 1,4-addition reaction conditions used previously. This reaction afforded adduct **(*RS*)-346** in 52% yield contaminated with small amount of impurity **347** (1:0.18), which arises from methanol addition to the enone catalysed by the rhodium complex (**Scheme 2-43**). It should be noted that impurity **347** does not form under the reaction conditions without the presence of the rhodium catalyst. The adduct **(*RS*)-346** was clearly a mixture of two diastereomers at the α-keto position, and whilst the exact ratio could not be determined from the ^1H NMR, the number of ^{13}C NMR peaks were clearly doubled and twinned.



Scheme 2-43: Rhodium-catalysed 1,4-addition of model C ring boronate **317** with racemic model E ring enone **(*RS*)-346**.

2.4.3.2 Enantiopure E ring enone

The enantiopure variant of the E ring enone was accessed is a similar manner to the racemic enone. Swern oxidation of **(*R*)-343** followed by nucleophilic addition of vinyl magnesium bromide afford a diastereomeric mixture **(*R*)-345** in 35% yield and 1.15:1 dr. Oxidation to the enone with DMP accessed the volatile enone **(*R*)-346** in 89% yield (**Scheme 2-44**).

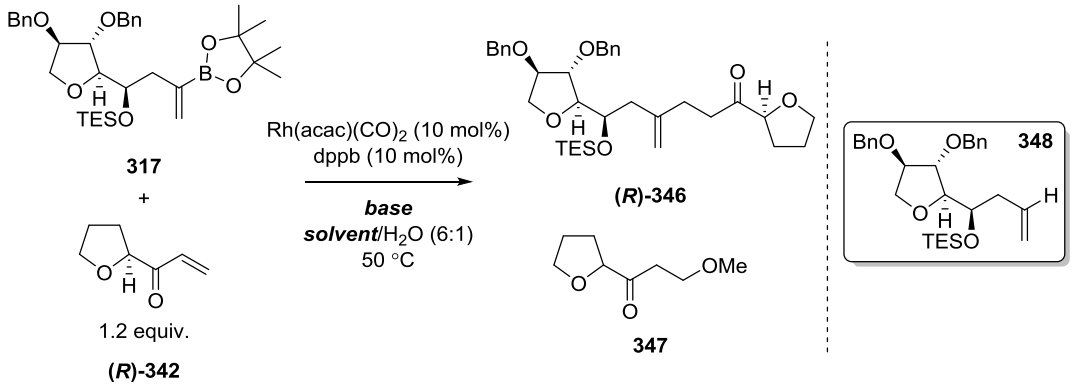


Scheme 2-44: Synthesis of the chiral E ring model **(*R*)-342**.
Reagents and conditions: a) DMSO, $(COCl)_2$, Et_3N, DCM, –78 °C; b) vinyl magnesium bromide, Et_2O, –78 °C, 35% over two steps, 1.15:1 dr; c) DMP, DCM, 89%.

The model for the E ring **(*R*)-342** was subjected to the rhodium-catalysed 1,4-addition reaction conditions used for previous model systems. Pleasingly, adduct **(*R*)-346** was isolated in 39% yield (**entry 1**, **Table 2-3**). There was no epimerisation at the α-keto centre during the reaction; only one set of ^{13}C peaks in **(*R*)-346** compared to **(*RS*)-346**. However, this product was still contaminated with the methanol-adduct **347**.

To eliminate this impurity, alternative solvents were explored. Replacing MeOH with THF afforded the product in 63% yield without the production of impurity **347** (**entry 2**). However, traces of the lower polarity by-product **348**, formed from protodeborylation, were also isolated. Other alcoholic solvents did not improve the yield but did produce more of by-product **348** (**entries 3** and **4**). Using 1,4-dioxane did not deliver any of the desired product **(*R*)-346** (**entry 5**). It should be noted that replacing $Rh(acac)(CO)_2$ with 5 mol% $[Rh(cod)Cl]_2$, known to be a more active catalyst for rhodium-catalysed 1,4-addition,[75, 111] provided no product at all (under the conditions described in **entry 1**).

The addition of a small number of bases were also explored because these are proposed to catalyse the reaction by aiding the formation of the hydroxyrhodium species (the active catalyst).[111] However, the base additives in **entries 6** to **8** did not improve the yield in comparison with the neutral conditions of **entry 2**, and seemed to promote the formation of the protodeborylation product **348**.



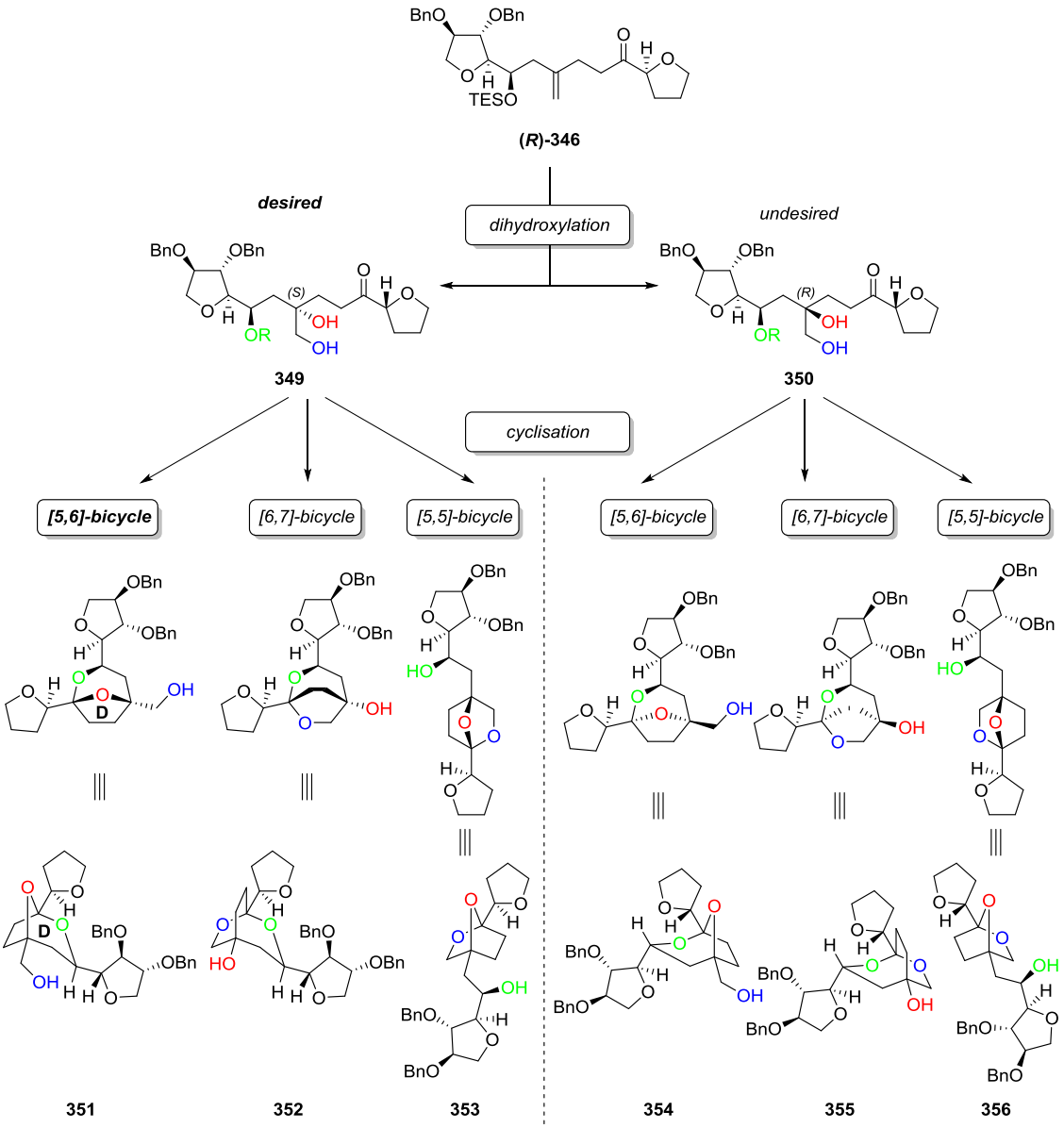
Entry	Base [a]	Solvent	Yield of **(*R*)-346**	Yield of **348**	Ratio of **(*R*)-346**:**347** [b]
1	-	MeOH	39%	Not isolated	1:0.45
2	**-**	**THF**	**63%**	**trace**	**-**
3	-	HFIP	51%	4%	-
4	-	*i*-PrOH	<4%	27%	-
5	-	1,4-dioxane	0%	Not isolated	-
6	KOH	THF	18%	12%	-
7	K_2CO_3	THF	36%	18%	-
8	Et_3N	THF	0%	Not isolated	-

Table 2-3: Optimisation of the rhodium-catalysed 1,4-addition of **317** and **(*R*)-342**. >20:1 dr for all entries. [a] 2 equiv.; [b] No entry means formation of **347** was not detected.

The best conditions for the rhodium-catalysed 1,4-addition reaction of the model C ring boronate **317** and enantiopure model E ring enone **(*R*)-342** was **entry 2** in **Table 2-3**, using THF as the solvent to eliminate the formation of by-product **(*R*)-346**. These conditions would be used in further rhodium-catalysed 1,4-addition reactions.

2.4.4 The asymmetric dihydroxylation/cyclisation sequence

The previous sections outlined the development of the rhodium-catalysed 1,4-addition reaction as the key C–C bond forming reaction in our synthesis of the D ring. The final steps to complete the synthesis of the D ring were to be asymmetric dihydroxylation of the olefin in **(*R*)-346** and cyclisation to form the bicyclic acetal motif. However, as shown in **Scheme 2-45**, this could potentially form up to six different bicyclic acetals, dependent on the stereoselectivity of the initial dihydroxylation. The desired D ring structure **351** originates from the (*S*)-isomer of the diol **349**, where the secondary and tertiary alcohols (highlighted in green and red respectively) cyclise onto the ketone, leaving the primary (blue) alcohol unreacted. The other potential bicyclic acetals ([6,7] and [5,5]) are formed when the primary hydroxyl group (blue) is involved in acetal formation. Presumably, as the D ring acetal appears in the majority of the PTXs, and so is likely to be thermodynamically favourable compared to the other possible structures.



Scheme 2-45: Asymmetric dihydroxylation/cyclisation sequence of **(*R*)-346** to form 6 possible bicyclic acetals **351** to **356**.

2.4.4.1 Introduction: Sharpless Asymmetric Dihydroxylation

To prevent the formation of bicycles **354** to **356** from the undesired (*R*)-diol **350**, dihydroxylation of the alkene of **(*R*)-346** must be facially-selective for the desired (*S*)-diol **349**.

One method for the stereoselective catalytic asymmetric dihydroxylation of olefins is the Sharpless asymmetric dihydroxylation (SAD) reaction.[112-114] This reaction employs catalytic potassium osmate and the phthalazine class of the dihydroquinine and

dihydroquinidine ligands ($(DHQ)_2PHAL$, **357** and $(DHQD)_2PHAL$, **358** respectively) with potassium ferricyanide[115] and potassium carbonate in a 1:1 mixture of *tert*-butanol/water.[113] The *pseudo*-enantiomeric ligands **357** and **358** have opposite facial selectivity, as shown by the mnemonic in the **Figure 2-2**. $(DHQ)_2PHAL$ **357** conditions dihydroxylate olefins from the bottom, whilst $(DHQD)_2PHAL$ **358** conditions dihydroxylate from the top when the alkene is positioned as shown (R_L = largest substituent; R_M = medium-sized; R_S = smallest).

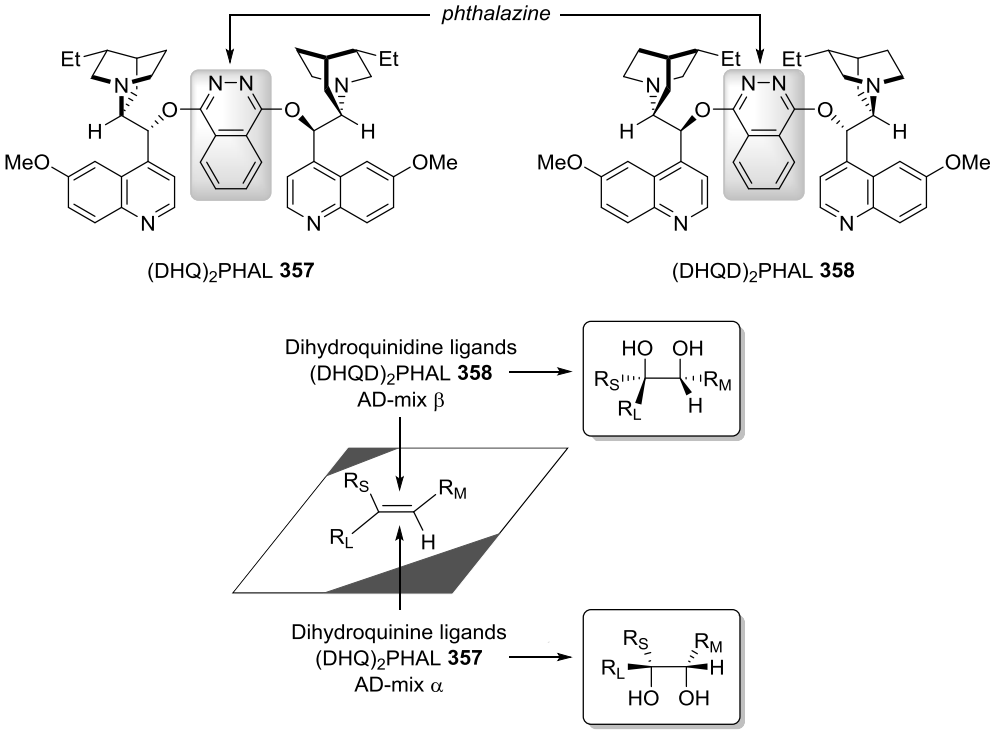
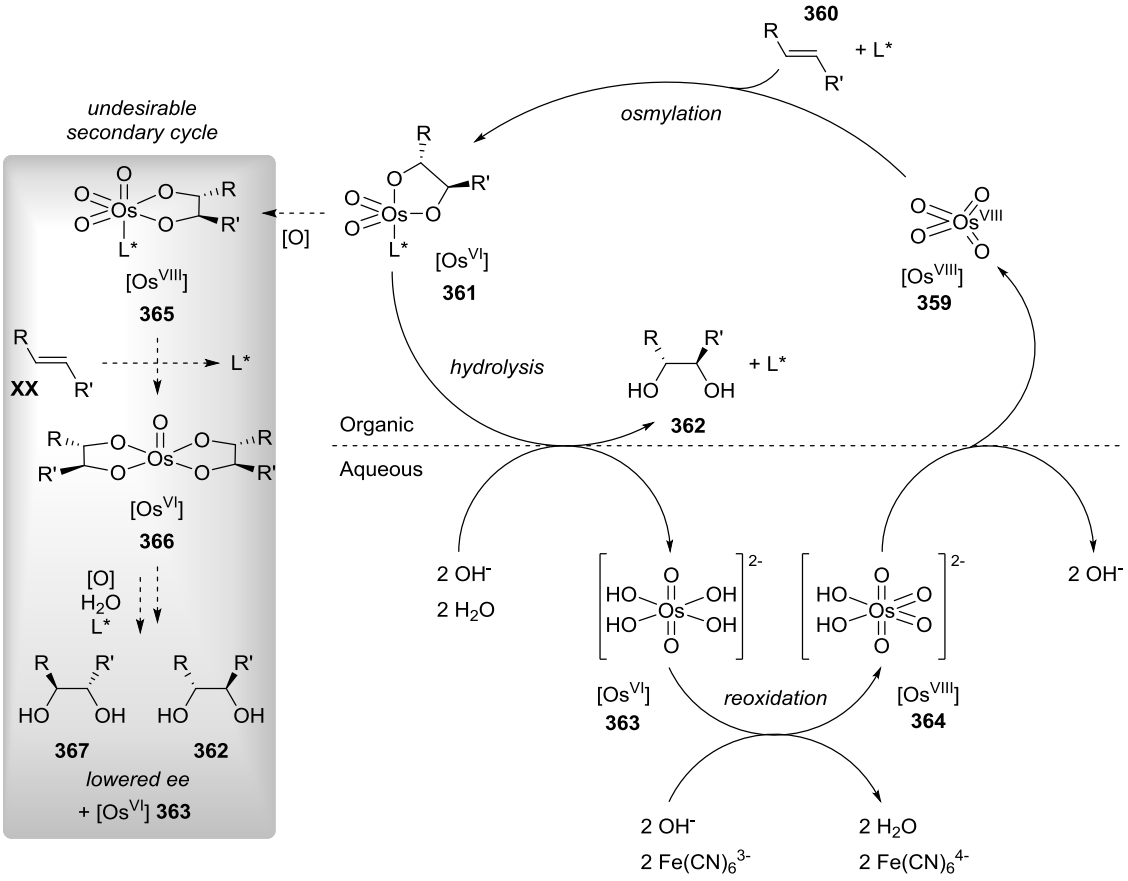


Figure 2-2: Sharpless asymmetric dihydroxylation ligands and mnemonic.

To simplify reaction set-up, Sharpless designed the combination of reagents for asymmetric dihydroxylation (AD) as mixes α and β for $(DHQ)_2PHAL$ **357** and $(DHQD)_2PHAL$ **358** respectively (typical composition: 0.4988:0.0016:0.0007 mol for $K_3Fe(CN)_6/K_2CO_3$:ligand **357** or **358**:$K_2OsO_2(OH)_4$ from Sigma Aldrich).

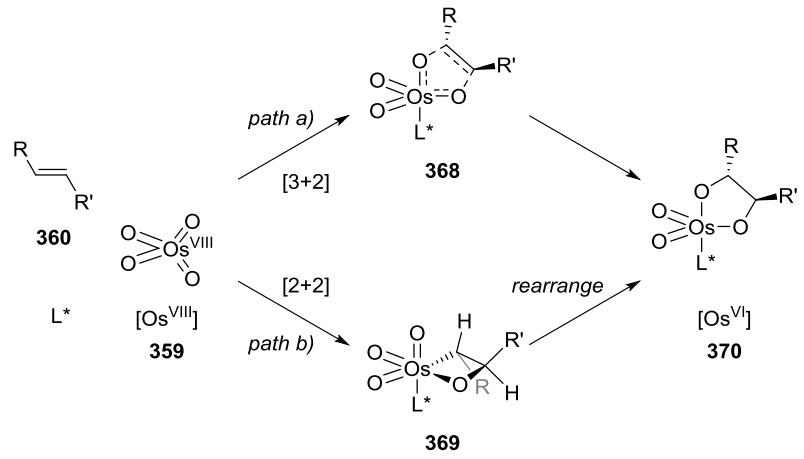
The catalytic cycle proposed for the SAD with potassium ferricyanide as the co-oxidant is shown in **Scheme 2-46**.[112, 116, 117] The osmium(VIII) tetroxide **359** forms osmate(VI)

ester **361** *via* osmylation with alkene substrate **360** and pre-coordination to the chiral ligand (L*). The osmate(VI) ester **361** is hydrolysed to release diol **362** and ligand, and the osmium(VI) species **363** is reoxidised to osmium(VIII) by the $Fe(CN)_6^{3-}$ to continue the catalytic cycle. The *tert*-butanol/water solvent system is biphasic, which boosts enantioselectivity compared to homogenous solutions because osmate(VI) ester **361** is not further oxidised by the reoxidant $Fe(CN)_6^{3-}$ as they exist in separate phases. This prevents the formation of osmate diester **366** consisting of two equivalents of the alkene starting material in the undesirable secondary cycle, which has been shown to decrease enantioselectivity and lower turnover.[116] SAD reactions are often performed in the presence of an equivalent of methanesulfonamide, particularly for non-terminal olefins, as this is proposed to enhance the rate-limiting osmate(VI) ester **361** hydrolysis.[113]



Scheme 2-46: The catalytic cycle of Sharpless asymmetric dihydroxylation.

Two mechanisms have been proposed for the osmylation step of the catalytic cycle: a concerted [3+2]-pathway (*path a*));[118-120] and a stepwise addition reaction of osmium tetroxide *via* an osmaoxetane intermediate **369** (*path b*), **Scheme 2-47**).[112, 121] There has been experimental evidence that support both *path a*)[122, 123] and *path b*),[124, 125] but the current accepted mechanism is the concerted [3+2]-pathway (*path a*)).



Scheme 2-47: Proposed mechanisms for the osmylation step of SAD.

A transition state that accounts for the enantioselectivity has also been proposed.[126-128] The ligand adopts a U-shaped geometry with the osmium coordinated to the quinuclidine nitrogen shown in **Figure 2-3a**.[128] The alkene fits into the chiral pocket and exposes one π-face to the coordinated osmium tetroxide to dihydroxylate. This led Sharpless to the proposed mnemonic (as already shown in **Figure 2-2**) where the south east, and to a lesser extent the north west, quadrants are sterically crowded and smaller substituents are preferred here. The southwest quadrant is considered to be an attractive area for flat aromatic substituents (**Figure 2-3b**).[127]

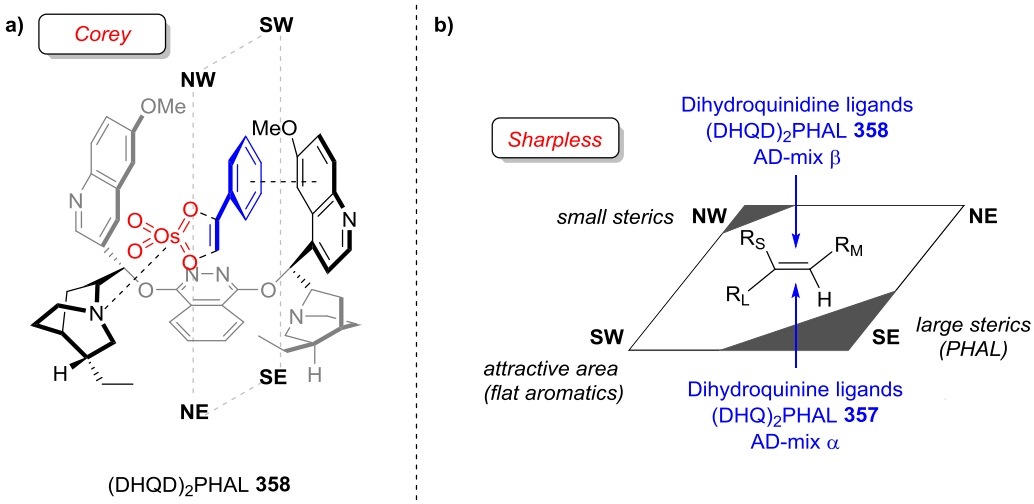


Figure 2-3: Transition state model for facial selectivity using (DHQD)$_2$PHAL **358** proposed by Corey and the mnemonic for SAD proposed by Sharpless.

However, the mnemonic has been updated using computational studies by Norrby.[129, 130] The new mnemonic proposes the northwest quadrant is open and not subject to weak crowding as Sharpless had proposed. The northeast and southwest quadrants are proposed to be attractive due to non-bonded stabilisation of substrate substituents. Additionally, the south side of the alkene is stabilised by the quinoline (**Figure 2-4**).

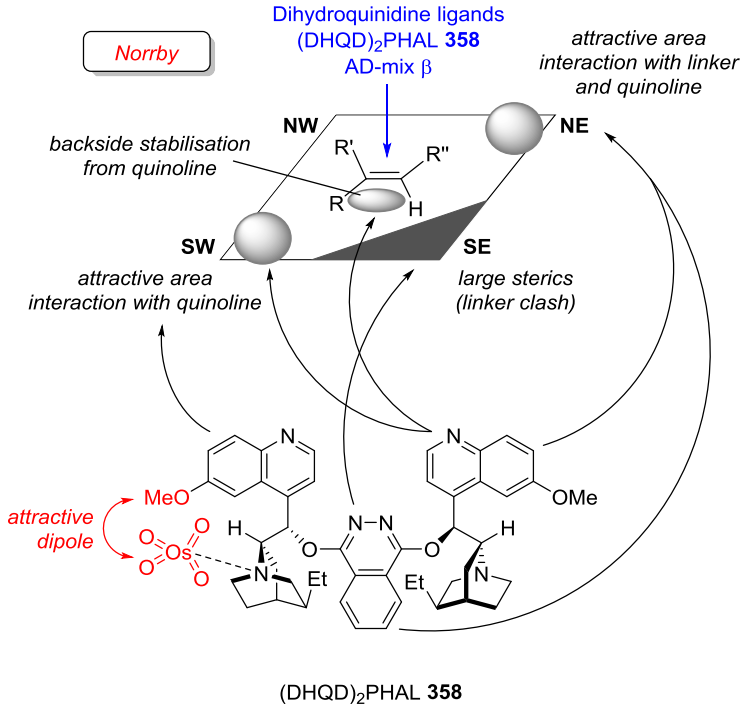
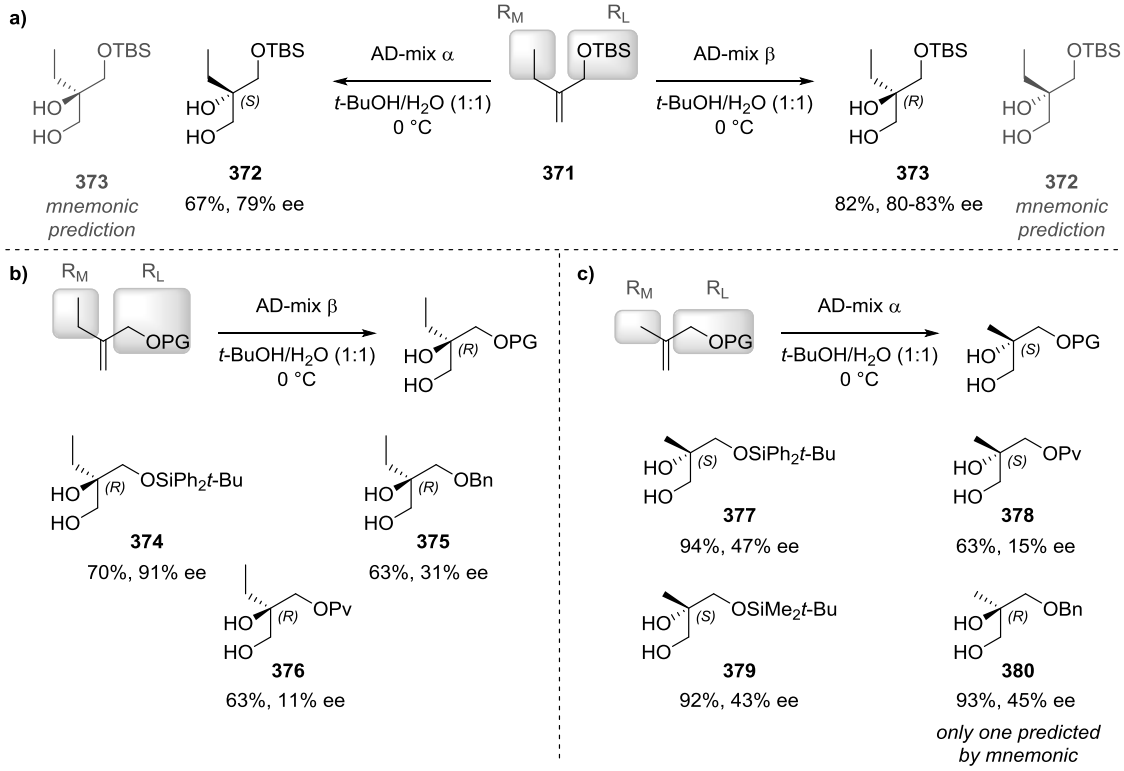


Figure 2-4: Mapped interactions of (DHQD)$_2$PHAL **358** to the mnemonic for SAD proposed by Norrby.

2.4.4.2 SAD on 1,1-disubstituted alkenes

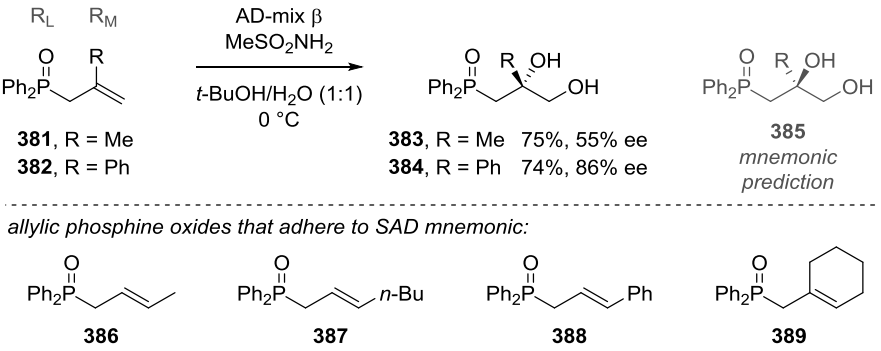
The original mnemonic developed by Sharpless[113, 127] is commonly used to predict and determine the correct stereochemistry of the diol products, and behaves well with *trans*-disubstituted alkenes. However, there have been several cases where the mnemonic has failed to predict the correct stereochemistry,[131] particularly for mono-substituted[132-135] and 1,1-disubstituted alkenes.

The first reported caveat to the SAD mnemonic for 1,1-disubstituted alkenes was discovered by Hale and co-workers in 1994.[136] Several protected allylic alcohols displayed reversed facial selectivity using the PHAL ligand class ((DHQ)$_2$PHAL **357**, (DHQD)$_2$PHAL **358**, **Scheme 2-48**). The unusual asymmetric dihydroxylation to give diol **374** was used in the synthesis of the top half of (+)-A83586C, a cyclodepsipeptide from *Streptomyces karnatakensis* by Hale,[137, 138] and in the synthesis of plakortone G by Nishiyama.[139]



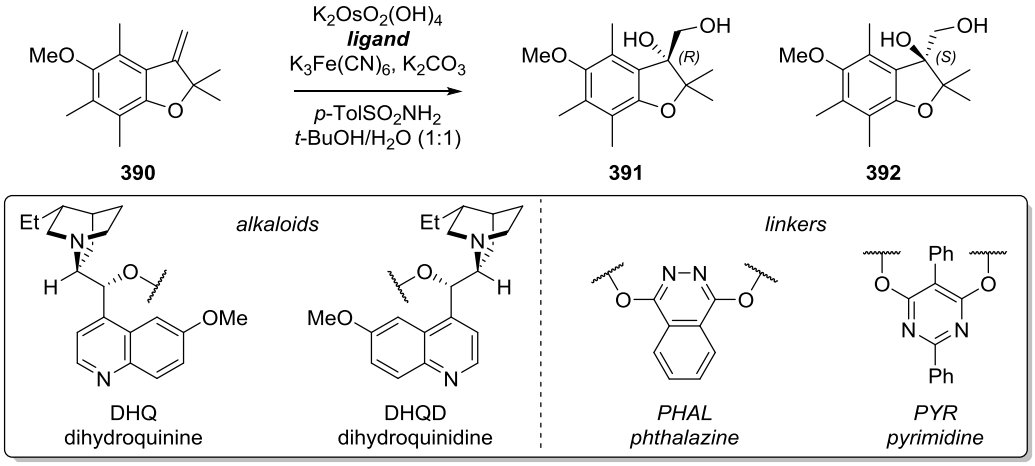
Scheme 2-48: First reported caveat to the original SAD mnemonic discovered by Hale.

Since this discovery, there have been more reports of anomalous behaviour with respect to the mnemonic. Warren reported the atypical behaviour of 1,1-*gem*-disubstituted allylic phosphine oxides;[140] where the opposite sense of asymmetric induction to that expected was observed (**Scheme 2-49**). However, other allylic phosphine oxides (**386** to **389**) conformed to the original mnemonic.



Scheme 2-49: Anomalous behaviour of 1,1-*gem*-disubstituted allylic phosphine oxides in SAD reaction.

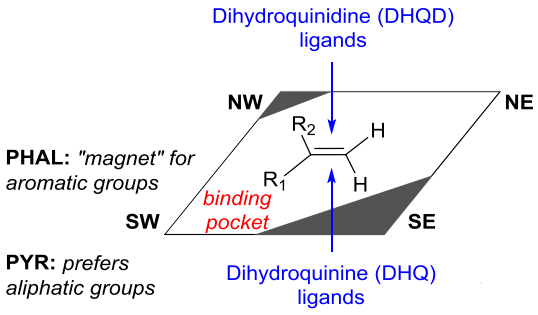
There have also been reports that changes in the linker from phthalazine to pyrimidine can change the facial selectivity. Krysan reported when using phthalazine ligands in the SAD of **390**, the compound followed the mnemonic, albeit with low enantioselectivities of 32% and 36% ee (**Table 2-4**, **entries 1** and **2**). However, swapping the linker to pyrimidine ($(DHQ)_2PYR$ and $(DHQD)_2PYR$, **entries 3** and **4**) reversed the selectivity, in contrast to the mnemonic. These reactions exhibited higher enantioselectivities: 86% and 93% ee for $(DHQ)_2PYR$ and $(DHQD)_2PYR$ respectively.[141]



Entry	Ligand alkaloid	Ligand linker	ee	Configuration	Mnemonic?
1	DHQ	PHAL	32%	*S*, **392**	Y
2	DHQD	PHAL	36%	*R*, **391**	Y
3	DHQ	PYR	86%	*R*, **391**	N
4	DHQD	PYR	93%	*S*, **392**	N

Table 2-4: Experimental results of switching ligand linkers in the SAD reaction by Krysan.

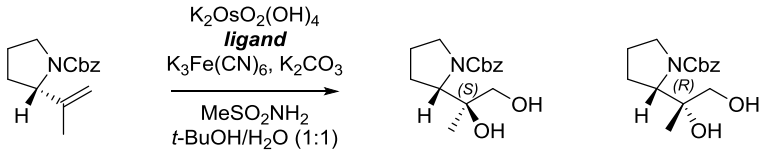
In light of these caveats, Vanhessche and Sharpless modified the mnemonic for PHAL and PYR ligands ($(DHQ)_2PHAL$, $(DHQD)_2PHAL$ and $(DHQ)_2PYR$, $(DHQD)_2PYR$) for mono- and 1,1-disubstituted alkenes based upon their own experimental observations (**Figure 2-5**).[142] The SW quadrant was referred to as a binding pocket for either aromatic groups when using PHAL ligands ($(DHQ)_2PHAL$, $(DHQD)_2PHAL$), or for aliphatic groups when PYR ligands ($(DHQ)_2PYR$, $(DHQD)_2PYR$) were used. Taken together with preference for hydrogen to occupy the sterically hindered SE quadrant, this would explain the switch in enantiofacial selectivity when changing between these ligand classes and dihydroxylating the same substrate, as demonstrated by Krysan.[141]



Substitution	Best Ligand
R_1 = aromatic R_2 = H	PHAL
R_1 = aliphatic R_2 = H	PYR
R_1 = aromatic R_2 = aliphatic	PHAL
R_1 = aliphatic R_2 = aromatic	PYR

Figure 2-5: Proposed mnemonic for SAD on mono- and 1,1-disubstituted alkenes proposed by Sharpless.

However, this new model for 1,1-disubstituted alkenes failed for proline-derived 1,1-disubstuted alkene **393** reported by Gardiner.[143] Both $(DHQ)_2PHAL$ **357** and $(DHQD)_2PHAL$ **358** ligands in the SAD reaction produced diol **394** as the major diastereomer (**Table 2-5**, **entries 2** and **3**). However, $(DHQ)_2PYR$ and $(DHQD)_2PYR$ produced the diols predicted by Sharpless' original model (**entries 3** and **4**).



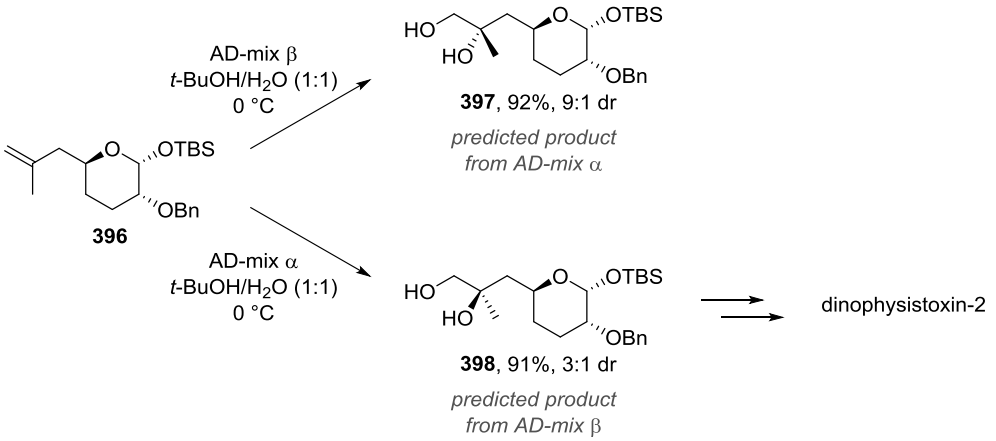
393 **394** **395**

Entry	Ligand	**394**:**395**	Mnemonic?
1	$(DHQ)_2PHAL$	1.9:1	Y
2	$(DHQD)_2PHAL$	3.5:1	N
3	$(DHQ)_2PYR$	1.8:1	Y
4	$(DHQD)_2PYR$	1:2.5	Y

Table 2-5: Atypical facial selectivity of the SAD reaction on proline-derived alkene **393**.

Forsyth and co-workers reported unusual reversal in selectivity in their synthesis of dinophysistoxin-2.[144] When dihydroxylating alkene **396**, they found that the β-mix of SAD produced undesired diol **397** in 9:1 dr, despite predicting desired diol **398**. Indeed, the use of α-mix furnished diol **398** in 3:1 dr (**Scheme 2-50**). They hypothesised the levels

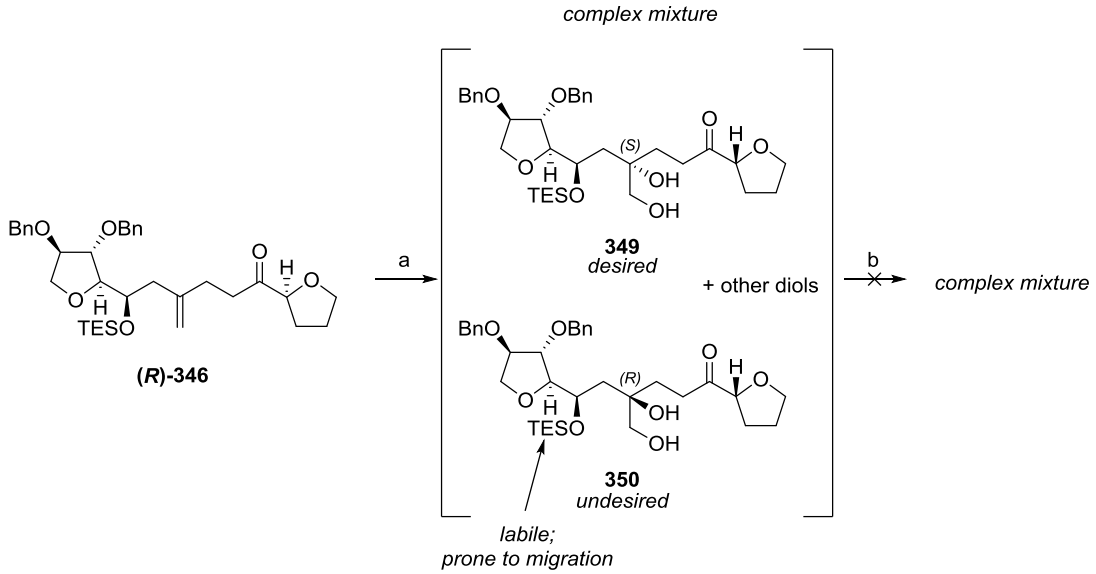
of diastereoselectivity of AD-mix β compared to α may represent matched and mismatched diastereomeric transition states respectively.



Scheme 2-50: Unusual reversal of facial selectivity in the synthesis of dinophysistoxin-2 by Forsyth.

2.4.4.3 Results & Discussion: SAD and acid-catalysed cyclisation to form the D ring

These anomalies demonstrate that it is difficult to predict the facial selectivity of SAD, for the dihydroxylation of the proposed 1,1-disubstituted alkene **(*R*)-346**. To analyse if there was an inherent substrate bias towards a particular face of **(*R*)-346**, Upjohn dihydroxylation conditions[145] were employed to dihydroxylate **(*R*)-346**. Purification and separation of the diol(s) generated was difficult because the TES-group appeared to migrate, which resulted in a complex mixture. Based upon work done in the group previously where the cyclisation of a similar diol could be achieved with a catalytic amount of 4 M HCl in dioxane without prior purification,[67] it was decided to perform the dihydroxylation, deprotection and cyclisation sequentially without prior purification of intermediates. However, this sequence resulted in a complex mixture of products without the identification of the desired D ring structure (**Scheme 2-51**). Nevertheless, some of the products contained a peak at 105.6 ppm in the ^{13}C NMR (126 MHz, C_6D_6) spectrum which could represent the acetal quaternary carbon centre.[49, 62]



Scheme 2-51: Attempted Upjohn dihydroxylation and cyclisation sequence of **(*R*)-346**.
Reagents and conditions: a) $K_2OsO_2(OH)_4$, NMO, acetone/H_2O (4:1); b) 4 M HCl in dioxane, THF.

Despite this failure, we pursued the SAD/cyclisation route, in the hope that enforcing facial selectivity would create fewer potential products. Based upon the mnemonics proposed by Sharpless (both general[113] and for 1,1-disubstituted alkenes)[142] and Norrby (modified from Sharpless for general alkenes),[146] $(DHQ)_2PHAL$ ligands (AD-mix α) should provide the desired facial selectivity (**Figure 2-6**). However, because the mnemonics often are not accurate for 1,1-disubstituted alkenes, both AD-mixes α and β were investigated.

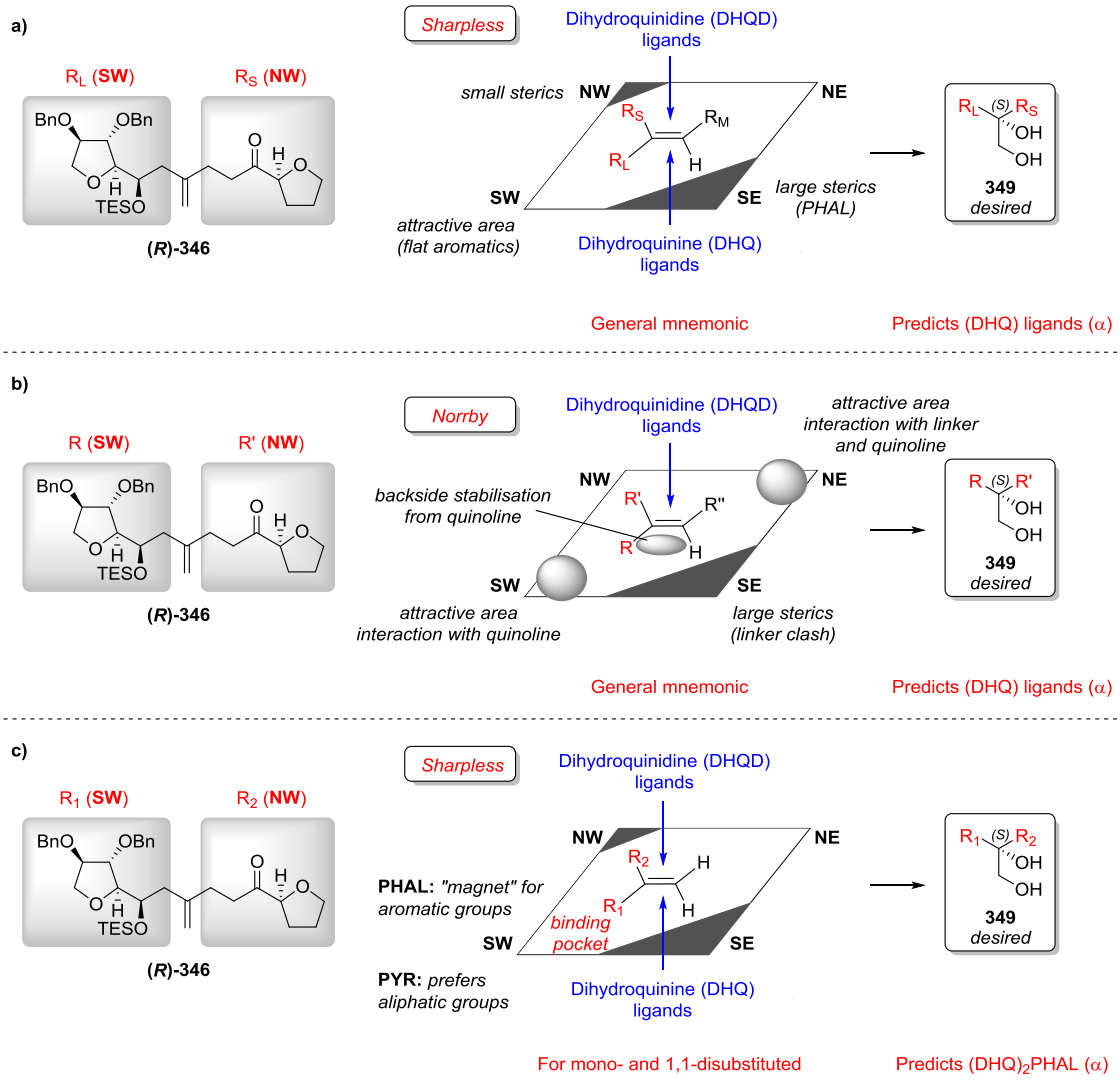
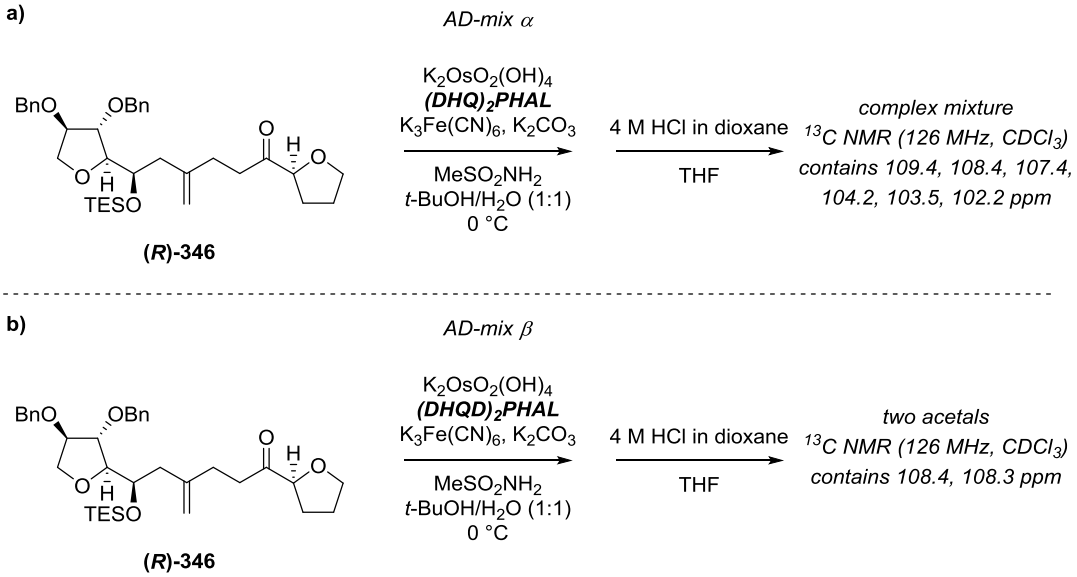


Figure 2-6: Analysis of the mnemonics proposed by Sharpless (**a)** and **c)**) and Norrby (**b)**) to predict the ligands to achieve the desired SAD product **349** of **(*R*)-346**.

Subjecting **(*R*)-346** to AD-mix α conditions followed by deprotection/cyclisation with 4 M HCl in dioxane produced a complex mixture of products with several peaks in the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum that could represent an acetal carbon (109.4, 108.4, 107.4, 104.2, 103.5, 102.2 ppm; **Scheme 2-52a**).

However, the use of AD-mix β to dihydroxylate **(*R*)-346** followed by the same deprotection/cyclisation sequence afforded a mixture of two bicyclic acetal systems, based upon the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum (108.4, 108.3 ppm for the acetal

carbons; **Scheme 2-52b**). Unfortunately, the two potential acetals could not be identified from the mixture.

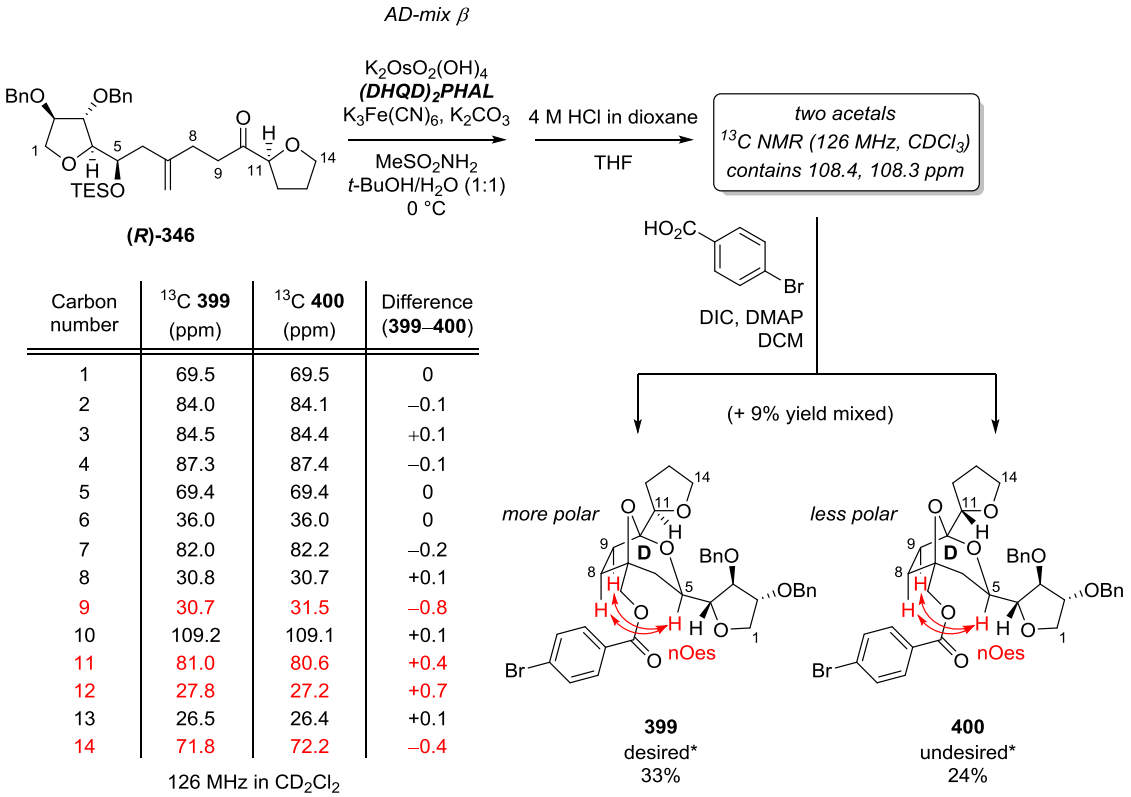


Scheme 2-52: First attempts at SAD reaction on **(*R*)-346**.

It was decided to derivatise the mixtures of products in an attempt to i) separate them by decreasing the polarity of the respective compounds; and ii) make the compounds crystalline to obtain X-ray crystal structures to confirm stereochemical assignments. As the AD-mix β reaction was less complicated, this mixture of compounds was derivatised with 4-bromobenzoic acid, in order to form esters with the free hydroxyl group of the possible bicyclic acetals.

Pleasingly, after derivatisation, the two acetals could be separated to give a 24% yield of a lower-polarity compound and a 33% yield of a higher-polarity compound (with 9% isolated as a mixture of the two), although neither ester was crystalline (**Scheme 2-53**). Upon careful analysis of the NMR spectra in different NMR solvents ($CDCl_3$, C_6D_6, CD_2Cl_2), it was revealed the two acetals contained the same connectivity (COSY/HSQC/HMBC), and both had nOes from C-5H to the other side of the ring (C-8 and C-9) suggesting the same bicyclic acetal structure despite their differences in the

NMR spectra for each compound (see **Appendix 6.2.2** and **6.2.3**). Examining at the differences in the ^{13}C NMR spectra (the table in **Scheme 2-53**), the larger differences were observed around C-11 suggesting that this carbon configuration (originally α to the ketone) had epimerised under the reaction conditions, probably upon treatment with the 4 M HCl in dioxane cyclisation step. This was not observed in the previous model as an α-keto proton was not present.[67] Variable temperature NMR experiments showed these acetals **399** and **400** do not interconvert.

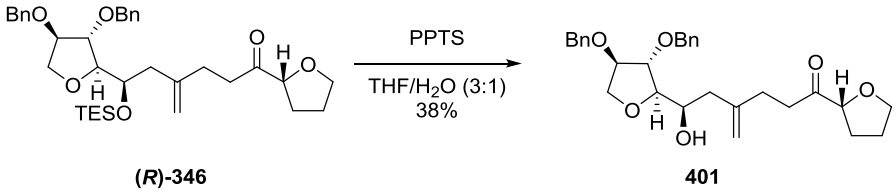


Carbon number	^{13}C **399** (ppm)	^{13}C **400** (ppm)	Difference (**399**–**400**)
1	69.5	69.5	0
2	84.0	84.1	–0.1
3	84.5	84.4	+0.1
4	87.3	87.4	–0.1
5	69.4	69.4	0
6	36.0	36.0	0
7	82.0	82.2	–0.2
8	30.8	30.7	+0.1
9	30.7	31.5	–0.8
10	109.2	109.1	+0.1
11	81.0	80.6	+0.4
12	27.8	27.2	+0.7
13	26.5	26.4	+0.1
14	71.8	72.2	–0.4

Scheme 2-53: Derivatisation of AD-mix β acetal mixture from **(*R*)-346**, with a table comparing the ^{13}C NMR (126 MHz, CD_2Cl_2) peaks of the two acetals **399** and **400**. The red entries in the table highlight the larger differences in ^{13}C peak values.

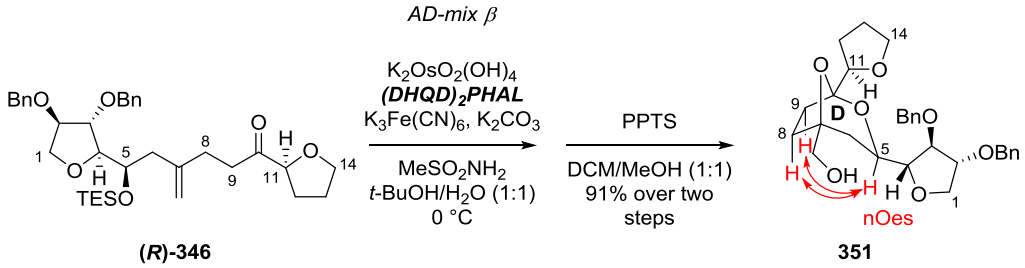
With the potential for epimerisation at C-11 α to the ketone before acetalisation complicating analysis of the bicyclic structures, possibly due to the overly acidic conditions, an alternative deprotection/cyclisation sequence was investigated. Taking inspiration from Evans' synthesis of PTX-4,[23, 49] PPTS was utilised. To simplify the

reaction sequence, the TES protecting group of **(*R*)-346** was removed with PPTS. Gratifyingly, the TES group could be removed, albeit in a moderate yield of 38%, by exposure to PPTS in THF/H_2O (**Scheme 2-54**).



Scheme 2-54: Test reaction of PPTS removal of TES group of **(*R*)-346**.

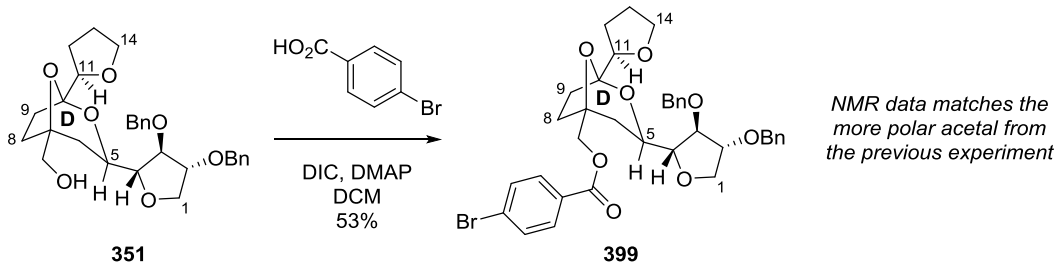
With this promising result, the SAD of **(*R*)-346** with AD-mix β followed by treatment with PPTS was attempted. Pleasingly, only one bicyclic acetal was isolated in 91% yield and this compound was confirmed to be the desired D ring acetal **351** by NMR analysis (**Scheme 2-55**). A NOESY spectrum in CD_2Cl_2 identified the same nOes as the acetals **399** and **400** (see **Appendix 6.2.1**). It was presumed that the use of the weaker acid PPTS avoided epimerisation of C-11, resulting in the desired bicyclic acetal **351**. Re-subjecting acetal **351** to the 4 M HCl conditions showed that the acetal was stable once it had formed, and no observable epimerisation occurred.



Scheme 2-55: Successful attempt at synthesising the desired bicyclic acetal D ring **351** from **(*R*)-346**.

To confirm this structure did indeed correspond to one of the acetal derivatives **399** and **400**, the acetal **351** was esterified with 4-bromobenzoic acid in 53% yield (**Scheme 2-56**). The NMR spectra of this acetal matched the data obtained from the original SAD/cyclisation reaction involving HCl, supporting the hypothesis that the HCl

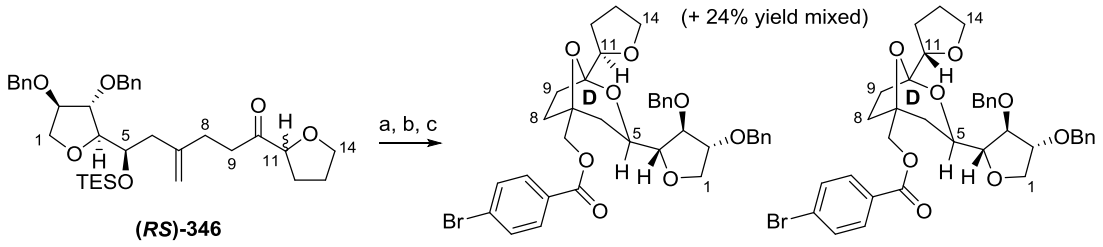
conditions were responsible for epimerisation at the α-keto C-11 position before cyclisation.



351 **399**

Scheme 2-56: Derivatisation of the unepimerised acetal **351**. NMR data matches derivatised acetal **399** from **Scheme 2-53**.

To confirm the hypothesis, **(*RS*)-346** was subjected to the AD-mix β and PPTS conditions (**Scheme 2-57**). Pleasingly, the data for the two acetals matched the NMR data of acetals **399** and **400** isolated from the reaction of **(*R*)-346** with the AD-mix β/4 M HCl in dioxane in **Scheme 2-53**. This confirms the hypothesis that the HCl conditions were causing epimerisation at C-11 before cyclisation, and therefore PPTS should be used for future cyclisation reactions.



(*RS*)-346

399
desired
30%

400
undesired
18%

Scheme 2-57: Derivatisation of AD-mix β acetal mixture from **(*RS*)-346**.
Reagents and conditions: a) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C; b) PPTS, DCM/MeOH (1:1); c) 4-bromobenzoic acid, DIC, DMAP, DCM.

Repeating the dihydroxylation/cyclisation sequence with AD-mix α on **(*R*)-346** furnished a complex mixture of compounds which could not be identified. The peaks in the ^1H NMR spectrum did not match with peaks in the spectrum of the desired D ring acetal **351** (**Figure 2-7**).

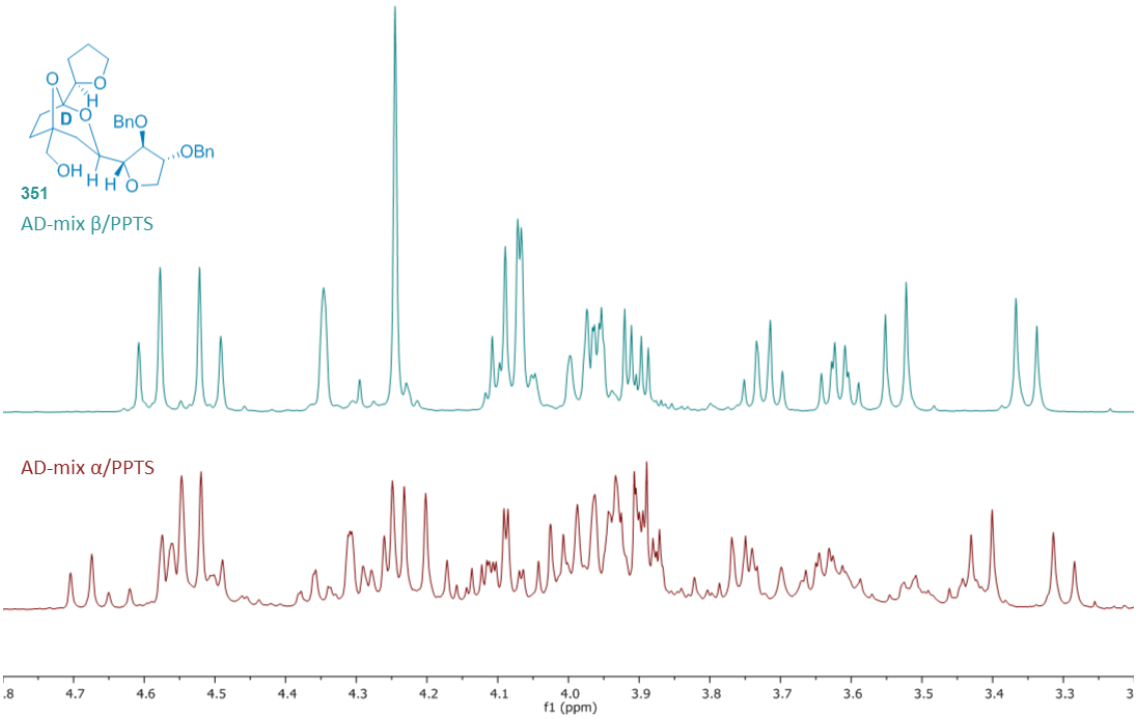
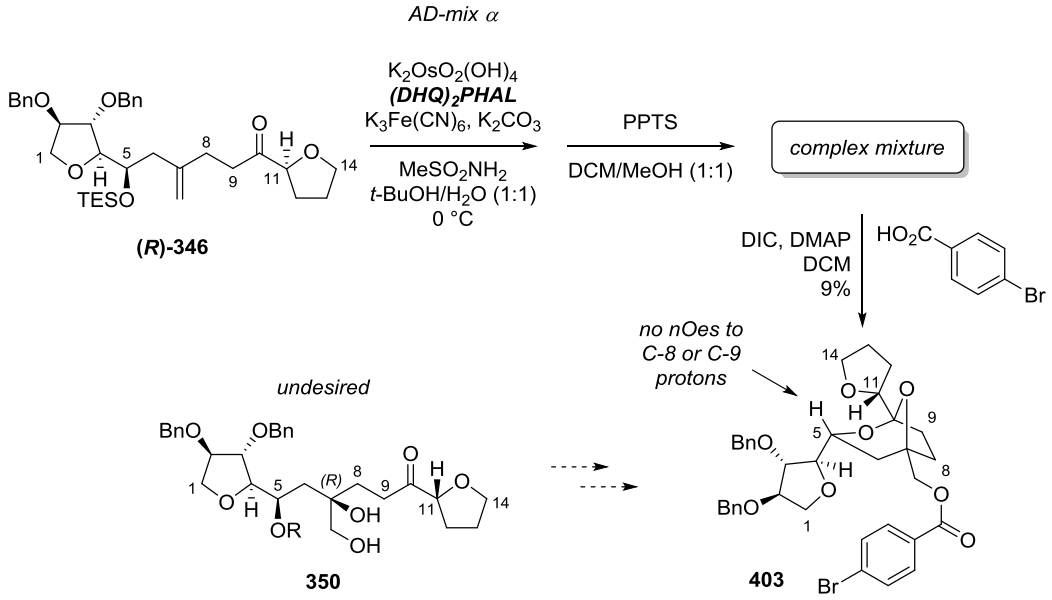


Figure 2-7: ^{1}H NMR (400 MHz, C_6D_6, 4.80 ppm to 3.20 ppm) comparing the desired D ring acetal **351** from AD-mix β and the mixture of compounds isolated from AD-mix α.

However, upon derivatisation of this mixture with 4-bromobenzoic acid, the only identifiable acetal product (isolated in 9% yield) was not the same as either acetals **399** or **400** previously identified. After careful analysis of the NMR data, the connectivity appeared to be the same as for the previous acetals **399** and **400** by COSY/HSQC/HMBC. However, there was no nOe from C-5H to the other side of the ring (C-8 or C-9 protons, see **Appendix 6.2.4**), suggesting that bicyclic acetal **403** is produced upon derivatisation of the product arising from the undesired diol **350** (**Scheme 2-58**).



Scheme 2-58: Derivatisation of AD-mix α reaction mixture using PPTS for the cyclisation step.

Interestingly, this type of bicyclic acetal has not been reported in the synthesis of the D ring of the PTXs. Brimble had proposed that steric strain in the cyclisation process, coupled with facile degradation during purification (by HPLC) of other bicyclic acetal isomers prevents other structural isomers from being identified.[62] A comparison of the ^{1}H NMR data for of each of the functionalised bicyclic acetals is shown in **Figure 2-8**.

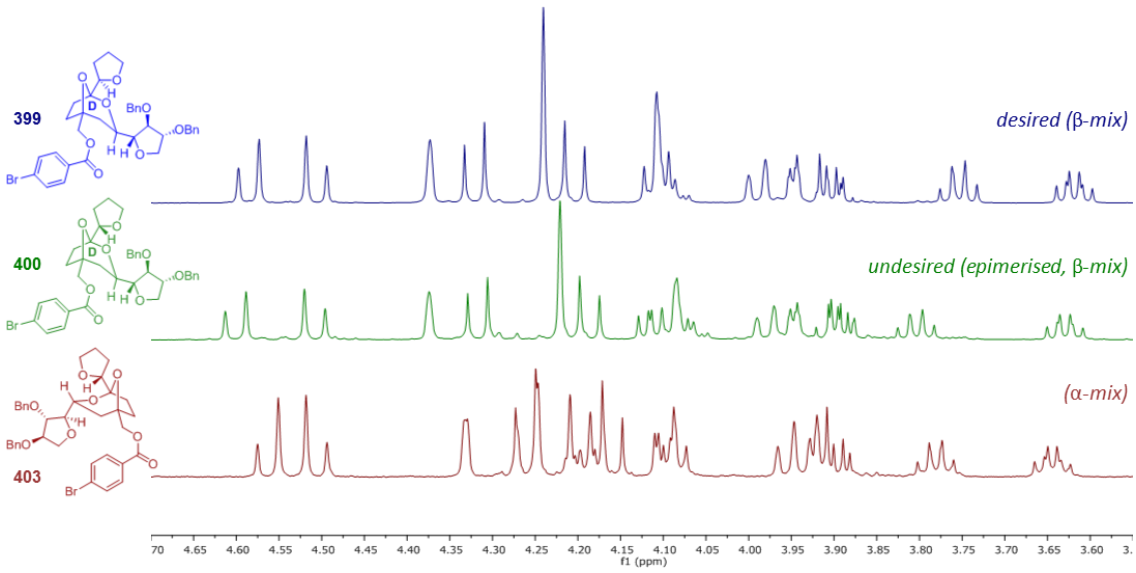
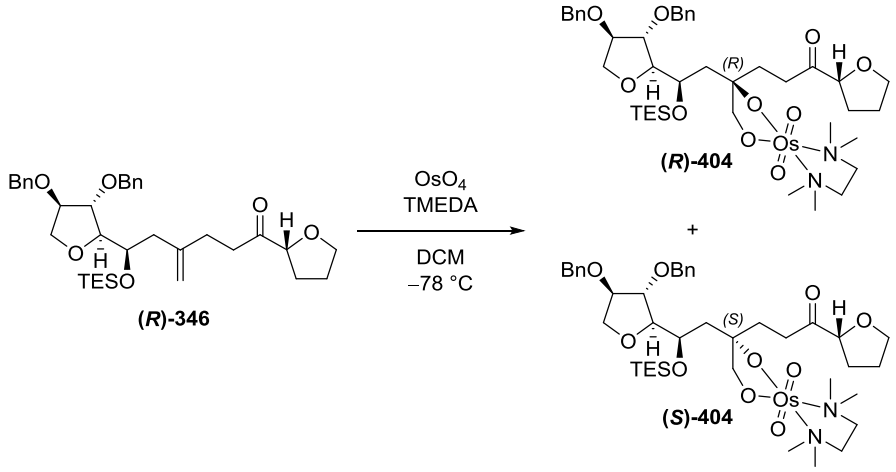


Figure 2-8: Comparison of the ^{1}H NMR (500 MHz, C_6D_6, 4.70 ppm to 3.55 ppm) of the functionalised acetals **399** (desired, from AD-mix β), **400** (undesired, from AD-mix β with epimerisation at C-11) and **403** (from AD-mix α).

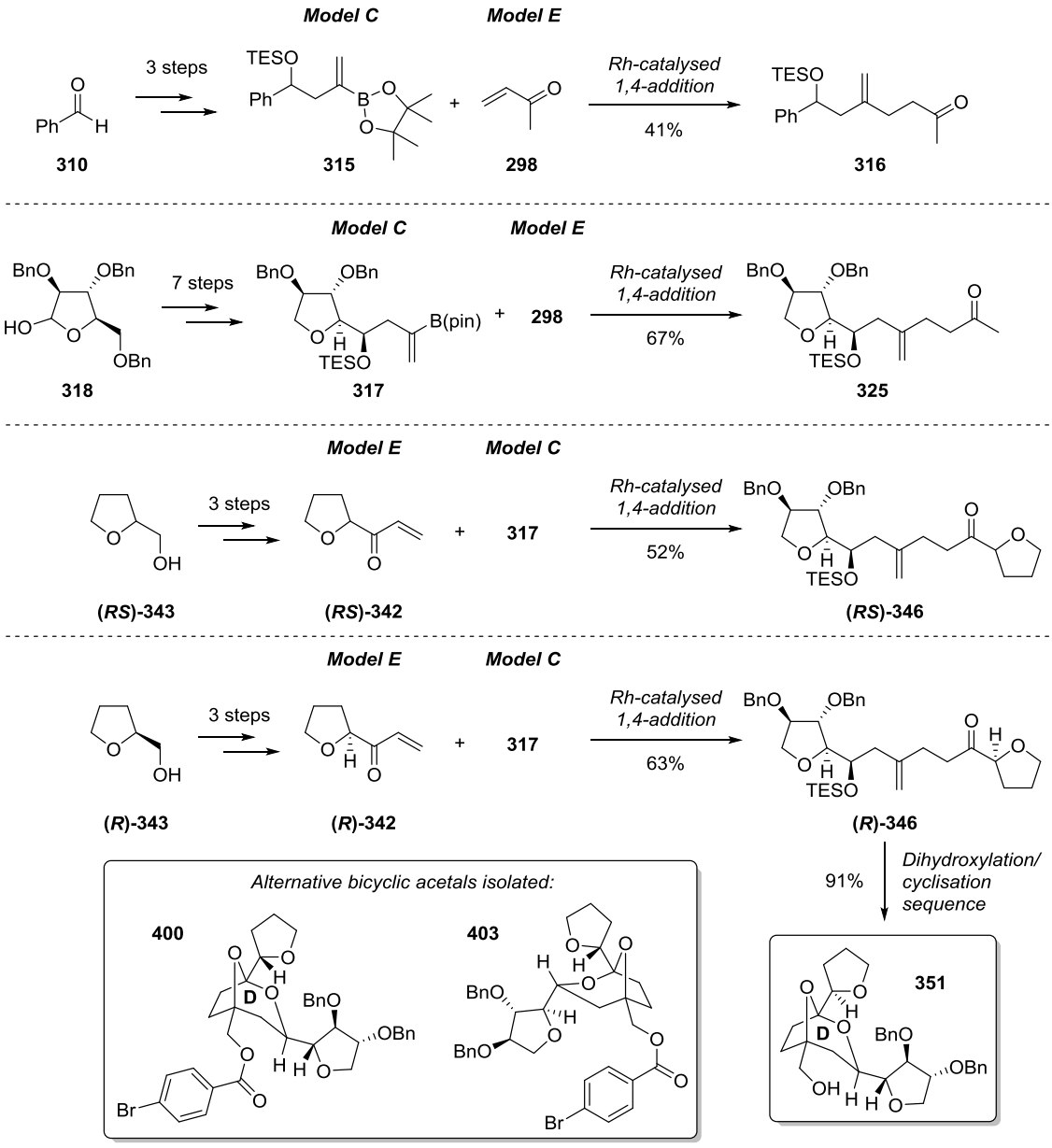
In an attempt to unequivocally identify what happens to each of the isomers **349** and **350**, **(*R*)-346** was osmylated with OsO_4 and TMEDA to form the osmate ester complexes **(*R*)-404** and **(*S*)-404**, which were separable *via* preparative TLC (**Scheme 2-59**).[147] It was hoped these would be crystalline enough to determine the stereochemistry at C-7, and could be decomplexed[148] separately to determine the fate of each isomer. Unfortunately, an X-ray crystal structure could not be successfully obtained for either complex **(*R*)-404** or **(*S*)-404**.



Scheme 2-59: Synthesis of osmate esters **(*R*)-404** and **(*S*)-404**.

2.5 Conclusions

The rhodium-catalysed 1,4-addition step has proven to work with increasingly more complex model systems and appears to be a good C–C bond bond-forming method for our synthesis of PTX-4 (**Scheme 2-60**). Utilising tetrahydrofuran rings as models for the C and E rings of PTX-4 in our model substrate **(*R*)-346** permitted the synthesis of the desired D ring structure **351** by a dihydroxylation/cyclisation sequence. During this process, we have observed the opposite facial selectivity of the SAD reaction of **(*R*)-346**, identified other bicyclic acetals through functionalisation with 4-bromobenzoic acid (**400** and **403**), and have identified suitable cyclisation conditions using PPTS to avoid epimerisation of the α-keto centre.



Scheme 2-60: Summary of **Chapter 2**.

Chapter 3

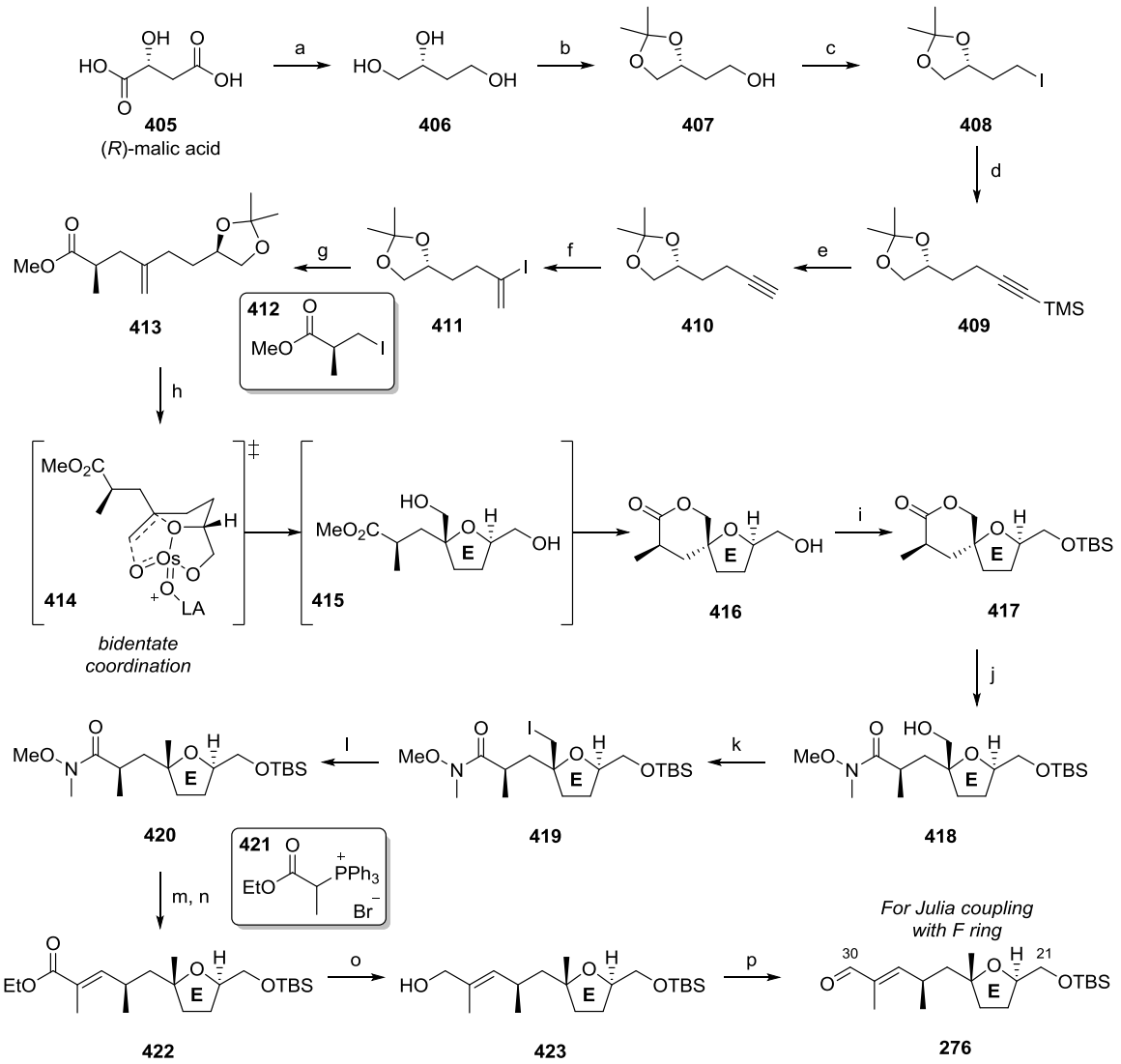
Chapter 3: Synthesis of the desired E ring fragment

As outlined in **Chapter 2**, the D ring bicyclic acetal structure was successfully synthesised using a model system. This chapter outlines our current synthesis of the E ring and the elaborations on the E ring side chain to utilise the rhodium-catalysed 1,4-addition reaction and dihydroxylation/cyclisation sequence described in **Chapter 2**.

