

Synthesis of the CDE & EFG Ring Systems of Pectenotoxin-4

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by

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and

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Declaration

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

Yifan Liu

University of Oxford, Hilary Term 2016

Abstract

A thesis submitted for the degree of Doctor of Philosophy.

Yifan Liu, Wolfson College and the Chemistry Research Laboratory, HT 2016

This thesis explores new synthetic routes for the formation of CDE & EFG fragments of pectenotoxin-4.

Chapter 1: Introduction and Previous Work

This chapter reviews the discovery and biological activities of members of the pectenotoxin family. Two previous total syntheses are discussed, and previous work regarding the synthesis of ABC, E and FG fragments within the group is introduced.

Chapter 2: Synthesis of the E Ring Fragment of Pectenotoxin-4

The synthesis of the E ring fragment is discussed. Key reactions include Negishi coupling and osmium mediated oxidative cyclisation.

Chapter 3: First Generation Strategy for the Synthesis of the D ring

A simple model towards the D ring core was completed using alkyne-epoxide opening strategy. The application on a more sophisticated system was tested.

Chapter 4: Second Generation Strategy for the Synthesis of the D ring

Sonogashira coupling was successfully tested as key step to unite two coupling partners; and further functionalisation towards the D ring skeleton was studied.

Chapter 5: Third Generation Strategy for the Synthesis of the D ring

The new strategy including a Lewis acid assisted coupling and mercury mediated hydration of alkyne sequence was completed on a simple model. The application on a more sophisticated system was tested.

Chapter 6: Synthesis of EFG Fragment of Pectenotoxin-4

Key Julia–Kocienski olefination between E ring fragment and FG ring fragment was examined. The further functionalisation of the resulting coupling product towards EFG fragment was finished.

Chapter 7: Experimental

Full experimental procedures and characterisation of compounds are reported.

Acknowledgements

I would like to thank Professor Tim Donohoe for his support during my DPhil research in the group. He is so approachable that I can always pop in the office to discuss any problems and thoughts in the research.

Thanks to CSC Scholarship for their financial support to fund my DPhil.

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I will really miss Team Pectenotoxin, Xuezheng, Ahria, Mike, Matt... We have done so much together and it was really a wonderful time of collaborations.

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Now it comes to the end of my student life (hopefully). I will miss everyone I met here...

Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
AD	asymmetric dihydroxylation
aq.	aqueous
Ar	aryl
atm	atmosphere
BMS	borane dimethyl sulfide
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
br.	Broad
brsm	based on recovery of starting material
Bt	benzothiazole
Bu	butyl
C	Celsius
cm ⁻¹	wavenumbers
CSA	camphorsulfonic acid
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQ	dihydroquinyl
DHQD	dihydroquinidyl
DET	diethyl tartrate
DIBAL	diisobutyl aluminium hydride
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
eq.	equivalents
ESI ⁺	electrospray ionization (positive ion detection)
Et	ethyl
g	gas
H	hour(s)
Hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphorotriamide
HPLC	high performance liquid
HRMS	high resolution mass spectrometry
Hz	hertz
<i>i</i>	<i>iso</i>
Im	imidazole
IR	infra-red
J	coupling constant (Hz)
L	generic ligand
LDA	lithium diisopropylamide
M	molar

mM	millimolar
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mL	millitres
mol	mole
M.P.	melting point
MOM	methoxymethyl
m.s.	molecular sieves
<i>n</i>	normal
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMP	<i>N</i> -methylpyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	generic nucleophile
P	generic protecting group (n = number)
PG	protecting group
Ph	phenyl
pH	$-\log_{10}[\text{H}_3\text{O}^+]$
PHAL	phthalazinyl
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
PTX	pectenotoxin
Py	pyridine
R	generic alkyl group
R*	non-racemic alkyl group
R _L	generic large substituent
R _M	generic medium substituent
R _S	generic small substituent
RSM	recovered starting material
r.t.	room temperature
SAE	Sharpless asymmetric epoxidation
Super-Hydride	lithium triethylborohydride
<i>t</i>	<i>tert</i>
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butyl ammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBODPS	<i>tert</i> -butoxide diphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

Ts
X

tosyl
generic halogen

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Chapter 1

Introduction and Previous Work

1.1 The Family of Pectenotoxins

1.1.1 Discovery

The first five members of the pectenotoxin (PTX) family, which originated from plankton (dinoflagellates *Dinophysis Fortii*), were isolated off the northeastern coast of Japan by Yamamoto and co-workers in 1983.^[1] They have also been found in sponges and shellfish globally.^{[2],[3],[4]} Currently, more than 20 compounds from the family have been isolated and their structures determined.^[5] Initially, they were classified as a group of toxins associated with diarrhetic shell fish poisoning,^[6] but later *in vivo* experiments demonstrated that liver seems to be their target organ and PTXs do not induce diarrhetic symptoms.^[7] It is now widely accepted that the actin cytoskeleton is the principal molecular target of PTXs.^[8]

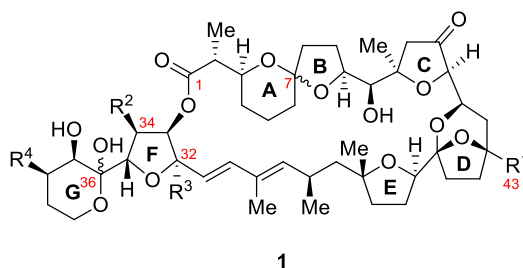


Figure 1.1 Structures of PTXs

Since 1990s, it has been discovered that some PTXs are potently cytotoxic in human cancer cell lines.^{[9],[10]} Structure-activity relationship studies suggest that the lactone ring integrity is essential for the toxicity, and oxidation at C43 decreases the toxicity.^{[6],[7]} PTX-2 is recognised as the parent compound and the most toxic among the PTX family, showing excellent LC₅₀ values against colon (7.82 nmol/L, COLO

205), lung (25.1 nmol/L, HOP-62) and breast cancer (62.7 nmol/L, BT-549).^[11]

The structures of fully characterised compounds in the PTX family are presented in Table 1.1.

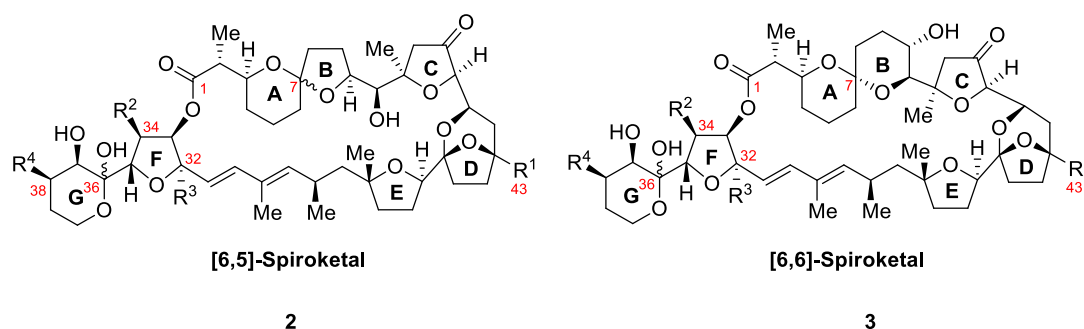


Table 1.1 Fully characterised compounds in PTX family

Entry	Name	Spiroketal	R ¹	R ²	R ³	R ⁴	C-7	C-36
1	PTX-1	[6,5]	CH ₂ OH	H	H	CH ₃	<i>R</i>	α -OH
2	PTX-2	[6,5]	CH ₃	H	H	CH ₃	<i>R</i>	α -OH
3	PTX-2b	[6,5]	CH ₃	H	H	CH ₃	<i>S</i>	α -OH
4	PTX-2c	[6,6]	H	H	H	CH ₃	<i>S</i>	α -OH
5	PTX-3	[6,5]	CHO	H	H	CH ₃	<i>R</i>	α -OH
6	PTX-4	[6,5]	CH ₂ OH	H	H	CH ₃	<i>S</i>	α -OH
7	PTX-6	[6,5]	COOH	H	H	CH ₃	<i>R</i>	α -OH
8	PTX-7	[6,5]	COOH	H	H	CH ₃	<i>S</i>	α -OH
9	PTX-8	[6,6]	H	H	H	CH ₃	<i>S</i>	α -OH
10	PTX-9	[6,6]	H	H	H	CH ₃	<i>S</i>	α -OH
11	PTX-11	[6,5]	CH ₃	OH	H	CH ₃	<i>R</i>	α -OH
12	PTX-11b	[6,5]	CH ₃	OH	H	CH ₃	<i>S</i>	α -OH
13	PTX-11c	[6,6]	CH ₃	OH	H	CH ₃	<i>S</i>	α -OH
14	36S-PTX-12	[6,5]	CH ₃	H	H	=CH ₂	<i>R</i>	α -OH
15	36R-PTX-12	[6,5]	CH ₃	H	H	=CH ₂	<i>R</i>	β -OH
16	PTX-13	[6,5]	CH ₃	H	OH	CH ₃	<i>R</i>	α -OH
17	PTX-14	[6,5]	CH ₃	H	O-C36	CH ₃	<i>R</i>	α -OH

Most of the compounds differ in the AB spiroketal ring stereochemistry, oxidation state at C43 and C34. The skeleton of PTXs features a 26-membered macrolactone, 8 highly functionalised THF or THP rings and 19 or 20 stereocentres. The 7 continuous stereogenic centres from C32 to C38, the highly-oxidised CDE system and the

stereocentre of the AB spiroketal are considered to be the major challenges towards the syntheses of PTXs.

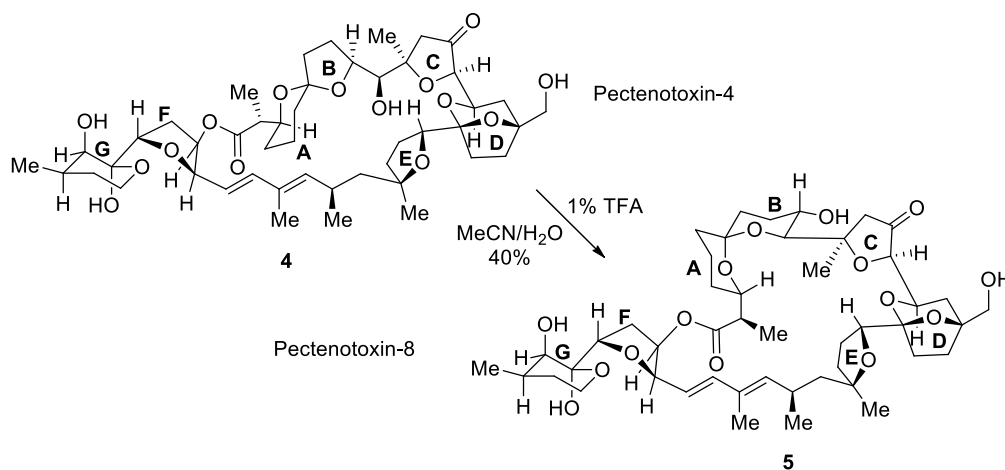
Normally, PTXs are labelled as ABCDEFG rings (Figure 1.1), yet some research groups preferred to separate dioxabicyclic D ring into two rings.^[12] In this report, we will use ABCDEFG ring systems to name all the fragments.

1.2 Previous Total Syntheses

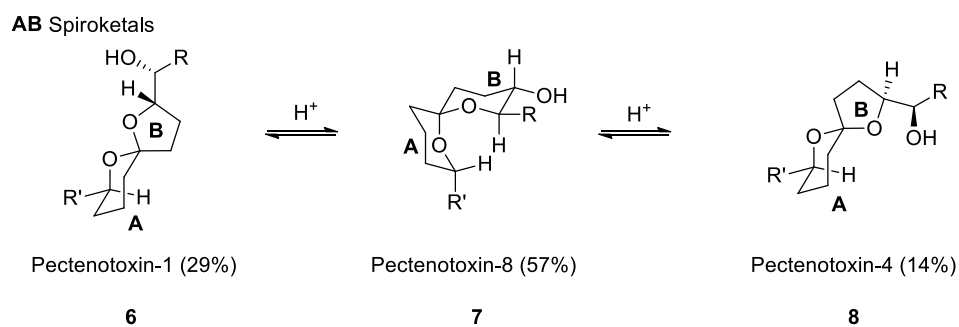
The unique structure as well as the excellent biological activities of PTXs has attracted the attention of many synthetic chemists.^[13–23] To date, only two total syntheses of members of the PTX family have been reported. Evans *et al.*^[24,25] first finished the total synthesis of PTX-4 and PTX-8 in 2002, and Fujiwara *et al.*^[26] finished the total synthesis of PTX-2 in 2014. In addition to the two total syntheses, more than 20 fragment syntheses towards PTXs have been published.^[12,14,15,17,20–46]

1.2.1 Evans' Total Synthesis (2002)

Evans and co-workers published their total synthesis of Pectenotoxin-4 and Pectenotoxin-8, the first two compounds in PTX family that had been synthesised. PTX-4 was synthesised as parent compound in a 36 longest linear step sequence and 0.3% overall yield. Based on the results of initial studies on isomerisation by Murai^[18] (Scheme 1.02), PTX-8 was obtained in 40% yield under acidic conditions (Scheme 1.01).

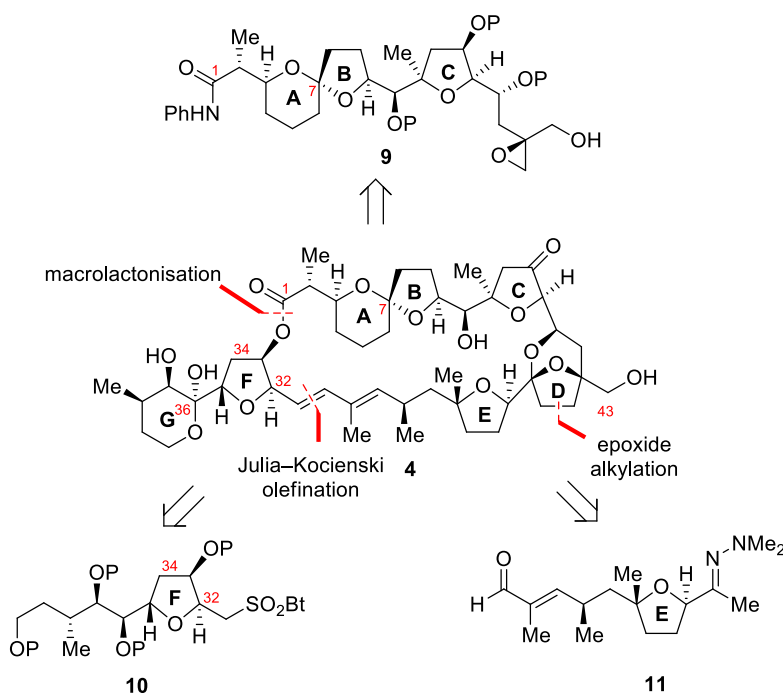


Scheme 1.01 Evans' synthesis of PTX-8



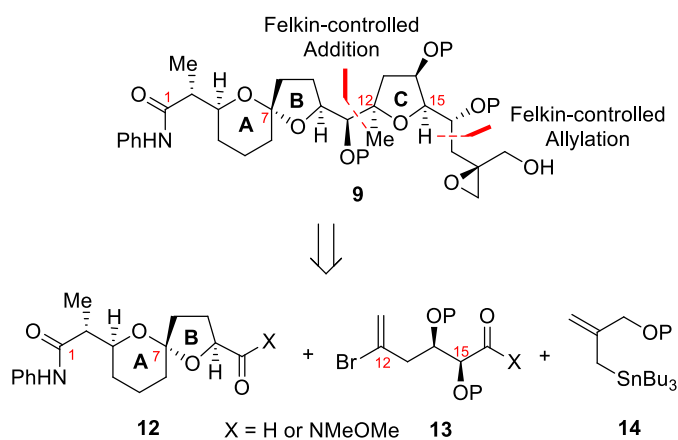
Scheme 1.02 Isomerisation studies by Murai

The disconnection strategy of PTX-4 is illustrated in Scheme 1.03, where macrolactonisation, Julia–Kocienski olefination^[47] and epoxide alkylation were used to couple three major fragments ABC, E and FG together. The G ring was cyclised at a later stage after the major coupling reactions.



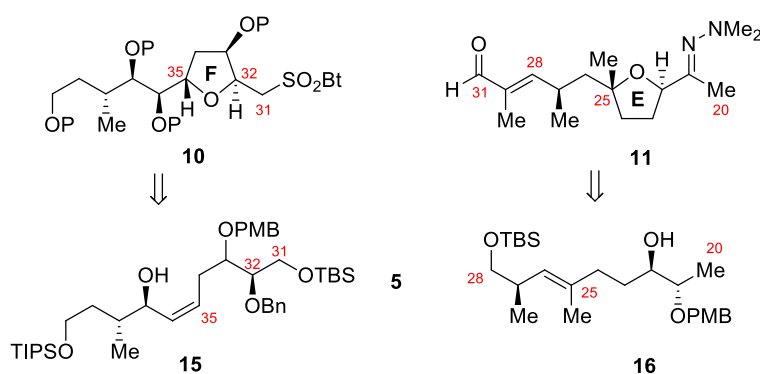
Scheme 1.03 Major disconnections of PTX-4 by Evans

Based on the disconnections described in Scheme 1.03, the ABC ring system can be further disconnected to fragments **9**, **10** and **11** using Felkin-controlled addition to the corresponding aldehydes or Weinreb amides (Scheme 1.04). Hydroxy-directed epoxidation (C12) and cyclisation of a subsequent epoxide by O15 constructed the C ring with the correct stereocentre (C12) with over 95:5 *d.r.*.



Scheme 1.04 Disconnections of the ABC ring system of PTX-4 by Evans

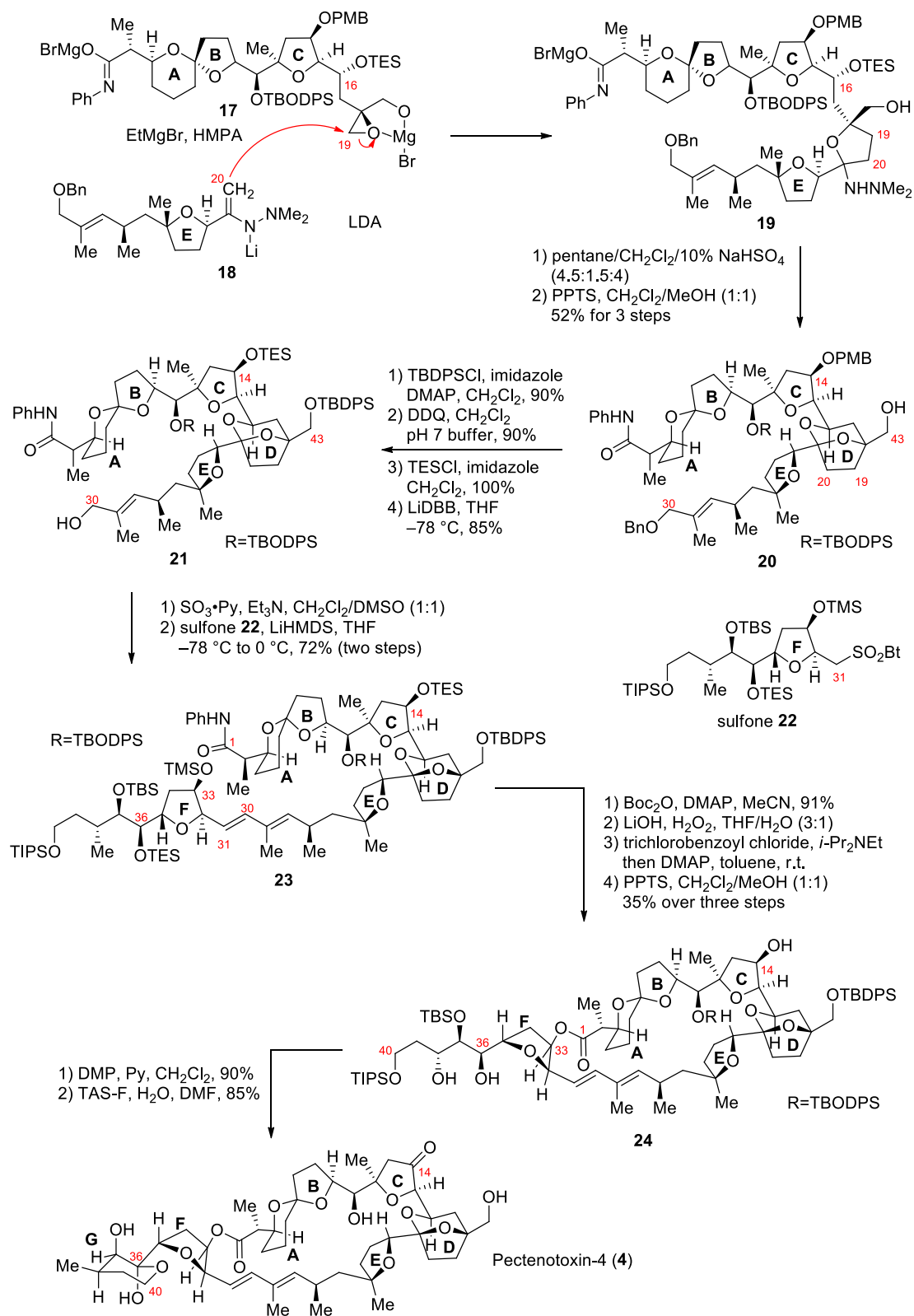
Having obtained the ABC fragment, Evans prepared E and F ring fragments *via* similar methods. The F ring fragment was formed using hydroxyl-directed epoxidation (C35) and an acidic cyclisation strategy (C32, over 95:5 *d.r.*) similar to the one performed in ABC fragment synthesis. The E ring fragment was synthesised using an iodo-assisted cyclisation (NIS, MeCN, $-40\text{ }^{\circ}\text{C}$, 89%), and moderate *d.r.* (72:28) was achieved.