3.1 Donohoe's synthesis of the E ring

Our next challenge was to expose the real E ring fragment to the conditions described in **Chapter 2** to synthesise the D ring. The model C ring boronate **317** was still to be used as opposed to the real ABC fragment in order to simplify the task at hand.

The Donohoe group's synthesis of the E ring was developed by Dr Paul Winship and Dr Yifan Liu and was published recently.[43, 68, 69] The E ring fragment **276**, used in the Julia coupling[66] to the F ring sulfone (which will be discussed in **Chapter 4**), was synthesised in 16 steps from (*R*)-malic acid **405** (**Scheme 3-1**). Reduction with borane dimethyl sulfide to triol **406** followed by acetal protection of the 1,2-diol afforded acetonide **407** in 81% yield over two steps. An Appel reaction on the unprotected primary alcohol of **407** with iodine provided iodide **408** in 90% yield. Alkynylation with trimethylsilylacetylene, followed by removal of the TMS group provided terminal alkyne **410** in 92% yield over two steps. A nickel-catalysed hydroalumination and iodination reaction developed by Hoveyda[105] allowed regioselective formation of the α-vinyl iodide **411**. Negshi coupling of **411** with **412** (derived from an Appel reaction on (*R*)-Roche ester/methyl (*R*)-(−)-3-hydroxy-2-methylpropionate) afforded adduct **413** in 90% yield.



Scheme 3-1: Donohoe's synthesis of the E ring developed by Dr Paul Winship and Dr Yifan Liu. *Reagents and conditions:* a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF; b) 2,2-dimethoxypropane, PTSA, acetone, 81% over two steps; c) I_2, PPh_3, imidazole, Et_2O/MeCN (25:8), 90%; d) trimethylsilylacetylene, *n*-BuLi, DMPU; e) K_2CO_3, MeOH, 92% over two steps; f) Ni(dppp)Cl_2, DIBAL-H, NIS, THF, 87%; g) **412**, Zn/Cu, benzene/DMA (10:1), 45 °C then $Pd(PPh_3)_4$, benzene/HMPA (10:1), 80 °C, 90%; h) $K_2OsO_2(OH)_4$, PNO, $Sc(OTf)_3$, citric acid, MeCN/H_2O (3:2); i) TBSCl, imidazole, DMAP, DCM, 69% over two steps; j) MeNHOMe·HCl, $AlMe_3$, THF, 99%; k) I_2, PPh_3, imidazole, PhMe, 79%; l) Pd/C, H_2, Et_3N, MeOH, 98%; m) DIBAL-H, THF, –78 °C; n) **421**, *n*-BuLi, benzene, 88% over two steps; o) $LiEt_3BH$, DCM, –78 °C, 92%; p) DMP, $NaHCO_3$, DCM (assumed quant. as used crude).

The key step was osmium-mediated oxidative cyclisation to afford the *cis*-tetrahydrofuran **416**, followed by TBS protection of the primary alcohol in 69% yield over two steps. The acidic conditions utilised in the cyclisation reaction were enough to deprotect the diol to allow for chelation to the osmium and thus provide the *cis*-stereochemistry, as shown in the transition state **414**. Pyridine *N*-oxide is a necessary reoxidant in the reaction as it oxidises Os(IV) to Os(VI) in the catalytic cycle but prevents the formation of unwanted Os(VIII)

which would dihydroxylate double bonds instead.[45] The initially formed diol **415** cyclises onto the methyl ester spontaneously *in situ* to generate lactone **416**, the free hydroxyl group of which is then protected with TBSCl. Nucleophilic opening of the lactone with *N*,*O*-dimethylhydroxylamine hydrochloride formed the Weinreb amide **418** in 99% yield. A two-step procedure to deoxygenate the primary alcohol **418** to form the methyl group **420** *via* the iodide **419** was accomplished in 77% yield over two steps. Reduction of the amide followed by a Wittig reaction generated the desired (*E*)-alkene **422** in 88% yield. Finally, a reduction of the ethyl ester with Super-Hydride® to the corresponding alcohol **423** and oxidation back to aldehyde **276** generated the desired fragment for the Julia coupling[66] with the F ring sulfone.

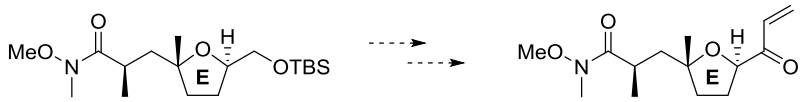
Dr Yifan Liu had prepared a significant amount of **420** to use for further studies,[68] and this sequence has recently been repeated by co-worker Timothy Kwok up to this compound,[48] which was the E ring fragment used for further modifications discussed in this chapter.

3.2 Results & Discussion: Modifications of the E ring side chain

3.2.1 Weinreb amide E ring enone

3.2.1.1 Synthesis of the Weinreb amide E ring enone

With E ring fragment **420** in hand, our attention turned to elaborating the TBS-protected alcohol into enone **424** for the rhodium-catalysed 1,4-addition reaction.

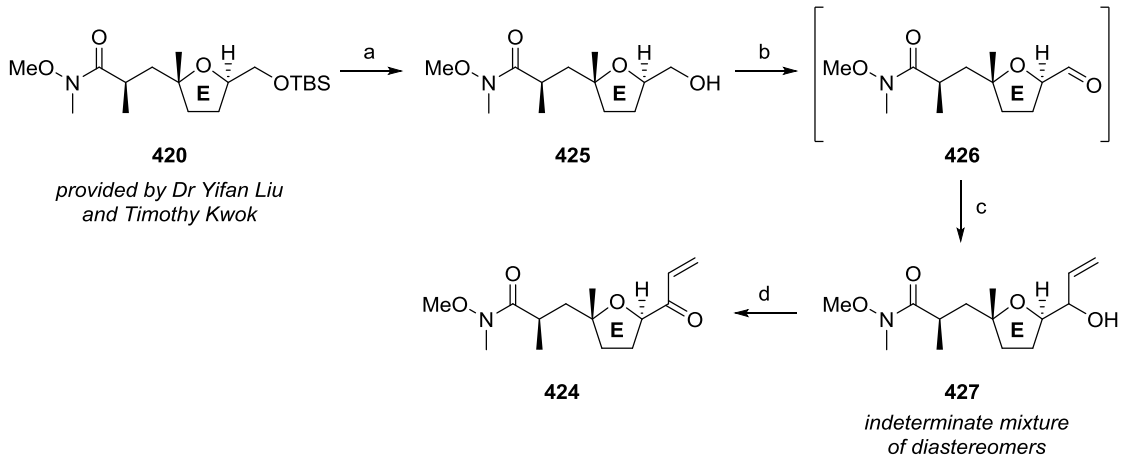


420 **424**

Scheme 3-2: Proposed E ring enone **424** to synthesis for the rhodium-catalysed 1,4-addition.

Enone **424** was prepared in four steps from E fragment **420** (**Scheme 3-3**). The TBS group of **420** was removed using TBAF which resulted in 96% yield of alcohol **425**. A Parikh–Doering oxidation to aldehyde **426** followed by the addition of vinyl magnesium bromide

provided vinyl alcohol **427** in 69% yield as an indeterminable mixture of diastereomers at the hydroxyl-bearing stereoentre. Finally, oxidation using DMP afforded E ring enone **424** in 53% yield (unoptimised).



Scheme 3-3: Synthesis of E ring enone **424**.
Reagents and conditions: a) TBAF, THF, 0 °C, 96%; b) SO_3·py, Et_3N, DMSO, DCM, 0 °C; c) vinyl magnesium bromide, Et_2O, 0 °C, 69% over two steps; d) DMP, DCM, 53%.

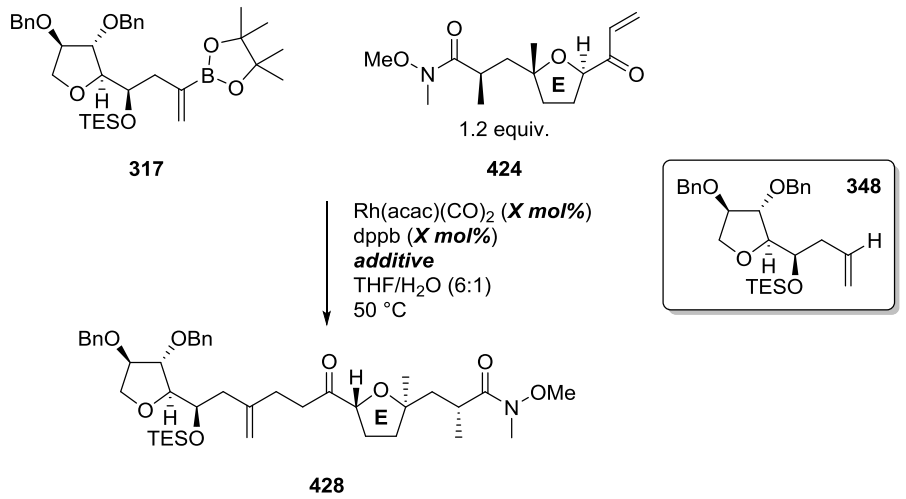
3.2.1.2 Attempts to perform the rhodium-catalysed 1,4-addition with model C ring

Using the conditions developed in **Chapter 2**, we subjected model C ring boronate **317** and E ring enone **424** to the rhodium-catalysed 1,4-addition reaction. However, the desired product **428** was not formed (**entry 1**, **Table 3-1**). Interestingly, no protodeborylated by-product **348** was detected in this reaction, which is often observed if the reaction is not successful. This suggested the rhodium catalyst was not transmetallating with the boronate. However, the batch of catalyst had not degraded because it was used to successfully repeat reactions which were known to work.

Our hypothesis was that the Weinreb amide could sequester the rhodium catalyst, despite evidence that Weinreb amides can participate in rhodium-catalysed 1,4-addition reactions.[149] To test the hypothesis, the reaction was repeated with an increased catalyst loading. A small amount of product was isolated from the reaction when the catalyst loading

was increased to 120 mol%, and trace amounts of deborylated starting material **348** were formed (**entry 2**), supporting the proposed hypothesis.

An attempt was made to out-compete the rhodium for complexation to the Weinreb amide by addition of magnesium chloride (**entry 3**). However, this approach was not successful. It was clear the E ring enone **424** was not a suitable substrate to use in this reaction and other E ring enones with alternative side chains should be examined.



Entry	**X** mol%	Additive	Yield **428**	Yield **348**
1	10	-	0%	None observed
2	**120**	**-**	**6%**	**Trace**
3	10	$MgCl_2$ (1.1 equiv.)	0%	None observed

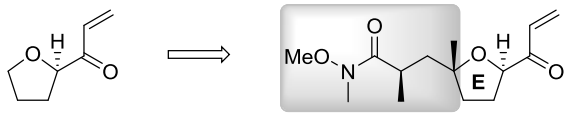
Table 3-1: Attempts at the rhodium-catalysed 1,4-addition reaction with model C ring boronate **317** and E ring enone **424**.

3.2.2 Methyl ketone E ring enone

3.2.2.1 Synthesis of the methyl ketone E ring enone

Comparing the differences between **(*R*)-342** (which worked in the rhodium-catalysed 1,4-addition reaction with model C ring boronate **317**) and E ring enone **424** (which did not), the only change was the addition of the side chain containing the Weinreb amide (**Figure 3-1**). As stated in **Chapter 3.2.1.2**, we proposed the rhodium catalyst was being sequestered

by the Weinreb amide functionality. However, the steric bulk of the side chain highlighted could also affect the reactivity of the enone.

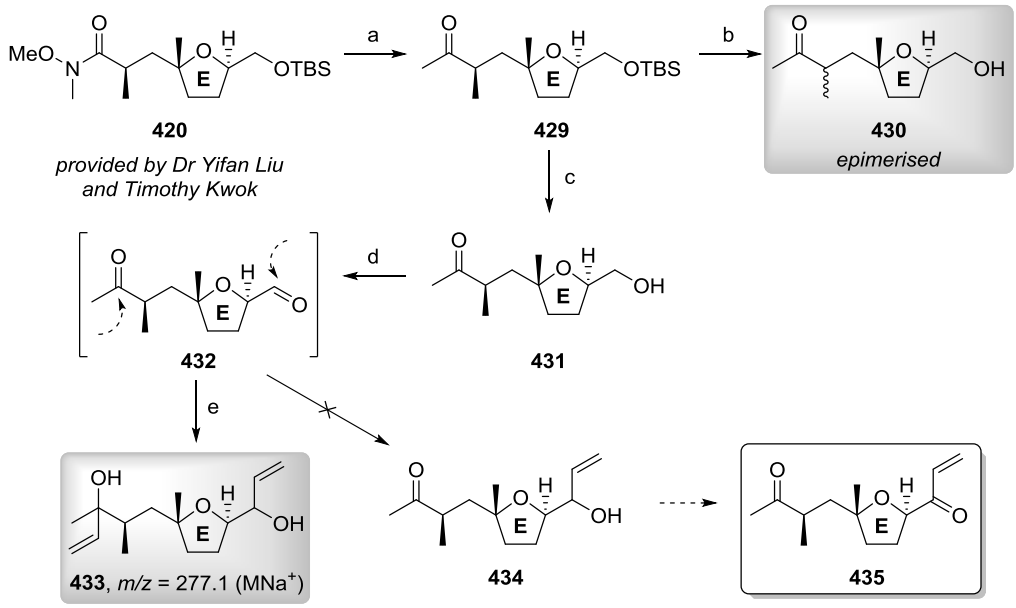


(*R*)-342 424

Figure 3-1: Comparing the differences in structure with **(*R*)-342** and E ring enone **424**.

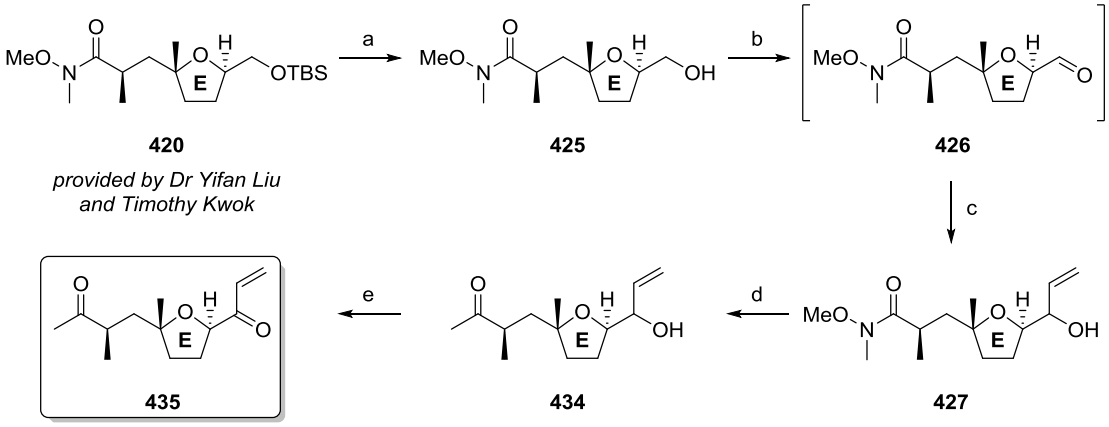
To unequivocally determine whether the rhodium-catalysed 1,4-addition reaction is feasible with an E ring enone derivative despite the steric bulk of the side chain, the Weinreb amide was converted into a methyl ketone.

Our first route to the desired methyl ketone **435** was to react Weinreb amide **420** with methyl magnesium bromide to synthesise ketone **429** in 72% yield. Deprotection of the TBS-protected alcohol with TBAF resulted in epimerisation of the α-keto stereocentre, presumably from the presence of basic tetra-*n*-butylammonium hydroxide.[150] In contrast, the TBS group was removed with TASF in DMF without epimerisation. The resulting alcohol **431** was then oxidised using Parikh–Doering conditions to aldehyde **432**. However, selective addition of vinyl magnesium bromide to the aldehyde instead of the ketone was not achieved, and the over-addition product **433** was observed by mass spectrometry (**Scheme 3-4**).



Scheme 3-4: First attempted route to E ring enone **435**.
Reagents and conditions: a) methyl magnesium bromide, Et_2O, –78 °C, 72%; b) TBAF, THF, 0 °C, 55%; c) TASF, DMF, 84%; d) SO_3·py, Et_3N, DMSO, DCM, 0 °C; e) vinyl magnesium bromide, Et_2O, 0 °C.

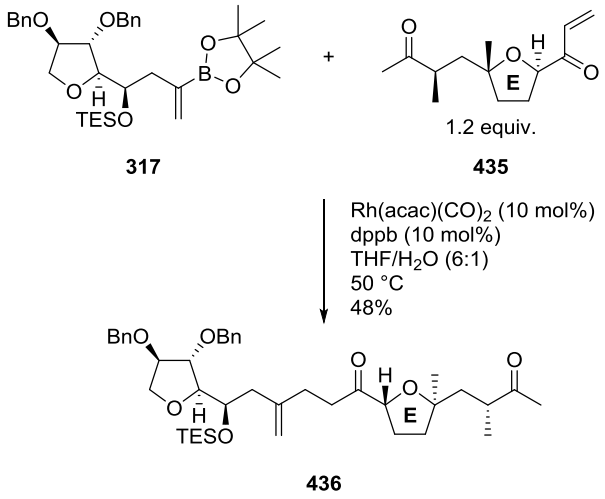
To avoid over-addition of the vinyl Grignard, the steps were reordered. Deprotection of **420** with TBAF, Parikh–Doering oxidation and vinyl Grignard reagent addition provided alcohol **427**, synthesised previously. Nucleophilic addition of methyl magnesium bromide delivered ketone **434** in 99% yield. Finally, DMP oxidation of the secondary allylic alcohol afforded the desired E ring enone **435** in 98% yield (**Scheme 3-5**).



Scheme 3-5: Second attempted route to E ring enone **435**.
Reagents and conditions: a) TBAF, THF, 0 °C, 96%; b) SO_3·py, Et_3N, DMSO, DCM, 0 °C; c) vinyl magnesium bromide, Et_2O, 0 °C, 69% over two steps; d) methyl magnesium bromide, Et_2O, –78 °C, 99%; e) DMP, DCM, 98%.

3.2.2.2 The attempt at the rhodium-catalysed 1,4-addition with model C ring

The ketone E ring enone **435** was then subjected to the rhodium-catalysed 1,4-addition conditions with the model C ring boronate **317**. Pleasingly, the desired adduct **436** was afforded in 41% yield (unoptimised, **Scheme 3-6**). This supports the hypothesis proposed in **Chapter 3.2.1.2** that the original Weinreb amide functionality was not compatible with our reaction conditions, and the presence of the sterically bulky side chain does not prevent the reaction from occurring. However, as the ketone functionality is not useful in our synthesis of PTX-4, a different synthetically useful functional group would need to be explored.



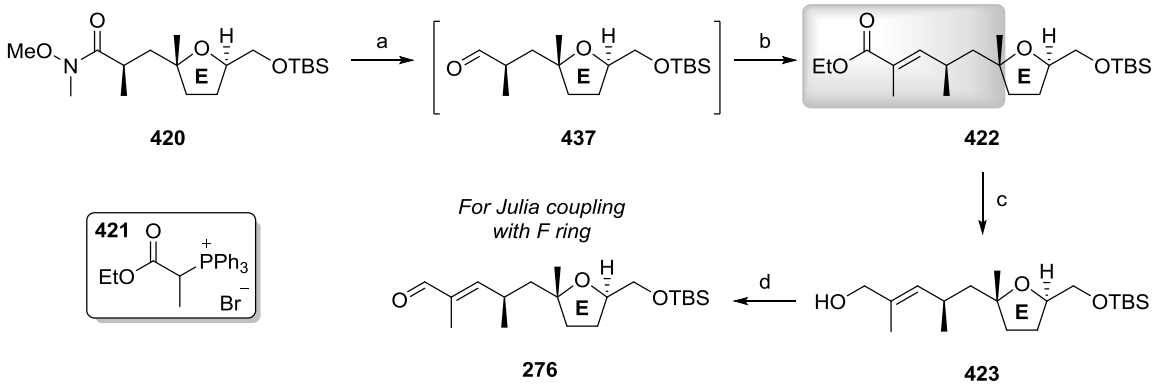
Scheme 3-6: Successful attempt at the rhodium-catalysed 1,4-addition with model C ring boronate **317** and E ring enone **435**.

3.2.3 Unsaturated ethyl ester E ring enone

With the successful coupling of the model C ring boronate **317** and the ketone-functionalised E ring fragment **435**, the replacement of the methyl ketone group with an alternative functional group that is compatible with the rhodium-catalysed 1,4-addition reaction and the future synthesis of PTX-4 needed to be investigated.

Referring to the synthetic plan for the E ring side chain outlined in **Chapter 3.1**, the side chain was to be modified by conversion of Weinreb amide **420** into the unsaturated aldehyde

276 *via* aldehyde **437**, unsaturated ethyl ester **422** and allyl alcohol **423** (**Scheme 3-7**).[43, 68, 69]



Scheme 3-7: Donohoe's synthesis of the E ring described in **Chapter 3.1**.
Reagents and conditions: a) DIBAL-H, THF, –78 °C; b) **421**, *n*-BuLi, benzene, 88% over two steps; c) $LiEt_3BH$, DCM, –78 °C, 92%; d) DMP, $NaHCO_3$, DCM (assumed quant. as used crude).

It was proposed that the E ring enone **438** with the unsaturated ethyl ester side chain of **422** because both aldehydes **437** and **276** were likely to be unstable and allylic alcohol **423** may require protection. However, the unsaturated ethyl ester might also undergo rhodium-catalysed 1,4-addition[151] and this possibility needed to be investigated (**Figure 3-2**).

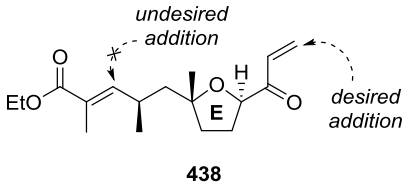
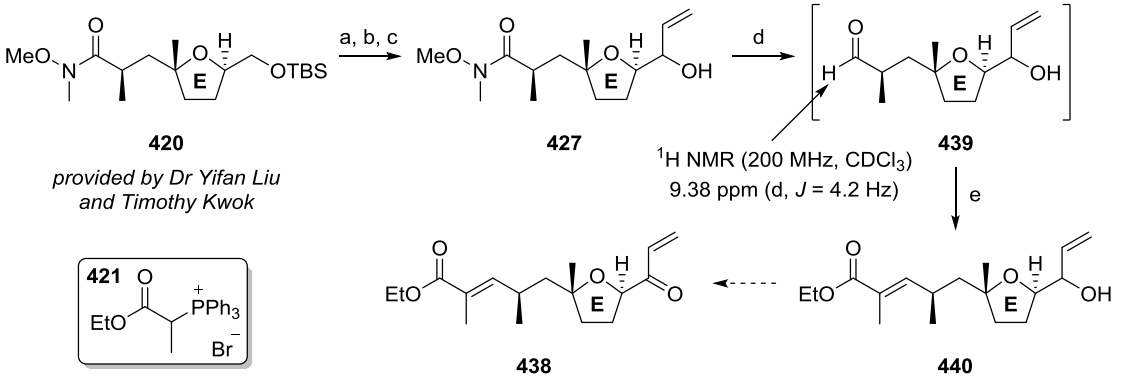


Figure 3-2: Proposed E ring fragment **438** for the rhodium-catalysed 1,4-addition with two possible sites of addition.

3.2.3.1 Synthesis of the unsaturated ethyl ester E ring enone

The synthesis of the required E ring enone **438** was prepared from the same allylic alcohol **427**, accessed in three steps from E ring fragment **420**. An attempt to reduce the Weinreb amide of **427** to aldehyde **439** (identified by ^{1}H NMR (200 MHz, $CDCl_3$) 9.38 Hz (d, J = 4.2 Hz) for aldehyde proton) without prior protection of the allylic alcohol, followed by a Wittig reaction with the ylide generated *in situ* from phosphonium salt **421** resulted in 31% yield of **440** (**Scheme 3-8**). However, because of the low yield and formation of multiple

unidentified by-products, a route in which the alcohol was protected before reduction of the Weinreb was explored.

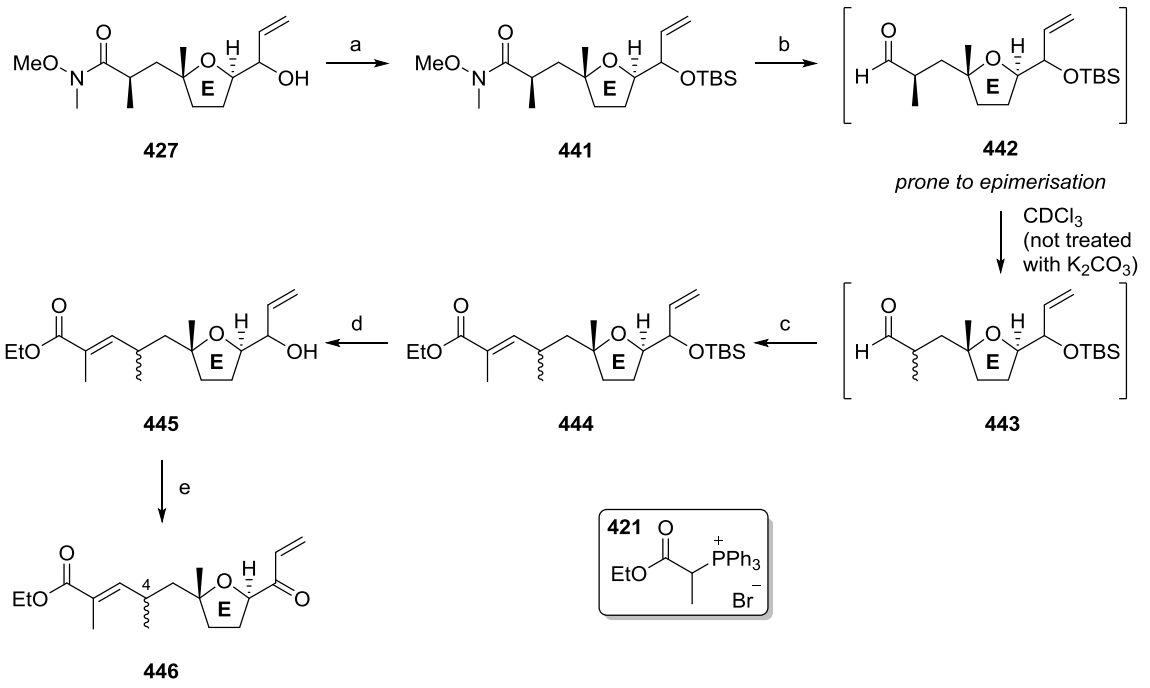


Scheme 3-8: First attempted synthesis of E ring enone **438**.
Reagents and conditions: a) TBAF, THF, 0 °C, 96%; b) SO_3·py, Et_3N, DMSO, DCM, 0 °C; c) vinyl magnesium bromide, Et_2O, 0 °C, 69% over two steps; d) DIBAL-H, THF, –78 °C; e) **421**, *n*-BuLi, benzene, 31% over two steps.

Protection of allylic alcohol **427** was accomplished by treatment with TBSCl in 88% yield (**Scheme 3-9**). The Weinreb amide **441** was reduced with DIBAL-H to provide aldehyde **442**, which appeared to epimerise at the α-keto stereocentre in $CDCl_3$ (when not treated with K_2CO_3). This was observed in the ^{1}H NMR (200 MHz, $CDCl_3$) of the aldehyde, where two doublets for the aldehyde protons were observed at 9.57 ppm (J = 3.2 Hz) and 9.39 ppm (J = 4.0 Hz). However, as the stereocentre at the TBS-protected alcohol was not defined, it is possible these pairs of doublets are simply the two epimers, although only one doublet was observed for related aldehyde **439**.

Despite the possible epimerisation, we decided to continue with the synthesis regardless, and the Wittig product **444** was obtained in 37% yield (**Scheme 3-9**). Removal of the TBS group revealed alcohol **445** in 80% yield, and the DMP oxidation of the allylic alcohol afforded the epimerised E ring enone **446** in 64% yield. The enone **446** had twinned peaks in both the ^{1}H and ^{13}C NMR spectra, indicating a mixture of two closely related diastereomers, despite loss of the undefined stereocentre from the allylic alcohol upon oxidation. This supports the hypothesis that epimerisation had occurred at C-4, originally

the α-keto stereocentre in aldehyde **442**. Nevertheless, enone **446** was used in the first rhodium-catalysed 1,4-addition reactions described in **Chapter 3.2.3.2**.

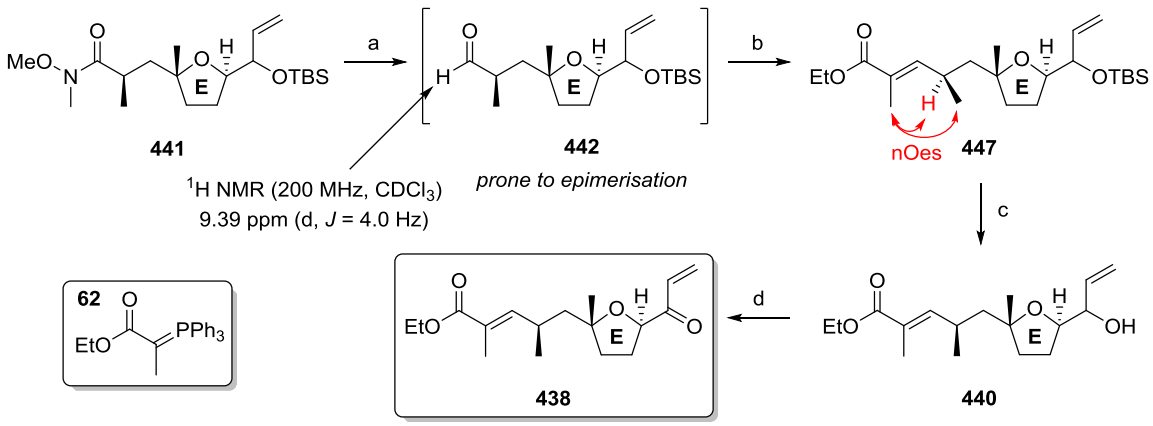


Scheme 3-9: Second attempted synthesis of the E ring enone **438**.
Reagents and conditions: a) TBSCl, imidazole, DMAP, DCM, 88%; b) DIBAL-H, THF, –78 °C; c) **421**, *n*-BuLi, benzene, Δ, 37% over two steps; d) TBAF, THF, 80%; e) DMP, DCM, 64%.

To obtain the unepimerised E ring enone **438**, the route was repeated with some adjustments to improve the yield (**Scheme 3-10**). The DIBAL-H reduction of the Weinreb amide **441** to aldehyde **442** remained the same, although NMR analysis of the aldehyde **442** was performed in $CDCl_3$ treated with K_2CO_3 (to remove HCl, a decomposition product of $CDCl_3$),[152] to prevent epimerisation of the α-keto stereocentre. The ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of the unepimerised aldehyde **442** showed one doublet for the aldehyde proton at 9.39 ppm (J = 4.0 Hz), matching one of the two doublet peaks observed in the spectrum for epimerised aldehyde **443**.

The Wittig reaction was improved by use of pre-formed ylide **62** instead of material generated *in situ* by treatment of the phosphonium salt **421** with *n*-BuLi, providing an 87% yield of **447** over two steps. The (*E*)-geometry of **447** was confirmed by nOes (see

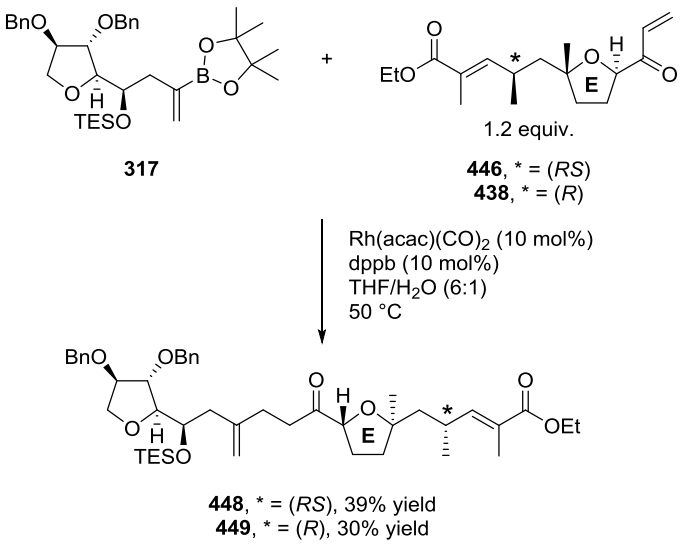
Appendix 6.2.5). Deprotection of the allylic alcohol with TBAF afforded **440** in 78% yield. Finally, the oxidation of the alcohol with DMP was improved by buffering the reaction with $NaHCO_3$, increasing the yield of the desired E ring enone **438** to 90% (**Scheme 3-10**). Both the ^{1}H and ^{13}C NMR spectra of **438** showed one set of peaks compared to the spectra of enone **446**, which confirmed that epimerisation had not occurred during the synthesis.



Scheme 3-10: Successful synthesis of E ring enone **438**.
Reagents and conditions: a) DIBAL-H, THF, –78 °C; b) **62**, benzene, Δ, 87% over two steps; c) TBAF, THF, 78%; d) DMP, $NaHCO_3$, DCM, 90%.

3.2.3.2 Attempts at the rhodium-catalysed 1,4-addition with model C ring

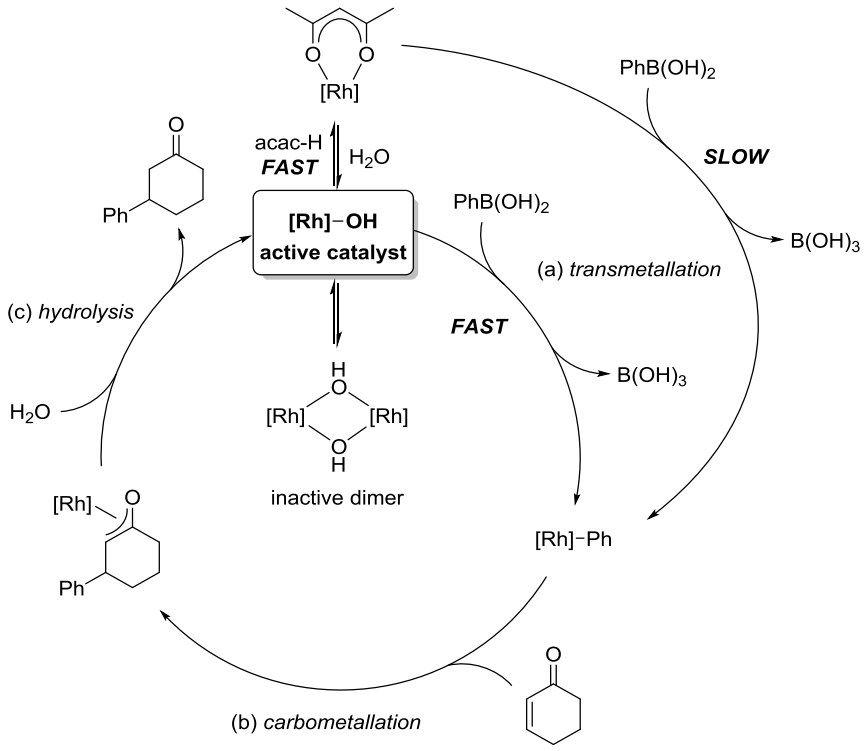
The rhodium-catalysed 1,4-addition reaction was initially attempted with epimerised E ring enone **446** and model C ring boronate **317**. Pleasingly, this reaction gave the desired adduct **448** in 39% yield using a 10 mol% catalyst loading of $Rh(acac)(CO)_2$ and dppb. A repeat of the reaction with unepimerised E ring enone **438** afforded a similar yield of 30% of the desired adduct **449** (**Scheme 3-11**).



Scheme 3-11: First attempts at the rhodium-catalysed 1,4-addition with model C ring boronate **317** and E ring enones **446** and **438**.

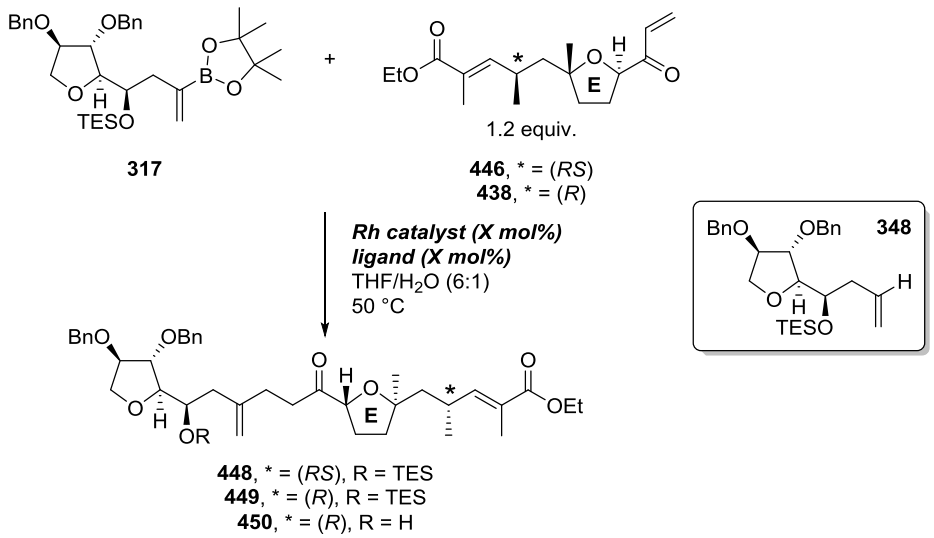
The lower observed yield (compared to previous models) was not due to overreaction at the unsaturated ester, as addition was not observed here. A control experiment in which product **449** was resubmitted to the reaction conditions (without the presence of either boronate **317** or enone **438**) showed the product **449** was stable under the reaction conditions.

To improve the yield, a variety of catalysts more active than $Rh(acac)(CO)_2$ were explored.[75] It has been reported that the acetylacetonato (acac) ligand inhibits the reaction because the protonated acac (acac–H) readily reacts with the active monomeric catalytic species (**Scheme 3-12**).[83] Also, the carbon monoxide (CO) binds strongly to the rhodium centre, which means displacement with other more active ligands is inhibited.[82] Rhodium complexes bearing dienes and other π-accepting ligands typically exhibit an increase in reaction rate over systems that possess diphosphine ligands (such as dppb), as it is proposed that they have a lower rate of catalyst dimerisation (the active species is the monomer[84]) and a higher rate of transmetallation.[153]



Scheme 3-12: Catalytic cycle for the rhodium-catalysed 1,4-addition from **Chapter 2.3**, with interactions of the monomeric [Rh]-OH active catalytic species with acac-H and with its inactive dimer.

The optimisation of this reaction is described in **Table 3-2**, with the previously discussed attempts in **entries 1** and **2**. Catalyst $[Rh(cod)Cl]_2$ did not provide any desired product **449** (**entry 3**), analogous to the attempt in the previous model described in **Chapter 2.4.3.2**. However, $[Rh(cod)OH]_2$ successfully afforded adduct **449** in 16% yield (**entry 4**).[153] Despite the lower yield, there was a better mass recovery from this reaction because no protodeborylation by-product **348** was observed and boronate **317** could be recovered (24% mass recovery therefore the yield of **449** was 22% brsm). Increasing the catalyst loading to 15 mol% afforded **449** in 53% yield, yet increasing it to 30 mol% did not increase the yield further (**entries 5** and **6** respectively).

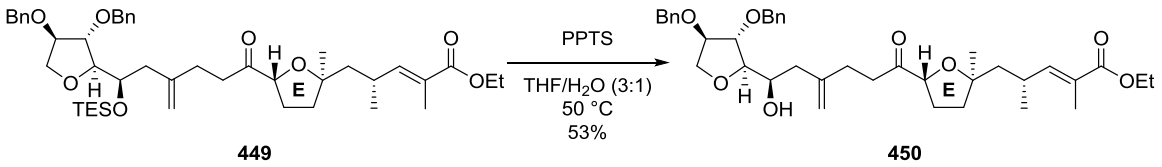


Entry	Rh catalyst	Ligand	**X** mol%	Yield **449**	Yield **450**
1 †	$Rh(acac)(CO)_2$	dppb	10	39%	-
2	$Rh(acac)(CO)_2$	dppb	10	30%	-
3	$[Rh(cod)Cl]_2$	-	5	0%	-
4	$[Rh(cod)OH]_2$	-	5	16%	-
5	**$[Rh(cod)OH]_2$**	**-**	**15**	**53%**	**-**
6	$[Rh(cod)OH]_2$	-	30	49%	-
7	$Rh(nbd)_2BF_4$	-	15	5%	41%
8	$Rh(nbd)_2BF_4$	-	30	0%	40%

Table 3-2: Optimisation of the rhodium-catalysed 1,4-addition with model C ring boronate **317** and E ring enone **438**. † Used epimerised E ring enone **446** to form adduct **448**.

Using cationic rhodium catalyst $Rh(nbd)_2BF_4$[154] in the rhodium-catalysed 1,4-addition reaction produced the TES-deprotected product **450** in 40% yield, with only small amounts of the TES protected product **449** isolated at lower catalyst loadings (**entries 7** and **8**). The increased Lewis-acidity of the cationic rhodium species may have aided deprotection of the TES group, as this product was not observed with the other rhodium catalysts. This deprotected alcohol **450** may still be useful in the cyclisation step, depending on whether the TES group needs to be present to improve facial selectivity in the subsequent dihydroxylation/cyclisation sequence, or if the free hydroxyl group can help direct the

oxidation reagent. The deprotected alcohol **450** could also be accessed upon treatment of **449** with PPTS in 53% yield (**Scheme 3-13**).



Scheme 3-13: Deprotection of the TES group of **449**.

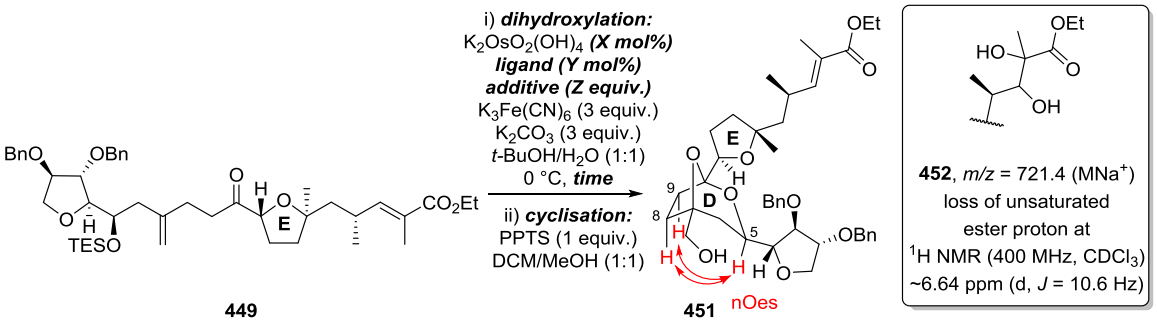
With an acceptable yield of 53% for the rhodium-catalysed 1,4-addition with model C ring boronate **317** to the real E ring enone fragment **438**, our focus turned to the dihydroxylation/cyclisation sequence on adduct **449**.

3.2.3.3 Acid-catalysed cyclisation to form the CDE ring

Adduct **449** was subjected to the same dihydroxylation/cyclisation conditions as the previous model described in **Chapter 2.4.4.3**. Without careful monitoring of the SAD reaction (TLC every 10 minutes), over-oxidation can occur at the unsaturated ester double bond (**entry 1**, **Table 3-3**). This was indicated by mass spectrometry, with a peak of *m/z* = 721.4 for the molecular ion plus sodium, as well as the loss of the unsaturated ester proton at ~6.64 ppm in the ^{1}H NMR spectrum. However, with careful monitoring, the SAD reaction was completed in just over 40 minutes, and after cyclisation with PPTS, it afforded the desired bicyclic D ring **451** in 27% yield (**entry 2**). The structure was confirmed by extensive COSY/HSQC/HMBC analysis to have the same connectivity as the previous D ring model **351**, the nOes between C-5 and C-8/C-9 protons confirmed that the compound was the desired bicyclic acetal. However, the methanesulfonamide additive, proposed to aid osmate ester hydrolysis,[113] was difficult to remove from the desired product **451**.

To aid purification, methanesulfonamide was omitted from the reaction (**entry 3**). Pleasingly, **451** was obtained in 40% yield despite the dihydroxylation reaction taking longer to reach completion in the absence of methanesulfonamide. Use of the *pseudo*-

enantiomer ligand, $(DHQ)_2PHAL$, produced a complex mixture which did not contain any of the desired product **451**, and no other bicyclic acetals were observed by NMR analysis, in contrast to the previous model (**entry 4**). A non-chiral variant of the SAD reaction was attempted using the quinuclidine HCl salt (neutralised *in situ* with additional K_2CO_3), which afforded **451** in a reduced yield of 14% (**entry 5**).



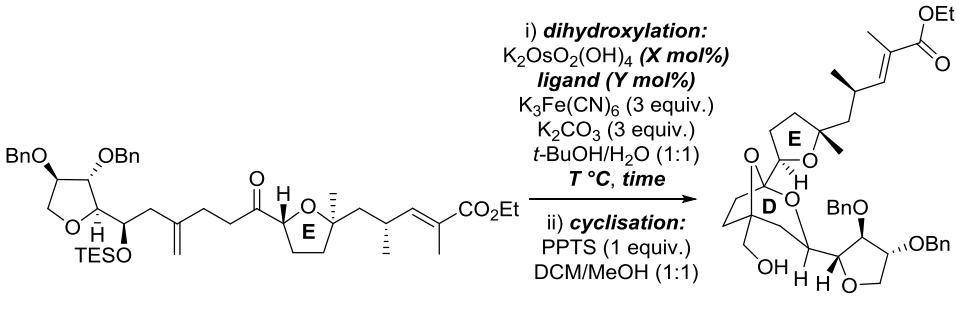
Entry	**X** mol%	Ligand	**Y** mol%	Additive (**Z** equiv.)	Time	Yield **451**
1 *	10	$(DHQD)_2PHAL$	20	$MeSO_2NH_2$ (1 equiv.)	1 h 25 min	0% *
2	10	$(DHQD)_2PHAL$	20	$MeSO_2NH_2$ (1 equiv.)	47 min	27%
3	**10**	**$(DHQD)_2PHAL$**	**20**	**-**	1 h 25 min	**40%**
4	10 × 2	$(DHQ)_2PHAL$	20 × 2	-	3 h 40 min	0%
5	10	Quinuclidine·HCl	20	K_2CO_3 (0.2 equiv.)		14%

Table 3-3: Dihydroxylation/cyclisation sequence on **449**. * 7.8 equiv. $K_3Fe(CN)_6$ and K_2CO_3, detected **452** by *m/z* instead of **451**.

Attempts to optimise the dihydroxylation/cyclisation sequence on **449** did not improve the yield. The best conditions from **entry 3**, **Table 3-3** are identical to those in **entry 1**, **Table 3-4** for comparison. Using ligands with other linkers, such as pyrimidine ($(DHQD)_2PYR$)[155] and anthraquinone ($(DHQD)_2AQN$), did not improve the yield. The pyrimidine ligand linker afforded the desired product **451** in 24% yield, whereas the anthraquinone linker did not afford **451** despite additional catalyst/ligand loading (**entries 2** and **3** respectively).

Increasing the catalyst and ligand loading from the onset of the reaction decreased the yield to 16% of **451**, suggesting poorer facial selectivity in the dihydroxylation reaction (**entry 4**). Lowering the temperature to –10 °C to aid facial selectivity was unsuccessful because

the reaction solvent froze (**entry 5**). Finally, changing the order of addition from **449** being added first, to being added last to allow for pre-coordination of the ligand to the osmium before reaction with **449** did not improve the yield, because an additional solvent was required to transfer **449** into the reaction and this slowed the reaction (**entry 6**).

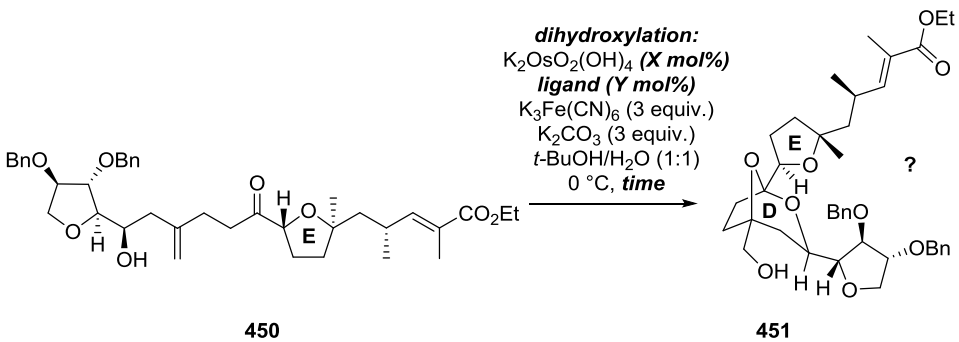


449 **451**

Entry	**X** mol%	Ligand	**Y** mol%	T °C	Time	Yield **451**
1	**10**	**$(DHQD)_2PHAL$**	**20**	**0 °C**	**1 h 25 min**	**40%**
2	10	$(DHQD)_2PYR$	20	0 °C	3 h 10 min	24%
3	10 × 2	$(DHQD)_2AQN$	20 × 2	0 °C	7 h 35 min	0%
4	20	$(DHQD)_2PHAL$	40	0 °C	1 h	16%
5 [a]	10	$(DHQD)_2PHAL$	20	–10 °C [a]	3 h 40 min	30%
6 [b]	10 × 2	$(DHQD)_2PHAL$	20 × 2	0 °C		19% [b]

Table 3-4: Optimisation of the dihydroxylation/cyclisation sequence on **449**. [a] solvent froze, warmed to 0 °C after 30 min. [b] 70% more dilute as added **449** last as opposed to first.

Dihydroxylation of the unprotected adduct **450** did not require treatment with PPTS to promote cyclisation because the TES group had already been removed. Whilst we had not attempted to dihydroxylate an adduct without the alcohol being TES-protected and could not predict the change in facial selectivity accordingly, the use of both *pseudo*-enantiomeric ligands was explored. However, neither the $(DHQ)_2PHAL$ nor $(DHQD)_2PHAL$ ligands provided the desired product **451** (**Table 3-5**). The ^{13}C NMR spectrum of the products from of both reactions indicated the possible presence of acetal quaternary carbons, but these spectra did not match that of the desired product **451** and so the compounds could not be identified upon further analysis.



450 **451**

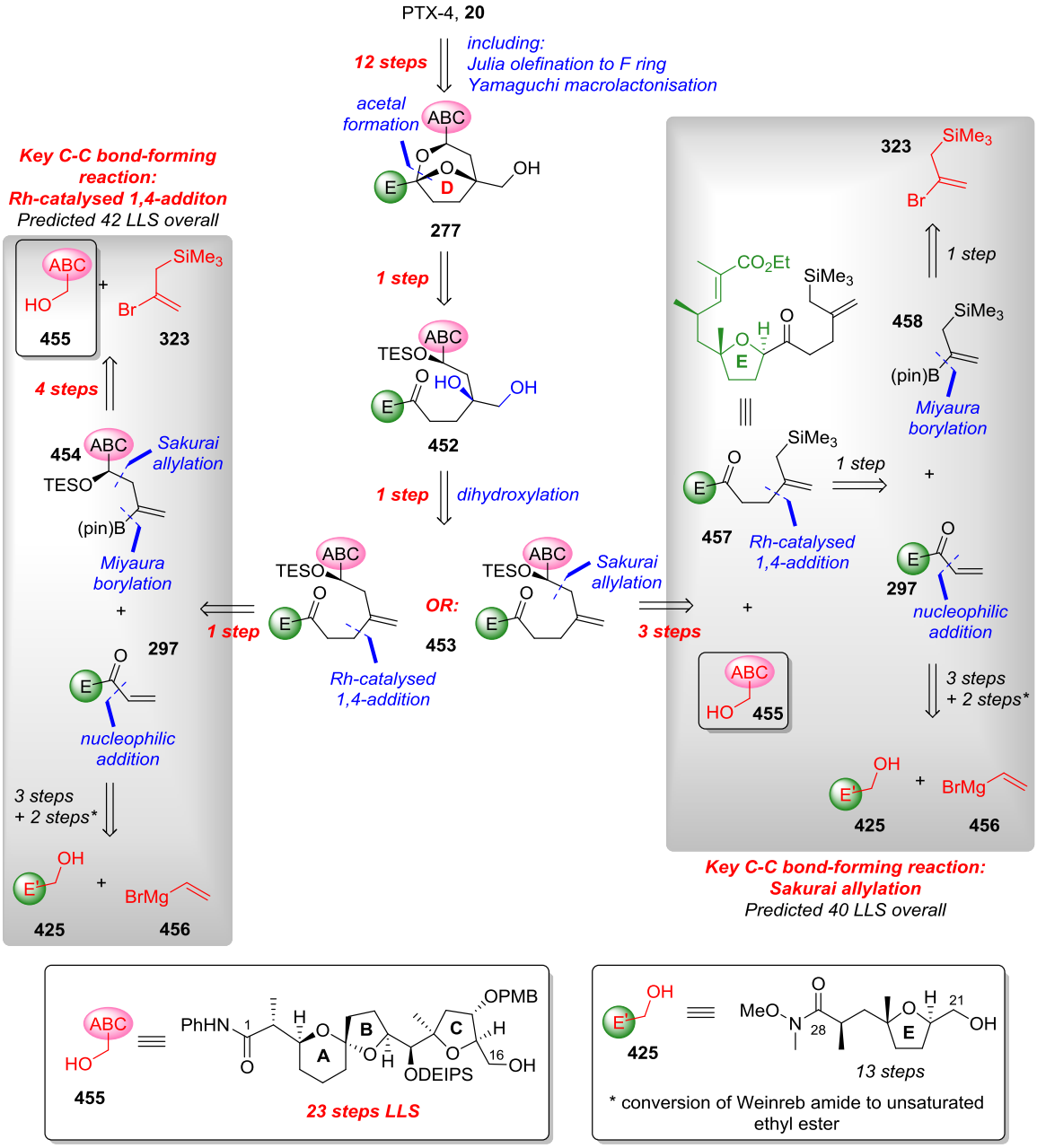
Entry	**X** mol%	Ligand	**Y** mol%	Time	Yield **451**	Comment
1	10 × 2	$(DHQ)_2PHAL$	20 × 2	6 h 45 min	0%	Unidentified products: ^{13}C NMR 107.1, 106.9 ppm *
2	10	$(DHQD)_2PHAL$	20		0%	Unidentified products: ^{13}C NMR 108.7, 105.9 ppm *

Table 3-5: Dihydroxylation/cyclisation sequence on **450**. * ^{13}C NMR (126 MHz, $CDCl_3$).

3.2.4 Alternative order of steps: E ring allyl silane

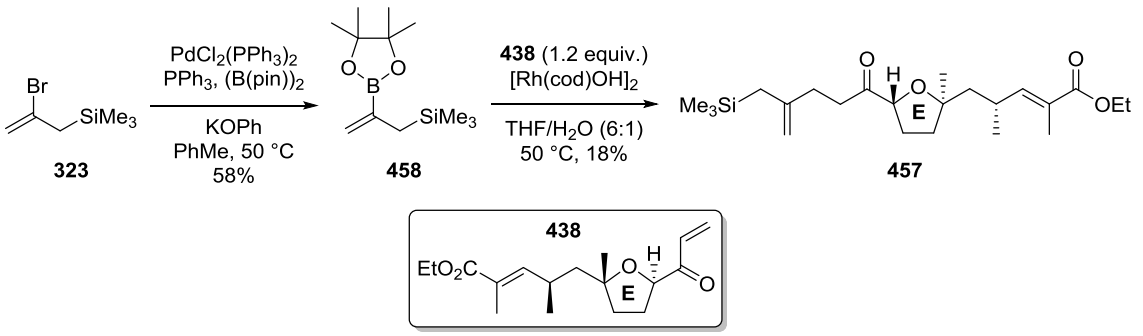
As an alternative route to the synthesis of PTX-4, the order of steps could be switched to shorten the longest linear sequence (our current total synthesis is predicted to be approximately 42 steps LLS), as well as rely upon a different reaction as the key C–C bond forming reaction to couple the ABC fragment to the E ring.

By switching the order of steps to utilise the Sakurai reaction as the key C–C bond forming step as opposed to the original proposal to use the rhodium-catalysed 1,4-addition reaction, the longest linear sequence could potentially be decreased to 40 steps (**Scheme 3-14**). This would require the synthesis of E ring fragment **457** (where the E ring substituent is highlighted in green) as the Sakurai allylating reagent.



Scheme 3-14: Divergent retrosynthetic pathways by switching the order of rhodium-catalysed 1,4-addition and Sakurai reactions as the key C–C bond forming step. The steps highlighted in bold, italic red are for the LLS.

To synthesise E ring fragment **457**, vinyl bromide **323** was converted into the volatile boronate **458** in 58% yield (**Scheme 3-15**). The rhodium-catalysed 1,4-addition reaction with boronate **458** and E ring enone **438** provided **457** in an unoptimised yield of 18%. To improve this yield, alteration of the limiting reagent would be considered, but because material was limited this was not conducted at the time. Further work will be undertaken by co-workers.

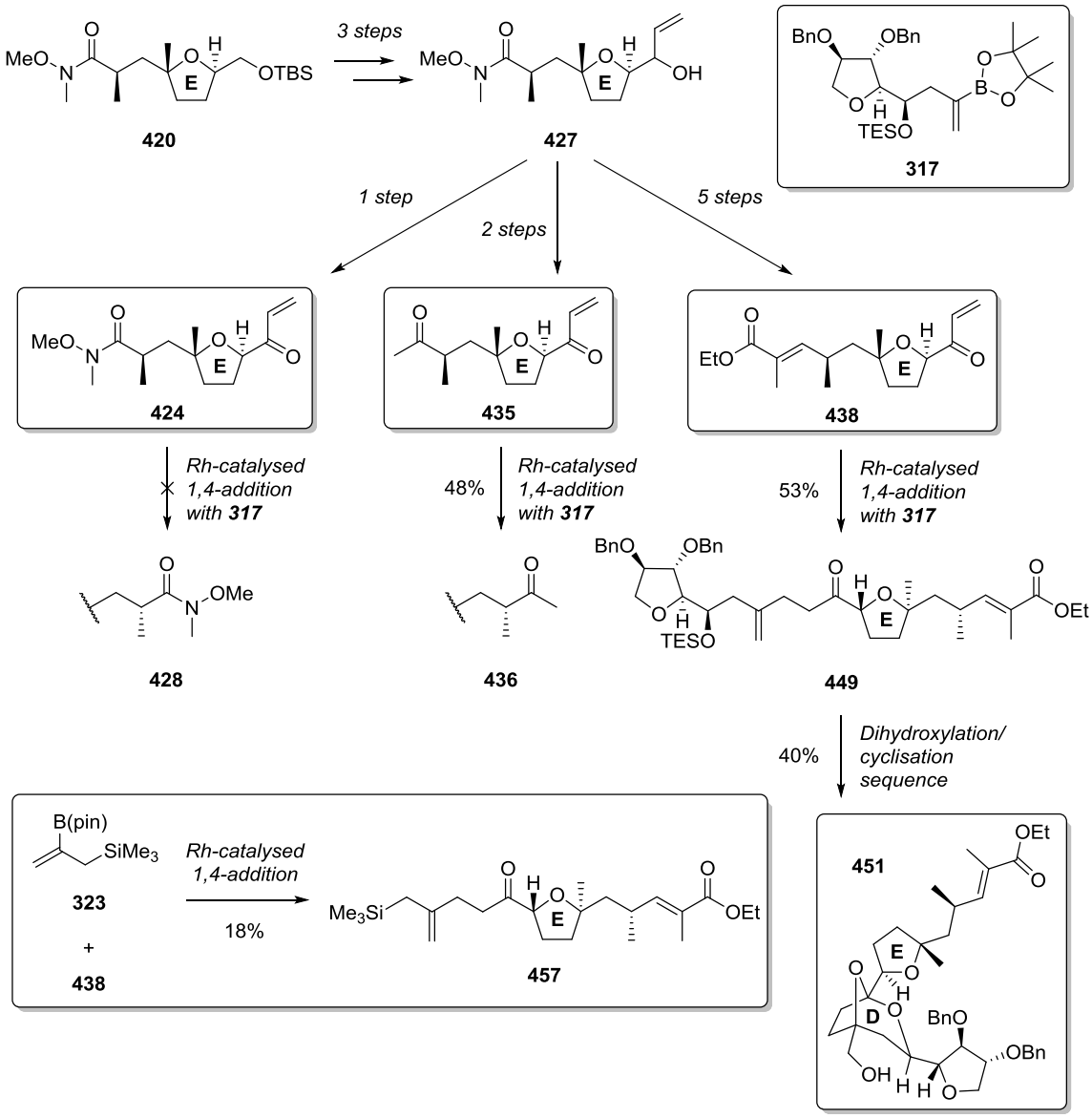


Scheme 3-15: Synthesis of E ring allyl silane **457**.

3.3 Conclusions & Future Work

Various modifications of the E ring side chain were explored and tested in the rhodium-catalysed 1,4-addition reaction with model C ring boronate **317** (**Scheme 3-16**). The Weinreb amide functionality was not compatible with the rhodium-catalysed 1,4-addition reaction conditions. A substrate bearing a methyl ketone functionality could participate in the rhodium-catalysed 1,4-addition reaction with C ring boronate **317**, but it is not synthetically useful. The unsaturated ethyl ester functionality was chosen based upon the planned conversion *en route* to the Julia coupling[66] with the F ring. This E ring enone **438** was coupled with C ring boronate in 53% yield after optimisation.

The D ring was successfully synthesised with the real E ring fragment **451** in 40% yield after extensive optimisation. An alternative E ring fragment, the allyl silane **457**, was synthesised in anticipation of altering the order of steps in the synthesis of PTX-4.

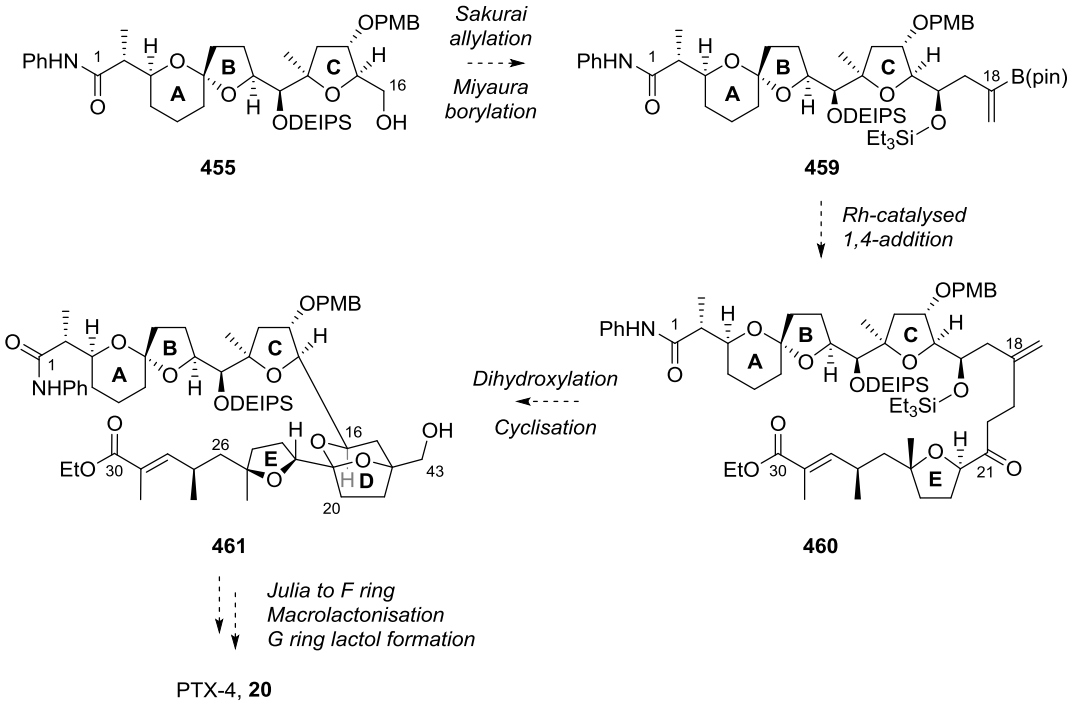


Scheme 3-16: Summary of **Chapter 3**.

Future work would consist of using the conditions for the Sakurai allylation reaction, Miyaura borylation reaction, rhodium-catalysed 1,4-addition reaction, and the dihydroxylation/cyclisation sequence developed in **Chapters 2** and **3** with the real ABC fragment and E ring enone **438** to continue the synthesis of PTX-4 (**Scheme 3-17**). The alternative route described in **Chapter 3.2.4** could also be explored and compared to find the best route.

Alternative boronates could also be explored, as pinacol boronate may not be optimal and was chosen because of ease of synthesis and stability. Other boronates, such as potassium

trifluoroborates,[92, 156, 157] are thought to be more nucleophilic[158] and may speed up the rate-determining transmetallation step in the rhodium-catalysed 1,4-addition reaction.[75]



Scheme 3-17: Future work to complete the synthesis of PTX-4.

Chapter 4

Chapter 4: Synthesis of the desired F ring fragment

As outlined in **Chapter 3**, the E ring side chain was modified to allow for the synthesis of the D ring with a model C ring, using our proposed rhodium-catalysed 1,4-addition disconnection and our dihydroxylation/cyclisation sequence. This chapter outlines the reoptimisation and scale-up of the previously published F ring synthesis,[43] with modifications to the protecting group strategy employed in preparation for the Julia coupling with the ABCDE fragment in our total synthesis of PTX-4.

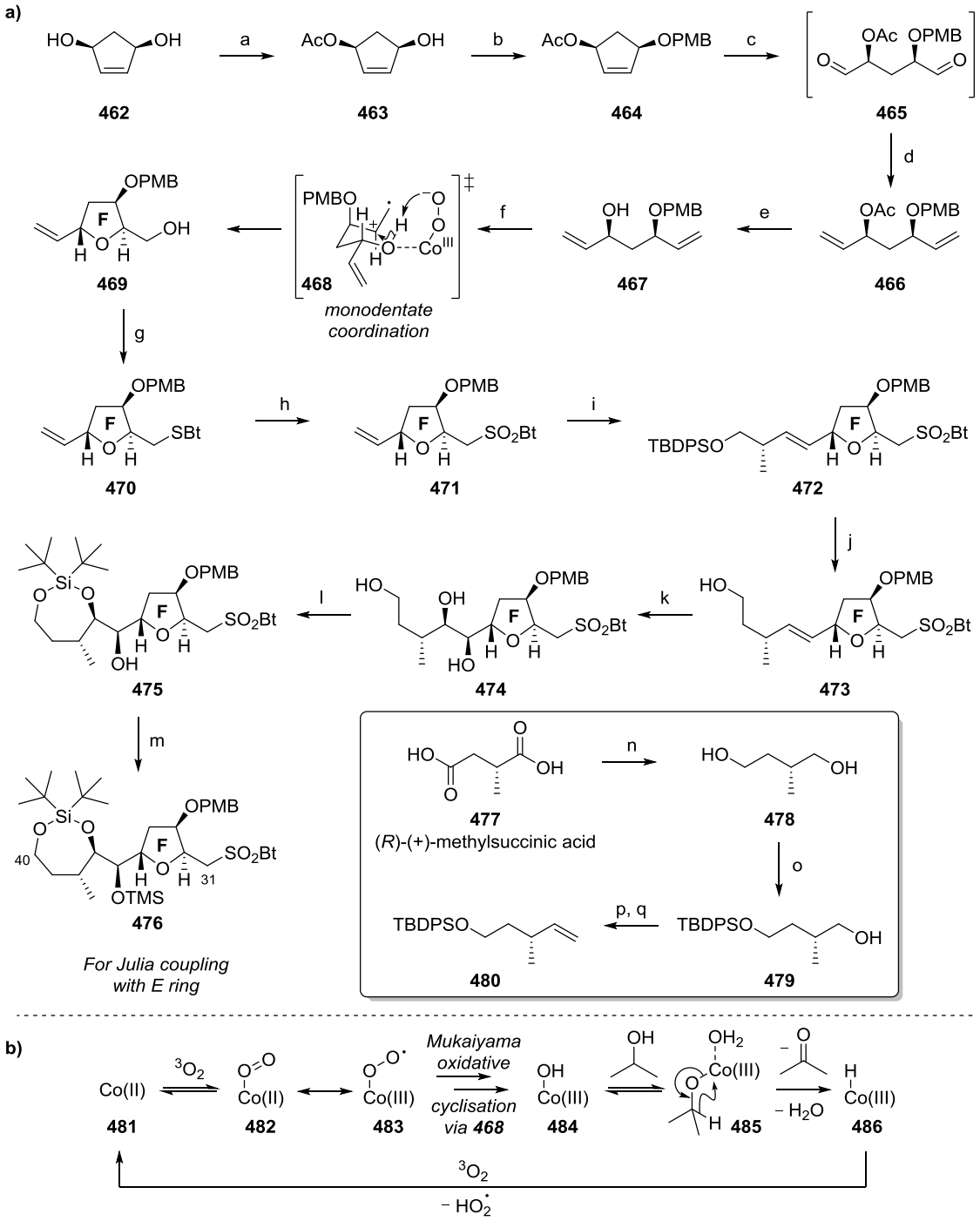
4.1 Donohoe's synthesis of the F ring

The Donohoe's group synthesis of the F ring was developed by Dr Kirsty Luscombe,[159] Dr Michael Tucker[160] and Dr Ahria Roushanbakhti,[161] and has been published recently.[43] The F ring fragment **476**, which was utilised for the Julia coupling[66] to the E ring fragment (**276** discussed in **Chapter 3.1**), was synthesised in 13 steps from *cis*-diol **462** (**Scheme 4-1a**). Diol **462** was enzymatically desymmetrised using pancreatin from porcine pancreas to mono-acetate **463** in 70% yield. The remaining hydroxyl group was protected with PMB trichloroacetimidate to afford the PMB ether **464** in 99% yield. Ozonolysis to dialdehyde **465**, followed by a double Wittig reaction and subsequent acetate removal gave access to **467** in 71% yield over three steps.

The key step was the cobalt-mediated Mukaiyama oxidative cyclisation reaction[162] using Pangenkopf's second generation $Co(nmp)_2$ catalyst[163] to afford the *trans*-tetrahydrofuran **469** in 48–56% yield. The catalytic cycle of the cobalt species is outlined in **Scheme 4-1b**.[164] The cobalt(II) precursor **481** is activated with molecular oxygen to generate cobalt(III) species **483**. The monodenate coordination of the O_2-activated cobalt complex **483** allows for the radical oxidation of the alkene to a radical cation, followed by a 5-*exo* ring closure of the hydroxyl group attached to the cobalt complex, shown in transition

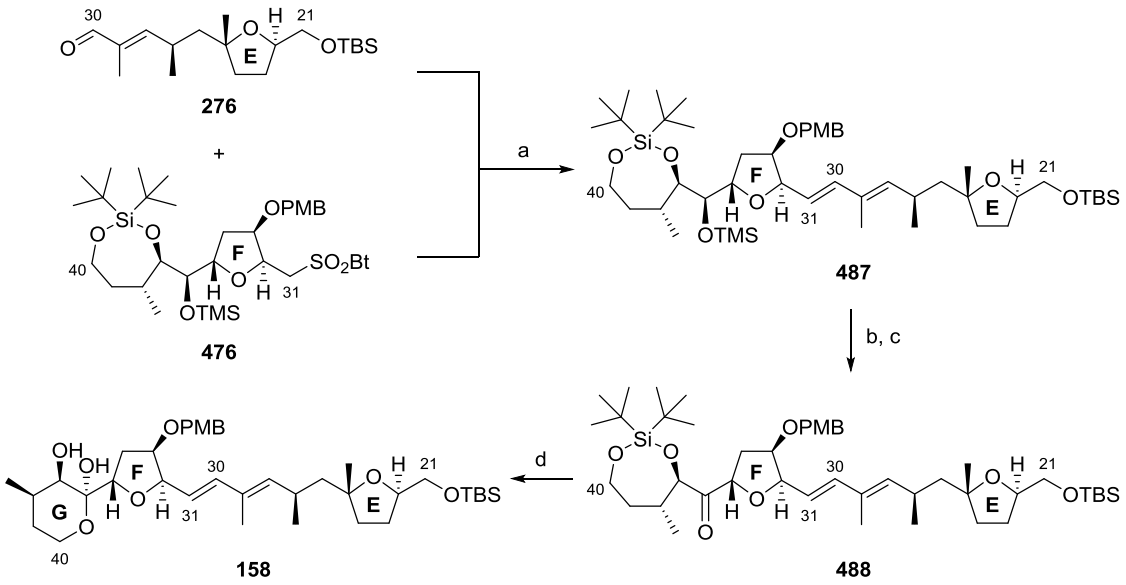
state **468** in **Scheme 4-1a**. The O–O bond of hydroperoxide cobalt(III) species is readily cleaved by the exocyclic radical to form the *trans*-tetrahydrofuran **469** and Co(III) hydroxide **484**. The activated cobalt complex is regenerated by a hydride shift from coordinated *i*-PrOH (**485**) to generate hydridocobalt(III) complex **486**. This species is decomposed by molecular oxygen, releasing a hydroperoxyl radical and cobalt(II) species **481** to complete the catalytic cycle.

A Mitsunobu reaction[165] with mercaptobenzothiazole followed by oxidation of the corresponding sulfide **470** to the sulfone **471** with an ammonium molybdate catalyst was achieved in 64% yield over two steps. Olefin cross metathesis of **471** with alkene **480** (derived from (*R*)-(+)-methyl succinic acid **477** in 4 steps, shown in the box of **Scheme 4-1a**) mediated by Hoveyda–Grubbs second generation catalyst followed by acidic deprotection of the primary TBDPS group delivered **473** in 83% yield and with a 92:8 *E*/*Z* diastereomeric ratio. The (*E*)-alkene was oxidised to give the diol **474** using AD-mix β in 66% yield. Subsequent 1,4-diol protection with t-$Bu_2Si(OTf)_2$ and TMSCl afforded the desired F ring fragment **476** in 59% yield over two steps, in preparation for the Julia coupling with the E ring fragment **276** (the synthesis was discussed in **Chapter 3.1**). Dr Ahria Roushanbakhti had also obtained an X-ray crystal structure of **476**, confirming the relative stereochemistry of the *trans*-tetrahydrofuran, the outcome of the Sharpless asymmetric dihydroxylation and the position of the silyl tether.



Scheme 4-1: Donohoe's synthesis of the E ring developed by Dr Kirsty Luscombe, Dr Michael Tucker and Dr Ahria Roushanbakhti, with the catalytic cycle of the key Mukaiyama oxidative cyclisation. *Reagents and conditions:* a) vinyl acetate, pancreatin, Et_3N, THF, 70%, >90% ee, ; b) 4-methoxybenzyl-2,2,2-trichloroacetimidate, CSA, DCM/pentane (4:1), 0 °C, 99%; c) O_3, PPh_3, DCM, –78 °C; d) $MePPh_3Br$, KHMDS, THF –78 °C to rt; e) KOH, MeOH, 71% over three steps; f) $Co(nmp)_2$ (10–30 mol%), *t*-BuOOH, *i*-PrOH, O_2, 55 °C, 48–56%; g) BtSH, PPh_3, DIAD, 0 °C; h) H_2O_2, $(NH_4)_2MoO_4$ (10 mol%), EtOH/THF (4:1), 64% over two steps; i) **480**, HG-II (5 mol%), DCM, 40 °C; j) AcCl, MeOH, 83% over two steps, *E*/*Z* = 92:8; k) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 °C to rt, 66%; l) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DCM, 4 Å MS, –78 °C, 65%; m) TMSCl, imidazole, DCM, 91%; n) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C, 87%; o) TBDPSCl, imidazole, DMAP, DCM, 0 °C, 64%; p) DMSO, $(COCl)_2$, Et_3N, DCM, –78 °C; q) $MePPh_3Br$, *n*-BuLi, THF, 0 °C, 51% over two steps.

The Julia coupling reaction[66] of the E and F fragments and cyclisation to form the G ring was achieved in four steps in 46% overall yield (**Scheme 4-2**). The slight degradation of the *trans*-stereochemistry of the F ring was proposed to be due to the reversible ring opening of the lithiated sulfone (at C-31 of **476**) before coupling to E ring aldehyde **276**.



Scheme 4-2: The Julia coupling of the E and F fragments **276** and **476**, and cyclisation of the G ring. *Reagents and conditions:* a) LiHMDS, THF, –78 °C to 0 °C, 99%, *cis*/*trans* = 8:92, *E*/*Z* = 95:5; b) PPTS, MeOH/DCM (1:1), 0 °C to rt, 76%; c) DMP, pyridine, DCM, 95%; d) TASF, 1.5 M H_2O solution in DMF, 64%.

Despite the successful union of the E and F rings, EFG fragment **158** was not coupled to the ABC fragment to form the D ring because the 1,3-diene between C-28 to C-31 would not survive the conditions required to synthesise the D ring, as discussed in **Chapter 2.2**. Additionally, the conditions for the removal of the PMB group on the F ring were incompatible with the 1,3-diene, because the use of DDQ resulted in exclusive allylic oxidation as observed by Evans.[23]

It was proposed to synthesise F ring **489** in preparation for the Julia coupling with the ABCDE fragment **490**, with the C-33 hydroxyl PMB group replaced by a TMS group at a late-stage (**Figure 4-1**). The original TMS group on the C-36 hydroxyl was to be replaced by a TES group because the G ring cyclisation reaction would occur after the

Yamaguchi macrolactonisation[34] onto the C-33 hydroxyl group. Therefore, the protecting group on the C-36 hydroxyl group was to remain attached after deprotection of the C-33 hydroxyl group and macrolactonisation.

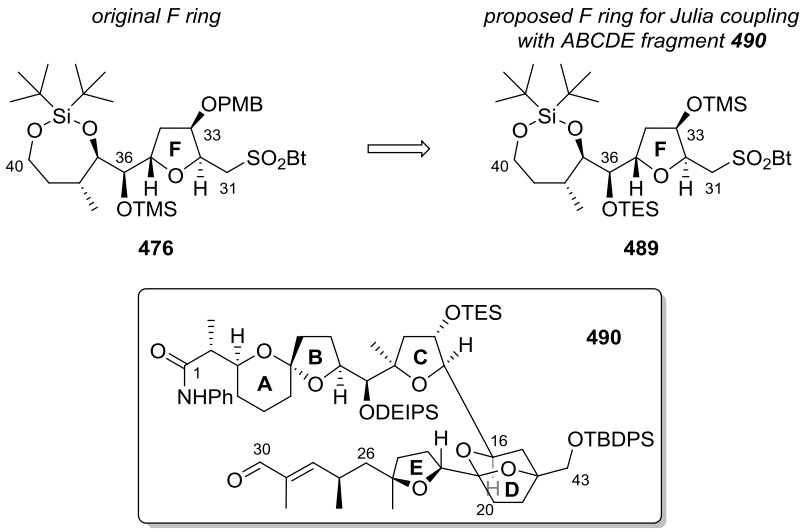
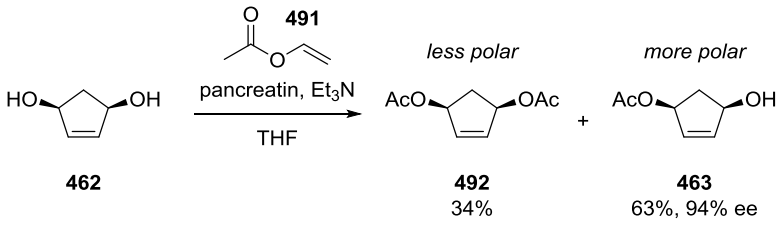


Figure 4-1: Proposed new F ring fragment **489** for Julia coupling to ABCDE fragment **490**.

4.2 Results & Discussion: Reoptimisation of the F ring synthesis

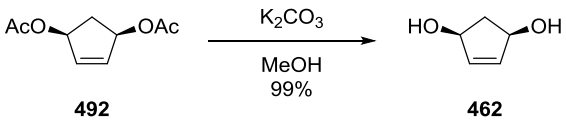
4.2.1 Desymmetrisation of the cis-diol

Cis-diol **462** was desymmetrised using pancreatin from porcine pancreas and vinyl acetate **491** to selectively acetate-protect one of the hydroxyl groups. The reaction was run until complete consumption of starting material **462** was observed, which resulted in a 63% yield of desired monoacetate **463** and a 34% yield of diacetate **492** (**Scheme 4-3**). Analysis of the Mosher's esters of a derivative of **463** confirmed the absolute stereochemistry (see **Appendix 6.1.3**).



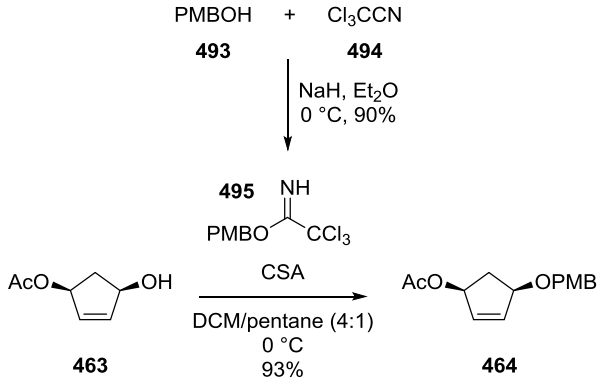
Scheme 4-3: Enzymatic desymmetrisation of *cis*-diol **462**.

The diacetate **492** could be recycled to give the corresponding *cis*-diol starting material **462** using mildly basic conditions in 99% yield (**Scheme 4-4**). The use of KOH instead of K_2CO_3 in MeOH resulted in in a complex mixture of products. The recovered starting material **462** was resubjected to the enzymatic desymmetrisation conditions in **Scheme 4-3** to minimise loss of material.



Scheme 4-4: Hydrolysis of undesired diacetate **492** to starting material *cis*-diol **462**.

The remaining hydroxyl group of **463** was protected with PMB trichloroacetimidate **495** and CSA to give **464** in 93% yield (**Scheme 4-5**). The PMB trichloroacetimidate **495** was accessed in one step from trichloroacetontrile **494** and PMB alcohol **493**.[166]

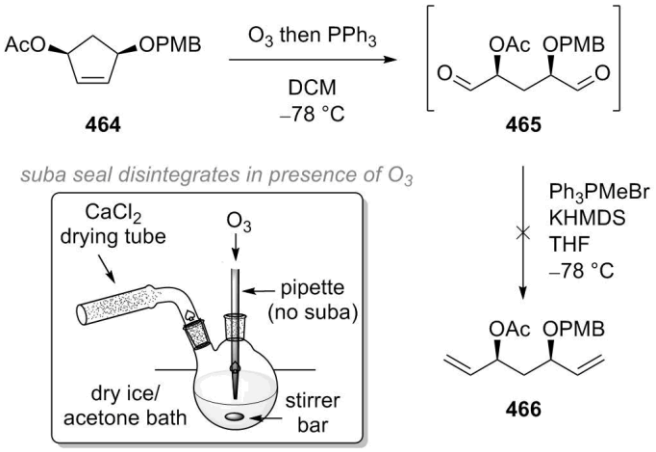


Scheme 4-5: PMB-protection of hydroxyl **463** using PMB trichloroacetimidate **495**.

4.2.2 Ozonolysis-Wittig-deprotection sequence

With desymmetrised cyclopentene **464** in hand, attempts were made to replicate the original ozonolysis-Wittig-deprotection sequence. To simplify the sequence, the deprotection step was not performed initially. The ozonolysis set up is shown in **Scheme 4-6**. A two-necked flask was equipped with a drying tube, and ozone was bubbled through the solution *via* a pipette. After addition of triphenylphosphine, the solvent was removed on a rotary evaporator in the two-neck flask to avoid decomposition of dialdehyde **465**

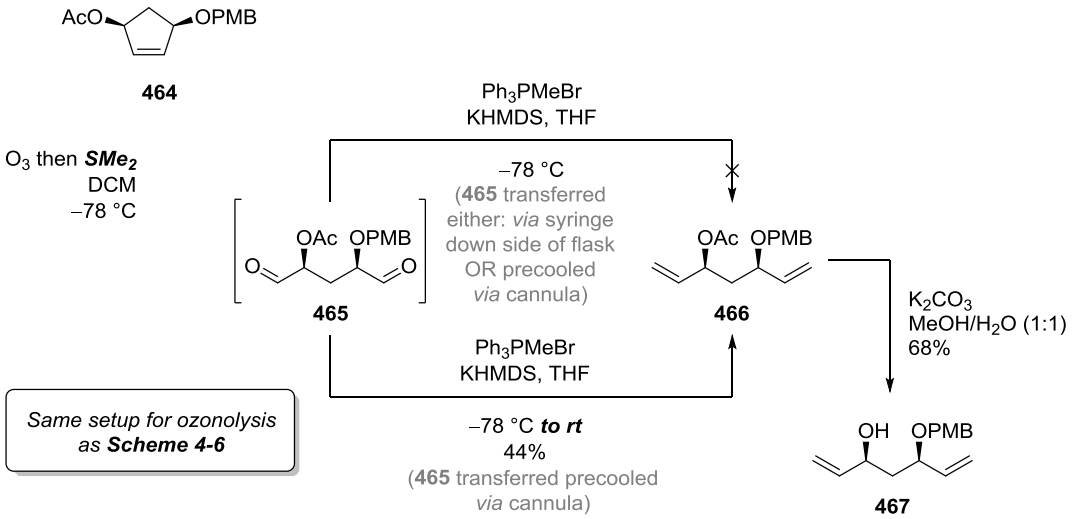
before the crude orange oil was added by syringe to the ylide in a separate flask. However, this attempt failed to give the desired diene **466**. The crude ^{1}H NMR spectrum of dialdehyde **465** before the Wittig reaction was difficult to analyse due to an abundance of aromatic protons from the triphenylphosphine and so it was difficult to see if dialdehyde **465** had been formed.



Scheme 4-6: Initial attempt at replicating ozonolysis-Wittig sequence. The ozonolysis setup is in the box.

After communication with Dr Ahria Roushanbakhti, it was noted that the aldehyde should be treated as volatile and unstable when exposed to air, and therefore should be concentrated on a rotary evaporator under N_2 and at only 200 mbar with a cold-water bath. It was also recommended to transfer dialdehyde **465** in THF by syringe down the side of the flask containing the ylide to allow the solution to cool down before addition, or alternatively to use a cannula when dialdehyde **465** in THF was pre-cooled to –78 °C. However, repeating the ozonolysis-Wittig sequence described in **Scheme 4-6** with these modifications still did not afford the desired diene **466**. Again, the crude ^{1}H NMR spectrum of dialdehyde **465** was difficult to analyse due to the triphenylphosphine quench, but four aldehyde peaks were now observed in the ^{1}H NMR (200 MHz, $CDCl_3$) spectrum at 9.81, 9.53, 9.52 and 9.40 ppm.

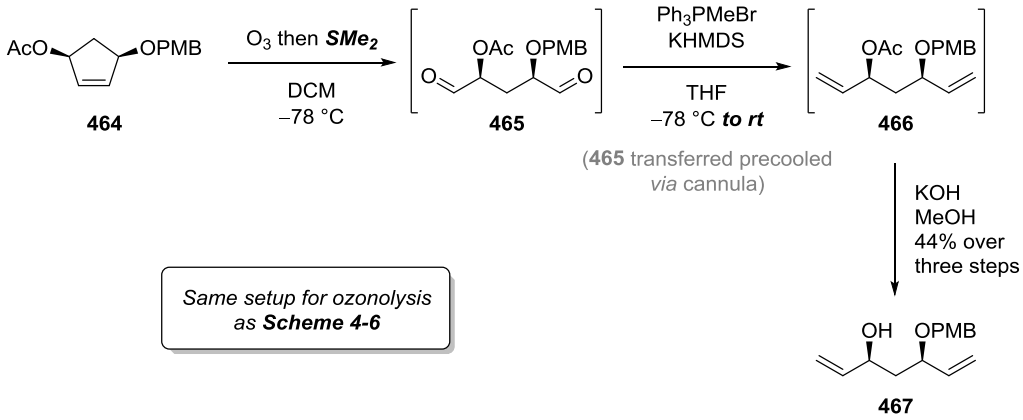
To aid ^{1}H NMR analysis of the dialdehyde **465**, triphenylphosphine was replaced with dimethylsulfide because dimethylsulfide is volatile and would be removed upon concentration of dialdehyde **465**. However, dimethylsulfide did not completely quench the ozonide at –20 °C as indicated by TLC analysis, and therefore the reaction was warmed to room temperature after an hour. Pleasingly, the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of the crude dialdehyde **465** contained peaks at 9.88, 2 × 9.59 and 9.46 ppm. After careful concentration, a THF solution of dialdehyde **465** was precooled and transferred *via* cannula into the ylide suspension. TLC analysis of the Wittig reaction showed the desired product. However, after the reaction had been quenched at –78 °C, none of the desired product **466** was observed in the crude ^{1}H NMR spectrum (**Scheme 4-7**). The Wittig reaction may require warming to room temperature before quenching because it might have reacted upon warming for the TLC. Gratifyingly, alkene **466** was isolated in 44% yield over two steps upon warming. The acetate group was removed by treatment of **466** with K_2CO_3 in MeOH/H_2O (1:1) to give the alcohol **467** in 68% yield.



Scheme 4-7: Modifications to the ozonolysis-Wittig sequence and subsequent acetate-deprotection.

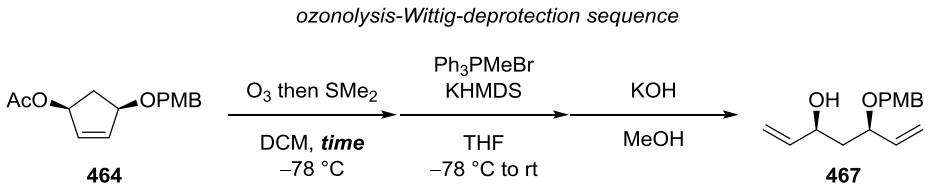
Additionally, the TLC analysis the Wittig reaction shown in **Scheme 4-7** also showed traces of the acetate-deprotected alcohol **467**, as reported by Dr Ahria Roushanbakhti.[161]

The ozonolysis-Wittig-deprotection sequence was repeated to access alcohol **467** directly. Use of KOH and MeOH as the quench for the Wittig reaction led to hydrolysis of the acetate group. Pleasingly, alcohol **467** was isolated in 44% yield over three steps on a 100 mg scale (**Scheme 4-8**).



Scheme 4-8: Successful ozonolysis-Wittig-deprotection sequence to access alcohol **467**.

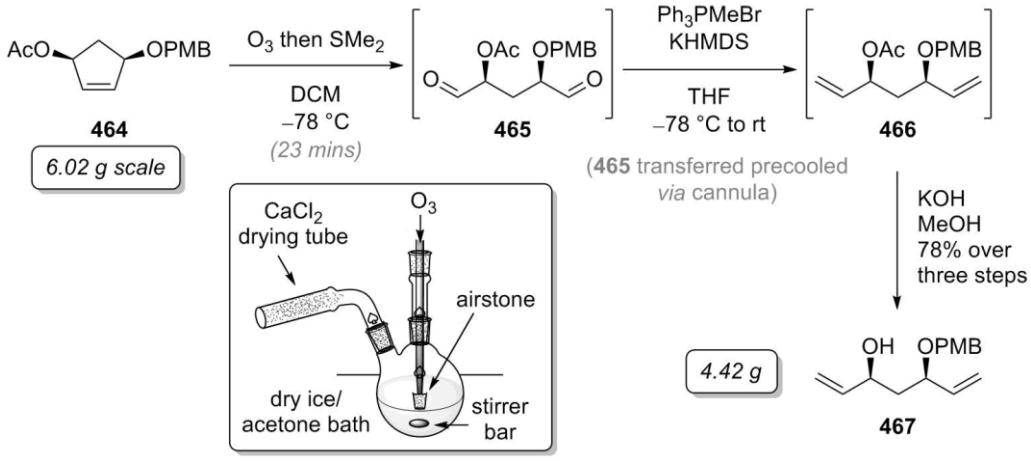
However, scaling up the reaction using the setup shown in **Scheme 4-6** resulted in increased reaction times for the ozonolysis reaction, as shown in **Table 4-1**. The increase in reaction time does not appear to be linearly correlated with the scale, as **entry 3** with 2.5 g of the starting material **464** was expected to be completed in around 1 hour and 15 minutes but took nearly 4 hours instead.



Entry	Scale (**464**)	Time (O_3)*	Yield **467**
1	100 mg	5 min	44%
2	500 mg	14 min	58%
3	2.5 g	3 h 52 min	51%

Table 4-1: Scale-up of ozonolysis-Wittig-deprotection sequence. * Time taken for the solution to turn blue (indicating saturation of O_3) using the setup shown in **Scheme 4-6**.

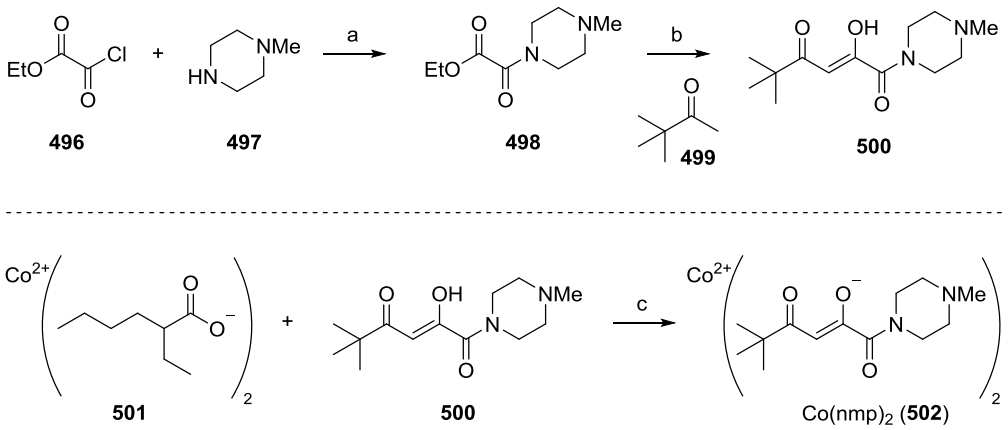
Replacing the pipette with an airstone for the ozone to bubble through was remarkably effective (set up shown in **Scheme 4-9**), and reduced the time required for ozonolysis of 2.5 g of **464** to 8 minutes and afforded **467** in 56% yield (*cf.* **entry 3**, **Table 4-1**). This reaction was scaled up to 6.02 g of **464**, which required 23 minutes for ozonolysis, and provided 78% yield of **467** (**Scheme 4-9**).



Scheme 4-9: Scaled up ozonolysis-Wittig-deprotection sequence with alternative setup for ozonolysis.

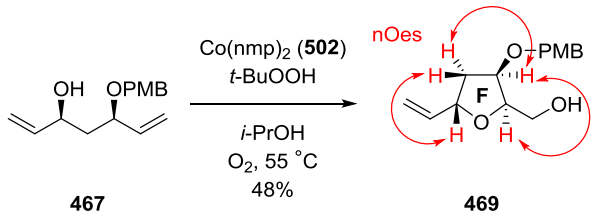
4.2.3 Mukaiyama oxidative cyclisation

For the Mukaiyama oxidative cyclisation of alcohol **467**, the $Co(nmp)_2$ catalyst was synthesised according to the procedure described by Pagenkopf (**Scheme 4-10**).[163] Ethyl oxalyl chloride **496** and *N*-methylpiperazine **497** were coupled together to form amide **498** in quantitative yield. A Claisen reaction with pinacolone **499** afforded adduct **500**, the nmp ligand, in 47% yield which existed exclusively as the enol form. Ligand exchange with cobalt(II) ethyl-2-hexanoate **501** and nmp **500** provided $Co(nmp)_2$ (**502**) for the use in the Maikyama oxidative cyclisation.



Scheme 4-10: Synthesis of $Co(nmp)_2$ (**502**) for the Mukaiyama oxidative cyclisation.
Reagents and conditions: a) Et_3N, DCM, 0 °C, quant.; b) **499**, *t*-BuOK, THF, 0 °C, 47%; c) benzene, 0 °C, 95%.

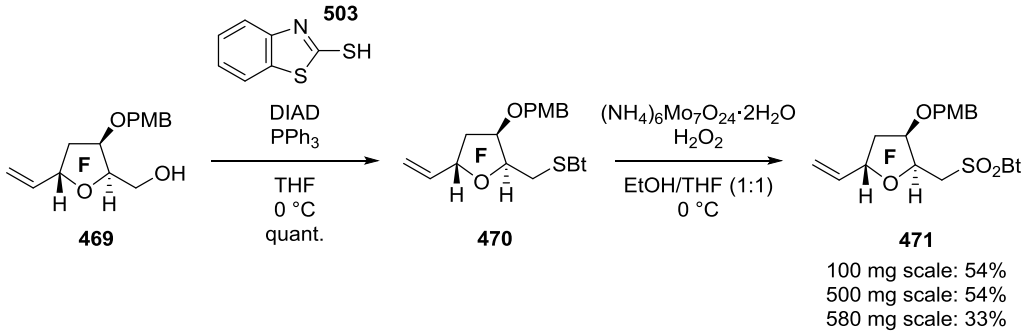
The Mukaiyama oxidative cyclisation reaction of **467** afforded *trans*-tetrahydrofuran ring **469** in 48% yield as a single diastereomer (**Scheme 4-11**). The *trans*-junction was confirmed by nOe analysis and matched the reported characterisation data.[43]



Scheme 4-11: Mukaiyama oxidative cyclisation of **467**.

4.2.4 Mitsunobu and sulfide oxidation

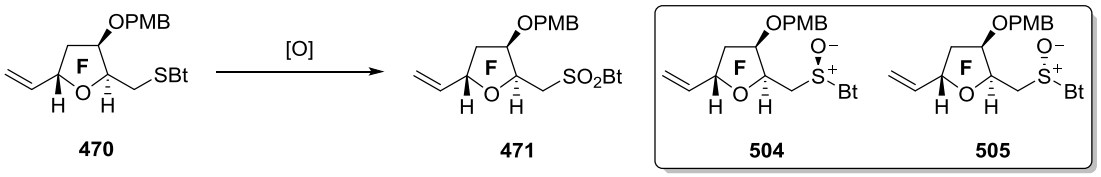
In preparation for the Julia reaction with the E ring fragment, the primary hydroxyl group of **469** was converted into the sulfone in two steps. The Misunobu reaction[165] with mercaptobenzothiazole **503** gave a quantitative yield of sulfide **470** (**Scheme 4-12**). However, the original conditions to oxidise sulfide **470** to the corresponding sulfone **471** did not give consistently reproducible results. Upon scaling up, the yield of **471** dropped from 54% to 33% yield.[159, 167]



Scheme 4-12: Mitsunobu reaction and sulfide oxidation.

Alternative oxidation conditions were explored, as shown in **Table 4-2**. **Entries 1** and **2** are the summarised conditions from **Scheme 4-12**. Various equivalents of *m*-CPBA were used, based upon Evans' synthesis.[23] Reaction of **470** with 2.2 equivalents provided the diastereomeric sulfoxides **504** and **505**, but the desired sulfone **471** was not isolated (**entry 3**). Increasing the number of equivalents of the oxidant used to 6.3 afforded the sulfone in 41% yield (**entry 4**), but increasing the oxidant further to 10 equivalents did not improve the yield much more (**entry 5**). Interestingly, epoxidation of the terminal alkene was not observed.

Oxone[168] failed to oxidise sulfide **470** and the starting material was returned from the reaction (**entry 6**). Reaction with ruthenium(III) chloride hydrate and sodium periodate[169] produced sulfone **471** in 11% yield, with a 25% yield of sulfoxide **504**/**505** and recovery of 53% yield of the starting sulfide **470** (**entry 7**). However, Na_2WO_4 was found to be reliable and reproducible, and delivered yields of 54%, 53% and 60% when reactions were performed on 50 mg, 200 mg and 1 g scales respectively (**entries 8**, **9** and **10**).[159, 170] Interestingly, it appears one diastereomer of the sulfoxides **504** and **505** is converted to the sulfone faster than the other because only one diastereomer was isolated. It proved difficult to push the reaction to completely oxidise the remaining sulfoxide but the yields obtained from the reaction with Na_2WO_4 were acceptable to progress with the synthesis.



470 **471** **504** **505**

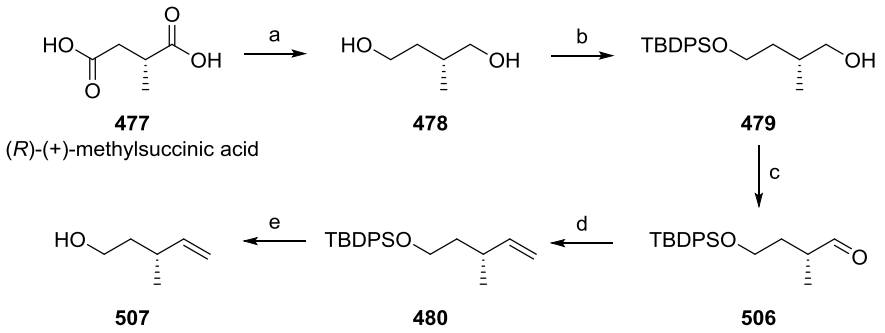
Entry	[O]	Yield **471**	Yield **504**/**505** [a]
1 [b, c]	$(NH_4)_6Mo_7O_{24}\cdot 2H_2O$ (10 mol%), H_2O_2 (12 equiv.), EtOH/THF (1:1), 0 °C	54%	-
2 [d]	$(NH_4)_6Mo_7O_{24}\cdot 2H_2O$ (10 mol%), H_2O_2 (12 equiv.), EtOH/THF (1:1), 0 °C	33%	-
3	*m*-CPBA (2.2 equiv.), $NaHCO_3$ (2.2 equiv.), DCM, 0 °C	0%	46%
4	*m*-CPBA (6.3 equiv.), $NaHCO_3$ (6.3 equiv.), DCM, 0 °C	41%	-
5	*m*-CPBA (10 equiv.), $NaHCO_3$ (10 equiv.), DCM, 0 °C	49%	-
6 [e]	Oxone (1.5 equiv.), H_2O, rt	0%	-
7 [f]	$RuCl_3\cdot xH_2O$ (25 mol%). $NaIO_4$ (2.5 equiv.), DCM/MeCN/H_2O (1:1:1), rt	11%	25%
8 [g]	**Na_2WO_4 (10 mol%), H_2O_2 (12 equiv.), MeOH/THF (4:1), 0 °C**	**54%**	**16% (>95:5 dr)**
9 [h]	**Na_2WO_4 (10 mol%), H_2O_2 (12 equiv.), MeOH/THF (4:1), 0 °C**	**53%**	**-**
10 [i]	**Na_2WO_4 (10 mol%), H_2O_2 (12 equiv.), MeOH/THF (4:1), 0 °C**	**60%**	**-**

Table 4-2: Optimisation of sulfide oxidation. A dash means data was not collected. [a] Indeterminable mixture of the sulfoxide diastereomers unless stated otherwise. [b] 100 mg scale. [c] 500 mg scale. [d] 580 mg scale. [e] 87% recovered starting material **470**. [f] 53% recovered starting material **470**. [g] 50 mg scale. [h] 200 mg scale. [i] 1 g scale.

4.2.5 Alkene cross metathesis with side chain fragment

The side chain fragments **480** and **507** required for the cross metathesis reaction were synthesised by co-worker Timothy Kwok[48] in four or five steps respectively from (*R*)-(+)-methylsuccinic acid **477**,[171] as described in the original publication (**Scheme 4-13**).[43] Both side chain fragments **480** and **507** were used in the attempted cross metathesis reactions with F ring **471** because use of the unprotected alcohol **507** would slightly

shorten the linear sequence for the synthesis of the F ring, despite the published route using the TBDPS-protected fragment **480**.



Scheme 4-13: Synthesis of the side chain fragment by co-worker Timothy Kwok.
Reagents and conditions: a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C to rt, 93%; b) TBDPSCl, imidazole, DMAP, DCM, 0 °C to rt, 69%; c) DMSO, $(COCl)_2$, Et_3N, DCM, –78 °C; d) $MePPh_3Br$, *n*-BuLi, THF, 0 °C, 62% over two steps; e) TBAF, THF, 50 °C, 79%.

Based on the model for selective olefin cross metathesis published by Grubbs in 2002, both alkene partners **480** and **507** as well as the F ring **471** are classed as Type I olefins and undergo rapid homodimerization.[172] To disfavour homodimerization, it was reported that 4 equivalents of the least precious alkene partner (either **480** or **507**) could be used.[160] From the model proposed by Grubbs, it was suggested to use Grubbs Second Generation catalyst (G-II, **509**)[173] should be used instead of the First Generation catalyst (G-I, **508**)[174] because it has higher activity (**Figure 4-2**). However, Hoveyda–Grubbs Second Generation Catalyst (HG-II, **510**)[175] was not reviewed in the model, and it is known to have superior activity and stability so it was the chosen catalyst for our cross metathesis reactions.[176]

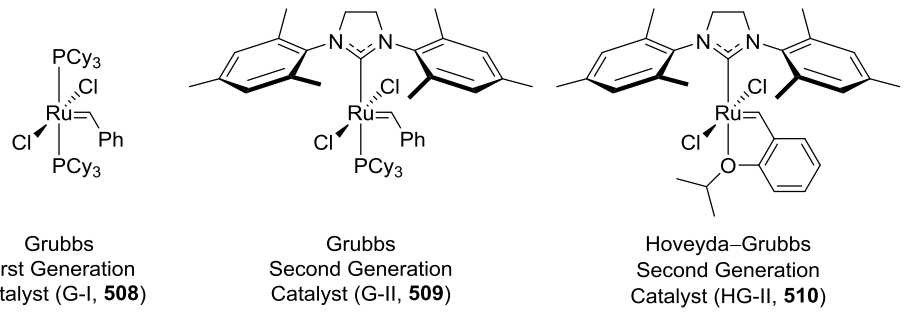
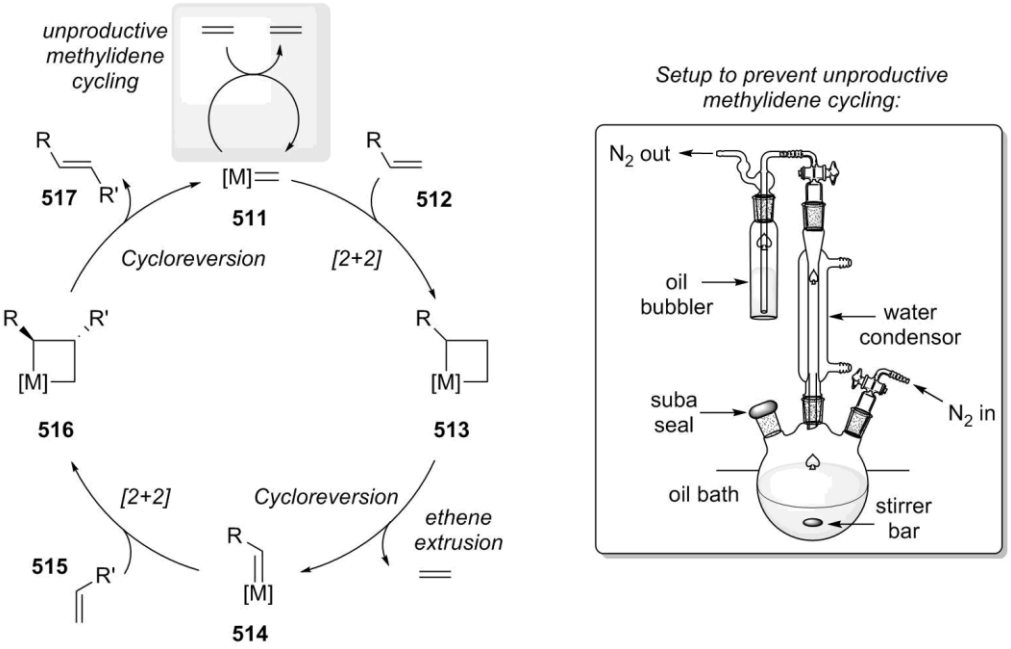


Figure 4-2: A selection of cross metathesis catalysts.

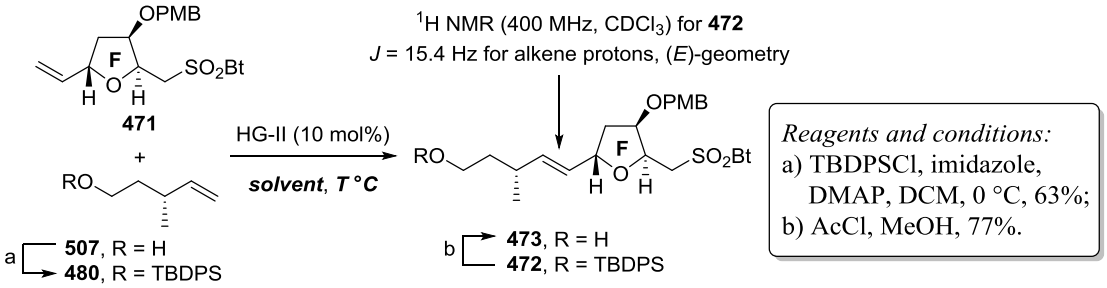
The cross metathesis reaction produces an equivalent of ethene per catalytic cycle, as shown in **Scheme 4-14**.[177] It was previously noted within the Donohoe group that despite the volatility of ethene (bp = –104 °C), the headspace accumulated a significant amount of ethene which was detrimental to the catalytic cycle and catalyst longevity.[178, 179] It was suggested that the accumulated ethene would react with active catalyst **511** in an unproductive methylidene cycle, preventing normal catalytic turnover and accelerating catalyst decomposition. To prevent this, a gentle stream of nitrogen gas was passed across the reaction headspace by use of the setup shown in **Scheme 4-14**.



Scheme 4-14: Catalytic cycle for a cross metathesis reaction and the set up used for our cross metathesis.

The cross metathesis reaction with unprotected side chain fragment **507** and the F ring **471** did not proceed cleanly, as reported previously,[161] and produced 41% yield of **473** (**entry 1**, **Table 4-3**). After alcohol **507** had been protected with TBDPSCl to afford 63% yield of **480**, this side chain fragment was used in subsequent cross metathesis reactions. Repeating the reaction in DCM delivered the desired adduct **472** cleanly in 62% yield (**entry 2**). However, the solvent in both **entries 1** and **2** evaporated overnight.

To prevent solvent evaporation, alternative less-volatile solvents were explored. Performing the reaction in toluene prevented solvent evaporation overnight but the reaction only afforded a 36% yield of **42** (**entry 3**). DCE also did not evaporate and an increased yield of 44% of **472** was obtained (**entry 4**). The use of chlorobenzene as the solvent did not improve the yield further despite not evaporating (**entry 5**). However, replacing the suba seal with a glass stopper and lowering the temperature to 40 °C afforded **472** in 80% yield without loss of solvent (**entry 6**). Adduct **472** can was deprotected with AcCl in MeOH in 77% yield.



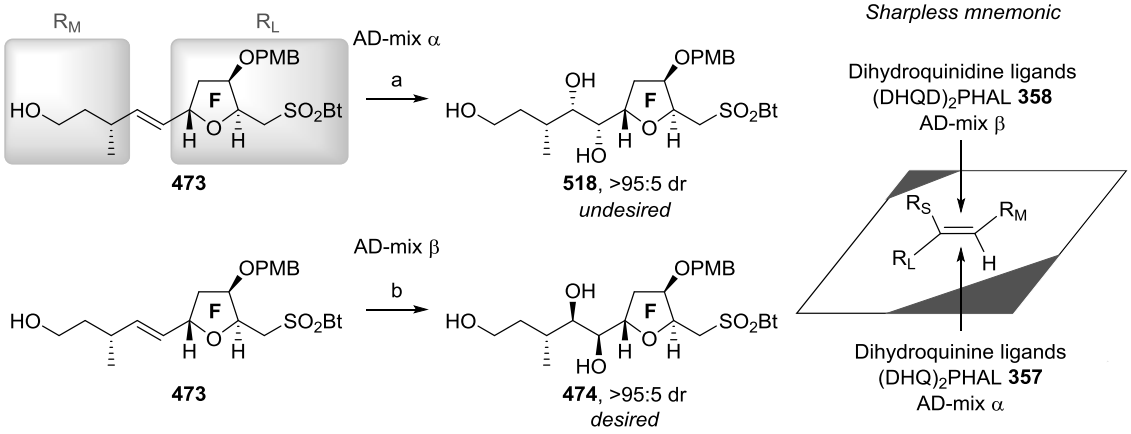
Entry	R	Solvent	T °C	Yield **472**
1 †, ‡	H	DCM	45 °C	41%
2 [b]	TBDPS	DCM	45 °C	62%
3	TBDPS	PhMe	45 °C	36%
4	TBDPS	DCE	45 °C	44%
5	TBDPS	PhCl	45 °C	24%
6 *	**TBDPS**	**DCM**	**40 °C**	**80%**

Table 4-3: Optimisation of the cross metathesis reaction using 4 equiv. of **480** or **507**. † Yield of **473**. ‡ Solvent evaporated. * Replaced suba seal with glass stopper to prevent solvent evaporation.

4.2.6 Dihydroxylation and silyl tether

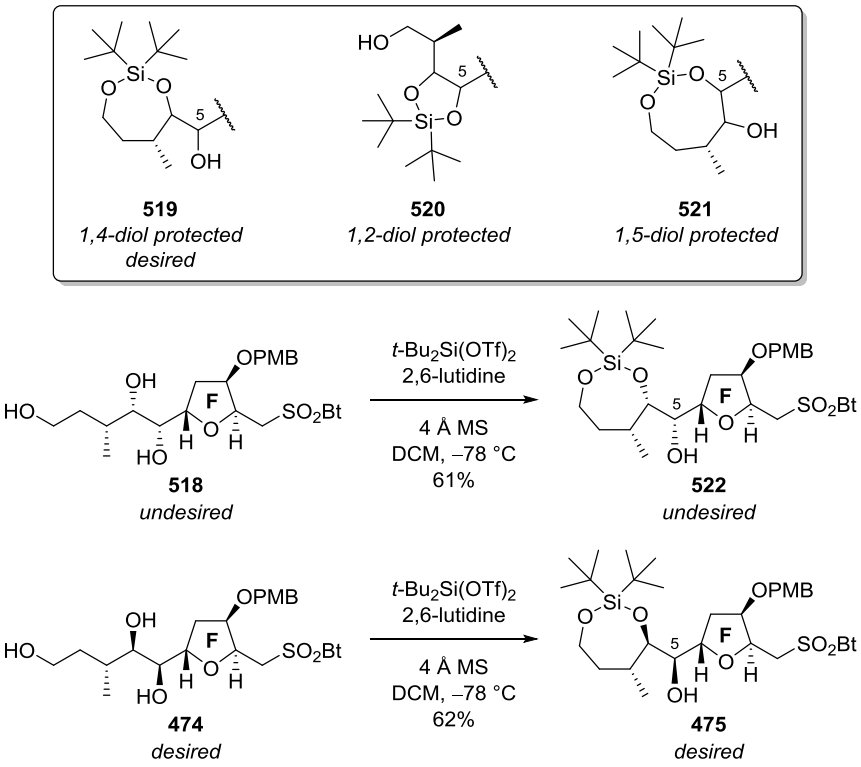
The facial selectivity of the dihydroxylation reaction of alkene **473** was predicted by the Sharpless mnemonic.[113, 127] With the F ring as the R_L substituent and the alcohol side chain as the R_M substituent, the mnemonic predicts that AD-mix β should dihydroxylate the correct face of alkene **473**. Both AD-mix α and β were used to confirm that each

produces a different isomer. The α mix afforded undesired triol **518** in 70% yield (>95:5 dr) and the β mix produced desired triol **474** in 74% yield (>95:5 dr, **Scheme 4-15**), the NMR data for which was compared to the data previously reported in order to confirm the relative stereochemistry.[161]



Scheme 4-15: Dihydroxylation of alkene **473**.
Reagents and conditions: a) $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 °C to rt, 70%, >95:5 dr; b) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 °C to rt, 74%, >95:5 dr.

With both triols in hand, the protection of 1,4-diol motif (**519**) over the 1,2- or 1,5-diol motif (**520** or **521**) with *t*-$Bu_2Si(OTf)_2$ was attempted on each, using undesired triol **518** to test the reaction. Pleasingly, both reactions afforded the desired 1,4-diol protected with the silyl tether, with a 61% yield of undesired **522** and a 62% yield of desired **475**. The proton of the C-5 hydroxyl group has a COSY correlation to the C-5 methine, which in turn correlates *via* COSY and HMBC to the adjacent protons and carbons, confirming the connectivity of the desired 1,4-diol tether. Additionally, the NMR data for compound **475** also matches data previously reported for this compound.[43, 161] As Dr Ahria Roushanbakhti had previously obtained an X-ray crystal structure for a derivative of **475** (as mentioned in **Chapter 4.1**), the relative stereochemistry of the *trans*-tetrahydrofuran, the 1,2-diol resulting from the Sharpless asymmetric dihydroxylation reaction and the silyl tether had been confirmed.[43, 161]



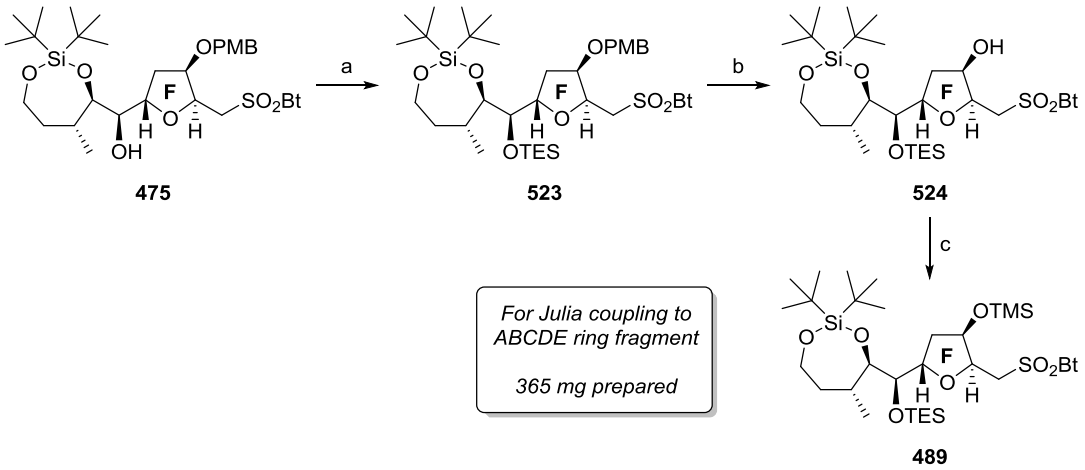
Scheme 4-16: Silyl tether protection of triols **518** and **474**.

4.2.7 Final steps to complete synthesis of F ring

The final steps for the synthesis of the F ring required TES protection of the alcohol **475**, followed by a protecting group interchange from PMB to TMS. The TES protection of the alcohol **475** was accomplished in quantitative yield (**Scheme 4-17**). The protocol described by Evans[23] for PMB group removal with DDQ in 1 M pH 7 buffer (NaH_2PO_4/Na_2HPO_4) and DCM revealed alcohol **524** in 87% yield.

The final step of TMS protection of the alcohol **524** gave the desired F ring fragment **489** in 89% yield. The TMS group is relatively labile, and hydrolysed on silica gel column purification, including when the eluent was doped with 1% Et_3N. However, it was found that using neutral alumina instead of silica gel for purification prevented hydrolysis of the TMS group.

A total of 365 mg of F ring **489** was prepared ready for the Julia coupling with the ABCDE ring fragment in the total synthesis of PTX-4.



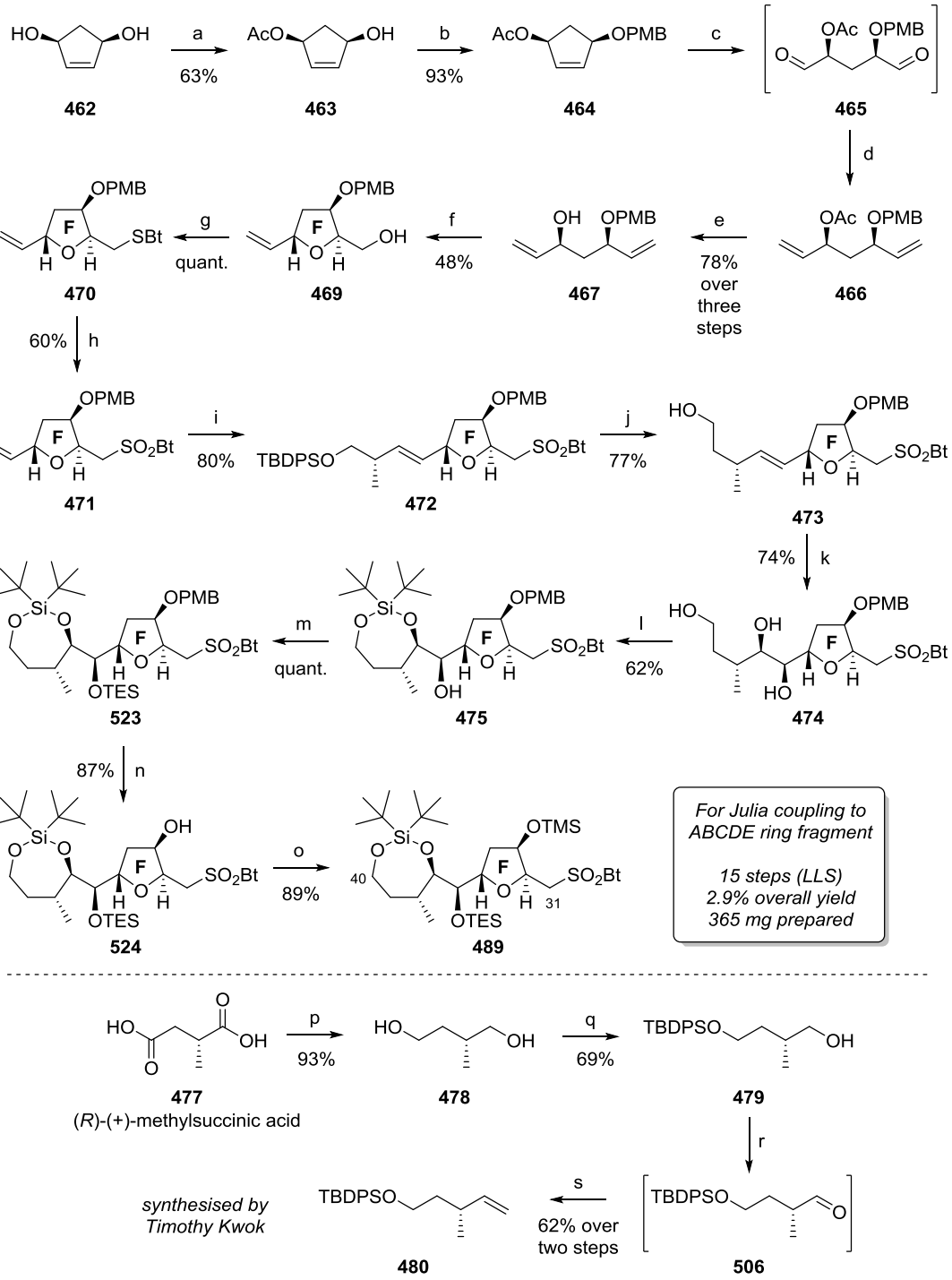
Scheme 4-17: Final steps in the synthesis of F ring **489**, in preparation for the Julia olefination with ABCDE ring fragment.
Reagents and conditions: a) TESCl, imidazole, DCM, 0 °C, quant.; b) DDQ, 1 M pH 7 buffer, DCM, 87%; c) TMSCl, imidazole, DCM, 0 °C, 89%.

4.3 Conclusions & Future Work

The synthesis of F ring fragment **489** (C-31 to C-40) was achieved in 15 steps (LLS) in 2.9% overall yield from commercially available *cis*-diol **462** (**Scheme 4-18**). Various steps, including the ozonolysis-Wittig-deprotection sequence, were reoptimised *en route* to the F ring fragment. A total of 365 mg of **489** was synthesised and stored in preparation for the Julia coupling to the ABCDE fragment.

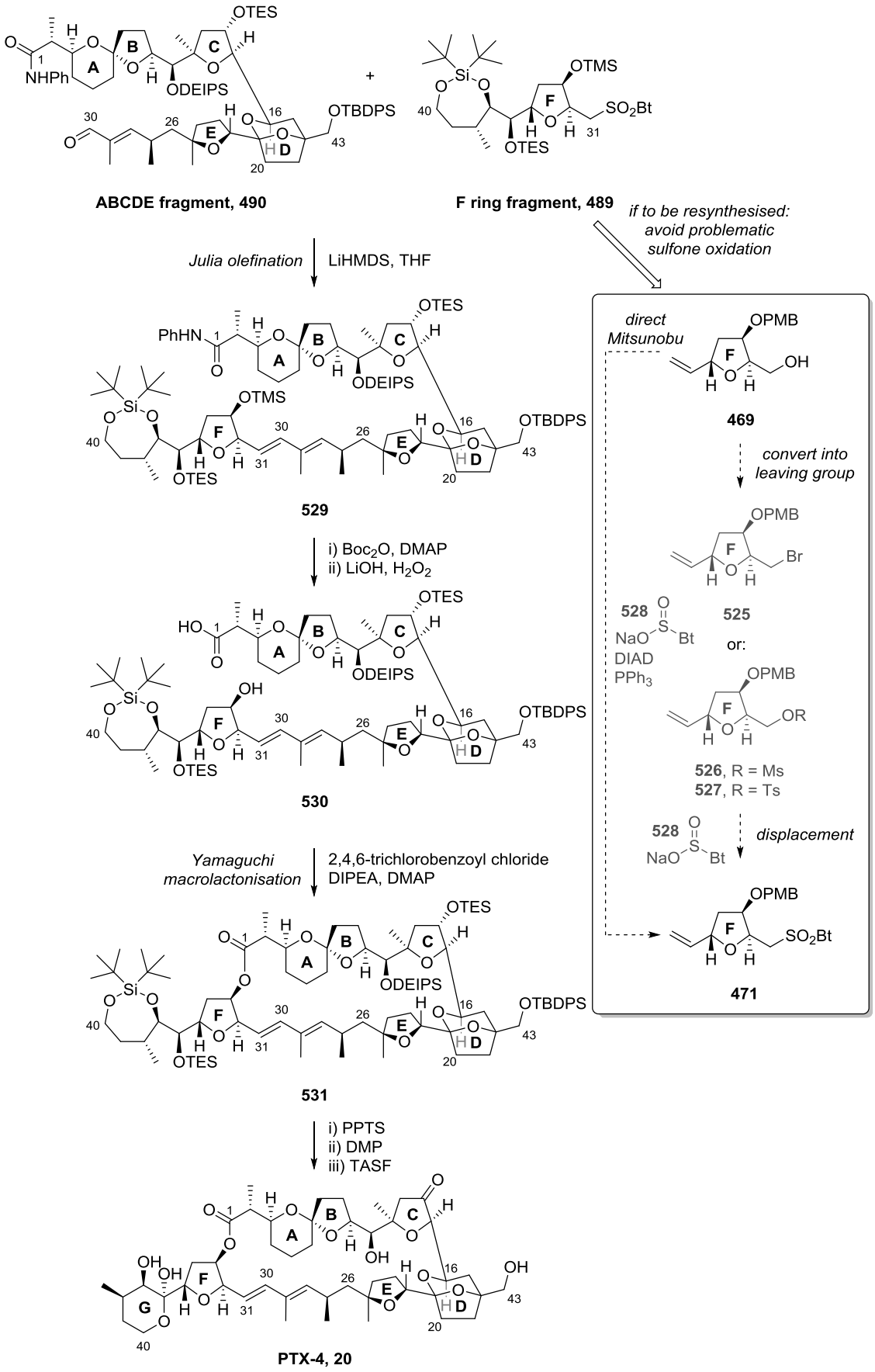
In the event that the F ring needs to be resynthesised, future work could be to research if the sulfinate salt of 2-mercaptobenzothiazole **528** could be used to access the sulfone directly from F ring **469** (**Scheme 4-19**). This could possibly be achieved by a Mitsunobu reaction, or a simple displacement of the alcohol when converted to a better leaving group (for example, a mesylate **526** or bromide **527**).[180]

The final steps after the Julia coupling reaction would be the Yamaguchi macrolactonisation,[34] lactonisation of the G ring, late-stage oxidation of the hydroxyl groups at C-14 and C-36, and global deprotection (**Scheme 4-19**). This would complete the synthesis of PTX-4. This work is currently ongoing within the group.



Scheme 4-18: Summary of **Chapter 4**.

Reagents and conditions: a) vinyl acetate, pancreatin, Et_3N, THF, 63%; b) 4-methoxybenzyl-2,2,2-trichloroacetimidate, CSA, DCM/pentane (4:1), 0 °C, 93%; c) O_3, SMe_2, DCM, –78 °C; d) $MePPh_3Br$, KHMDS, THF –78 °C to rt; e) KOH, MeOH, 78% over three steps; f) $Co(nmp)_2$ (30 mol%), *t*-BuOOH, *i*-PrOH, O_2, 55 °C, 48%; g) BtSH, PPh_3, DIAD, 0 °C, quant.; h) H_2O_2, Na_2WO_4 (10 mol%), MeOH/THF (4:1), 60%; i) **480**, HG-II (10 mol%), DCM, 40 °C, 80%; j) AcCl, MeOH, 77%; k) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 °C to rt, 74%; l) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DCM, 4 Å MS, –78 °C, 62%; m) TESCl, imidazole, DCM, 0 °C, quant.; n) DDQ, 1 M pH 7 buffer, DCM, 87%; o) TMSCl, imidazole, DCM, 0 °C, 89%; p) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C to rt, 93%; q) TBDPSCl, imidazole, DMAP, DCM, 0 °C to rt, 69%; r) DMSO, $(COCl)_2$, Et_3N, DCM, –78 °C; s) $MePPh_3Br$, *n*-BuLi, THF, 0 °C, 62% over two steps.



Scheme 4-19: Future work to complete the synthesis of PTX-4.

Chapter 5

Chapter 5: Experimental

5.1 General experimental

5.1.1 Solvents and reagents

All reactions were performed using flame-dried reaction vessels under an atmosphere of argon unless stated otherwise. Anhydrous diethyl ether (Et_2O), dichloromethane (DCM), methanol (MeOH), acetonitrile (MeCN), toluene (PhMe) and tetrahydrofuran (THF) were obtained from MBRAUN SPS-5 solvent purification system by passage through double filtration columns under N_2. Brine refers to a sat. aq. solution of NaCl. The 1 M pH 7 buffer was made as follows: 4.680 g of NaH_2PO_4 and 8.662 g Na_2HPO_4 were dissolved in a 100 mL volumetric flask with up to 100 mL distilled H_2O. 2,3-Dibromopropene was purchased from Sigma Aldrich (80% purity, technical grade, 106003-25G). Methyl vinyl ketone (MVK) was purchased from Alfa Aesar (90% purity, technical grade, stabilised with 0.5% hydroquinone, A11910). Potassium phenoxide (KOPh) was prepared according to the procedure described by Kornblum and Lurie.[181] Propargyl bromide was purchased from Sigma Aldrich (purum, ~80% in toluene, 81831-250ML). Zinc dust was purchased from Sigma Aldrich (dust, <10 μm, ≥98%, 209988-100G), and was freshly activated before use by stirring in 1 M aq. HCl for 1 h, washing with H_2O (2 × 100 mL) and dried under vacuum at 150 °C. The resulting powder was then ground using a mortar and pestle.[182] TMEDA was freshly distilled over sodium under Ar.[183] (1*R*,3*S*)-Cyclopent-4-ene-1,3-diol was purchased from Sigma Aldrich (≥99.0% (GC), 29823-2.5G). Pancreatin was purchased from Sigma Aldrich (from porcine pancreas, 8 × USP specifications, P7545-25G). Potassium *tert*-butoxide was purchased from Sigma Aldrich (sublimed grade, 99.99% trace metals basis, 659878-5G). *tert*-Butyl hydroperoxide solution was purchased from Sigma Aldrich (packed in FEP bottles,

~5.5 M in decane (over molecular sieve 4Å), 19997-25ML). Other reagents were used as supplied.

5.1.2 Chromatography

Thin layer chromatography (TLC) was carried out using Merck aluminium-backed TLC Silica Gel 60 F_{254} pre-coated plates (particle size 0.2 mm). Preparative TLC was performed using glass-backed (500 μm) Merck Kieselgel 60 F_{254} plates. Plates were visualised by the quenching of fluorescence under ultraviolet light (λ_{max} = 254 nm) and by staining and heating with potassium permanganate, anisaldehyde, vanillin, ammonium molybdate or ceric ammonium molybdate as appropriate. Flash column chromatography was performed using Merck Geduran® 60 silica gel (particle size 40–63 μm) unless stated otherwise, with the solvent system given in parentheses. Flash column chromatography using alumina was performed using Sigma Aldrich (06300) activated neutral (pH 7.0 ± 0.5) Brockmann Activity I alumina (0.05–0.15 mm). All solvents used for chromatography purification were HPLC grade or equivalent and supplied by Honeywell, Sigma Aldrich or Thermo Fisher Scientific.

5.1.3 Optical rotation

Specific optical rotations were measured on a Schmidt Haensch Unipol L2000 Polarimeter with a 100 mm quartz glass microtube (1 cm^3 volume) at the sodium D line (589.3 nm) at 25 °C in $CHCl_3$ or ACS photo spectroscopic grade CH_2Cl_2 and are reported in the units of 10^{-1} deg cm^2 g^{-1}. Solution concentrations are given in units of 10^{-2} g mL^{-1}.

5.1.4 Melting points

Melting points (m.p.) were obtained using a Leica VMTG heated-stage microscope equipped with a Testo 720 thermometer and are uncorrected.

5.1.5 Infrared spectroscopy

Infrared spectra were recorded using a Bruker Tensor 27 fourier-transform infrared (FT-IR) spectrometer as neat samples on the Pike Miracle Attenuated Total Reflectance (ATR) diamond module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w), and broad (br.).

5.1.6 NMR spectroscopy

Proton (^{1}H), carbon (^{13}C), boron (^{11}B) and fluorine (^{19}F) spectra were recorded on Bruker AVB-500 (AVII 500, 500/126 MHz), Bruker AVC-500 (AVII 500 with He cryoprobe, 500/126 MHz), Bruker AVF-400 (AVIII HD 400 nanobay, 400/101/377 MHz) or Bruker DPX-200 (200 MHz) spectrometers in deuterated solvents. ^{13}C spectra were recorded with broadband decoupling. Chemical shifts (δ_H, δ_C or δ_F) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR or 0.1 ppm for ^{13}C, ^{11}B and ^{19}F NMR. ^{1}H and ^{13}C NMR spectra were referenced to the solvent residual peak ($CDCl_3$, δ 7.26 and 77.16 ppm respectively; CD_2Cl_2, δ 5.32 and 54.00 ppm respectively; C_6D_6, 7.16 and 128.06 ppm respectively). ^{11}B and ^{19}F NMR spectra are not externally referenced. Peak assignments were made on the basis of chemical shifts, integrations and coupling constants, using COSY, HSQC, HMBC, DEPT135, DEPTQ, NOESY and TOCSY experiments where appropriate. Multiplets are described as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), double triplet (dt), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), quadruple doublet (qd), multiplet (m), broad (br.) and apparent (app.). Coupling constants (*J*) are rounded to the nearest 0.1 Hz. Mosher's ester analyses of compounds **282**, **331**, **463**, and **539** are in the **Appendix 6.1**. ^{1}H, ^{13}C NMR and nOe analyses of compounds **351, 399, 400, 403, 447, 451**, and **469** are also in the **Appendix 6.2**.

5.1.7 Mass spectrometry

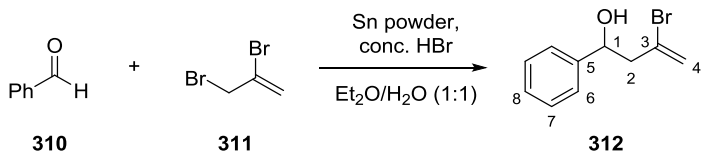
Low resolution mass spectra were recorded on an Agilent 6120 Quadrupole spectrometer equipped with an Agilent 1260 Infinity LC pump, with a flow rate of 0.2 mL/min using H_2O/MeOH/HCO_2H (10:89.9:0.1) as eluent. The mass reported is that containing the most abundant isotopes under electrospray ionisation (ESI). High resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory mass-spec facilities. For the ESI accurate mass service, analyses were performed using a Thermo Exactive mass spectrometer equipped with Waters Acquity liquid chromatography system using the same flow rate and eluent as above. Instrument control and data processing were performed using Thermo Xcalibur Software. The mass spec was operated using the heated electrospray (HESI-II) probe and resolution was set to 50,000 FWHM. Electrospray source conditions were adjusted to maximise sensitivity. For the electron ionisation (EI) and Chemical ionisation (CI) accurate mass service, analyses were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. Source conditions for both EI and CI were adjusted to maximise sensitivity, the reagent gas used in CI was ammonia. Both systems were calibrated on the day of the analysis and its mass accuracy with external calibration (as used for these experiments) is better than 5 ppm for 24 h following calibration. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass. Mass to charge ratios (*m/z*) are reported in Daltons.

5.1.8 Reporting of compounds

Compounds that are not assigned a compound number are labelled S1, S2 etc. Systematic names were generated by the computer programme ChemDraw according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). However, the numbering on the structures may not correspond to the systematic name. The NMR assignments follow the numbering system shown on the structures for straightforward comparison of data.

5.2 Experimental procedures for D ring model studies

3-Bromo-1-phenylbut-3-en-1-ol (312)*



310 **311** **312**

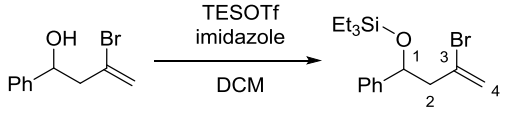
To a suspension of Sn powder (1.82 g, 15.4 mmol) and 2,3-dibromopropene **311** (80% purity, 3.0 mL, 31 mmol) in Et_2O (10 mL) and H_2O (10 mL) was added benzaldehyde **310** (1.04 mL, 10.2 mmol) followed by 3 drops of concentrated HBr (48% aq. HBr). The reaction mixture was stirred at rt for 10 h. The suspension was filtered through a silica plug eluting with Et_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 95:5 pentane:EtOAc) to afford the title compound **312** (2.31 g, 99%) as a colourless oil.

R_f: 0.63 (50:50 pentane:EtOAc); **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.43–7.27 (5H, m, ArH), 5.69 (1H, s, C-4H_AH$_B$), 5.55 (1H, d, J = 1.6 Hz, C-4H$_A$$H_B$), 5.04 (1H, ddd, J = 8.6, 4.2, 2.3 Hz, C-1H), 2.85 (1H, ddd, J = 14.5, 8.8, 0.8 Hz, C-2H_AH$_B$), 2.75 (1H, ddd, J = 14.5, 4.3, 1.2 Hz, C-2H$_A$$H_B$), 2.09 (1H, d, J = 2.7 Hz, OH); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 143.0 (C-5), 130.2 (C-3), 128.7 (2C, 2 × C-6), 128.0 (2C, 2 × C-7), 126.0 (C-8),

* Compound **312** was prepared according to the procedure detailed by Reeves.[67]

120.2 (C-4), 71.7 (C-1), 51.5 (C-2); Spectroscopic data were consistent with those in the literature.[184]

((3-Bromo-1-phenylbut-3-en-1-yl)oxy)triethylsilane (314)

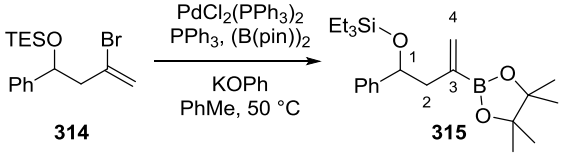


312 **314**

To a stirred solution of **312** (250 mg, 1.10 mmol) and imidazole (300 mg, 4.41 mmol) in DCM (11 mL) was added TES triflate (400 μL, 2.21 mmol) and strried at rt for 22 h. The reaction was quenched with H_2O (22 mL), the layers separated, and the aq. layer was extracted with DCM (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 99:1 pentane:Et_2O) to afford the title compound **314** (374 mg, 99%) as a colourless oil.

R_f: 0.72 (90:10 pentane:EtOAc); **IR:** ν_{max} (thin film/cm^{-1}) 2955, 2912, 2877, 1632, 1494, 1455, 1414, 1364, 1239, 1196, 1093, 1069, 1007, 944, 888, 841, 772, 744, 700; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.37–7.21 (5H, m, ArH), 5.51 (1H, dt, *J* = 1.7, 0.9 Hz, C-4H_AH_B), 5.40 (1H, d, *J* = 1.6 Hz, C-4H_AH_B), 4.96 (1H, dd, *J* = 7.9, 4.8 Hz, C-1H), 2.80 (1H, ddd, *J* = 14.0, 7.9, 0.8 Hz, C-2H_AH_B), 2.61 (1H, ddd, *J* = 14.1, 4.8, 1.1 Hz, C-2H_AH_B), 0.87 (9H, t, *J* = 7.9 Hz, $Si(CH_2CH_3)_3$), 0.54 (6H, qd, *J* = 8.3, 7.9, 3.1 Hz, $Si(CH_2CH_3)_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 144.4 (quaternary Ar), 130.7 (C-3), 128.2 (2C, Ar), 127.4 (2C, Ar), 126.0 (Ar), 119.6 (C-4), 72.6 (C-1), 53.3 (C-2), 6.9 (3C, $Si(CH_2CH_3)_3$), 4.9 (3C, $Si(CH_2CH_3)_3$); a mass spectrum could not be obtained for this compound.

4,4,5,5-Tetramethyl-2-(4-phenyl-4-((triethylsilyl)oxy)but-1-en-2-yl)-1,3,2-dioxaborolane (315)*

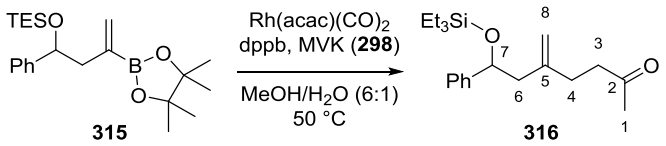


To a flask containing $PdCl_2(PPh_3)_2$ (23 mg, 33 μmol), PPh_3 (17 mg, 66 μmol), bis(pinacolato)diboron (307 mg, 1.21 mmol) and KOPh[181] (218 mg, 1.65 mmol) was added compound **314** (376 mg, 1.10 mmol) in PhMe (6.6 mL). The reaction was flushed under argon and heated to 50 °C for 6 h and then cooled to rt. Water (5.5 mL) was added and the layers were separated. The aq. layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:1 → 97:3 pentane:Et_2O) to afford the title compound **315** (315 mg, 74%) as a colourless oil.

R_f: 0.70 (90:10 pentane:Et_2O); **IR:** ν_{max} (thin film/cm^{-1}) 2954, 2876, 1618, 1417, 1369m, 1307, 1196, 1140, 1085, 1066, 1005, 960, 941, 868, 849, 818, 780, 725, 699, 670; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.30–7.14 (5H, m, ArH), 5.78 (1H, d, J = 3.6 Hz, C-4H_AH$_B$), 5.49 (1H, d, J = 3.6 Hz, C-4H$_A$$H_B$), 4.80 (1H, app. t, J = 6.6 Hz, C-1H), 2.57 (1H, dd, J = 12.7, 6.8 Hz, C-2H_AH$_B$), 2.46 (1H, dd, J = 12.5, 6.1 Hz, C-2H$_A$$H_B$), 1.25 (12H, s, 2 × C(C$H_3$)$_2$), 0.86 (9H, t, J = 7.9 Hz, Si(CH$_2$CH_3)$_3$), 0.50 (6H, qd, J = 7.9, 3.6 Hz, Si(CH_2CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 145.6 (quaternary Ar), 132.8 (C-4), 127.9 (2C, Ar), 126.8 (Ar), 126.4 (2C, Ar), 83.4 (C-3), 74.6 (C-1), 47.5 (C-2), 25.1 (2C, 2 × C(CH$_3$)$_2$), 24.9 (4C, 2 × C(CH$_3$)$_2$), 7.0 (3C, Si(CH$_2$$CH_3$)$_3$), 5.0 (3C, Si($CH_2CH_3$)$_3$); a mass spectrum could not be obtained for this compound.

* Compound **315** was prepared according to the procedure detailed by Miyaura.[94]

5-Methylene-7-phenyl-7-((triethylsilyl)oxy)heptan-2-one (316)*

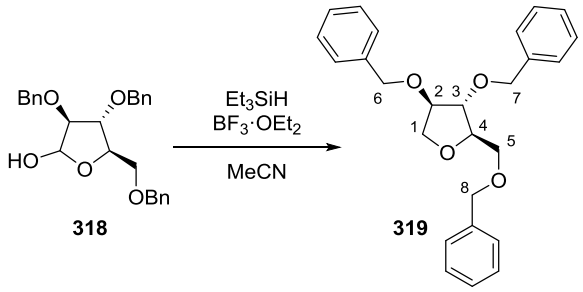


To a solution of compound **315** (100 mg, 257 μmol), $Rh(acac)(CO)_2$ (2 mg, 7.7 μmol) and dppb (3.3 mg, 7.7 μmol) in MeOH (0.90 mL) and H_2O (0.15 mL) was added MVK (**298**, 90% purity, 28 μL, 342 μmol) and the vial was flushed with argon. The reaction heated to 50 °C for 21 h and then cooled to rt. EtOAc (5 mL) and H_2O (5 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 95:5 pentane:Et_2O) to afford the title compound **316** (35 mg, 41%) as a colourless oil.

R_f: 0.45 (75:25 pentane:Et_2O); **IR:** ν_{max} (thin film/cm^{-1}) 2954, 2912, 2877, 1717, 1646, 1493, 1454, 1414, 1359, 1310, 1238, 1159, 1089, 1070, 1007, 943, 910, 894, 841, 772, 740, 701; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.28–7.15 (5H, m, ArH), 4.71 (1H, dd, J = 7.6, 5.4 Hz, C-7H), 4.69 (2H, s, C-8H_AH_B) 2.48 (2H, dd, J = 9.0, 6.4 Hz, C-3H_2), 2.41 (1H, dd, J = 13.7, 7.6 Hz, C-6$H_A$$H_B$), 2.30–2.19 (3H, m, C-4$H_2$, C-6$H_A$$H_B$), 2.09 (3H, s, C-1$H_3$), 0.81 (9H, t, J = 7.9 Hz, Si(CH_2CH_3)$_3$), 0.45 (6H, qd, J = 7.9, 2.6 Hz, Si(CH_2CH_3)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 208.6 (C-2), 145.4 (quaternary Ar), 145.1 (C-5), 128.1 (2C, Ar), 127.2 (Ar), 126.1 (2C, Ar), 112.6 (C-7), 74.6 (C-8), 47.9 (C-6), 42.0 (C-3), 30.5 (C-4), 30.0 (C-1), 6.9 (3C, Si(CH_2CH_3)$_3$), 4.9 (3C, Si(CH_2CH_3)$_3$); **HRMS:** (ESI+, *m/z*) $C_{20}H_{32}O_2{}^{28}SiNa$ (MNa^+) Calculated: 355.20638, Found: 355.20645 (Δ +0.20 ppm).

* Compound **316** was prepared according to the procedure detailed by Suginome and Ito.[86]

(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)tetrahydrofuran (319)*

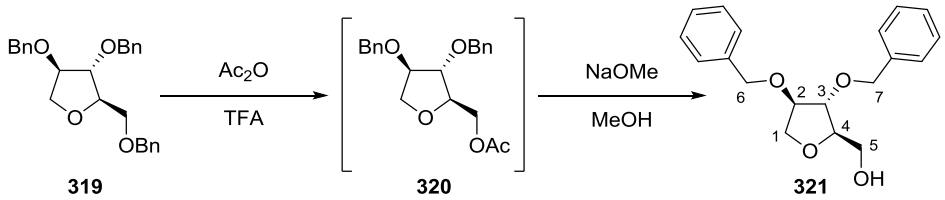


To a solution of commercially available furanose **318** (9.66 g, 23.0 mmol) in MeCN (100 mL) was added triethylsilane (14.7 mL, 91.9 mmol) followed by $BF_3{\cdot}OEt_2$ (5.7 mL, 46 mmol) dropwise. The reaction was stirred at rt for 22 h, after which sat. aq. $NaHCO_3$ (100 mL) was added. The layers were separated, and the aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 90:10 pentane:EtOAc) to afford the title compound **319** (8.88 g, 95%) as a colourless oil.

R_f: 0.69 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ –0.8 (*c* = 1.00, $CHCl_3$; lit.[185] $[\alpha]_D^{25}$ 0.0, *c* = 1.00, $CHCl_3$); **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.37–7.25 (15H, m, ArH), 4.62–4.42 (6H, m, C-6H_2, C-7H_2, C-8H_2), 4.10–3.99 (3H, m, C-2H, C-3H, C-4H), 4.02 (1H, dd, *J* = 10.1, 2.0 Hz, C-1H_AH$_B$), 3.94 (1H, dd, *J* = 10.0, 4.4 Hz, C-1H$_A$$H_B$), 3.65 (1H, dd, *J* = 10.0, 6.1 Hz, C-5H_AH$_B$), 3.60 (1H, dd, *J* = 10.0, 5.7 Hz, C-5H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 138.3 (quaternary Ar), 137.9 (2C, 2 quaternary Ar), 128.6 (2C, Ar), 128.5 (2C, Ar), 128.0 (Ar), 127.9 (5C, 4 Ar), 127.8 (2C, Ar), 127.7 (Ar), 84.7 (C-3), 83.3, 82.9 (C-2/4), 71.9 (C-1), 73.5, 71.7, 71.3 (C-6/7/8), 70.5 (C-5); Spectroscopic data were consistent with those in the literature.[185]

* Compound **319** was prepared according to the procedure detailed by Reeves and Liu.[67, 68]

((2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)methanol (321)*



To a solution of **319** (8.81 g, 21.8 mmol) in acetic anhydride (88.0 mL, 931 mmol) was added trifluoroacetic acid (21.7 mL, 283 mmol) and stirred at rt for 6 h. The reaction was poured into a stirred mixture of Na_2CO_3 (100 g) in ice water (500 mL). The layers were separated, and the aq. layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **320** was obtained as a yellow oil and was carried into the next step without further purification.

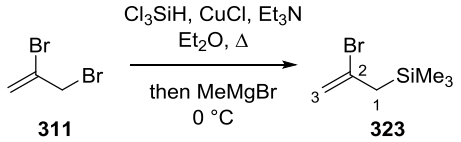
Crude product **320** (assumed quant., 21.8 mmol) was redissolved in MeOH (58 mL) and NaOMe (2.35 g, 43.6 mmol) in MeOH (8.9 mL) was added. The reaction was stirred at rt for 17 h before concentrated *in vacuo*. The mixture was redissolved in Et_2O (100 mL) and H_2O (100 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 90:10 → 80:20 → 1:1 pentane:EtOAc) to afford the title compound **321** (6.08 g, 89% over two steps) as a colourless oil.

R_f: 0.40 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +22.0 (*c* = 1.00, $CHCl_3$; lit.[185] $[\alpha]_D^{25}$ +24.0, *c* = 1.00, $CHCl_3$); **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.40–7.26 (10H, m, ArH), 4.56 (2H, d, *J* = 1.5 Hz, C-6H_2), 4.52 (2H, s, C-7H_2), 4.09–3.96 (4H, m, C-1H_AH_B, C-2H, C-3H, C-4H), 3.93 (1H, dd, *J* = 10.3, 4.2 Hz, C-1H_AH_B), 3.80 (1H, dd, *J* = 11.8, 3.2 Hz, C-5H_AH_B), 3.69

* Compound **321** was prepared according to the procedure detailed by Reeves and Liu.[67, 68]

(1H, dd, J = 11.7, 4.6 Hz, C-5$H_A H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 137.7 (quaternary Ar), 137.5 (quaternary Ar), 128.7 (4C, 2Ar), 128.1 (2C, Ar), 127.9 (2C, Ar), 127.8 (2C, 2Ar), 84.7, 83.8, 82.9 (C-2/3/4), 72.2 (C-6), 71.8 (C-1), 71.3 (C-7), 63.1 (C-5); Spectroscopic data were consistent with those in the literature.[185]

(2-Bromoallyl)trimethylsilane (323)*

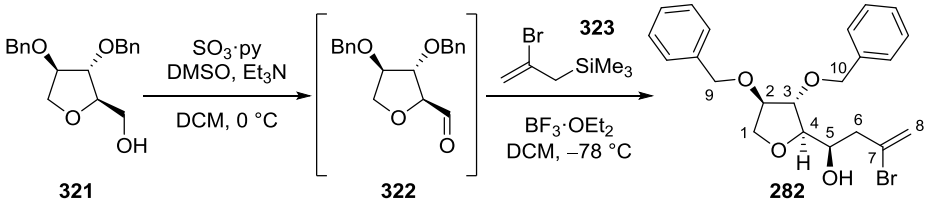


To a three-necked 1 L flask attached to a condenser and an overhead stirrer, was charged with CuCl (665 mg, 6.71 mmol) and Et_3N (18.7 mL, 134 mmol) in Et_2O (64 mL). To this mechanically stirred suspension was added a mixture of 2,3-dibromopropene **311** (80% purity, 13.1 mL, 134 mmol) and trichorosilane (14.9 mL, 148 mmol) dropwise at a rate-maintaining gentle reflux. The reaction was stirred for 6 h then cooled to 0 °C. Methyl magnesium bromide solution (3 M in Et_2O, 201 mL, 604 mmol) was added carefully *via* cannula dropwise. The reaction was warmed to rt over 15 h before cooling back to 0 °C. The reaction was quenched carefully with sat. aq. NH_4Cl (320 mL, gas released *via* vent) and this was poured into Et_2O (120 mL) and H_2O (120 mL). The layers were separated and the organic layer was washed with H_2O (3 × 120 mL). The combined aq. layers were extracted Et_2O (5 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (volatile, 400 mbar, rt). The crude product was purified by vacuum distillation (26 mbar, 52 °C) to afford the title compound **323** (10.75 g, 38%) as a colourless oil.