Scheme 1.05 Disconnections of the FG and E ring system of PTX-4 by Evans

With all three portions in hand, the end game assembly could then be examined (Scheme 1.06).

Note that the coupling of the ABC fragment and the E ring fragment was achieved by the addition of MgBr_2 activated epoxide complex **17** to 5.7 equivalents of the metalloenamine **18** derived from corresponding hydrazone. The subsequent hydrazinyl alcohol **19** was subjected to acidic conditions to remove OTES (C16) and promote cyclisation. Therefore, the resulting D ring core was constructed in 52% yield (based on **17**) in three steps.



Scheme 1.06 End-game assembling of PTX-4 by Evans

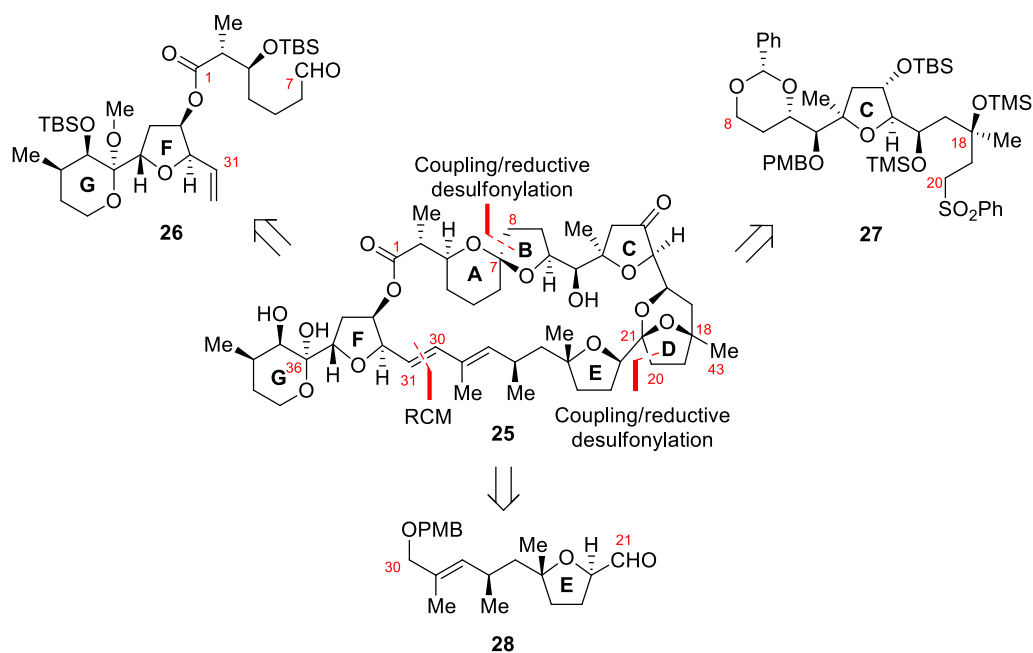
Protection group manipulations of ABCDE moiety **20** gave allylic alcohol **21**.

Oxidation of the primary alcohol (C30) gave the subsequent aldehyde, which was employed as the electrophilic partner in a Julia–Kocienski olefination. The key Julia coupling then united the final F ring fragment **22**, giving ABCDEF moiety **23** in 72% yield over two steps. Due to the E1cB elimination of sulfone **22**, Julia product **23** was isolated as an 88:12 mixture of C32 epimers.

The resulting *N*-phenylamide **23** was treated with Boc₂O/DMAP, and LiOH/H₂O₂/THF/H₂O hydrolysed the subsequent imide to corresponding carboxylic acid, which was then subjected to Yamaguchi macrolactonisation conditions. Afterwards the cyclised adduct was transformed to diol **24** under PPTS/MeOH conditions. Then, DMP oxidation of diol **24** and final TAS-F global deprotection gave the desired Pectentoxin-4 in 76% yield and thus finished the whole synthetic sequence.

1.2.2 Fujiwara's Total Synthesis (2014)

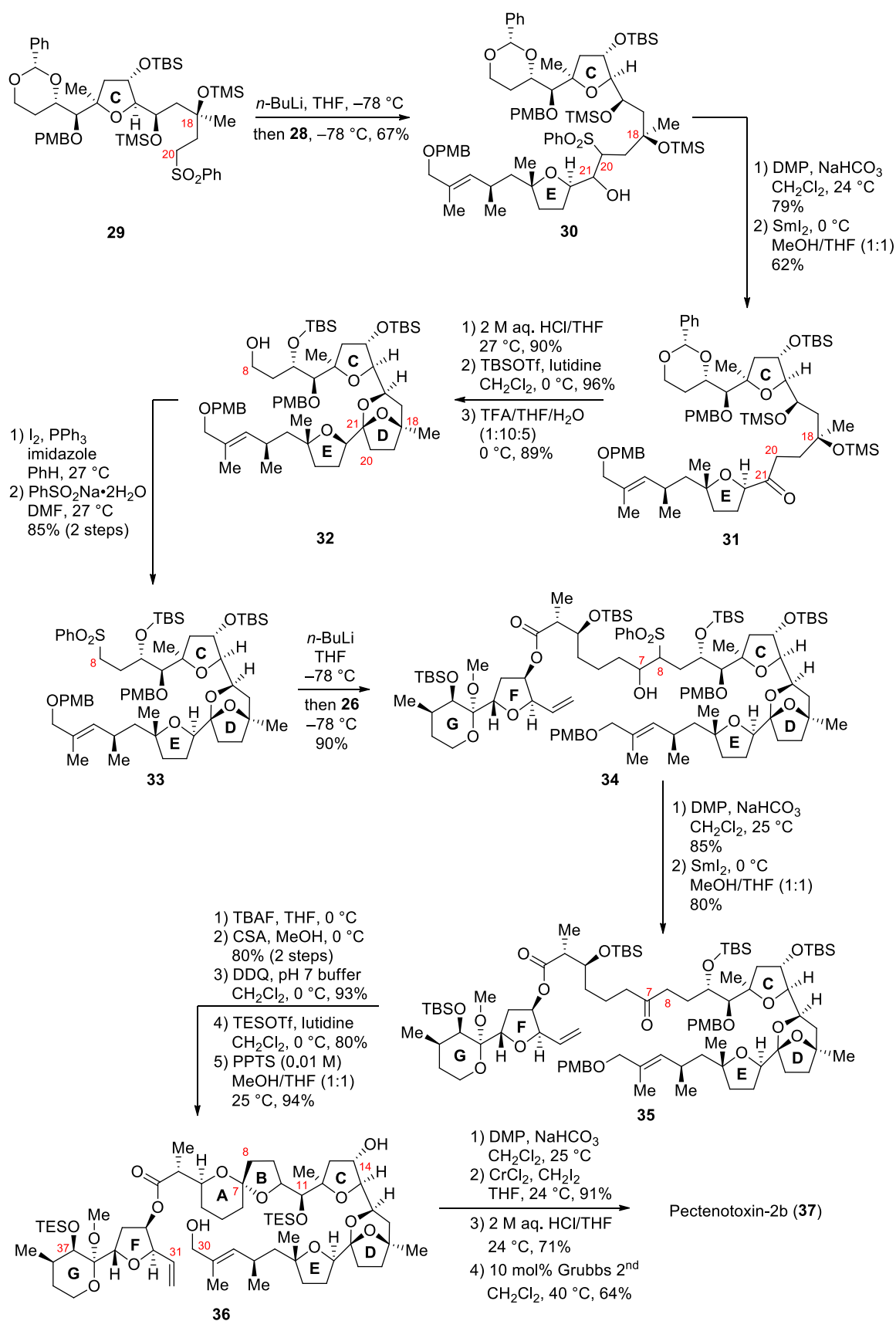
Fujiwara and co-workers finished the total synthesis of Pectenotoxin-2 in 2014. PTX-2 and PTX-4 differs in the C7 carbon configuration and C43 oxidation state (PTX-2, C7-*R*, C43-Me; PTX-4, C7-*S*, C43-CH₂OH). The major disconnection of PTX-2 by Fujiwara is presented in Scheme 1.07. Different from Evans' retrosynthetic strategy, Fujiwara chose to construct FG ring prior to fragment assembling,^[34] and ring close metathesis (C30–C31) was employed as the key step to form the 26-membered macrolactone.^[26] Sulfone-aldehyde coupling/reductive desulfonylation sequence was used to achieve the other two key coupling (C7–C8 and C20–C21).



Scheme 1.07 Major disconnections of PTX-2 by Fujiwara

Fujiwara's end-game strategy towards PTX-2 is illustrated in Scheme 1.08. Deprotonation of sulfone **29** (C ring portion) with *n*-BuLi and subsequent alkylation with aldehyde **28** (E ring portion) produced adduct **30** (C20–C21).^[18,20,33] DMP oxidation of subsequent alcohol **30** (C21) and radical cleavage of the sulfone group resulted in the formation of ketone **31**, which was subjected to PG manipulation to give alcohol **32** (C8).

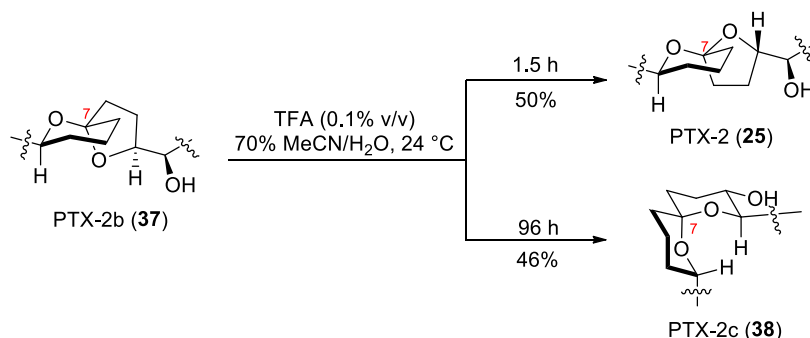
After treatment of alcohol **32** (C8) with I₂/PPh₃/imidazole, the resulting iodide was then transformed to subsequent sulfone **33**, which was again deprotonated and subjected to a coupling/reductive desulfonylation sequence (C7–C8) with aldehyde **26** (A ring skeleton) to give ketone (C7) **35**.



Scheme 1.08 End-game assembly of PTX-2b by Fujiwara

AB spiroketal was formed from ketone **35** upon treatment with TBAF and CSA sequentially, and the resulting spiroketal moiety was subjected to protecting group manipulation to produce primary alcohol **36** (C30). The DMP oxidation of alcohol **36** followed by Takai olefination^[48] produced C30 diene, which was then had protecting group removed, followed by an RCM reaction using Grubbs second generation catalyst. The resulting PTX-2b was successfully isolated in 64% yield without isomerisation of the spiroketal moiety.

When PTX-2b was subjected to mild acidic conditions, PTX-2 could be isolated in 50% yield in 1.5 h and PTX-2c could be isolated in 46% yield after 96 h.



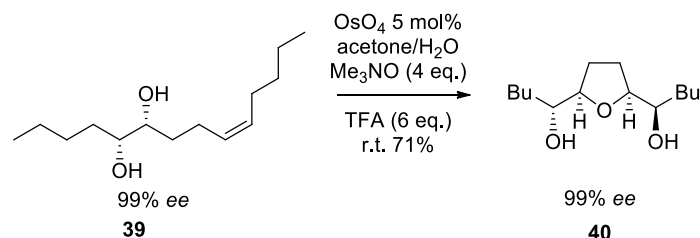
Scheme 1.09 Isomerisation of PTX-2b to PTX-2 and PTX-2c under mild acidic conditions

1.3 Our Strategy

1.3.1 Background

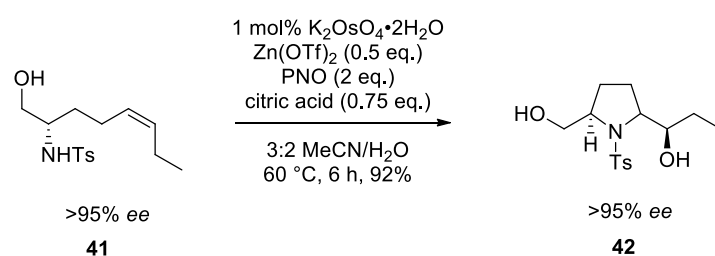
In 2005, Donohoe and co-workers^[49] reported a new catalytic oxidation reaction that promotes the cyclisation of vicinal diols onto a proximal alkene with a high level of

stereocontrol. The osmium species could be condensed onto a pre-formed diol to give an intermediate osmate ester that could undergo the oxidative cyclisation.



Scheme 1.10 Oxidative cyclisation developed by Donohoe in 2005

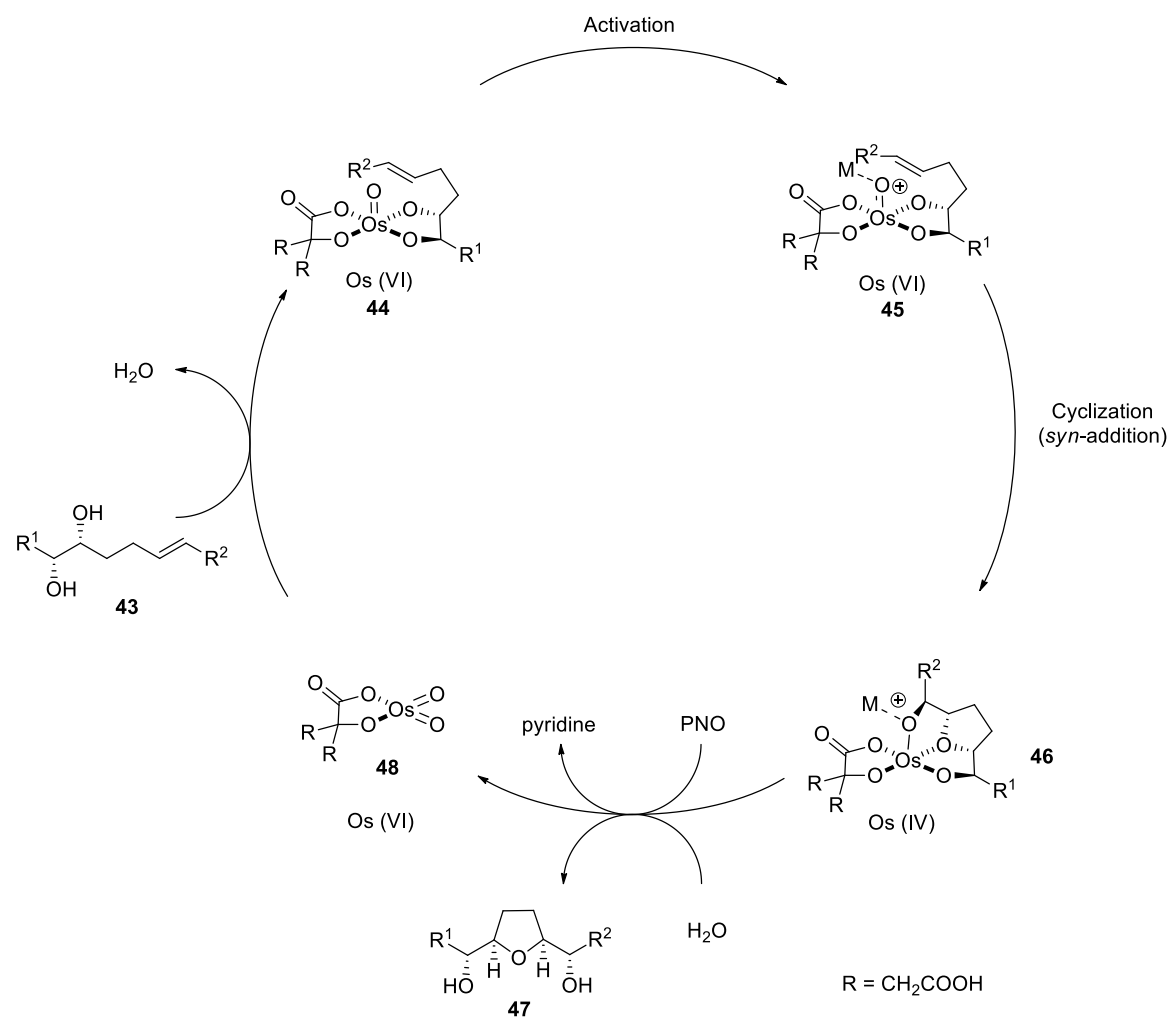
The reaction was then further developed within the group (Scheme 1.11).^[50] The milder oxidising agent PNO was used instead of NMO as it can avoid the oxidation to unwanted Os(VIII), which can result in the dihydroxylation of the starting material. The addition of citric acid was found to stabilise Os(VI)^[51] with respect to disproportion in acidic media, and the presence of Lewis acid can accelerate the reaction rate.^[50]



Scheme 1.11 Optimised conditions for an oxidative cyclisation

The detailed mechanism of oxidative cyclisation is illustrated in Scheme 1.12. The first step includes the attachment of osmium(VI) to the diol substrate **43**. Coordination of the Lewis acid to the osmium centre, activates the intermediate **45** to react to give

the *syn*-cyclisation product **46**. Following this, **46** is hydrolysed to give cyclised THF product **47**. PNO re-oxidises osmium(IV) to osmium(VI), completing the catalytic cycle. Notably, the stereochemistry of the product is fully controlled by the stereogenic centre in the substrate.



Scheme 1.12 Mechanism of oxidative cyclisation

This methodology is simple to perform and tolerant of substitution on the THF backbone, giving a reliable and predictable stereochemically defined formation of *cis*-THF rings directed by the chiral secondary alcohol. A number of natural products have been synthesised within the group using this methodology.^[17,49,52–54] Therefore,

we hoped to use this methodology to efficiently construct the highly functionalised THF rings of PTXs.

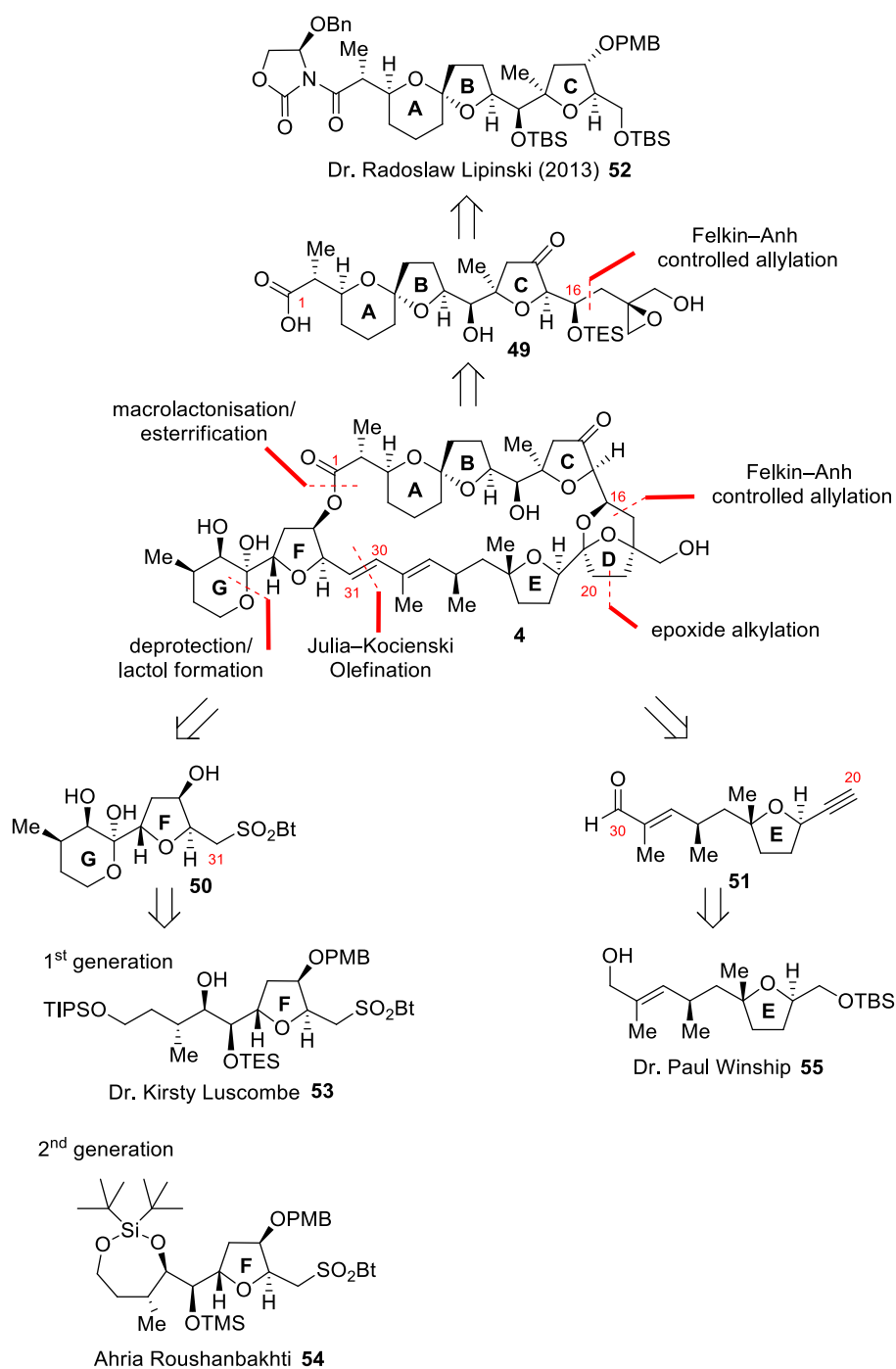
1.3.2 Retrosynthesis and Previous Work in the Group

Our strategy to disconnect PTX-4 is presented in Scheme 1.13. The major disconnection includes macrolactonisation (C1), Julia–Kocienski olefination (C30) epoxide alkylation (C20) and Felkin–Anh controlled allylation (C16).

ABC moiety **52** was prepared by Dr. Radoslaw Lipinski^[17] (2013) in 18 linear steps in 2.6% overall yield in the group. A cascade oxidative cyclisation and hydride shifts strategy was employed to synthesise the AB spiroketal.

The E ring portion **55** was initially synthesised by Dr. Paul Winship^[55] (2011) in 15 linear steps in 7.5% overall yield. Key reaction included Negishi coupling and oxidative cyclisation. Details regarding the original route and optimisation of it will be discussed in Chapter 2.

The FG ring portion was accessed in two generation strategies in Donohoe group. Dr. Kirsty Luscombe^[56] (2012) first prepared the FG ring portion **53** in 12 linear steps in 0.69% overall yield. Ahria Roushanbakhti developed second generation strategy (2015) towards FG portion **54** in 12 linear steps in 5.7% yield^[57] based on preliminary results from Dr. Michael Tucker.^[58]



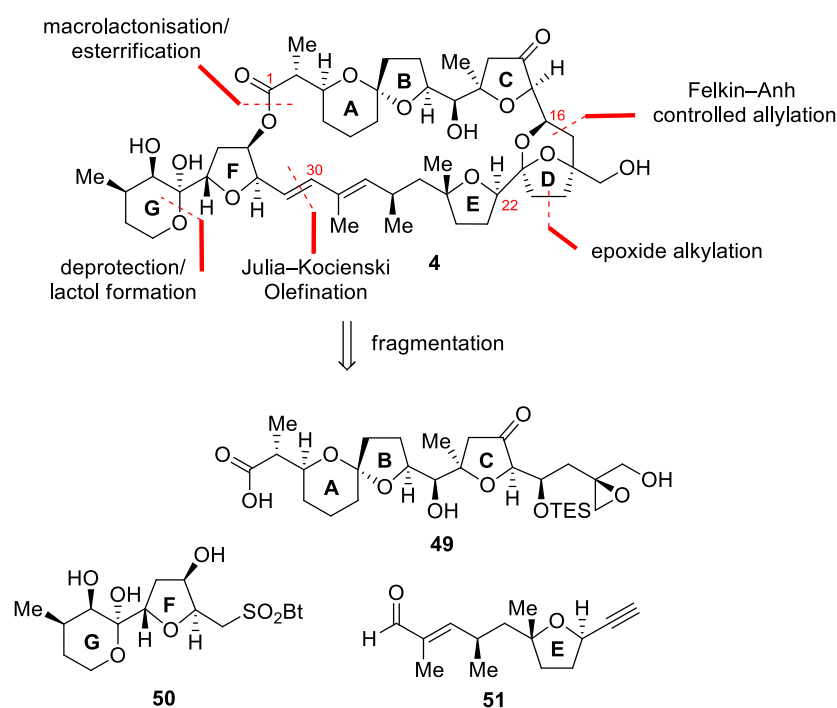
Scheme 1.13 Our strategy and previous work towards PTX-4 in the group

Chapter 2

Synthesis of the E Ring Fragment of Pectenotoxin-4

2.1 Introduction

As described in Chapter 1, our strategy towards the synthesis of pectenotoxin-4 (PTX-4) follows a similar retrosynthetic analysis to the route previously described by Evans (Scheme 2.01).^[25]

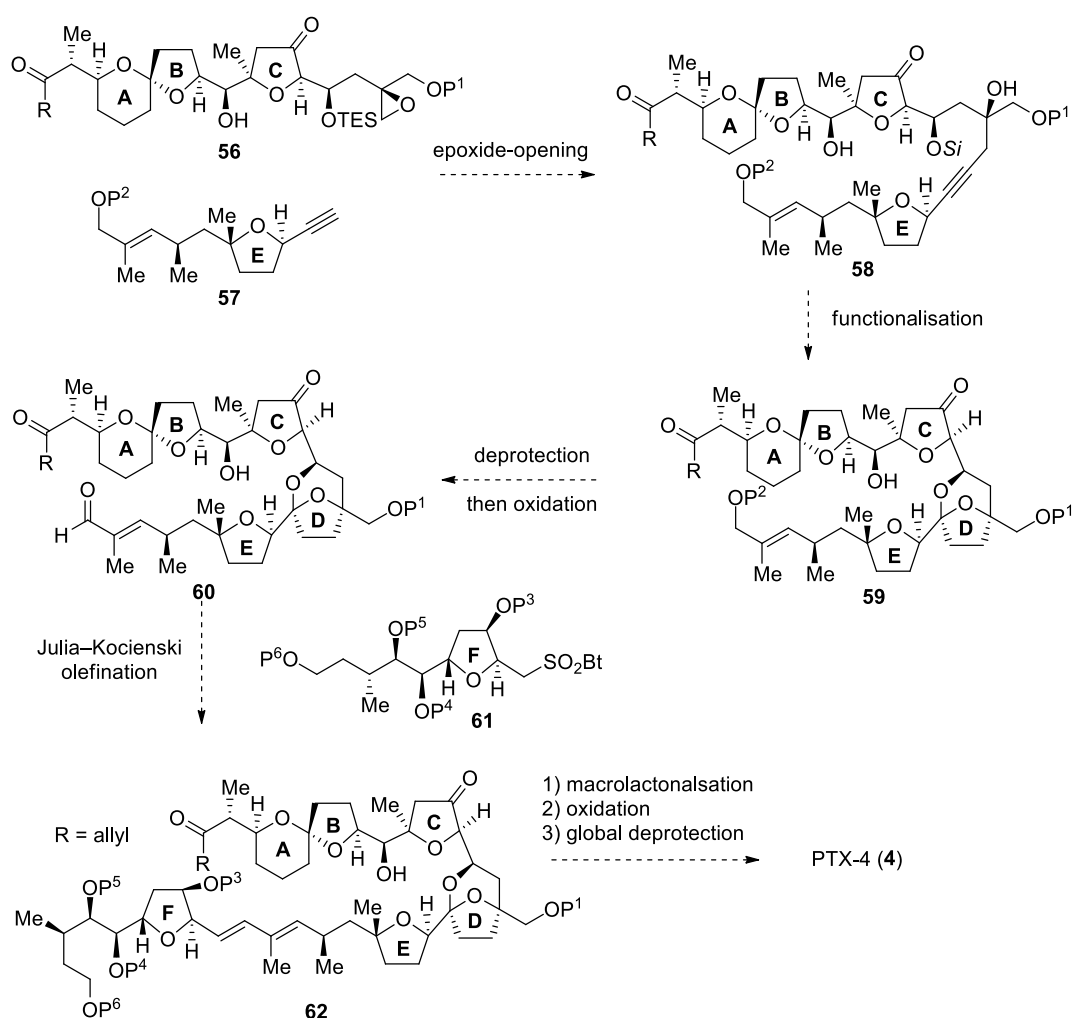


Scheme 2.01 Retrosynthesis of PTX-4

Based on this strategy, PTX-4 can be disconnected into three different parts comprising of the ABC, E and FG ring fragments. The key coupling reactions involve esterification to connect the ABC and FG, Julia-Kocienski olefination to combine E and FG, and then epoxide-alkynylation to unite ABC and E fragments. Finally, the D ring can be generated through functionalisation of the alkyne.

It was determined that the most practical plan for the synthesis of PTX-4 (Scheme

2.02) was to first assemble the ABC and E ring fragments, utilising further functionalisation of the alkyne moiety to furnish an advanced intermediate **59** containing the D ring. Selective deprotection of OP² and oxidation of the corresponding alcohol to aldehyde gives the Julia–Kocienski precursor **60**; which can then be coupled with the F ring fragment **61**. Subsequent macrolactonisation would then form the 26-membered ring of PTX-4. Final deprotection of OP⁴, oxidation, and removal of all remaining protecting groups will complete PTX-4.



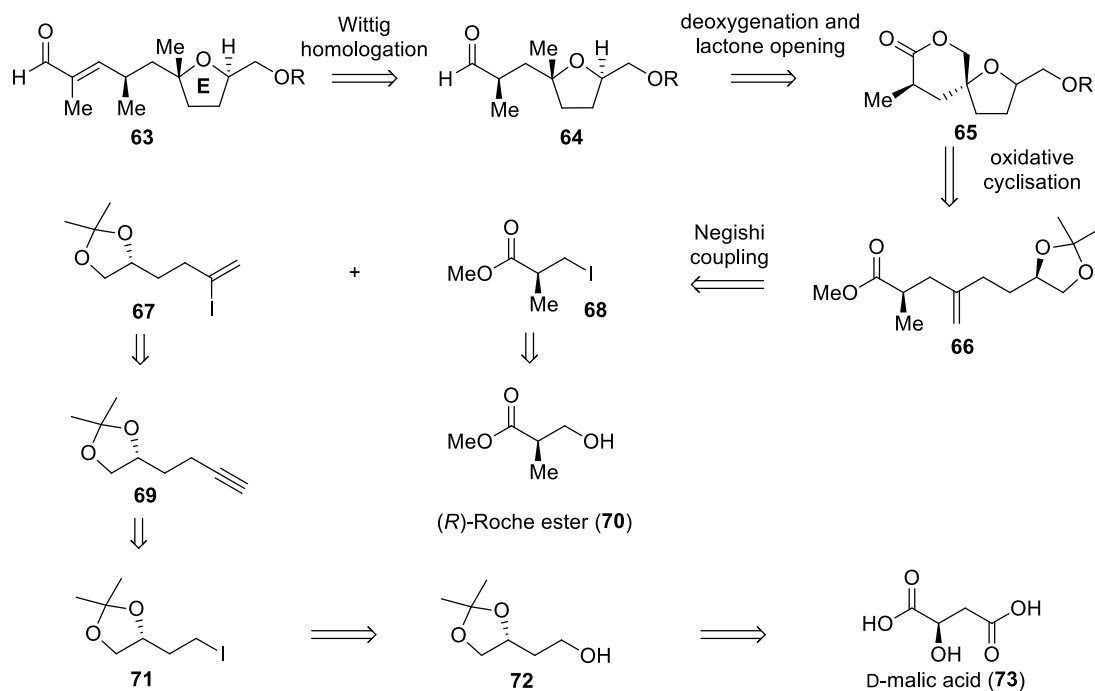
Scheme 2.02 Proposed late stage coupling strategy to complete PTX-4

The next sections in this chapter will focus on the following issues: 1) synthesis of the E ring fragment; 2) comparison with the work of others; 3) future applications.

2.2 Retrosynthetic Analysis of the E Ring Fragment

Initially, the synthetic route first developed by a former group member Dr. Paul Winship^[55] was examined, with the aim of repeating the synthetic route, before optimisation and scale-up to provide a solid base for the total synthesis. The retrosynthetic analysis is shown in Scheme 2.03.

In order to obtain aldehyde **63**, a strategy utilising the direct Wittig homologation^[59] or Wittig-reduction-oxidation could be applied. A lactone opening/deoxygenation strategy furnishes **64** from spiro-lactone **65**, which itself is a product of osmium mediated oxidative cyclisation^[50] from **66**. The oxidative cyclisation precursor can be accessed by the Negishi coupling^[60] of vinyl iodide **67** and iodide **68**. Both coupling fragments can easily be synthesised from commercially available chiral compounds (*R*)-Roche ester and D-malic acid.

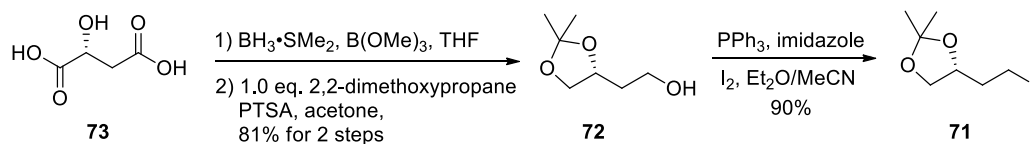


Scheme 2.03 Retrosynthetic analysis of the PTX-4 E ring

2.3 Synthetic Route

2.3.1 Synthesis of Negishi Precursor: Vinyl Iodide **67**

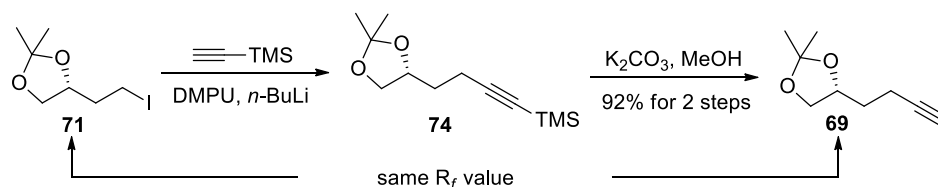
Starting from commercially available material D-malic acid, alcohol **72** was easily obtained following a two-step reduction-protection process (Scheme 1.04). An Appel reaction using I_2/PPh_3 /imidazole condition then converted subsequent alcohol **72** into iodide **71** in 90% yield.^[61]



Scheme 2.04 Synthesis of iodide **71**

With iodide **71** in hand, alkylation with lithium TMS-acetylene, followed by

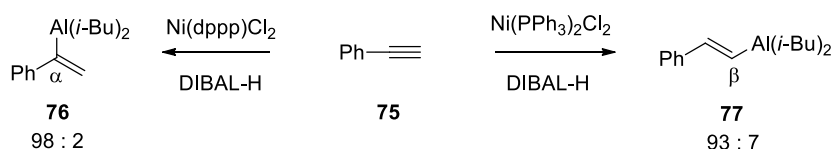
deprotection to the alkyne was then examined. Conducting this sequence as a stepwise procedure gave 85% for alkynylation and 90% yield for TMS deprotection.



Scheme 2.05 Synthesis of alkyne **69**

Initially, the alkynylation reaction was thought to be difficult to push to completion as indicated by TLC. ^1H NMR analysis of the unreacted ‘starting material’ in the reaction revealed that this was not actually starting material **71**, but the product of deprotection, terminal alkyne **69**. The formation of **69** was postulated to be due to nucleophilic attack of the excess base onto TMS-alkyne **74**. Therefore, since iodide **71** and terminal alkyne **69** have the same retention value (TLC), it was viewed as impractical to judge reaction completion by TLC monitoring, and as a result more than 1.5 equivalents of nucleophile were used to ensure full consumption of the starting material. Finally, a more convenient protocol was developed by performing a one-pot deprotection by the addition of potassium carbonate and methanol directly into the reaction mixture producing alkyne **69** in 92% yield over two steps. This avoided the use of laborious column chromatography and minimised potential loss of the volatile product during solvent removal.

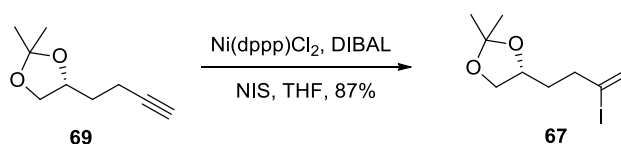
Inspired by methodology developed by Hoveyda^[62] (Scheme 2.06), we then chose to perform a nickel-catalysed hydroalumination to access vinyl iodide **67**.



Scheme 2.06 Selectivity of alkyne metalation

Hoveyda noted that when the hydroalumination of a terminal alkyne was performed in the absence of a catalyst, DIBAL-H was found to react with the acetylene bond to afford the β -vinylaluminium. However, when different nickel catalysts were applied, the selectivity could be controlled to selectively give either α or β products.

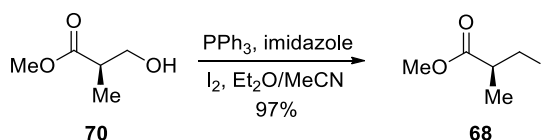
Using literature conditions, vinyl iodide **67** was synthesised as a single product in 87% yield. The coupling constant between the two protons of the double bond was 1.2 Hz, providing strong evidence for the formation of the desired 1,1-disubstituted alkene instead of the 1,2-disubstituted derivative.



Scheme 2.07 Synthesis of coupling partner **67**

2.3.2 Synthesis of the Negishi Precursor **68**

In order to perform the desired Negishi coupling, coupling partner **68** was synthesised as depicted in Scheme 2.08. Similar to the formation of iodide **71**, a simple iodination process furnished iodide **68** in almost quantitative yield.

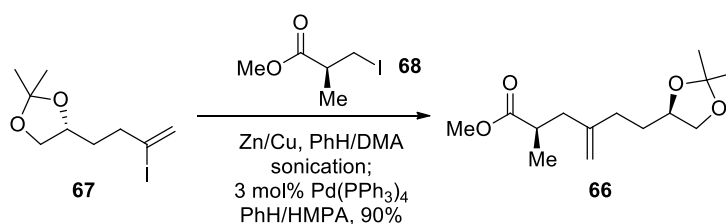


Scheme 2.08 Synthesis of coupling partner **68**

2.3.3 Negishi Coupling and Further Functionalisation

With easy access to both coupling partners **67** and **68**, the conditions required for the Negishi coupling were investigated.

Using the conditions developed previously by Dr. Paul Winship, iodide **68** was treated with a zinc/copper couple and sonicated at 40 °C to 50 °C for two hours for the purpose of activation. Following this, the suspension was added to a solution of vinyl iodide **67**, HMPA, $\text{Pd}(\text{PPh}_3)_4$ and benzene *via* cannula. The reaction mixture was then heated at reflux for two hours to provide the coupled product **66** in an excellent yield of 90%. All the data were consistent with Dr. Paul Winship's report.^[55]

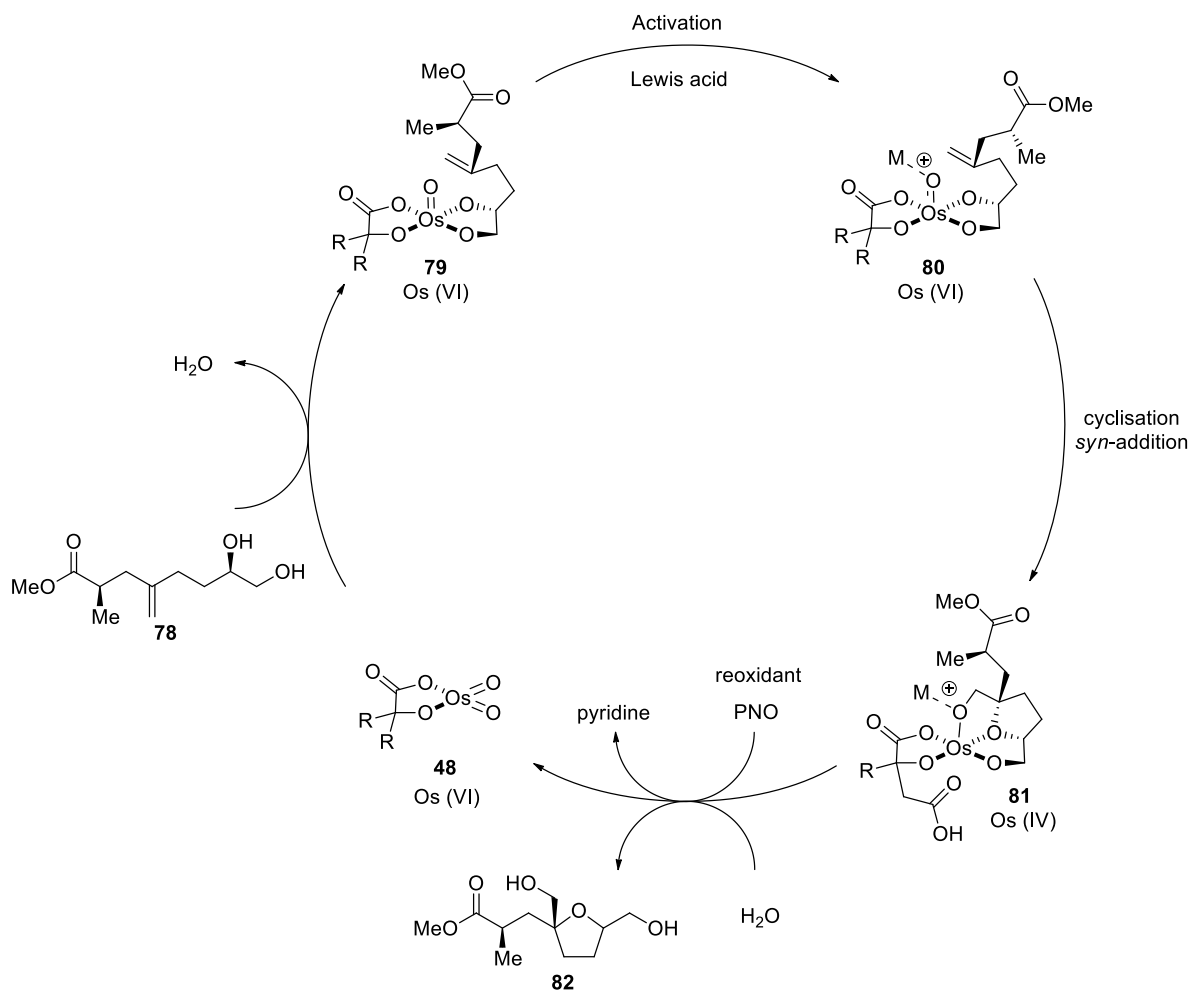


Scheme 2.09 Negishi coupling

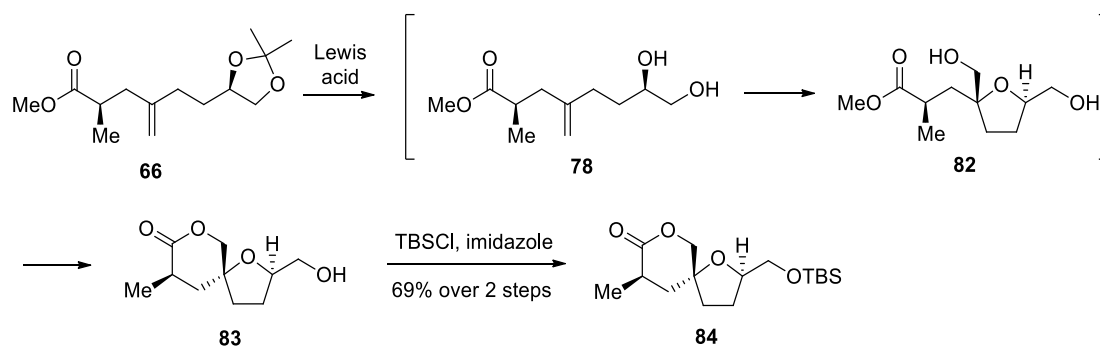
As described in Scheme 2.03, the key oxidative cyclisation was then performed on substrate **66**. Addition of the Lewis acid first deprotected the acetal to give diol **78** *in situ*, which then chelated to potassium osmate to form intermediate **79**. When activated by the metal cation of the Lewis acid, the oxidative cyclisation proceeded

smoothly, generating cyclised complex **81**. At this stage, citric acid was found to accelerate the hydrolysis process in the next step.^[51] Sharpless proposed that the neighbouring group participation of the carboxylic acid oxygen in citric acid (Scheme 2.10, R=CH₂COOH) was responsible for aiding the hydrolysis of the osmate ester, possibly from the open coordination site of the square-pyramidal intermediate. Once the oxidation and hydrolysis were finished, the generated hydroxyl group attacks the methyl ester to form the spiro-lactone product **84**. Sc(OTf)₃ was found to effectively promote the reaction, but the high loading (0.5 eq.) required and high molecular weight of Sc(OTf)₃ makes the reaction very expensive to perform on large scale (the cost is around £30/g for the Lewis acid). When a more cost-effective Lewis acid, eg. Cu(OTf)₂ (£6/g) was used, the yield dropped from 76 % to 63 % (yield based on three times purification by column chromatography). As a result, a compromise was found, with 0.1 eq. of Sc(OTf)₃ and 0.4 eq. of Cu(OTf)₂ used, which gave a reproducible yield of 76% on 10 gram scale.