* Compound **323** was prepared according to the procedure detailed by Trost.[186]

R_f: 0.75 (50:50 pentane:Et_2O); **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 5.31 (1H, dt, *J* = 1.3, 0.7 Hz, C-3H_AH_B), 5.22 (1H, dd, *J* = 1.6, 0.5 Hz, C-3H_AH_B), 2.11 (2H, s, C-1H_2), 0.11 (9H, s, Si$(CH_3)_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 131.3 (C-2), 114.1 (C-3), 33.5 (C-1), –1.4 (3C, Si$(CH_3)_3$); Spectroscopic data were consistent with those in the literature.[186]

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-3-bromobut-3-en-1-ol (282)



To a solution of **321** (105 mg, 0.33 mmol) and Et_3N (0.55 mL, 3.18 mmol) in DCM (2 mL) at 0 °C was added SO_3·py (253 mg, 1.59 mmol) in DMSO (1.69 mL, 23.9 mmol). The reaction was warmed to rt and stirred for 3 h 30 min before it was diluted with a 1:1 mixture of hexane:EtOAc (20 mL). The solution was washed with 1 M aq. HCl (2 × 15 mL), sat. aq. $NaHCO_3$ (20 mL) and brine containing ice (5 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **322** was obtained as a pale yellow oil and was carried into the next step without further purification.

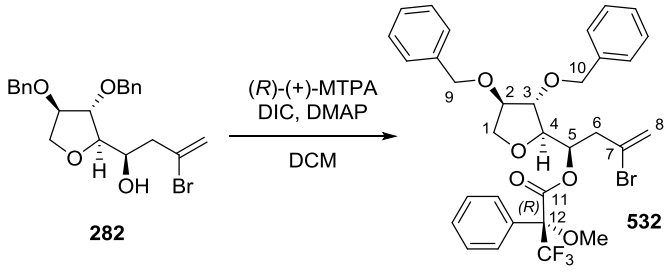
Crude product **322** (assume quant., 0.33 mmol) was transferred to a flask and was dried azeotropically with anhydrous benzene (3 × 3 mL) before redissolving in anhydrous DCM (3 mL) and cooled to –78 °C. Bromide **323** (258 mg, 1.33 mmol) in DCM (2 mL) was added, followed by BF_3·OEt_2 (82 µL, 0.67 mmol) dropwise. The reaction was warmed to rt for 17 h before it was quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (30 mL) and H_2O (10 mL). The layers were separated, and the aq. layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 70:30 pentane:Et_2O) to afford the title compound **282** (78.9 mg, 56% over two steps, >20:1 dr) as a colourless oil.

The stereochemistry of C-5 was assigned the (*R*)-configuration by Mosher's ester analysis (see **Appendix 6.1.1**).

R_f: 0.37 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +25.4 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3450, 2866, 1632, 1496, 1454, 1207, 1075, 1028, 893, 737, 698; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.43–7.26 (10H, m, ArH), 5.68 (1H, q, *J* = 1.3 Hz, C-8H_AH_B), 5.55 (1H, d, *J* = 1.7 Hz, C-8H_AH_B), 4.57 (2H, q, *J* = 11.8 Hz, C-10H_2), 4.55 (2H, s, C-9H_2), 4.22–4.15 (1H, m, C-5H), 4.17 (1H, d, *J* = 3.2 Hz, C-3H), 4.12–4.06 (2H, m, C-1H_AH_B, C-2H), 3.89 (1H, dd, *J* = 9.9, 3.5 Hz, C-1H_AH_B), 3.87–3.83 (1H, m, C-4H), 2.67 (1H, dd, *J* = 14.8, 3.8 Hz, C-6H_AH_B), 2.48 (1H, ddd, *J* = 14.7, 8.9, 0.8 Hz, C-6H_AH_B), 2.44 (1H, d, *J* = 2.0 Hz, O*H*); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 137.6 (quaternary Ar), 137.5 (quaternary Ar), 130.1 (C-7), 128.7 (4C, 2Ar), 128.2 (2C, Ar), 128.1 (2C, 2Ar), 127.9 (2C, Ar), 119.8 (C-8), 86.7 (C-4), 82.6 (C-3), 82.4 (C-2), 72.0 (C-10), 71.6 (C-1), 71.2 (C-9), 68.9 (C-5), 45.3 (C-6); **HRMS:** (Ammonia CI-MS, *m/z*) $C_{22}H_{25}{}^{79}BrO_4$ (MH^+) Calculated: 433.1009, Found: 433.1009 (Δ +0.00 ppm).

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-3-bromobut-3-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (532)*



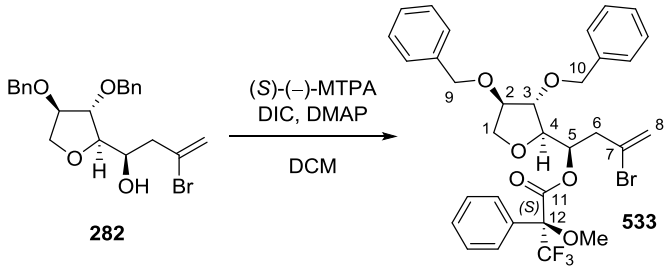
* Compound **532** was prepared according to the procedure detailed by Hoye.[99]

To a solution of **282** (20 mg, 46 μmol) in DCM (0.5 mL), were added DIC (8.6 μL, 56 μmol) and DMAP (2.8 mg, 23 μmol). (*R*)-(+)-MTPA (13 mg, 56 μmol) was added in DCM (0.73 mL) and the reaction was stirred at rt for 18 h. TLC analysis indicated incomplete reaction so additional (*R*)-(+)-MTPA (13 mg, 56 μmol) and DIC (10 μL, 65 μmol) in DCM (1 mL) were added and stirring was continued for 6 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA (13 mg, 56 μmol) and DIC (10 μL, 65 μmol) in DCM (1 mL) were added and stirring was continued for a further 2 h. The reaction was then filtered through a Celite® plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 pentane:Et_2O) to afford the title compound **532** (20 mg, 67%) as a colourless oil.

R_f: 0.54 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +25.6 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2950, 1752, 1714, 1670, 1497, 1454, 1254, 1168, 1120, 1081, 1018, 899, 798; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.57 (2H, m, ArH), 7.44 (1H, m, ArH), 7.42–7.21 (12H, m, ArH), 5.71 (1H, ddd, *J* = 8.6, 4.6, 3.8 Hz, C-5H), 5.36 (1H, s, C-8H_AH_B), 5.23 (1H, d, *J* = 1.8 Hz, C-8H_AH_B), 4.57–4.38 (4H, m, C-9H_2, C-10H_2), 4.06 (2H, td, *J* = 4.3, 1.2 Hz, C-1H_AH_B, C-3H), 4.02 (1H, s, C-2H), 3.98 (1H, t, *J* = 4.5 Hz, C-4H), 3.90 (1H, dd, *J* = 10.1, 3.9 Hz, C-1H_AH_B), 3.53 (3H, d, *J* = 1.2 Hz, OCH_3), 2.77 (1H, dd, *J* = 15.0, 3.8 Hz, C-6H_AH_B), 2.70 (1H, dd, *J* = 15.3, 8.8 Hz, C-6H_AH_B); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.1 (C-11), 137.6 (quaternary Ar), 137.3 (quaternary Ar), 132.3 (C-7), 129.9 (Ar), 129.6 (Ar), 128.7 (Ar), 128.6 (2C, Ar), 128.4 (Ar), 128.2 (quaternary Ar), 128.1 (Ar), 128.0 (2C, Ar), 127.7 (2C, Ar), 126.9 (Ar), 123.5 (q, *J* = 288.6 Hz, CF_3), 120.7 (C-8), 84.8 (q, *J* = 27.6 Hz, C-12), 83.9 (C-2), 83.8 (C-4), 82.9 (C-3), 73.2 (C-5), 72.2 (C-1), 72.1 (C-10), 71.4 (C-9), 55.7 (OCH_3), 42.0 (C-6); **^{19}F NMR:** δ_F (377 MHz, $CDCl_3$) –71.4; **HRMS:** (ESI+,

m/z) $C_{32}H_{32}O_6{}^{79}BrF_3Na$ (MNa^+) Calculated: 671.12266, Found: 671.12268 (Δ –0.03 ppm).

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-3-bromobut-3-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (533)*



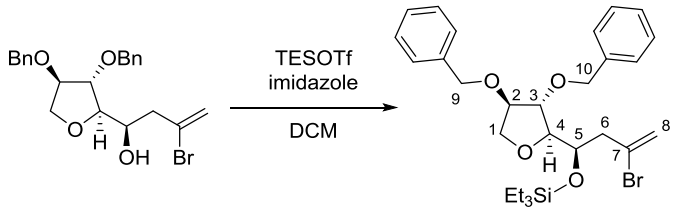
To a solution of **282** (20 mg, 46 μmol), DIC (8.6 μL, 56 μmol) and DMAP (2.8 mg, 23 μmol) in DCM (0.5 mL) was added (*S*)-(–)-MTPA (13 mg, 56 μmol) in DCM (0.73 mL) and the reaction was stirred at rt for 18 h 30 min. TLC analysis indicated incomplete reaction so additional (*S*)-(–)-MTPA (13 mg, 56 μmol) and DIC (10 μL, 65 μmol) in DCM (1 mL) were added and stirring was continued for 6 h. The reaction was filtered through a Celite® plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 pentane:Et_2O) to afford the title compound **533** (30 mg, quant.) as a colourless oil.

R_f: 0.54 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ –19.1 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2977, 1752, 1714, 1670, 1498, 1454, 1368, 1254, 1169, 1119, 1001, 900, 724; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.61–7.51 (2H, m, ArH), 7.48–7.42 (1H, m, ArH), 7.41–7.27 (12H, m, ArH), 5.68 (1H, ddd, *J* = 9.4, 5.1, 3.2 Hz, C-5H), 5.56 (1H, s, C-8H_AH_B), 5.44 (1H, d, *J* = 1.2 Hz, C-8H_AH_B), 4.54–4.33 (4H, m, C-9H_2, C-10H_2), 4.03 (1H, dt, *J* = 4.3, 1.7 Hz, C-3H), 3.95 (3H, ddd, *J* = 7.8, 6.3, 2.8 Hz, C-1H_AH_B, C-2H, C-4H), 3.88 (1H, dd, *J* = 10.1, 4.3 Hz, C-1H_AH_B), 3.54–3.49 (3H, m, OCH_3), 2.89 (1H, dd, *J* = 15.4, 2.8 Hz, C-

* Compound **533** was prepared according to the procedure detailed by Hoye.[99]

6H_AH$_B$), 2.78 (1H, dd, J = 15.5, 9.2 Hz, C-8H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.1 (C-11), 137.6 (quaternary Ar), 137.4 (quaternary Ar), 132.0 (C-7), 129.9 (Ar), 129.7 (Ar), 128.9 (Ar), 128.8 (quaternary Ar), 128.6 (2C, Ar), 128.5 (2C, Ar), 128.1 (Ar), 128.0 (2C, Ar), 127.9 (2C, Ar), 127.8 (2C, Ar), 126.9 (Ar), 123.4 (q, J = 288.6 Hz, CF_3), 120.5 (C-8), 84.8 (q, J = 27.5 Hz, C-12), 83.7 (C-2), 83.7 (C-4), 82.7 (C-3), 73.6 (C-5), 72.1 (C-1), 71.8 (C-10), 71.4 (C-9), 55.6 (OCH_3), 42.2 (C-6); **^{19}F NMR:** δ_F (377 MHz, $CDCl_3$) –71.3; **HRMS:** (ESI+, *m/z*) $C_{32}H_{32}O_6{}^{79}BrF_3Na$ (MNa^+) Calculated: 671.12266, Found: 671.12285 (Δ +0.28 ppm).

(((*R*)-1-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-3-bromobut-3-en-1-yl)oxy)triethylsilane (324)



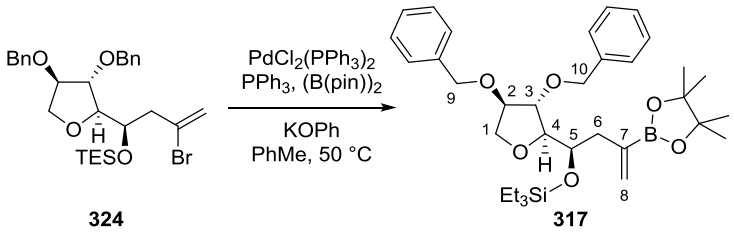
282 **324**

To a stirred solution of **282** (708 mg, 1.64 mmol) and imidazole (446 mg, 6.55 mmol) in DCM (17 mL) was added TES triflate (593 μL, 3.28 mmol) and stirred at rt for 22 h. The TLC showed some starting material present so more TES triflate was added (300 μL) and stirred for a further 2 h. The reaction was quenched with H_2O (40 mL), the layers separated, and the aq. layer was extracted with DCM (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 99:1 → 95:5 pentane:Et_2O) to afford the title compound **324** (764 mg, 85%) as a colourless oil.

R_f: 0.58 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ +11.1 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2954, 2875, 1632, 1496, 1455, 1392, 1240, 1101, 1009, 891, 735, 698; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.40–7.23 (10H, m, ArH), 5.59 (1H, d, J = 1.3 Hz, C-8H_AH$_B$), 5.43

(1H, d, J = 1.5 Hz, C-8H$_A$$H_B$), 4.59 (1H, d, J = 11.6 Hz, C-10H_AH$_B$), 4.56 (1H, d, J = 11.6 Hz, C-10H$_A$$H_B$), 4.54 (1H, d, J = 12.0 Hz, C-9H_AH$_B$), 4.49 (1H, d, J = 12.0 Hz, C-9H$_A$$H_B$), 4.21 (1H, dt, J = 7.3, 4.3 Hz, C-5H), 4.14 (1H, ddd, J = 5.0, 2.1, 0.9 Hz, C-3H), 4.09 (1H, dt, J = 4.6, 2.3 Hz, C-2H), 3.99 (1H, dd, J = 10.1, 2.4 Hz, C-1H_AH$_B$), 3.90 (1H, dd, J = 10.0, 4.8 Hz, C-1H$_A$$H_B$), 3.78 (1H, dd, J = 4.9, 3.9 Hz, C-4H), 2.67 (1H, ddd, J = 14.6, 4.5, 1.1 Hz, C-6H_AH$_B$), 2.54 (1H, ddd, J = 14.5, 7.3, 0.8 Hz, C-6H$_A$$H_B$), 0.96 (9H, dt, J = 13.3, 7.9 Hz, Si(CH$_2$CH_3)$_3$), 0.66–0.55 (6H, m, Si(CH_2CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, CDCl$_3$) 138.0 (2C, 2 quaternary Ar), 131.0 (C-7), 128.6 (2C, Ar), 128.5 (2C, Ar), 127.9 (4C, 3 Ar), 127.8 (2C, Ar), 119.8 (C-8), 86.2 (C-4), 83.9 (C-3), 83.6 (C-2), 72.0 (C-10), 71.6 (C-1), 71.4 (C-9), 69.9 (C-5), 46.0 (C-6), 7.1 (3C, Si(CH$_2$$CH_3$)$_3$), 5.3 (3C, Si($CH_2CH_3$)$_3$); **HRMS:** (ESI+, *m/z*) C$_{28}$H$_{39}$O$_4$^{79}Br^{28}SiNa (MNa$^+$) Calculated: 569.16932, Found: 569.16917 (Δ –0.26 ppm).

(((*R*)-1-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)oxy)triethylsilane (317)[*]



324 **317**

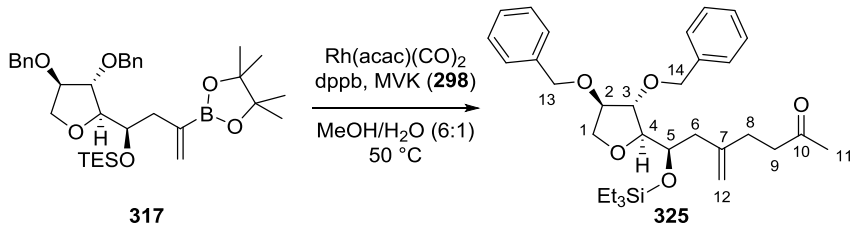
To a flask charged with $PdCl_2(PPh_3)_2$ (59 mg, 84 μmol), PPh_3 (44 mg, 0.17 mmol), bis(pinacolato)diboron (785 mg, 3.09 mmol) and KOPh[181] (557 mg, 4.21 mmol) was added compound **324** (1.54 g, 2.80 mmol) in PhMe (17 mL). The reaction was flushed under argon and heated to 50 °C for 19 h before adding additional bis(pinacolato)diboron (150 mg, 0.591 mmol). The reaction was heated to 50 °C for a further 21 h and then cooled to rt. Water (20 mL) was added and the layers were separated. The aq. layer was

[*] Compound **317** was prepared according to the procedure detailed by Miyaura.[94]

extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 pentane:Et_2O) to afford the title compound **317** (1.32 g, 79%) as a colourless oil.

R_f: 0.48 (80:20 pentane:Et_2O); $[\alpha]_D^{25}$ +2.8 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2951, 2875, 1617, 1455, 1390, 1370, 1310, 1209, 1143, 1095, 967, 899, 864, 736, 698; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.36–7.25 (10H, m, ArH), 5.82 (1H, d, *J* = 3.7 Hz, C-8H_AH$_B$), 5.63 (1H, d, *J* = 3.6 Hz, C-8H$_A$$H_B$), 4.62 (1H, d, *J* = 11.4 Hz, C-10H_AH$_B$), 4.57 (1H, d, *J* = 11.4 Hz, C-10H$_A$$H_B$), 4.51 (2H, s, C-9$H_2$), 4.27 (1H, dd, *J* = 5.0, 2.2 Hz, C-3H), 4.12–4.15 (2H, m, C-2H, C-5H), 3.93 (1H, dd, *J* = 9.8, 3.3 Hz, C-1H_AH$_B$), 3.89 (1H, dd, *J* = 9.8, 5.2 Hz, C-1H$_A$$H_B$), 3.78 (1H, dd, *J* = 5.1, 3.6 Hz, C-4H), 2.45 (1H, dd, *J* = 13.2, 6.4 Hz, C-6H_AH$_B$), 2.28 (1H, dd, *J* = 13.4, 6.3 Hz, C-6H$_A$$H_B$), 1.23 (12H, s, 2 × C(C$H_3$)$_2$), 0.93 (9H, t, *J* = 7.9 Hz, Si(CH$_2$CH_3)$_3$), 0.59 (6H, q, *J* = 7.8 Hz, Si(CH_2CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 138.3 (quaternary Ar), 138.2 (quaternary Ar), 137.9 (v. br., C-7), 132.8 (C-8), 129.7 (Ar), 128.5 (4C, 2Ar), 127.9 (2C, Ar), 127.8 (3C, 2Ar), 86.2 (C-4), 84.2 (C-2), 83.9 (C-3), 83.5 (2C, 2 × *C*(CH$_3$)$_2$), 72.1 (C-10), 71.4 (2C, C-1, C-9), 71.3 (C-5), 41.0 (C-6), 25.0 (2C, 2 × C(*C*H$_3$)$_2$), 24.9 (2C, 2 × C(*C*H$_3$)$_2$), 7.1 (3C, Si(CH$_2$*C*H$_3$)$_3$), 5.3 (3C, Si(*C*H$_2$CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{34}H_{51}O_6{}^{11}B^{28}SiNa$ (MNa^+) Calculated: 617.34402, Found: 617.34363 (Δ –0.63 ppm).

(*R*)-7-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-5-methylene-7-((triethylsilyl)oxy)heptan-2-one (325)*



317 325

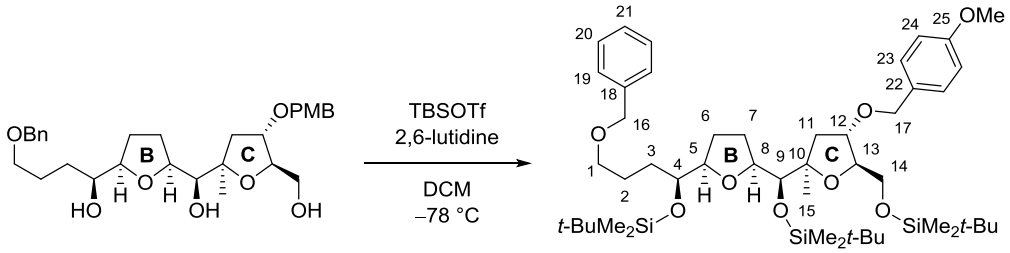
To a solution of compound **317** (50 mg, 84 μmol), $Rh(acac)(CO)_2$ (2.2 mg, 8.4 μmol) and dppb (3.6 mg, 8.4 μmol) in a 6:1 mixture of MeOH and H_2O (0.35 mL) was added MVK (**298**, 90% purity, 9.2 μL, 0.10 mmol) and the vial was flushed with argon. The reaction was heated to 50 °C for 23 h and then cooled to rt. The reaction mixture was diluted with EtOAc (1 mL) and H_2O (1 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 → 70:30 pentane:Et_2O) to afford the title compound **325** (31 mg, 67%) as a colourless oil.

R_f: 0.29 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ +2.7 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3031, 2952, 2911, 2876, 1717, 1646, 1497, 1455, 1415, 1358, 1237, 1208, 1098, 1011, 895, 737, 698; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.39–7.24 (10H, m, ArH), 4.83 (1H, s, C-12$H_A$$H_B$), 4.77 (1H, q, *J* = 1.6 Hz, C-12$H_A$$H_B$), 4.57 (2H, s, C-14$H_2$), 4.53 (1H, d, *J* = 11.9 Hz, C-13$H_A$$H_B$), 4.49 (1H, d, *J* = 11.9 Hz, C-13$H_A$$H_B$), 4.18 (1H, ddd, *J* = 4.5, 2.0, 0.8 Hz, C-2H), 4.08 (1H, dt, *J* = 4.5, 2.2 Hz, C-5H), 4.01 (1H, dd, *J* = 10.7, 5.9 Hz, C-4H), 3.97 (1H, dd, *J* = 10.0, 2.4 Hz, C-1$H_A$$H_B$), 3.89 (1H, dd, *J* = 9.9, 4.7 Hz, C-1$H_A$$H_B$), 3.76 (1H, t, *J* = 4.6 Hz, C-3H), 2.53 (2H, t, *J* = 7.7 Hz, C-9H_2), 2.37–2.16 (4H, m, C-6$H_A$$H_B$, C-8$H_2$), 2.11 (3H, s, C-11$H_3$), 0.93 (9H, t, *J* = 7.9 Hz, Si($CH_2C$$H_3$)$_3$), 0.58 (6H,

* Compound **325** was prepared according to the procedure detailed by Suginome and Ito.[86]

q, J = 7.8 Hz, Si(CH_2CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 208.5 (C-10), 144.8 (C-7), 138.1 (2C, 2 quaternary Ar), 128.5 (4C, 2Ar), 127.9 (4C, 2Ar), 127.8 (2C, 2Ar), 112.6 (C-12), 86.1 (C-3), 83.9 (C-5), 83.8 (C-2), 71.9 (C-14), 71.5 (C-13), 71.4 (C-4), 70.9 (C-1), 42.0 (C-9), 40.9 (C-6), 30.6 (C-8), 30.0 (C-11), 7.1 (3C, Si(CH$_2$*C*H$_3$)$_3$), 5.3 (3C, Si(*C*H$_2$CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{32}H_{46}O_5{}^{28}SiNa$ (MNa^+) Calculated: 561.30067, Found: 561.30037 (Δ –0.53 ppm).

((*S*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butoxy)(*tert*-butyl)dimethylsilane (326)



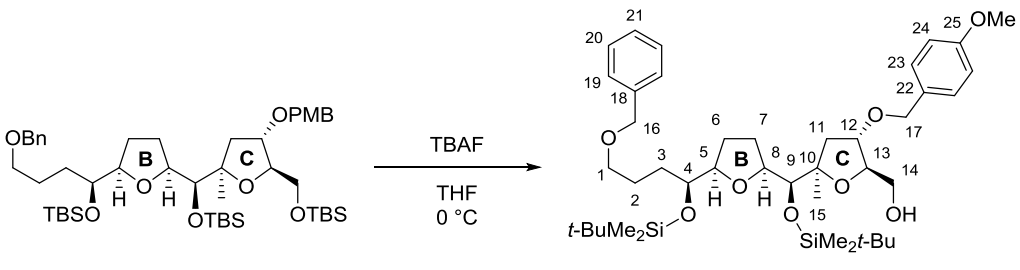
170 **326**

To a stirred solution of **170** (100 mg, 0.188 mmol) and 2,6-lutidine (219 µL, 1.88 mmol) in DCM (2 mL) was added TBS triflate (216 µL, 0.942 mmol) dropwise at –78 °C. The reaction was warmed to rt for 5 h 30 min before the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 95:5 → 90:0 pentane:Et_2O) to afford the title compound **326** (111 mg, 67%) as a colourless oil.

R_f: 0.48 (80:20 pentane:Et_2O); $[\alpha]_D^{25}$ –5.5 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2954, 2929, 2884, 2856, 2360, 113, 1558, 1514, 1471, 1463, 1388, 1361, 1302, 1250, 1172, 1099, 1073, 1042, 1006, 936, 899. 835, 776, 697, 668, 576; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.32–7.21 (5H, m, ArH), 7.21–7.15 (2H, m, C-23H), 6.84–6.76 (2H,

m, C-24H), 4.43 (2H, s, C-16H_2), 4.40 (1H, d, J = 11.5 Hz, C-17H_AH$_B$), 4.33 (1H, d, J = 11.5 Hz, C-17H$_A$$H_B$), 4.05 (1H, ddd, J = 7.0, 4.3, 2.6 Hz, C-13H), 3.99–3.89 (1H, m, C-4H, C-12H), 3.73 (3H, s, OCH_3), 3.67–3.60 (2H, m, C-5H, C-9H), 3.58 (1H, dd, J = 10.4, 4.3 Hz, C-14H_AH$_B$), 3.42–3.31 (4H, m, C-1H_2, C-8H, C-14H$_A$$H_B$), 1.96–1.83 (2H, m, C-3$H_AH_B$, C-11$H_AH_B$), 1.83–1.76 (1H, m, C-11H$_A$$H_B$), 1.76–1.42 (5H, m, C-2$H_AH_B$, C-6$H_AH_B$, C-7$H_2$), 1.40–1.21 (2H, m, C-2H$_A$$H_B$, C-6H$_A$$H_B$), 1.16 (3H, s, C-15H), 0.85–0.78 (27H, m, 3 × Si(CH$_3$)$_2$C(CH_3)$_3$), 0.03– –0.05 (18H, m, 3 × Si(CH_3)$_2$C(CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 159.2 (C-25), 138.8 (C-22), 130.7 (C-18), 129.3 (2C, 2 × C-23), 128.5 (2C, 2 × C-19), 127.7 (2C, 2 × C-20), 127.6 (C-21), 113.9 (2C, 2 × C-24), 85.2 (C-10), 84.6 (C-13), 82.6 (C-8), 81.5 (C-12), 79.7 (C-4), 79.5 (C-5), 74.3 (C-9), 72.9 (C-16), 71.0 (C-17), 70.7 (C-1), 64.3 (C-14), 42.7 (C-11), 30.7 (C-6), 28.0 (C-2), 26.2 (6C, 2 × Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 26.1 (3C, 2 × Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 25.6 (C-7), 24.0 (C-3), 21.8 (C-15), 18.5 (2C, 2 × Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 18.4 (Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), –2.6 (Si(*C*H$_3$)(CH$_3$)C(CH$_3$)$_3$), –3.7 (Si(CH$_3$)(*C*H$_3$)C(CH$_3$)$_3$), –4.4 (Si(*C*H$_3$)(CH$_3$)C(CH$_3$)$_3$), –4.8 (Si(CH$_3$)(*C*H$_3$)C(CH$_3$)$_3$), –5.2 (Si(*C*H$_3$)(CH$_3$)C(CH$_3$)$_3$), –5.3 (Si(CH$_3$)(*C*H$_3$)C(CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{48}H_{85}O_8{}^{28}Si_3$ (MH^+) Calculated: 873.55468, Found: 873.55487 (Δ +0.22 ppm).

((2*R*,3*S*,5*R*)-5-((*S*)-((2*S*,5*R*)-5-((*S*)-4-(Benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)butyl)tetrahydrofuran-2-yl)((*tert*-butyldimethylsilyl)oxy)methyl)-3-((4-methoxybenzyl)oxy)-5-methyltetrahydrofuran-2-yl)methanol (327)



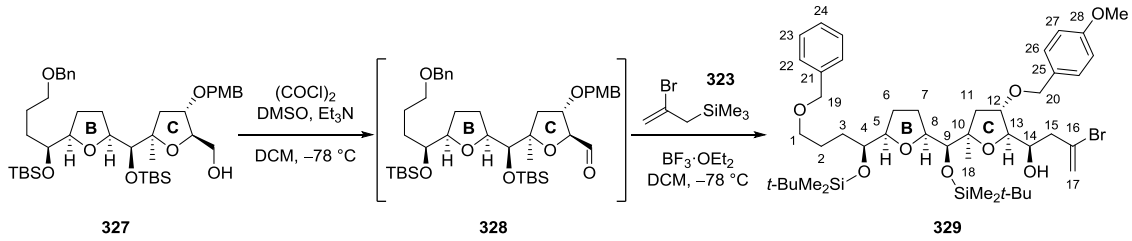
326 **327**

To a stirred solution of **326** (20 mg, 23 μmol) in THF (0.55 mL) was added TBAF (1 M in THF, 70 μL, 69 μmol) at 0 °C. The reaction was stirred for 1 h before the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL), diluted with EtOAc (2 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 2:1 → 50:50 pentane:Et_2O) to afford the title compound **327** (15.4 mg, 89%) as a colourless oil.

R_f: 0.34 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +5.4 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3658, 3446, 2980, 2956, 2930, 2884, 2856, 1613, 1514, 1462, 1388, 1302, 1249, 1121, 1072, 1042, 1006, 956, 899, 835, 776, 736, 698; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.28–7.24 (4H, m, C-19H, C-20H), 7.23–7.15 (3H, m, C-21H, C-23H), 6.82–6.78 (2H, m, C-24H), 4.43 (2H, s, C-16H_2), 4.36 (2H, s, C-17H_2), 4.02–3.89 (3H, m, C-5H, C-12H, C-13H), 3.73 (3H, s, OCH_3), 3.69–3.60 (3H, m, C-4H, C-9H, C-14H_AH_B), 3.52 (1H, dt, *J* = 9.2, 6.3 Hz, C-8H), 3.46 (1H, ddd, *J* = 12.1, 8.3, 4.0 Hz, C-16H_AH_B), 3.40 (2H, t, *J* = 6.5 Hz, C-1H_2), 2.30 (1H, dd, *J* = 8.4, 4.7 Hz, OH), 2.12 (1H, dd, *J* = 13.2, 7.1 Hz, C-11H_AH_B), 1.80 (1H, tdd, *J* = 11.5, 8.4, 4.6 Hz, C-6H_AH_B), 1.74–1.64 (2H, m, C-7H_AH_B, C-11H_AH_B), 1.64–1.53 (3H, m, C-2H_2, C-6H_AH_B), 1.53–1.45 (1H, m, C-3H_AH_B), 1.45–1.38 (1H, m, C-7H_AH_B), 1.38–1.30 (1H, m, C-3H_AH_B), 1.19 (3H, s, C-15H_3), 0.81 (18H, d, *J* = 3.3 Hz, 3 × $Si(CH_3)_2C(CH_3)_3$), 0.00 (12H, dd, *J* = 8.9, 3.3 Hz, 3 × $Si(CH_3)_2C(CH_3)_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 159.4 (C-25), 138.8 (C-18), 130.4 (C-22), 129.4 (2C, 2 × C-23), 128.5 (2C, 2 × C-19), 127.7 (2C, 2 × C-20), 127.6 (C-21), 114.0 (2C, 2 × C-24), 85.0 (C-10), 83.9 (C-13), 82.4 (C-8), 80.0 (C-5), 79.7 (C-12), 78.9 (C-9), 74.0 (C-4), 72.9 (C-16), 71.7 (C-17), 70.7 (C-1), 63.2 (C-14), 55.4 (OCH_3), 42.6 (C-11), 30.2 (C-3), 27.2 (C-7), 26.2 (3C, $Si(CH_3)_2C(CH_3)_3$), 26.1 (3C, $Si(CH_3)_2C(CH_3)_3$),

25.6 (C-6), 22.3 (C-15), 18.4 (2C, 2 × $Si(CH_3)_2C(CH_3)_3$), –2.8 ($Si(CH_3)(CH_3)C(CH_3)_3$), –3.9 ($Si(CH_3)(CH_3)C(CH_3)_3$), –4.4 ($Si(CH_3)(CH_3)C(CH_3)_3$), –4.5 ($Si(CH_3)(CH_3)C(CH_3)_3$); **HRMS:** (ESI+, *m/z*) $C_{42}H_{70}O_8{}^{28}Si_2Na$ (MNa^+) Calculated: 781.45014, Found: 781.44970 (Δ –0.56 ppm).

(*R*)-1-((2*R*,3*S*,5*R*)-5-((*S*)-((2*S*,5*R*)-5-((*S*)-4-(Benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)butyl)tetrahydrofuran-2-yl)((*tert*-butyldimethylsilyl)oxy)methyl)-3-((4-methoxybenzyl)oxy)-5-methyltetrahydrofuran-2-yl)-3-bromobut-3-en-1-ol (329)



327 **328** **329**

To a solution of oxalyl chloride (102 µL, 1.21 mmol) in DCM (0.5 mL) at –78 °C was added DMSO (90 µL, 1.25 mmol) dropwise (gas released). The reaction was stirred for 20 min before **327** (31.7 mg, 41.8 µmol) in DCM (0.5 mL) was added dropwise. The reaction was stirred for a further 40 min before Et_3N (0.36 mL, 2.09 mmol) was added dropwise (gas released). The reaction was warmed to rt and stirred for 2 h 15 min before it was diluted with DCM (3 mL), quenched with sat. aq. NH_4Cl (3 mL) and the layers were separated. The aq. layer was extracted with DCM (3 × 3 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **328** was obtained as a yellow oil and was carried into the next step without further purification.

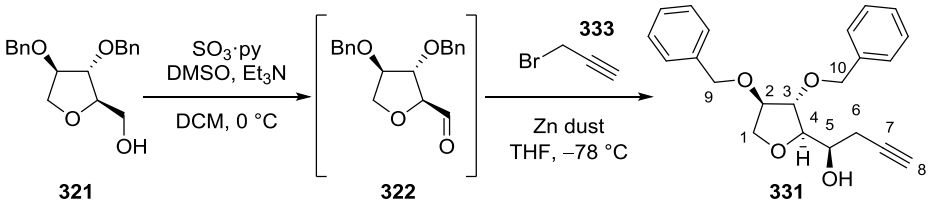
Crude product **328** (assume quant., 41.8 µmol) was transferred to a flask and was dried azeotropically with anhydrous benzene (3 × 3 mL). Bromide **323** (32 mg, 0.17 mmol) in DCM (0.65 mL) was added and cooled to –78 °C, before the addition of $BF_3{\cdot}OEt_2$ (82 µL, 0.67 mmol) dropwise. The reaction was stirred for 1 h 15 min before it was quenched

with sat. aq. $NaHCO_3$ (2 mL). The mixture was diluted with Et_2O (2 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 90:10 → 85:15 pentane:Et_2O) to afford the title compound **329** (8.1 mg, 22% over two steps, >20:1 dr) as a colourless oil.

R_f: 0.61 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +12.8 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3428, 2954, 2928, 2885, 2856, 2361, 2342, 1733, 1632, 1613, 1587, 1514, 1471, 1463, 1361, 1303, 1249, 1172, 1118, 1072, 1039, 1007, 936, 890, 836, 776, 735, 697, 669, 611; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.35–7.31 (4H, m, C-22H, C-23H), 7.30–7.22 (3H, m, C-24H, C-26H), 6.90–6.85 (2H, m, C-27H), 5.65 (1H, d, *J* = 1.4 Hz, C-17$H_A$$H_B$), 5.49 (1H, d, *J* = 1.6 Hz, C-17$H_A$$H_B$), 4.49 (2H, s, C-19$H_2$), 4.45 (1H, d, *J* = 11.4 Hz, C-20$H_A$$H_B$), 4.40 (1H, d, *J* = 11.3 Hz, C-20$H_A$$H_B$), 4.14 (1H, dt, *J* = 7.4, 4.2 Hz, C-12H), 4.04 (1H, dd, *J* = 9.0, 4.7 Hz, C-14H), 3.99 (1H, td, *J* = 6.8, 6.2, 3.4 Hz, C-4H), 3.95 (t, *J* = 4.3 Hz, C-13H), 3.80 (3H, s, OCH_3), 3.72–3.67 (2H, m, C-5H, C-9H), 3.59 (1H, dt, *J* = 9.3, 6.2 Hz, C-8H), 3.46 (2H, t, *J* = 6.5 Hz, C-1H_2), 2.73 (1H, s, OH), 2.61 (1H, dd, *J* = 14.6, 3.8 Hz, C-15$H_A$$H_B$), 2.46 (1H, dd, *J* = 14.9, 8.9 Hz, C-15$H_A$$H_B$), 2.15 (1H, dd, *J* = 13.2, 7.4 Hz, C-11$H_A$$H_B$), 1.92–1.83 (1H, m, C-3$H_A$$H_B$), 1.79 (1H, dd, *J* = 13.1, 4.0 Hz, C-11$H_A$$H_B$), 1.78–1.61 (4H, m, C2$H_2$, C-3$H_A$$H_B$, C-7$H_A$$H_B$), 1.61–1.51 (1H, m, C-6$H_A$$H_B$), 1.51–1.36 (2H, m, C-6$H_A$$H_B$, C-7$H_A$$H_B$), 1.25 (3H, s, C-18$H_3$), 0.90–0.86 (18H, m, 3 × Si(CH_3)$_2$C(CH_3)$_3$), 0.09–0.04 (12H, m, 3 × Si(CH_3)$_2$C(CH_3)$_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 159.4 (C-28), 138.8 (C-21), 130.6 (C-25), 130.2 (C-16), 129.5 (2C, 2 × C-27), 128.5 (2C, 2 × C-22), 127.7 (2C, 2 × C-23), 127.6 (C-24), 119.5 (C-17), 114.0 (2 × C-26), 85.6 (C-13), 85.0 (C-10), 82.4 (C-8), 80.0 (C-4), 78.8 (C-12), 78.7 (C-5), 74.0 (C-9), 73.0 (C-19), 71.4 (C-20), 70.7 (C-1), 69.3 (C-14), 55.4 (OCH_3), 44.6 (C-15), 42.6

(C-11), 30.4 (C-6), 27.3 (C-7), 26.2 (6C, 2 × $Si(CH_3)_2C(\mathit{C}H_3)_3$), 25.8 (C-2), 25.6 (C-3), 22.2 (C-18), 18.4 (2C, 2 × $Si(CH_3)_2\mathit{C}(CH_3)_3$), –2.8 ($Si(\mathit{C}H_3)(CH_3)C(CH_3)_3$), –3.8 ($Si(CH_3)(\mathit{C}H_3)C(CH_3)_3$), –4.4 ($Si(\mathit{C}H_3)(CH_3)C(CH_3)_3$), –4.4 ($Si(CH_3)(\mathit{C}H_3)C(CH_3)_3$); **HRMS:** (ESI+, *m/z*) $C_{45}H_{74}O_8{}^{79}Br^{28}Si_2$ (MH^+) Calculated: 877.41001, Found: 877.40968 (Δ –0.38 ppm).

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)but-3-yn-1-ol (331)



321 322 331

To a solution of **321** (101 mg, 0.321 mmol) and Et_3N (0.55 mL, 3.2 mmol) in DCM (2 mL) at 0 °C was added SO_3·py (253 mg, 1.59 mmol) in DMSO (1.69 mL, 23.9 mmol). The reaction was warmed to rt and stirred for 3 h 15 min before it was diluted with a 1:1 mixture of hexane:EtOAc (20 mL). The solution was washed with 1 M aq. HCl (2 × 10 mL), sat. aq. $NaHCO_3$ (20 mL) and brine containing ice (5 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **322** was obtained as a pale yellow oil and was carried into the next step without further purification.

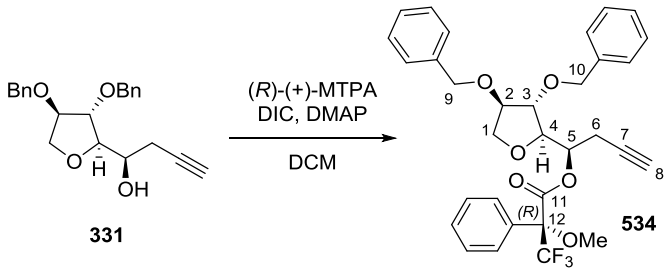
To a suspension of freshly activated Zn dust[182] (105 mg, 1.61 mmol) in THF (11 mL) at 0 °C was added propargyl bromide (80% wt in PhMe, 0.24 mL, 2.3 mmol) dropwise. The suspension was stirred for 30 min before cooling to –78 °C. Crude product **322** (assume quant., 0.32 mmol) was dried azeotropically with anhydrous benzene (3 × 2 mL). before redissolving in anhydrous THF (10 mL) and added dropwise to the suspension. The reaction was kept at –78 °C and stirred for 1 h 10 min before it was quenched with sat. aq. NH_4Cl (20 mL) and warmed to rt. The mixture was extracted with EtOAc (3 ×

30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 70:30 pentane:Et_2O) to afford the title compound **331** (59.2 mg, 52% over two steps, >20:1 dr) as a colourless oil.

The stereochemistry of C-5 was assigned the (*R*)-configuration by Mosher's ester analysis (see **Appendix 6.1.2**).

R_f: 0.31 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ –7.3 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3454, 3290, 3088, 3063, 3031, 2868, 2359, 2341, 1496, 1454, 1394, 1370, 1332, 1207, 1074, 1028, 738 698, 641; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.39–7.29 (10H, m, ArH), 4.59 (1H, d, *J* = 11.9 Hz, C-10$H_A$$H_B$), 4.56 (1H, d, *J* = 11.9 Hz, C-10$H_A$$H_B$), 4.53 (1H, d, *J* = 11.8 Hz, C-9$H_A$$H_B$), 4.51 (1H, d, *J* = 11.8 Hz, C-9$H_A$$H_B$), 4.18 (1H, dt, *J* = 2.7, 1.1 Hz, C-3H), 4.07–4.03 (2H, m, C-1$H_A$$H_B$, C-2H), 4.00 (1H, dd, *J* = 5.2, 2.7 Hz, C-4H), 3.94 (1H, tdd, *J* = 6.3, 5.2, 3.8 Hz, C-5H), 3.90 (1H, dd, *J* = 10.4, 3.8 Hz, C-1$H_A$$H_B$), 2.61 (1H, d, *J* = 3.8 Hz, OH), 2.49 (1H, ddd, *J* = 16.9, 6.3, 2.7 Hz, C-6$H_A$$H_B$), 2.44 (1H, ddd, *J* = 16.9, 6.2, 2.7 Hz, C-6$H_A$$H_B$), 2.08 (1H, t, *J* = 2.7 Hz, C-8H); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 137.8 (quaternary Ar), 137.4 (quaternary Ar), 128.7 (4C, 2Ar), 128.1 (2C, 2Ar), 127.9 (4C, 2Ar), 86.3 (C-4), 82.5 (C-2), 82.4 (C-3), 80.3 (C-7), 71.8 (C-10), 71.7 (C-1), 71.2 (2C, C-8, C-9), 69.7 (C-5), 23.9 (C-6); **HRMS:** (ESI+, *m/z*) $C_{22}H_{24}O_4Na$ (MNa^+) Calculated: 375.15673, Found: 375.15668 (Δ +0.13 ppm).

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)but-3-yn-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (534)*



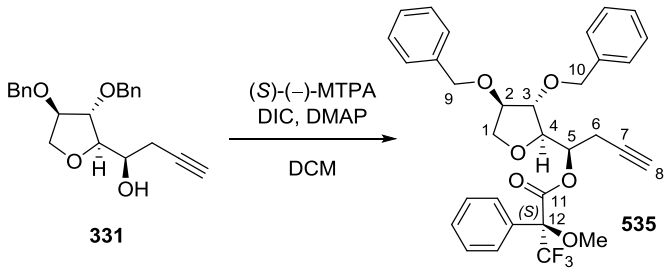
To a solution of **331** (12 mg, 34 μmol) in DCM (0.5 mL), were added DIC (6.3 μL, 41 μmol) and DMAP (2.1 mg, 17 μmol). (*R*)-(+)-MTPA (12.3 mg, 52.5 μmol) was added in DCM (0.5 mL) and the reaction was stirred at rt for 20 h 45 min. TLC analysis indicated incomplete reaction so additional (*R*)-(+)-MTPA (9.7 mg, 41 μmol) and DIC (7 μL, 45 μmol) in DCM (0.5 mL) were added and stirring was continued for 23 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA (20.5 mg, 87.5 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 23 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA (20.6 mg, 88.0 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 19 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA (20.2 mg, 86.3 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 30 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA (20.6 mg, 88.0 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 19 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA (20.1 mg, 85.8 μmol), DIC (14 μL, 90 μmol) and DMAP (2.9 mg, 23 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 24 h. TLC analysis still indicated incomplete reaction so additional (*R*)-(+)-MTPA

* Compound **534** was prepared according to the procedure detailed by Hoye.[99]

(20.3 mg, 86.7 μmol), DIC (14 μL, 90 μmol) and DMAP (3.4 mg, 28 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 24 h. The reaction was then filtered through a Celite® plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 95:5 → 90:10 pentane:EtOAc) to afford the title compound **534** (10.3 mg, 53%) as a colourless oil.

R_f: 0.37 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ +12.7 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3297, 2979, 1752, 1714, 1670, 1498, 1454, 1369, 1338, 1253, 1168, 1119, 1081, 1028, 1000, 798, 699, 642; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.65–7.19 (15H, m, ArH), 5.34 (1H, ddd, *J* = 7.4, 5.8, 4.6 Hz, C-5H), 4.50 (1H, d, *J* = 11.9 Hz, C-10H_AH_B), 4.47 (1H, d, *J* = 11.6 Hz, C-9H_AH_B), 4.46 (1H, d, *J* = 11.9 Hz, C-10H_AH_B), 4.39 (1H, d, *J* = 11.6 Hz, C-9H_AH_B), 4.16 (1H, dd, *J* = 7.4, 2.9 Hz, C-4H), 4.06–3.99 (3H, m, C-1H_AH_B, C-2H, C-3H), 3.96 (1H, dd, *J* = 10.1, 4.1 Hz, C-1H_AH_B), 3.49 (3H, s, OCH_3), 2.76 (1H, ddd, *J* = 17.5, 4.6, 2.7 Hz, C-6H_AH_B), 2.66 (1H, ddd, *J* = 17.4, 5.8, 2.7 Hz, C-6H_AH_B), 1.90 (1H, t, *J* = 2.7 Hz, C-8H); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 166.1 (C-11), 137.6 (2C, 2 quaternary Ar), 131.8 (quaternary Ar), 129.9 (Ar), 129.8 (Ar), 128.9 (Ar), 128.7 (2C, Ar), 128.6 (2C, Ar), 128.1 (Ar), 128.0 (2C, Ar), 127.9 (2C, Ar), 127.8 (2C, Ar), 127.0 (Ar), 123.4 (q, *J* = 288.5 Hz, CF_3), 85.0 (q, *J* = 27.8 Hz, C-12), 84.0 (C-2), 82.7 (2C, C-3, C-4), 78.7 (C-7), 73.4 (C-5), 72.4 (C-1), 71.9 (C-9), 71.5 (C-10), 71.1 (C-8), 55.6 (OCH_3), 20.7 (C-6); **^{19}F NMR:** δ_F (470 MHz, $CDCl_3$) –71.6; **HRMS:** (ESI+, *m/z*) $C_{32}H_{31}O_6F_3Na$ (MNa^+) Calculated: 591.19649, Found: 591.19648 (Δ –0.02 ppm).

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)but-3-yn-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (535)*



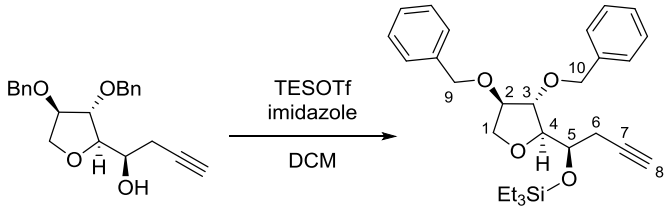
To a solution of **331** (12 mg, 34 μmol) in DCM (0.5 mL), were added DIC (6.3 μL, 41 μmol) and DMAP (2.1 mg, 17 μmol). (*S*)-(–)-MTPA (10 mg, 43 μmol) was added in DCM (0.5 mL) and the reaction was stirred at rt for 20 h 45 min. TLC analysis indicated incomplete reaction so additional (*S*)-(–)-MTPA (11 mg, 47 μmol) and DIC (7 μL, 45 μmol) in DCM (0.5 mL) were added and stirring was continued for 23 h. TLC analysis still indicated incomplete reaction so additional (*S*)-(–)-MTPA (20.2 mg, 86.3 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 23 h. TLC analysis still indicated incomplete reaction so additional (*S*)-(–)-MTPA (20.2 mg, 86.3 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 19 h. TLC analysis still indicated incomplete reaction so additional (*S*)-(–)-MTPA (20.5 mg, 87.5 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 30 h. TLC analysis still indicated incomplete reaction so additional (*S*)-(–)-MTPA (20.7 mg, 88.4 μmol) and DIC (14 μL, 90 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 19 h. TLC analysis still indicated incomplete reaction so additional (*S*)-(–)-MTPA (20.1 mg, 85.8 μmol), DIC (14 μL, 90 μmol) and DMAP (2.9 mg, 23 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 24 h. TLC analysis still indicated incomplete reaction so additional (*S*)-(–)-MTPA (20.0 mg, 85.4 μmol), DIC

* Compound **535** was prepared according to the procedure detailed by Hoye.[99]

(14 μL, 90 μmol) and DMAP (3.4 mg, 28 μmol) in DCM (0.5 mL) were added and stirring was continued for a further 24 h. The reaction was then filtered through a Celite® plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 95:5 → 90:10 pentane:EtOAc) to afford the title compound **535** (18.4 mg, 95%) as a colourless oil.

R_f: 0.34 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ –39.3 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3429, 2980, 1752, 1714, 1670, 1498, 1454, 1369, 1339, 1255, 1168, 1120, 1081, 1029, 1001, 798, 709, 642; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.67–7.12 (15H, m, ArH), 5.20 (1H, ddd, *J* = 9.0, 4.9, 3.9 Hz, C-5H), 4.49 (1H, d, *J* = 11.9 Hz, C-10H_AH_B), 4.43 (1H, d, *J* = 11.9 Hz, C-10H_AH_B), 4.19–4.14 (2H, m, C-4H, C-9H_AH_B), 3.98–3.91 (4H, m, 3H,C-1H_2, C-3H, C-9H_AH_B), 3.70–3.68 (1H, m, C-2H), 3.66 (3H, dd, *J* = 4.1, 2.6 Hz, OCH_3), 2.89 (1H, ddd, *J* = 17.6, 3.9, 2.7 Hz, C-6H_AH_B), 2.76 (1H, ddd, *J* = 17.7, 4.9, 2.7 Hz, C-6H_AH_B), 2.03 (1H, t, *J* = 2.7 Hz, C-28H); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 165.9 (C-11), 137.7 (quaternary Ar), 137.5 (quaternary Ar), 132.6 (quaternary Ar), 129.9 (Ar), 129.8 (Ar), 128.9 (Ar), 128.7 (2C, Ar), 128.6 (Ar), 128.5 (2C, Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (2C, Ar), 127.6 (Ar), 127.4 (Ar), 127.0 (Ar), 123.5 (q, *J* = 291.2 Hz, CF_3), 84.5 (q, *J* = 27.2 Hz, C-12), 84.1 (C-2), 82.5 (C-3), 82.2 (C-4), 78.9 (C-7), 73.3 (C-5), 72.4 (C-1), 71.6 (2C, C-8, C-9), 71.4 (C-10), 56.1 (OCH_3), 20.9 (C-6); **^{19}F NMR:** δ_F (470 MHz, $CDCl_3$) –71.3; **HRMS:** (ESI+, *m/z*) $C_{32}H_{31}O_6F_3Na$ (MNa^+) Calculated: 591.19649, Found: 591.19621 (Δ –0.47 ppm).

(((*R*)-1-((2*S*,3*S*,4*S*)-4-(Benzyloxy)-3-phenethyltetrahydrofuran-2-yl)but-3-yn-1-yl)oxy)triethylsilane (334)



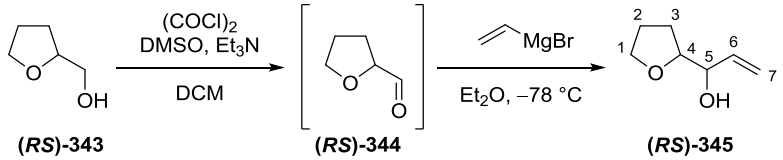
331 **334**

To a stirred solution of **331** (59 mg, 0.17 mmol) and imidazole (37 mg, 0.54 mmol) in DCM (1.55 mL) was added TES triflate (50 µL, 0.27 mmol) and stirred at rt for 2 h. The reaction was quenched with H_2O (3 mL), the layers separated, and the aq. layer was extracted with DCM (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 pentane:Et_2O) to afford the title compound **334** (63.4 mg, quant.) as a colourless oil.

R_f: 0.58 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ –20.0 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3117, 3032, 3003, 2934, 2872, 2836, 2360, 2341, 1637, 1608, 1577, 1511, 1466, 1442, 1420, 1374, 1320, 1293, 1247, 1194, 1175, 1150, 1113, 1073, 1035, 995, 966, 846, 817, 753, 703, 639; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.42–7.22 (10H, m, ArH), 4.64 (1H, d, *J* = 11.7 Hz, C-10H_AH_B), 4.54 (1H, d, *J* = 11.8 Hz, C-10H_AH_B), 4.53 (2H, s, C-9H_2), 4.18 (1H, dd, *J* = 2.9, 1.3 Hz, C-4H), 4.11–4.07 (1H, m, C-2H), 4.04–3.89 (4H, m, C-1H_2, C-3H, C-5H), 2.55 (1H, ddd, *J* = 17.0, 4.7, 2.7 Hz, C-6H_AH_B), 2.51 (1H, ddd, *J* = 17.0, 4.8, 2.7 Hz, C-6H_AH_B), 2.01 (1H, t, *J* = 2.6 Hz, C-8H), 0.97 (9H, t, *J* = 7.9 Hz, Si(CH_2CH_3)$_3$), 0.69–0.59 (6H, m, Si(CH_2CH_3)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 138.2 (quaternary Ar), 137.9 (quaternary Ar), 128.5 (4C, 2Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (4C, 2Ar), 85.5 (C-3), 84.1 (C-4), 83.3 (C-2), 81.1 (C-7), 71.8 (C-1), 71.6 (C-10), 71.4 (C-9), 70.4 (C-8), 70.2 (C-5), 24.5 (C-6), 7.0 (3C, Si(CH_2CH_3)$_3$), 5.2 (3C, Si(CH_2CH_3)$_3$); **HRMS:**

(ESI+, *m/z*) $C_{28}H_{38}O_4{}^{28}SiNa$ (MNa^+) Calculated: 489.24316, Found: 489.24292 (Δ –0.49 ppm).

1-(Tetrahydrofuran-2-yl)prop-2-en-1-ol ((*RS*)-345)



(*RS*)-343 (*RS*)-344 (*RS*)-345

To a solution of DMSO (8.90 mL, 103 mmol) in DCM (140 mL) under argon at –78 °C was added oxalyl chloride (5.40 mL, 61.9 mmol) dropwise. The mixture was stirred for 30 min before tetrahydrofurfuryl alcohol **(*RS*)-343** (5.0 mL, 52 mmol) was added dropwise. The reaction was stirred at –78 °C for a further 30 min before Et_3N (36.0 mL, 258 mmol) was added. The solution was warmed to rt and H_2O (140 mL) was added. The layers were separated and the aq. layer was extracted with DCM (3 × 100 mL). NaCl was added to the aq. layer until saturated, and then the aq. layer was extracted further with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (volatile, 400 mbar, rt). The crude product **(*RS*)-344** was obtained as a pale yellow oil and white precipitate and was carried into the next step without further purification.*

Crude **(*RS*)-344** (assumed quant., 51.6 mmol) was transferred to a flask in anhydrous Et_2O (55 mL) and cooled to –78 °C. Vinyl magnesium bromide (1 M in THF, 77 mL, 77.0 mmol) was added at –78 °C and was warmed to rt over 2 h. TLC analysis indicated incomplete reaction so additional vinyl magnesium bromide (20.0 mL, 20.0 mmol) was added, and stirring was continued for 15 h. The reaction was quenched with sat. aq. NH_4Cl (80 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3

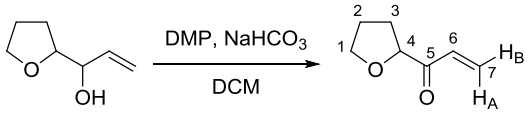
* Compound **(*RS*)-344** was prepared according to the procedure detailed by Riva.[110]

× 100 mL) and DCM (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (azeotropes, 400 mbar, rt). The crude product was purified by column chromatography (SiO_2, 1:1 pentane:Et_2O) to afford the title compound **(*RS*)-345** (1.55 g, 23% over two steps, 1:1.15 dr) as a colourless oil.

Diastereomeric ratio at C-5 was ascertained by ^{1}H NMR spectroscopy of the crude mixture; δ_H 5.29 (1 H, dt, *J* = 6.1, 1.7 Hz, C-7H$_A$*H$_B$* minor), 5.20–5.17 (1 H, m, C-7'*H$_A$*H$_B$ major). The diastereoisomers are identified by prime notation.

R$_f$: 0.34 (50:50 pentane:EtOAc); **IR:** ν_{max} (thin film/cm^{-1}) 3424, 3082, 2977, 2872, 1645w, 1424, 1291, 1185, 1136, 1061, 994, 924, 702; **^{1}H NMR:** δ_H (400 MHz, CD_2Cl_2) 5.82 (2H, dddd, *J* = 17.2, 10.6, 5.8, 5.0 Hz, C-6H, C-6'H), 5.34 (1H, dt, *J* = 6.2, 1.6 Hz, C-7*H$_A$*H$_B$), 5.29 (1H, dt, *J* = 6.3, 1.7 Hz, C-7H$_A$*H$_B$*), 5.20–5.17 (1H, m, C-7'*H$_A$*H$_B$), 5.17–5.14 (1H, m, C-7'H$_A$*H$_B$*), 4.24 (1H, dtt, *J* = 5.3, 3.4, 1.6 Hz, C-5H), 3.93–3.69 (7H, m, C-1H$_2$, C-1'H$_2$, C-4H, C-4'H, C-5'H), 2.46 (1H, t, *J* = 3.2 Hz, OH), 2.13 (1 H, td, *J* = 3.7, 2.0 Hz, OH'), 1.95–1.57 (8H, m, C-2H$_2$, C-2'H$_2$, C-3H$_2$, C-3'H$_2$); **^{13}C NMR:** δ_C (101 MHz, CD_2Cl_2) 138.1 (C-6), 137.6 (C-6'), 116.7 (C-7), 116.2 (C-7'), 82.5 (C-4), 82.2 (C-4'), 75.8 (C-5), 74.0 (C-5'), 69.3 (C-1), 68.8 (C-1'), 28.1 (C-3), 26.6 (2 C, C-2, C-3'), 25.7 (C-2'); **HRMS:** (ESI+, *m/z*) $C_7H_{12}O_2Na$ (MNa^+) Calculated: 151.07295, Found: 151.07300 (Δ +0.33 ppm).

1-(Tetrahydrofuran-2-yl)prop-2-en-1-one ((*RS*)-342)



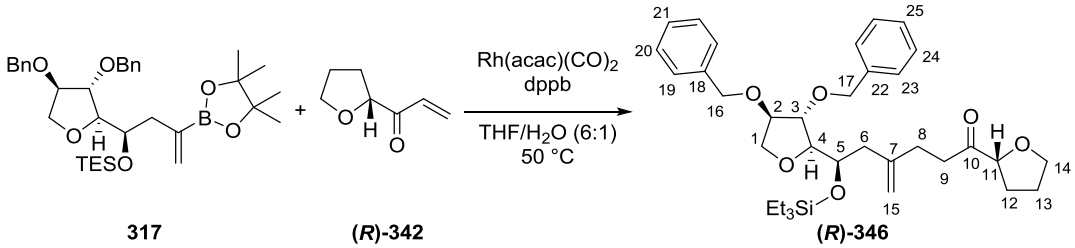
(*RS*)-345 (*RS*)-342

To a solution of **(*RS*)-345** (1.14 g, 8.93 mmol) and $NaHCO_3$ (3.75 g, 44.6 mmol) in DCM (from Winchester, 103 mL) was added DMP (7.57 g, 17.9 mmol) and the reaction was

stirred at rt for 28 h. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and the layers were separated. The aq. layer was extracted with DCM (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (volatile, cool bath). The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 → 80:20 pentane:Et_2O) to afford the title compound **(*RS*)-342** (736 mg, 65%) as a colourless oil.

R_f: 0.30 (50:50 pentane:Et_2O); **IR:** ν_{max} (thin film/cm^{-1}) 2979, 2874, 1697, 1611, 1448, 1403, 1289, 1177, 1053, 1027, 989, 927, 788, 682; **^{1}H NMR:** δ_H (400 MHz, CD_2Cl_2) 6.65 (1H, dd, *J* = 17.5, 10.6 Hz, C-6H), 6.32 (1H, dd, *J* = 17.5, 1.7 Hz, C-7H_AH_B), 5.79 (1H, dd, *J* = 10.6, 1.6 Hz, C-7H_AH_B), 4.54–4.46 (1H, m, C-4H), 3.94–3.85 (2H, m, C-1H_2), 2.24–2.12 (1H, m, C-3H_AH_B), 1.97–1.83 (3H, m, C-2H_2, C-3H_AH_B); **^{13}C NMR:** δ_C (101 MHz, CD_2Cl_2) 200.7 (C-5), 132.5 (C-6), 129.5 (C-7), 82.7 (C-4), 69.8 (C-1), 29.7 (C-3), 26.1 (C-2); **HRMS:** (ESI+, *m/z*) $C_7H_{10}O_2Na$ (MNa^+) Calculated: 149.05730, Found: 149.05746 (Δ +1.07 ppm).

(6*R*)-6-((2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)tetrahydrofuran-2-yl)-4-methylene-1-(tetrahydrofuran-2-yl)-6-((triethylsilyl)oxy)hexan-1-one ((*RS*)-346)*



317 **(*R*)-342** **(*R*)-346**

To a solution of compound **317** (50 mg, 84 μmol), $Rh(acac)(CO)_2$ (2.2 mg, 8.4 μmol) and dppb (3.6 mg, 8.4 μmol) in THF (0.30 mL) and H_2O (0.05 mL) was added enone **(*RS*)-342** (12.7 mg, 101 μmol) and the vial was flushed with argon. The reaction heated to

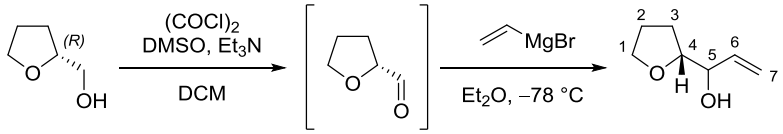
* Compound **(*RS*)-346** was prepared according to the procedure detailed by Suginome and Ito.[86]

50 °C for 21 h and then cooled to rt. EtOAc (1 mL) and H_2O (1 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 → 70:30 pentane:Et_2O) to afford the title compound **(*RS*)-346** (31.4 mg, 52%) as a colourless oil contaminated with **347** (**(*RS*)-346**:**347**, 1:0.18). The diastereomeric ratio could not be determined at C-11. The diastereoisomers are identified by prime notation. The * in the ^{13}C NMR denotes defined twinned peaks for each diastereomer.

R_f: 0.22 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ +2.1 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2952, 2911, 2875, 1716, 1645, 1496, 1455, 1412, 1368, 1308, 1261, 1207, 1077, 1016, 970, 896, 801, 736, 698; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.38–7.24 (10H, m, ArH, ArH'), 4.83 (1H, s, C-15$H_A$$H_B$, C-15'$H_A$$H_B$), 4.79 (1H, q, *J* = 1.6 Hz, C-15$H_A$$H_B$, C-15'$H_A$$H_B$), 4.59 (1H, d, *J* = 11.6 Hz, C-17$H_A$$H_B$, C-17'$H_A$$H_B$), 4.56 (1H, d, *J* = 11.6 Hz, C-17$H_A$$H_B$, C-17'$H_A$$H_B$), 4.53 (1H, d, *J* = 12.0 Hz, C-16$H_A$$H_B$, C-16'$H_A$$H_B$), 4.50 (1H, d, *J* = 12.0 Hz, C-16$H_A$$H_B$, C-16'$H_A$$H_B$), 4.30 (1H, dd, *J* = 8.2, 6.0 Hz, C-11H, C-11'H), 4.18 (1H, ddd, *J* = 4.6, 2.0, 0.7 Hz, C-3H, C-3'H), 4.08 (1H, dt, *J* = 4.6, 2.2 Hz, C-2H, C-2'H), 4.02 (1H, ddd, *J* = 6.5, 5.6, 4.6 Hz, C-5H, C-5'H), 3.99–3.86 (4H, m, C-1$H_A$$H_B$, C-1'$H_A$$H_B$, C-14$H_2$, C-14'$H_2$), 3.76 (1H, t, *J* = 4.6 Hz, C-4H, C-4'H), 2.76–2.67 (1H, m, C-9$H_A$$H_B$, C-9'$H_A$$H_B$), 2.66–2.58 (1H, C-9$H_A$$H_B$, C-9'$H_A$$H_B$), 2.37–2.25 (3H, m, C-6$H_A$$H_B$, C-6'$H_A$$H_B$, C-8$H_2$, C-8'$H_2$), 2.25–2.19 (1H, m, C-6$H_A$$H_B$, C-6'$H_A$$H_B$) 2.19–2.10 (1H, m, C-12$H_A$$H_B$, C-12'$H_A$$H_B$), 1.93–1.83 (3H, m, C-12$H_A$$H_B$, C-12'$H_A$$H_B$, C-13$H_2$, C-13'$H_2$), 0.93 (9H, t, *J* = 7.9 Hz, Si(CH_2CH_3)$_3$, Si(CH_2CH_3)$_3$'), 0.58 (6H, q, *J* = 8.1 Hz, Si(CH_2CH_3)$_3$, Si(CH_2CH_3)$_3$'); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 211.8* (C-10, C-10'), 144.9 (C-7, C-7'), 138.1 (2 × 2C, C-18, C-18', C-22, C-22'), 128.5 (2 × 4C, 2 × C-20, 2 ×

C-20', 2 × C-24, 2 × C-24'), 127.9 (2 × 2C, 2 × C-23, 2 × C-23'), 127.8 (4C, 2 × C-19, C-21, C-25), 112.6* (C-15, C-15'), 86.1 (C-4, C-4'), 83.9* (C-3, C-3'), 83.8 (C-2, C-2'), 83.5* (C-11, C-11'), 71.9 (C-17, C-17'), 71.4 (2 × 2C, C-1, C-1', C-16, C-16'), 70.8 (C-5, C-5'), 69.5 (C-14, C-14'), 41.0* (C-6, C-6'), 36.7 (C-9, C-9'), 29.8* (C-8, C-8'), 29.2* (C-12, C-12'), 25.8 (C-13, C-13'), 7.1 (2 × 3C, $Si(CH_2\mathit{C}H_3)_3$, $Si(CH_2\mathit{C}H_3)_3$'), 5.3 (2 × 3C, $Si(\mathit{C}H_2CH_3)_3$, $Si(\mathit{C}H_2CH_3)_3$'); **HRMS:** (ESI+, *m/z*) $C_{35}H_{50}O_6{}^{28}SiNa$ (MNa^+) Calculated: 617.32689, Found: 617.32644 (Δ –0.73 ppm).

1-((*R*)-Tetrahydrofuran-2-yl)prop-2-en-1-ol ((*R*)-345)



(*R*)-343 (*R*)-344 (*R*)-345

To a solution of DMSO (1.89 mL, 26.6 mmol) in DCM (26.6 mL) under argon at –78 °C was added oxalyl chloride (1.03 mL, 11.8 mmol) dropwise. The mixture was stirred for 30 min before (*R*)-tetrahydrofurfuryl alcohol **(*R*)-343** (0.92 mL, 9.49 mmol) was added dropwise. The reaction was stirred at –78 °C for a further 30 min before Et_3N (6.8 mL, 49 mmol) was added. The solution was warmed to rt and H_2O (27 mL) was added. When the solution cleared, the layers were separated, and the aq. layer was extracted with DCM (3 × 30 mL). NaCl was added to the aq. layer until saturated, and then the aq. layer was extracted further with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under a stream of N_2 (volatile). The crude product **(*R*)-344** was obtained as a pale yellow oil and white precipitate and was carried into the next step without further purification.*

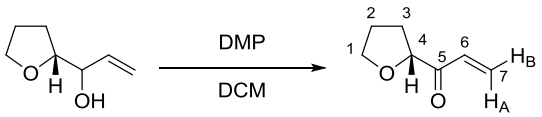
* Compound **(*R*)-344** was prepared according to the procedure detailed by Riva.[110]

Crude **(*R*)-344** (assumed quant., 9.49 mmol) was transferred to a flask in anhydrous Et_2O (14.3 mL) and cooled to –78 °C. Vinyl magnesium bromide (1 M in THF, 14.3 mL, 14.3 mmol) was added at –78 °C and was warmed to rt over 15 h. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3 × 30 mL) and DCM (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under a stream of N_2 (azeotropes). The crude product was purified by column chromatography (SiO_2, 1:1 pentane:Et_2O) to afford the title compound **(*R*)-345** (431 mg, 35% over two steps, 1:1.15 dr) as a colourless oil.

Diastereomeric ratio at C-5 was ascertained by ^{1}H NMR spectroscopy of the crude mixture; δ_H 5.29 (1 H, dt, *J* = 6.1, 1.7 Hz, C-7H$_A$*H$_B$* minor), 5.20–5.17 (1 H, m, C-7'*H$_A$*H$_B$ major). The diastereoisomers are identified by prime notation.

R$_f$: 0.34 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +6.4 (*c* = 1.00, DCM); **IR:** ν_{max} (thin film/cm^{-1}) 3437, 3088, 2976, 2875, 1644, 1428, 1261, 1185, 1064, 995, 924, 802, 617; **^{1}H NMR:** δ_H (400 MHz, CD_2Cl_2) 5.82 (2H, dddd, *J* = 17.3, 10.5, 5.8, 4.8 Hz, C-6H, C-6'H), 5.34 (1H, dt, *J* = 6.1, 1.7 Hz, C-7*H$_A$*H$_B$), 5.29 (1H, dt, *J* = 6.1, 1.7 Hz, C-7H$_A$*H$_B$*), 5.20–5.17 (1H, m, C-7'*H$_A$*H$_B$), 5.17–5.14 (1H, m, C-7'H$_A$*H$_B$*), 4.27–4.22 (1H, m, C-5H), 3.92–3.69 (7H, m, C-1H$_2$, C-1'H$_2$, C-4H, C-4'H, C-5'H), 2.45 (1H, d, *J* = 3.8 Hz, OH), 2.10 (1H, d, *J* = 3.3 Hz, OH'), 1.95–1.60 (8H, m, C-2H$_2$, C-2'H$_2$, C-3H$_2$, C-3'H$_2$); **^{13}C NMR:** δ_C (101 MHz, CD_2Cl_2) 138.0 (C-6), 137.5 (C-6'), 116.7 (C-7), 116.2 (C-7'), 82.5 (C-4), 82.2 (C-4'), 75.8 (C-5), 74.0 (C-5'), 69.3 (C-1), 68.7 (C-1'), 28.1 (C-3), 26.6 (2C, C-2, C-3'), 25.6 (C-2'); **HRMS:** (Ammonia CI-MS, *m/z*) $C_7H_{16}O_2N$ (MNH_4^+) Calculated: 146.1176, Found: 146.1171 (Δ +3.42 ppm).

(*R*)-1-(Tetrahydrofuran-2-yl)prop-2-en-1-one ((*R*)-342)

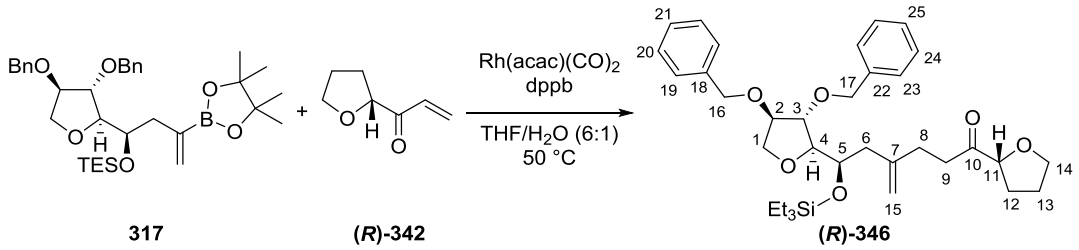


(*R*)-345 (*R*)-342

To a solution of **(*R*)-345** (431 mg, 3.36 mmol) in wet DCM (39 mL) was added DMP (2.85 g, 6.73 mmol) and was stirred at rt for 2 h. Sat. aq. $NaHCO_3$ (40 mL) was added and the layers were separated. The aq. layer was extracted with DCM (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated by a stream of N_2 (volatile). The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 pentane:Et_2O) to afford the title compound **(*R*)-342** (376 mg, 89%) as a colourless oil.

R_f: 0.30 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +49.4 (*c* = 1.00, DCM); **IR:** ν_{max} (thin film/cm^{-1}) 2955, 2874, 1698, 1612, 1458, 1403, 1178, 1056, 990, 929, 792, 683; **^{1}H NMR:** δ_H (400 MHz, CD_2Cl_2) 6.65 (1H, dd, *J* = 17.5, 10.6 Hz, C-6H), 6.32 (1H, dd, *J* = 17.5, 1.7 Hz, C-7H_AH$_B$), 5.79 (1H, dd, *J* = 10.6, 1.7 Hz, C-7H$_A$$H_B$), 4.53–4.47 (1H, m, C-4H), 3.94–3.86 (2H, m, C-1H_2), 2.25–2.12 (1H, m, C-3H_AH$_B$), 1.97–1.83 (3H, m, C-2H_2, C-3H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, CD_2Cl_2) 200.7 (C-5), 132.5 (C-6), 129.5 (C-7), 82.7 (C-4), 69.8 (C-1), 29.7 (C-3), 26.1 (C-2); **HRMS:** (ESI+, *m/z*) $C_7H_{11}O_2$ (MH^+) Calculated: 127.07536, Found: 127.07551 (Δ +1.18 ppm).

(*R*)-6-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-4-methylene-1-((*R*)-tetrahydrofuran-2-yl)-6-((triethylsilyl)oxy)hexan-1-one ((*R*)-346)[*]



317 **(*R*)-342** **(*R*)-346**

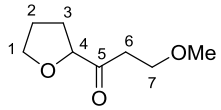
To a solution of compound **317** (50 mg, 84 μmol), $Rh(acac)(CO)_2$ (2.2 mg, 8.4 μmol) and dppb (3.6 mg, 8.4 μmol) in THF (0.30 mL) and H_2O (0.05 mL) was added enone **(*R*)-342** (12.7 mg, 101 μmol) and the vial was flushed with argon. The reaction heated to 50 °C for 23 h and then cooled to rt. EtOAc (1 mL) and H_2O (1 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 → 70:30 pentane:Et_2O) to afford the title compound **(*R*)-346** (31.4 mg, 63%, >20:1 dr) as a colourless oil.

R_f: 0.22 (70:30 pentane:Et_2O); $[\alpha]_D^{25}$ +12.1 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2952, 2911, 2875, 1716, 1645, 1496, 1455, 1412, 1368, 1308, 1261, 1207, 1077, 1016, 970, 896, 801, 736, 698; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.41–7.23 (10H, m, ArH), 4.83 (1H, s, C-15H_AH_B), 4.79 (1H, q, *J* = 1.6 Hz, C-15H_AH_B), 4.59 (1H, d, *J* = 11.6 Hz, C-17H_AH_B), 4.55 (1H, d, *J* = 11.6 Hz, C-17H_AH_B), 4.53 (1H, d, *J* = 11.9 Hz, C-16H_AH_B), 4.49 (1H, d, *J* = 11.9 Hz, C-16H_AH_B), 4.30 (1H, dd, *J* = 8.1, 6.0 Hz, C-11H), 4.18 (1H, ddd, *J* = 4.6, 2.0, 0.8 Hz, C-3H), 4.08 (1H, dt, *J* = 4.6, 2.2 Hz, C-2H), 4.02 (1H, ddd, *J* = 6.5, 5.6, 4.6 Hz, C-5H), 3.99–3.85 (4H, m, C-1H_AH_B, C-14H_2), 3.76 (1H, t, *J* = 4.5 Hz, C-4H), 2.76–2.58 (2H, m, C-9H_2), 2.39–2.26 (3H, m, C-6H_AH_B, C-8H_2), 2.26–2.10 (2H,

[*] Compound **(*R*)-346** was prepared according to the procedure detailed by Suginome and Ito.[86]

m, C-6H$_A$*H$_B$*, C-12*H$_A$*H$_B$), 1.88 (3H, ddd, *J* = 6.1, 3.7, 2.1 Hz, C-12H$_A$*H$_B$*, C-13H$_2$), 0.93 (9H, t, *J* = 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$), 0.58 (6H, q, *J* = 7.8 Hz, Si(C*H*$_2$CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 211.8 (C-10), 144.9 (C-7), 138.1 (2C, C-18, C-22), 128.5 (4C, 2 × C-20, 2 × C-24), 127.9 (2C, 2 × C-23), 127.8 (4C, 2 × C-19, C-21, C-25), 112.6 (C-15), 86.1 (C-4), 83.9 (C-3), 83.8 (C-2), 83.5 (C-11), 71.9 (C-17), 71.4 (2C, C-1, C-16), 70.8 (C-5), 69.5 (C-14), 41.0 (C-6), 36.7 (C-9), 29.8 (C-8), 29.2 (C-12), 25.8 (C-13), 7.1 (3C, Si(CH$_2$*C*H$_3$)$_3$), 5.3 (3C, Si(*C*H$_2$CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{35}H_{50}O_6{}^{28}SiNa$ (MNa^+) Calculated: 617.32689, Found: 617.32655 (Δ –0.55 ppm).