Purification of the lactone **84** was not so straightforward and the product was often found to be contaminated with a small amount of the Lewis acids after the column, possibly due to the high loading of the reagents. Therefore the crude product **84** was directly treated with standard TBS protection conditions to avoid the problematic purification procedure. Interestingly, lactone **84** was found to be a white solid when stored in the freezer, but melted at room temperature.



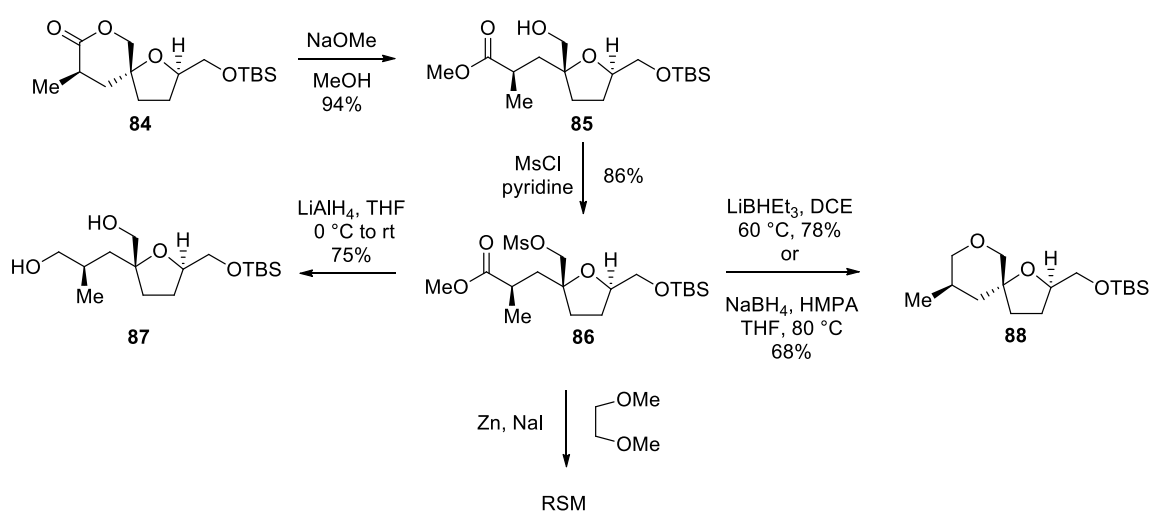
Scheme 2.10 Catalytic cycle for Os(VI) oxidative cyclisation



Scheme 2.11 Formation of lactone **84** from substrate **66**

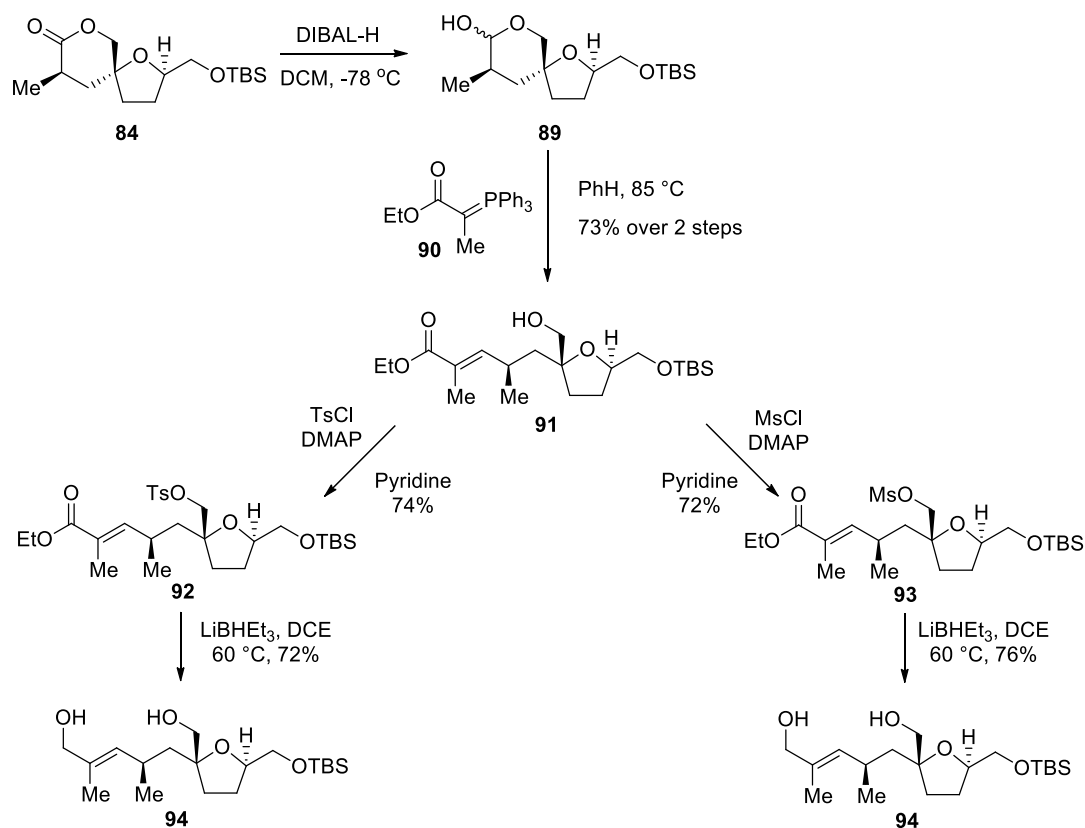
Having obtained lactone **84** on a multi-gram scale, the next job was to deoxygenate the hydroxyl group of the neo-pentyl position (Scheme 2.12). Functionalisation of

compound **84** proved to be a nontrivial process, and previous work by Dr. Paul Winship towards deoxygenation had been met with some difficulty. As shown in Scheme 2.12, lactone **84** could be opened by NaOMe to provide **85**. Mesylation of the primary hydroxyl group was then performed in order to provide a better leaving group. However, three different reduction strategies using Super-Hydride[®], Lithium Aluminium Hydride or radical conditions did not result in deoxygenation.^[63–66]



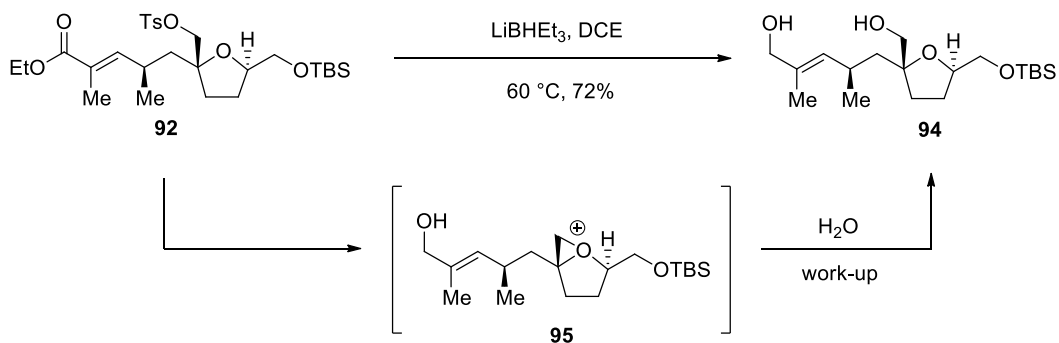
Scheme 2.12 Failed deoxygenation attempts by Dr. Paul Winship

Therefore, another strategy was carried out by forming the conjugated ester **91** first, followed by deoxygenation. Similar efforts to those described above were then made to deoxygenate the hydroxyl group. Apart from mesylates, tosylate protected alcohols have previously proved to be ideal substrates to undergo deoxygenation.^[67] Unfortunately, when Super-Hydride[®] was applied to both substrates, compound **94** was the only product observed.



Scheme 2.13 Failed deoxygenation attempts by Dr. Paul Winship

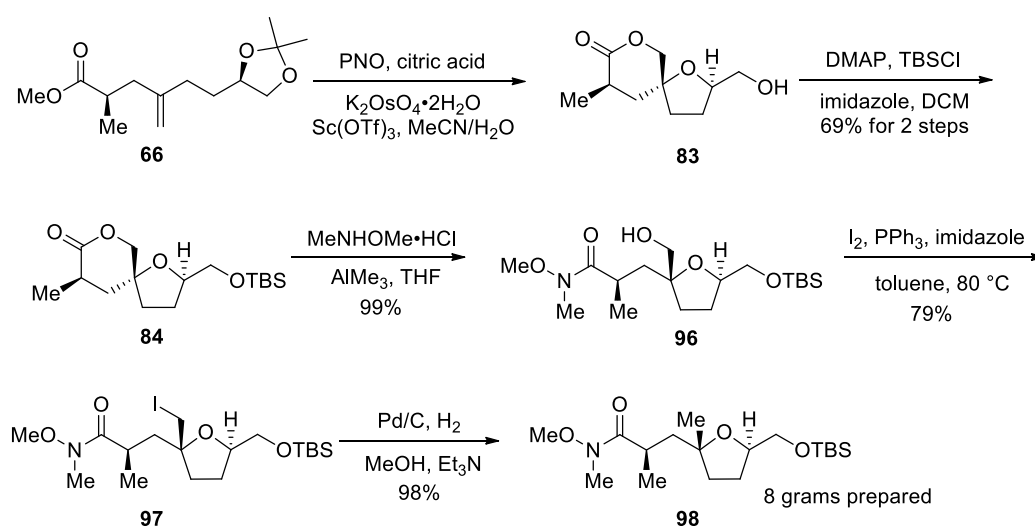
Dr. Paul Winship proposed that the lone pair of the THF-oxygen could attack the neopentyl centre to give an oxonium intermediate, which is then reluctant to react further, but could be quenched by water during work-up (Scheme 2.14).



Scheme 2.14 Proposed intermediate for failed deoxygenation

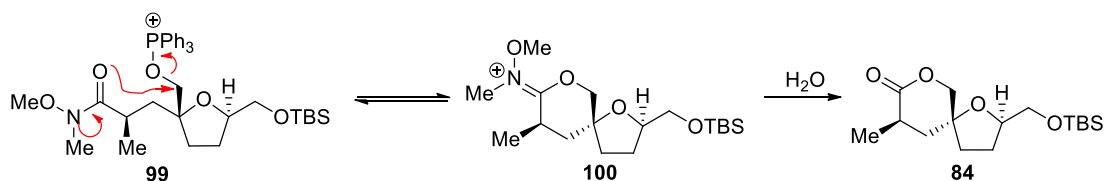
Since both of these strategies did not provide the desired deoxygenated product, an

alternative approach was sought. Instead of deoxygenating the neopentyl alcohol by reduction of mesylated or tosylated derivatives, it was decided that hydrogenation of the corresponding iodide **97** might be beneficial. This was indeed the case and Weinreb amide formation, iodination and hydrogenation provided target structure **98** in very good yield. All the spectroscopic data including ^1H , ^{13}C NMR were consistent with Dr. Paul Winship's.^[55]



Scheme 2.15 Successful attempts to scale-up the route to deoxygenation product **98**

When performing this chemistry, we discovered that lactone **84** formed as a byproduct during the iodination process. A possible explanation for this involves the reversible formation of intermediate **100**, which could then collapse back to lactone **84** by hydrolysis during the work-up of the reaction.

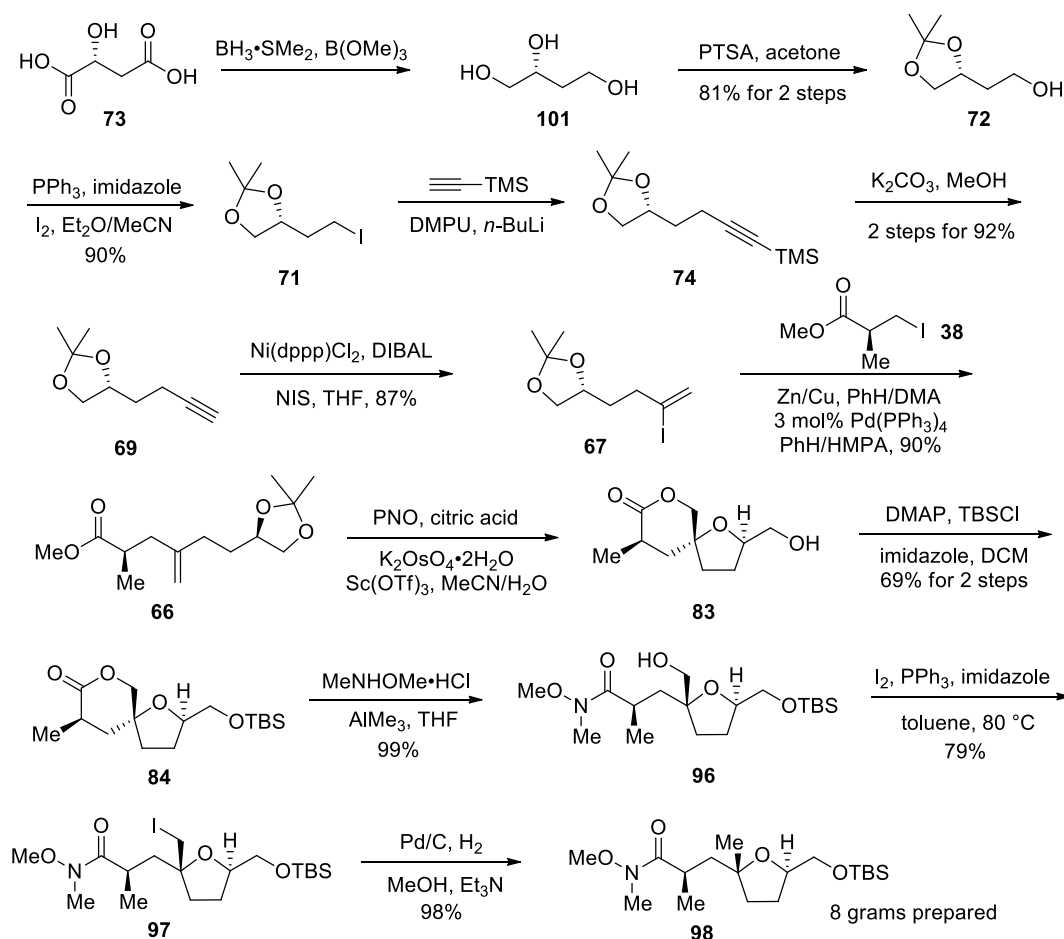


Scheme 2.16 Proposed mechanism for lactone formation in iodination reaction

2.4 Conclusion and Future Application

2.4.1 Conclusion of the Synthesis

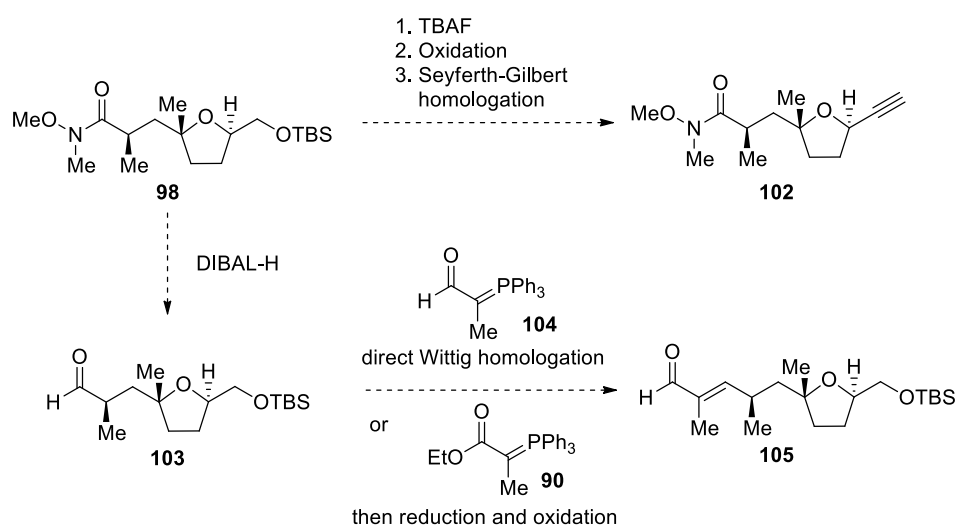
In summary, starting from commercially available material D-malic acid, the desired Weinreb amide **98** could be synthesised in 12 linear steps and 27% overall yield (compared to 14% yield as reported in Dr. Paul Winship's thesis). This compares favourably with the route described by Evans, who reported a sequence that involves marginally fewer steps (10 steps) but significantly lower overall yield (7% from Evans' auxiliary). The overall route is summarised in Scheme 2.17.



Scheme 2.17 Summary of the synthesis to **98**

2.4.2 Future Application of Compound 98

As introduced at the beginning of this chapter, compound **98** requires further functionalisation to alkyne **102** in order to access the proposed alkyne-epoxide coupling strategy to connect the ABC ring fragment. In order to achieve this, the TBS-protecting group will be removed, and the alcohol functionality oxidised to the aldehyde. Seyferth–Gilbert homologation^[68] will then deliver desired alkyne **102**.



Scheme 2.18 Further functionalisation proposals

Furthermore, the western part of **98** (as drawn) needs to be developed into conjugated aldehyde **105**, a key precursor for Julia–Kocienski olefination. This can be achieved either by direct Wittig homologation using aldehyde **104**, or a stepwise procedure by homologation with ester **90**, DIBAL reduction and then oxidation to aldehyde **105**. Further details concerning this functionalisation and coupling will be discussed in Chapter 6.

Chapter 3

First Generation Strategy for the Synthesis of the D Ring

3.1 Introduction

3.1.1 Previously Reported Syntheses of the D Ring of the PTXs

So far there have been seven synthetic approaches towards the D ring of the PTXs including the two total syntheses by Evans and Fujiwara. Since most of the examples have chosen to form the D ring at a late stage of the synthesis, special attention has been paid here to the number of equivalents of the two advanced coupling partners used.

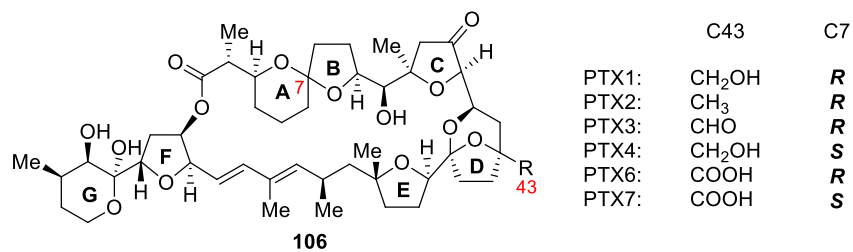
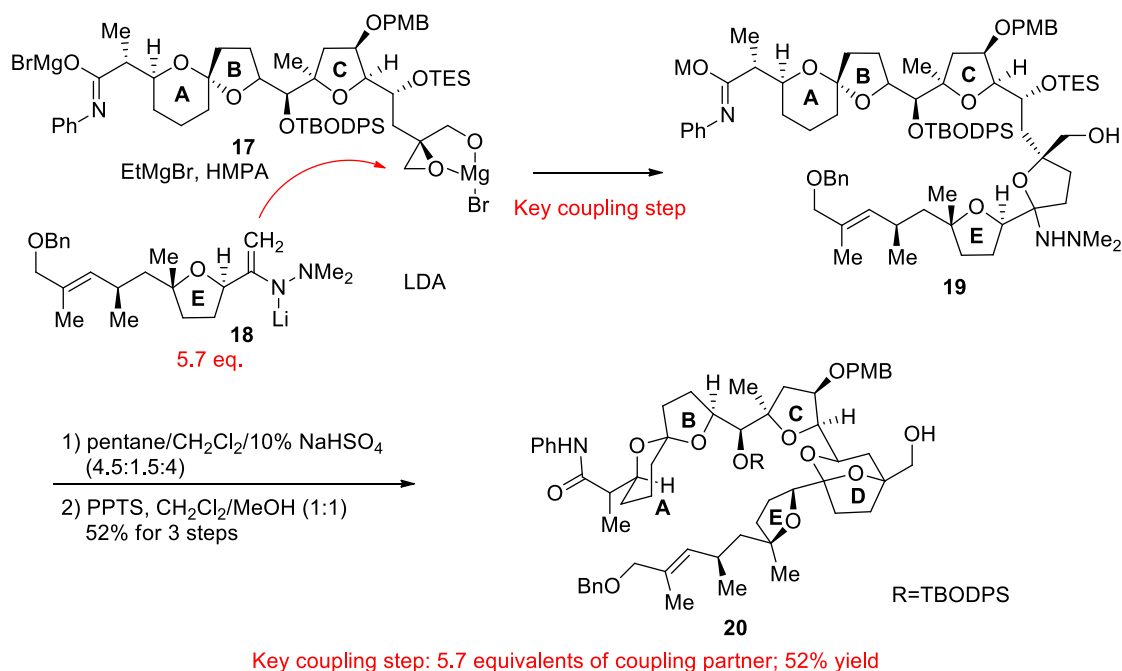


Figure 3.1 Members of the PTX family

3.1.1.1 Evans' synthesis of the ABCDE system

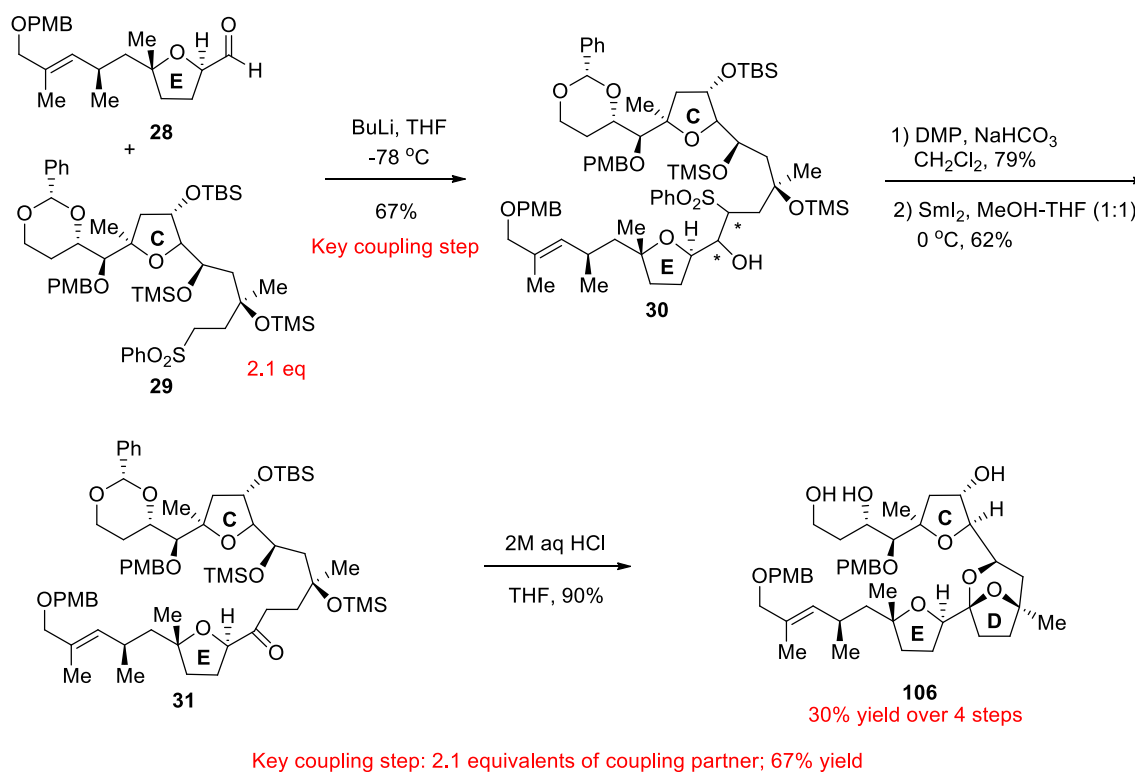
Evans and co-workers completed the first total synthesis of pectenotoxin-4^[24,25] in 2002. They used an epoxide opening strategy to unite the two major building blocks **17** and **18**. The resulting unstable hydrozinyllactol **19** was hydrolysed to the corresponding lactol, which was then treated under acidic conditions to desilylate the secondary TES group, affording the D ring moiety **20** *via* ketal formation. The overall yield was 52% over three steps, although 5.7 equivalents of an advanced hydrazone were used in the synthesis (no recovery of the excess amount of hydrazone **18**).



Scheme 3.01 Evans' synthesis of ABCDE system

3.1.1.2 Fujiwara's synthesis of the CDE ring system

Scheme 3.02 illustrates the formation of the CDE system in Fujiwara's total synthesis of PTX-2.^[26] The strategy utilised was a Julia type condensation, giving **30** as a mixture of diastereoisomers. Following DMP oxidation of the secondary alcohol **30** and cleavage of the phenylsulfonyl group using stoichiometric SmI₂, ketone **31** was generated as a single compound in 49% yield over 2 steps. Final deprotection of the two TMS groups produced the desired CDE fragment **106**, completing the sequence in 4 steps and 30% overall yield.

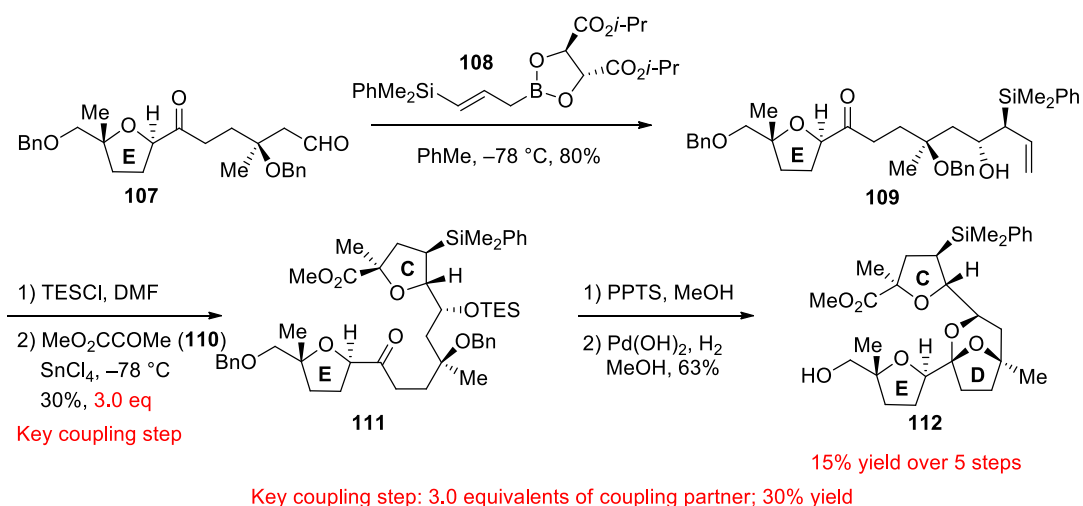


Scheme 3.02 Fujiwara's synthesis of the CDE ring system

3.1.1.3 Roush's synthesis of the CDE ring system

Roush and co-workers reported their route to the CDE fragment of PTX-2 in 2001.^[42]

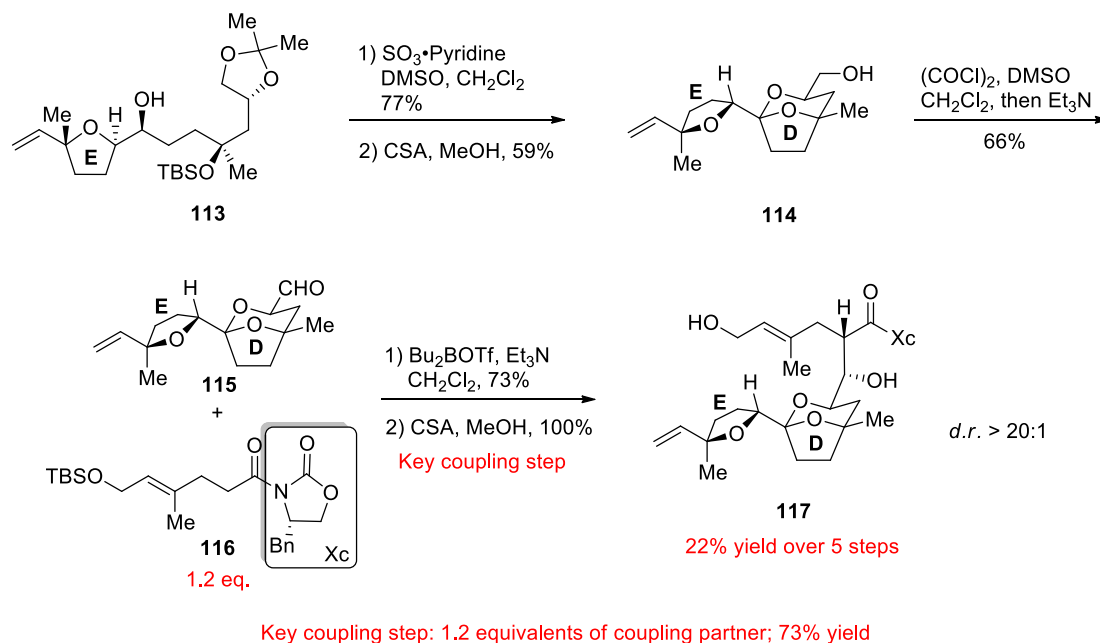
Starting from aldehyde **107**, their synthetic route featured a diastereoselective crotylation with **108** and then a [3+2] annulation with methyl pyruvate **110** to form compound **111**. This convergent methodology using a three-component coupling sequence for THF synthesis had previously been developed in their group. Acid-mediated deprotection and hydrogenation of **111** produced the CDE fragment **112** in 5 steps (Scheme 3.03) and 15% overall yield. Notably, although methyl pyruvate **110** was a small building block for [3+2] annulation in Scheme 3.03, it would be a huge coupling partner in the total synthesis. Therefore it was considered as major coupling partner.



Scheme 3.03 Roush's synthesis of the CDE ring system

3.1.1.4 Micalizio's synthesis of the DE ring system

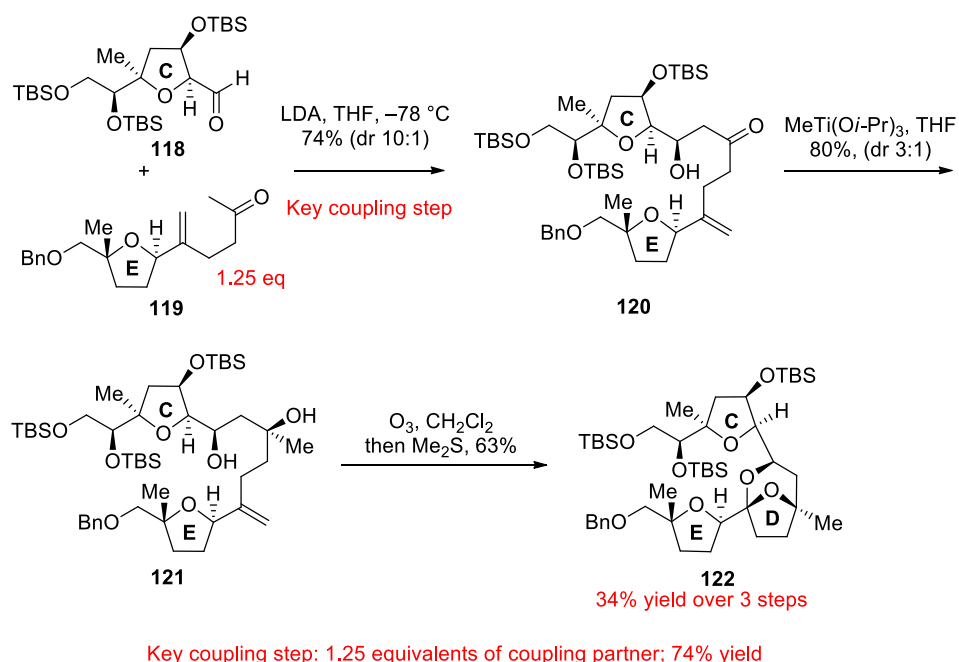
Micalizio and co-workers chose to synthesise the D ring skeleton **114** of PTX-2 before adding the C ring by using a sequence of Parikh–Doering oxidation^[69] and acidic deprotection from **113**.^[30] Swern oxidation of the resulting alcohol provided aldehyde **115**, which was then subjected to Evans aldol and deprotection conditions to give the functionalised DE ring system **117**. Notably, the key coupling reaction produced **117** in 73% yield using only 1.2 equivalents of nucleophile, and a very high diastereoselectivity (over 20:1) was achieved.



Scheme 3.04 Micalizio's synthesis of the DE ring system

3.1.1.5 Pihko's synthesis of the CDE ring system

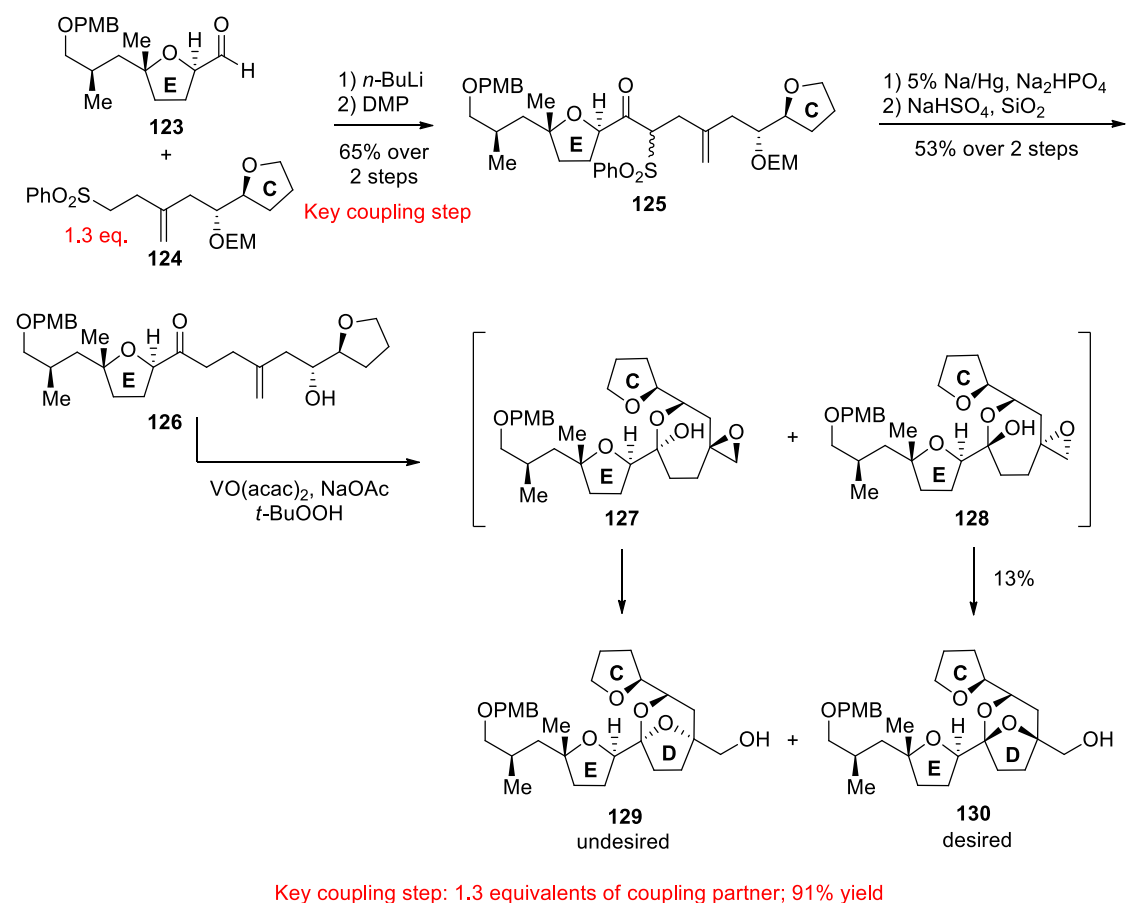
In Pihko's route, starting from ketone **119** and aldehyde **118**, a Felkin–Anh controlled alkylation product **120** was obtained in 10:1 *d.r.* using 1.25 equivalents of ketone **119**.^[27] The corresponding coupling product **120** was then subjected to an intramolecular hydroxyl-directed methyltitanation and ozonolysis of the double bond to give CDE ring system **122**. Although the results were excellent for the key coupling reaction between **118** and **119** (1.25 equivalents, 74% yield), the subsequent methyltitanation gave a 3:1 mixture of inseparable diastereoisomers (major product was the desired one). This resulted in a lower yield for the final cyclisation, as the undesired epimer was unreactive.



Scheme 3.05 Pihko's synthesis of the CDE ring system

3.1.1.6 Brimble's synthesis of the CDE ring system

Similar to Fujiwara's coupling strategy, a sequence of Julia type coupling, oxidation and radical cleavage of phenylsulfonyl group was also applied in Brimble's route starting from aldehyde **123** (Scheme 3.06).^[31] The key coupling was optimised to 91% yield with only 1.3 equivalents of nucleophile. Deprotection of the corresponding product **125** gave the epoxidation precursor **126**. However, substrate-directed vanadium-catalysed epoxidation of homoallylic alcohol **126** gave a pair of diastereoisomers **127** and **128**, which could then be trapped intramolecularly by the seven-membered lactol to form the desired D ring structure. The isolated yield of **130** was only 13% at this stage due to the poor diastereoselectivity of the epoxidation.

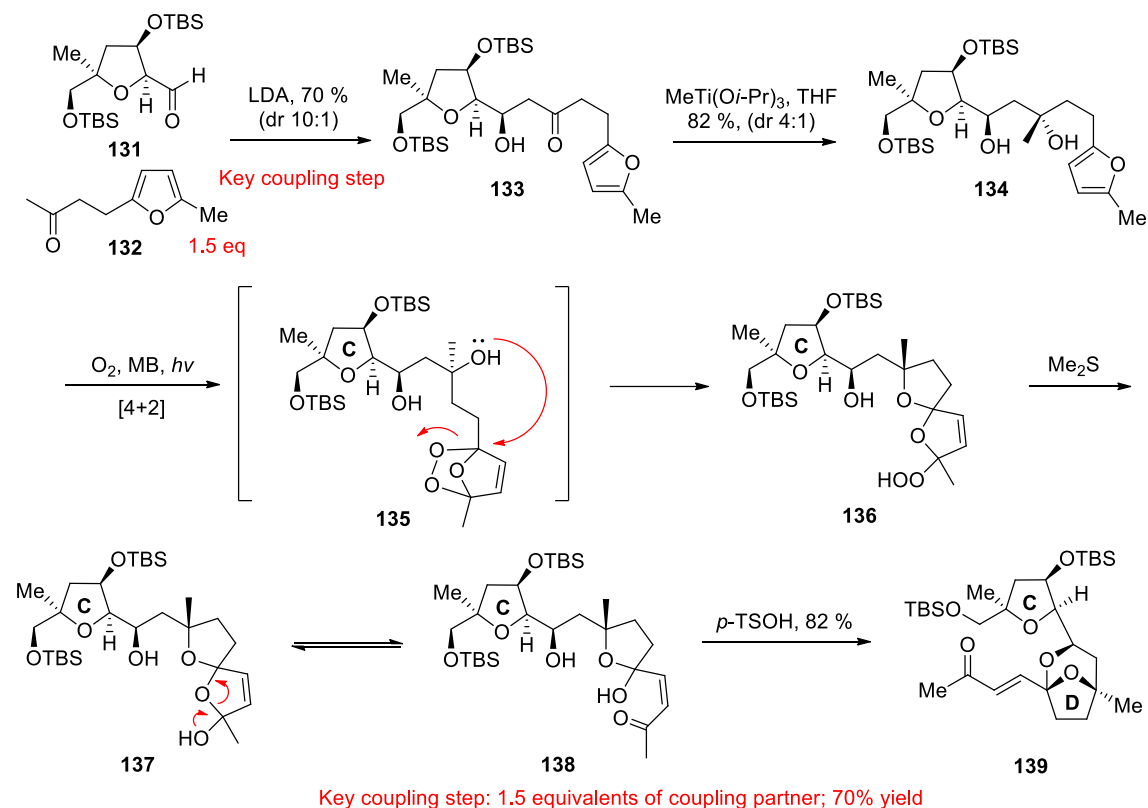


Scheme 3.06 Brimble's synthesis of the CDE ring system

3.1.1.7 Vassilikogiannakis' synthesis of the CD ring system

Vassilikogiannakis and co-workers reported a unique strategy for the synthesis of the CD skeleton.^[39] Applying the methodology developed in their group, the D ring could be synthesised using a singlet oxygen initiated rearrangement from hydroxyl-furan species **134**. The proposed mechanism suggests that initial [4+2] cycloaddition of singlet oxygen to the furan **134** yields ozonide **135**, which is rapidly opened by an internal hydroxyl group to afford the [5,5]-spirocyclic hydroperoxide **136**. Reduction of the product to hemiketal **137** is followed by rearrangement of spirocycle and acid catalysed *cis-trans* isomerisation of the double bond, giving the final product **139** via

intermediate **138**.