3-Methoxy-1-(tetrahydrofuran-2-yl)propan-1-one (347)

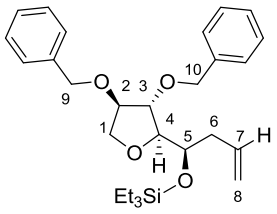


347

A small amount of **347** was isolated from the Rh-catalysed 1,4-addition reactions in MeOH/H$_2$O with boronate **317** and enones **(*RS*)-342** and **(*R*)-342**.

R$_f$: 0.11 (70:30 pentane:Et$_2$O); **IR:** ν_{max} (thin film/cm^{-1}) 2954, 2929, 2876, 1718, 1456, 1390, 1227, 1118, 1075, 1020, 968, 933, 741, 700; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 4.33 (1H, dd, *J* = 8.4, 6.3 Hz, C-4H), 3.99–3.88 (2H, m, C-1H$_2$), 3.71–3.61 (2H, m, C-7H$_2$), 3.33 (3H, s, OCH$_3$), 2.87–2.72 (2H, m, C-6H$_2$), 2.23–2.11 (1H, m, C-3*H$_A$*H$_B$), 2.00–1.85 (3H, m, H-2, C-3H$_A$*H$_B$*); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 210.8 (C-5), 83.7 (C-4), 69.6 (C-1), 67.3 (C-7), 59.0 (OCH$_3$), 38.6 (C-6), 28.9 (C-3), 25.8 (C-2); **HRMS:** (ESI+, *m/z*) $C_8H_{14}O_3Na$ (MNa^+) Calculated: 181.08352, Found: 181.08349 (Δ –0.17 ppm).

(((*R*)-1-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)but-3-en-1-yl)oxy)triethylsilane (348)

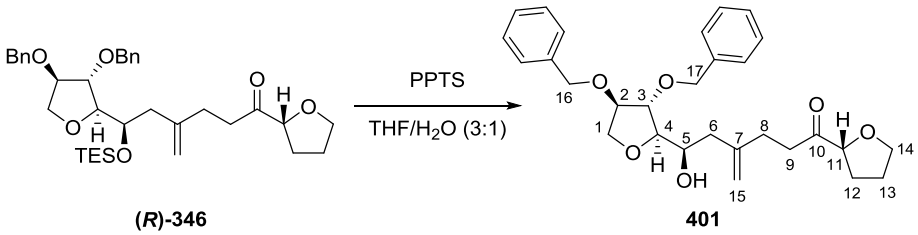


348

A small amount of **348** was isolated from the Rh-catalysed 1,4-addition reactions with boronate **317**.

R_f: 0.66 (70:30 pentane:Et_2O); **IR:** ν_{max} (thin film/cm^{-1}) 3066, 3031, 2953, 2911, 2876, 1641, 1497, 1455, 1414, 1334, 1239, 1208, 1100, 1078, 1006, 913, 734, 697; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.39–7.23 (10H, m, ArH), 5.89 (1H, ddt, *J* = 17.3, 10.2, 7.1 Hz, C-7H), 5.14–5.03 (2H, m, C-8H_AH_B), 4.60 (1H, d, *J* = 11.7 Hz, C-10H_AH_B), 4.52 (2H, s, C-9H_2), 4.51 (1H, d, *J* = 11.7 Hz, C-10H_AH_B), 4.15 (1H, ddd, *J* = 3.4, 1.5, 0.7 Hz, C-3H), 4.08–4.05 (1H, m, C-2H), 3.97 (1H, dd, *J* = 10.0, 2.2 Hz, C-1H_AH_B), 3.92 (1H, dd, *J* = 9.9, 4.3 Hz, C-1H_AH_B), 3.88 (1H, td, *J* = 5.1, 2.5 Hz, C-5H), 3.80 (1H, dd, *J* = 6.6, 3.3 Hz, C-4H), 2.35 (2H, m, C-6H_AH_B), 0.94 (9H, t, *J* = 7.9 Hz, Si(CH_2CH_3)$_3$), 0.60 (6H, q, *J* = 8.1 Hz, Si(CH_2CH_3)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 138.2 (quaternary Ar), 138.1 (quaternary Ar), 134.5 (C-7), 130.9 (Ar), 128.5 (2C, Ar), 127.8 (5C, 3 Ar), 127.7 (2C, Ar), 117.6 (C-8), 85.8 (C-4), 84.3 (C-3), 83.6 (C-2), 71.7 (C-10), 71.6 (2C, C-1, C-5), 71.4 (C-9), 38.6 (C-6), 7.1 (3C, Si(CH_2CH_3)$_3$), 5.3 (3C, Si(CH_2CH_3)$_3$); **HRMS:** (ESI+, *m/z*) $C_{28}H_{40}O_4{}^{28}SiNa$ (MNa^+) Calculated: 491.25881, Found: 491.25856 (Δ –0.51 ppm).

(*R*)-6-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-6-hydroxy-4-methylene-1-((*R*)-tetrahydrofuran-2-yl)hexan-1-one (401)



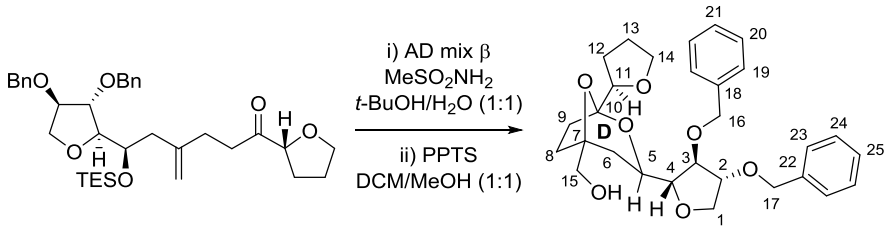
(*R*)-346 401

To a solution of compound **(*R*)-346** (72 mg, 0.12 mmol) in THF (1.2 mL) and H_2O (0.4 mL) was added PPTS (61 mg, 0.24 mmol). The reaction was stirred at rt for 23 h before EtOAc (1 mL) and H_2O (1 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 → 70:30 pentane:Et_2O) to afford the title compound **401** (22 mg, 38%) as a colourless oil.

R_f: 0.43 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +26.1 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3468, 3064, 3031, 2919, 2868, 2357, 2341, 1714, 1646, 1497, 1454, 1402, 1367, 1332, 1207, 1072, 1028, 901, 739, 699; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.39–7.27 (10H, m, ArH), 4.87 (1H, s, C-15$H_A$$H_B$), 4.84 (1H, d, *J* = 1.6 Hz, C-15$H_A$$H_B$), 4.56 (2H, s, C-17$H_2$), 4.54 (1H, d, *J* = 11.8 Hz, C-16$H_A$$H_B$), 4.50 (1H, d, *J* = 12.0 Hz, C-16$H_A$$H_B$), 4.31 (1H, dd, *J* = 8.1, 6.1 Hz, C-11H), 4.19 (1H, d, *J* = 3.1 Hz, C-3H), 4.06–4.02 (2H, m, C-1$H_A$$H_B$, C-2H), 3.99–3.89 (3H, m, C-5H, C-14H_2), 3.87 (1H, dd, *J* = 10.4, 3.9 Hz, C-1$H_A$$H_B$), 3.80 (1H, dd, *J* = 4.8, 3.1 Hz, C-4H), 2.84–2.75 (1H, m, C-9$H_A$$H_B$), 2.72–2.64 (1H, m, C-9$H_A$$H_B$), 2.57 (1H, s, O*H*), 2.40–2.26 (3H, m, C-6$H_A$$H_B$, C-8$H_2$), 2.22–2.13 (1H, m, C-12$H_A$$H_B$), 2.10 (1H, dd, *J* = 14.3, 9.2 Hz, C-6$H_A$$H_B$), 1.95–1.84 (3H, m, C-12$H_A$$H_B$, C-13$H_2$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 212.0 (C-10), 144.9 (C-7), 137.8 (quaternary Ar), 137.6 (quaternary Ar), 128.6 (4C, 2Ar), 128.1 (2C, Ar), 128.0 (2Ar), 127.9 (2C, Ar), 112.3 (C-15), 87.5 (C-4), 83.6 (C-11), 82.8 (C-3), 82.6 (C-2), 71.9 (C-17), 71.6 (C-1),

71.1 (C-16), 69.5 (C-14), 69.2 (C-5), 40.9 (C-6), 36.5 (C-9), 29.2 (C-12), 29.0 (C-8), 25.8 (C-13); **HRMS:** (ESI+, *m/z*) $C_{29}H_{36}O_6Na$ (MNa^+) Calculated: 503.24041, Found: 503.24017 (Δ –0.48 ppm).

((1*S*,3*R*,5*R*)-3-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-1-((*R*)-tetrahydrofuran-2-yl)-2,8-dioxabicyclo[3.2.1]octan-5-yl)methanol (351)



(*R*)-346 351

To a suspension of compound **(*R*)-346** (23 mg, 39 μmol), $K_3Fe(CN)_6$ (33 mg, 0.10 mmol), K_2CO_3 (14 mg, 0.10 mmol), methanesulfonamide (3.2 mg, 34 μmol), $(DHQD)_2PHAL$ (5.2 mg, 6.7 μmol) in *t*-BuOH (0.5 mL) at 0 °C was added $K_2OsO_2(OH)_4$ (1.2 mg, 3.4 μmol) in H_2O (0.5 mL). The reaction was warmed to rt for 20 h before the reaction was quenched with sat. aq. Na_2SO_3 (1 mL) and stirred for a further 3 h. The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude diol product was obtained as a pale yellow oil and was carried into the next step without further purification.

Crude diol (assumed quant., 39 μmol) was transferred to a flask in DCM (1 mL) and MeOH (1 mL). PPTS (9.7 mg, 38.7 μmol) was added and the reaction was stirred at rt for 17 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL), diluted with EtOAc (2 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 60:40 →

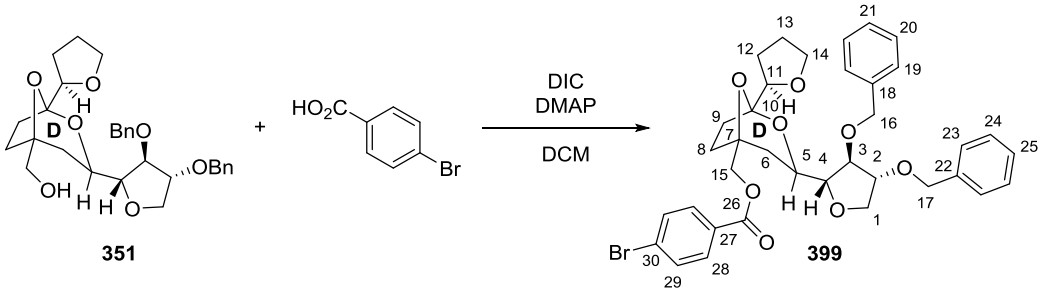
50:50 → 40:60 → 25:75 → 0:100 pentane:EtOAc) to afford the title compound **351** (17.5 mg, 91%) as a colourless oil.

The bicyclic ring configuration was confirmed by nOes between C-5H to C-8H$_B$ and C-9H$_B$ in CD_2Cl_2 (see **Appendix 6.2.1**).

R$_f$: 0.12 (60:40 pentane:EtOAc); $[\alpha]_D^{25}$ +2.0 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3543, 2919, 2871, 1496, 1455, 1327, 1210, 1076, 1028, 979, 908, 738, 699; **^{1}H NMR:** δ_H (500 MHz, C_6D_6) 7.38–7.32 (2H, m, ArH), 7.28–7.22 (2H, m, ArH), 7.22–7.06 (6H, m, ArH), 4.59 (1H, d, *J* = 12.0 Hz, C-16*H$_A$*H$_B$), 4.51 (1H, d, *J* = 12.1 Hz, C-16H$_A$*H$_B$*), 4.34 (1H, m, C-3H), 4.25 (2H, s, C-17H$_2$), 4.12–4.03 (3H, m, C-4H, C-5H, C-11H), 4.00–3.94 (2H, m, 2H, C-1*H$_A$*H$_B$, C-2H), 3.93–3.89 (1H, m, C-1H$_A$*H$_B$*), 3.72 (1H, dt, *J* = 8.2, 6.9 Hz, C-14*H$_A$*H$_B$), 3.61 (td, *J* = 7.6, 5.7 Hz, 1H, C-14H$_A$*H$_B$*), 3.54 (1H, d, *J* = 11.8 Hz, C-15*H$_A$*H$_B$), 3.35 (1H, d, *J* = 11.8 Hz, 1H, C-15H$_A$*H$_B$*), 2.02 (1H, td, *J* = 13.2, 4.6 Hz, C-9*H$_A$*H$_B$), 1.97–1.88 (2H, m, C-9H$_A$*H$_B$*, C-12*H$_A$*H$_B$), 1.84 (1H, tdd, *J* = 12.9, 4.9, 1.6 Hz, C-8*H$_A$*H$_B$), 1.81–1.72 (2H, m, C-6*H$_A$*H$_B$, C-12H$_A$*H$_B$*), 1.64–1.58 (1H, m, 1H, C-13*H$_A$*H$_B$), 1.55 (dd, *J* = 12.8, 3.4 Hz, C-6H$_A$*H$_B$*), 1.50–1.40 (1H, m, C-13H$_A$*H$_B$*), 1.27 (1H, ddd, *J* = 12.2, 9.4, 4.5 Hz, C-8H$_A$*H$_B$*); **^{1}H NMR:** δ_H (500 MHz, CD_2Cl_2) 7.45–7.06 (10H, m, ArH), 4.62–4.44 (4H, m, C-16H$_2$, C-17H$_2$), 4.12–4.04 (2H, m, C-2H, C-3H), 4.00–3.85 (4H, m, C-1H$_2$, C-5H, C-11H), 3.83–3.70 (3H, m, C-4H, C-14H$_2$), 3.63 (1H, d, *J* = 11.9 Hz, C-15*H$_A$*H$_B$), 3.51 (1H, d, *J* = 11.9 Hz, C-15H$_A$*H$_B$*), 2.01 (1H, dd, *J* = 13.4, 5.1 Hz, C-9*H$_A$*H$_B$), 1.97–1.74 (6H, m, C-8*H$_A$*H$_B$, C-9H$_A$*H$_B$*, C-12H$_2$, C-13H$_2$), 1.69–1.60 (2H, m, C-8H$_A$*H$_B$*, C-6*H$_A$*H$_B$), 1.51 (1H, dd, *J* = 12.9, 3.9 Hz, C-6H$_A$*H$_B$*); **^{13}C NMR:** δ_C (126 MHz, C_6D_6) 138.8 (C-18), 138.6 (C-22), 128.7 (2C, 2Ar), 128.4 (2C, Ar), 128.2 (2C, Ar), 128.0 (4C, 2Ar), 108.4 (C-10), 87.4 (C-4), 84.5 (C-3), 84.1 (C-2), 84.0 (C-7), 81.4 (C-11), 71.8 (C-1), 71.7 (C-16), 71.4 (C-17), 69.5 (C-5), 69.0 (C-14), 66.9 (C-15),

36.0 (C-6), 31.8 (C-9), 28.5 (C-8), 27.4 (C-12), 26.3 (C-13); **^{13}C NMR:** δ_C (126 MHz, CD_2Cl_2) 138.8 (C-18), 138.7 (C-22), 128.9 (4C, 2Ar), 128.3 (3C, 2Ar), 128.2 (3C, 2Ar), 108.8 (C-10), 87.3 (C-4), 84.5 (C-3), 84.1 (C-2), 83.9 (C-7), 81.0 (C-11), 72.2 (C-1), 72.1 (C-16), 71.8 (C-17), 69.5 (C-14), 69.3 (C-5), 67.3 (C-15), 35.6 (C-6), 31.0 (C-9), 28.9 (C-8), 27.8 (C-12), 26.5 (C-13); **HRMS:** (ESI+, *m/z*) $C_{29}H_{37}O_7$ (MH^+) Calculated: 497.25338, Found: 497.25380 (Δ +0.84 ppm).

((1*S*,3*R*,5*R*)-3-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-1-((*R*)-tetrahydrofuran-2-yl)-2,8-dioxabicyclo[3.2.1]octan-5-yl)methyl 4-bromobenzoate (399)



To compound **351** (10.8 mg, 21.7 μmol) in DCM (2.5 mL), were added 4-bromobenzoic acid (8.8 mg, 44 μmol), DMAP (1 crystal, cat.), and DIC (6.7 μL, 43.5 μmol). The reaction was stirred at rt for 21 h before the reaction was diluted with H_2O (3 mL) and DCM (3 mL). The mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 pentane:EtOAc) to afford the title compound **399** (7.8 mg, 53%) as a colourless oil.

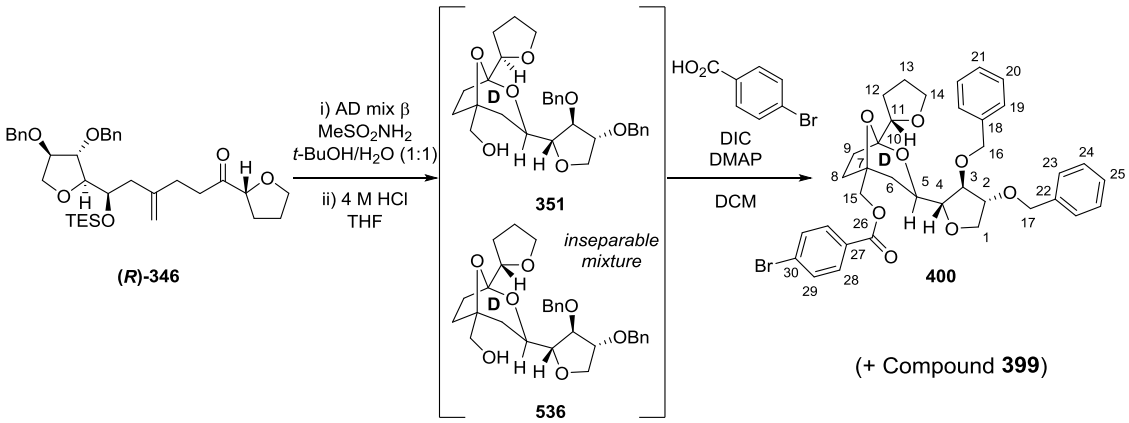
The bicyclic ring configuration was confirmed by nOes between C-5H to C-8H_B and C-9H_B in CD_2Cl_2 (see **Appendix 6.2.2**).

R_f: 0.58 (60:40 pentane:EtOAc); $[\alpha]_D^{25}$ –1.6 (*c* = 0.50, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2872, 1721, 1590, 1484, 1454, 1398, 1271, 1174, 1101, 1071, 1012, 956, 848, 756, 699;

^{1}H NMR: δ_H (500 MHz, C_6D_6) 7.75–7.69 (2H, m, C-28H), 7.35–7.29 (2H, m, ArH), 7.27–7.21 (2H, m, ArH), 7.21–7.18 (3H, m, ArH), 7.14–7.08 (3H, m, ArH), 7.08–7.04 (2H, m, C-29H), 4.59 (1H, d, J = 12.1 Hz, C-16H_AH$_B$), 4.51 (1H, d, J = 12.0 Hz, C-16H$_A$$H_B$), 4.37 (1H, s, C-3H), 4.32 (1H, d, J = 11.7 Hz, C-15H_AH$_B$), 4.24 (2H, s, C-17H$_2$), 4.20 (1H, d, J = 11.7 Hz, C-15H$_A$$H_B$), 4.14–4.06 (3H, m, C-4H, C-5H, C-11H), 3.99 (1H, dt, J = 9.7, 1.0 Hz, C-1H_AH$_B$), 3.95 (1H, dt, J = 4.0, 1.3 Hz, C-2H), 3.93–3.87 (1H, dd, J = 9.7, 3.9 Hz, C-1H$_A$$H_B$), 3.75 (1H, dt, J = 8.1, 6.9 Hz, C-14H_AH$_B$), 3.62 (1H, td, J = 7.7, 5.7 Hz, C-14H$_A$$H_B$), 2.11–1.91 (4H, m, C-9H$_2$, C-6H_AH$_B$, C-12H_AH$_B$), 1.82–1.71 (2H, m, C-7H$_A$$H_B$, C-12H$_A$$H_B$), 1.69–1.60 (1H, m, C-13H_AH$_B$), 1.50–1.40 (2H, m, C-8H_AH$_B$, C-13H$_A$$H_B$), 1.33 (1H, ddd, J = 12.4, 9.2, 4.9 Hz, C-8H$_A$$H_B$); **^{1}H NMR:** δ_H (500 MHz, CD_2Cl_2) 7.94–7.87 (2H, m, C-28H), 7.62–7.55 (2H, m, C-29H), 7.39–7.21 (10H, m, ArH), 4.57 (1H, d, J = 11.8 Hz, C-16H_AH$_B$), 4.52 (1H, d, J = 11.8 Hz, C-17H_AH$_B$), 4.51 (1H, d, J = 11.8 Hz, C-16H$_A$$H_B$), 4.49 (1H, d, J = 11.8 Hz, C-17H$_A$$H_B$), 4.38 (1H, d, J = 11.7 Hz, C-15H_AH$_B$), 4.30 (1H, d, J = 11.7 Hz, C-15H$_A$$H_B$), 4.12 (1H, dt, J = 2.3, 1.0 Hz, C-3H), 4.08 (1H, dt, J = 3.9, 1.5 Hz, C-2H), 4.00–3.89 (4H, m, C-5H, C-11H, C-14H$_2$) 3.82–3.72 (3H, m, C-1H$_2$, C-4H), 2.08 (1H, ddd, J = 13.1, 10.3, 7.2 Hz, C-9H_AH$_B$), 1.95 (1H, ddd, J = 13.3, 7.8, 6.4 Hz, C-9H$_A$$H_B$), 1.90–1.73 (7H, m, C-8H$_2$, C-6H_AH$_B$, C-12H$_2$, C-13H$_2$), 1.70 (1H, dd, J = 12.9, 3.8 Hz, C-6H$_A$$H_B$); **^{13}C NMR:** δ_C (126 MHz, C_6D_6) 165.3 (C-26), 138.8 (C-18), 138.5 (C-22), 131.9 (2C, 2 × C-29), 131.5 (2C, 2 × C-28), 129.4 (Ar), 128.7 (2C, 2Ar), 128.4 (4C, 2Ar), 128.2 (2C, Ar), 128.0 (3C, 2Ar), 108.8 (C-10), 87.4 (C-4), 84.5 (C-3), 84.0 (C-2), 81.9 (C-7), 81.7 (C-11), 71.9 (C-1), 71.7 (C-16), 71.4 (C-17), 69.5 (C-5), 69.0 (C-14), 68.9 (C-15), 36.2 (C-6), 32.1 (C-9), 30.4 (C-8), 27.2 (C-12), 26.4 (C-13); **^{13}C NMR:** δ_C (126 MHz, CD_2Cl_2) 165.9 (C-26), 138.7 (C-18), 138.6 (C-22), 132.3 (2C, 2 × C-29), 131.7 (2C, 2 × C-28), 129.6 (quaternary Ar), 129.0 (2C, 2Ar), 128.9 (2C, Ar), 128.6 (quaternary Ar), 128.3 (2C, Ar), 128.2 (4C, 2Ar), 109.2 (C-

10), 87.3 (C-4), 84.5 (C-3), 84.0 (C-2), 82.0 (C-7), 81.0 (C-11), 72.3 (C-16), 72.0 (C-17), 71.8 (C-14), 69.5 (C-1), 69.4 (C-5), 69.3 (C-15), 36.0 (C-6), 30.8 (C-8), 30.7 (C-9), 27.8 (C-12), 26.5 (C-13); **HRMS:** (ESI+, *m/z*) $C_{36}H_{40}O_8{}^{79}Br$ (MH^+) Calculated: 679.19011, Found: 679.19004 (Δ –0.10 ppm).

((1*S*,3*R*,5*R*)-3-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-1-((*S*)-tetrahydrofuran-2-yl)-2,8-dioxabicyclo[3.2.1]octan-5-yl)methyl 4-bromobenzoate (400)



To a suspension of compound **(*R*)-346** (20 mg, 34 μmol), $K_3Fe(CN)_6$ (33 mg, 0.10 mmol), K_2CO_3 (14 mg, 0.10 mmol), methanesulfonamide (3.2 mg, 34 μmol), $(DHQD)_2PHAL$ (5.2 mg, 6.7 μmol) in *t*-BuOH (0.5 mL) at 0 °C was added $K_2OsO_2(OH)_4$ (1.2 mg, 3.4 μmol) in H_2O (0.5 mL). The reaction was warmed to rt for 19 h before the reaction was quenched with sat. aq. Na_2SO_3 (1 mL) and stirred for a further 1 h. The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude diol product was obtained as a pale yellow oil and was carried into the next step without further purification.

Crude diol (assumed quant., 34 μmol) was transferred to a flask in THF (1 mL). Two drops of 4 M HCl in dioxane were added and the reaction was stirred at rt for 25 h. Another drop of 4 M HCl in dioxane was added and the reaction was stirred for a further 2 h. Another drop of 4 M HCl in dioxane was added and the reaction was stirred for

another 17 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL), diluted with EtOAc (1 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 60:40 → 50:50 → 25:75 pentane:EtOAc) to afford an inseparable mixture of compounds **351** and **536** (11.7 mg, 70%) as a colourless oil.

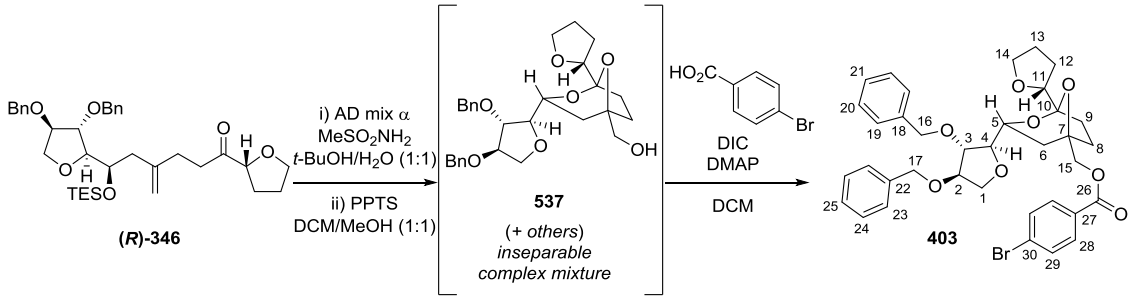
To the inseparable mixture of compounds **351** and **536** (11.7 mg, 23.6 μmol) in DCM (2.5 mL), were added 4-bromobenzoic acid (9.5 mg, 47 μmol), DMAP (1 crystal, cat.), and DIC (7.3 μL, 47 μmol). The reaction was stirred at rt for 21 h before the reaction was diluted with H_2O (3 mL) and DCM (3 mL). The mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 80:20 pentane:EtOAc) to afford the title compound **400** (3.8 mg, 24%) as a colourless oil, as well as compound **399** (5.0 mg, 31%) and an indeterminable mixture of the **399** and **400** (1.5 mg, 9%).

The bicyclic ring configuration was confirmed by nOes between C-5H to C-8H_B and C-9H_B in CD_2Cl_2 (see **Appendix 6.2.3**).

R_f: 0.65 (60:40 pentane:EtOAc); $[\alpha]_D^{25}$ –0.2 (*c* = 0.20, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2924, 1722, 1590, 1484, 1455, 1398, 1271, 1209, 1174, 1101, 1080, 1012, 901, 848, 756, 698; **^{1}H NMR:** δ_H (500 MHz, C_6D_6) 7.74 (2H, d, *J* = 8.5 Hz, C-28H), 7.36 (2H, d, *J* = 7.2 Hz, ArH), 7.25–7.10 (8H, m, ArH), 7.08 (2H, d, *J* = 8.6 Hz, C-29H), 4.60 (1H, d, *J* = 12.1 Hz, C-16$H_A$$H_B$), 4.51 (1H, d, *J* = 12.1 Hz, C-16$H_A$$H_B$), 4.37 (1H, s, C-3H), 4.32 (1H, d, *J* = 11.6 Hz, C-15C$H_A$$H_B$), 4.22 (2H, s, C-17$H_2$), 4.19 (1H, d, *J* = 11.6 Hz, C-15C$H_A$$H_B$), 4.12 (1H, dd, *J* = 7.8, 5.8 Hz, C-11H), 4.08 (1H, s, C-4H), 4.08–4.04 (1H, m,

C-5H), 3.98 (1H, d, *J* = 9.9 Hz, C-1H_AH$_B$), 3.96–3.93 (1H, m, C-2H), 3.90 (1H, dd, *J* = 5.6, 1.6 Hz, C-1H$_A$$H_B$), 3.80 (1H, q, *J* = 7.0 Hz, C-14H_AH$_B$), 3.63 (1H, td, *J* = 7.5, 5.8 Hz, C-14H$_A$$H_B$), 2.32 (1H, td, *J* = 13.2, 4.5 Hz, C-9H_AH$_B$), 2.20 (1H, ddt, *J* = 12.4, 8.4, 6.3 Hz, C-12H_AH$_B$), 1.94–1.79 (2H, m, C-6H_AH$_B$, C-12H$_A$$H_B$), 1.79–1.71 (3H, m, C-6H$_A$$H_B$, C-9H$_A$$H_B$, C-13$H_AH_B$), 1.55–1.46 (2H, m, C-8$H_AH_B$, C-13H$_A$$H_B$), 1.33 (1H, ddd, *J* = 12.5, 9.6, 4.6 Hz, C-8H$_A$$H_B$); **^{1}H NMR:** δ_H (500 MHz, CD_2Cl_2) 7.93–7.88 (2H, m, C-28), 7.61–7.57 (2H, m, C-29H), 7.38–7.24 (10H, m, ArH), 4.58 (1H, d, *J* = 11.9 Hz, C-17H_AH$_B$), 4.53–4.45 (3H, m, C-16H$_2$, C-17HAH_B), 4.40 (1H, d, *J* = 11.6 Hz, C-15H_AH$_B$), 4.29 (1H, d, *J* = 11.6 Hz, C-15H$_A$$H_B$), 4.12 (1H, dt, *J* = 2.3, 1.0 Hz, C-3H), 4.07 (1H, dt, *J* = 4.0, 1.5 Hz, C-2H), 4.00–3.95 (1H, m, C-5H), 3.95–3.88 (3H, m, C-11H, C-14H$_2$), 3.80–3.69 (3H, m, C-1H$_2$, C-4H), 2.16–2.08 (1H, m, C-9CH_AH$_B$), 2.01–1.93 (1H, m, C-12H_AH$_B$), 1.93–1.83 (5H, m, C-9H$_A$$H_B$, C-8H$_2$, C-12H$_A$$H_B$, C-13$H_AH_B$), 1.83–1.72 (2H, m, C-6$H_AH_B$, C-13H$_A$$H_B$), 1.70 (1H, dd, *J* = 12.9, 4.0 Hz, C-6H$_A$$H_B$); **^{13}C NMR:** δ_C (126 MHz, C_6D_6) 165.3 (C-26), 138.8 (C-18), 138.6 (C-22), 131.9 (2C, 2 × C-29), 131.5 (2C, 2 × C-28), 128.7 (2C, 2Ar), 128.4 (5C, 3Ar), 128.2 (Ar), 128.0 (4C, 2Ar), 109.2 (C-10), 87.6 (C-4), 84.2 (C-3), 84.1 (C-2), 81.8 (C-7), 79.8 (C-11), 71.8 (C-1), 71.4 (C-16), 71.3 (C-17), 69.5 (C-5), 69.1 (C-14), 68.8 (C-15), 36.4 (C-6), 30.8 (C-9), 30.4 (C-8), 27.0 (C-12), 26.2 (C-13); **^{13}C NMR:** δ_C (126 MHz, CD_2Cl_2) 165.9 (C-26), 138.7 (2C, C-18, C-22), 132.3 (2C, 2 × C-29), 131.7 (2C, 2 × C-28), 129.6 (C-30), 128.9 (3C, 2Ar), 128.6 (C-27), 128.3 (3C, 2Ar), 128.2 (3C, 2Ar), 125.4 (Ar), 109.1 (C-10), 87.4 (C-4), 84.4 (C-3), 84.1 (C-2), 82.2 (C-7), 80.6 (C-11), 72.2 (C-14), 71.9 (C-16), 71.7 (C-17), 69.5 (C-1), 69.4 (C-5), 69.1 (C-15), 36.0 (C-6), 31.5 (C-9), 30.7 (C-8), 27.2 (C-12), 26.4 (C-13); **HRMS:** (ESI+, *m/z*) $C_{36}H_{40}O_8{}^{79}Br$ (MH^+) Calculated: 679.19011, Found: 679.19031 (Δ +0.29 ppm).

((3*R*,5*S*)-3-((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-1-((*R*)-tetrahydrofuran-2-yl)-2,8-dioxabicyclo[3.2.1]octan-5-yl)methyl 4-bromobenzoate (403)



To a suspension of compound **(*R*)-346** (21 mg, 36 μmol), $K_3Fe(CN)_6$ (33 mg, 0.10 mmol), K_2CO_3 (14 mg, 0.10 mmol), methanesulfonamide (3.2 mg, 34 μmol), $(DHQD)_2PHAL$ (5.2 mg, 6.7 μmol) in *t*-BuOH (0.5 mL) at 0 °C was added $K_2OsO_2(OH)_4$ (1.2 mg, 3.4 μmol) in H_2O (0.5 mL). The reaction was warmed to rt for 19 h before the reaction was quenched with sat. aq. Na_2SO_3 (1 mL) and stirred for a further 30 min. The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude diol product was obtained as a pale yellow oil and was carried into the next step without further purification.

Crude diol (assumed quant., 36 μmol) was transferred to a flask in DCM (1 mL) and MeOH (1 mL). PPTS (9.7 mg, 39 mmol) was added and the reaction was stirred at rt for 22 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL), diluted with EtOAc (2 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 60:40 → 25:75 pentane:EtOAc) to afford an inseparable mixture of compounds including **537** (9.2 mg, 53%) as a colourless oil.

To the inseparable mixture of compounds including **537** (9.2 mg, 19 μmol) in DCM (2.5 mL), were added 4-bromobenzoic acid (7.5 mg, 37 μmol), DMAP (1 crystal, cat.),

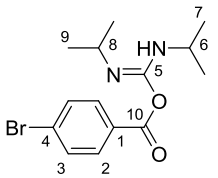
and DIC (10 μL, 65 μmol). The reaction was stirred at rt for 28 h before the reaction was diluted with H_2O (3 mL) and DCM (3 mL). The mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 → 80:20 pentane:EtOAc) to afford the title compound **403** (1.1 mg, 9%) as a colourless oil.

The bicyclic ring configuration was confirmed by the lack of nOes between C-5H to C-8$H_{A/B}$ and C-9$H_{A/B}$ in C_6D_6 (see **Appendix 6.2.4**).

R_f: 0.67 (60:40 pentane:EtOAc); $[\alpha]_D^{25}$ +11.9 (*c* = 0.10, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3064, 3028, 2946, 2870, 2360, 2338, 1722, 1651, 1590, 1496, 1484, 1454, 1398, 1368, 1271, 1207, 1173, 1102, 1070, 1028, 1012, 957, 903, 848, 830, 755, 738, 698, 638, 612; **^{1}H NMR:** δ_H (500 MHz, C_6D_6) 7.80–7.73 (2H, m, C-28H), 7.38–6.98 (12H, m ,C-29H, ArH), 4.56 (1H, d, *J* = 12.2 Hz, C-16H_AH_B), 4.51 (1H, d, *J* = 12.3 Hz, C-16H_AH_B), 4.33 (1H, d, *J* = 2.1 Hz, C-3H), 4.26 (1H, d, *J* = 11.7 Hz, C-15H_AH_B), 4.26 (1H, d, *J* = 11.9 Hz, C-17H_AH_B), 4.23–4.16 (1H, m, C-5H), 4.20 (1H, d, *J* = 11.9 Hz, C-17H_AH_B), 4.16 (1H, d, *J* = 11.7 Hz, C-15H_AH_B), 4.12–4.06 (2H, m, C-4H, C-11H), 3.98–3.86 (3H, m, C-1H_2, C-2H), 3.81–3.75 (1H, m, C-14H_AH_B), 3.64 (1H, m, C-14H_AH_B), 2.41 (1H, dd, *J* = 13.8, 5.5 Hz, C-6H_AH_B), 2.30 (1H, td, *J* = 12.5, 4.4 Hz, C-9H_AH_B), 2.09–1.99 (1H, m, C-12H_AH_B), 1.87 (1H, ddd, *J* = 12.7, 9.2, 5.1 Hz, C-9H_AH_B), 1.76–1.60 (4H, m, C-6H_AH_B, C-8H_AH_B, C-12H_AH_B, C-13H_AH_B), 1.47 (2H, m, C-8H_AH_B, C-13H_AH_B); **^{1}H NMR:** δ_H (500 MHz, CD_2Cl_2) 7.90–7.86 (2H, m, C-28H), 7.58–7.54 (2H, m, C-29H), 7.41–7.23 (10H, m, ArH), 4.57 (1H, d, *J* = 11.8 Hz, C-16H_AH_B), 4.56 (1H, d, *J* = 11.8 Hz, C-16H_AH_B), 4.50 (1H, d, *J* = 11.7 Hz, C-17H_AH_B), 4.48 (1H, d, *J* = 11.7 Hz, C-17H_AH_B), 4.42 (1H, d, *J* = 11.7 Hz, C-15H_AH_B), 4.31 (1H, d, *J* = 11.7 Hz, C-15H_AH_B), 4.09 (1H, d,

J = 2.7 Hz, C-3H), 4.08–4.05 (1H, m, C-2H), 3.95–3.87 (4H, m, C-1H$_2$, C-5H, C-11H), 3.80 (1H, dd, J = 8.5, 2.7 Hz, C-4H), 3.77–3.70 (2H, m, C-14H$_2$), 2.32 (1H, dd, J = 13.4, 5.7 Hz, C-6H_AH$_B$), 2.04 (1H, td, J = 11.4, 3.9 Hz, C-9H_AH$_B$), 1.96 (1H, dd, J = 11.3, 3.6 Hz, C-8H_AH$_B$), 1.93–1.79 (5H, m, C-8H$_A$$H_B$, C-9H$_A$$H_B$, C-12H$_2$, C-13$H_AH_B$), 1.79–1.69 (1H, m, C-13H$_A$$H_B$), 1.73 (1H, dd, J = 13.4, 8.5 Hz, C-6H$_A$$H_B$); **^{13}C NMR:** δ_C (126 MHz, C_6D_6) 165.3 (C-26), 138.7 (C-18), 138.5 (C-22), 131.9 (2C, 2 × C-29), 131.4 (2C, 2 × C-28), 129.5 (Ar), 128.7 (Ar), 128.6 (2C, Ar), 128.4 (3C, 2Ar), 128.2 (2C, Ar), 128.0 (2C, Ar), 127.5 (Ar), 108.4 (C-10), 86.8 (C-4), 84.5 (C-3), 83.8 (C-2), 80.7 (C-7), 80.1 (C-11), 71.9 (C-1), 71.6 (C-16), 71.2 (C-17), 69.2 (C-14), 68.5 (C-5), 68.1 (C-15), 37.5 (C-6), 33.3 (C-9), 32.7 (C-8), 26.7 (C-12), 26.3 (C-13); **^{13}C NMR:** δ_C (126 MHz, CD_2Cl_2) 165.9 (C-26), 138.7 (C-18), 138.6 (C-22), 132.3 (2C, 2 × C-29), 131.7 (2C, 2 × C-28), 129.6 (Ar), 128.9 (4C, 2Ar), 128.5 (Ar), 128.4 (2C, Ar), 128.3 (2C, 2Ar), 128.2 (2C, Ar), 108.4 (C-10), 86.7 (C-4), 84.7 (C-3), 83.9 (C-2), 81.0 (C-7), 80.7 (C-11), 72.2 (C-1), 72.0 (C-16), 71.7 (C-17), 69.6 (C-14), 68.5 (C-15), 68.4 (C-5), 37.6 (C-6), 33.8 (C-9), 33.0 (C-8), 26.9 (C-12), 26.5 (C-13); **HRMS:** (ESI+, *m/z*) $C_{36}H_{39}O_8{}^{79}BrNa$ (MNa^+) Calculated: 701.17205, Found: 701.17162 (Δ –0.61 ppm).

(*E*)-4-Bromobenzoic (*E*)-*N*,*N′*-diisopropylcarbamimidic anhydride (538)



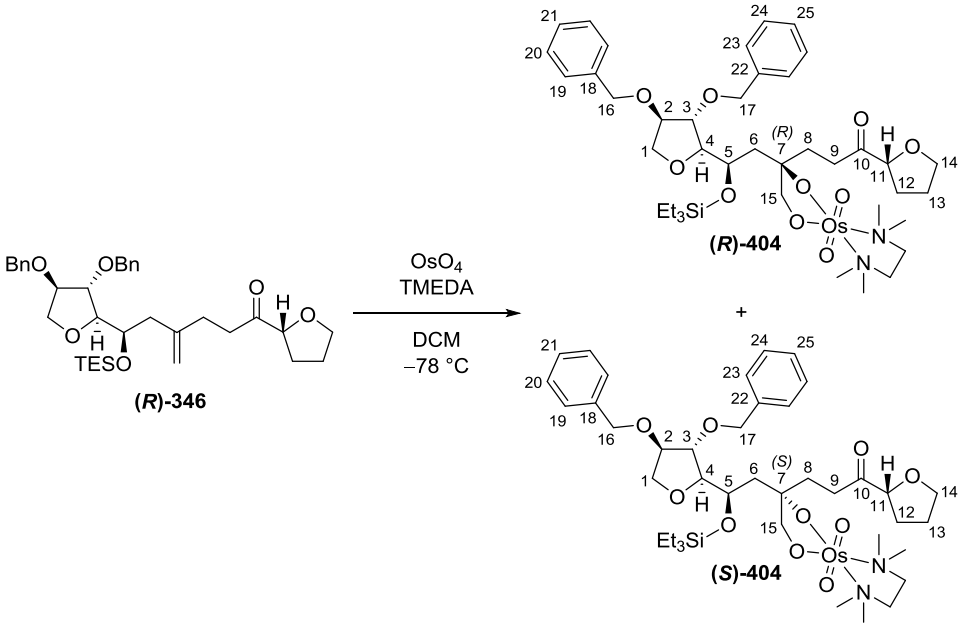
538

A small amount of **538** was isolated from the esterification reactions with 4-bromobenzoic acid and DIC.

R_f: 0.63 (60:40 pentane:EtOAc); **IR:** ν_{max} (thin film/cm^{-1}) 3519, 3304, 3057, 2974, 2934, 2876, 2360, 1689, 1636, 1591, 1535, 1484, 1458, 1396, 1366, 1258, 1198, 1179, 1162,

1132, 1070, 1054, 1013, 931, 867, 850, 832, 808, 752, 714, 689, 626; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.58–7.54 (2H, m, 2 × C-2H), 7.42–7.37 (2H, m, 2 × C-3H), 6.63 (1H, d, *J* = 6.4 Hz, NH), 4.36 (1H, hept, *J* = 6.8 Hz, C-8H), 3.85 (1H, dp, *J* = 7.7, 6.5 Hz, C-6H), 1.42 (6H, d, *J* = 6.8 Hz, 2 × C-9H_3), 1.01 (6H, d, *J* = 6.6 Hz, 2 × C-7H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 171.4 (C-10), 154.0 (C-5), 136.0 (C-4), 132.0 (C-2), 128.2 (C-3), 125.2 (C-1), 50.5 (C-8), 43.0 (C-6), 22.4 (C-7), 21.0 (C-9); **HRMS:** (ESI+, *m/z*) $C_{14}H_{19}N_2O_2{}^{79}BrNa$ (MNa^+) Calculated: 349.05221, Found: 349.05236 (Δ +0.43 ppm).

Osmate esters (*R*)-404 and (*S*)-404



To a solution of compound **(*R*)-346** (60.6 mg, 0.102 mmol) and freshly distilled TMEDA[183] (17 µL, 0.107 mmol) in DCM (10 mL), were added solid OsO_4 (32.5 mg, 0.128 mmol) in DCM (3 mL) at –78 °C. The reaction was warmed to rt for 22 h before the solvent was evaporated *via* a stream of N_2. The crude mixture was purified by preparative TLC (90:10 $CHCl_3$:MeOH) to afford one major isomer of **404** (47.5 mg, 56%), one minor isomer of **404** (16.3 mg, 19%) and an indeterminable mixture of the two

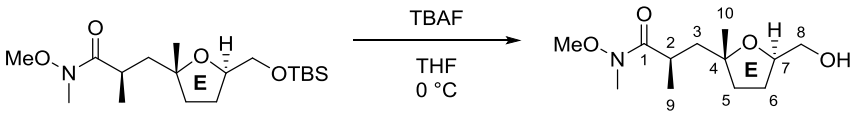
(21.5 mg, 25%) as dark brown solids. Both NMR analysis and X-ray crystallography could not confirm which diastereomer was the major and minor.

R_f: 0.50 (**major**) and 0.48 (**minor**) (90:10 DCM:MeOH); $[\alpha]_D^{25}$ –73.6 (**major**) and –796.8 (**minor**) (*c* = 0.10, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3401, 3028, 2916, 2875, 1712, 1455, 1402, 1353, 1286, 1241, 1206, 1074, 1014, 959, 926, 877, 836, 799, 739, 699, 606 (**major**); 3403, 3029, 2918, 2875, 1711, 1455, 1403, 1353, 1286, 1240, 1207, 1092, 1015, 960, 925, 878, 837, 800, 739, 699, 607 (**minor**); **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.38–7.20 (10H, m, ArH), 4.59 (1H, d, *J* = 11.5 Hz, C-17H_AH_B), 4.54 (1H, d, *J* = 11.5 Hz, C-17H_AH_B), 4.51 (1H, d, *J* = 11.7 Hz, C-16H_AH_B), 4.46 (1H, d, *J* = 11.8 Hz, C-16H_AH_B), 4.37–4.32 (1H, m, C-11H), 4.29–4.23 (2H, m, C-3H, C-5H), 4.14 (1H, d, *J* = 9.9 Hz, C-15H_AH_B), 4.10 (1H, d, *J* = 9.9 Hz, C-15H_AH_B), 4.03 (1H, dt, *J* = 4.9, 2.3 Hz, C-2H), 3.95 (1H, dd, *J* = 9.9, 2.4 Hz, C-14H_AH_B), 3.93–3.87 (1H, m, C-1H_AH_B), 3.87–3.80 (3H, m, C-1H_AH_B, C-7H, C-14H_AH_B), 3.11–2.94 (4H, m, NCH_2CH_2N), 2.83 (3H, s, NCH_3), 2.79 (6H, 2 × s, 2 × NCH_3), 2.73 (3H, s, NCH_3), 2.66 (1H, ddd, *J* = 17.5, 10.7, 5.3 Hz, C-9H_AH_B), 2.52 (1H, ddd, *J* = 17.5, 10.6, 4.9 Hz, C-9H_AH_B), 2.31 (1H, ddd, *J* = 14.1, 10.6, 5.4 Hz, C-8H_AH_B), 2.25 (1H, dd, *J* = 14.8, 3.3 Hz, C-6H_AH_B), 2.21–2.08 (2H, m, C-8H_AH_B, C-12H_AH_B), 1.93–1.81 (4H, m, C-6H_AH_B, C-12H_AH_B, C-13H_AH_B), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$), 0.68 (H, q, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$) (**major**); 7.38–7.21 (10H, m, ArH), 4.65 (1H, d, *J* = 11.5 Hz, C-17H_AH_B), 4.59 (1H, d, *J* = 11.5 Hz, C-17H_AH_B), 4.50 (2H, s, C-16H_2), 4.40 (1H, d, *J* = 10.0 Hz, C-15H_AH_B), 4.33–4.27 (3H, m, C-3H, C-5H, C-11H), 4.11–4.07 (1H, m, C-4H), 4.07 (1H, d, *J* = 10.0 Hz, C-15H_AH_B), 4.01 (1H, dd, *J* = 5.8, 2.0 Hz, C-2H), 3.92 (1H, dd, *J* = 9.7, 3.5 Hz, C-1H_AH_B), 3.87–3.78 (3H, m, C-1H_AH_B, C-14H_2), 3.05–2.97 (4H, m, NCH_2CH_2N), 2.83 (3H, s, NCH_3), 2.80 (3H, s, NCH_3), 2.74 (6H, s, 2 × NCH_3), 2.56 (2H, t, *J* = 8.0 Hz, C-9H_2), 2.33–2.23 (2H,

m, C-6H_AH$_B$, C-8H_AH$_B$), 2.06–1.98 (1H, m, C-12H_AH$_B$), 1.96 (1H, dd, J = 14.9, 4.3 Hz, C-6H$_A$$H_B$), 1.93–1.81 (1H, m, C-8H$_A$$H_B$), 1.81–1.74 (3H, m, C-12H$_A$$H_B$, C-13H$_2$), 0.93 (9H, t, J = 7.9 Hz, Si(CH$_2$CH_3)$_3$), 0.62 (6H, q, J = 7.7 Hz, 6H, Si(CH_2CH$_3$)$_3$) (**minor**); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 212.4 (C-10), 138.6 (C-22), 138.3 (C-18), 128.5 (Ar), 128.4 (Ar), 128.0 (Ar), 127.7 (2C, 2Ar), 127.6 (Ar), 88.6 (C-15), 88.4 (C-7), 88.1 (C-4), 84.3 (C-2), 84.1 (C-3), 83.3 (C-11), 72.0 (C-17), 71.6 (C-14), 71.2 (C-16), 69.6 (C-5), 69.3 (C-1), 64.4 (NCH$_2$CH$_2$N), 64.2 (NCH$_2$$CH_2$N), 52.2 (NCH$_3$), 51.6 (NCH$_3$), 51.5 (NCH$_3$), 50.9 (NCH$_3$), 38.4 (C-6), 34.1 (C-9), 29.2 (2C, C-8, C-12), 25.7 (C-13), 7.3 (3C, Si(CH$_2$$CH_3$)$_3$), 5.4 (3C, Si($CH_2CH_3$)$_3$) (**major**); 212.7 (C-10), 138.6 (C-22), 138.4 (C-18), 128.5 (Ar), 128.4 (Ar), 127.8 (2C, 2Ar), 127.7 (Ar), 127.6 (Ar), 88.0 (C-7), 87.2 (C-15), 87.1 (C-2), 84.8 (C-4), 83.8 (C-3), 83.1 (C-11), 72.2 (C-17), 71.4 (C-16), 71.3 (C-1), 69.7 (C-5), 69.2 (C-14), 64.5 (NCH$_2$CH$_2$N), 64.2 (NCH$_2$$CH_2$N), 52.2 (NCH$_3$), 51.8 (NCH$_3$), 51.3 (NCH$_3$), 51.1 (NCH$_3$), 39.1 (C-6), 33.6 (C-9), 31.7 (C-8), 29.1 (C-12), 25.6 (C-13), 7.2 (3C, Si(CH$_2$$CH_3$)$_3$), 5.3 (3C, Si($CH_2CH_3$)$_3$) (**minor**); a mass spectrum could not be obtained for these compounds.

5.3 *Experimental procedures for E ring modifications*

(*R*)-3-((2*R*,5*R*)-5-(Hydroxymethyl)-2-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide (425)*



420 **425**

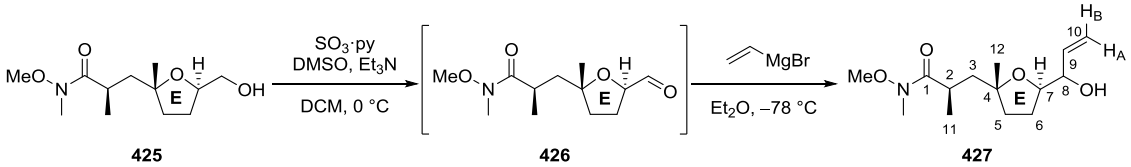
To a stirred solution of **420** (503 mg, 1.40 mmol) in THF (6.75 mL) was added TBAF (1 M in THF, 70 μL, 69 μmol) at 0 °C. The reaction was stirred for 2 h 30 min before the reaction was quenched with sat. aq. NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 98:2 DCM:MeOH) to afford the title compound **425** (331 mg, 96%) as a colourless oil.

R_f: 0.56 (90:10 DCM:MeOH); $[\alpha]_D^{25}$ –33.2 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3438, 2967, 2935, 2873, 16556, 1462, 1387, 1180, 1150, 1104, 1041, 996, 883, 747; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 4.09–3.99 (1H, m, C-7H), 3.71 (3H, s, OCH_3), 3.64 (1H, ddd, *J* = 15.2, 7.4, 4.1 Hz, C-8H_AH$_B$), 3.44 (1H, dt, *J* = 11.0, 5.2 Hz, C-8H$_A$$H_B$), 3.17 (3H, s, NCH_3), 3.14 (1H, s, C-2H), 2.15 (1H, dd, *J* = 14.1, 9.1 Hz, C-3H_AH$_B$), 2.09–2.01 (1H, m, OH), 1.96–1.84 (1H, m, C-6H_AH$_B$), 1.84–1.70 (2H, m, C-5H_AH$_B$, C-6H$_A$$H_B$), 1.70–1.58 (1H, m, C-5H$_A$$H_B$), 1.51 (1H, dd, *J* = 14.2, 3.5 Hz, C-3H_AH$_B$), 1.16 (3H, s, C-10H_3), 1.15 (3H, d, *J* = 7.0 Hz, C-9H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 179.1 (C-1), 83.2 (C-4), 79.2 (C-7), 65.4 (C-8), 61.6 (OCH_3), 44.2 (C-3), 37.9 (C-5), 32.7 (NCH_3), 31.1 (C-2),

* Compound **425** was prepared according to the procedure detailed by Liu.[68]

27.4 (C-6), 26.9 (C-10), 19.9 (C-9); **HRMS:** (ESI+, *m/z*) $C_{12}H_{23}O_4NNa$ (MNa^+) Calculated: 268.15193, Found: 268.15235 (Δ +1.57 ppm).

(2*R*)-3-((2*R*,5*R*)-5-(1-Hydroxyallyl)-2-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide (427)



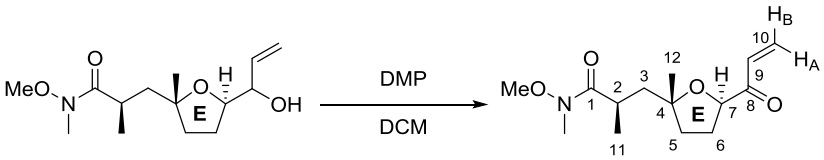
To a solution of **425** (100 mg, 0.41 mmol) and Et_3N (0.55 mL, 3.18 mmol) in DCM (2 mL) at 0 °C was added SO_3·py (253 mg, 1.59 mmol) in DMSO (1.69 mL, 23.9 mmol). The reaction was warmed to rt and stirred for 2 h 20 min before it was diluted with a 1:1 mixture of hexane:EtOAc (15 mL). The solution was washed with 1 M aq. HCl (2 × 5 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The aq. layer was saturated with NaCl, extracted with EtOAc (5 × 10 mL) and DCM (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **426** was obtained as a colourless oil and was carried into the next step without further purification.

Crude **426** (assumed quant., 0.41 mmol) was transferred to a flask in anhydrous Et_2O (4.0 mL) and cooled to –78 °C. Vinyl magnesium bromide (1 M in THF, 0.45 mL, 0.45 mmol) was added at –78 °C and was stirred for 1 h. TLC analysis still indicated incomplete reaction so additional vinyl magnesium bromide (1 M in THF, 0.45 mL, 0.45 mmol) was added and stirred for a further 40 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2,

1:1 pentane:Et_2O) to afford the title compound **427** (76 mg, 69% over two steps) as a colourless oil. The diastereomeric ratio could not be determined at C-8.

R_f: 0.42 (90:10 DCM:MeOH); $[\alpha]_D^{25}$ –9.8 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3441, 2969, 2937, 1659, 1462, 1387, 1316, 1180, 1102, 1048, 996, 924, 746; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 5.83–5.69 (1H, m, C-9H), 5.31 (1H, dt, *J* = 17.3, 1.7 Hz, C-10H_AH_B), 5.16 (1H, dt, *J* = 10.6, 1.6 Hz, C-10H_AH_B), 4.23 (1H, dtd, *J* = 5.7, 2.9, 1.6 Hz, C-8H), 3.99–3.89 (1H, m, C-7H), 3.71 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 3.13 (1H, s, C-2H), 2.30 (d, *J* = 2.8 Hz, OH), 2.19– 2.13 (1H, dd, *J* = 14.3, 9.0 Hz, C-3H_AH_B), 1.94–1.80 (1H, m, C-6H_AH_B), 1.80–1.66 (2H, m, C-5H_AH_B, C-6H_AH_B), 1.66–1.56 (1H, m, C-5H_AH_B), 1.50 (1H, dd, *J* = 14.2, 3.6 Hz, C-3H_AH_B), 1.16 (3H, s, C-12H_3), 1.14 (3H, d, *J* = 7.0 Hz, C-11H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 178.8 (C-1), 136.4 (C-9), 116.3 (C-10), 83.2 (C-4), 81.5 (C-7), 72.8 (C-8), 61.6 (OCH_3), 44.1 (C-3), 37.8 (C-5), 32.7 (NCH_3), 31.1 (C-2), 26.4 (C-12), 24.9 (C-6), 19.9 (C-11); **HRMS:** (ESI+, *m/z*) $C_{14}H_{26}O_4N$ (MH^+) Calculated: 272.18563, Found: 272.18497 (Δ –2.42 ppm).

(*R*)-3-((2*R*,5*R*)-5-Acryloyl-2-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide (424)



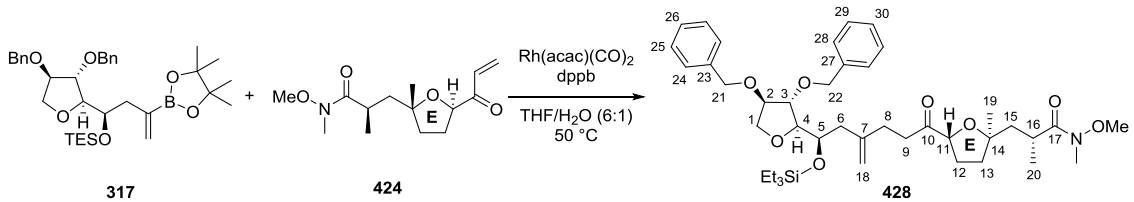
427 424

To a solution of **427** (76 mg, 0.28 mmol) in DCM (from Winchester, 3.2 mL) was added DMP (238 mg, 0.56 mmol) and the reaction was stirred at rt for 16 h 30 min. The reaction was quenched with sat. aq. $NaHCO_3$ (6 mL) and the layers were separated. The aq. layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude

product was purified by column chromatography (SiO_2, 50:50 pentane:Et_2O) to afford the title compound **424** (45 mg, 53%) as a colourless oil.

R_f: 0.53 (90:10 DCM:MeOH); $[\alpha]_D^{25}$ +23.7 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2970, 2936, 2360, 1698, 1662, 1613, 1462, 1404, 1387, 1284, 1179, 1069, 996, 934, 886, 748, 671; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 6.75 (1H, dd, *J* = 17.5, 10.6 Hz, C-9H), 6.37 (1H, dd, *J* = 17.5, 1.7 Hz, C-10H_AH_B), 5.76 (1H, dd, *J* = 10.6, 1.8 Hz, C-10H_AH_B), 4.52 (1H, t, *J* = 7.7 Hz, C-7H), 3.73 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 3.16 (1H, s, C-2H), 2.30–2.14 (2H, m, C-3H_AH_B, C-6H_AH_B), 2.10–1.97 (1H, m, C-6H_AH_B), 1.80 (1H, dt, *J* = 12.3, 7.9 Hz, C-5H_AH_B), 1.71–1.61 (1H, m, C-5H_AH_B), 1.55 (1H, dd, *J* = 14.2, 3.7 Hz, C-3H_AH_B), 1.21 (3H, s, C-12H_3), 1.17 (3H, d, *J* = 7.0 Hz, C-11H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 200.6 (C-8), 178.6 (C-1), 131.7 (C-9), 129.3 (C-10), 84.9 (C-4), 82.4 (C-7), 61.5 (OCH_3), 44.1 (C-3), 37.4 (C-5), 31.2 (NCH_3), 29.1 (C-2), 25.8 (C-12), 19.7 (C-11); **HRMS:** (ESI+, *m/z*) $C_{14}H_{23}O_4NNa$ (MNa^+) Calculated: 292.15193, Found: 292.15160 (Δ –1.13 ppm).

(*R*)-3-((2*R*,5*R*)-5-((*R*)-6-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-4-methylene-6-((triethylsilyl)oxy)hexanoyl)-2-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide (428)



317 424 428

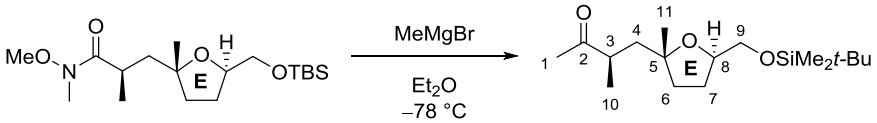
To compound **317** (50 mg, 84 μmol), $Rh(acac)(CO)_2$ (2.2 mg, 8.5 μmol) and dppb (3.6 mg, 8.5 μmol) in a vial was added enone **424** (27.3 mg, 101 μmol) in THF (0.30 mL) and H_2O (0.05 mL) and the vial was flushed with argon. The reaction heated to 50 °C for 42 h. TLC analysis still indicated incomplete reaction so additional $Rh(acac)(CO)_2$ (2.18 mg, 8.5 μmol) and dppb (3.60 mg, 8.5 μmol) were added and stirred for a further

6 h. TLC analysis still indicated incomplete reaction so additional $Rh(acac)(CO)_2$ (21.8 mg, 85 μmol) and dppb (36 mg, 85 μmol) in THF (0.1 mL) were added and stirred for a further 21 h. The reaction was cooled to rt and EtOAc (3 mL) and H_2O (3 mL) were added and the layers were separated. The aq. layer was saturated with NaCl and extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography twice (SiO_2, 100:0 → 90:10 → 80:20 → 50:50 → 0:100 pentane:Et_2O; then the flush was purified again: SiO_2, 80:20 → 70:30 pentane:EtOAc) to afford the title compound **428** (3.7 mg, 6%) as a colourless oil.

R_f: 0.47 (60:40 pentane:EtOAc); $[\alpha]_D^{25}$ +1.3 (*c* = 0.10, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2928, 2875, 2364, 1770, 1716, 1666, 1455, 1386, 1263, 1095, 1003, 797, 740, 699; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.38–7.23 (10H, m, ArH), 4.82 (1H, s, C-18H_AH_B), 4.76 (1H, d, *J* = 1.8 Hz, C-18H_AH_B), 4.58 (1H, d, *J* = 11.6 Hz, C-22H_AH_B), 4.55 (1H, d, *J* = 11.9 Hz, C-22H_AH_B), 4.53 (1H, d, *J* = 12.1 Hz, C-21H_AH_B), 4.50 (1H, d, *J* = 12.0 Hz, C-21H_AH_B), 4.31 (1H, t, *J* = 7.8 Hz, C-11H), 4.20–4.16 (1H, m, C-3H), 4.07 (1H, dt, *J* = 4.6, 2.2 Hz, C-2H), 4.01 (1H, q, *J* = 5.8 Hz, C-5H), 3.95 (1H, dd, *J* = 10.1, 2.3 Hz, C-1H_AH_B), 3.88 (1H, dd, *J* = 9.9, 4.7 Hz, C-1H_AH_B), 3.75 (1H, t, *J* = 4.6 Hz, C-4H), 3.72 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 3.16 (1H, s, C-16H), 2.68 (2H, ddd, *J* = 8.6, 6.7, 2.2 Hz, C-9H_2), 2.33–2.24 (3H, m, C-6H_AH_B, C-8H_AH_B, C-15H_AH_B), 2.23–2.12 (2H, m, C-6H_AH_B, C-12H_AH_B), 1.97–1.87 (1H, m, C-12H_AH_B), 1.76 (1H, dt, *J* = 12.4, 8.0 Hz, C-13H_AH_B), 1.64 (1H, ddd, *J* = 12.6, 8.1, 5.1 Hz, C-13H_AH_B), 1.52 (1H, dd, *J* = 14.3, 3.8 Hz, C-15H_AH_B), 1.28–1.23 (1H, m, C-8H_AH_B), 1.20 (3H, s, C-19H_3), 1.16 (3H, d, *J* = 7.0 Hz, C-20H_3), 0.92 (9H, t, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$), 0.58 (6H, q, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 212.0 (C-10), 178.8 (C-17), 145.1 (C-7), 138.2 (C-27),

138.1 (C-23), 128.6 (Ar), 128.5 (Ar), 127.9 (2C, 2Ar), 127.8 (2C, 2Ar), 112.4 (C-18), 86.1 (C-4), 84.8 (C-14), 83.9 (C-3), 83.8 (C-2), 83.5 (C-11), 71.9 (C-22), 71.5 (C-1), 71.4 (C-21), 70.8 (C-5), 61.7 (OCH_3), 44.2 (C-15), 41.1 (C-6), 37.6 (C-13), 36.5 (C-9), 32.7 (NCH_3), 31.1 (C-16), 29.8 (C-8), 29.2 (C-12), 26.0 (C-19), 19.9 (C-20), 7.1 (3C, $Si(CH_2\mathit{C}H_3)_3$), 5.3 (3C, $Si(\mathit{C}H_2CH_3)_3$); **HRMS:** (ESI+, *m/z*) $C_{42}H_{63}O_8N^{28}SiNa$ (MNa^+) Calculated: 760.42152, Found: 760.42122 (Δ –0.39 ppm).

(*R*)-4-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3-methylbutan-2-one (429)



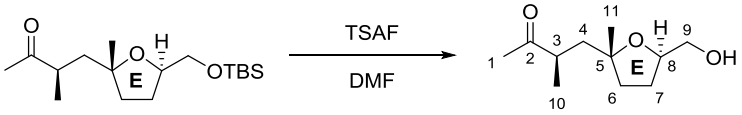
420 **429**

To a stirred solution of **420** (100 mg, 0.28 mmol) in Et_2O (2 mL) was added methyl magnesium bromide (3 M in Et_2O, 0.56 mL, 1.67 mmol) at –78 °C. The reaction was warmed to rt and stirred for 12 h 45 min. TLC analysis indicated incomplete reaction so additional methyl magnesium bromide (3 M in Et_2O, 0.1 mL, 0.30 mmol) was added and stirred for a further 4 h. The reaction was quenched with sat. aq. NH_4Cl (15 mL) and the mixture was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 85:15 pentane:Et_2O) to afford the title compound **429** (63.3 mg, 72%) as a colourless oil.

R_f: 0.58 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +21.9 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2959, 2930, 2858, 1717, 1461, 1360, 1255, 1106, 1018, 982, 938, 837, 777, 665, 609; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 3.85 (1H, dddd, *J* = 9.7, 5.2, 4.4, 1.9 Hz, C-8H), 3.57 (1H, dd, *J* = 10.5, 4.4 Hz, C-9H_AH_B), 3.51 (1H, dd, *J* = 10.5, 5.3 Hz, C-9H_AH_B), 2.72–2.61 (1H, m, C-3H), 2.12 (3H, s, C-1H_3), 2.08 (1H, dd, *J* = 14.4, 9.0 Hz, C-4H_AH_B), 1.97–1.86

(1H, m, C-7H_AH$_B$), 1.84–1.72 (2H, m, C-6H_AH$_B$, C-7H$_A$$H_B$), 1.69–1.59 (1H, m, C-6H$_A$$H_B$), 1.48 (1H, dd, J = 14.4, 3.9 Hz, C-4H$_A$$H_B$), 1.12 (3H, s, C-11H$_3$), 1.10 (3H, d, J = 7.1 Hz, C-10H$_3$), 0.87 (9H, s, Si(CH$_3$)$_2$C(CH_3)$_3$), 0.05 (6H, d, J = 1.2 Hz, (Si(CH_3)$_2$C(CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, CDCl$_3$) 212.8 (C-2), 82.7 (C-5), 80.0 (C-8), 66.2 (C-9), 44.1 (C-4), 43.8 (C-3), 36.8 (C-6), 28.2 (C-7), 27.9 (C-11), 27.1 (C-1), 26.1 (3C, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 18.7 (C-10), 18.5 (Si(CH$_3$)$_2$$C$(CH$_3$)$_3$), –5.1 (Si($CH_3$)(CH$_3$)C(CH$_3$)$_3$), –5 (Si(CH$_3$)($CH_3$)C(CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) C$_{17}$H$_{34}$O$_3$^{28}SiNa (MNa$^+$) Calculated: 337.21694, Found: 337.21703 (Δ +0.27 ppm).

(*R*)-4-((2*R*,5*R*)-5-(Hydroxymethyl)-2-methyltetrahydrofuran-2-yl)-3-methylbutan-2-one (431)



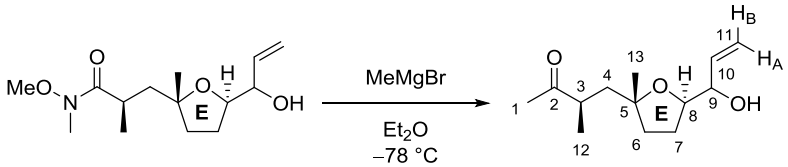
429 **431**

To **429** (26 mg, 82.7 μmol) in a flask was added TSAF (68 mg, 24.8 μmol) in DMF (1 mL) at rt. The reaction was stirred for 24 h before the addition of EtOAc (2 mL) and sat. aq. LiCl (2 mL). The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. LiCl (10 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO$_2$, 75:25 → 50:50 pentane:EtOAc) to afford the title compound **431** (12.7 mg, 84%) as a colourless oil.

R$_f$: 0.17 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +9.4 (*c* = 1.00, CHCl$_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3434, 29667, 2928, 2874, 1711, 1458, 1355, 1237, 1162, 1105, 1039, 957, 884, 820, 761; **^{1}H NMR:** δ_H (400 MHz, CDCl$_3$) 3.93 (1H, ddt, J = 10.7, 8.8, 4.1 Hz, C-8H), 3.64 (1H, dd, J = 11.5, 3.2 Hz, C-9H_AH$_B$), 3.43 (1H, ddd, J = 11.5, 5.3, 0.9 Hz, C-9H$_A$$H_B$), 2.74–2.63 (1H, m, C-3H), 2.18–2.09 (4H, m, C-1H$_3$, C-4H_AH$_B$), 1.92–1.75 (3H, m, C-

6H_AH$_B$, C-7H$_2$), 1.73–1.62 (1H, m, C-6H$_A$$H_B$), 1.51 (1H, dd, J = 14.5, 3.6 Hz, C-4H$_A$$H_B$), 1.16 (3H, s, C-11H$_3$), 1.11 (3H, d, J = 7.1 Hz, C-10H$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 212.8 (C-2), 82.9 (C-5), 79.8 (C-8), 65.1 (C-9), 44.1 (C-4), 43.7 (C-3), 37.1 (C-6), 28.1 (C-11), 27.3 (C-1), 27.2 (C-7), 18.6 (C-10); **HRMS:** (ESI+, *m/z*) $C_{11}H_{21}O_3$ (MH^+) Calculated: 201.14852, Found: 201.14862 (Δ +0.50 ppm).

(3*R*)-4-((2*R*,5*R*)-5-(1-Hydroxyallyl)-2-methyltetrahydrofuran-2-yl)-3-methylbutan-2-one (434)



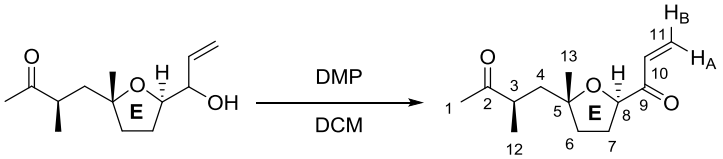
427 434

To a stirred solution of **427** (24.4 mg, 67.9 μmol) in Et_2O (0.5 mL) was added methyl magnesium bromide (3 M in Et_2O, 0.14 mL, 0.41 mmol) at –78 °C. The reaction was warmed to rt and stirred for 45 min. TLC analysis indicated incomplete reaction so additional methyl magnesium bromide (3 M in Et_2O, 0.14 mL, 0.41 mmol) was added and stirred for a further 1 h 15 min. The reaction was quenched with sat. aq. NH_4Cl (1 mL) and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 75:25 pentane:Et_2O) to afford the title compound **434** (15.3 mg, 99%) as a colourless oil. The diastereomeric ratio could not be determined at C-9.

R_f: 0.44 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +11.6 (c = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3452, 2970, 2931, 2876, 1705, 1458, 1428, 1375, 1355, 1312, 1239, 1160, 1104, 1047, 995, 924, 849, 742; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 5.81–5.71 (1H, m, C-10H), 5.33 (1H, dt, J = 17.3, 1.6 Hz, C-11H_AH$_B$), 5.18 (1H, dt, J = 10.6, 1.6 Hz, C-11H$_A$$H_B$), 4.21

(1H, ddd, J = 5.7, 3.6, 1.7 Hz, C-9H), 3.84 (1H, ddd, J = 9.2, 5.8, 3.7 Hz, C-8H), 2.73–2.62 (1H, m, C-3H), 2.18–2.09 (4H, m, C-1H$_3$, C-4H_AH$_B$), 1.96–1.69 (4H, m, C-6H_AH$_B$, C-7H$_2$, OH), 1.69–1.60 (1H, m, C-6H$_A$$H_B$), 1.52 (1H, dd, J = 14.5, 3.8 Hz, C-4H$_A$$H_B$), 1.17 (3H, s, C-13H$_3$), 1.12 (3H, d, J = 7.1 Hz, C-12H$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 212.6 (C-2), 136.2 (C-10), 116.4 (C-11), 83.0 (C-5), 82.2 (C-8), 72.7 (C-9), 44.1 (C-4), 43.8 (C-3), 36.9 (C-6), 27.7 (C-13), 27.0 (C-1), 24.9 (C-7), 18.6 (C-12); **HRMS:** (ESI+, *m/z*) $C_{13}H_{22}O_3Na$ (MNa^+) Calculated: 249.14612, Found: 249.14588 (Δ –0.96 ppm).

(*R*)-4-((2*R*,5*R*)-5-Acryloyl-2-methyltetrahydrofuran-2-yl)-3-methylbutan-2-one (435)



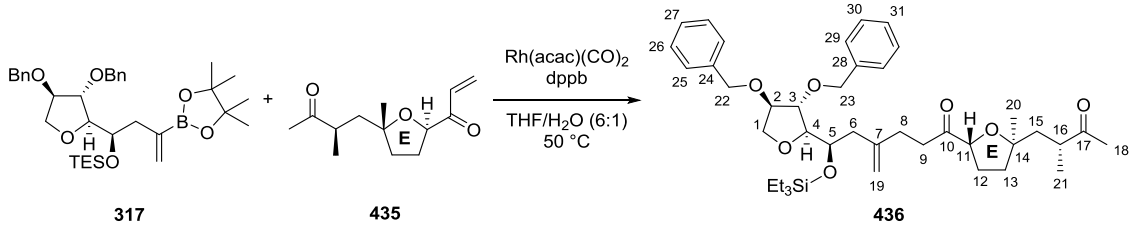
434 **435**

To a solution of **434** (23.1 mg, 0.102 mmol) in DCM (from Winchester, 1.2 mL) was added DMP (86.6 mg, 0.204 mmol) and the reaction was stirred at rt for 15 h 40 min. The reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and the layers were separated. The aq. layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 80:20 pentane:EtOAc) to afford the title compound **435** (22.4 mg, 98%) as a colourless oil.

R_f: 0.46 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +60.4 (c = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2970, 2932, 2362, 1699, 1612, 1458, 1403, 1355, 1164, 1071, 991, 668; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 6.66 (1H, dd, J = 17.5, 10.6 Hz, C-10H), 6.35 (1H, dd, J = 17.5, 1.6 Hz, C-11H_AH$_B$), 5.78 (1H, dd, J = 10.6, 1.6 Hz, C-11H$_A$$H_B$), 4.42 (1H, t, J = 7.8 Hz, C-8H), 2.69 (1H, dtt, J = 14.1, 7.1, 3.6 Hz, C-3H), 2.30–2.11 (5H, m, C-1H$_3$, C-4H_AH$_B$,

C-7H_AH$_B$), 2.04 (dq, J = 12.6, 8.1 Hz, C-7H$_A$$H_B$), 1.87 (1H, dt, J = 12.3, 8.3 Hz, C-6H_AH$_B$), 1.71–1.63 (1H, m, C-6H$_A$$H_B$), 1.54 (1H, dd, J = 14.5, 3.8 Hz, C-4H$_A$$H_B$), 1.20 (3H, s, C-13H$_3$), 1.13 (3H, d, J = 7.1 Hz, C-12H$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 212.6 (C-2), 200.3 (C-9), 132.0 (C-10), 129.6 (C-11), 84.8 (C-5), 82.7 (C-8), 44.0 (C-4), 43.9 (C-3), 36.4 (C-6), 29.1 (C-7), 27.3 (C-13), 26.9 (C-1), 18.6 (C-12); **HRMS:** (ESI+, *m/z*) $C_{13}H_{20}O_3Na$ (MNa^+) Calculated: 247.13047, Found: 247.13051 (Δ +0.16 ppm).