Scheme 3.07 Vassilikogiannakis' synthesis of the CD ring system

3.2 Design of a Model System and Retrosynthetic Analysis

3.2.1 Principles of the Design

As introduced in the Chapter One, the structure of PTX-4 can be divided into 4 segments. The ABC fragment, FG fragment and E ring fragment have already been synthesised in the Donohoe group.^[17,55–58] The penultimate task, before completing the molecule, was to construct the D ring in a way which would be compatible with the other fragments during the final steps of the synthesis (Figure 3.2).

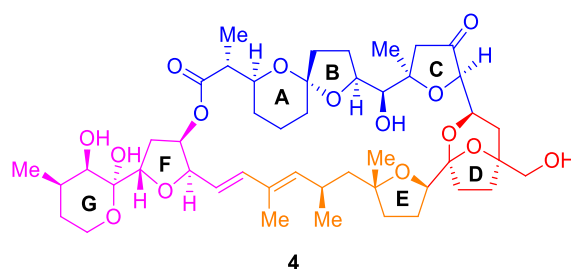
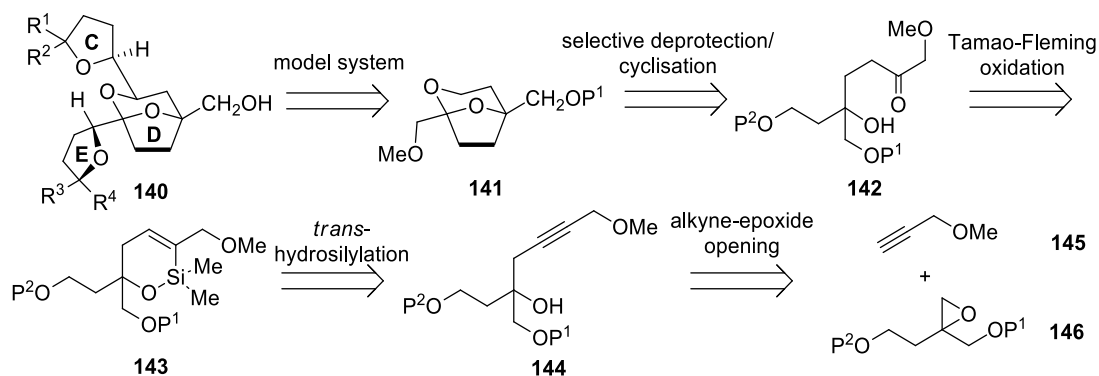


Figure 3.2 Synthetic analysis of PTX-4

Additionally, the number of equivalents of the two valuable partners required was a significant factor that needed to be considered in the coupling step. Since we had planned a late stage union of the E and ABC fragment, both already highly functionalised and extremely precious, it was critical that the stoichiometry was kept as close to 1:1 as possible.

3.2.2 Retrosynthetic Analysis

With these principles in mind, we proposed a retrosynthetic analysis as shown in Scheme 3.08.



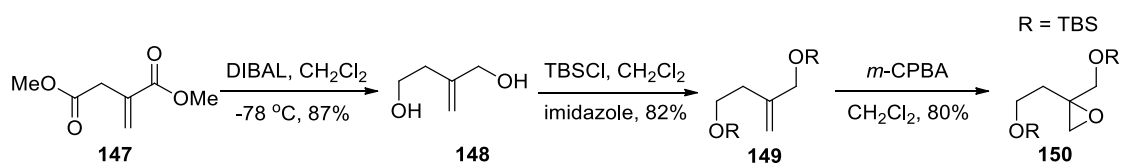
Initially, a model spiroketal **141** was designed to be used as a simplification of

structure **140**, in order to test if the key conversions (shown in Scheme 3.08) would be successful. Compound **141** could be prepared from **142** using a selective deprotection/cyclisation strategy. In order to synthesise **142**, we proposed a regio- and stereoselective hydrosilylation^[70] of **144** followed by Tamao–Fleming oxidation^[71,72]. Alcohol **144** could then be synthesised by the nucleophilic attack of terminal alkyne **145** onto epoxide **146**.

3.3 Results and Discussion

3.3.1 First Attempts to Prepare the Model System

Starting from commercially available starting material dimethyl itaconate **147**, epoxide **150** was synthesised by a sequence of DIBAL reduction, double silyl protection and epoxidation in 57% over three steps. The ¹H NMR spectrum of **150** showed an AB system at δ 2.75 ppm (d, J = 5.1 Hz) and δ 2.70 ppm (d, J = 5.1 Hz), which was assigned as CH_2 of the epoxide. With epoxide **150** in hand, ring opening with the anion of alkyne **145** was investigated (Table 3.1).



Scheme 3.09 Synthetic route to epoxide **11**

Although various conditions, such as BuLi with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ^[73] or Et_2AlCl ^[74], are known in the literature for alkyne epoxide opening, the desired product was not obtained when were applied in our system (Entry 1 & 3, Table 3.1).

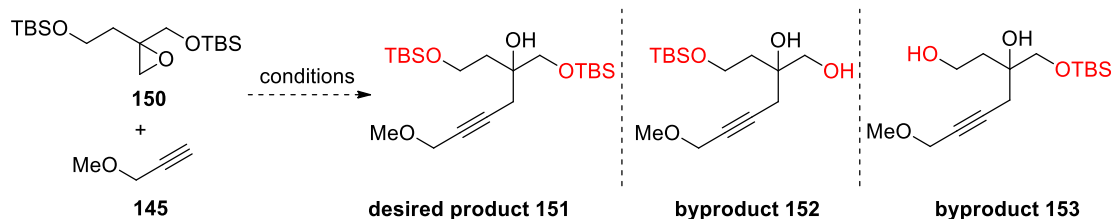


Table 3.1 Initial screening of alkyne-epoxide opening condition

Entry	Reagents ^a	Result
1	<i>n</i> -BuLi, BF ₃ ·Et ₂ O	silyl PG deprotection of 150
2	<i>n</i> -BuLi	no conversion
3	<i>n</i> -BuLi, Et ₂ AlCl	no desired product
4	<i>n</i> -BuLi, DMPU ^b	byproduct 152 and 153
5	KHMDS	no conversion
6	NaHMDS	no conversion
7	<i>n</i> -BuLi, MeAl ₃	byproduct 152 and 153

a) 2.0 equiv. of nucleophile **145** was used unless specified; b) 10.0 equiv. of nucleophile **145** was used

c) General conditions: THF, -78 °C to 0 °C, 2 h

When 10.0 eq. of alkyne and BuLi were used together with DMPU (Entry 4), the product obtained was the mono-deprotected form of the desired structure **152** and **153**. The ¹³C NMR spectrum of the inseparable mixture isolated from both Entry 4 & 7 both gave two sets of C-OTBS signals in a 1:1 ratio, which suggested that there was no preference for which TBS group was deprotected. When the amount of nucleophile **145** was reduced to 1.5 equivalents, TBS deprotection occurred in preference to epoxide opening (not shown in Table 3.1). We postulated that there was a chelation effect between the epoxide, protected alcohols and Li⁺, which acts as a hard Lewis acid, resulting in activation of the silyl protecting group (Figure 3.3). Various deprotonation conditions were also examined, but no conversion of starting material could be observed (Entry 2, 5 & 6).

In conclusion, it appeared that it was important to employ a suitable Lewis acid to activate the epoxide (see Entry 2, 5 & 6; no reaction without a Lewis acid). Additionally, due to the lack of selectivity of the epoxide opening and high loading of the nucleophile (10 equivalents), epoxide **150** was not an ideal compound.

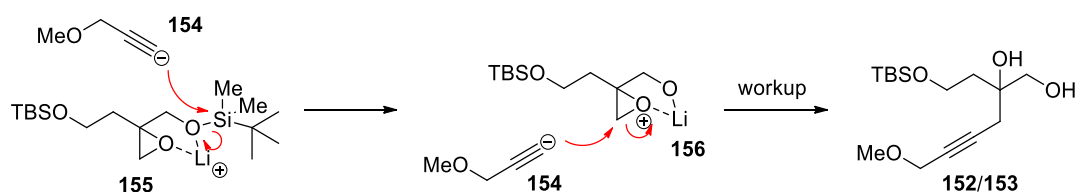
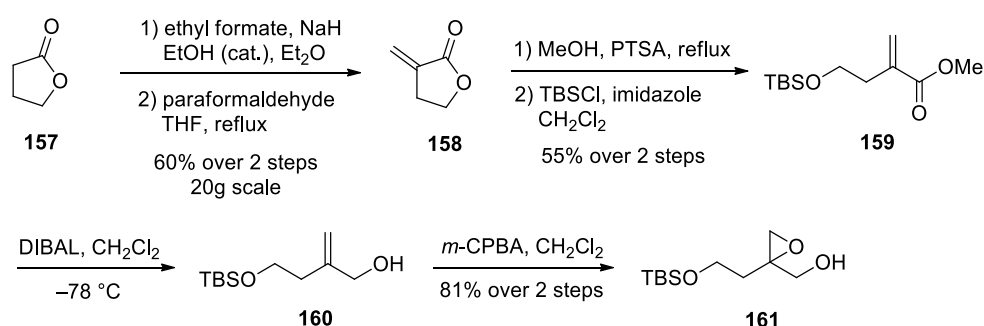


Figure 3.3 Proposed mechanism for the deprotection of **150**

3.3.2 Revised Route for the Model System

Using the preliminary results from model epoxide **150** and taking Evans' free-alcohol-activation strategy^[25] into consideration (Scheme 3.01), epoxide **161** was thought to be as an ideal substrate, since attack of the alkyne on the epoxide may benefit from metal chelation between the deprotonated alcohol and epoxide (Scheme 3.10).



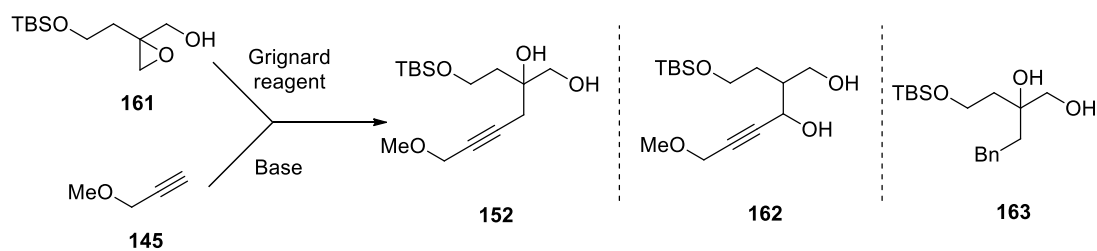
Scheme 3.10 Synthetic route to epoxide **161**

Starting from the commercially available γ -butyrolactone **157**, following the procedure of Jenkins and co-workers^[75], compound **158** was obtained in acceptable

yield on a 20 gram scale. Transesterification and TBS protection of **158** resulted in the formation of compound **159**. DIBAL reduction followed by *m*-CPBA epoxidation led to the desired epoxide **161** in excellent yield. The ¹H NMR data of compound **161** showed a doublet that counted for one proton at δ 2.86 ppm (*J* = 4.8 Hz), which was assigned as one proton of the epoxide CH₂. The other proton was assigned at δ 2.77-2.68 ppm, together with the OH proton. With epoxide **161** in hand, the ring opening was then investigated.

Epoxide **161** was first treated with 1.0 equivalent of a Grignard reagent before the addition of a nucleophile (alkyne, 2 equivalents). We believe the resulting alkoxide species contains a chelated Mg²⁺ centre, which likely assists the activation of epoxide. Thus, the various conditions tested are shown in Table 3.2.

The application of *i*-PrMgCl as the activating Grignard reagent made the reaction work to give desired product **152** in 31% yield; Changing to BnMgCl resulted in little improvement (Entry 3). Entries 4-5 showed the failure of attempts to utilise Grignard reagents as a base, whether it was in a one-pot procedure or two-pot sequence, and only products incorporating a benzyl group **163** could be observed. The slow deprotonation of the alkyne using Grignard reagents was believed to be responsible for the formation of **163**. Therefore, Et₃N and MgBr₂ (Entry 6-8) were used in order to accelerate this process.^[76-78]



Scheme 3.11 Optimisation of alkyne-epoxide opening

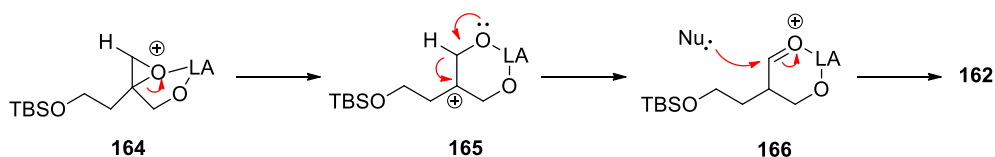
Table 3.2 Screening of alkyne-epoxide opening conditions

Entry	Base (alkyne)	Grignard reagent (epoxide)	Solvent	Additive	Result
1	<i>n</i> -BuLi	<i>i</i> -PrMgCl	THF	DMPU	152 , 31% (49% brsm)
2^a	LDA	-	Et ₂ O	DMPU	mainly S.M.
3	<i>n</i> -BuLi	BnMgCl	Et ₂ O	DMPU	152 , 33%
4^a	BnMgCl	BnMgCl	Et ₂ O	-	163 , 43%
5	BnMgCl	BnMgCl	Et ₂ O	-	163 , 32%
6	BnMgCl	BnMgCl	THF	Et ₃ N	162 , 58%
7	<i>t</i> -BuMgCl	<i>t</i> -BuMgCl	THF	Et ₃ N	162 , 31%
8	<i>t</i> -BuMgCl	<i>t</i> -BuMgCl	THF	MgBr ₂ ·Et ₂ O	152 , < 10%
9	<i>n</i> -BuLi	<i>t</i> -BuMgCl	THF	DMPU	152 , 41% (69% brsm)
10	NaHMDS	<i>t</i> -BuMgCl	THF	DMPU	152 , 17%

a) A one-pot procedure was examined

b) All reactions were performed with two equivalents of alkyne **145** compared to epoxide

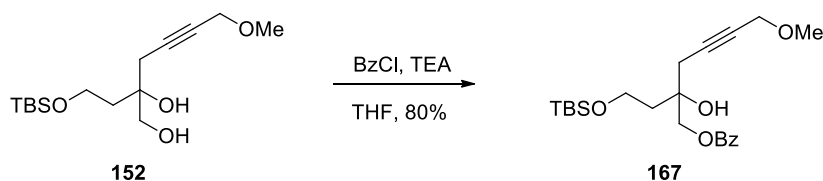
Interestingly, when Et₃N was used as an additive in the reaction, an unexpected product **162** was isolated in 58%. It is proposed that the epoxide may first undergo a Meinwald rearrangement to an aldehyde prompted by the Lewis acid in the presence of Et₃N (Scheme 3.12), followed by the deprotonated alkyne attacking the aldehyde to give product **162**. This type of [1,2] hydride shift process usually occurs under Lewis acidic medium^[79], and it is the first time we have observed a Et₃N promoted Meinwald rearrangement under basic conditions, although the role of Et₃N is still not clear.



Scheme 3.12 Proposed mechanism for the formation of **162**

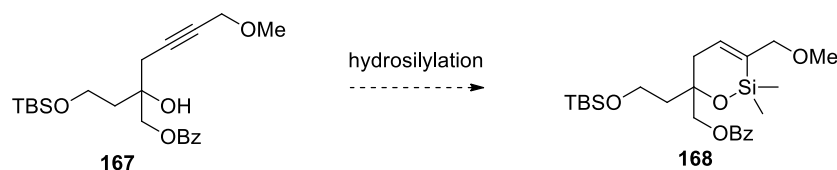
In Entry 8, the desired product **152** could be obtained by using MgBr_2 as additive, but a low conversion of starting material and the resulting low yields were also recorded. The best conditions involved treating the alkyne (2 eq.) with $n\text{-BuLi}$ and the epoxide with $t\text{-BuMgCl}$, giving **152** in 41% yield (69% brsm, Entry 9, Table 3.2).

With this successful coupling of alkyne and epoxide, further reactions were then investigated towards the synthesis of a D ring model (Scheme 3.13).



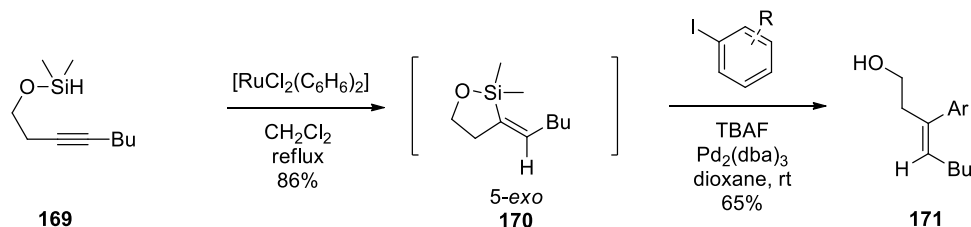
Scheme 3.13 Selective protection of coupling product **152**

Benzoyl protection of compound **152** gave **167** in 80% yield. The ^1H NMR data of **167** suggested that the chemical shift of the corresponding CH_2 changed from around δ 3.90 (CH_2OH) to δ 4.41 (CH_2OBz) as a two-proton-singlet. In order to obtain desired product **168**, the hydrosilylation reaction was then studied.



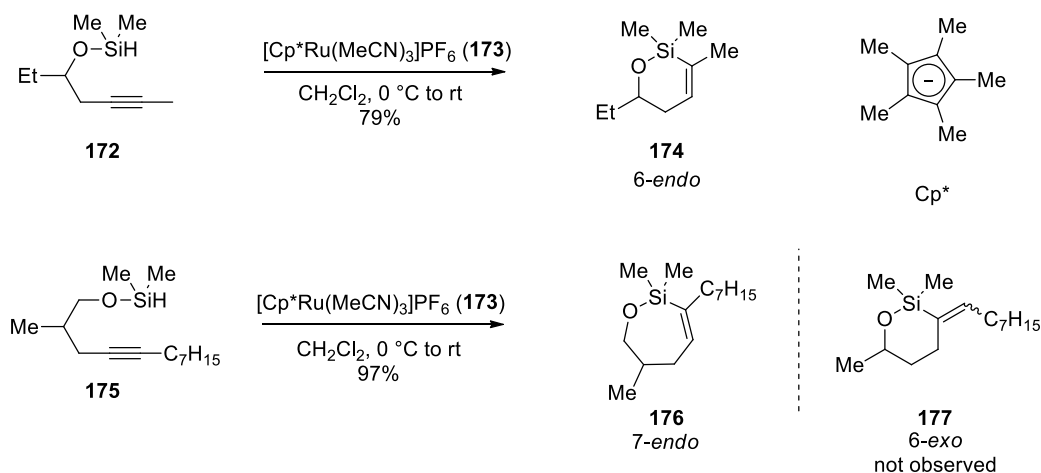
Scheme 3.14 Proposal for alkyne hydrosilylation

In 2002, Denmark reported an intramolecular hydrosilylation reaction^[80], catalysed by $[\text{RuCl}_2\text{Ph}_2]$, that proceeds *trans*-addition in a 5-*exo* manner (Scheme 3.15).



Scheme 3.15 Denmark's 5-*exo* intramolecular hydrosilylation

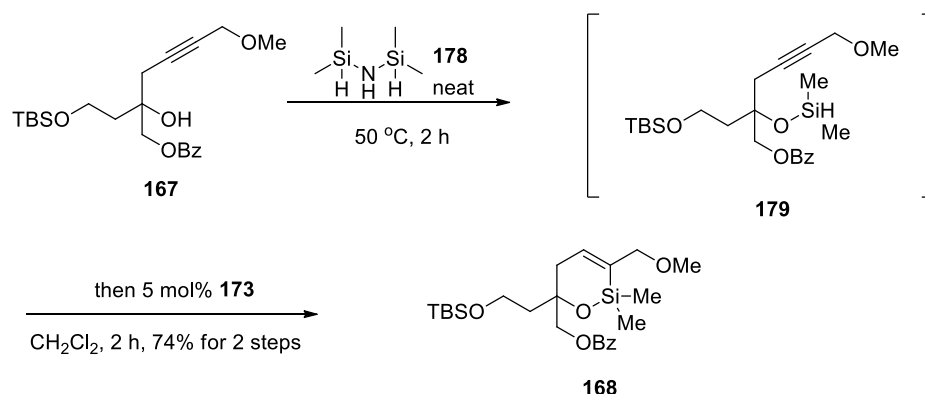
In 2003, Trost reported a hydrosilylation reaction which provided a 6-*endo-dig* product using $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ as catalyst (Scheme 3.16).^[81] *Trans* addition across the alkyne was observed in each case, which was computationally later shown to involve an unusual direct *trans* addition rather than the more commonly observed *cis* addition followed by *E/Z* isomerisation.^[70]



Scheme 3.16 Trost's hydrosilylation reaction on different substrates

In terms of regioselectivity, the second example in Scheme 3.16 implies that the

7-*endo* process was more favourable than 6-*exo* reaction on the same substrate. There is still no experimental evidence to support the mechanism behind these results; however, Trost's method provided us with an ideal way to realise our strategy.



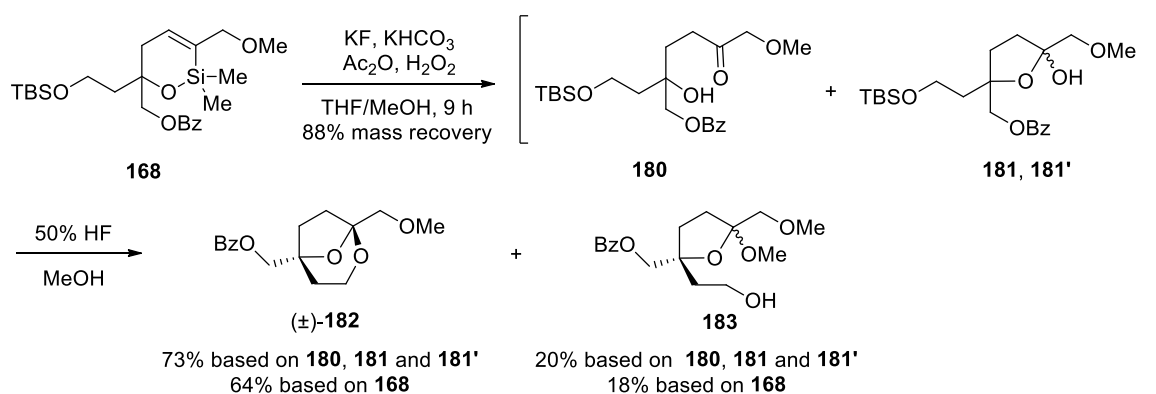
Scheme 3.17 Synthetic approach to hydrosilylation

Upon treatment of **167** with bis(trimethylsilyl)amine **178** and Ru catalyst **173**, silane **168** was obtained in 30 % yield; TLC monitoring of the first step showed that the reaction was not complete after one day, indicating slow formation of the corresponding silylated intermediate **179**. Furthermore, it was also discovered that the silylated intermediate **179** was difficult to isolate by column chromatography because of its sensitivity to moisture. Therefore, **167** was treated with neat disilazane **178** at 50 °C for two hours to increase the reaction rate, and then excess **178** was removed under vacuum. Afterwards, Ru catalyst **173** and CH₂Cl₂ were added and silane **168** could then be synthesised in 74% yield over 2 steps. ¹H NMR spectroscopy of **168** showed a distinctive CR₂=CHR peak (br. s.) at δ 6.47 ppm; ¹³C NMR spectroscopy showed a pair of double bond peaks at δ 138.4 ppm and 138.2 ppm; high resolution mass spectrometry also found the right mass (m/z at 487.2302, M+Na⁺, Δ – 0.9 ppm),

which provided strong evidence for the success of the hydrosilylation.

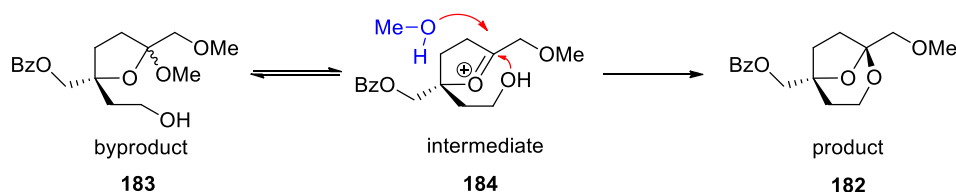
With compound **168** in hand, the Tamao–Fleming oxidation could then be examined. The reaction was found to be slow under neutral (KHF_2) and basic (KHCO_3) conditions^[71], with the starting material not fully consumed even after 18 h. When applying an acidic medium (Scheme 3.18, using Ac_2O as additive), the reaction of **168** was finished in 9 h and the desired product **180** was formed together with its hemiacetal **181** and **181'**. ^1H NMR spectroscopic analysis then showed that the product was an almost 1:1:1 mixture of **180**, **181** and **181'**. Treatment of the mixture of **180**, **181** and **181'** in 50 % HF solution in water promoted TBS deprotection followed by cyclisation to give **182** in one pot in 64% yield over 2 steps from **168**.

The structure of **182** was supported by spectroscopic data. Two protons of $\text{CH}_2\text{CH}_2\text{OR}$ appear at δ 2.30–2.19 ppm and δ 1.39 ppm (doublet, $J = 12.6$ Hz) respectively; ^{13}C NMR spectroscopy gives a distinctive peak at δ 106.6 ppm for the ketal carbon; high resolution mass spectrometry also provides the right mass of the product ($\text{C}_{16}\text{H}_{20}\text{O}_5$ predicted 315.1203 ($\text{M}+\text{Na}^+$), found 315.1205).



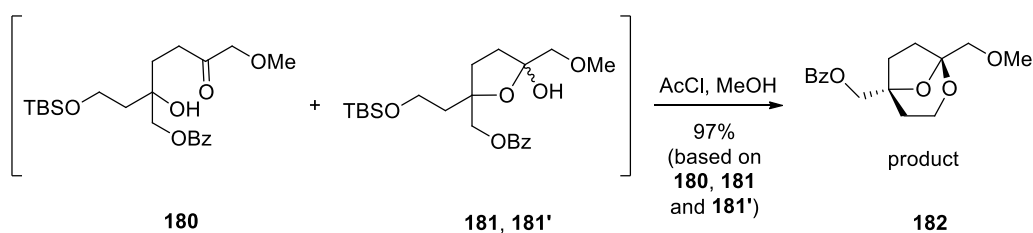
Scheme 3.18 Synthesis of D ring skeleton **26**

In addition to bicycle **182**, compound **183** was obtained as a major byproduct, isolated in 20% yield. The mechanism for the generation of **183** is shown in Scheme 3.19. When intermediate **184** is formed, methanol competes with the pendent hydroxyl group to trap the oxonium ion to generate byproduct **183**.



Scheme 3.19 Mechanism of the final step

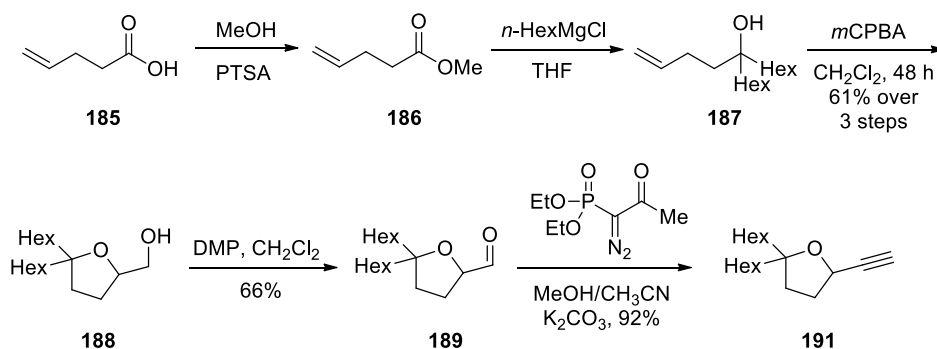
It is reasonable to propose that, under acidic equilibrium conditions, **184** could be transformed into **182** with the removal of MeOH. Hence, as shown in Scheme 3.20, we developed new conditions using anhydrous HCl generated *in situ* from AcCl and MeOH, followed by concentration *in vacuo* to remove the acid and MeOH, leading to almost quantitative transformation to the final product **182** by shifting the equilibrium.



Scheme 3.20 Optimisation of the final step

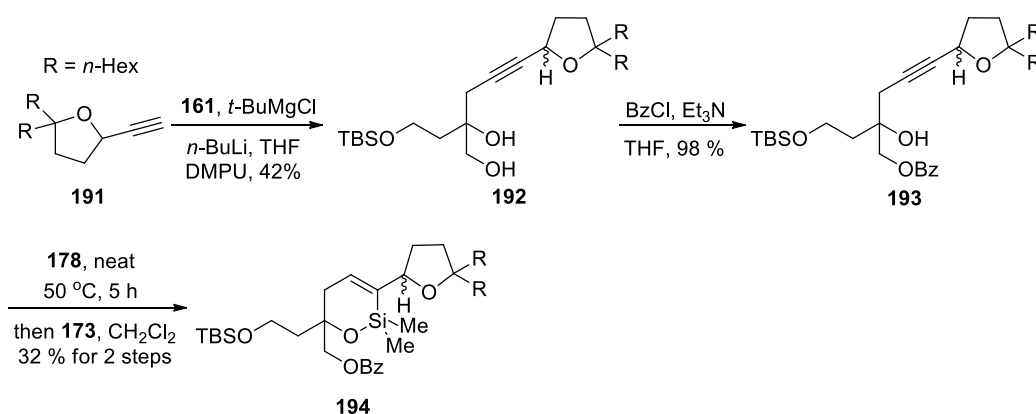
3.3.3 A More Sophisticated Model System

With a proof-of-concept on a simple model system, we chose to apply the conditions to a more advanced model alkyne substrate **191**.



Scheme 3.21 Synthesis of alkyne **191**

Starting from commercially available acid **185**, compound **188** could be obtained on a 10-gram scale in 61% overall yield through an esterification, Grignard reaction and epoxidation sequence. Subsequent DMP oxidation and Seyferth–Gilbert homologation^[68] gave the desired alkyne **191** in good yield. The ¹H NMR of **191** showed a doublet at δ 2.41 ppm (J = 2.0 Hz) for the alkyne proton $\text{CHC}\equiv\text{CH}$, which matches the other coupling constant of $\text{CHC}\equiv\text{CH}$ at δ 4.58 ppm as a doublet of triplets (J = 6.6, 1.9 Hz), giving evidence for the formation of the alkyne.

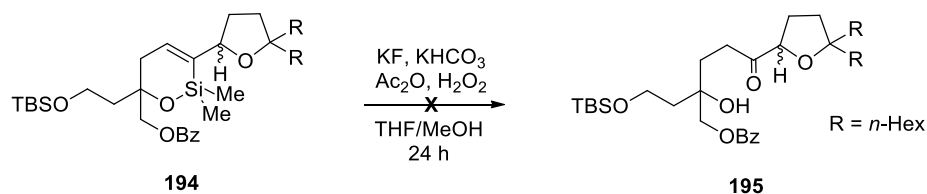


Scheme 3.22 Test of key reactions on advanced materials

Using the conditions optimised on the earlier model system (Entry 9, Table 3.2), **192**

could be obtained by the nucleophilic attack of alkyne **191** onto epoxide **161** (Scheme 3.22). Compound **194** could then be synthesised by benzoyl protection of the primary alcohol and hydrosilylation. However, the reaction rates were slower than that of the simple model **168** due to steric hindrance (2 h versus 12 h). The ^1H NMR spectroscopic data of **194** showed a triplet at δ 6.46 ppm ($J = 4.3$ Hz), which was assigned as the double bond proton $\text{CR}_2=\text{CHR}$. Since alkyne **191** was a racemic mixture, the corresponding products **192**, **193** and **194** were all obtained as a mixture of diastereoisomers.

Having obtained hydrosilylation product **194**, the Tamao–Fleming oxidation could again be investigated. However, treating **194** under the same conditions applied in Scheme 3.18 (KF, KHCO_3 , Ac_2O , H_2O_2 , THF/MeOH) lead to no reaction. One of the possible explanations is that the hexyl group on THF ring partially blocks the silyl group and increases the steric hindrance of the substrate. However, the reaction was only tried once because of a lack of material. Due to the long sequence and the consideration of the efficiency of this model system, it was decided not to continue on this route.

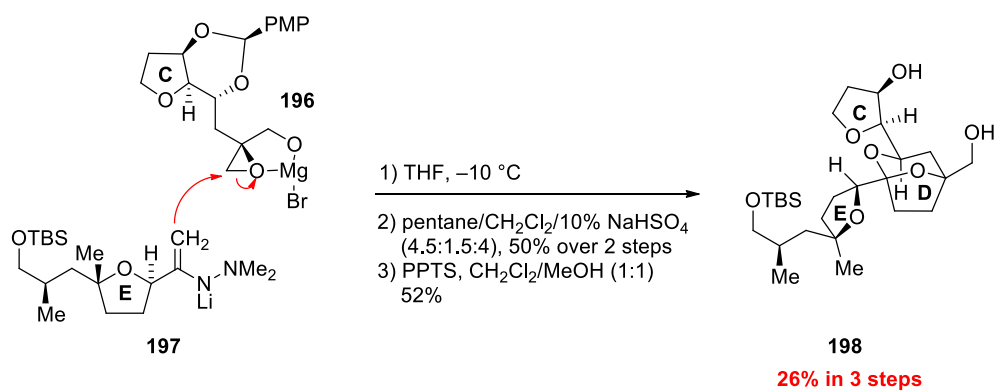


Scheme 3.23 Preliminary investigation of Tamao–Fleming oxidation on advanced materials

3.4 Summary and Future plan

The synthetic plan outlined in Scheme 3.08 has been investigated for two model systems. The synthetic plan was successfully implemented on a simplified model with hydrosilylation, Tamao–Fleming oxidation and deprotection/cyclisation. The coupling of the alkyne and epoxide needs to be further optimised, although the stoichiometry (2:1) of the coupling partners would be feasible for the final route. In addition to the simplified model, an advanced model was synthesised and pleasingly the key coupling reaction worked in similar yields (41%). Potential steric issues need to be carefully considered if this strategy were to be applied in the total synthesis as the Tamao–Fleming oxidation did not work easily in the more sophisticated model system.

In comparison with Evans' synthesis of D ring model^[82], this method increased the number of equivalents of coupling partners from 1.3 to 2 (Scheme 3.24), and achieved marginally better isolated yield (35% of this method vs 26% of Evans'). Attempt to improve the yield and reduce the number of equivalents of nucleophile in the key coupling step is ongoing in the Donohoe group, and part of these results will be discussed in Chapter 5.



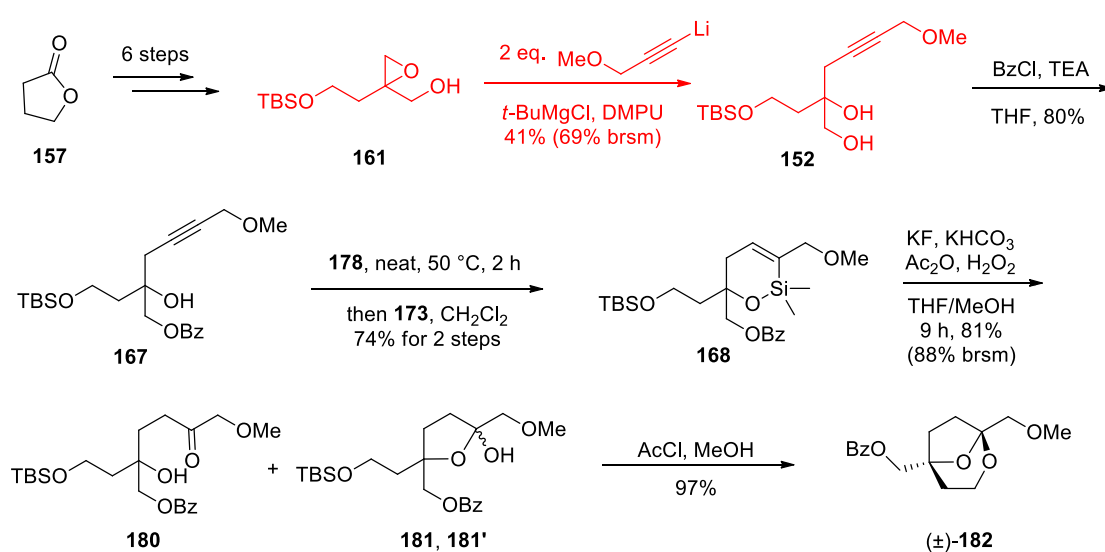
Scheme 3.24 Evan' synthesis of D ring model

Chapter 4

Second Generation Strategy for the Synthesis of the D Ring

4.1 Introduction to the New Strategy

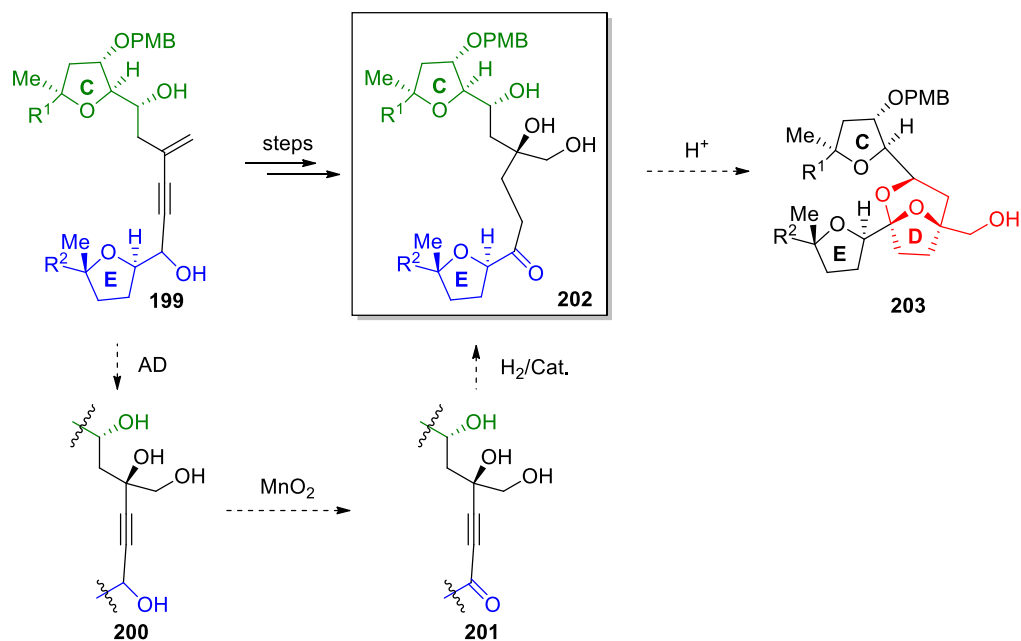
As described in Chapter 3 (outlined in Scheme 4.01), the First Generation Strategy towards the D ring was implemented on a simplified model, but the key epoxide opening reaction and subsequent functionalisation on more advanced systems gave poor results. Therefore, a new strategy was needed.



Scheme 4.01 First generation approach to the D ring

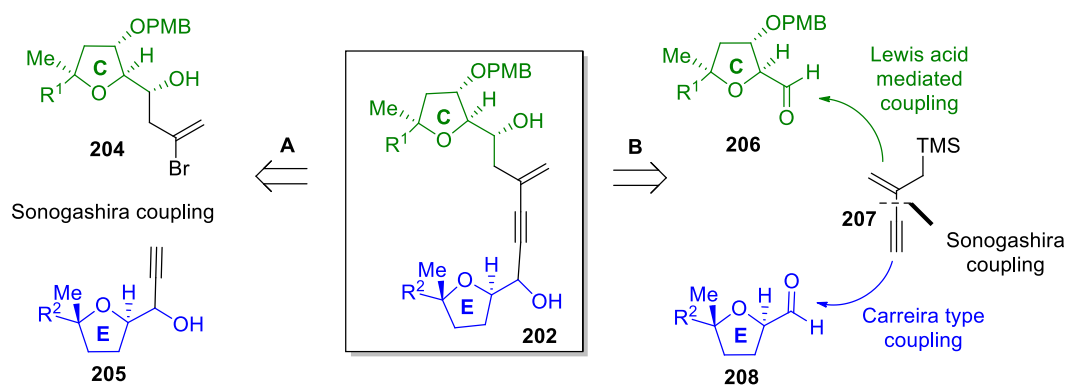
4.2 Retrosynthetic Analysis

Our new strategy towards key intermediate **202** is outlined in Scheme 4.02. From enyne **199** we envisaged a Sharpless asymmetric dihydroxylation^[83] (AD), followed by selective oxidation of the propargylic alcohol **200** and hydrogenation of the triple bond. The subsequent alkyl triol **202** could then be subjected to acidic media to generate the final D ring core **203**.



Scheme 4.02 Proposed synthesis of a D ring structure **203**

We hoped that enyne **199** could be prepared by one of two possible routes. In Plan A, **202** could be synthesised by direct Sonogashira coupling^[84] between vinyl bromide **204** and propargylic alcohol **205**. In Plan B, a Lewis acid promoted alkylation and Carreira type^[85] alkyne-aldehyde coupling would provide the desired framework.