(*R*)-6-((2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-1-((2*R*,5*R*)-5-methyl-5-((*R*)-2-methyl-3-oxobutyl)tetrahydrofuran-2-yl)-4-methylene-6-((triethylsilyl)oxy)hexan-1-one (436)



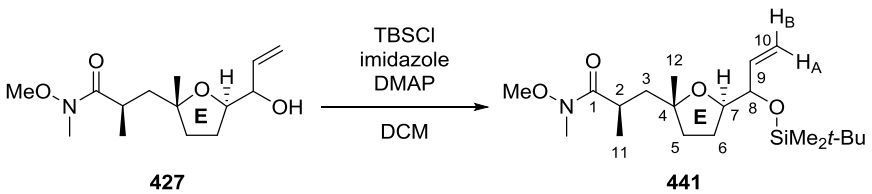
317 435 436

To compound **317** (37.6 mg, 63.2 μmol), Rh(acac)(CO)$_2$ (1.6 mg, 6.3 μmol) and dppb (2.7 mg, 6.3 μmol) in a vial was added enone **435** (17 mg, 76 μmol) in THF (0.23 mL) and H_2O (37 μL) and the vial was flushed with argon. The reaction heated to 50 °C for 24 h. The reaction was cooled to rt and Et_2O (1 mL), EtOAc (1 mL) and H_2O (1 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 75:25 → 0:100 pentane:EtOAc) to afford the title compound **436** (21.1 mg, 48%) as a colourless oil.

R_f: 0.24 (50:50 pentane:Et_2O); $[\alpha]_D^{25}$ +18.1 (c = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3031, 2918, 2875, 1715, 1646, 1497, 1455, 1354, 1238, 1097, 1008, 897, 738, 698; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.39–7.20 (10H, m, ArH), 4.82 (1H, s, C-19H_AH$_B$), 4.77

(1H, q, J = 1.6 Hz, C-19H$_A$*H$_B$*), 4.58 (1H, d, J = 11.6 Hz, C-23*H$_A$*H$_B$), 4.55 (1H, d, J = 11.7 Hz, C-23H$_A$*H$_B$*), 4.53 (1H, d, J = 12.3 Hz, C-22*H$_A$*H$_B$), 4.50 (1H, d, J = 12.0 Hz, C-22H$_A$*H$_B$*), 4.23–4.16 (2H, m, C-3H, C-11H), 4.08 (1H, dt, J = 4.6, 2.2 Hz, C-2H), 4.03–3.99 (1H, m, C-5H), 3.95 (1H, dd, J = 9.9, 2.4 Hz, C-1*H$_A$*H$_B$), 3.89 (1H, dd, J = 9.9, 4.8 Hz, C-1H$_A$*H$_B$*), 3.76 (1H, t, J = 4.6 Hz, C-4H), 2.73–2.60 (3H, m, C-9H$_2$, C-16H), 2.35–2.23 (3H, m, C-6*H$_A$*H$_B$, C-8H$_2$), 2.23–2.21 (3H, m, C-6*H$_A$*H$_B$, C-12*H$_A$*H$_B$, C-15*H$_A$*H$_B$), 2.14 (3H, s, C-18H$_3$), 1.98–1.89 (1H, m, C-12H$_A$*H$_B$*), 1.83 (1H, ddd, J = 12.3, 8.9, 7.8 Hz, C-13*H$_A$*H$_B$), 1.65 (1H, ddd, J = 12.4, 8.0, 4.5 Hz, C-13H$_A$*H$_B$*), 1.52 (1H, dd, J = 14.5, 4.0 Hz, C-15H$_A$*H$_B$*), 1.19 (3H, s, C-20H$_3$), 1.13 (3H, d, J = 7.1 Hz, C-21H$_3$), 0.92 (9H, t, J = 8.0 Hz, Si(CH$_2$C*H$_3$)$_3$), 0.58 (6H, q, J = 8.0 Hz, Si(C*H$_2$*CH$_3$)$_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 212.4 (C-17), 211.4 (C-10), 145.0 (C-7), 138.2 (C-28), 138.1 (C-24), 128.5 (4C, 3Ar), 127.9 (2C, Ar), 127.8 (4C, 2Ar), 112.5 (C-19), 86.1 (C-4), 84.6 (C-14), 83.9 (C-3), 83.8 (2C, C-2, C-11), 71.9 (C-23), 71.4 (2C, C-1, C-22), 70.8 (C-5), 43.9 (2C, C-15, C-16), 41.1 (C-6), 36.7 (C-13), 36.6 (C-9), 29.8 (C-8), 29.0 (C-12), 27.3 (C-20), 26.9 (C-18), 18.6 (C-21), 7.1 (3C, Si(CH$_2$*C*H$_3$)$_3$), 5.3 (3C, Si(*C*H$_2$CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{41}H_{60}O_7N^{28}SiNa$ (MNa^+) Calculated: 715.40005, Found: 715.39944 (Δ –0.85 ppm).

(2*R*)-3-((2*R*,5*R*)-5-(1-((*tert*-butyldimethylsilyl)oxy)allyl)-2-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide (441)



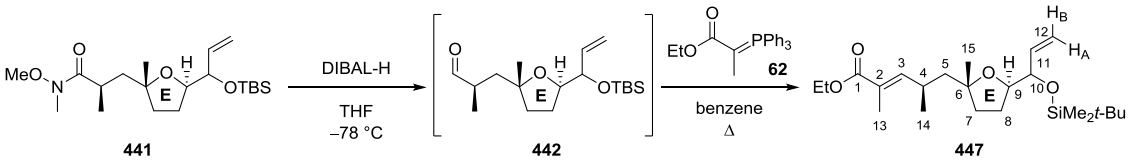
427 **441**

To a stirred solution of **427** (307 mg, 1.13 mmol) in DCM (9.3 mL) was added imidazole (462 mg, 6.78 mmol), DMAP (13.8 mg, 0.11 mmol) and TBSCl (511 mg, 3.39 mmol) at rt. The reaction was stirred for 7 h before the reaction was quenched with H_2O (20 mL).

The mixture was diluted with EtOAc (30 mL), separated and the aq. layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 85:15 pentane:EtOAc) to afford the title compound **441** (384 mg, 88%) as a colourless oil. The diastereomeric ratio could not be determined at C-8.

R_f: 0.61 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ –22.2 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2958, 2931, 2856, 2363, 2335, 1670, 1463, 1409, 1387, 1322, 1253, 1219, 1161, 1105, 1064, 1027, 1002, 938, 922, 837, 775, 679, 669; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddd, *J* = 16.4, 10.4, 5.5 Hz, C-9H), 5.22 (1H, d, *J* = 17.2 Hz, C-10H_AH_B), 5.08 (1H, d, *J* = 10.5 Hz, C-10H_AH_B), 4.11 (1H, t, *J* = 4.8 Hz, C-8H), 3.79 (1H, td, *J* = 7.2, 4.4 Hz, C-7H), 3.72 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 3.12 (1H, s, C-2H), 2.07 (1H, dd, *J* = 14.0, 8.6 Hz, C-3H_AH_B), 1.94–1.73 (2H, m, C-6H_2), 1.70–1.55 (2H, m, C-5H_2), 1.49 (1H, dd, *J* = 14.1, 3.8 Hz, C-3H_AH_B), 1.14 (3H, s, C-12H_3), 1.14 (3H, d, *J* = 7.4 Hz, C-11H_3), 0.89 (9H, s, $Si(CH_3)_2C(CH_3)_3$), 0.05 (3H, s, $Si(CH_3)(CH_3)C(CH_3)_3$), 0.02 (3H, s, $Si(CH_3)(CH_3)C(CH_3)_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 171.2 (C-1), 139.3 (C-9), 114.9 (C-10), 82.9 (C-4), 82.1 (C-7), 75.2 (C-8), 61.5 (OCH_3), 44.0 (C-3), 38.0 (C-5), 32.6 (NCH_3), 31.4 (C-2), 26.2 (C-12), 26.2 (C-6), 26.0 (3C, $Si(CH_3)_2C(CH_3)_3$), 19.8 (C-11), 18.3 ($Si(CH_3)_2C(CH_3)_3$), –4.3 ($Si(CH_3)(CH_3)C(CH_3)_3$), –4.5 ($Si(CH_3)(CH_3)C(CH_3)_3$); **HRMS:** (ESI+, *m/z*) $C_{20}H_{39}O_4N^{28}SiNa$ (MNa^+) Calculated: 408.25406, Found: 408.25379 (Δ –0.66 ppm).

Ethyl (4*R*,*E*)-5-((2*R*,5*R*)-5-(1-((*tert*-butyldimethylsilyl)oxy)allyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (447)



To a solution of **441** (952 mg, 2.47 mmol) in THF (45 mL) at –78 °C was added DIBAL-H (1 M in THF, 12.3 mL, 12.3 mmol) dropwise. The reaction was stirred for 2 h 30 min. TLC analysis indicated incomplete reaction so additional DIBAL-H (1 M in THF, 5.0 mL, 5.0 mmol) was added and stirred for a further 1 h. TLC analysis still indicated incomplete reaction so additional DIBAL-H (1 M in THF, 5 mL, 5 mmol) was added and stirred for a further 1 h. The reaction was quenched with EtOAc (90 mL) and warmed to rt before sat. aq. Rochelle's salt (potassium sodium tartrate, 100 mL) was added and the layers were separated. The aq. layer was extracted with EtOAc (5 × 100 mL). The combined organic layers were washed with H_2O (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product **442** was obtained as a colourless oil and was carried into the next step without further purification.

Crude **442** (assumed quant., 2.47 mmol) was dried azeotropically in benzene (3 × 5 mL). To a 2-necked flask equipped with a condenser, was dissolved (carboxyethylidene)triphenylphosphorane **62** (3.13 g, 8.64 mmol) in benzene (56 mL). Crude **442** was added as a solution in THF (12.2 mL) and the reaction was heated to reflux and stirred for 15 h. The reaction was cooled to rt before it was quenched with sat. aq. NH_4Cl (60 mL). The mixture was diluted with EtOAc (75 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 97:3 → 95:5 pentane:Et_2O) to afford the title compound **447** (877 mg, 87% over two steps) as a colourless oil. The diastereomeric ratio could not be determined at C-10. The diastereoisomers are identified by prime notation.

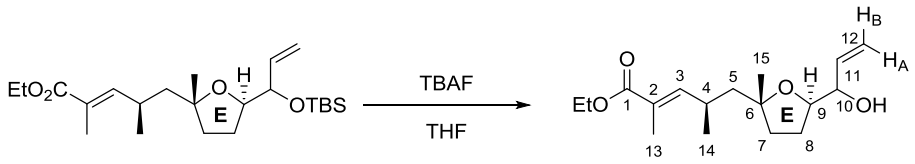
Aldehyde **442** is identified by the presence of ^{1}H NMR (200 MHz, $CDCl_3$) 9.39 ppm (*J* = 4.0 Hz) for the aldehyde proton. Epimerisation at the α-keto stereocentre is diagnosed by the presence of ^{1}H NMR (200 MHz, $CDCl_3$) 9.57 (*J* = 3.2 Hz, epimer of **442**) and 9.39 ppm (*J* = 4.0 Hz) for the aldehyde protons.

The (*E*)-geometry of the double bond was confirmed by nOes between C-13H_3 to C-4H and C-14H_3 in $CDCl_3$ (see **Appendix 6.2.5**).

R_f: 0.40 (85:15 pentane:Et_2O); $[\alpha]_D^{25}$ –10.8 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2958, 2930, 2858, 1711, 1648, 1462, 1388, 1368, 1251, 1151, 1118, 1098, 106, 1028, 939, 922, 837, 776, 751, 671; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 6.63 (1H, dd, *J* = 6.5, 1.5 Hz, C-3'H), 6.61 (dd, *J* = 6.5, 1.5 Hz, C-3H), 5.79 (1H, ddd, *J* = 17.3, 10.5, 5.7 Hz, C-11H), 5.79 (1H, ddd, *J* = 17.3, 10.5, 5.6 Hz, C-11'H), 5.22 (1H, dq, *J* = 17.2, 1.9 Hz, C-12H_AH$_B$, C-12'H_AH$_B$), 5.08 (1H, dt, *J* = 10.5, 1.6 Hz, C-12H$_A$$H_B$), 5.07 (dt, *J* = 10.5, 1.6 Hz, C-12'H$_A$$H_B$), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$, OCH_2CH$_3$'), 4.13–4.06 (1H, m, C-10H, C-10'H), 3.74 (1H, ddd, *J* = 10.8, 8.4, 4.4 Hz, C-9H, C-9'H), 2.74–2.61 (1H, m, C-4H, C-4'H), 1.94–1.85 (1H, m, C-8H_AH$_B$, C-8'H_AH$_B$), 1.85 (3H, d, *J* = 1.4 Hz, C-13H_3), 1.84 (3H, d, *J* = 1.4 Hz, C-13'H$_3$), 1.82–1.74 (1H, m, C-8H$_A$$H_B$, C-8'H$_A$$H_B$), 1.73–1.52 (4H, m, C-5$H_2$, C-5'H$_2$, C-7H$_2$, C-7'H$_2$), 1.29 (2H, t, *J* = 7.1 Hz, OCH$_2$CH_3, OCH$_2$CH_3'), 1.16 (3H, s, C-15H$_3$), 1.15 (3H, s, C-15'H$_3$), 1.01 (3H, d, *J* = 6.7 Hz, C-14H$_3$), 1.00 (3H, d, *J* = 6.8 Hz, C-14'H$_3$), 0.90 (9H, s, Si(CH$_3$)$_2$C(CH_3)$_3$), 0.89 (9H, s, Si(CH$_3$)$_2$C(CH_3)$_3$'), 0.06 (6H, s, Si(CH_3)(CH$_3$)C(CH$_3$)$_3$), 0.04 (6H, s, Si(CH_3)(CH$_3$)C(CH$_3$)$_3$'), 0.02 (3H, s, Si(CH$_3$)(CH_3)C(CH$_3$)$_3$), 0.01 (3H, s, Si(CH$_3$)(CH_3)C(CH$_3$)$_3$'); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 168.7 (C-1, C-1'), 149.5 (C-3'), 149.2 (C-3), 139.4 (C-11, C-11'), 125.0 (C-2), 124.7 (C-2'), 115.1 (C-12), 115.0 (C-12'), 83.2 (C-6), 83.0 (C-6'), 82.4 (C-9'), 82.2 (C-9), 75.4 (C-10), 75.2 (C-10'), 60.5 (O*C*H$_2$CH$_3$, O*C*H$_2$CH$_3$'), 48.0 (C-5, C-5'), 37.8 (C-7), 37.5

(C-7'), 30.3 (C-4), 30.1 (C-4'), 27.3 (C-15'), 26.9 (C-15), 26.5 (C-8), 26.4 (C-8'), 26.1 (3C, 3C', $Si(CH_3)_2C(\mathit{C}H_3)_3$, $Si(CH_3)_2C(\mathit{C}H_3)_3$'), 21.7 (C-14'), 21.6 (C-14), 18.4 ($Si(CH_3)_2\mathit{C}(CH_3)_3$, $Si(CH_3)_2\mathit{C}(CH_3)_3$'), 14.5 ($OCH_2\mathit{C}H_3$, $OCH_2\mathit{C}H_3$'), 12.5 (C-13, C-13'), –4.3 ($Si(\mathit{C}H_3)(CH_3)C(CH_3)_3$, $Si(\mathit{C}H_3)(CH_3)C(CH_3)_3$'), –4.4 ($Si(CH_3)(\mathit{C}H_3)C(CH_3)_3$), –4.5 ($Si(CH_3)(\mathit{C}H_3)C(CH_3)_3$'); **HRMS:** (ESI+, *m/z*) $C_{23}H_{42}O_4{}^{28}SiNa$ (MNa^+) Calculated: 433.27446, Found: 433.27433 (Δ –0.30 ppm).

Ethyl (4*R*,*E*)-5-((2*R*,5*R*)-5-(1-hydroxyallyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (440)



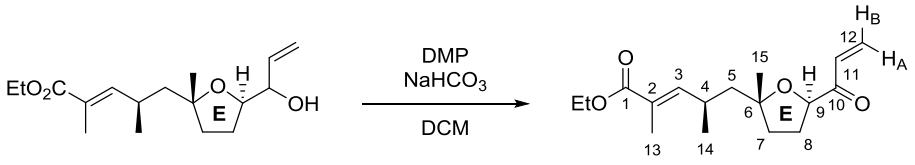
447 **440**

To a stirred solution of **447** (877 mg, 2.14 mmol) in THF (85 mL) was added TBAF (1 M in THF, 6.95 mL, 6.95 mmol) at rt. The reaction was stirred for 8 h at rt. TLC analysis indicated incomplete reaction so additional TBAF (1 M in THF, 6.95 mL, 6.95 mmol) was added and stirred for a further 18 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL). The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 85:15 pentane:EtOAc) to afford the title compound **440** (494 mg, 78%) as a colourless oil. The diastereomeric ratio could not be determined at C-10. The diastereoisomers are identified by prime notation.

R_f: 0.21 (85:15 pentane:EtOAc); $[\alpha]_D^{25}$ –12.0 (*c* = 0.50, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3466, 2963, 2927, 2871, 2362, 2340, 1709, 1647, 1456, 1372, 1273, 1245, 1098, 1046, 996, 924, 751, 668; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 6.64 (1H, dd, *J* = 10.0, 1.4 Hz, C-3H'), 6.64 (1H, dd, *J* = 10.1, 1.5 Hz, C-3H), 5.78 (1H, ddd, *J* = 16.8, 10.7, 5.8 Hz, C-11,

C-11'), 5.32 (1H, dq, J = 17.4, 1.8 Hz, C-12H_AH$_B$, C-12'H_AH$_B$), 5.19 (1H, dt, J = 10.7, 1.5 Hz, C-12H$_A$$H_B$, C-12'H$_A$$H_B$), 4.28–4.17 (1H, m, C-10H, C-10'H), 4.18 (2H, qd, J = 7.1, 1.5 Hz, OCH_2CH$_3$), 4.18 (2H, q, J = 7.1 Hz, OCH_2CH$_3$'), 3.93 (1H, ddd, J = 8.6, 5.7, 3.6 Hz, C-9'H), 3.88 (1H, ddd, J = 9.4, 5.7, 3.6 Hz, C-9H), 2.77–2.64 (1H, m, C-4H, C-4'H), 2.22 (1H, d, J = 3.0 Hz, OH'), 2.19 (1H, d, J = 2.8 Hz, OH), 1.94–1.84 (1H, m, C-8H_AH$_B$, C-8'H_AH$_B$), 1.86 (3H, d, J = 1.5 Hz, C-13H$_3$), 1.85 (3H, d, J = 1.4 Hz, C-13'H$_3$), 1.81–1.57 (5H, m, C-5H$_2$, C-5'H$_2$, C-7H$_2$, C-7'H$_2$, C-8H$_A$$H_B$, C-8'H$_A$$H_B$), 1.29 (3H, t, J = 7.1 Hz, OCH$_2$CH_3, OCH$_2$CH_3'), 1.19 (3H, s, C-15H$_3$, C-15'H$_3$), 1.03 (3H, d, J = 6.8 Hz, C-14H$_3$), 1.02 (3H, d, J = 6.9 Hz, C-14'H$_3$); **^{13}C NMR:** δ_C (126 MHz, CDCl$_3$) 168.7 (C-1'), 168.6 (C-1), 149.1 (C-3'), 148.8 (C-3), 136.4 (C-11, C-11'), 125.1 (C-2), 124.9 (C-2'), 116.5 (C-12, C-12'), 83.5 (C-6), 83.4 (C-6'), 81.6 (C-9'), 81.5 (C-9), 72.9 (C-10, C-10'), 60.6 (OCH$_2$CH$_3$, OCH$_2$CH$_3$'), 48.0 (C-5), 47.8 (C-5'), 37.8 (C-7), 37.7 (C-7'), 30.2 (C-4), 30.0 (C-4'), 27.1 (C-15'), 26.9 (C-15), 25.2 (C-8, C-8'), 21.7 (C-14'), 21.5 (C-14), 14.5 (OCH$_2$$CH_3$, OCH$_2$$CH_3$'), 12.5 (C-13, C-13'); **HRMS:** (ESI+, *m/z*) $C_{17}H_{28}O_4Na$ (MNa^+) Calculated: 319.18798, Found: 319.18760 (Δ –1.19 ppm).

Ethyl (*R*,*E*)-5-((2*R*,5*R*)-5-acryloyl-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (438)



440 **438**

To a solution of **440** (62.8 mg, 0.212 mmol) in DCM (from Winchester, 2.4 mL) was added NaHCO$_3$ (89 mg, 1.06 mmol) and DMP (180 mg, 0.424 mmol) and the reaction was stirred at rt for 3 h. The reaction was quenched with sat. aq. NaHCO$_3$ (10 mL) and the layers were separated. The aq. layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with sat. aq. Na$_2$S$_2$O$_3$ (2 × 10 mL), dried over

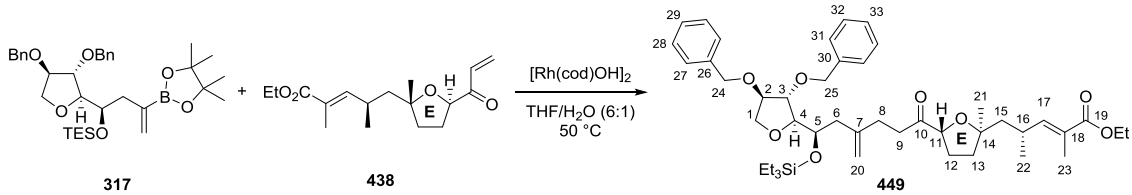
$MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 pentane:EtOAc) to afford the title compound **438** (56 mg, 90%) as a colourless oil.

R_f: 0.35 (85:15 pentane:EtOAc); $[\alpha]_D^{25}$ –5.6 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2970, 2930, 2872, 174, 108, 168, 1613, 1454, 1401, 1368, 1271, 1245, 1176, 1143, 1095, 1071, 1000, 937, 858, 752; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 6.74 (1H, dd, *J* = 17.5, 10.6 Hz, C-11H), 6.64 (1H, dq, *J* = 10.1, 1.5 Hz, C-3H), 6.37 (1H, dd, *J* = 17.5, 1.8 Hz, C-12$H_A$$H_B$), 5.78 (1H, dd, *J* = 10.6, 1.7 Hz, C-12$H_A$$H_B$), 4.46 (1H, t, *J* = 7.8 Hz, C-9H), 4.18 (2H, qd, *J* = 7.1, 1.4 Hz, OC$H_2$$CH_3$), 2.80–2.67 (1H, m, C-4H), 2.20 (1H, dtd, *J* = 12.9, 7.8, 5.1 Hz, C-8$H_A$$H_B$), 2.05 (1H, dq, *J* = 12.7, 8.1 Hz, C-8$H_A$$H_B$), 1.86 (3H, d, *J* = 1.4 Hz, C-13H_3), 1.82–1.59 (4H, m, C-5H_2, C-7H_2), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.22 (3H, s, C-15H_3), 1.04 (3H, d, *J* = 6.8 Hz, C-14H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 200.6 (C-10), 168.6 (C-1), 148.6 (C-3), 132.0 (C-11), 129.6 (C-12), 125.3 (C-2), 85.3 (C-6), 82.3 (C-9), 60.6 (O*C*$H_2$$CH_3$), 48.1 (C-5), 37.4 (C-7), 30.2 (C-4), 29.4 (C-8), 26.5 (C-15), 21.5 (C-14), 14.5 (OCH_2*C*H_3), 12.5 (C-13); **HRMS:** (ESI+, *m/z*) $C_{17}H_{26}O_4Na$ (MNa^+) Calculated: 317. 17233, Found: 317.17228 (Δ –0.16 ppm).

A sample containing a pair of C-4 epimers will contain the following additional peaks, denoted by prime notation for the undesired epimer: ^{1}H NMR (400 MHz, $CDCl_3$) twinned multiplets at 6.74 (1H, dd, *J* = 17.5, 10.6 Hz, C-11H)/6.72 (1H, dd, *J* = 17.5, 10.6 Hz, C-11'H), 6.65 (1H, dq, *J* = 10.0, 1.5 Hz, C-3'H)/6.64 (1H, dq, *J* = 10.1, 1.5 Hz, C-3H), 6.37 (1H, dd, *J* = 17.5, 1.8 Hz, C-12$H_A$$H_B$)/6.35 (1H, dd, *J* = 17.5, 1.8 Hz, C-12'$H_A$$H_B$), 5.78 (1H, dd, *J* = 10.6, 1.7 Hz, C-12$H_A$$H_B$)/5.76 (1H, dd, *J* = 10.4, 2.0 Hz, C-12'$H_A$$H_B$), 4.48 (1H, t, *J* = 7.7 Hz, C-9'H)/4.46 (1H, t, *J* = 7.8 Hz, C-9H), 1.22 (3H, s, C-15H_3)/1.20 (3H, s, C-15'H_3), 1.04 (3H, d, *J* = 6.8 Hz, C-14H_3)/1.02 (3H, d, *J* = 6.7 Hz, C-14'H_3); ^{13}C NMR

(101 MHz, $CDCl_3$) twinned peaks at 168.6 × 2 (C-1, C-1'), 149.0 (C-3')/148.6 (C-3), 125.3 (C-2)/125.1 (C-2'), 85.3 (C-6)/85.1 (C-6'), 82.5 (C-9')/82.3 (C-9), 60.6 × 2 (OCH_2CH_3, OCH_2CH_3'), 48.1 (C-5)/47.8 (C-5'), 37.4 (C-7)/37.1 (C-7'), 30.2 (C-4)/30.0 (C-4'), 29.4 (C-8)/29.1 (C-8'), 26.7 (C-15')/26.5 (C-15), 21.7 (C-14')/21.5 (C-14).

Ethyl (*R*,*E*)-5-((2*R*,5*R*)-5-((*R*)-6-((2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)tetrahydrofuran-2-yl)-4-methylene-6-((triethylsilyl)oxy)hexanoyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (449)



317 438 449

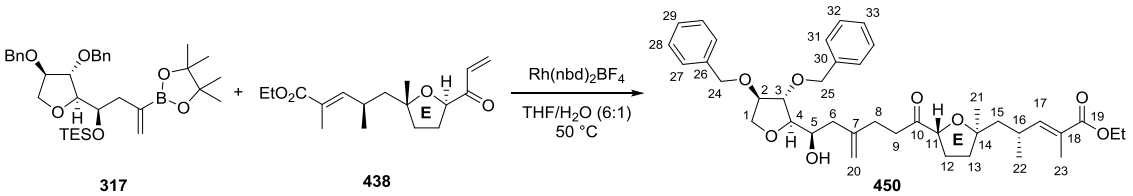
To compound **317** (33.6 mg, 56.6 μmol) and $[Rh(cod)OH]_2$ (3.9 mg, 8.5 μmol) in a vial was added enone **438** (20 mg, 67.9 μmol) in THF/H_2O (6:1, 0.24 mL) and the vial was flushed with argon. The reaction heated to 50 °C for 24 h. The reaction was cooled to rt and EtOAc (1 mL) and H_2O (1 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 95:5 → 90:10 → 80:20 pentane:EtOAc) to afford the title compound **449** (22.9 mg, 53%) as a colourless oil.

R_f: 0.48 (80:20 pentane:EtOAc); $[\alpha]_D^{25}$ –7.1 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3438, 2970, 1708, 1647, 1454, 1369. 1251, 1095, 751, 699; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.39–7.24 (10H, m, ArH), 6.62 (1H, dq, *J* = 10.1, 1.4 Hz, C-17H), 4.82 (1H, s, C-20H_AH$_B$), 4.77 (1H, q, *J* = 1.6 Hz, C-20H$_A$$H_B$), 4.59 (1H, d, *J* = 11.6 Hz, C-25H_AH$_B$), 4.55 (1H, d, *J* = 11.7 Hz, C-25H$_A$$H_B$), 4.53 (1H, d, *J* = 12.4 Hz, C-24H_AH$_B$), 4.49 (1H, d, *J* = 12.0 Hz, C-24H$_A$$H_B$), 4.25 (1H, t, *J* = 7.8 Hz, C-11H), 4.21–4.14 (3H, m, C-3H, O$CH_2$$CH_3$), 4.08 (1H, dt, *J* = 4.6, 2.3 Hz, C-2H), 4.04–3.99 (1H, m, C-5H), 3.95 (1H, dd,

J = 9.9, 2.4 Hz, C-1H_AH$_B$), 3.89 (1H, dd, *J* = 9.9, 4.8 Hz, C-1H$_A$$H_B$), 3.76 (1H, t, *J* = 4.5 Hz, C-4H), 2.77–2.64 (3H, m, C-9H$_2$, C-16H), 2.36–2.24 (3H, m, C-6H_AH$_B$, C-8H$_2$), 2.24–2.10 (2H, m, C-6H$_A$$H_B$, C-12$H_AH_B$), 1.99–1.88 (1H, m, C-12H$_A$$H_B$), 1.86 (3H, d, *J* = 1.5 Hz, C-23H$_3$), 1.76–1.66 (2H, m, C-13H_AH$_B$, C-15H_AH$_B$), 1.66–1.58 (2H, m, C-13H$_A$$H_B$, C-15H$_A$$H_B$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.21 (3H, s, C-21H$_3$), 1.04 (3H, d, *J* = 6.7 Hz, C-22H$_3$), 0.92 (9H, t, *J* = 8.0 Hz, Si(CH$_2$CH_3)$_3$), 0.58 (6H, q, *J* = 8.0 Hz, Si(CH_2CH$_3$)$_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 211.9 (C-10), 168.5 (C-19), 148.6 (C-17), 145.0 (C-7), 138.2 (C-30), 138.1 (C-26), 128.5 (4C, 3Ar), 127.9 (2C, Ar), 127.8 (4C, 2Ar), 125.3 (C-18), 112.4 (C-20), 86.1 (C-4), 85.1 (C-14), 83.9 (C-3), 83.8 (C-2), 83.3 (C-11), 71.9 (C-25), 71.4 (2C, C-1, C-24), 70.8 (C-5), 60.6 (O*C*H$_2$CH$_3$), 47.9 (C-15), 41.1 (C-6), 37.6 (C-13), 36.6 (C-9), 30.2 (C-16), 29.8 (C-8), 29.3 (C-12), 26.4 (C-21), 21.5 (C-22), 14.5 (OCH$_2$*C*H$_3$), 12.5 (C-23), 7.1 (3C, Si(CH$_2$*C*H$_3$)$_3$), 5.3 (3C, Si(*C*H$_2$CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{45}H_{66}O_8{}^{28}SiNa$ (MNa^+) Calculated: 785.44192, Found: 785.44164 (Δ –0.36 ppm).

Ethyl (*R*,*E*)-5-((2*R*,5*R*)-5-((*R*)-6-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)tetrahydrofuran-2-yl)-6-hydroxy-4-methylenehexanoyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (450)

Method 1:

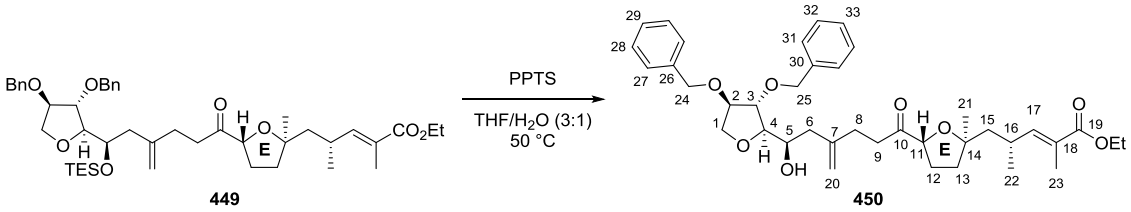


317 438 450

To compound **317** (34.5 mg, 58 μmol) and Rh(nbd)$_2$BF$_4$ (3.3 mg, 8.7 μmol) in a vial was added enone **438** (20.5 mg, 69.6 μmol) in THF/H$_2$O (6:1, 0.24 mL) and the vial was flushed with argon. The reaction heated to 50 °C for 24 h. The reaction was cooled to rt and Et$_2$O (2 mL) and H$_2$O (2 mL) were added and the layers were separated. The aq. layer

was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography twice (SiO_2, 100:0 → 95:5 → 90:10 → 80:20 → 0:100 pentane:EtOAc; then the flush was purified again: SiO_2, 70:30 pentane:EtOAc) to afford the title compound **450** (15.5 mg, 41%) as a colourless oil, as well as small amount of compound **449** (1.2 mg, 5%).

Method 2:

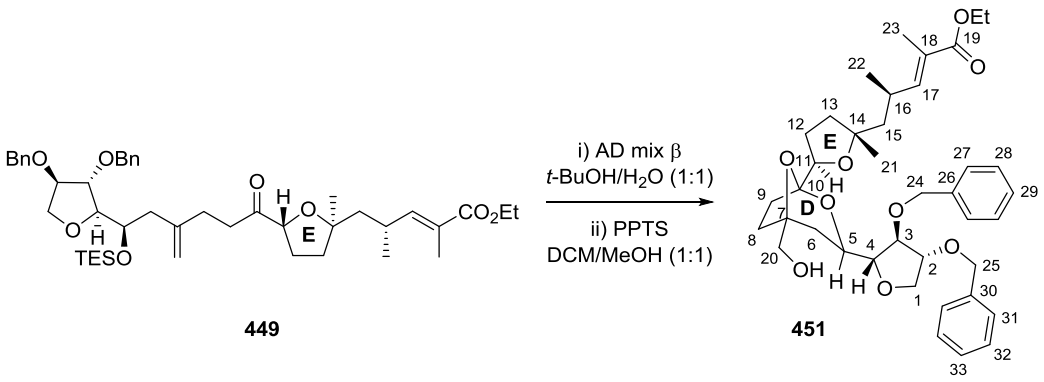


To a solution of compound **449** (16.8 mg, 22.0 μmol) in THF/H_2O (3:1, 0.3 mL) was added PPTS (11 mg, 44 μmol). The reaction was stirred at rt for 21 h 40 min. TLC analysis indicated incomplete reaction so additional PPTS (11 mg, 44 μmol) was added and stirred at rt for a further 5 h 30 min. TLC analysis still indicated incomplete reaction, so the reaction was heated to 50 °C for a further 3 h. The reaction was cooled to rt before EtOAc (1 mL) and H_2O (1 mL) were added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 75:25 pentane:EtOAc) to afford the title compound **450** (7.5 mg, 53%) as a colourless oil.

R_f: 0.21 (70:30 pentane:EtOAc); $[\alpha]_D^{25}$ +8.8 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3490, 3064, 3031, 2961, 2918, 2869, 2850, 1708, 1646, 1497, 1454, 1391, 1369, 1271, 1245, 1202, 1177, 1094, 1073, 1029, 1002, 906, 751, 739, 699, 659; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.39–7.23 (10H, m, ArH), 6.63 (1H, dq, *J* = 10.1, 1.4 Hz, C-17H),

4.87 (1H, s, C-20H_AH$_B$), 4.82 (1H, q, J = 1.6 Hz, C-20H$_A$$H_B$), 4.56 (2H, s, C-25H$_2$), 4.53 (1H, d, J = 11.9 Hz, C-24H_AH$_B$), 4.50 (1H, d, J = 11.9 Hz, C-24H$_A$$H_B$), 4.25 (1H, t, J = 7.9 Hz, C-11H), 4.21–4.15 (3H, m, C-3H, OCH_2CH$_3$), 4.06–4.02 (2H, m, C-1H_AH$_B$, C-2H), 3.95 (1H, ddd, J = 9.4, 5.0, 2.0 Hz, C-5H), 3.87 (1H, dd, J = 10.3, 3.8 Hz, C-1H$_A$$H_B$), 3.79 (1H, dd, J = 4.8, 3.0 Hz, C-4H), 2.82–2.67 (3H, m, C-8H$_2$, C-16H), 2.60 (1H, d, J = 2.3 Hz, OH), 2.39–2.23 (3H, m, C-6H_AH$_B$, C9H$_2$), 2.21–2.13 (1H, m, C-12H$_A$$H_B$), 2.10 (1H, dd, J = 14.3, 9.1 Hz, C-6H$_A$$H_B$), 1.95 (1H, dq, J = 12.8, 8.3 Hz, C-12H$_A$$H_B$), 1.86 (3H, d, J = 1.4 Hz, C-23H$_3$), 1.78–1.59 (4H, m, C-13H$_2$,C-15H$_2$), 1.28 (3H, t, J = 7.1 Hz, OCH$_2$CH_3), 1.21 (3H, s, C-21H$_3$), 1.04 (3H, d, J = 6.8 Hz, C-22H$_3$); **^{13}C NMR:** δ_C (126 MHz, CDCl$_3$) 212.2 (C-10), 168.5 (C-19), 148.6 (C-17), 145.0 (C-7), 137.8 (C-30), 137.7 (C-26), 128.6 (4C, 2Ar), 128.1 (2C, Ar), 128.0 (2C, 2Ar), 127.9 (2C, Ar), 125.3 (C-18), 112.2 (C-20), 87.5 (C-4), 85.1 (C-14), 83.4 (C-11), 82.8 (C-3), 82.6 (C-2), 71.9 (C-25), 71.6 (C-1), 71.1 (C-24), 69.2 (C-5), 60.6 (OCH$_2$CH$_3$), 47.9 (C-15), 41.0 (C-6), 37.5 (C-13), 36.4 (C-8), 30.2 (C-16), 29.3 (C-12), 28.9 (C-9), 26.5 (C-21), 21.5 (C-22), 14.5 (OCH$_2$$CH_3$), 12.5 (C-23); **HRMS:** (ESI+, *m/z*) C$_{39}$H$_{52}$O$_8$Na (MNa$^+$) Calculated: 671.35544, Found: 671.35504 (Δ –0.60 ppm).

Ethyl (*R*,*E*)-5-((2*R*,5*R*)-5-((1*S*,3*R*,5*R*)-3-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)tetrahydrofuran-2-yl)-5-(hydroxymethyl)-2,8-dioxabicyclo[3.2.1]octan-1-yl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (451)


BnO
OBn
O
H
O
E
O
H
TESO
CO2Et
i) AD mix β
t-BuOH/H2O (1:1)
ii) PPTS
DCM/MeOH (1:1)
OEt
O
E
D
O
OH
H
H
O
O
O
O
O
O
H
O
O
O
O
O
O

To a suspension of compound **449** (11.6 mg, 15.2 μmol), $K_3Fe(CN)_6$ (14.9 mg, 45.6 μmol), K_2CO_3 (6.3 mg, 46 μmol), $(DHQD)_2PHAL$ (2.4 mg, 3.0 μmol) in *t*-BuOH (0.5 mL) at 0 °C was added $K_2OsO_2(OH)_4$ (0.6 mg, 1.5 μmol) in H_2O (0.5 mL). The reaction was stirred and monitored closely for 1 h 25 min before the reaction was quenched with sat. aq. Na_2SO_3 (1 mL) and stirred for a further 15 min. The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude diol product was obtained as a pale yellow oil and was carried into the next step without further purification.

Crude diol (assumed quant., 15.2 μmol) was transferred to a flask in DCM (1 mL) and MeOH (1 mL). PPTS (3.8 mg, 15.2 μmol) was added and the reaction was stirred at rt for 17 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL), diluted with EtOAc (2 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 → 80:20 → 70:30 → 60:40 → 50:50 → 0:100 pentane:EtOAc) to afford the title compound **451** (4.0 mg, 40%) as a colourless oil.

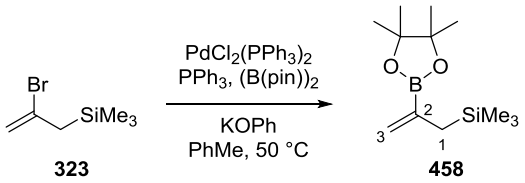
The bicyclic ring configuration was confirmed by nOes between C-5H to C-$8H_B$ and C-$9H_B$ in $CDCl_3$ (see **Appendix 6.2.6**).

R_f: 0.14 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ –3.4 (*c* = 0.50, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3734, 3690, 3475, 3030, 2962, 2926, 2361, 2342, 1706, 1648, 1497, 1455, 1369, 1272, 1246, 1177, 1095, 1028, 909, 751, 698, 669, 655, 636, 608; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.39–7.21 (10H, m, ArH), 6.63 (1H, dd, *J* = 10.1, 1.6 Hz, C-17H), 4.57 (1H, d, *J* = 11.9 Hz, C-24$H_A$$H_B$), 4.51 (2H, s, C-25$H_2$), 4.49 (1H, d, *J* = 11.7 Hz, C-24$H_A$$H_B$), 4.18 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 4.15 (1H, s, C-3H), 4.09–4.06 (1H, m, C-2H), 3.99–3.92

(3H, m, C-1H_2, C-5H), 3.92–3.87 (1H, m, C-11H), 3.83–3.77 (1H, m, C-4H), 3.66 (1H, d, *J* = 12.0 Hz, C-20H_AH$_B$), 3.55 (1H, d, *J* = 11.9 Hz, C-20H$_A$$H_B$), 2.73–2.62 (1H, m, C-16H), 2.12–2.03 (1H, m, C-9H_AH$_B$), 1.99–1.77 (7H, m, C-8H_AH$_B$, C-9H$_A$$H_B$, C-12$H_2$, C-23$H_3$), 1.71–1.50 (7H, m, C-6$H_2$, C-8H$_A$$H_B$, C-13$H_2$, C-15$H_2$), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.15 (3H, s, C-21H_3), 1.01 (3H, d, *J* = 6.7 Hz, C-22H_3); **^{1}H NMR:** δ_H (500 MHz, C_6D_6) 7.38–7.08 (10H, m, ArH), 6.94–6.90 (1H, m, C-17H), 4.63 (1H, d, *J* = 12.1 Hz, C-24H_AH$_B$), 4.56 (1H, d, *J* = 12.1 Hz, C-24H$_A$$H_B$), 4.43 (1H, s, C-3H), 4.29 (d, *J* = 11.6 Hz, C-25H_AH$_B$), 4.27 (1H, d, *J* = 11.7 Hz, C-25H$_A$$H_B$), 4.14–4.04 (4H, m, C-4H, C-5H, OCH_2CH$_3$), 4.03–3.93 (4H, m, C-1H_2, C-2H, C-11H), 3.45 (1H, d, *J* = 11.7 Hz, C-20H_AH$_B$), 3.31 (1H, d, *J* = 11.7 Hz, C-20H$_A$$H_B$), 2.69–2.58 (1H, m, C-16H), 2.14–2.03 (2H, m, C-9H_AH$_B$, C-12H_AH$_B$), 2.00–1.93 (1H, m, C-9H$_A$$H_B$), 1.91 (3H, d, *J* = 1.5 Hz, C-23H_3), 1.90–1.71 (3H, m, 1H, C-6H_AH$_B$, C-8H_AH$_B$, C-12H$_A$$H_B$), 1.57–1.38 (5H, m, C-6H$_A$$H_B$, C-13$H_2$, C-15$H_2$), 1.27–1.19 (1H, m, C-8H$_A$$H_B$), 1.16 (3H, s, C-21$H_3$), 1.02 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 0.89 (3H, d, *J* = 6.7 Hz, C-22H_3); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 168.7 (C-19), 149.0 (C-17), 138.1 (C-26), 137.9 (C-30), 128.6 (4C, 2Ar), 128.0 (Ar), 127.9 (3C, 2Ar), 127.8 (2C, Ar), 125.0 (C-18), 108.0 (C-10), 87.0 (C-4), 83.9 (C-7), 83.7 (C-14), 83.6 (C-3), 83.3 (C-2), 80.5 (C-11), 71.9 (C-1), 71.7 (C-24), 71.4 (C-25), 68.8 (C-5), 66.9 (C-20), 60.6 (O*C*H$_2$CH$_3$), 48.0 (C-15), 37.4 (C-13), 35.5 (C-6), 30.5 (C-9), 30.2 (C-16), 28.4 (C-8), 27.6 (C-12), 27.0 (C-21), 21.6 (C-22), 14.5 (OCH$_2$*C*H$_3$), 12.5 (C-23); **^{13}C NMR:** δ_C (126 MHz, C_6D_6) 168.2 (C-19), 149.2 (C-17), 138.9 (C-26), 138.6 (C-30), 128.7 (2C, 2Ar), 128.4 (3C, Ar), 128.2 (2C, Ar), 128.0 (2C, Ar), 127.5 (Ar), 125.3 (C-18), 107.9 (C-10), 87.5 (C-4), 84.4 (C-3), 83.9 (2C, C-2, C-14), 83.4 (C-7), 83.1 (C-11), 81.7 (C-1), 71.9 (C-24), 71.7 (C-25), 71.4 (C-5), 69.4 (C-20), 60.4 (O*C*H$_2$CH$_3$), 48.1 (C-15), 37.8 (C-13), 36.0 (C-6), 32.0 (C-9), 30.2 (C-16), 28.7 (C-8), 27.5 (C-12), 27.4

(C-21), 21.4 (C-22), 14.4 (OCH_2CH_3), 12.6 (C-23); **HRMS:** (ESI+, *m/z*) $C_{39}H_{52}O_9Na$ (MNa^+) Calculated: 687.35035, Found: 687.35055 (Δ +0.29 ppm).

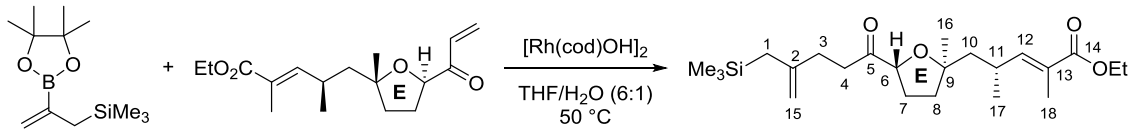
Trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)silane (458)



To a flask charged with $PdCl_2(PPh_3)_2$ (5.5 mg, 7.8 μmol), PPh_3 (4 mg, 15.5 μmol), bis(pinacolato)diboron (72 mg, 0.29 mmol) and KOPh[181] (51 mg, 0.39 mmol) was added compound **323** (50 mg, 0.26 mmol) in PhMe (1.6 mL). The reaction was flushed under argon and heated to 50 °C for 3 h. The reaction was cooled to rt and water (2 mL) was added. The layers were separated, and the aq. layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 99:1 pentane:Et_2O) to afford the title compound **458** (36.2 mg, 58%) as a volatile, colourless oil.

R_f: 0.52 (90:10 pentane:Et_2O); **IR:** ν_{max} (thin film/cm^{-1}) 2958, 2925, 2856, 2363, 2344, 1731, 1599, 1493, 1458, 1362, 1261, 1143, 1073, 1023, 922, 856, 841, 802, 751, 704, 692, 662, 628, 611; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 5.65 (1H, d, J = 3.6 Hz, C-3H_AH_B), 5.40 (1H, d, J = 3.5 Hz, C-3H_AH_B), 1.66 (2H, s, C-1H_2), 1.25 (12H, s, 2 × C(CH_3)$_2$), –0.02 (9H, s, Si(CH_3)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 138.5 (v. br., C-2), 126.9 (C-3), 83.5 (2C, 2 × *C*(CH_3)$_3$), 25.5 (C-1), 25.0 (4C, 2 × C(CH_3)$_2$), –1.7 (3C, Si(CH_3)$_3$); **^{11}B NMR:** δ_B (128 MHz, $CDCl_3$) 29.9; a mass spectrum could not be obtained for this compound.

Ethyl (*R*,*E*)-2,4-dimethyl-5-((2*R*,5*R*)-2-methyl-5-(4-((trimethylsilyl)methyl)pent-4-enoyl)tetrahydrofuran-2-yl)pent-2-enoate (457)



458 438 457

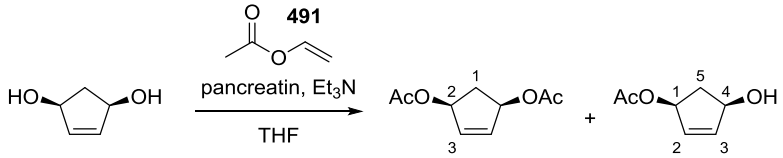
To compound **458** (17.6 mg, 59.7 μmol) and enone **438** (10 mg, 42 μmol) in a vial was added $[Rh(cod)OH]_2$ (3.9 mg, 8.5 μmol) and THF/H_2O (6:1, 0.24 mL) and the vial was flushed with argon. The reaction was heated to 50 °C for 22 h and then was cooled to rt. DCM (2 mL) and H_2O (2 mL) were added and the layers were separated. The aq. layer was extracted with DCM (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 97:3 pentane:EtOAc) to afford the title compound **457** (4.4 mg, 18%) as a colourless oil.

R_f: 0.69 (90:10 pentane:EtOAc); $[\alpha]_D^{25}$ –9.2 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2957, 2927, 2872, 2850, 2361, 2337, 1712, 1647, 1635, 1455, 1367, 1262, 1247, 1175, 1096, 1071, 854, 801, 772, 751, 696, 653, 631, 619, 609; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 6.63 (1H, dq, *J* = 10.2, 1.5 Hz, C-12H), 4.55 (1H, q, *J* = 1.5 Hz, C-15$H_A$$H_B$), 4.52 (1H, dt, *J* = 1.7, 0.9 Hz, C-15$H_A$$H_B$), 4.26 (1H, t, *J* = 7.9 Hz, C-6H), 4.18 (2H, qd, *J* = 7.1, 1.7 Hz, OC$H_2$$CH_3$), 2.78–2.63 (3H, m, C-4$H_2$, C-11H), 2.26–2.13 (3H, m, C-3H_2, C-7$H_A$$H_B$), 2.01–1.91 (1H, m, C-7$H_A$$H_B$), 1.86 (3H, d, *J* = 1.5 Hz, C-18H_3), 1.79–1.60 (4H, m, C-8H_2, C-10H_2), 1.29 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.22 (3H, s, C-16H_3), 1.04 (3H, d, *J* = 6.7 Hz, C-17H_3), 0.07 (2H, s, C-1H_2), 0.02 (9H, s, Si(CH_3)$_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 212.3 (C-5), 168.6 (C-14), 148.6 (C-12), 146.7 (C-2), 125.3 (C-13), 107.0 (C-15), 85.1 (C-9), 83.4 (C-6), 60.6 (O*C*$H_2$$CH_3$), 48.0 (C-10), 37.5 (C-8), 36.8 (C-4), 31.5 (C-3), 30.2 (C-11), 29.3 (C-7), 26.5 (C-16), 21.5 (C-17), 14.5 (OCH_2*C*H_3), 12.5

(C-18), 1.2 (C-1), –1.2 (3C, $Si(CH_3)_3$); **HRMS:** (ESI+, *m/z*) $C_{23}H_{40}O_4{}^{28}SiNa$ (MNa^+) Calculated: 431.25881, Found: 431.25847 (Δ –0.79 ppm).

5.4 *Experimental procedures for the synthesis of the F ring*

(1*R*,3*S*)-Cyclopent-4-ene-1,3-diyl diacetate (492) and (1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate (463)*



To a suspension of pancreatin (0.94 g) and (*1R*,3*S*)-cyclopent-4-ene-1,3-diol **462** (250 mg, 25.0 mmol) in THF (5 mL) was added vinyl acetate (1.60 mL, 17.5 mmol) and Et_3N (0.24 mL, 1.75 mmol). The reaction mixture was shaken in an incubator at rt until the starting material was completely consumed, as indicated by TLC (20 h 30 min). The reaction was filtered through Celite®, rinsed with Et_2O and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 80:20 → 50:50 pentane:EtOAc) to afford the title compound **492** first (157 mg, 34%) as a yellow oil, and the title compound **463** second (223 mg, 63%, 94% ee) as a yellow solid.

The stereochemistry of C-1 of monoacetate **463** was assigned the (*S*)-configuration and in 94% ee by Mosher's ester analysis (see **Appendix 6.1.3**).

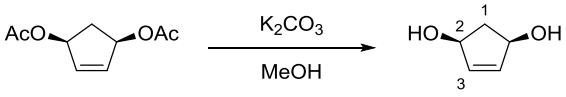
Diacetate 492: **R_f:** 0.57 (50:50 pentane:EtOAc); **IR:** ν_{max} (thin film/cm^{-1}) 2946, 1731, 1434, 1365, 1224, 1074, 1016, 989, 958, 909, 74, 644, 608; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 6.09 (2H, d, *J* = 0.9 Hz, 2 × C-3H), 5.55 (2H, ddd, *J* = 7.6, 3.8, 0.9 Hz, 2 × C-2H), 2.88 (1H, dt, *J* = 15.1, 7.6 Hz, C-1H_AH_B), 2.06 (6H, s, 2 × $OCOCH_3$), 1.74 (1H, dt, *J* = 14.9, 3.8 Hz, C-1H_AH_B); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 170.8 (2C, 2 × O*C*OCH$_3$), 134.7 (2C, 2 × C-3), 76.7 (2C, 2 × C-2), 37.2 (C-1), 21.3 (2C, 2 × OCO*C*H$_3$); **HRMS:**

* Compounds **492** and **463** was prepared according to the procedure detailed by Donohoe.[43]

(ESI+, *m/z*) $C_9H_{12}O_4Na$ (MNa^+) Calculated: 207.06278, Found: 207.06286 (Δ +0.39 ppm); Spectroscopic data were consistent with those in the literature.[187]

Monoacetate 463: **R_f:** 0.29 (50:50 pentane:EtOAc); **m.p.:** 47–49 °C; $[\alpha]_D^{25}$ –67.9 (*c* = 1.00, $CHCl_3$; lit.[43] –64.4 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3400, 2944, 2363, 1733, 1434, 1362, 1332, 1242, 1090, 1059, 1019, 981, 910, 882, 773; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 6.11 (1H, ddd, *J* = 5.5, 2.2, 1.2 Hz, C-2H), 5.99 (1H, ddd, *J* = 5.5, 2.2, 1.1 Hz, C-3H), 5.52–5.47 (1H, m, C-4H), 4.75–4.69 (1H, m, C-1H), 2.80 (1H, dt, *J* = 14.7, 7.4 Hz, C-5H_AH_B), 2.05 (3H, s, $OCOCH_3$), 1.66 (1H, dt, *J* = 14.6, 3.8 Hz, C-5H_AH_B), 1.61 (1H, s, OH); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 170.9 (O*C*OCH_3), 138.6 (C-2), 132.8 (C-3), 77.2 (C-4), 75.0 (C-1), 40.7 (C-5), 21.4 ($OCOCH_3$); **HRMS:** (ESI+, *m/z*) $C_7H_{10}O_3Na$ (MNa^+) Calculated: 165.05222, Found: 165.05239 (Δ +1.03 ppm); Spectroscopic data were consistent with those in the literature.[43, 188, 189]

(1*R*,3*S*)-Cyclopent-4-ene-1,3-diol (462)



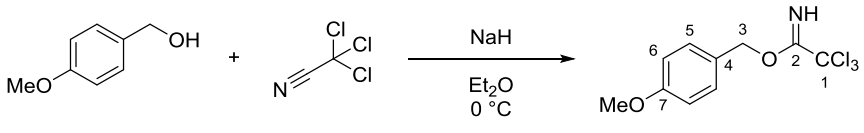
492 **462**

To a solution of compound **492** (1.37 g, 7.45 mmol) in MeOH (45 mL) was added K_2CO_3 (2.10 g, 14.9 mmol). The reaction was stirred for 24 h at rt. The reaction was filtered through a cotton plug and the solvent removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, 95:5 DCM:MeOH) to afford the title compound **462** (706 mg, 99%) as a yellow solid.

R_f: 0.07 (50:50 pentane:EtOAc); **m.p.:** 51–53 °C (lit. 55–59 °C); **IR:** ν_{max} (thin film/cm^{-1}) 3296, 2927, 1422, 1348, 1319, 1261, 1118, 1062, 1000, 876, 762; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 6.05–5.96 (2H, m, 2 × C-3H), 4.73 – 4.58 (2H, m, 2 × C-2H), 3.49–

3.46 (2H, m, 2 × OH), 2.70 (1H, dtd, J = 14.5, 7.2, 1.0 Hz, C-1H_AH_B), 1.55 (1H, dt, J = 14.5, 3.5 Hz, C-1H_AH_B); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 136.6 (2C, 2 × C-3), 75.2 (2C, 2 × C-2), 43.8 (C-1); Spectroscopic data were consistent with those in the literature.[190]

4-Methoxybenzyl-2,2,2-trichloroacetimidate (495)*



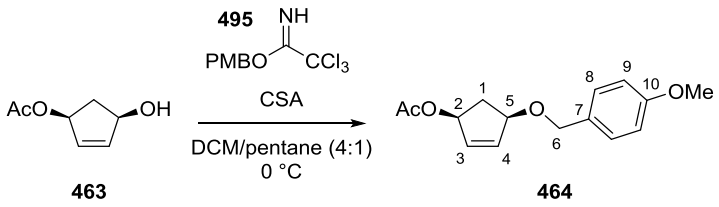
493 **494** **495**

Sodium hydride (60% dispersion in mineral oil, 64.4 mg, 0.16 mmol) under argon was washed with pentane (3 × 2 mL) before it was dissolved in dry Et_2O (5 mL). 4-Methoxybenzyl alcohol **493** (2.0 mL, 16 mmol) was added and stirred at rt for 30 min. The solution was cooled to 0 °C and trichloroacetonitrile **494** (1.78 mL, 17.7 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt. The reaction was diluted with pentane/MeOH (275:1, 17 mL) and stirred for a further 30 min. The mixture was filtered through Celite® and concentrated afford the title compound **495** (4.09 g, 90%) as a yellow oil.

R_f: 0.70 (EtOAc); **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.36 (1H, s, NH), 7.37 (2H, d, J = 8.7 Hz, 2 × C-5H), 6.91 (2H, d, J = 8.7 Hz, 2 × C-6H), 5.27 (2H, s, C-3H_2), 3.82 (3H, s, OCH_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 162.8 (C-2), 159.8 (C-7), 129.9 (2C, 2 × C-5), 127.6 (C-4), 114.0 (2C, 2 × C-6), 91.5 (C-1), 70.8 (C-3), 55.4 (OCH_3); Spectroscopic data were consistent with those in the literature.[166]

* Compound **495** was prepared according to the procedure detailed by Tokuyama.[166]

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl acetate (464)*



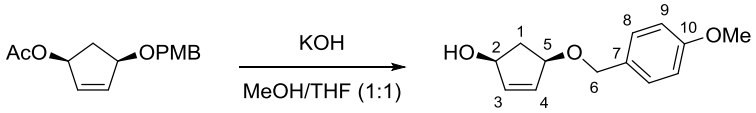
To a solution of compound **463** (873 mg, 5.85 mmol) and (+/–)-10-camphorsulfonic acid (136 mg, 0.59 mmol) in DCM/pentane (4:1, 15 mL) at 0 °C was added trichloroacetimidate **495** (1.82 g, 6.44 mmol) in DCM/pentane (4:1, 5 mL). The reaction was warmed to rt and stirred for 21 h. TLC analysis indicated incomplete reaction so additional trichloroacetimidate **495** (0.91 g, 3.22 mmol) in DCM/pentane (4:1, 2 mL) was added and the resulting mixture was stirred at rt for a further 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and the mixture was extracted with DCM (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 15:1 → 90:10 pentane:EtOAc) to afford the title compound **464** (1.43 g, 93%) as a white solid.

R_f: 0.38 (80:20 pentane:EtOAc); **m.p.:** 30–31 °C (lit.[43] 30–35 °C); $[\alpha]_D^{25}$ –5.9 (*c* = 1.00, $CHCl_3$; lit.[43] –5.6 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 2938, 2838, 1732, 1612, 1585, 1513, 1464, 1441, 1365, 1302, 1244, 1175, 1072, 1032, 823, 794; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.6 Hz, 2 × C-8H), 6.88 (2H, d, *J* = 8.7 Hz, 2 × C-9H), 6.11 (1H, ddd, *J* = 5.7, 2.0, 1.3 Hz, C-3H), 5.98 (1H, ddd, *J* = 5.7, 2.1, 1.3 Hz, C-4H), 5.53–5.48 (1H, m, C-2H), 4.52 (1H, d, *J* = 11.4 Hz, C-6H_AH_B), 4.51–4.45 (1H, m, C-5H), 4.47 (1H, d, *J* = 11.3 Hz, C-6H_AH_B), 3.80 (3H, s, OCH_3), 2.76 (1H, dt, *J* = 14.2, 7.4 Hz, C-1H_AH_B), 2.05 (3H, s, $OCOCH_3$), 1.74 (1H, dt, *J* = 14.2, 4.4 Hz, C-1H_AH_B); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 171.0 (O*C*OCH_3), 159.4 (C-10), 136.4 (C-3), 132.9 (C-4),

* Compound **464** was prepared according to the procedure detailed by Donohoe.[43]

130.5 (C-7), 129.5 (2C, 2 × C-8), 114.0 (2C, 2 × C-9), 81.0 (C-5), 77.0 (C-2), 70.9 (C-6), 55.4 (OCH_3), 37.7 (C-1), 21.3 ($OCOCH_3$); **HRMS:** (ESI+, *m/z*) $C_{15}H_{18}O_4Na$ (MNa^+) Calculated: 285.10973, Found: 285.10960 (Δ –0.46 ppm); Spectroscopic data were consistent with those in the literature.[43]

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-ol (539)



464 **539**

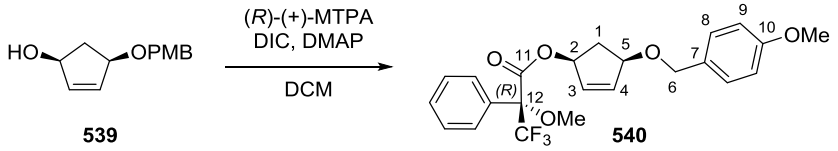
To a solution of compound **464** (103 mg, 0.393 mmol) in MeOH/THF (1:1, 10 mL) was added KOH (28 mg, 0.42 mmol). The reaction was stirred for 5 h before H_2O (10 mL) and EtOAc (15 mL) was added and the layers were separated. The aq. layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 60:40 pentane:EtOAc) to afford the title compound **539** (77 mg, 89%) as a colourless oil.

The stereochemistry of C-2 was assigned the (*S*)-configuration by Mosher's ester analysis (see **Appendix 6.1.3**).

R_f: 0.23 (60:40 pentane:EtOAc); $[\alpha]_D^{25}$ –18.8 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3393, 3060, 2999, 293, 2907, 2861, 2838, 2362, 2337, 1734, 1613, 1586, 1514, 1464, 1442, 1422, 1394, 1359, 1320, 1302, 1248, 1175, 1072, 1033, 877, 821, 768, 710, 681, 638, 615; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.29–7.25 (2H, m, 2 × C-8H), 6.90–6.85 (2H, m, 2 × C-9H), 6.01 (2H, s, C-3H, C-4H), 4.60 (1H, dd, *J* = 7.3, 4.1 Hz, C-2H), 4.50 (1H, d, *J* = 11.3 Hz, C-6H_AH_B), 4.46 (1H, d, *J* = 11.3 Hz, C-6H_AH_B), 4.41 (1H, ddd, *J* = 7.1, 4.1, 1.1 Hz, C-5H), 3.80 (3H, s, OCH_3), 2.63 (1H, dt, *J* = 14.2, 7.2 Hz, C-1H_AH_B), 2.40

(1H, s, OH), 1.64 (1H, dt, J = 14.1, 4.1 Hz, C-1H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 159.3 (C-10), 137.3 (C-4), 134.1 (C-3), 130.5 (C-7), 129.5 (2C, 2 × C-8), 113.9 (2C, 2 × C-9), 81.3 (C-5), 75.0 (C-2), 70.8 (C-6), 55.4 (OCH_3), 41.0 (C-1); **HRMS:** (ESI+, *m/z*) $C_{13}H_{16}O_3Na$ (MNa^+) Calculated: 243.09917, Found: 243.09925 (Δ –0.33 ppm).

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (540)*



539 **540**

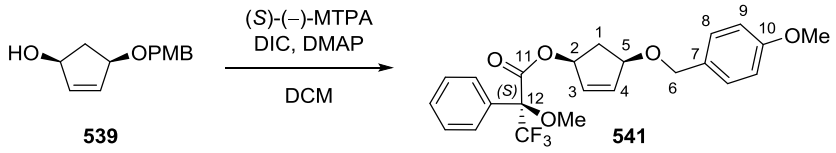
To a solution of **539** (10.1 mg, 45.8 μmol) in DCM (0.5 mL), were added DIC (8.4 μL, 55 μmol) and DMAP (2.8 mg, 23 μmol). (*R*)-(+)-MTPA (13.1 mg, 55.9 μmol) was added in DCM (0.5 mL) and the reaction was stirred at rt for 16 h. TLC analysis indicated incomplete reaction so additional (*R*)-(+)-MTPA (13.3 mg, 56.8 μmol) and DIC (10 μL, 64.6 μmol) in DCM (0.5 mL) were added and stirring was continued for 5 days. The reaction was then filtered through a Celite® plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 85:15 pentane:EtOAc) to afford the title compound **540** (13.6 mg, 68%) as a colourless oil.

R_f: 0.26 (85:15 pentane:EtOAc); $[\alpha]_D^{25}$ +15.0 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2953, 2361, 2333, 1744, 1716, 1670, 1614, 1514, 1454, 1368, 1250, 1170, 1122, 1081, 1018, 823, 767, 710, 644, 614; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.63–7.49 (2H, m, ArH), 7.49–7.32 (3H, m, ArH), 7.24 (2H, d, J = 8.3 Hz, 2 × C-8H), 6.87 (1H, d, J = 8.3 Hz, 2 × C-9H), 6.16 (1H, dd, J = 5.7, 1.6 Hz, C-4H), 5.98 (1H, dd, J = 5.8, 1.7 Hz, C-3H), 5.71 (1H, t, J = 6.4 Hz, C-2H), 4.53 (1H, t, J = 5.9 Hz, C-4H), 4.47 (1H, d, J = 11.3 Hz, C-6H_AH$_B$), 4.45 (1H, d, J = 11.5 Hz, C-6H$_A$$H_B$), 3.80 (3H, s, C-10$OCH_3$), 3.54 (3H, s, C-

* Compound **540** was prepared according to the procedure detailed by Hoye.[99]

12OCH$_3$), 2.85 (1H, dt, J = 14.3, 7.3 Hz, C-1H_AH$_B$), 1.86 (1H, dt, J = 14.2, 4.5 Hz, C-1H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, CDCl$_3$) 166.5 (C-11), 159.4 (C-10), 137.6 (C-4), 132.3 (Ar), 131.6 (C-3), 130.3 (C-7), 129.9 (Ar), 129.7 (quaternary Ar), 129.5 (2C, 2 × C-8), 128.9 (Ar), 128.5 (2C, Ar), 127.5 (2C, Ar), 123.4 (q, J = 288.5 Hz, CF$_3$), 114.0 (2C, 2 × C-9), 85.6 (q, J = 35.5 Hz, C-12), 80.8 (C-5), 79.3 (C-2), 70.8 (C-6), 55.6 (C-12O*C*H$_3$), 55.4 (C-10O*C*H$_3$), 37.5 (C-1); **^{19}F NMR:** δ_F (377 MHz, CDCl$_3$) –71.7; **HRMS:** (ESI+, *m/z*) C$_{23}$H$_{23}$O$_5$F$_3$Na (MNa$^+$) Calculated: 459.13898, Found: 459.13859 (Δ –0.85 ppm).

(1*S*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (541)*



539 **541**

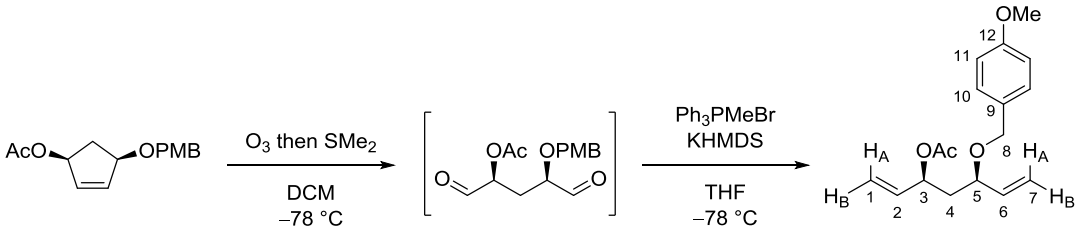
To a solution of **539** (9.7 mg, 44 μmol) in DCM (0.5 mL), were added DIC (8.4 μL, 55 μmol) and DMAP (2.8 mg, 23 μmol). (*S*)-(–)-MTPA (13.0 mg, 55.5 μmol) was added in DCM (0.5 mL) and the reaction was stirred at rt for 16 h. TLC analysis indicated incomplete reaction so additional (*S*)-(–)-MTPA (13.8 mg, 58.9 μmol) and DIC (10 μL, 64.6 μmol) in DCM (0.5 mL) were added and stirring was continued for 5 days. The reaction was then filtered through a Celite® plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO$_2$, 100:0 → 85:15 pentane:EtOAc) to afford the title compound **541** (19.2 mg, quant.) as a colourless oil.

R$_f$: 0.23 (85:15 pentane:EtOAc); $[\alpha]_D^{25}$ –54.2 (c = 1.00, CHCl$_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2950, 2850, 2359, 1744, 1715, 1670, 1613, 1586, 1514, 1453, 1368, 1250, 1170, 1122, 1081, 1019, 824, 766, 710, 638, 617; **^{1}H NMR:** δ_H (400 MHz, CDCl$_3$) 7.62–7.49 (2H, m, ArH), 7.49–7.33 (3H, m, ArH), 7.22 (2H, d, J = 8.6 Hz, 2 × C-8H), 6.86 (2H, d, J =

* Compound **541** was prepared according to the procedure detailed by Hoye.[99]

8.6 Hz, 2 × C-9H), 6.18 (1H, dt, *J* = 5.7, 1.6 Hz, C-4H), 6.05 (1H, dd, *J* = 5.6, 1.7 Hz, C-3H), 5.72 (1H, t, *J* = 6.4 Hz, C-2H), 4.52 (1H, t, *J* = 5.9 Hz, C-5H), 4.45 (1H, d, *J* = 11.2 Hz, C-6H_AH$_B$), 4.42 (1H, d, *J* = 11.3 Hz, C-6H$_A$$H_B$), 3.80 (3H, s, C-10OCH$_3$), 3.55 (3H, s, C-12OCH$_3$), 2.80 (1H, dt, *J* = 14.5, 7.4 Hz, C-1H_AH$_B$), 1.78 (1H, dt, *J* = 14.2, 4.5 Hz, C-1H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.4 (C-11), 159.4 (C-10), 137.8 (C-4), 132.3 (Ar), 131.6 (C-3), 130.3 (C-7), 129.9 (Ar), 129.7 (quaternary Ar), 129.5 (2C, 2 × C-8), 128.9 (Ar), 128.6 (2C, 2 × C-9), 127.4 (Ar), 123.4 (q, *J* = 287.5 Hz, CF_3), 114.0 (2C, 2 × C-9), 84.6 (q, *J* = 27.8 Hz, C-12), 80.8 (C-5), 79.3 (C-2), 70.7 (C-6), 55.6 (C-10O*C*H$_3$), 55.4 (C-12O*C*H$_3$), 37.1 (C-1); **^{19}F NMR:** δ_F (377 MHz, $CDCl_3$) –71.7; **HRMS:** (ESI+, *m/z*) $C_{23}H_{23}O_5F_3Na$ (MNa^+) Calculated: 459.13898, Found: 459.13870 (Δ –0.61 ppm).

(3*S*,5*R*)-5-((4-Methoxybenzyl)oxy)hepta-1,6-dien-3-yl acetate (466)*



464 **465** **466**

A 2-necked flask equipped with a drying tube was charged with a solution of compound **464** (100 mg, 0.381 mmol) in DCM (4 mL) at –78 °C. The solution was subjected to a stream of ozone gas through a pipette until the solution turned blue (3 min), at which point ozone was removed and nitrogen gas was passed through the solution until the blue colour disappeared (3 min). The reaction was quenched with dimethyl sulfide (0.11 mL, 1.5 mmol) and the reaction was warmed to –20 °C and stirred for 2 h. TLC analysis still indicated incomplete decomposition of the ozonide, so the reaction was warmed to rt and

* Compound **466** was prepared according to the procedure detailed by Roushanbakhti.[161]

stirred for a further 1 h. The solvent was removed *in vacuo* (treated as volatile and unstable: >200 mbar, cool water bath, avoid opening to air by concentrating in the 2-neck flask). The crude product **465** was obtained as a yellow oil and was carried into the next step without further purification.

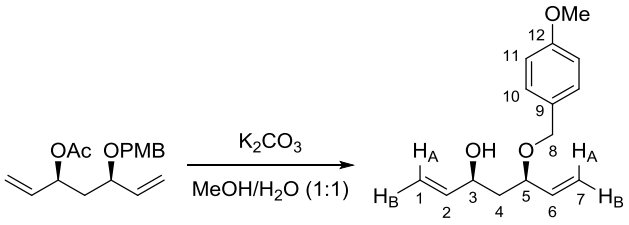
Triphenylmethylphosphonium bromide (586 mg, 1.64 mmol) was dried azeotropically in benzene (3 × 5 mL). To a suspension of dried triphenylmethylphosphonium bromide (586 mg, 1.64 mmol) in THF (4 mL) at 0 °C was added KHMDS (0.5 M in PhMe, 2.75 mL, 1.37 mmol) dropwise. The reaction was stirred for 15 min before it was cooled to –78 °C. Crude **465** (assumed quant., 0.38 mmol) was dissolved in THF (1 mL) and cooled to –78 °C before it was transferred *via* a cannula to the suspension of ylid. The reaction was warmed to rt and stirred for 1 h 10 min. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 90:10 pentane:EtOAc) to afford the title compound **466** (52 mg, 44% over two steps) as a colourless oil.

R_f: 0.67 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +28.2 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 2954, 2838, 1738, 1645, 1613, 1586, 1514, 1465, 1442, 1371, 1302, 1243, 1174, 1080, 1034, 993, 931, 821, 759; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.28–7.22 (2H, m, 2 × C-10H), 6.91–6.83 (2H, m, 2 × C-11H), 5.81–5.68 (2H, m, C-2H, C-6H), 5.39–5.33 (1H, m, C-3H), 5.28–5.12 (4H, m, C-1H_2, C-7H_2), 4.50 (1H, d, *J* = 11.3 Hz, C-8$H_A$$H_B$), 4.23 (1H, d, *J* = 11.2 Hz, C-8$H_A$$H_B$), 3.83–3.77 (1H, m, C-5H), 3.80 (3H, s, OCH_3), 2.06 (1H, dt, *J* = 14.0, 7.6 Hz, C-4$H_A$$H_B$), 2.00 (3H, s, $OCOCH_3$), 1.73 (1H, dt, *J* = 14.0, 6.1 Hz, C-4$H_A$$H_B$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 170.1 (O*C*OCH_3), 159.2 (C-12), 138.3 (C-6), 136.3 (C-2), 130.6 (C-9), 129.6 (2C, 2 × C-10), 118.0 (C-7), 117.1 (C-1), 113.9 (2C, 2 ×

C-11), 77.2 (C-5), 72.3 (C-3), 69.9 (C-8), 55.4 (OCH_3), 40.2 (C-4), 21.3 ($OCOCH_3$); **HRMS:** (ESI+, *m/z*) $C_{17}H_{22}O_4Na$ (MNa^+) Calculated: 313.14103, Found: 313.14107 (Δ +0.13 ppm); Spectroscopic data were consistent with those in the literature.[161]

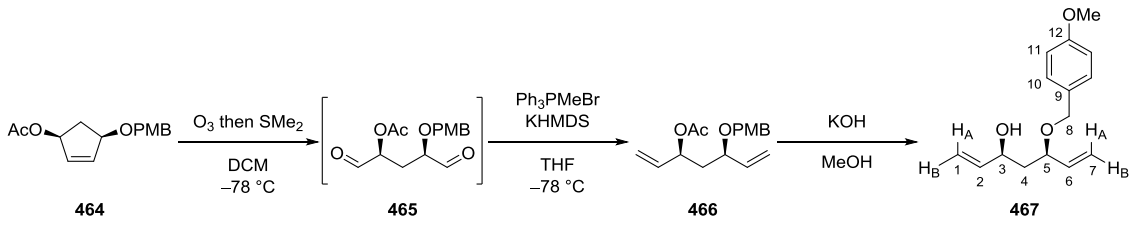
(3*S*,5*R*)-5-((4-Methoxybenzyl)oxy)hepta-1,6-dien-3-ol (467)

Method 1:



To a solution of compound **466** (52 mg, 0.18 mmol) in MeOH (1 mL) and H_2O (1 mL) was added K_2CO_3 (20 mg, 0.36 mmol). The reaction was stirred for 24 h at rt. TLC analysis indicated incomplete reaction so additional K_2CO_3 (20 mg, 0.36 mmol) was added and stirring was continued for 6 h. The reaction was diluted with EtOAc (3 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:0 pentane:EtOAc) to afford the title compound **467** (30 mg, 68%) as a colourless oil.

Method 2: [*]



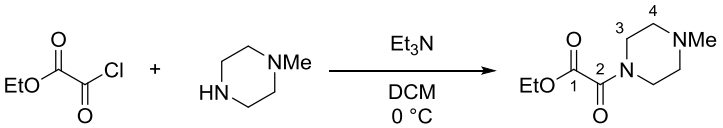
[*] Compound **467** was prepared according to the procedure detailed by Donohoe.[43]

A 2-necked flask equipped with a drying tube was charged with a solution of compound **464** (6.02 g, 23.0 mmol) in DCM (240 mL) at –78 °C. The solution was subjected to a stream of ozone gas through an airstone until the solution turned blue (23 min), at which point ozone was removed and nitrogen gas was passed through the solution until the blue colour disappeared (5 min). The reaction was quenched with dimethyl sulfide (6.75 mL, 91.9 mmol) and the reaction was warmed to –20 °C and stirred for 1 h. TLC analysis still indicated incomplete decomposition of the ozonide, so the reaction was warmed to rt and stirred for a further 2 h. The solvent was removed *in vacuo* (treated as volatile and unstable: >200 mbar, cool water bath, avoid opening to air by concentrating in the 2-neck flask). The crude product **465** was obtained as a yellow oil and was carried into the next step without further purification.

Triphenylmethylphosphonium bromide (36.1 g, 98.8 mmol) was dried azeotropically in benzene (3 × 10 mL). To a suspension of dried triphenylmethylphosphonium bromide (36.1 g, 98.8 mmol) in THF (240 mL) at 0 °C was added KHMDS (0.5 M in PhMe, 165 mL, 82.5 mmol) dropwise. The reaction was stirred for 15 min before it was cooled to –78 °C. Crude **465** (assumed quant., 23.0 mmol) was dissolved in THF (60 mL) and cooled to –78 °C before it was transferred *via* a cannula to the suspension of ylide. The reaction was warmed to rt and stirred for 1 h 30 min. The reaction was quenched with MeOH (180 mL) and KOH (1.55 g, 27.6 mmol) was added. The mixture was stirred for 15 h before the mixture was filtered through a pad of SiO_2 and washed with EtOAc. The filtrate solvent was removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, 90:10 pentane:EtOAc) to afford the title compound **467** (4.42 g, 78% over three steps) as a pale yellow oil.

R_f: 0.52 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ +70.8 (*c* = 1.00, $CHCl_3$; lit.[43] +70.7 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3442, 3078, 3003, 2916, 283, 1713, 1644, 1613, 1586, 1514, 1464, 1441, 1422, 1302, 1248, 1175, 1110, 1067, 1034, 993, 927, 822, 758, 702; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.27–7.23 (2H, m, 2 × C-10H), 6.90–6.85 (2H, m, 2 × C-11H), 5.82 (1H, ddd, *J* = 15.5, 9.6, 4.9 Hz, C-2H), 5.79–5.71 (1H, m, C-6H), 5.29–5.27 (1H, m, C-7$H_A$$H_B$), 5.26–5.24 (1H, m, C-7$H_A$$H_B$), 5.23 (1H, dt, *J* = 17.2, 1.6 Hz, C-1$H_A$$H_B$), 5.06 (1H, dt, *J* = 10.4, 1.4 Hz, C-1$H_A$$H_B$), 4.56 (1H, d, *J* = 11.3 Hz, C-8$H_A$$H_B$), 4.33–4.26 (1H, m, C-3H), 4.30 (1H, d, *J* = 11.2 Hz, C-8$H_A$$H_B$), 4.06–4.00 (1H, m, C-5H), 3.80 (3H, s, OCH_3), 3.48 (1H, s, OH), 1.83 (1H, dt, *J* = 14.5, 9.5 Hz, C-4$H_A$$H_B$), 1.67 (1H, ddd, *J* = 14.5, 3.8, 3.0 Hz, C-4$H_A$$H_B$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 159.4 (C-12), 140.6 (C-2), 138.2 (C-6), 130.0 (C-9), 129.7 (2C, 2 × C-10), 117.9 (C-7), 114.4 (C-1), 114.0 (2C, 2 × C-11), 80.5 (C-5), 72.2 (C-3), 70.0 (C-8), 55.4 (OCH_3), 42.6 (C-4); **HRMS:** (ESI+, *m/z*) $C_{15}H_{20}O_3Na$ (MNa^+) Calculated: 271.13047, Found: 271.13044 (Δ –0.11 ppm); Spectroscopic data were consistent with those in the literature.[43]

Ethyl 2-(4-methylpiperazin-1-yl)-2-oxoacetate (498)*



496 **497** **498**

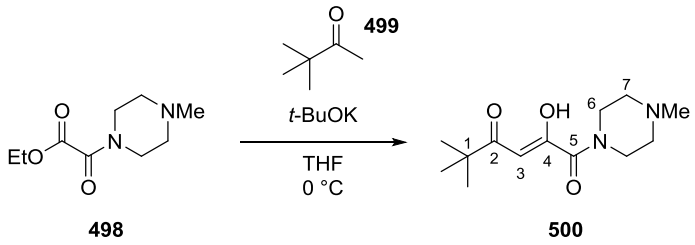
To a solution of *N*-methylpiperazine **497** (5.6 mL, 50 mmol) and Et_3N (6.7 mL, 50 mmol) in DCM (50 mL) at 0 °C was added ethyl oxalyl chloride **496** (5.6 mL, 50 mmol) dropwise. The reaction was warmed to rt and stirred for 17 h before being quenched with sat. aq. $NaHCO_3$ (50 mL). The layers were separated and the aq. layer was extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried

* Compound **498** was prepared according to the procedure detailed by Pagenkopf.[163]

over $MgSO_4$, filtered, and concentrated *in vacuo*. The title compound **498** was obtained as an orange oil (10.01 g, quant.) and was carried into the next step without further purification.

R_f: 0.10 (EtOAc); **IR:** ν_{max} (thin film/cm^{-1}) 2981, 2942, 2795, 1736, 1655, 1447, 1370, 1305, 1284, 1245, 1195, 1172, 1140, 1084, 1072, 1036, 999, 955, 925, 864, 833, 770, 672; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 4.33 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.70–3.60 (2H, m, C-3H_2), 3.50–3.40 (2H, m, C-3H_2), 2.50–2.40 (4H, m, 2 × C-4H_2), 2.32 (3H, s, NCH_3), 1.36 (3H, t, J = 7.1 Hz, OCH_2CH_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 162.9 (C-1), 160.3 (C-2), 62.3 (OCH_2CH_3), 55.0 (C-3), 54.3 (C-3), 46.1 (NCH_3), 41.4 (2C, 2 × C-4), 14.1 (OCH_2CH_3); **LRMS:** (ESI+, *m/z*) $C_9H_{17}N_2O_3$ (MH^+) Calculated: 201.1, Found: 201.2; Spectroscopic data were consistent with those in the literature.[163]

(*Z*)-2-Hydroxy-5,5-dimethyl-1-(4-methylpiperazin-1-yl)hex-2-ene-1,4-dione (500)*

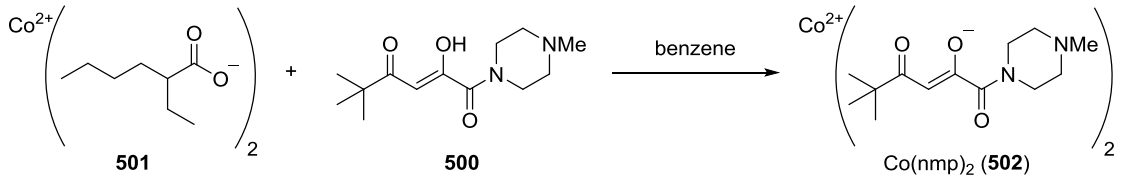


To a solution compound **498** (10 g, 50 mmol) and pinacolone **499** (6.25 mL, 50 mmol) in THF (250 mL) at 0 °C was added potassium *tert*-butoxide (sublimed grade, 11.2 g, 5.00 mmol) in THF (50 mL) *via* a cannula. The reaction mixture was warmed to rt then stirred for 19 h. The reaction was quenched with AcOH (1 M in DCM, 100 mL) and the mixture stirred for 1 h 30 min before being filtered through Celite® and concentrated *in vacuo*. The title compound **500** was obtained as an orange syrup (6.01 g, 47%) and was carried into the next step without further purification.

* Compound **500** was prepared according to the procedure detailed by Pagenkopf.[163]

R_f: 0.04 (95:5 EtOAc:MeOH); **IR:** ν_{max} (thin film/cm^{-1}) 2969, 2940, 2795, 1696, 1644, 1597, 1462, 1462, 1446, 1366, 1292, 1259, 1240, 1220, 1167, 1134, 1071, 1052, 1031, 1001, 906, 836, 815, 777, 724, 672, 653; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 5.98 (1H, s, C-3H), 3.74–3.56 (4H, m, 2 × C-6H_2), 2.57–2.40 (4H, m, 2 × C-7H_2), 2.32 (3H, s, NCH_3), 1.20 (9H, s, C-1(CH_3)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 201.0 (C-2), 185.5 (C-4), 164.0 (C-5), 95.5 (C-3), 55.2 (C-7), 54.5 (C-7), 46.1 (C-6), 46.0 (NCH_3), 41.8 (C-6), 27.3 (3C, C-1(CH_3)$_3$), 26.2 (C-1); **LRMS:** (ESI+, *m/z*) $C_{13}H_{23}N_2O_3$ (MH^+) Calculated: 255.3, Found: 255.2; Spectroscopic data were consistent with those in the literature.[163]

Co(nmp)$_2$ (502)*



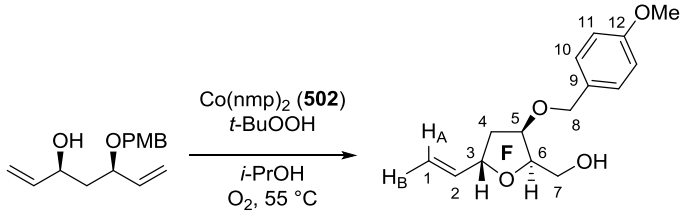
To a solution compound **500** (2.54 g, 10.0 mmol) in benzene (50 mL) at 0 °C was added cobalt(II) 2-ethylhexanoate **501** solution (65 wt% in mineral spirits, 2.65 mL, 5.00 mmol) followed by H_2O (0.36 mL, 20 mmol). The reaction mixture was stirred for 17 h before hexane (200 mL) was added to form a beige precipitate. The solvent was decanted and the solid residue was washed with hexane (2 × 100 mL). The remainder of the solvent was removed by filtration and the solid was dried under high vacuum line. The title compound **502** was obtained as a beige solid (2.67 g, 95%).

IR: ν_{max} (thin film/cm^{-1}) 3420, 2953, 2802, 2361, 2341, 1591, 1519, 1430, 1362, 1295, 1257, 1150, 1035, 1000, 838, 777, 669; **HRMS:** (ESI+, *m/z*) $C_{26}H_{43}O_6N_4Co$ (MNa^+)

* Compound **502** was prepared according to the procedure detailed by Pagenkopf.[163]

Calculated: 566.25091, Found: 566.25108 (Δ +0.30 ppm); Spectroscopic data were consistent with those in the literature.[163]

((2*R*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methanol (469)*



467 **469**

Oxygen was bubbled through a solution of $Co(nmp)_2$ (**502**, 34.2 mg, 60.4 μmol) in *i*-PrOH (1.43 mL) for 5 mins before replacing with stationary atmosphere of oxygen. To this solution was added alcohol **467** (50 mg, 0.20 mmol) in *i*-PrOH (0.48 mL) followed by *tert*-butyl hydroperoxide (5.5 M in decane, 11 μL, 60.4 μmol). The reaction stirred at 55 °C for 15 h and cooled to rt and purging with argon. Methyl iodide (13 μL, 0.20 mmol) was added and the reaction was stirred for a further 1 h 30 min. The solvent was removed *in vacuo* and the residue was redissolved in EtOAc (2 mL) and H_2O (2 mL). The layers were separated and the aq. layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 75:25 pentane:EtOAc) to afford the title compound **469** (26 mg, 48%) as a colourless oil.

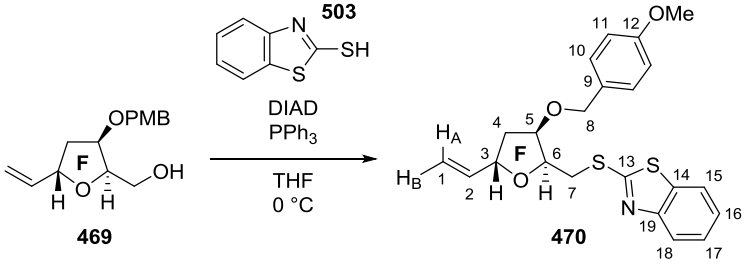
The *trans*-THF ring configuration was confirmed by nOes, including the lack of an nOe between C-3H and C-6H (see **Appendix 6.2.7**).

R_f: 0.26 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ –67.4 (*c* = 1.00, $CHCl_3$; lit.[43] –46.5 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3443, 2933, 1613, 1513, 1464, 1302, 1247, 1174,

* Compound **469** was prepared according to the procedure detailed by Donohoe.[43]

1035, 928, 884, 827; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, *J* = 8.2 Hz, 2 × C-10H), 6.88 (2H, d, *J* = 8.7 Hz, 2 × C-11H), 5.83 (1H, ddd, *J* = 17.2, 10.3, 6.6 Hz, C-2H), 5.28 (1H, dd, *J* = 17.1, 1.7 Hz, C-1H_AH$_B$), 5.13 (1H, d, *J* = 10.0 Hz, C-1H$_A$$H_B$), 4.64 (1H, q, *J* = 7.0 Hz, C-3H), 4.58 (1H, d, *J* = 11.5 Hz, C-8H_AH$_B$), 4.37 (1H, d, *J* = 11.4 Hz, C-8H$_A$$H_B$), 4.31–4.24 (1H, dt, *J* = 6.7, 3.2 Hz, C-5H), 4.13 (1H, q, *J* = 5.0 Hz, C-6H), 3.85 (1H, dd, *J* = 11.9, 5.1 Hz, C-7H_AH$_B$), 3.83–3.77 (1H, m, C-7H$_A$$H_B$), 3.81 (3H, s, OCH_3), 2.38 (1H, s, OH), 2.28 (1H, ddd, *J* = 13.3, 5.9, 1.9 Hz, C-4H_AH$_B$), 1.78 (1H, ddd, *J* = 13.7, 9.1, 5.2 Hz, C-4H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 159.5 (C-12), 138.4 (C-2), 129.8 (C-9), 129.3 (2C, 2 × C-10), 116.2 (C-1), 114.1 (2C, 2 × C-11), 81.2 (C-6), 80.3 (C-5), 79.0 (C-3), 71.4 (C-8), 62.3 (C-7), 55.4 (OCH_3), 38.3 (C-4); **HRMS:** (ESI+, *m/z*) $C_{15}H_{20}O_4Na$ (MNa^+) Calculated: 287.12538, Found: 287.12525 (Δ –0.45 ppm); Spectroscopic data were consistent with those in the literature.[43]

2-((((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)thio)benzo[*d*]thiazole (470)*



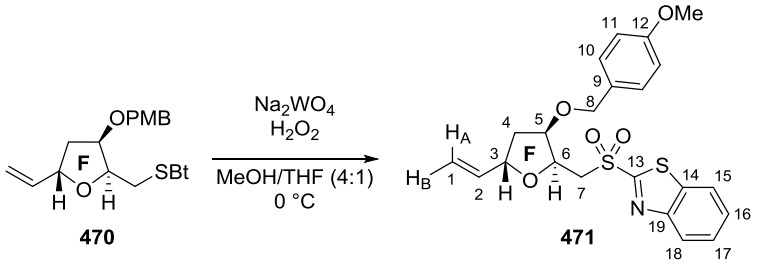
To a solution of alcohol **469** (1.40 g, 5.31 mmol), 2-mercaptobenzothiazole **503** (2.22 g, 13.3 mmol) and triphenylphosphine (3.48 g, 13.3 mmol) in THF (64 mL) at 0 °C was added DIAD (2.6 mL, 13.3 mmol) dropwise. The reaction was warmed to rt for 5 h before the reaction was quenched with 1 M aq. HCl (50 mL) and MeOH (50 mL). The mixture was stirred for 30 min before the MeOH and THF was removed *in vacuo*. The remaining

* Compound **470** was prepared according to the procedure detailed by Donohoe.[43]

solution was diluted with Et_2O (100 mL) and H_2O (50 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 95:5 → 90:10 pentane:EtOAc) to afford the title compound **470** (2.19 g, quant.) as a white solid.

R_f: 0.21 (90:10 pentane:EtOAc); $[\alpha]_D^{25}$ –98.8 (*c* = 1.00, $CHCl_3$; lit.[43] –105 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3073, 2955, 2932, 2903, 2836, 2361, 2342, 1612, 1586, 1513, 1461, 1427, 1320, 1247, 1150, 1036, 1016, 997, 931, 756, 705, 618; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 7.87–7.84 (1H, dt, *J* = 8.0, 0.9 Hz, C-15H), 7.75–7.71 (1H, m, C-18H), 7.46–7.37 (1H, m, C-17H), 7.34–7.22 (4H, m, 2 × C-10H, C-16H), 6.92–6.87 (2H, m, 2 × C-11H), 5.85 (1H, ddd, *J* = 17.1, 10.3, 6.9 Hz, C-2H), 5.29 (1H, dt, *J* = 17.1, 1.3 Hz, C-1H_AH$_B$), 5.13 (1H, dt, *J* = 10.2, 1.3 Hz, C-1H$_A$$H_B$), 4.68 (1H, dt, *J* = 9.7, 6.3 Hz, C-3H), 4.59 (1H, d, *J* = 11.2 Hz, C-8H_AH$_B$), 4.50 (1H, ddd, *J* = 7.8, 6.3, 4.2 Hz, C-6H), 4.46 (1H, d, *J* = 11.2 Hz, C-8H$_A$$H_B$), 4.26 (1H, td, *J* = 4.4, 1.5 Hz, C-5H), 3.81 (3H, s, OCH_3), 3.71 (1H, dd, *J* = 13.4, 6.3 Hz, C-7H_AH$_B$), 3.62 (1H, dd, *J* = 13.3, 7.8 Hz, C-7H$_A$$H_B$), 2.32 (1H, ddd, *J* = 13.2, 5.7, 1.6 Hz, C-4H_AH$_B$), 1.76 (1H, ddd, *J* = 13.3, 9.7, 4.6 Hz, C-4H$_A$$H_B$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 167.2 (C-13), 159.3 (C-12), 153.3 (C-19), 138.3 (C-2), 135.4 (C-14), 130.1 (C-9), 129.4 (2C, 2 × C-10), 126.1 (C-17), 124.2 (C-16), 121.6 (C-15), 121.0 (C-18), 116.3 (C-1), 113.9 (2C, 2 × C-11), 80.4 (C-6), 79.4 (C-5), 79.3 (C-3), 71.5 (C-8), 55.4 (OCH_3), 38.1 (C-4), 32.6 (C-7); **HRMS:** (ESI+, *m/z*) $C_{22}H_{24}O_3N^{32}S_2$ (MH^+) Calculated: 414.11921, Found: 414.11868 (Δ –1.28 ppm); Spectroscopic data were consistent with those in the literature.[43]

2-((((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)sulfonyl)benzo[*d*]thiazole (471)*



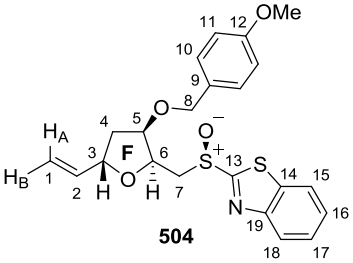
To a solution of compound **470** (1.00 g, 2.42 mmol) and sodium tungstate (71 mg, 0.24 mmol) in MeOH (16 mL) and THF (4 mL) at 0 °C was added H_2O_2 (30 wt% in H_2O, 3 mL, 29 mmol) dropwise. The reaction was warmed to rt for 28 h before the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL). The mixture was extracted with EtOAc (3 × 40 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 80:20 → 70:30 pentane:EtOAc) to afford the title compound **471** (647 mg, 60%) as a white solid.

R_f: 0.34 (70:30 pentane:EtOAc); $[\alpha]_D^{25}$ –6.4 (*c* = 1.00, $CHCl_3$; lit.[43] –11.1 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 2933, 2360, 1722, 1639, 1514, 1471, 1423, 1326, 1248, 1174, 1146, 1124, 1111, 1054, 1035, 991, 930, 851, 823, 762, 730, 690, 609; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.20 (1H, d, *J* = 8.0 Hz, C-15H), 7.98 (1H, d, *J* = 8.0 Hz, C-18H), 7.65–7.54 (2H, m, C-16H, C-17H), 7.22 (2H, d, *J* = 8.3 Hz, 2 × C-10H), 6.87 (2H, d, *J* = 8.5 Hz, 2 × C-11H), 5.64 (1H, ddd, *J* = 16.9, 10.4, 6.4 Hz, C-2H), 5.02 (1H, dd, *J* = 17.2, 1.5 Hz, C-1H_AH$_B$), 4.96 (1H, dd, *J* = 10.4, 1.4 Hz, C-1H$_A$$H_B$), 4.65 (1H, q, *J* = 5.8 Hz, C-6H), 4.50 (1H, d, *J* = 11.2 Hz, C-8H_AH$_B$), 4.41 (1H, dt, *J* = 10.2, 6.4 Hz, C-3H), 4.35 (1H, d, *J* = 11.1 Hz, C-8H$_A$$H_B$), 4.25 (1H, t, *J* = 4.7 Hz, C-5H), 3.96 (1H, dd, *J* = 14.9, 6.7 Hz, C-7H_AH$_B$), 3.90 (1H, dd, *J* = 14.9, 5.5 Hz, C-7H$_A$$H_B$), 3.81 (3H, s,

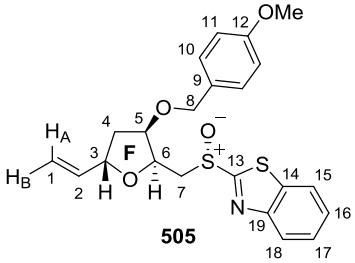
* Compound **471** was prepared according to the procedure detailed by Donohoe.[43]

OCH_3), 2.22 (1H, ddd, J = 13.4, 5.9, 1.6 Hz, C-4H_AH$_B$), 1.70 (1H, ddd, J = 13.8, 9.5, 4.8 Hz, C-4H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.5 (C-13), 159.4 (C-12), 152.7 (C-19), 137.6 (C-2), 137.1 (C-14), 129.7 (C-9), 129.4 (2C, 2 × C-10), 128.0 (C-17), 127.6 (C-16), 125.6 (C-15), 122.4 (C-18), 116.1 (C-1), 114.0 (2C, 2 × C-11), 79.3 (C-5), 78.7 (C-6), 75.6 (C-3), 71.5 (C-8), 55.4 (C-7), 55.2 (OCH_3), 37.9 (C-4); **HRMS:** (ESI+, *m/z*) $C_{22}H_{23}O_5N^{32}S_2Na$ (MNa^+) Calculated: 468.09099, Found: 468.09094 (Δ –0.11 ppm); Spectroscopic data were consistent with those in the literature.[43]

2-((*R*)-(((2*S*,3*R*,5*S*)-3-((4-Methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)sulfinyl)benzo[*d*]thiazole (504) and 2-((*S*)-(((2*S*,3*R*,5*S*)-3-((4-methoxybenzyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)sulfinyl)benzo[*d*]thiazole (505)



504



505

A small amount both **504** and **505** was isolated from the oxidation of sulfide **470** reactions. The stereochemistry of the sulfoxide could not be identified.

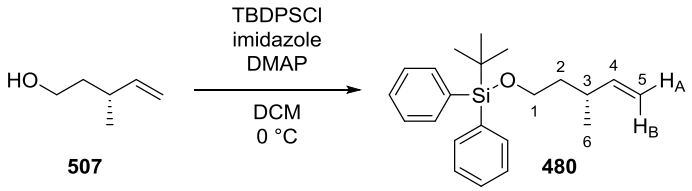
R$_f$: 0.29 (***Diastereoisomer A***), 0.23 (***Diastereoisomer B***) (70:30 pentane:EtOAc); **IR:** ν_{max} (thin film/cm^{-1}) 3064, 3035, 2927, 1612, 1514, 1473, 1426, 1395, 1304, 1248, 1148, 1083, 1060, 1034, 1000, 952, 929, 822, 761, 730, 661; **HRMS:** (ESI+, *m/z*) $C_{22}H_{24}O_4N^{32}S_2$ (MH^+) Calculated: 430.11413, Found: 430.11439 (Δ +0.60 ppm).

***Diasterisomer A:* ^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.09–8.05 (1H, m, C-15H), 8.02–7.96 (1H, m, C-18H), 7.59–7.51 (1H, m, C-16H), 7.48 (1H, m, C-17H), 7.29–7.24 (2H, m, 2 × C-10H), 6.90–6.85 (2H, m, 2 × C-11H), 5.70 (1H, ddd, J = 16.9, 10.3, 6.5 Hz, C-2H), 5.09 (1H, dt, J = 17.1, 1.4 Hz, C-1H_AH$_B$), 5.00 (1H, dt, J = 10.3, 1.3 Hz, C-1H$_A$$H_B$), 4.59

(2H, ddd, J = 7.3, 6.1, 4.4 Hz, C-6H), 4.55 (1H, d, J = 11.3 Hz, C-8H_AH$_B$), 4.54–4.44 (1H, m, C-3H), 4.41 (1H, d, J = 11.3 Hz, C-8H$_A$$H_B$), 4.25 (1H, td, J = 4.7, 1.8 Hz, C-5H), 3.80 (3H, s, OCH_3), 3.72 (1H, dd, J = 13.5, 6.0 Hz, C-7H_AH$_B$), 3.54 (1H, dd, J = 13.5, 7.2 Hz, C-7H$_A$$H_B$), 2.26 (1H, ddd, J = 13.3, 6.0, 1.8 Hz, C-4H_AH$_B$), 1.74 (1H, ddd, J = 13.3, 9.4, 4.9 Hz, C-4H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 177.8 (C-13), 159.4 (C-12), 154.0 (C-19), 137.9 (C-2), 136.3 (C-14), 129.9 (C-9), 129.5 (2C, 2 × C-10), 126.9 (C-16), 126.1 (C-17), 124.1 (C-15), 122.3 (C-18), 116.1 (C-1), 114.0 (2C, 2 × C-11), 79.5 (C-5), 78.6 (C-3), 74.9 (C-6), 71.4 (C-8), 56.3 (C-7), 55.4 (OCH_3), 38.1 (C-4).

Diasterisomer B: **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.07 (1H, ddd, J = 8.2, 1.3, 0.7 Hz, C-15H), 8.01 (1H, ddd, J = 8.0, 1.4, 0.7 Hz, C-18H), 7.56 (1H, ddd, J = 8.3, 7.2, 1.3 Hz, C-16H), 7.49 (1H, ddd, J = 8.4, 7.2, 1.3 Hz, C-17H), 7.21–7.17 (2H, m, 2 × C-10H), 6.84–6.80 (2H, m, 2 × C-11H), 5.86 (1H, ddd, J = 17.0, 10.3, 6.5 Hz, C-2H), 5.31 (1H, dt, J = 17.1, 1.4 Hz, C-1H_AH$_B$), 5.15 (1H, dt, J = 10.3, 1.3 Hz, C-1H$_A$$H_B$), 4.69 (1H, dt, J = 9.3, 6.3 Hz, C-3H), 4.64 (1H, ddd, J = 9.3, 4.5, 3.6 Hz, C-6H), 4.51 (1H, d, J = 11.5 Hz, C-8H_AH$_B$), 4.33 (1H, d, J = 11.5 Hz, C-8H$_A$$H_B$), 4.14 (1H, td, J = 4.6, 1.9 Hz, C-5H), 3.77 (3H, s, OCH_3), 3.56 (1H, dd, J = 13.2, 9.3 Hz, C-7H_AH$_B$), 3.35 (1H, dd, J = 13.3, 3.6 Hz, C-7H$_A$$H_B$), 2.31 (1H, ddd, J = 13.3, 6.0, 1.9 Hz, C-4H_AH$_B$), 1.82 (1H, ddd, J = 13.3, 9.3, 4.8 Hz, C-4H$_A$$H_B$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 178.1 (C-13), 159.5 (C-12), 154.0 (C-19), 138.1 (C-2), 136.1 (C-14), 129.8 (C-9), 129.4 (2C, 2 × C-10), 127.0 (C-16), 126.3 (C-17), 124.2 (C-15), 122.4 (C-18), 116.3 (C-1), 114.0 (2C, 2 × C-11), 79.7 (C-5), 79.1 (C-3), 74.9 (C-6), 71.4 (C-8), 59.1 (C-7), 55.4 (OCH_3), 38.4 (C-4).

(*R*)-*tert*-Butyl((3-methylpent-4-en-1-yl)oxy)diphenylsilane (480)*



507 **480**

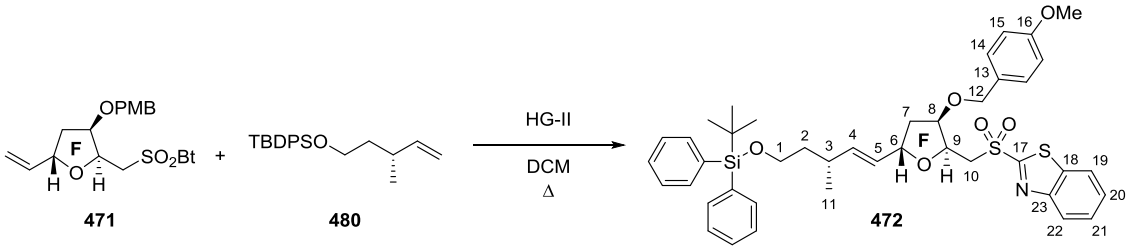
To a solution of compound **507** (150 mg, 1.50 mmol), imidazole (112 mg, 1.65 mmol) and DMAP (18 mg, 0.15 mmol) in DCM (16 mL) at 0 °C was added *tert*-butyl(chloro)diphenylsilane (0.43 mL, 1.65 mmol) dropwise. The reaction was warmed to rt for 24 h before the reaction was quenched with sat. aq. NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 98:2 pentane:DCM) to afford the title compound **480** (322 mg, 63%) as a colourless oil.

R_f: 0.39 (90:10 pentane:DCM); $[\alpha]_D^{25}$ –2.2 (*c* = 1.00, $CHCl_3$; lit.[43] –4.4 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3072, 3051, 2959, 2930, 2858, 1640, 1590, 1473, 1428, 1389, 1361, 1261, 1188, 1110, 997, 938, 912, 823, 788, 737, 701, 689, 614; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 7.72–7.62 (4H, m, ArH), 7.47–7.33 (6H, m, ArH), 5.66 (1H, ddd, *J* = 17.5, 10.3, 7.5 Hz, C-4H), 4.94 (1H, dt, *J* = 17.2, 1.5 Hz, C-5H_AH_B), 4.89 (1H, dt, *J* = 10.3, 1.2 Hz, C-5H_AH_B), 3.67 (2H, t, *J* = 6.6 Hz, C-1H_2), 2.35 (1H, dq, *J* = 13.9, 6.9 Hz, C-3H), 1.55 (2H, t, *J* = 6.7 Hz, C-2H_2), 1.05 (9H, s, $C(CH_3)_3$), 0.97 (3H, d, *J* = 6.7 Hz, C-6H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 144.5 (C-4), 135.7 (4C, Ar), 134.2 (2C, 2 × quaternary Ar), 129.6 (2C, Ar), 127.7 (4C, Ar), 112.8 (C-5), 62.1 (C-1), 39.4 (C-2), 34.3 (C-3), 27.0 (3C, $C(CH_3)_3$), 20.3 ($C(CH_3)_3$), 19.4 (C-6); **HRMS:** (ESI+, *m/z*)

* Compound **480** was prepared according to the procedure detailed by Donohoe.[43]

$C_{22}H_{31}O^{28}SiNa$ (MNa^+) Calculated: 339.21387, Found: 339.21385 (Δ –0.06 ppm); Spectroscopic data were consistent with those in the literature.[43]

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 (472)*



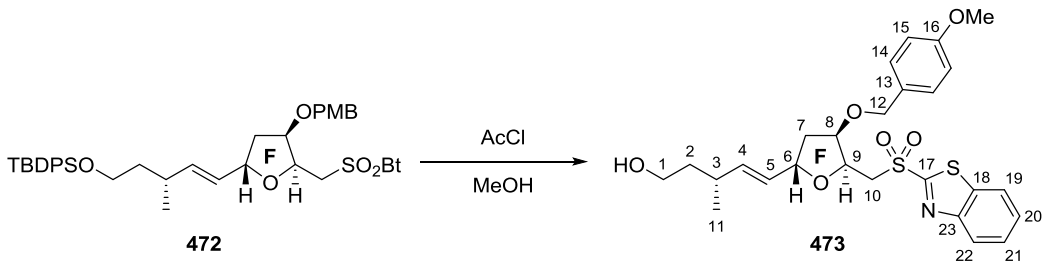
A 3-necked flask equipped with a condenser attached to a bubbler, and a neck attached to the N_2 line, was charged with a solution of compound **471** (920 mg, 2.07 mmol) and compound **480** (2.80 g, 8.26 mmol) in degassed DCM (N_2 was bubbled through for 5 min, 207 mL). Hoveyda–Grubbs second generation catalyst (129 mg, 0.206 mmol) was added and the neck was stoppered. The reaction was heated to 40 °C with a slow stream of N_2 flowing over the reaction and up through the condenser out of the bubbler for 22 h 30 min. The reaction was cooled to rt and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 95:5 → 90:10 → 85:15 → 70:30 pentane:EtOAc) to afford the title compound **472** (1.25 g, 80%) as a green oil (traces of catalyst present).

R_f: 0.46 (70:30 pentane:EtOAc); $[\alpha]_D^{25}$ –8.7 (*c* = 1.00, $CHCl_3$; lit.[43] –10.7 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3070, 2957, 2930, 2857, 2362, 1613, 1588, 1514, 1472, 1427, 1389, 1360, 1329, 1248, 1174, 1146, 1110, 1088, 1038, 1009, 986, 969, 940, 898, 852, 823, 762, 741, 704, 689, 614; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.19 (1H, dt, *J* = 8.3, 0.9 Hz, C-19H), 7.90 (1H, dt, *J* = 8.1, 0.9 Hz, C-22H), 7.70–7.63 (4H, m, ArH),

* Compound **472** was prepared according to the procedure detailed by Donohoe.[43]

7.58 (2H, ddd, J = 8.4, 7.2, 1.3 Hz, C-20H), 7.51 (1H, ddd, J = 8.3, 7.2, 1.3 Hz, C-21H), 7.46–7.35 (6H, m, ArH), 7.27–7.21 (2H, m, 2 × C-14H), 6.91–6.86 (2H, m, 2 × C-15H), 5.22 (1H, dd, J = 15.4, 6.7 Hz, C-4H), 5.17 (1H, dd, J = 15.4, 6.4 Hz, C-5H), 4.65 (1H, ddd, J = 6.9, 5.6, 4.5 Hz, C-9H), 4.50 (1H, d, J = 11.2 Hz, C-12H_AH$_B$), 4.35 (1H, d, J = 11.2 Hz, C-12H$_A$$H_B$), 4.30 (1H, dt, J = 9.6, 6.0 Hz, C-6H), 4.24 (1H, td, J = 4.9, 1.6 Hz, C-8H), 4.01 (1H, dd, J = 14.9, 7.0 Hz, C-10H_AH$_B$), 3.88 (1H, dd, J = 14.9, 5.6 Hz, C-10H$_A$$H_B$), 3.82 (3H, s, OCH_3), 3.61–3.50 (2H, m, C-1H_2), 2.22 (1H, quint, J = 6.8 Hz, C-3H), 2.14 (1H, ddd, J = 13.4, 5.8, 1.7 Hz, C-7H_AH$_B$), 1.61 (1H, ddd, J = 13.3, 9.7, 5.0 Hz, C-7H$_A$$H_B$), 1.39 (2H, q, J = 6.8 Hz, C-2H_2), 1.04 (9H, s, C(CH_3)$_3$), 0.84 (3H, d, J = 6.8 Hz, C-11H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.7 (C-17), 159.4 (C-16), 152.7 (C-23), 138.9 (C-4), 137.0 (C-18), 135.7 (4C, Ar), 134.1 (2C, 2 × quaternary Ar), 129.8 (C-13), 129.7 (2C, Ar), 129.4 (2C, 2 × C-14), 127.9 (C-21), 127.7 (4C, Ar), 127.5 (2C, C-5, C-20), 125.5 (C-19), 122.4 (C-22), 114.0 (2C, 2 × C-15), 79.4 (C-8), 78.5 (C-6), 75.5 (C-9), 71.5 (C-12), 61.8 (C-1), 55.4 (OCH_3), 55.0 (C-10), 39.2 (C-2), 38.2 (C-7), 32.4 (C-3), 27.0 (3C, C(CH_3)$_3$), 20.0 (C-3), 19.3 (C(CH_3)$_3$); **HRMS:** (ESI+, *m/z*) $C_{42}H_{50}O_6N^{32}S_2{}^{28}Si$ (MH^+) Calculated: 756.28433, Found: 756.28399 (Δ –0.45 ppm); Spectroscopic data were consistent with those in the literature.[43]

(*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 (473)*



472 **473**

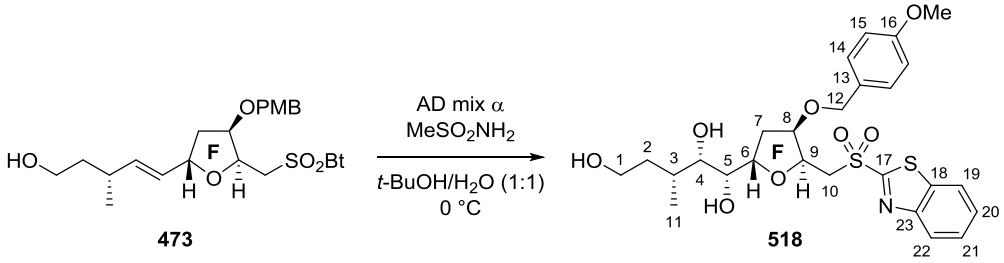
* Compound **473** was prepared according to the procedure detailed by Donohoe.[43]

To a flask containing compound **472** (1.20 g, 1.59 mmol) was added 0.1 M AcCl in MeOH (2.8 mL). The reaction was stirred for 2 h before the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and diluted with EtOAc (10 mL). The layers were separated and the aq. layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 50:50 pentane:EtOAc) to afford the title compound **473** (634 mg, 77%) as a colourless oil.

R_f: 0.23 (50:50 pentane:EtOAc); $[\alpha]_D^{25}$ –14.1 (*c* = 1.00, $CHCl_3$; lit.[43] –16.9 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3426, 2929, 2875, 2363, 2341, 1613, 1586, 1514, 1472, 1423, 1325, 1248, 1174, 1146, 1039, 972, 852, 822, 764, 730, 690, 669, 647, 624, 610; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.24–8.16 (1H, m, C-19H), 8.03–7.95 (1H, m, C-22H), 7.62 (1H, td, *J* = 8.3, 7.7, 1.5 Hz, C-20H), 7.57 (1H, td, *J* = 7.7, 7.2, 1.4 Hz, C-21H), 7.25–7.19 (2H, m, 2 × C-14H), 6.90–6.84 (2H, m, 2 × C-15H), 5.30–5.18 (2H, m, C-4H, C-5H), 4.64 (1H, dt, *J* = 7.1, 5.1 Hz, C-9H), 4.49 (1H, d, *J* = 11.2 Hz, C-12$H_A$$H_B$), 4.39–4.29 (1H, m, C-6H), 4.34 (1H, d, *J* = 11.0 Hz, C-12$H_A$$H_B$), 4.24 (1H, td, *J* = 4.8, 1.6 Hz, C-8H), 3.98 (1H, dd, *J* = 15.0, 7.1 Hz, C-10$H_A$$H_B$), 3.84 (1H, dd, *J* = 14.9, 5.4 Hz, C-10$H_A$$H_B$), 3.81 (3H, s, OCH_3), 3.49 (2H, tt, *J* = 10.7, 5.5 Hz, C-1H_2), 2.23–2.11 (2H, m, C-3H, C-7$H_A$$H_B$), 1.72 (1H, s, OH), 1.66 (1H, ddd, *J* = 13.3, 9.7, 4.9 Hz, C-7$H_A$$H_B$), 1.50–1.40 (1H, m, C-2$H_A$$H_B$), 1.40–1.29 (1H, m, C-2$H_A$$H_B$), 0.88 (3H, d, *J* = 6.7 Hz, C-11H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.7 (C-17), 159.4 (C-23), 152.8 (C-18), 138.9 (C-4), 137.1 (C-16), 129.7 (C-13), 129.4 (2C, 2 × C-14), 128.1 (C-5), 127.9 (C-21), 127.6 (C-20), 125.5 (C-19), 122.4 (C-22), 114.0 (2C, 2 × C-15), 79.4 (C-8), 78.5 (C-6), 75.5 (C-9), 71.5 (C-12), 61.0 (C-1), 55.4 (OCH_3), 55.1 (C-10), 39.3 (C-2), 38.2 (C-7), 33.2 (C-3), 20.5 (C-11); **HRMS:** (ESI+, *m/z*) $C_{26}H_{32}O_6N^{32}S_2$ (MH^+) Calculated: 518.16656,

Found: 518.16657 (Δ +0.02 ppm); Spectroscopic data were consistent with those in the literature.[43]

(1*R*,2*S*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methylpentane-1,2,5-triol (518)*



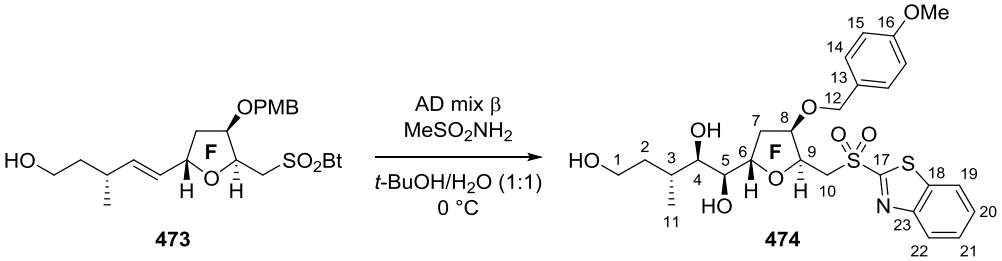
To a suspension of compound **473** (41 mg, 80 μmol), $K_3Fe(CN)_6$ (79 mg, 0.24 mmol), K_2CO_3 (33 mg, 0.24 mmol), $(DHQ)_2PHAL$ (5.0 mg, 6.4 μmol) in *t*-BuOH (0.5 mL) at 0 °C was added $K_2OsO_2(OH)_4$ (1.5 mg, 4.0 μmol) in H_2O (0.5 mL). The reaction was warmed to rt and stirred 3 h before the reaction was quenched with sat. aq. Na_2SO_3 (1 mL) and stirred for a further 15 min. The mixture was extracted with EtOAc (5 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, EtOAc) to afford the title compound **518** (31 mg, 70%, >95:5 dr) as a colourless oil (foams under high vacuum).

R_f: 0.20 (EtOAc); $[\alpha]_D^{25}$ –1.1 (*c* = 1.00, $CHCl_3$; lit.[161] –2.6 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3382, 2933, 2362, 2342, 1613, 1586, 1555, 1514, 1471, 1422, 1383, 1323, 1248, 1174, 1147, 1056, 852, 821, 764, 730, 691, 608; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.23–8.18 (1H, m, C-19H), 8.03–7.98 (1H, m, C-22H), 7.62 (1H, ddd, *J* = 8.2, 7.2, 1.5 Hz, C-20H), 7.58 (1H, ddd, *J* = 8.5, 7.2, 1.5 Hz, C-21H), 7.23–7.17 (2H, m, 2 × C-14H), 6.89–6.83 (2H, m, 2 × C-15H), 4.62 (1H, dt, *J* = 8.2, 4.0 Hz, C-9H), 4.50 (1H, d, *J* = 11.3 Hz, C-12H_AH$_B$), 4.31 (1H, d, *J* = 11.3 Hz, C-12H$_A$$H_B$), 4.19 (1H, t, *J* = 3.8 Hz,

* Compound **518** was prepared according to the procedure detailed by Roushanbakhti.[161]

C-8H), 4.02 (1H, dt, J = 10.3, 5.6 Hz, C-6H), 3.94 (1H, dd, J = 14.9, 8.3 Hz, C-10H_AH$_B$), 3.79 (3H, s, OCH$_3$), 3.76 (1H, dd, J = 15.0, 3.9 Hz, C-10H$_A$$H_B$), 3.72–3.64 (1H, m, C-1$H_AH_B$), 3.62–3.53 (1H, m, C-1H$_A$$H_B$), 3.48 (1H, d, J = 4.8 Hz, C-5H), 3.20 (1H, t, J = 4.2 Hz, C-4H), 2.96 (1H, s, OH), 2.53 (1H, s, OH), 2.10 (1H, ddd, J = 13.5, 6.0, 1.7 Hz, C-7H_AH$_B$), 1.93 (1H, ddd, J = 15.1, 10.2, 5.5 Hz, C-7H$_A$$H_B$), 1.91 (1H, s, OH), 1.70–1.55 (2H, m, C-2H_AH$_B$, C-3H), 1.45–1.32 (1H, m, C-2H$_A$$H_B$), 0.78 (3H, d, J = 6.6 Hz, C-11H$_3$); **^{13}C NMR:** δ_C (101 MHz, CDCl$_3$) 166.5 (C-17), 159.5 (C-23), 152.7 (C-18), 137.0 (C-16), 129.7 (C-13), 129.5 (2C, 2 × C-14), 128.2 (C-21), 127.8 (C-20), 125.5 (C-19), 122.5 (C-22), 114.0 (2C, 2 × C-15H), 79.6 (C-8), 79.2 (C-6), 75.9 (C-9), 73.6 (C-4), 72.3 (C-5), 71.3 (C-12), 60.4 (C-1), 55.7 (C-10), 55.4 (OCH$_3$), 36.4 (C-2), 33.1 (C-3), 32.1 (C-7), 14.5 (C-11); **HRMS:** (ESI+, *m/z*) $C_{26}H_{34}O_8N^{32}S_2$ (MH^+) Calculated: 552.17203, Found: 552.17187 (Δ –0.29 ppm); Spectroscopic data were consistent with those in the literature.[161]

(1*S*,2*R*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)-3-methylpentane-1,2,5-triol (474)[*43]



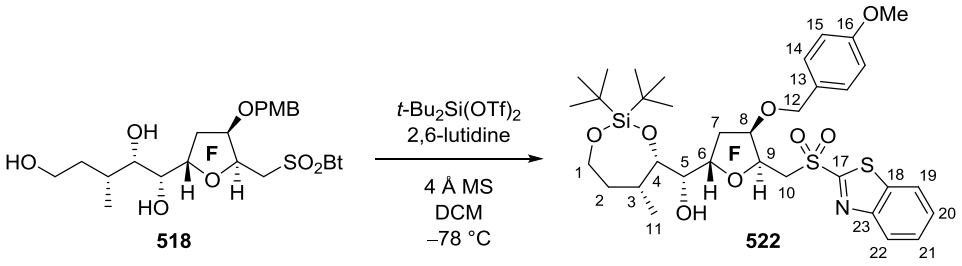
To a suspension of compound **473** (588 mg, 1.14 mmol), K$_3$Fe(CN)$_6$ (1.12 g, 3.41 mmol), K$_2$CO$_3$ (471 mg, 3.41 mmol), (DHQD)$_2$PHAL (71 mg, 91 μmol) in *t*-BuOH (6.8 mL) at 0 °C was added K$_2$OsO$_2$(OH)$_4$ (21 mg, 56.8 μmol) in H$_2$O (6.8 mL). The reaction was warmed to rt and stirred 14 h 30 min before the reaction was quenched with sat. aq.

[*] Compound **474** was prepared according to the procedure detailed by Donohoe.[43]

Na_2SO_3 (15 mL) and stirred for a further 15 min. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, EtOAc) to afford the title compound **474** (463 mg, 74%, >95:5 dr) as a colourless oil (foams under high vacuum).

R_f: 0.24 (EtOAc); $[\alpha]_D^{25}$ +3.1 (*c* = 1.00, $CHCl_3$; lit.[43] +1.4 (*c* = 1.00, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3423, 3067, 2932, 2359, 2333, 1613, 1586, 1555, 1514, 1471, 1423, 1388, 1324, 1248, 1175, 1146, 1112, 1062, 1034, 912, 851, 822, 763, 730, 692, 666, 620, 611; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.27–8.20 (1H, m, C-19H), 8.05–7.99 (1H, m, C-22H), 7.67–7.62 (1H, m, C-20H), 7.62–7.57 (1H, m, C-21H), 7.23–7.18 (2H, m, 2 × C-14H), 6.89–6.85 (2H, m, 2 × C-15H), 4.63 (1H, dt, *J* = 8.7, 3.7 Hz, C-9H), 4.52 (1H, d, *J* = 11.3 Hz, C-12H_AH$_B$), 4.34 (1H, d, *J* = 11.3 Hz, C-12H$_A$$H_B$), 4.22–4.11 (2H, m, C-6H, C-8H), 3.93 (1H, dd, *J* = 15.1, 8.8 Hz, C-10H_AH$_B$), 3.81 (3H, s, OCH_3), 3.73 (1H, dd, *J* = 15.1, 3.4 Hz, C-10H$_A$$H_B$), 3.72–3.65 (1H, m, C-1$H_AH_B$), 3.63–3.54 (1H, m, C-1H$_A$$H_B$), 3.42 (1H, d, *J* = 6.8 Hz, C-5H), 3.16 (1H, d, *J* = 7.8 Hz, C-4H), 2.71 (1H, d, *J* = 8.5 Hz, OH), 2.60 (1H, s, OH), 2.17–2.18 (2H, m, C-7H_2), 1.83–1.73 (1H, m, C-3H), 1.73–1.61 (2H, m, C-2H_AH$_B$, OH), 1.55–1.45 (1H, m, C-2H$_A$$H_B$), 0.84 (3H, d, *J* = 6.8 Hz, C-11H_3); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.4 (C-17), 159.6 (C-23), 152.8 (C-18), 137.0 (C-16), 129.5 (3C, 2 × C-14, C-13), 128.3 (C-21), 127.9 (C-20), 125.6 (C-19), 122.6 (C-22), 114.1 (2C, 2 × C-15), 82.1 (C-6), 79.3 (C-8), 77.3 (C-4), 76.8 (C-9), 71.4 (C-12), 70.8 (C-5), 61.0 (C-1), 55.8 (C-10), 55.4 (OCH_3), 36.5 (C-2), 33.7 (C-3), 33.0 (C-7), 17.2 (C-11); **HRMS:** (ESI+, *m/z*) $C_{26}H_{33}O_8N^{32}S_2Na$ (MNa^+) Calculated: 574.15398, Found: 574.15388 (Δ –0.17 ppm); Spectroscopic data were consistent with those in the literature.[43]

(*S*)-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*S*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanol (522)

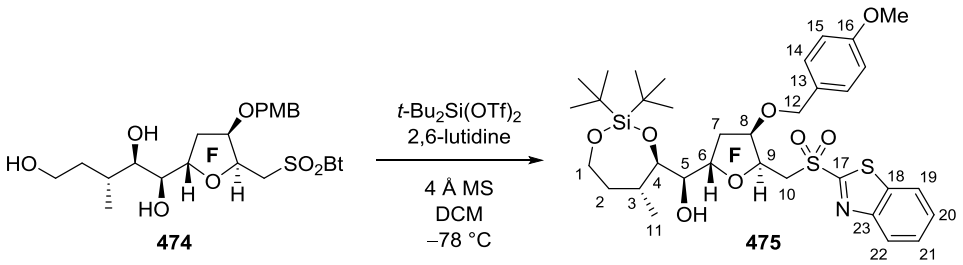


Compound **518** (76 mg, 0.14 mmol) was dried azeotropically with benzene (3 × 2 mL). To a flame-dried flask containing activated 4 Å powder molecular sieves was added dried compound **518** (76 mg, 0.14 mmol) in DCM (14 mL) followed by 2,6-lutidine (80 µL, 0.69 mmol). The mixture was cooled to –78 °C and 0.1 M *t*-$Bu_2Si(OTf)_2$ (in DCM, 0.15 mL, 0.15 mmol) was added dropwise. The reaction was warmed to rt and stirred 23 h before the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 6:1 pentane:EtOAc) to afford the title compound **522** (58 mg, 61%) as a colourless oil (foams under high vacuum).

R_f: 0.34 (75:25 pentane:EtOAc); $[\alpha]_D^{25}$ +6.5 (*c* = 1.00, $CHCl_3$); **IR:** ν_{max} (thin film/cm^{-1}) 3525, 2965, 2934, 2892, 2859, 1716, 1613, 1587, 1555, 1514, 1473, 1424, 1388, 1329, 1283, 1248, 1174, 1148, 1086, 1004, 976, 934, 906, 887, 852, 827, 791, 762, 731, 708, 691, 648, 610; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 8.21–8.17 (1H, m, C-19H), 8.01–7.96 (1H, m, C-22H), 7.62 (1H, td, *J* = 8.3, 7.8, 1.5 Hz, C-20H), 7.58 (1H, td, *J* = 7.7, 1.4 Hz, C-21H), 7.24–7.16 (2H, m, 2 × C-14H), 6.90–6.82 (2H, m, 2 × C-15H), 4.63–4.58 (1H, m, C-9H), 4.51 (1H, d, *J* = 11.3 Hz, C-12$H_A$$H_B$), 4.32 (1H, d, *J* = 11.2 Hz, C-12$H_A$$H_B$), 4.22 (1H, td, *J* = 4.5, 1.7 Hz, C-8H), 4.00 (1H, t, *J* = 11.7 Hz, C-1$H_A$$H_B$), 3.98–3.91 (1H, m, C-6H), 3.92–3.83 (3H, m, C-4H, C-10H_2), 3.82–3.75 (1H, m, C-1$H_A$$H_B$), 3.80 (3H, s,

OCH_3), 3.33–3.28 (1H, m, C-5H), 2.71 (1H, d, J = 5.4 Hz, OH), 2.22 (1H, ddd, J = 13.6, 6.3, 1.7 Hz, C-7H_AH$_B$), 1.98 (1H, ddd, J = 13.6, 8.8, 4.8 Hz, C-7H$_A$$H_B$), 1.80 (1H, dt, J = 7.5, 2.5 Hz, C-3H), 1.64 (1H, td, J = 11.7, 2.3 Hz, C-2H_AH$_B$), 1.50 (1H, dt, J = 14.9, 4.6 Hz, C-2H$_A$$H_B$), 1.02 (9H, s, Si(C(C$H_3$)$_3$)(C(CH$_3$)$_3$)), 0.92 (9H, s, Si(C(CH$_3$)$_3$)(C(C$H_3$)$_3$)), 0.87 (3H, d, J = 7.1 Hz, C-11H$_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 166.4 (C-17), 159.4 (C-23), 152.8 (C-18), 137.0 (C-16), 129.8 (C-13), 129.3 (2C, 2 × C-14), 128.0 (C-21), 127.7 (C-20), 125.6 (C-19), 122.4 (C-22), 113.9 (2C, 2 × C-15H), 79.3 (C-8), 78.7 (C-6), 77.4 (C-1), 76.0 (C-9), 75.0 (C-5), 71.1 (C-12), 60.7 (C-1), 55.5 (C-10), 55.4 (OCH_3), 39.6 (C-2), 36.2 (C-3), 33.7 (C-7), 28.4 (3C, Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 28.3 (3C, Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 22.0 (Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 21.5 (Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 11.1 (C-11); **HRMS:** (ESI+, *m/z*) $C_{34}H_{50}O_8N^{32}S_2{}^{28}Si$ (MH^+) Calculated: 692.27416, Found: 692.27394 (Δ –0.32 ppm).

(*R*)-((2*S*,4*R*,5*S*)-5-((Benzo[*d*]thiazol-2-ylsulfonyl)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 (475)*



Compound **474** (463 mg, 0.84 mmol) was dried azeotropically with PhMe (3 × 3 mL). To a flame-dried flask containing activated 4 Å powder molecular sieves was added dried compound **475** (463 mg, 0.84 mmol) in DCM (84 mL) followed by 2,6-lutidine (0.49 mL, 4.20 mmol). The mixture was cooled to –78 °C and 0.1 M t-Bu$_2$Si(OTf)$_2$ (in DCM, 10 mL, 1.0 mmol) was added dropwise. The reaction was warmed to rt and stirred

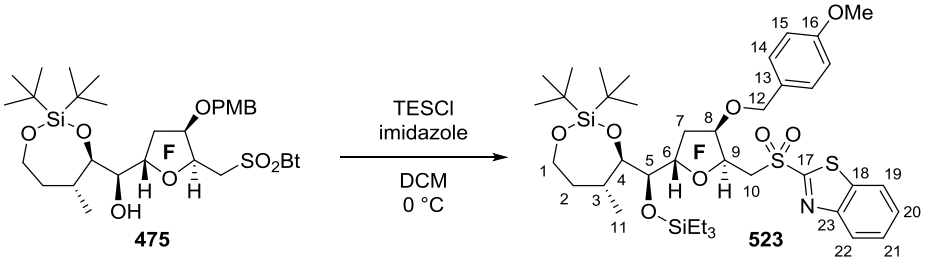
* Compound **475** was prepared according to the procedure detailed by Donohoe.[43]

17 h before the reaction was filtered through Celite®. The filtrate was quenched with sat. aq. $NaHCO_3$ (100 mL) and the layers were separated. The aq. layer was extracted with DCM (3 × 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 6:1 →3:1 pentane:EtOAc) to afford the title compound **475** (359 mg, 62%) as a white solid (foams under high vacuum).

R_f: 0.39 (75:25 pentane:EtOAc); **m.p.:** 137–140 °C; $[\alpha]_D^{25}$ –21.1 (*c* = 1.00, $CHCl_3$; lit.[43] –4.5 (*c* = 0.70, $CHCl_3$)); **IR:** ν_{max} (thin film/cm^{-1}) 3560, 2969, 2932, 2888, 2857, 1613, 1587, 1515, 1473, 1425, 1385, 1363, 1330, 1249, 1147, 1116, 969, 941, 916, 885, 827, 762, 731, 690, 649, 614; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 8.22–8.18 (1H, m, C-19H), 8.01–7.98 (1H, m, C-22H), 7.62 (1H, ddd, *J* = 8.2, 7.2, 1.4 Hz, C-20H), 7.58 (1H, ddd, *J* = 8.4, 7.2, 1.4 Hz, C-21H), 7.23–7.18 (2H, m, 2 × C-14H), 6.88–6.84 (2H, m, 2 × C-15H), 4.60 (1H, ddd, *J* = 6.7, 5.6, 3.9 Hz, C-9H), 4.49 (1H, d, *J* = 11.0 Hz, C-12$H_A$$H_B$), 4.34 (1H, d, *J* = 11.0 Hz, C-12$H_A$$H_B$), 4.29 (1H, t, *J* = 3.9 Hz, C-8H), 4.23 (1H, ddd, *J* = 9.6, 7.2, 5.9 Hz, C-6H), 4.00 (1H, dd, *J* = 14.8, 6.8 Hz, C-10$H_A$$H_B$), 4.00–3.93 (1H, m, C-1$H_A$$H_B$), 3.95 (2H, dd, *J* = 14.9, 5.7 Hz, C-10$H_A$$H_B$), 3.91–3.85 (1H, m, C-1$H_A$$H_B$), 3.81 (3H, s, OCH_3), 3.53 (1H, dd, *J* = 9.3, 1.3 Hz, C-4H), 3.39 (1H, td, *J* = 7.3, 1.3 Hz, C-5H), 2.26–2.21 (1H, m, C-7$H_A$$H_B$), 2.21 (1H, d, *J* = 7.5 Hz, OH), 1.94–1.84 (1H, m, C-3H), 1.74–1.65 (2H, m, C-2$H_A$$H_B$, C-7$H_A$$H_B$), 1.64–1.54 (1H, m, C-7$H_A$$H_B$), 0.98 (9H, s, Si(C($CH_3$)$_3$)(C($CH_3$)$_3$)), 0.95 (9H, s, Si(C($CH_3$)$_3$)(C($CH_3$)$_3$)), 0.88 (3H, d, *J* = 6.9 Hz, C-11H_3); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 166.3 (C-17), 159.4 (C-23), 152.8 (C-18), 137.0 (C-16), 129.6 (C-13), 129.5 (2C, 2 × C-14), 128.1 (C-21), 127.7 (C-20), 125.7 (C-19), 122.4 (C-22), 114.0 (2C, 2 × C-15), 80.7 (C-4), 80.0 (C-6), 79.1 (C-8), 75.8 (C-9), 74.9 (C-5), 71.5 (C-12), 65.9 (C-1), 55.4 (OCH_3), 54.7 (C-10), 42.2 (C-2), 38.7 (C-3),

34.5 (C-7), 28.2 (3C, Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 28.1 (3C, Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 21.8 (Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 21.6 (Si(C(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 19.4 (C-11); **HRMS:** (ESI+, *m/z*) $C_{34}H_{50}O_8N^{32}S_2{}^{28}Si$ (MH^+) Calculated: 692.27416, Found: 692.27408 (Δ –0.12 ppm); Spectroscopic data were consistent with those in the literature.[43]

2-((((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)((triethylsilyl)oxy)methyl)-3-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[*d*]thiazole (523)

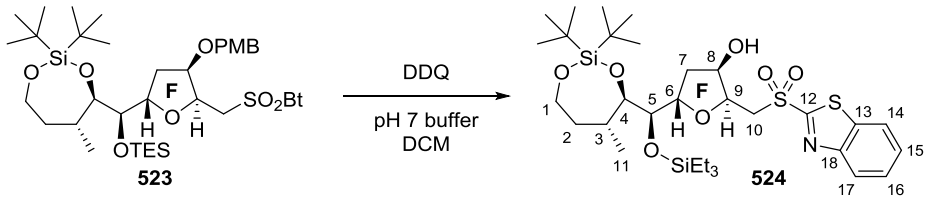


To a solution of compound **475** (334 mg, 0.483 mmol) and imidazole (328 mg, 4.82 mmol) in DCM (5 mL) at 0 °C was added chlorotriethylsilane (0.40 mL, 2.41 mmol) dropwise. The reaction was warmed to rt for 24 h before the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with DCM (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 100:0 → 90:10 pentane:EtOAc) to afford the title compound **523** (389 mg, quant.) as a colourless oil.

R_f: 0.27 (90:10 pentane:EtOAc); $[\alpha]_D^{25}$ –33.3 (*c* = 1.00, $CHCl_3$;); **IR:** ν_{max} (thin film/cm^{-1}) 2933, 2875, 2857, 1613, 1587, 1515, 1473, 1425, 1385, 1333, 1248, 1171, 1148, 1123, 1098, 1057, 1027, 1012, 985, 921, 886, 863, 827, 762, 729, 692, 648, 623; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.22–8.18 (1H, m, C-19H), 8.02–7.97 (1H, m, C-22H), 7.66–7.61 (1H, m, C-20H), 7.61–7.56 (1H, m, C-22H), 7.23–7.18 (2H, m, 2 × C-14H), 6.87–6.82 (2H, m, 2 × C-15H), 4.53 (1H, dt, *J* = 7.8, 3.8 Hz, C-9H), 4.49 (1H, d, *J* = 10.8 Hz, C-12H_AH$_B$), 4.40–4.32 (1H, m, C-6H), 4.33 (1H, d, *J* = 10.7 Hz, C-12H$_A$$H_B$), 4.26 (1H, t, *J*

= 4.0 Hz, C-8H), 4.20 (1H, dd, *J* = 14.7, 8.1 Hz, C-10H_AH$_B$), 3.96 (1H, dt, *J* = 11.7, 3.5 Hz, C-1H_AH$_B$), 3.90–3.80 (2H, m, C-1H$_A$$H_B$, C-10H$_A$$H_B$), 3.80 (3H, s, OCH_3), 3.49–3.43 (2H, m, C-4H, C-5H), 2.30 (1H, ddd, *J* = 13.2, 5.9, 1.1 Hz, C-7H_AH$_B$), 1.99–1.83 (1H, m, C-3H), 1.69–1.58 (3H, m, C-2H$_2$, C-7H$_A$$H_B$), 0.98 (18H, 2 × s, Si(C(CH_3)$_3$)(C(CH_3)$_3$)), 0.89–0.82 (12H, m, C-11H$_3$, Si($CH_2C$$H_3$)$_3$), 0.63–0.43 (6H, m, Si(C$H_2$$CH_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.3 (C-17), 159.4 (C-23), 152.8 (C-18), 136.9 (C-16), 129.8 (C-13), 129.6 (2C, 2 × C-14), 128.1 (C-21), 127.8 (C-20), 125.6 (C-19), 122.4 (C-22), 113.9 (2C, 2 × C-15), 82.0 (C-4), 80.1 (C-6), 79.1 (C-8), 77.5 (C-5), 75.2 (C-9), 71.5 (C-12), 66.3 (C-1), 55.4 (OCH_3), 54.3 (C-10), 42.2 (C-2), 38.5 (C-3), 34.3 (C-7), 28.0 (3C, Si(C(CH$_3$)$_3$)(C(CH_3)$_3$)), 27.9 (3C, Si(C(CH_3)$_3$)(C(CH$_3$)$_3$)), 22.1 (Si(C(CH$_3$)$_3$)(C(CH_3)$_3$)), 21.6 (Si(C(CH_3)$_3$)(C(CH$_3$)$_3$)), 19.5 (C-11), 7.2 (3C, Si($CH_2$$CH_3$)$_3$), 5.6 (3C, Si($CH_2CH_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{40}H_{63}O_8N^{32}S_2{}^{28}Si_2$ (MH^+) Calculated: 828.34258, Found: 828.34208 (Δ –0.60 ppm).

(2*S*,3*R*,5*S*)-2-((Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-5-((*R*)-((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)((triethylsilyl)oxy)methyl)tetrahydrofuran-3-ol (524)

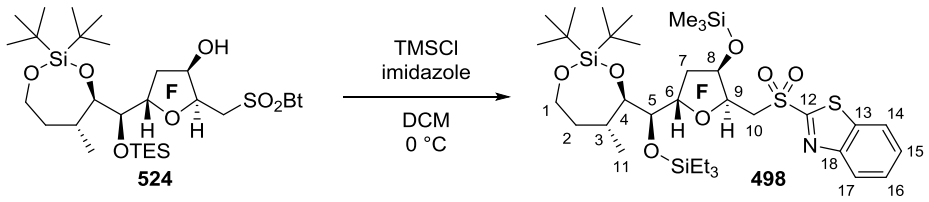


To a solution of compound **523** (389 mg, 0.482 mmol) in DCM (9.5 mL) and 1 M pH 7 buffer (0.95 mL) was added DDQ (274 mg, 1.21 mmol). The reaction was stirred for 16 h before the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column

chromatography (SiO_2, 100:0 → 95:5 → 90:10 pentane:EtOAc) to afford the title compound **524** (286 mg, 87%) as a white solid (foams under high vacuum).

R_f: 0.41 (80:20 pentane:EtOAc); **m.p.:** 48–51 °C; $[\alpha]_D^{25}$ –10.2 (*c* = 1.00, $CHCl_3$;); **IR:** ν_{max} (thin film/cm^{-1}) 3537, 2957, 2933, 2876, 2858, 2360, 1556, 1473, 1424, 13855, 1362, 1332, 1273, 1238, 1214, 1149, 1123, 1098, 1061, 1025, 1012, 984, 971, 922, 901, 887, 858, 827, 762, 729, 691, 669, 649, 625; **^{1}H NMR:** δ_H (400 MHz, $CDCl_3$) 8.25–8.21 (1H, m, C-14H), 8.04–8.00 (1H, m, C-17H), 7.68–7.63 (1H, m, C-15H), 7.63–7.58 (1H, m, C-16H), 4.59 (1H, q, *J* = 4.2 Hz, C-8H), 4.50–4.41 (2H, m, C-6H, C-9H), 4.17–4.08 (1H, m, C-10H_AH$_B$), 3.96 (1H, dt, *J* = 11.6, 3.3 Hz, C-1H_AH$_B$), 3.92–3.82 (2H, m, C-1H$_A$$H_B$, C-10H$_A$$H_B$), 3.51–3.43 (2H, m, C-4H, C-5H), 2.76 (1H, d, *J* = 4.6 Hz, OH), 2.21 (1H, dd, *J* = 13.3, 6.0 Hz, C-7H_AH$_B$), 1.95 (1H, dtd, *J* = 12.1, 6.7, 2.5 Hz, C-3H), 1.84 (1H, ddd, *J* = 13.3, 9.8, 4.9 Hz, C-7H$_A$$H_B$), 1.71–1.57 (2H, m, C-2$H_2$), 1.00 (9H, s, Si(C(C$H_3$)$_3$)(C(CH$_3$)$_3$)), 0.98 (9H, s, Si(C(CH$_3$)$_3$)(C(C$H_3$)$_3$)), 0.92–0.85 (12H, m, C-11H_3, Si(CH$_2$CH_3)$_3$), 0.66–0.47 (6H, m, Si(CH_2CH$_3$)$_3$); **^{13}C NMR:** δ_C (101 MHz, $CDCl_3$) 166.1 (C-12), 152.6 (C-18), 136.8 (C-13), 128.4 (C-16), 128.0 (C-15), 125.7 (C-14), 122.5 (C-17), 82.0 (C-4), 80.1 (C-6), 77.6 (C-5), 76.0 (C-9), 72.4 (C-8), 66.2 (C-1), 54.2 (C-10), 42.3 (C-2), 38.6 (C-3), 37.7 (C-7), 28.0 (6C, Si(C(*C*H$_3$)$_3$)(C(*C*H$_3$)$_3$)), 22.1 (Si(*C*(CH$_3$)$_3$)(C(CH$_3$)$_3$)), 21.6 (Si(C(CH$_3$)$_3$)(*C*(CH$_3$)$_3$)), 19.5 (C-11), 7.2 (3C, Si(CH$_2$*C*H$_3$)$_3$), 5.6 (3C, Si(*C*H$_2$CH$_3$)$_3$); **HRMS:** (ESI+, *m/z*) $C_{32}H_{55}O_7N^{32}S_2{}^{28}Si_2Na$ (MNa^+) Calculated: 708.28507, Found: 708.28463 (Δ –0.62 ppm).

2-((((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)((triethylsilyl)oxy)methyl)-3-((trimethylsilyl)oxy)tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[*d*]thiazole (498)



To a solution of compound **524** (102 mg, 0.149 mmol) and imidazole (102 mg, 1.49 mmol) in DCM (2.2 mL) at 0 °C was added chlorotrimethylsilane (95 µL, 0.75 mmol) dropwise. The reaction was warmed to rt for 13 h before the reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (alumina, 95:5 pentane:EtOAc) to afford the title compound **498** (101 mg, 89%) as a colourless oil (foams under high vacuum).

R_f: 0.28 (95:5 pentane:EtOAc); $[\alpha]_D^{25}$ –24.3 (*c* = 1.00, $CHCl_3$;); **IR:** ν_{max} (thin film/cm^{-1}) 2955, 2932, 2876, 2857, 1730, 1556, 1474, 1425, 1385, 1363, 1334, 1253, 1238, 1191, 1150, 1123, 1098, 1055, 1025, 1012, 962, 920, 861, 827, 761, 729, 691, 648, 623; **^{1}H NMR:** δ_H (500 MHz, $CDCl_3$) 8.24–8.20 (1H, m, C-17H), 8.03–7.99 (1H, m, C-14H), 7.72–7.61 (1H, m, C-15H), 7.61–7.51 (1H, m, C-16H), 4.52 (1H, t, *J* = 3.7 Hz, C-8H), 4.43–4.37 (2H, m, C-6H, C-9H), 4.04 (1H, dd, *J* = 14.9, 7.6 Hz, C-10H_AH_B), 3.95 (1H, dt, *J* = 11.7, 3.2 Hz, C-1H_AH_B), 3.88–3.82 (1H, m, C-1H_AH_B), 3.82 (1H, dd, *J* = 14.8, 3.7 Hz, C-10H_AH_B), 3.45–3.38 (2H, m, C-4H, C-5H), 2.06 (1H, dd, *J* = 12.8, 5.9 Hz, C-7H_AH_B), 1.94–1.84 (1H, m, C-3H), 1.73 (1H, ddd, *J* = 13.4, 9.7, 4.4 Hz, C-7H_AH_B), 1.64–1.60 (2H, m, C-2H_2), 0.99 (9H, s, Si(C(CH_3)$_3$)(C(CH_3)$_3$)), 0.97 (9H, s, Si(C(CH_3)$_3$)(C(CH_3)$_3$)), 0.85–0.80 (12H, m, C-11H_3, Si(CH_2CH_3)$_3$), 0.59–0.43 (6H, m,

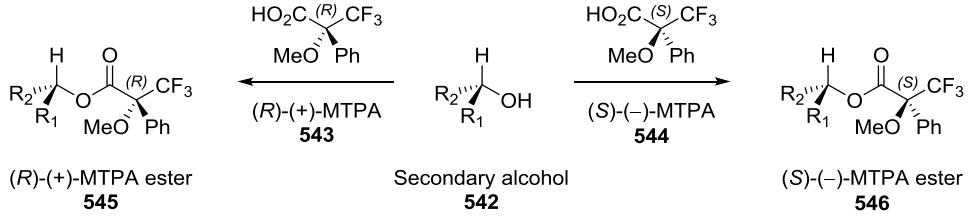
$Si(CH_2CH_3)_3$), 0.16 (9H, s, $Si(CH_3)_3$); **^{13}C NMR:** δ_C (126 MHz, $CDCl_3$) 166.4 (C-12), 152.8 (C-18), 136.9 (C-13), 128.2 (C-16), 127.8 (C-15), 125.7 (C-17), 122.4 (C-14), 81.9 (C-4), 79.8 (C-6), 77.5 (C-5), 75.9 (C-9), 73.1 (C-8), 66.3 (C-1), 54.3 (C-10), 42.3 (C-2), 38.7 (C-7), 38.5 (C-3), 28.0 (3C, $Si(C(CH_3)_3)(C(CH_3)_3)$), 27.9 (3C, $Si(C(CH_3)_3)(C(CH_3)_3)$), 22.1 ($Si(C(CH_3)_3)(C(CH_3)_3)$), 21.6 ($Si(C(CH_3)_3)(C(CH_3)_3)$), 19.5 (C-11), 7.2 (3C, $Si(CH_2CH_3)_3$), 5.6 (3C, $Si(CH_2CH_3)_3$), 0.2 (3C, $Si(CH_3)_3$); **HRMS:** (ESI+, *m/z*) $C_{35}H_{64}O_7N^{32}S_2{}^{28}Si_3$ (MH^+) Calculated: 758.34265, Found: 758.34218 (Δ +0.62 ppm)

Chapter 6

Chapter 6: Appendices

6.1 Appendix 1: Mosher's ester analysis

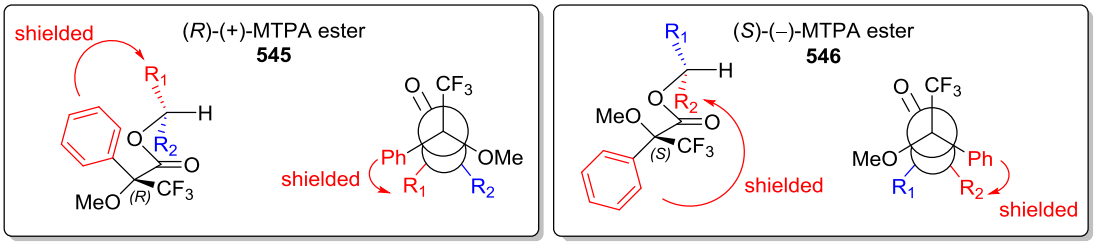
In 1973, Dale and Mosher reported an NMR-based method for determining the absolute configuration of the stereogenic carbon centre of secondary alcohols.[98] Derivatising the alcohol using a chiral, enantiomerically pure carboxylic acid, often using both enantiomers of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or Mosher's acid, to derivatise the secondary alcohol.[99] This generates the diastereomeric (therefore distinguishable by NMR)[100] MTPA esters **545** and **546** of the generic second alcohol **542** (**Scheme 6-1**).



Scheme 6-1: Synthesis of (*R*) and (*S*)-Mosher's esters **545** and **546** from secondary alcohol **542**.

These esters have been shown to predominantly adopt the usual *s-trans* arrangement about the O–CO bond, and the trifluoromethyl substituent as well as the proton attached to the stereogenic carbon of the esterified alcohol lie *syn*-coplanar to the carbonyl group. The phenyl ring of the MTPA ester imposes an anisotropic, magnetic shielding effect on protons residing above or below the plane of the aryl ring resulting in a more upfield chemical shift. As shown in **Scheme 6-2**, this results in R_2 protons of (*S*)-MTPA ester **546** will be relatively more shielded (upfield, lower δ_H value), whereas R_1 protons of (*R*)-MTPA ester **545** will be more shielded (upfield, lower δ_H value). Consequently, the sign of $\Delta\delta^{SR}$ (defined as $\delta_S - \delta_R$) for protons in R_1 will be positive whilst protons in R_2 will be negative. By determining which protons of a derivatised secondary alcohol with an unknown configuration have positive or negative $\Delta\delta^{SR}$ values, one can identify which of

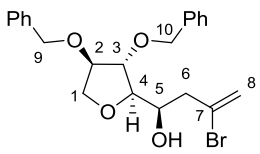
the substituents correspond to R_1 or R_2 and therefore determine the absolute configuration.



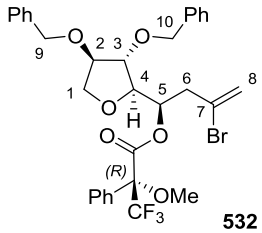
$\Delta\delta^{SR}$ ($\delta_S - \delta_R$): R_1 = positive; R_2 = negative

Scheme 6-2: Conformations of the Mosher's esters **545** and **546**.

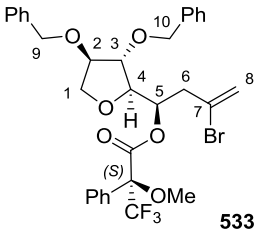
6.1.1 Mosher's ester analysis of compound 282



282



532

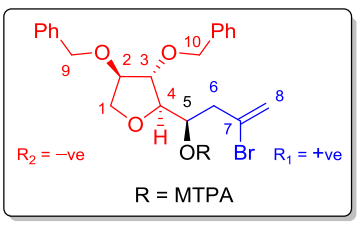


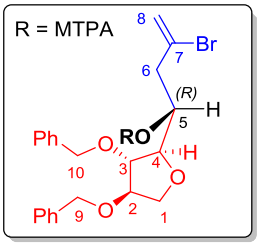
533

Proton	δ_S (**533**) ppm*	δ_R (**532**) ppm*	$\Delta\delta^{SR}$ ($\delta_S - \delta_R$) ppm	$\Delta\delta^{SR} \times 400$ (Hz)
C-8H_B	5.44	5.23	+0.21	+84
C-8H_A	5.56	5.36	+0.20	+80
C-6H_A	2.89	2.77	+0.12	+48
C-6H_B	2.78	2.70	+0.08	+32
C-1H_B	3.88	3.90	–0.02	–8
C-5H	5.68	5.71	–0.03	–12
C-4H	3.95	3.98	–0.03	–12
C-3H	4.03	4.06	–0.03	–12
C-2H	3.95	4.02	–0.07	–28
C-1H_A	3.95	4.06	–0.11	–44

^{1}H NMR (400 MHz, $CDCl_3$) shifts.

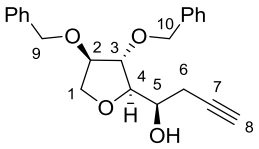
* For chemical shifts quoted as a multiplet, the midpoint of the range has been taken.



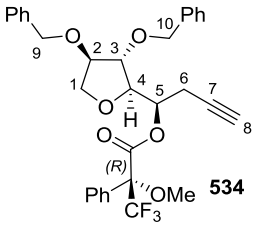


Based upon the model proposed by Mosher,[98-100] alcohol **282** was assigned the (*R*)-configuration at C-5.

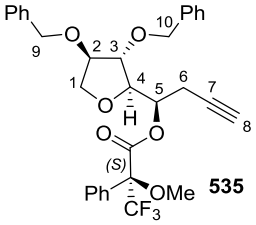
6.1.2 *Mosher's ester analysis of compound 331*



331



534

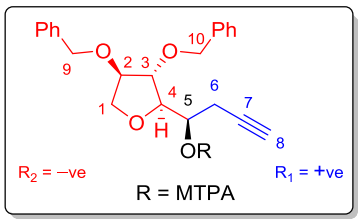


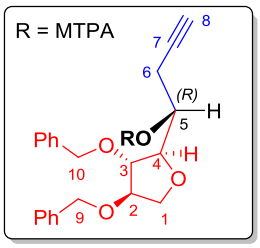
535

Proton	δ_S (**535**) ppm	δ_R (**534**) ppm	$\Delta\delta^{SR}$ ($\delta_S - \delta_R$) ppm	$\Delta\delta^{SR} \times 500$ (Hz)
C-8H	2.03	1.90	+0.13	+65
C-6H_A	2.89	2.76	+0.13	+65
C-6H_B	2.76	2.66	+0.10	+50
C-4H	4.16	4.16	0	0
C-1H_B	3.95	3.96	–0.01	–5
C-10H_A	4.49	4.50	–0.01	–5
C-10H_B	4.43	4.46	–0.03	–15
C-1H_A	3.95	4.00	–0.05	–25
C-3H	3.95	4.04	–0.09	–45
C-5H	5.20	5.34	–0.14	–70
C-9H_A	4.16	4.46	–0.30	–150
C-2H	3.69	4.04	–0.35	–175
C-9H_B	3.95	4.39	–0.44	–220

^{1}H NMR (500 MHz, $CDCl_3$) shifts.

* For chemical shifts quoted as a multiplet, the midpoint of the range has been taken.

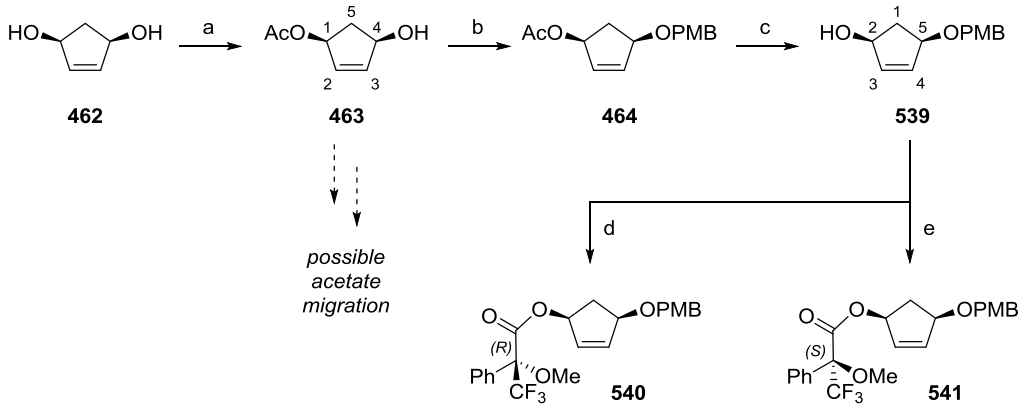




Based upon the model proposed by Mosher,[98-100] alcohol **331** was assigned the (*R*)-configuration at C-5.

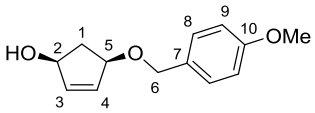
6.1.3 Mosher's ester analysis of compounds 463 and 539

To determine the absolute configuration of **463**, a Mosher's ester analysis of **539** was conducted (**Scheme 6-3**). Direct Mosher's ester analysis of the C-4 hydroxyl of **463** was not conducted as the possibility of acetate migrating to the C-4 hydroxyl under the esterification conditions would result in scrambling of the stereochemistry. Therefore, the C-4 hydroxyl was protected under acidic conditions with PMB trichloroacetimidate to afford **464**. The acetate was then hydrolysed to obtain **539**, which was derivatised using the Mosher's acids.

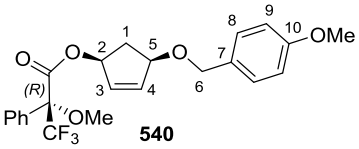


Scheme 6-3: Derivatisation of **463** for Mosher's ester analysis.
Reagents and conditions: a) vinyl acetate, pancreatin, Et_3N, THF, 63%; b) 4-methoxybenzyl-2,2,2-trichloroacetimidate, CSA, DCM/pentane (4:1), 0 °C, 93%; c) KOH, MeOH/THF (1:1), 89%; d) (*R*)-(+)-MTPA, DIC, DMAP, DCM, 68%; e) (*S*)-(–)-MTPA, DIC, DMAP, DCM, quant..

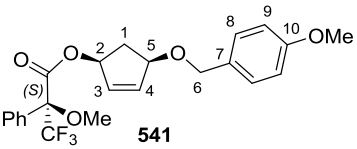
The Mosher's ester analysis was conducted on **539** to determine the stereochemistry at C-2. This configuration translates to C-1 of **463**, indirectly determining the absolute stereochemical assignment of **463**.



539



540

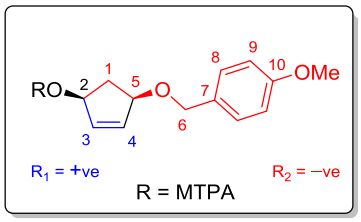


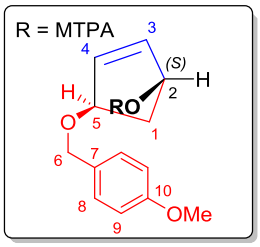
541

Proton	δ_S (**540**) ppm	δ_R (**541**) ppm	$\Delta\delta^{SR}$ ($\delta_S - \delta_R$) ppm	$\Delta\delta^{SR} \times 400$ (Hz)
C-3H	6.05	5.98	+0.07	+28
C-4H	6.18	6.16	+0.02	+8
C-2H	5.72	5.71	+0.01	+4
C-10OCH_3	3.80	3.80	0	0
C-5H	4.52	4.53	–0.01	–4
C-9H	6.86	6.87	–0.01	–4
C-6H_A	4.45	4.47	–0.02	–8
C-8H	7.22	7.24	–0.02	–8
C-6H_B	4.42	4.45	–0.03	–12
C-1H_A	2.80	2.85	–0.05	–20
C-1H_B	1.78	1.86	–0.08	–32

^{1}H NMR (400 MHz, $CDCl_3$) shifts.

* For chemical shifts quoted as a multiplet, the midpoint of the range has been taken.





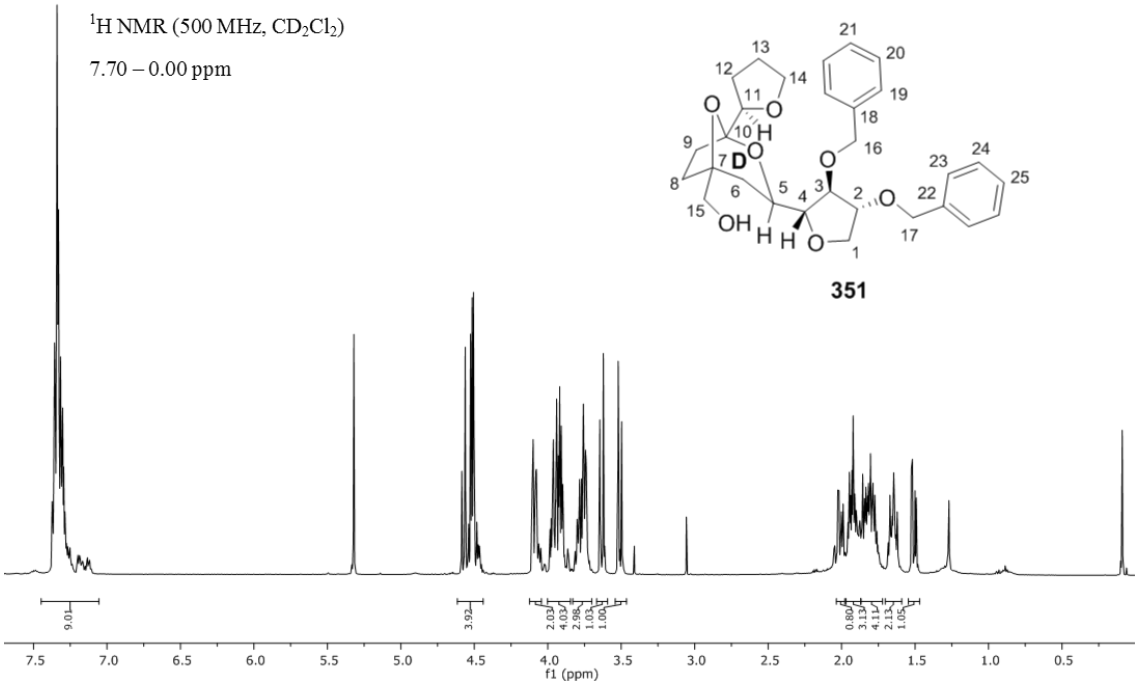
Based upon the model proposed by Mosher,[98-100] alcohol **539** was assigned the (*S*)-configuration at C-2. By translation, acetate **463** was assigned the (*S*)-configuration at the same carbon, C-1.

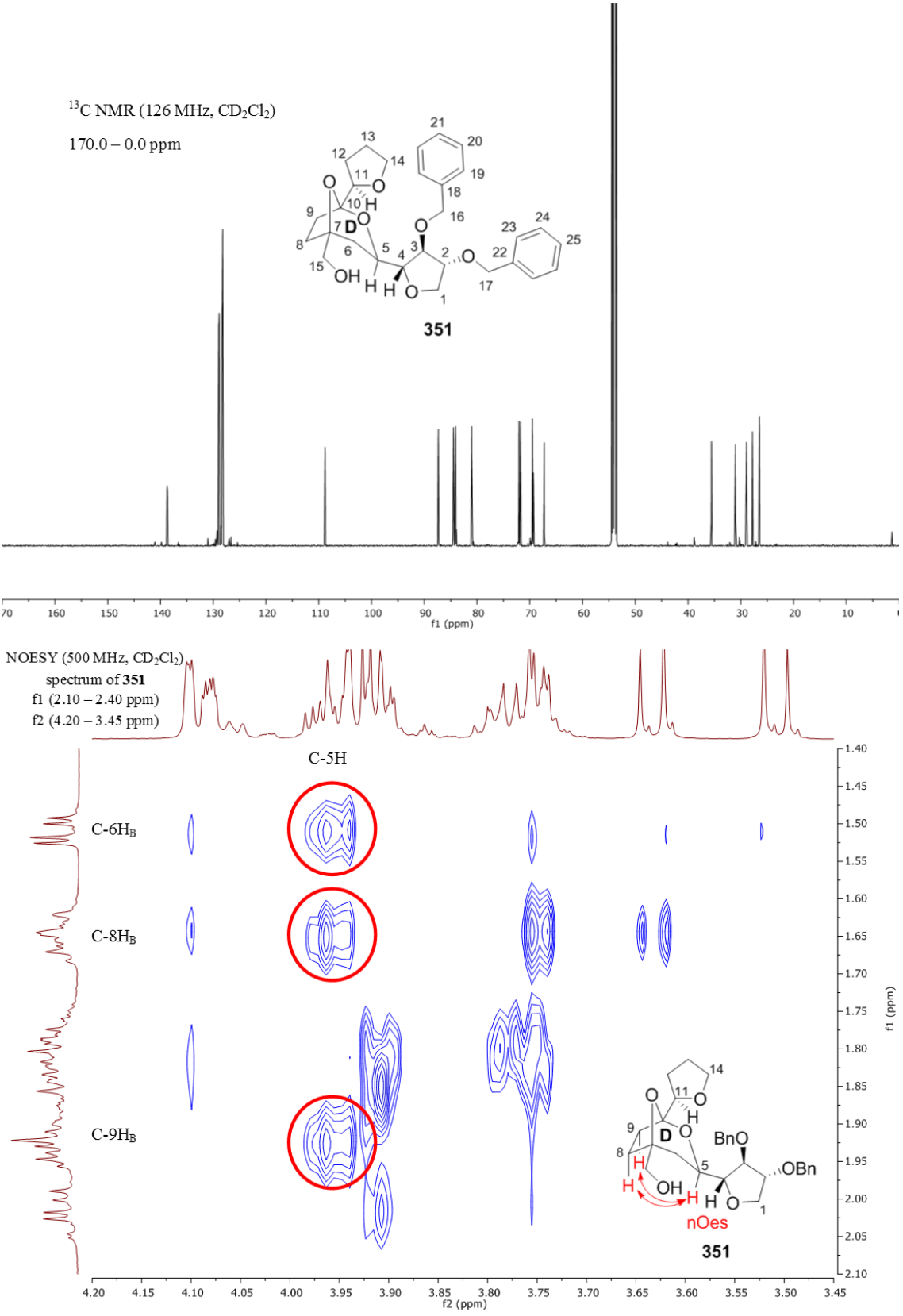
The ee was determined to be 94% by comparison with the ^{19}F NMR spectrum for **463** compared to the spectrum of a 1:1.3 mixture of diastereomers **541** and *C-2,5-epi*-**541**.[161]

6.2 Appendix 2: Nuclear Overhauser Effect analysis

The nuclear Overhauser effect (nOe) is the transfer of nuclear spin polarisation from one spin system to another *via* dipolar cross-relaxation through space.[191] A positive nOe or enhancement of the spin system after saturating a different spin system means the spins systems are close in space and are therefore nearby each other.

6.2.1 ^{1}H, ^{13}C NMR and nOe analysis of compound 351

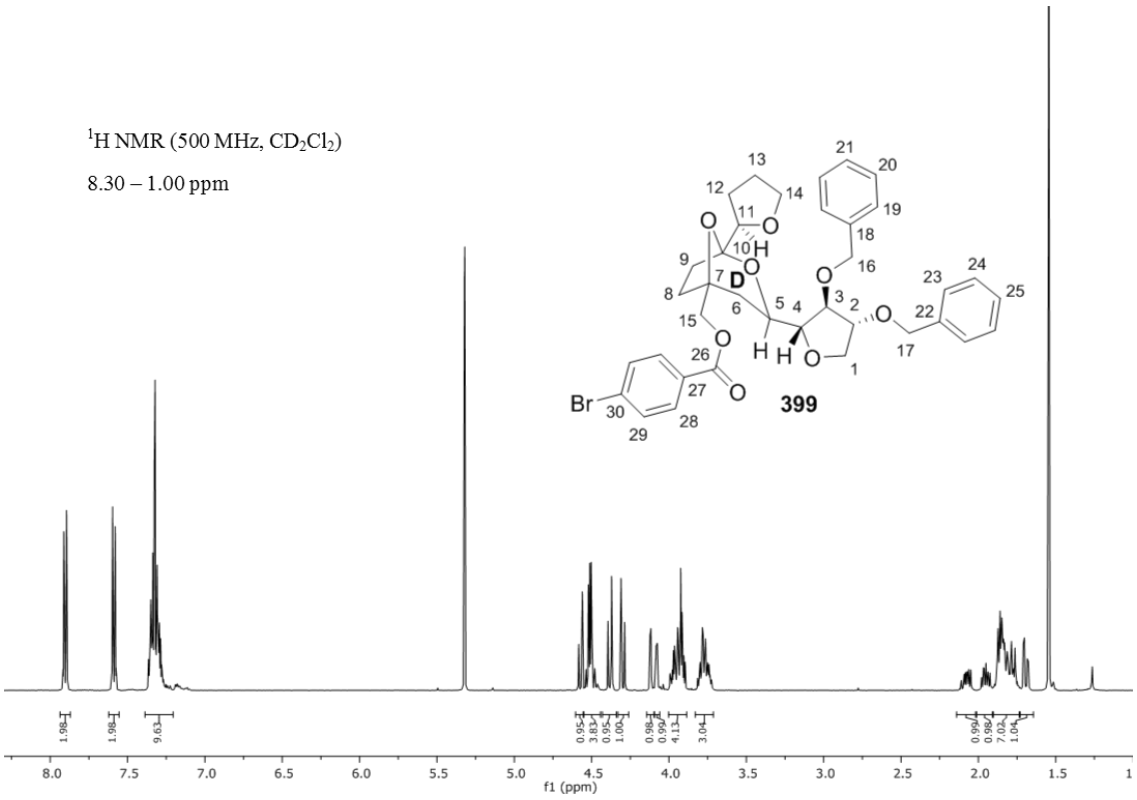


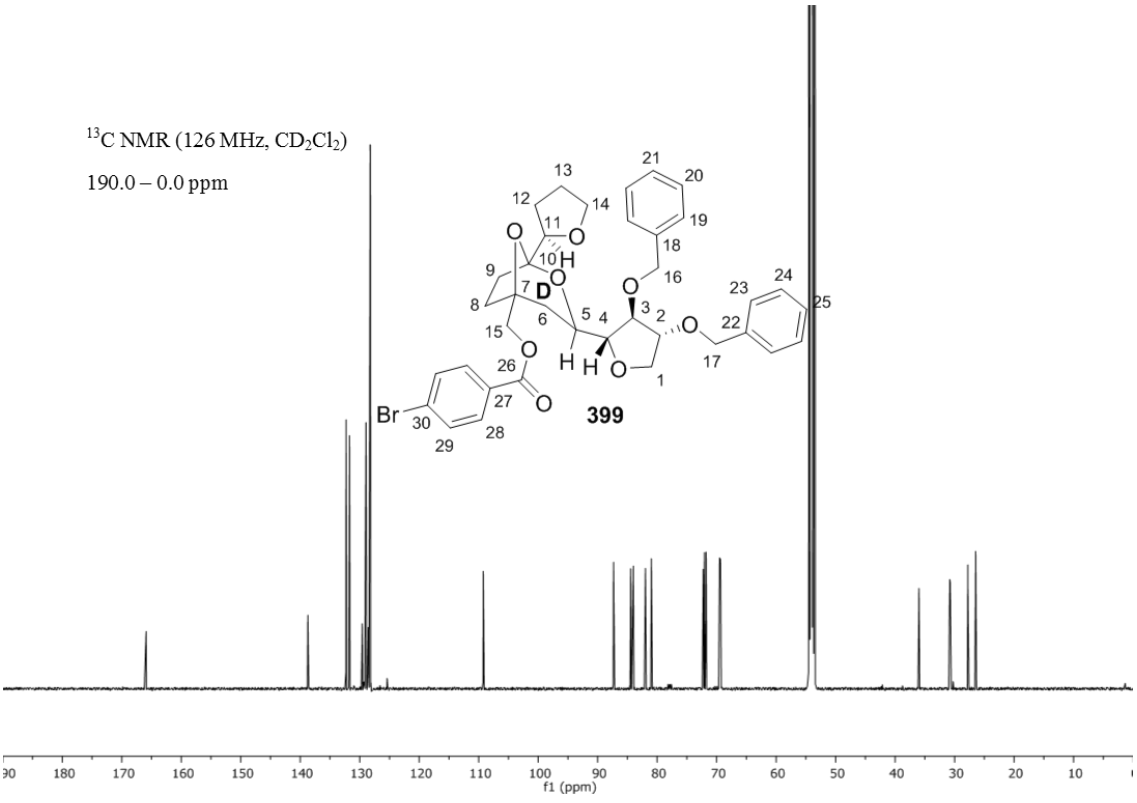


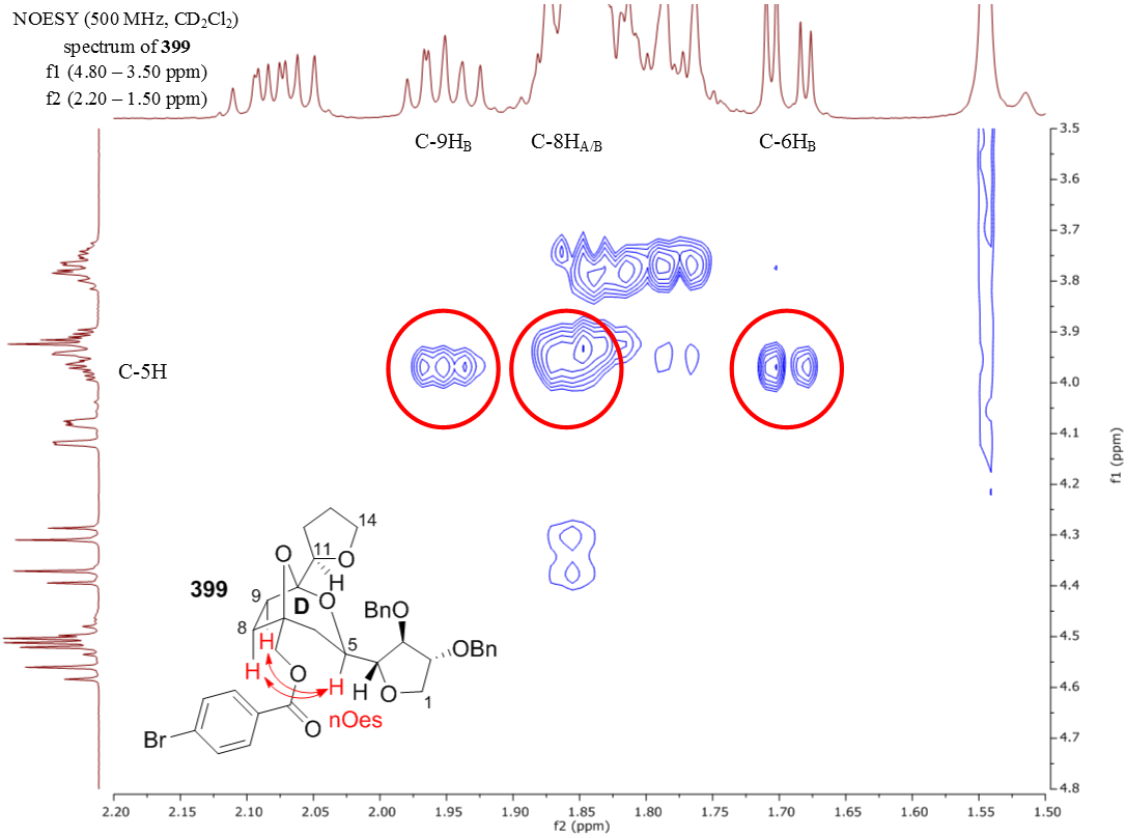
Key nOes observed: C-5H to C-8H$_B$ and C-9H$_B$.

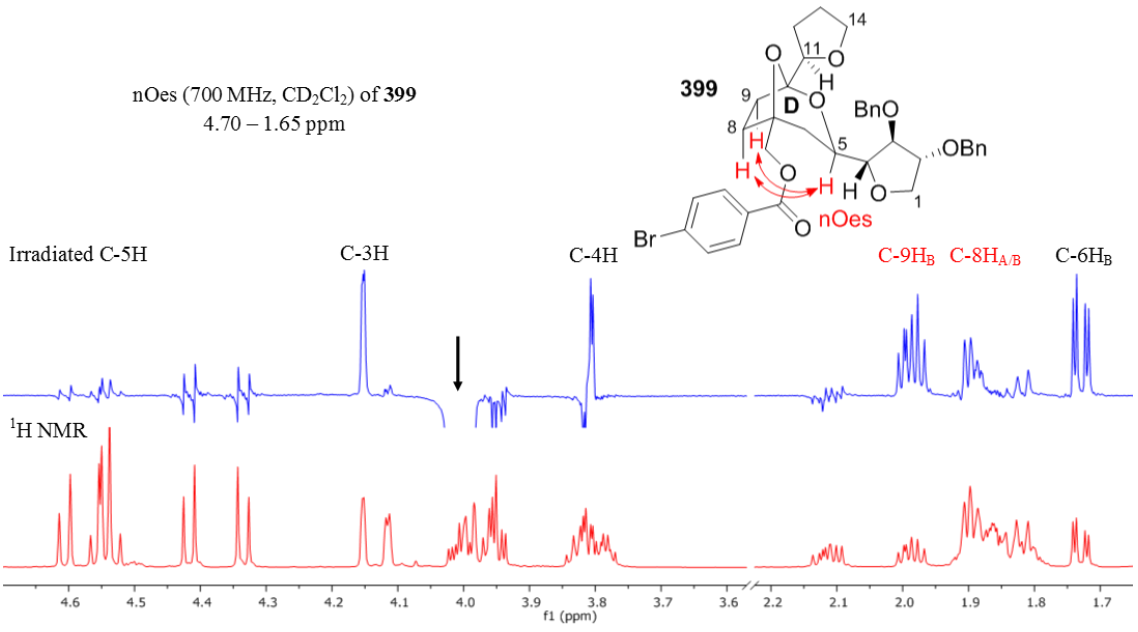
Also observe nOes to C-3H, C-4H (not shown) and C-6H$_B$.

6.2.2 ^{1}H, ^{13}C NMR and nOe analysis of compound 399





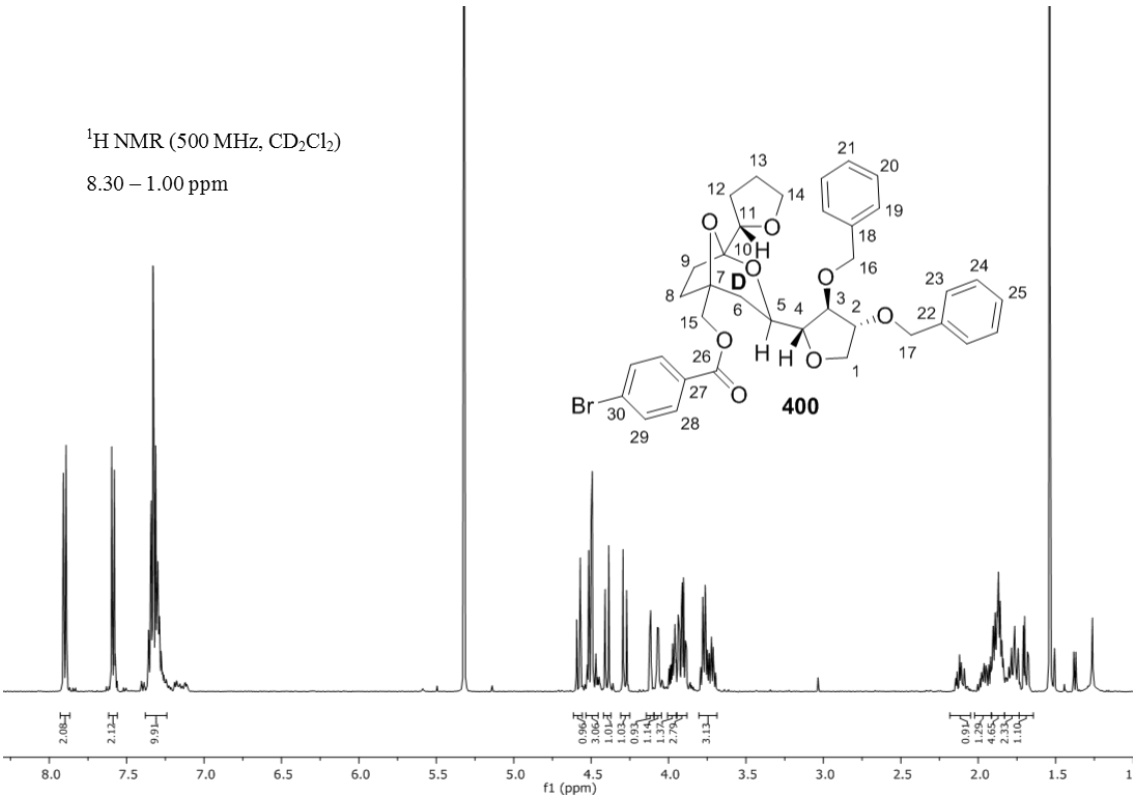


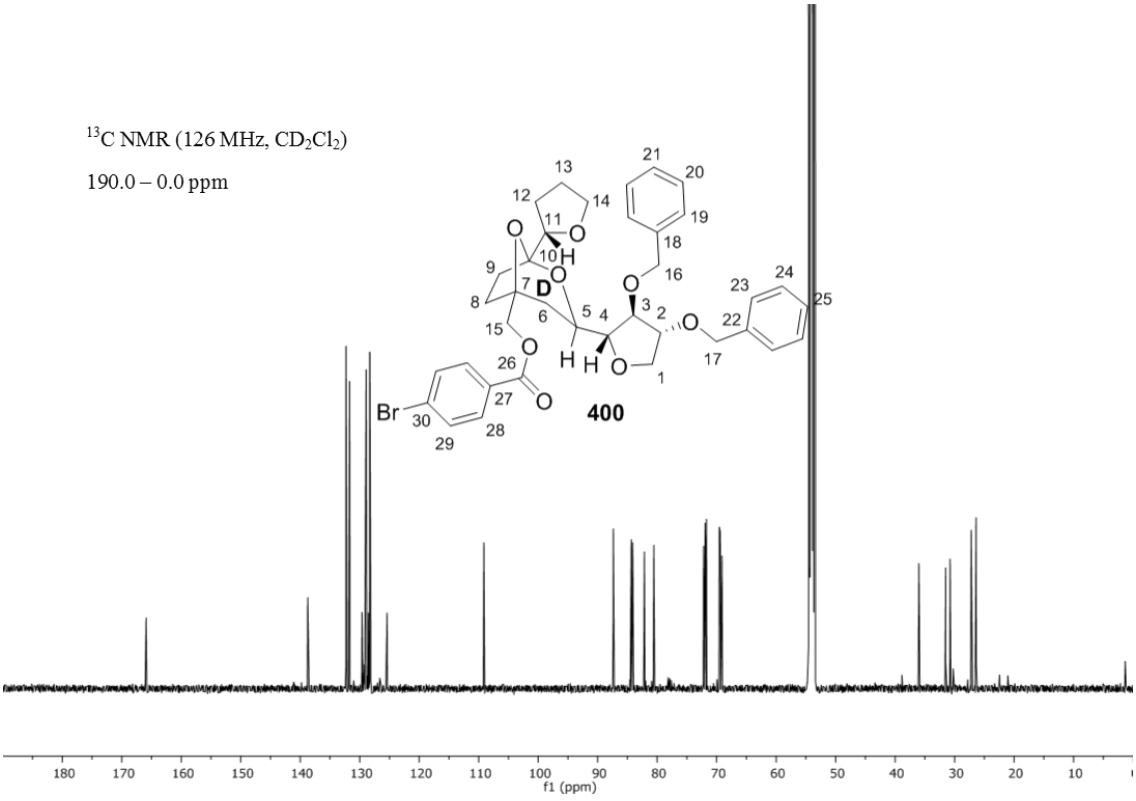


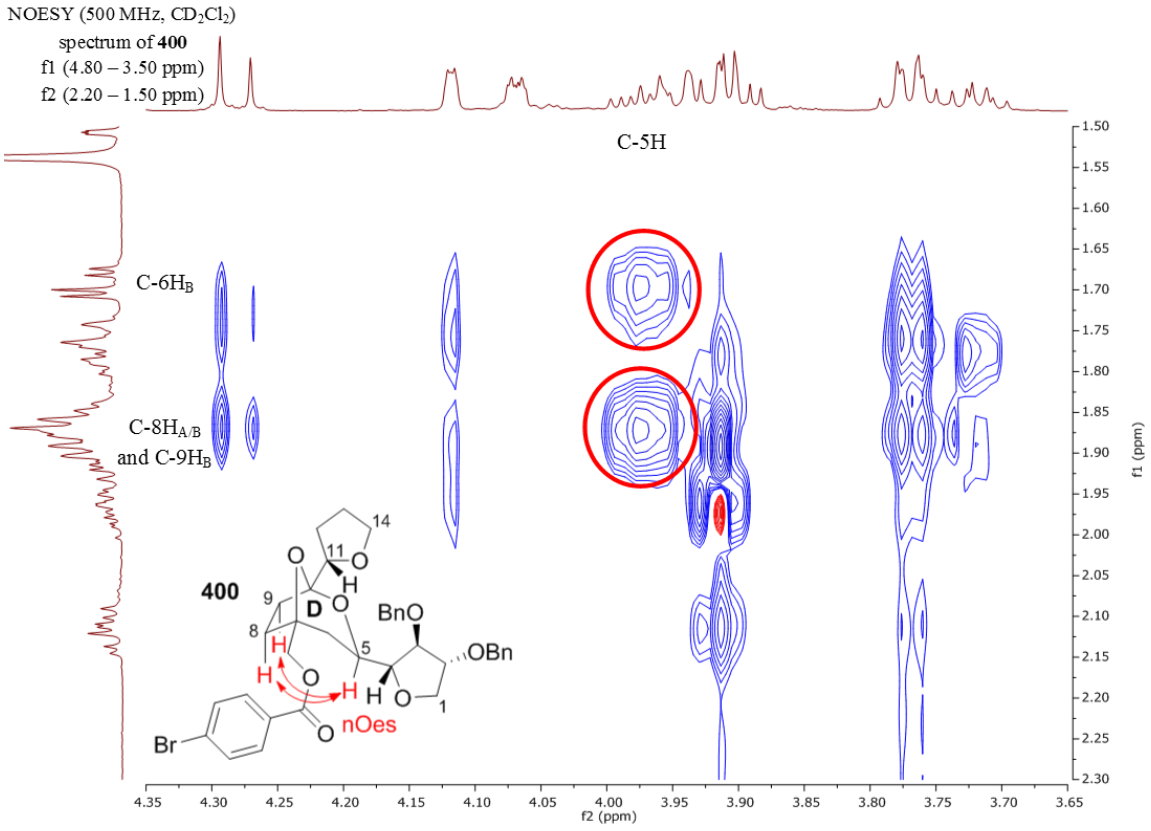
Key nOes observed: C-5H to C-8H$_{A/B}$ and C-9H$_B$.

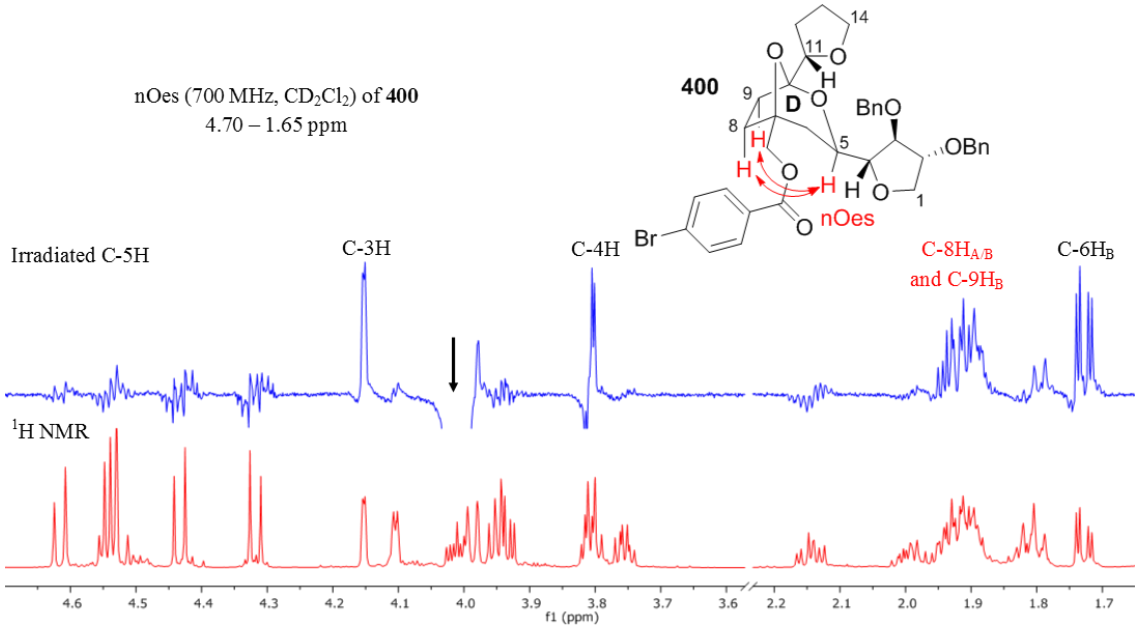
Also observe nOes to C-3H, C-4H and C-6H$_B$.

6.2.3 ^{1}H, ^{13}C NMR and nOe analysis of compound 400





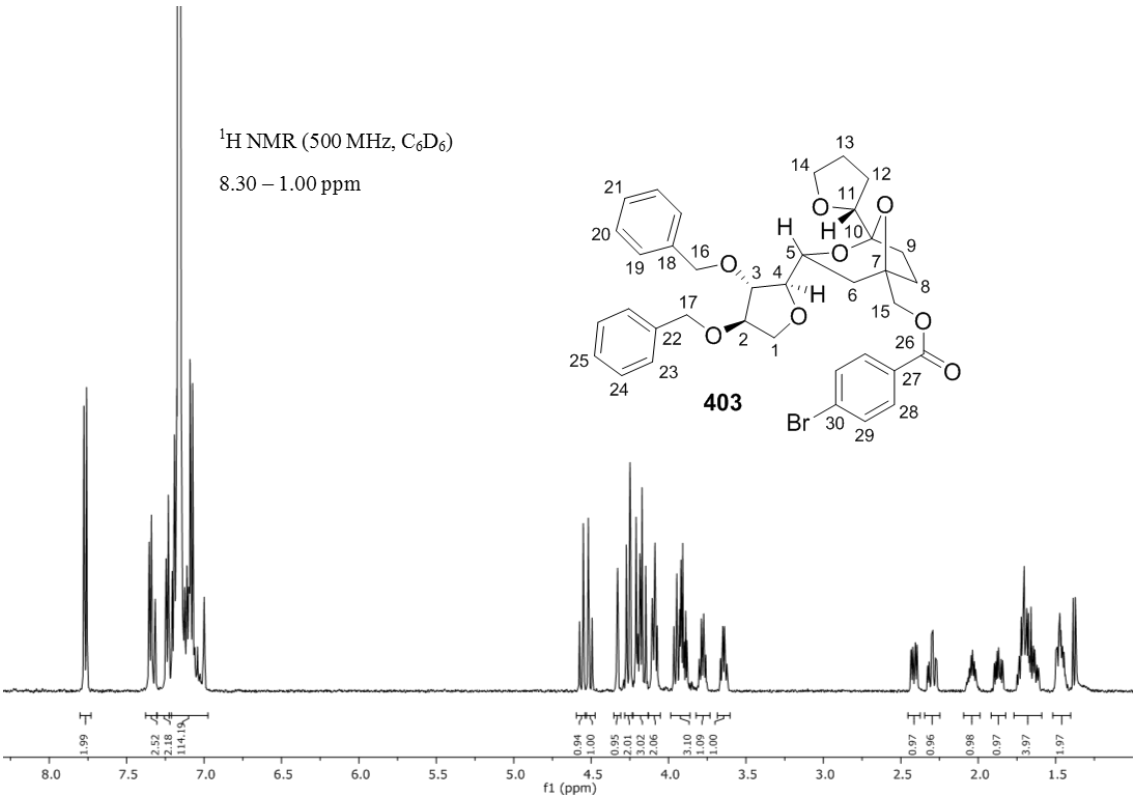


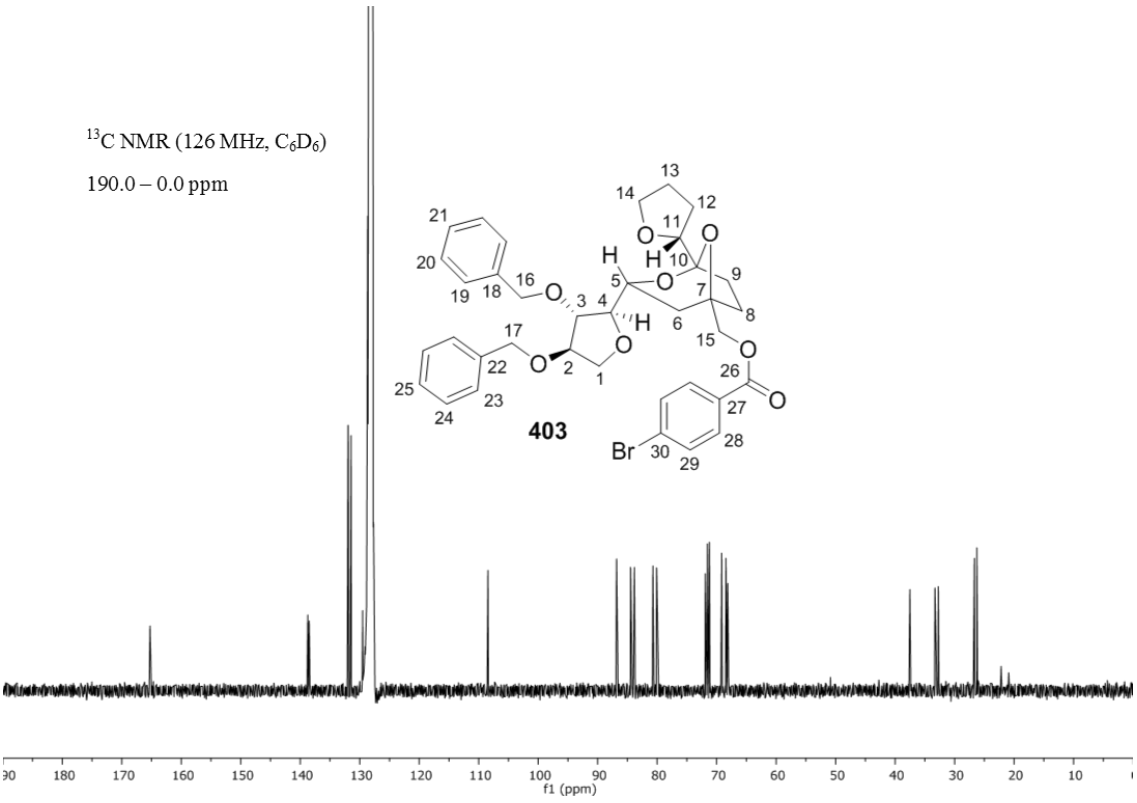


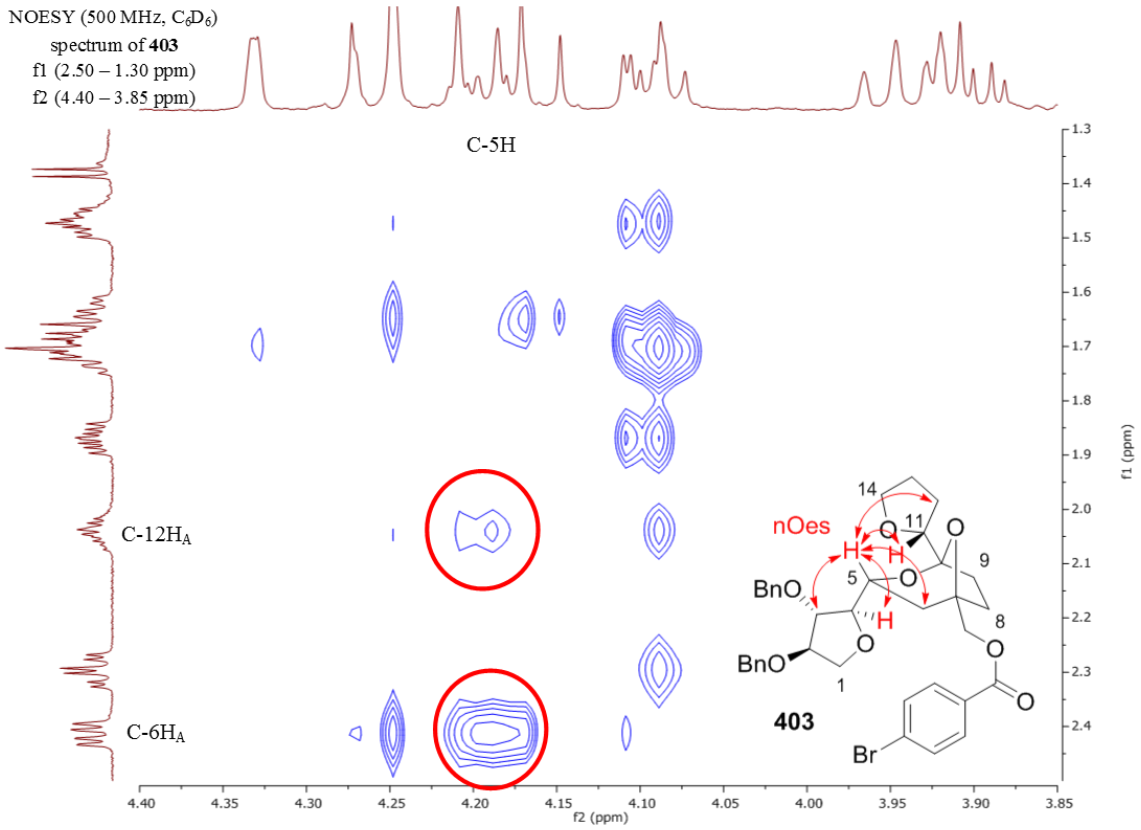
Key nOes observed: C-5H to C-8H$_{A/B}$ and C-9H$_B$.

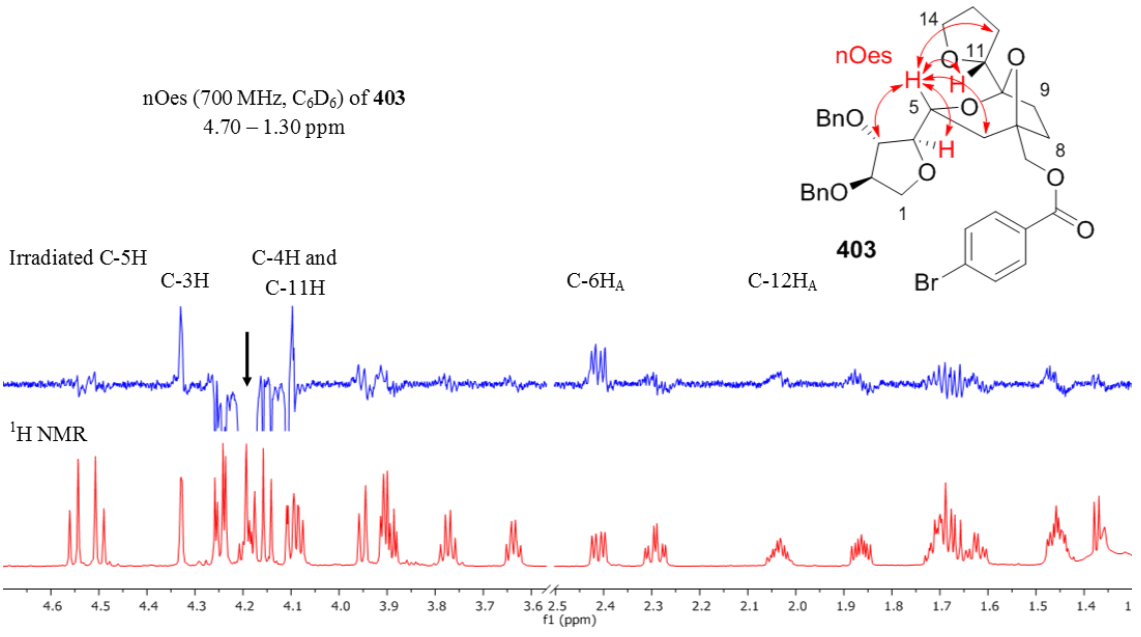
Also observe nOes to C-3H, C-4H and C-6H$_B$.

6.2.4 ^{1}H, ^{13}C NMR and nOe analysis of compound 403





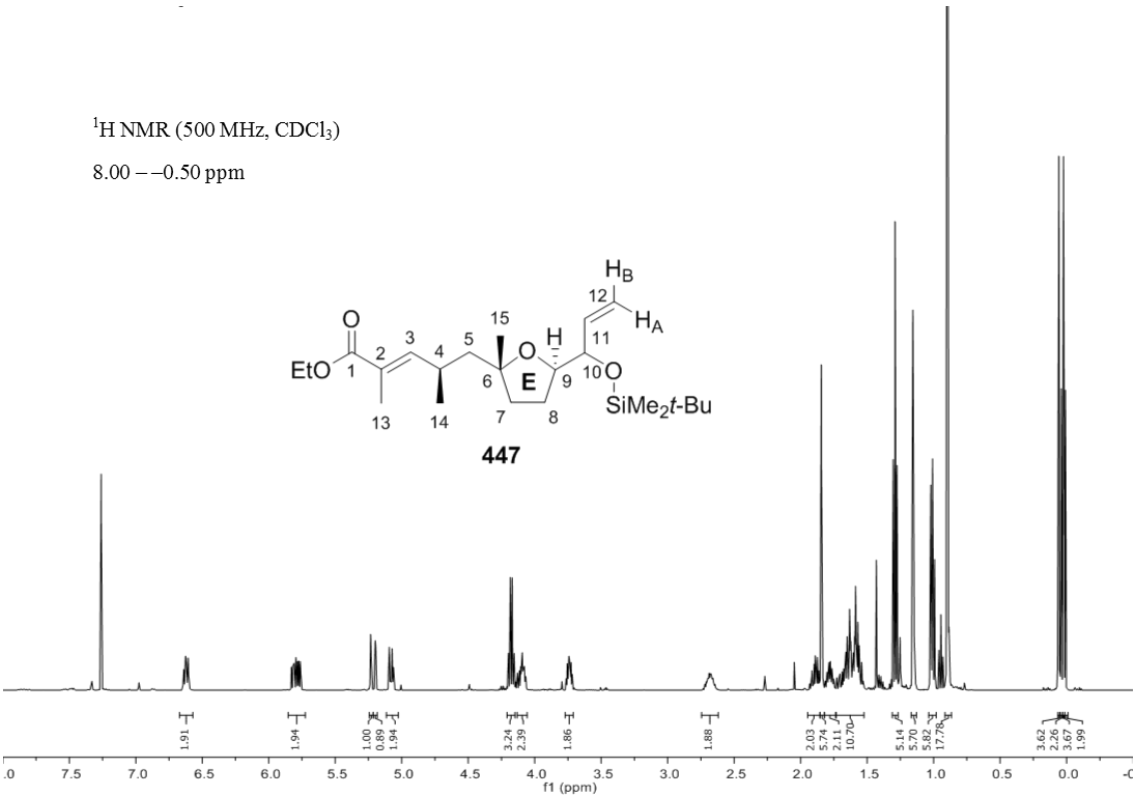


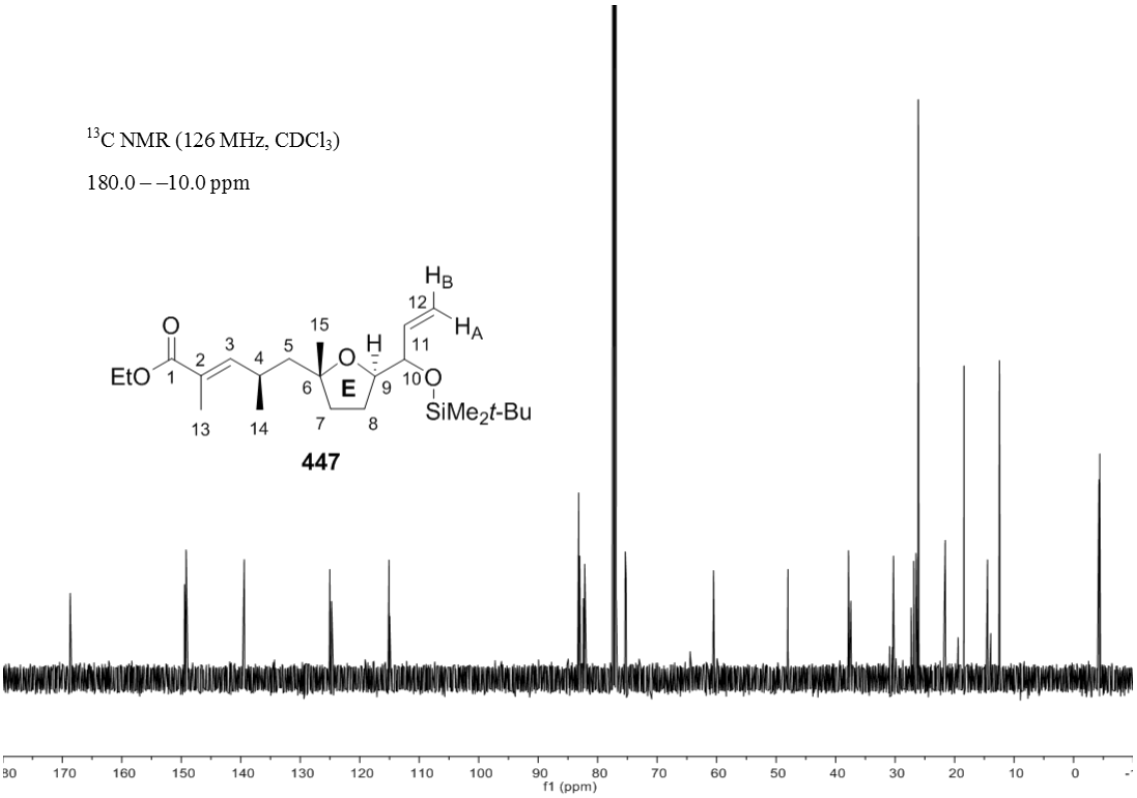


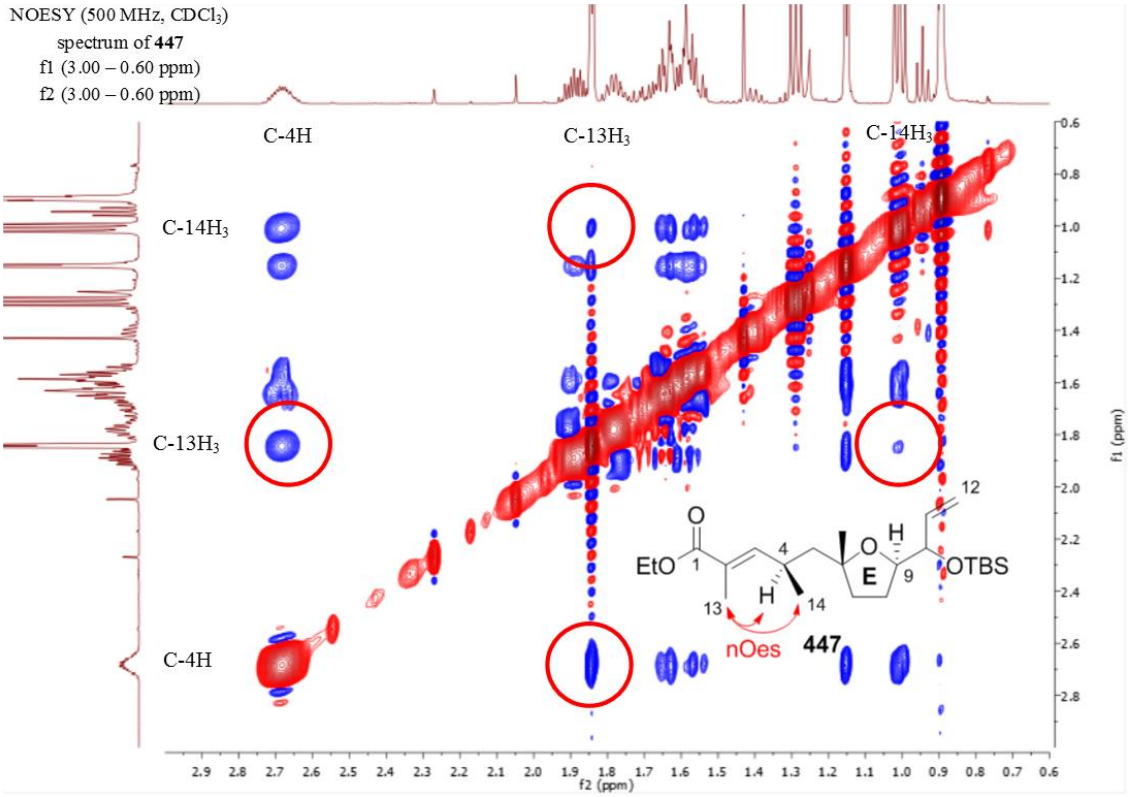
nOes observed: C-5H to C-3H, C-4H, C-6H_A, C-11H and C-12H_A.

No observed nOe to C-8$H_{A/B}$ or C-9$H_{A/B}$.

6.2.5 ^{1}H, ^{13}C NMR and nOe analysis of compound 447

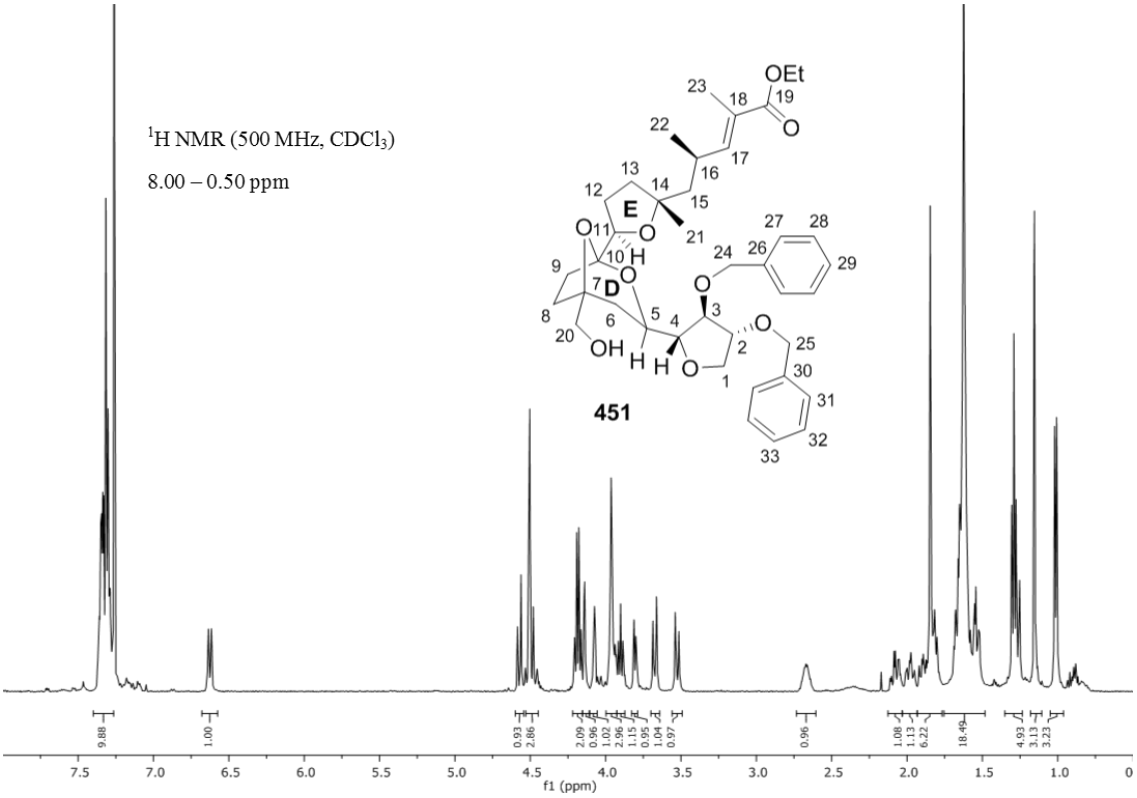


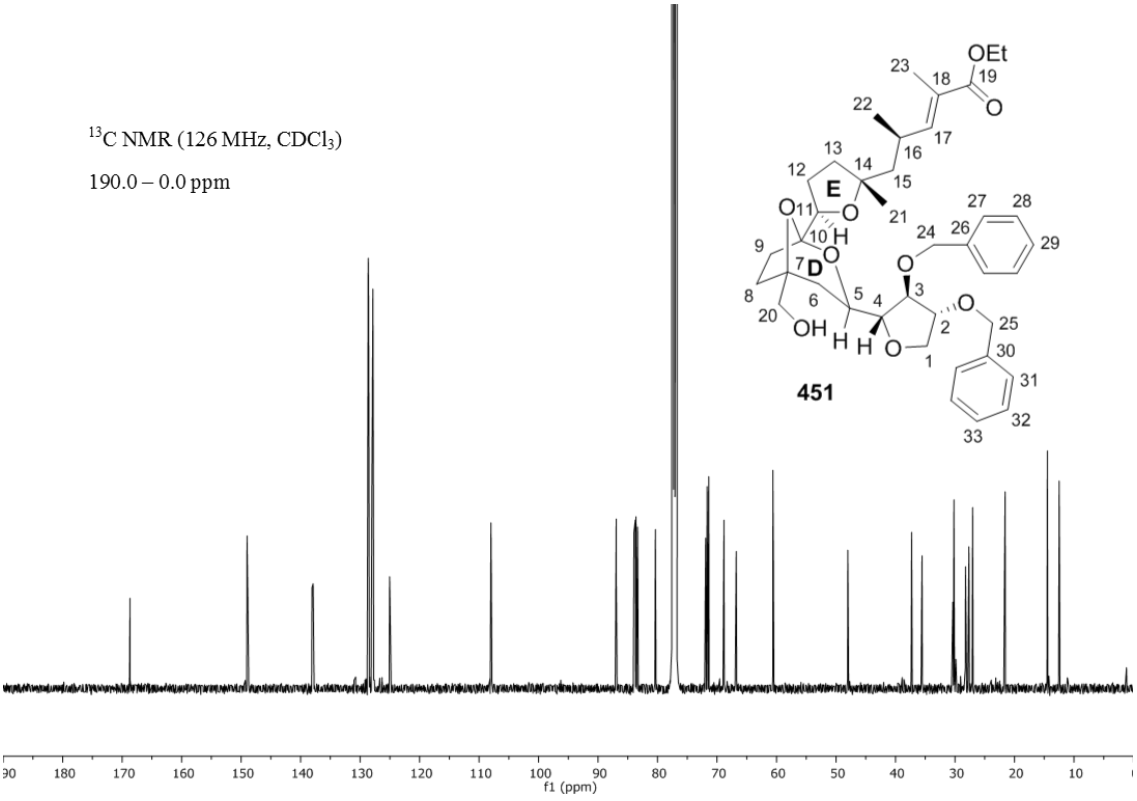


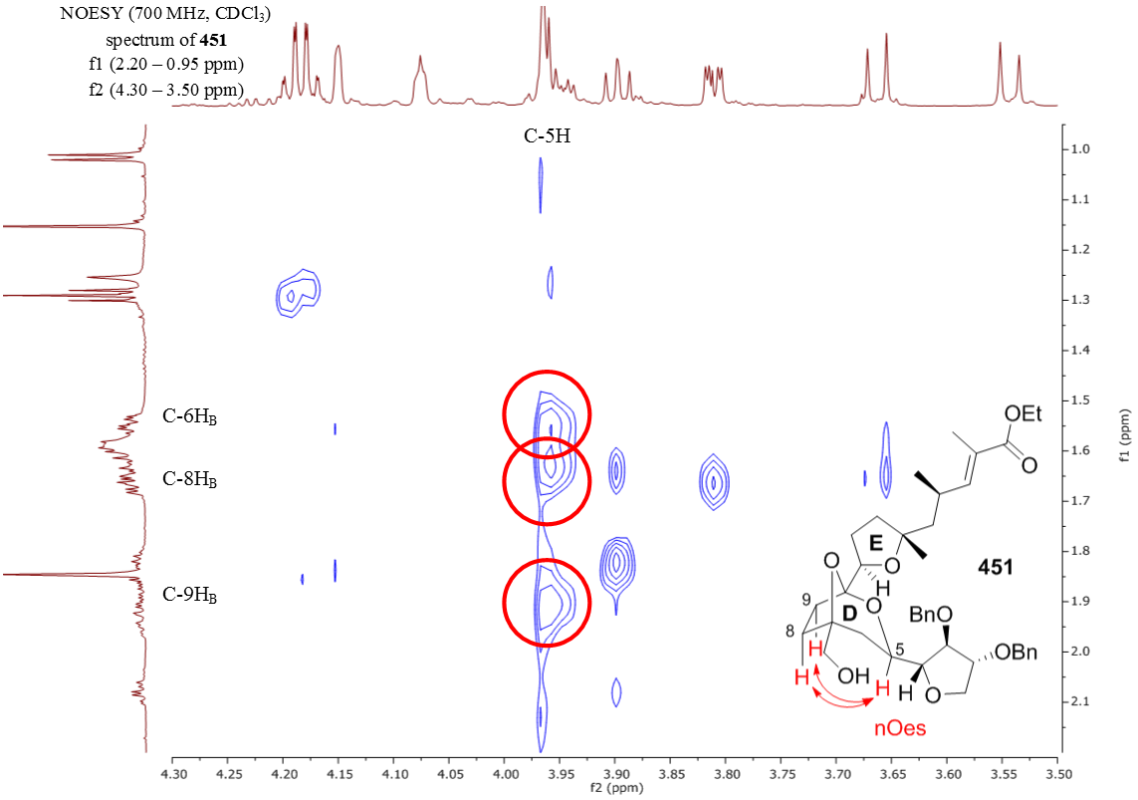


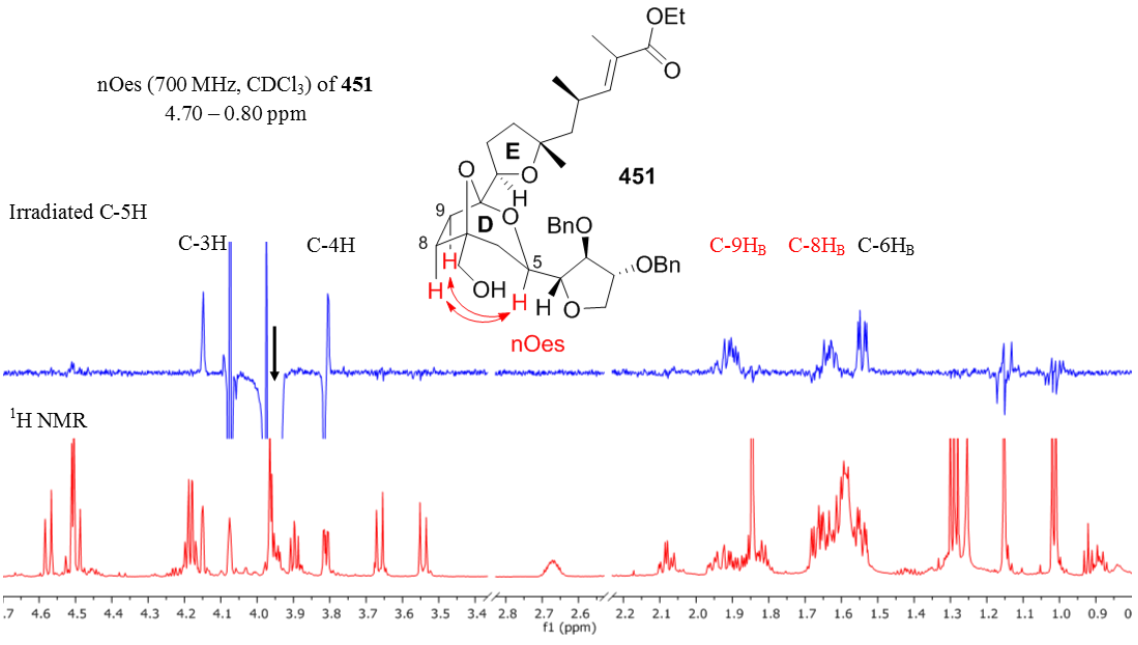
Key nOes observed: C-13H$_3$ to C-4H and C-14H$_3$, therefore (*E*) double bond geometry.

6.2.6 *^{1}H, ^{13}C NMR and nOe analysis of compound 451*





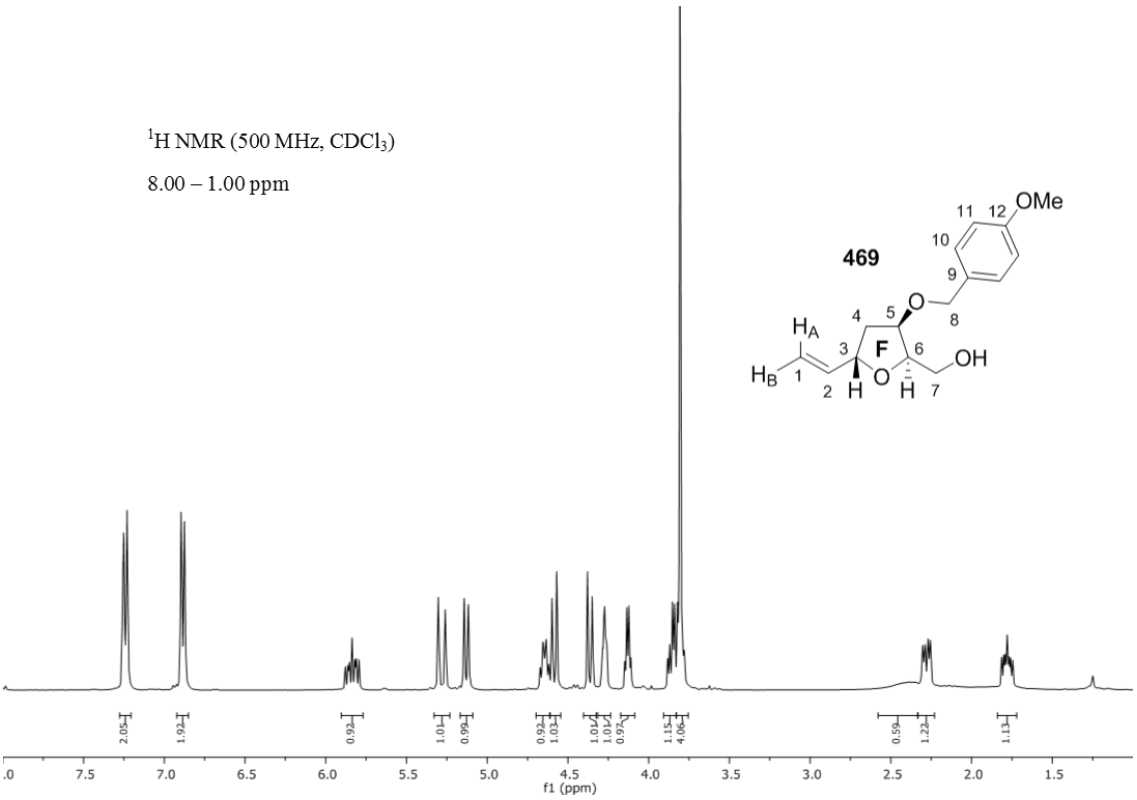


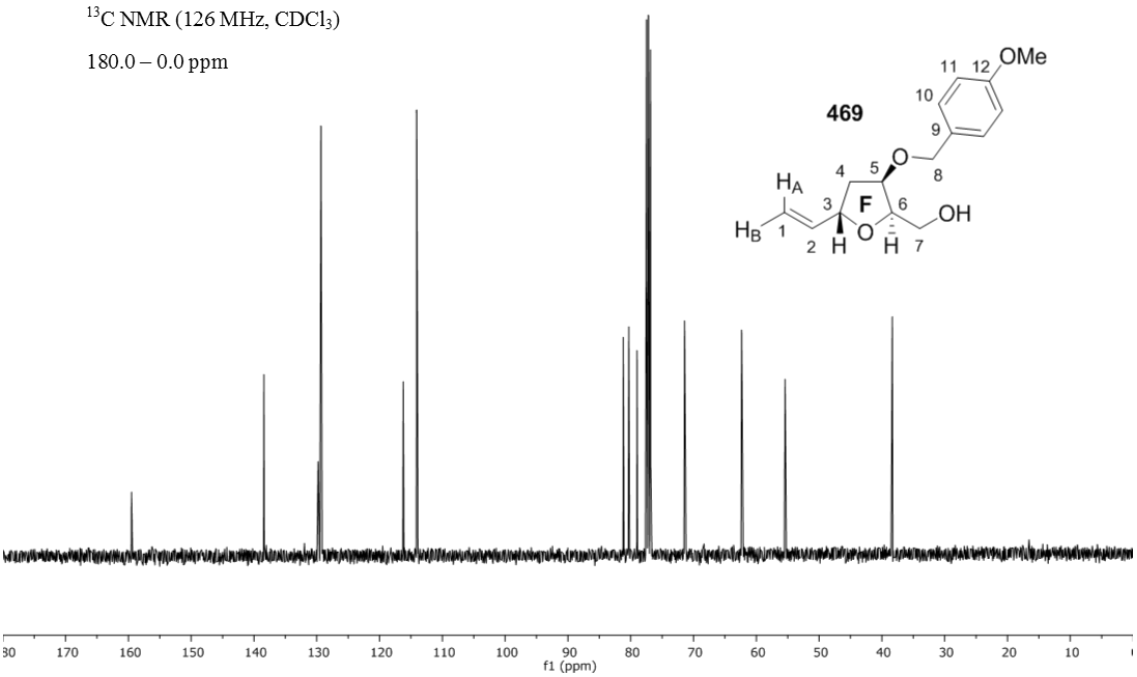


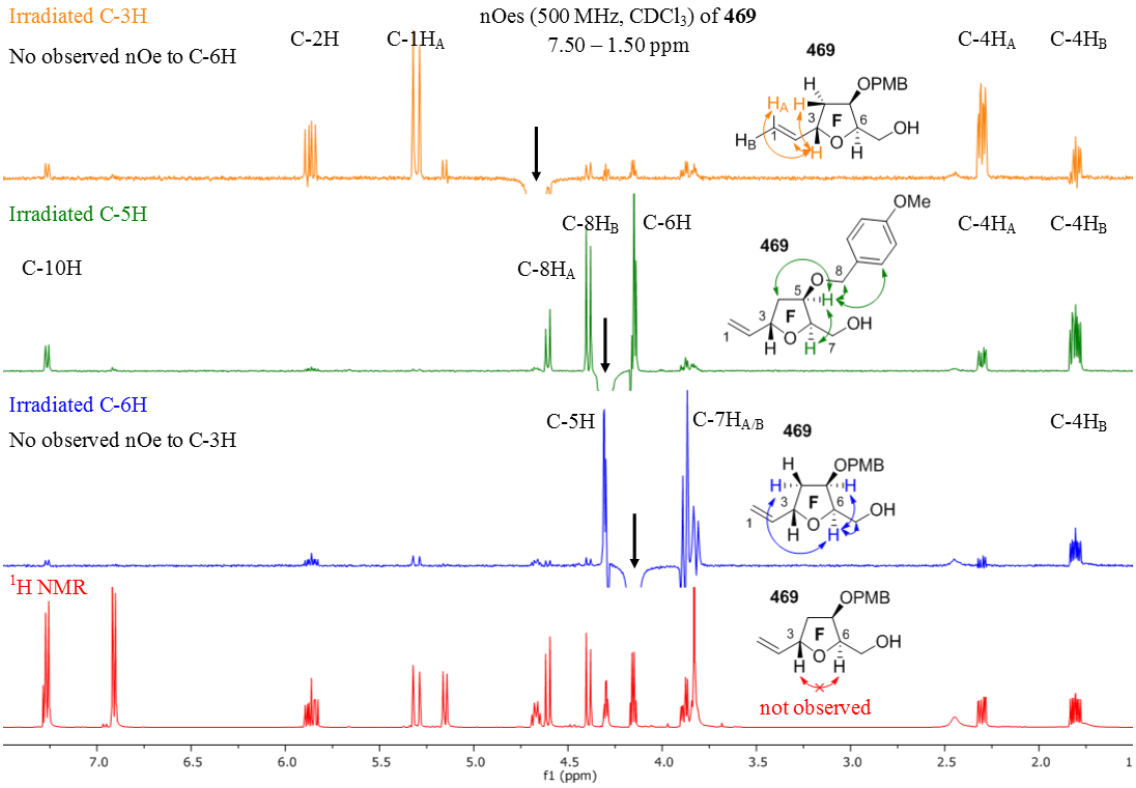
Key nOes observed: C-5H to C-8H$_B$ and C-9H$_B$.

Also observe nOes to C-3H, C-4H and C-6H$_B$.

6.2.7 ^{1}H, ^{13}C NMR and nOe analysis of compound 469







C-3H: nOes to C-1H_A, C-2H, C-4H_A and C-4H_B (weakly).

C-5H: nOes to C-4H_A (weakly), C-4H_B, C-6H, C-8H_A and C-8H_B.

C-6H: nOes to C-4H_B, C-5H and C-7H_A and H_B.

No observed nOe between C-3H and C-6H therefore *trans*-tetrahydrofuran geometry.

Chapter 7

Chapter 7: References

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