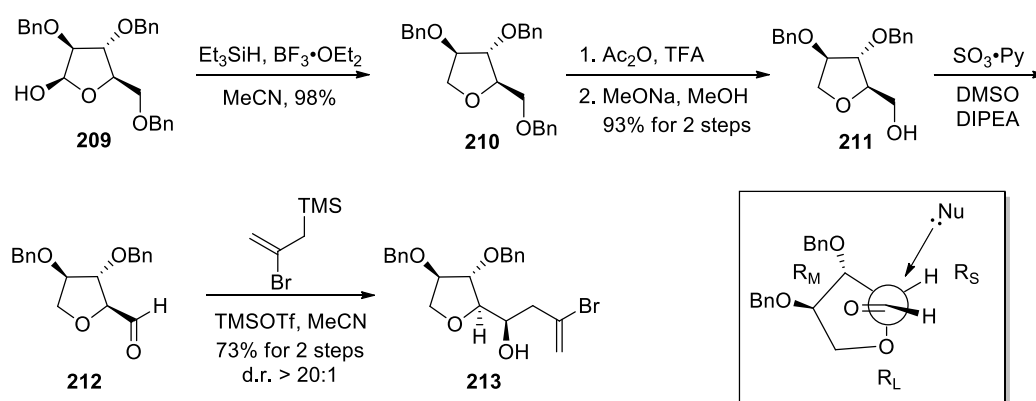


Scheme 4.03 Retrosynthesis of the D ring

4.3 Synthesis of Coupling Partners for a Sonogashira Coupling

4.3.1 Synthesis of Vinyl Bromide 213

Following a literature procedure,^[86] compound **211** could be obtained in a high-yielding three step sequence from commercially available material **209** (Scheme 4.04). The spectroscopic data for **211** were consistent with those previously reported.^[86] Parikh–Doering oxidation and subsequent Lewis acid promoted alkylation gave product **213** in excellent yield. The stereochemistry of **213** was predicted by the Felkin–Anh model, which puts oxygen perpendicular to the carbonyl plane due to the conjugation between oxygen's low-energy σ^* orbitals and neighbouring carbonyl π^* orbital.^[87] The newly formed stereocentre was achieved at high diastereoselectivity (*d.r.*>20:1), and assigned by Mosher's ester analysis (see SI for details).^[88]

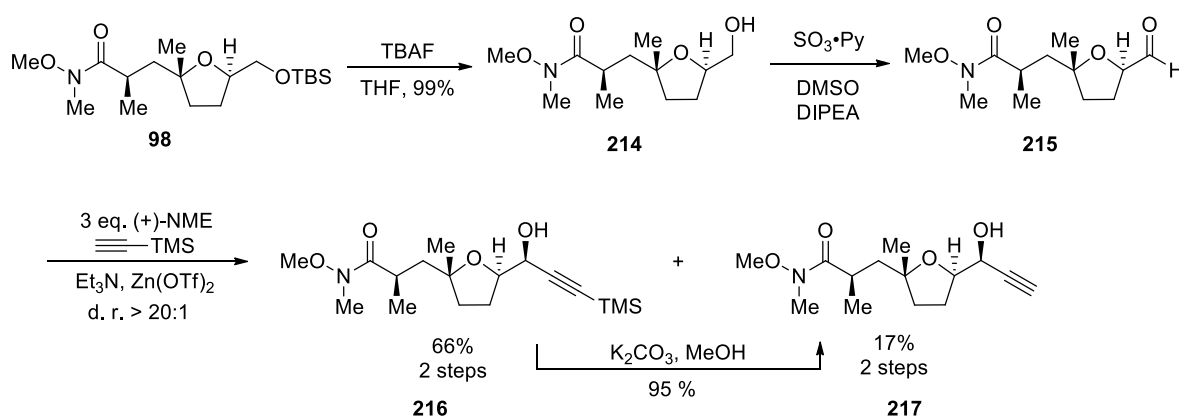


Scheme 4.04 Synthesis of vinyl bromide **213**

4.3.2 Synthesis of alkyne 217

Alkyne **217** could be synthesised from Weinreb Amide **98** using a similar method to

that outlined in Chapter 2. Initial TBS deprotection of **98** with TBAF provided alcohol **214** in 99% yield. Subsequent oxidation using Parikh–Doering conditions^[69] provided aldehyde **215**, which was used without further purification. Asymmetric addition of TMS-acetylene to this aldehyde using Carreira conditions gave **216** as a single diastereoisomer in 66% yield over the two steps. A small amount (17%) of deprotected terminal alkyne **217** was also produced. However, treatment of **216** with $K_2CO_3/MeOH$ resulted in TMS deprotection in almost quantitative yield to give **217**. The newly-generated stereocentre was assigned by comparison with the work of Tanaka.^[89] However, this factor was inconsequential as this stereocentre would later be oxidised to the corresponding ketone.



Scheme 4.05 Synthesis of alkyne **217**

4.4 Sonogashira Coupling and Further Functionalisation

4.4.1 Sonogashira Coupling

Having obtained both vinyl bromide **213** and terminal alkyne **217**, the Sonogashira reaction could now be examined. Conditions based on those reported by Chinchilla^[90]

yielded 22% of the desired product (Entry 1, Table 4.1). The ^1H NMR spectrum of **218** showed alkene peaks (δ 5.39, 5.26 ppm) as well as methoxy singlet (δ 3.66) of Weinreb amide, and a peak of m/z 401.1719 was found (predicted 401.1723 ($\text{M}+\text{Na}^+$)) by HRMS.

A major byproduct (~20%) was assigned to be homo-coupled product of alkyne **217** (δ 2.52–2.35 ppm alkyne proton missing; found m/z 559.3 (homo-coupled product + Na^+)), possibly formed due to trace amounts of oxygen in the presence of the copper co-catalyst.^[91]

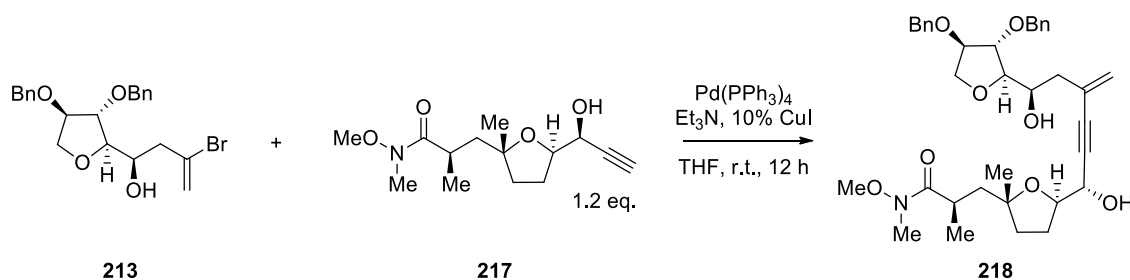


Table 4.1 Optimisation of Sonogashira coupling

Entry	Catalyst loading	Yield
1	10%	22%
2	100%	42% ^a
3	10%	27% ^a
4	10%	18% ^{a,b}

a) THF freshly distilled over Na; b) slow addition of alkyne *via* syringe pump

To better understand the reaction we elected to generate the vinyl palladium bromide

adduct in advance. We hoped that the copper(I)-alkyne complex, once generated, would undergo immediate transmetalation with palladium and avoid unwanted oxidation to copper(II). With this in mind, a stoichiometric amount of palladium catalyst was used (Entry 2), resulted in an improved yield of 42% along with around 10% of homo-coupled product.

Although the yield of **218** had been increased, further improvement was clearly necessary. Normally, three equivalents of the alkyne are used in Sonogashira coupling^[92] to increase yields and overcome possible side reactions, one being the previously mentioned dimerisation. However, it was not realistic for us to apply such high loadings of this coupling partner in the synthesis due to the advanced nature of the fragments so we needed to reduce the side reactions. In an attempt to remove oxygen from the solvent, THF was distilled over Na using benzophenone as indicator. However, this provided only marginally better yields (Entry 3). Slow addition of the alkyne *via* syringe pump even gave lower yields (Entry 4). Therefore, we turned to a copper-free protocol to avoid the unwanted homo-coupling.

Buchwald and co-workers^[93] have previously reported a copper-free Sonogashira coupling in 2003. Using XPhos as a soft ligand, they could use the palladium to both activate the alkyne and perform the cross coupling. Although only aryl halide compounds were tested in the original paper, we deemed it worthwhile to apply their conditions to our system.

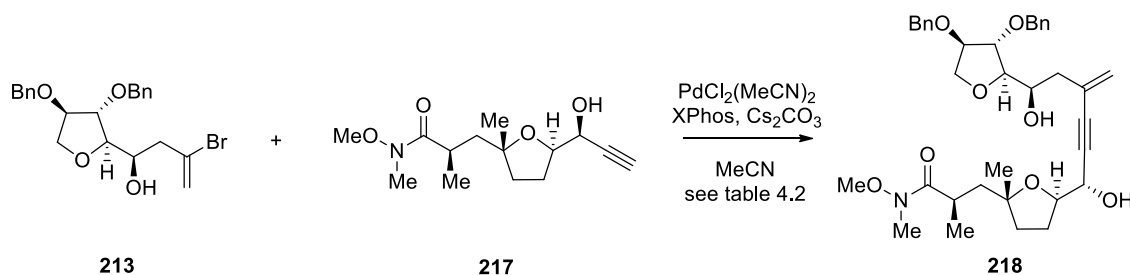


Table 4.2 Optimisation of copper-free Sonogashira coupling^a

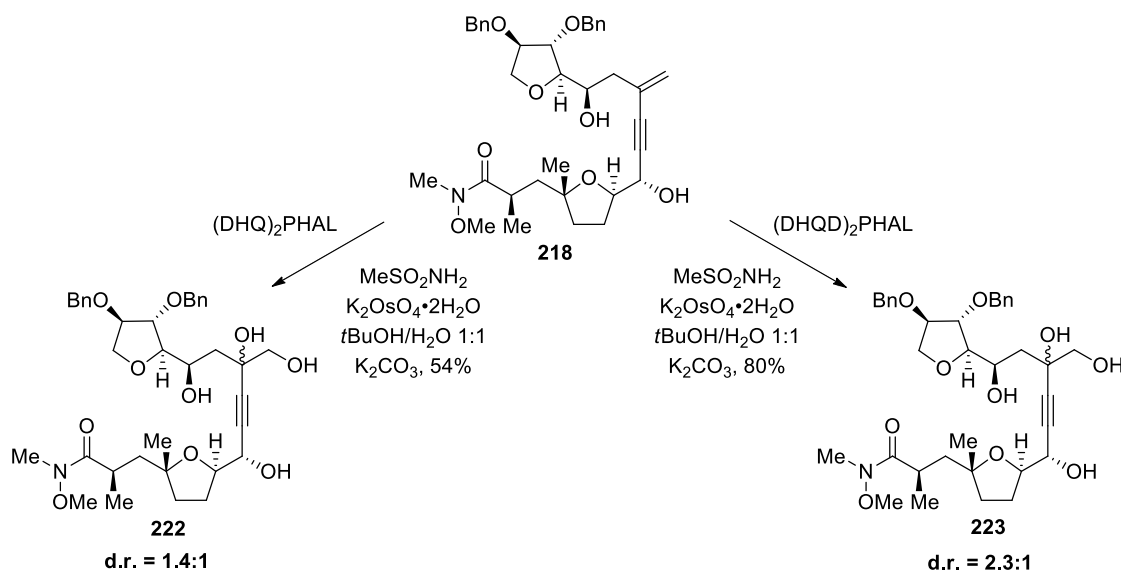
Entry	Pd Cat. (%)	Alkyne loading (eq.)	Time (h)	T (°C)	Yield (%)	Comments
1	2	1.2	16	70	15	-
2	5	1.2	6.5	70	10	-
3	5	1.2	4.5	30–60	42	-
4	5	1.02	3	50–60	51	-
5	10	1.2	2.5	65	54	45% S.M. recovered
6	10	0.5	3	55	51	yield calculated based on alkyne
7	10	1.2	2	65	33	120 mg scale

a) All reactions were performed at a scale of 20 mg of alkyne using $\text{PdCl}_2(\text{MeCN})_2$ as catalyst, XPhos as ligand (twice as the amount of $\text{PdCl}_2(\text{MeCN})_2$), Cs_2CO_3 as base (3.0 eq.); equivalents were calculated as alkyne/vinyl bromide b) pre-mix the vinyl bromide and catalyst/ligand/base at 70 °C

4.4.2 Dihydroxylation

With Sonogashira product **218** in hand, the subsequent dihydroxylation could be investigated. We chose to apply the conditions developed by Roberts *et al.*^[94,95] When ligands $(\text{DHQ})_2\text{PHAL}$ and $(\text{DHQD})_2\text{PHAL}$ were applied in the Sharpless asymmetric dihydroxylation, a modest 2.3:1 selectivity was observed, which was consistent with

the matched case (DHQD) and 1.4:1 for mismatched case (DHQ). (see SI for determination of *d.r.* value)



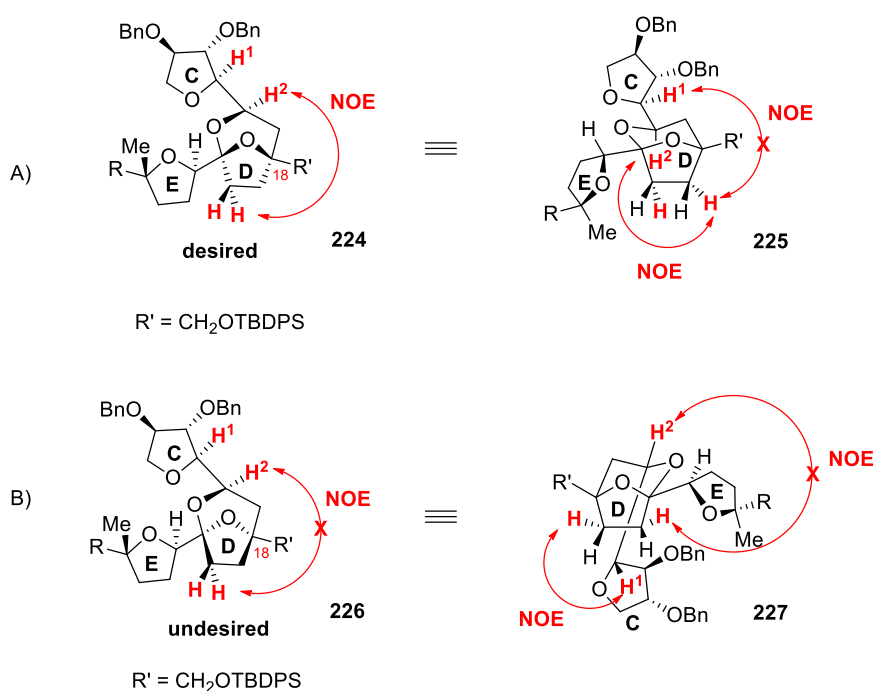
Scheme 4.08 Results of the Sharpless asymmetric dihydroxylation

Due to the difficulty of separating the diastereoisomers and of assigning the stereochemistry of the tertiary alcohol formed, we chose to take **223** forward as the pair of diastereoisomers might separate at a later stage.

4.4.3 Manganese Dioxide Oxidation

If we were able to achieve the propargylic alcohol oxidation and hydrogenation as outlined in Scheme 4.02, we would obtain the desired skeleton **224** and undesired skeleton **226** after acid catalytic cyclisation. The only difference between these two structures would be the configuration of the C18 centre formed during the dihydroxylation. We would then expect to observe nOe interactions between D ring protons and *H*² (around 4.1 ppm) in the desired structure, and nOe interactions between D ring protons and *H*¹ (around 3.7 ppm) in the undesired structure.

We also hoped that in case B, the final CDE structure would not be so favourable to form due to steric hindrance: the large group C ring would be in an axial position, and one of the OBn groups points towards the concave D ring side. In this case, it might even be possible to separate the pair of diastereoisomers which had been previously generated in the dihydroxylation reaction.

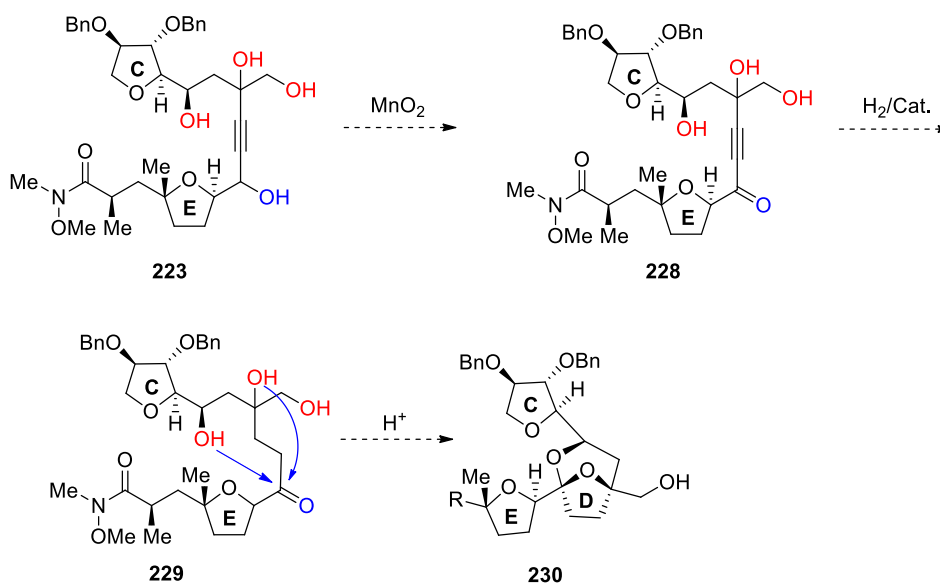


Scheme 4.09 Proposed nOe analysis of D ring product

Based on the above analysis, it was decided to take the AD product **223** to investigate further transformations.

In the original plan, the AD product would be treated with manganese dioxide for a propargylic oxidation to produce conjugated ketone **228** (Scheme 4.10). Further hydrogenation and cyclisation based on **228** could form the skeleton of D ring.

However, upon treatment of alcohol **223** (2.3:1 diastereoisomer) with manganese dioxide, we were unable to identify any desired product. Mass spectrometry analysis showed that the Weinreb amide group was missing, but the exact structure could not be identified by ^1H NMR due to the limited amount of material.

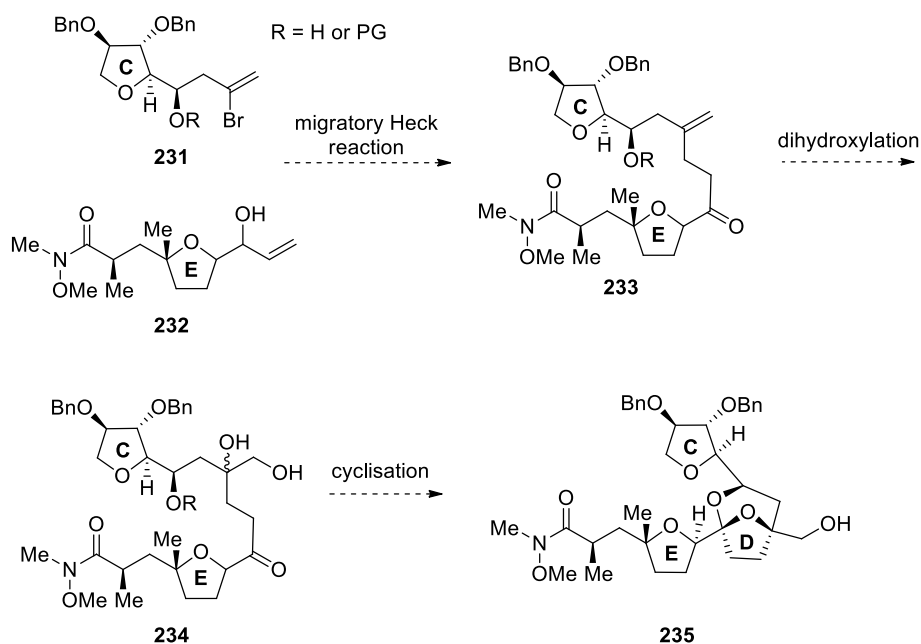


Scheme 4.10 Synthetic plan of the formation of D ring

In this case, if we chose to reduce the alkyne prior to oxidation, it would be unlikely to differentiate the four hydroxyl groups. Considering the long sequence (19 steps) and the efficiency of functionalisation, it was decided not to continue with this route.

4.4.4 Heck Coupling

Due to the difficulty in the functionalisation outlined in Scheme 6.02, we proposed a new route using a Heck coupling^[96] to make D ring skeleton (Scheme 4.11). If the Heck strategy succeeded, the functionalisation towards D ring would be simplified, only requiring dihydroxylation and acidic cyclisation based on ketone **233**.

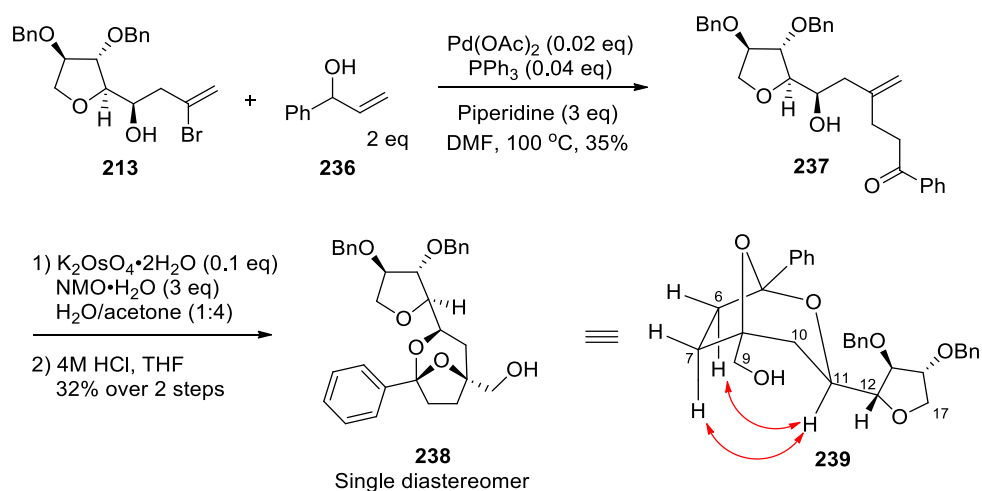


Scheme 4.11 Proposed synthetic route using migratory Heck strategy

The experimental work on this route was carried out on a model system by part II student Matthew Reeves.^[97] Scheme 4.12 showed some preliminary results from him. Based on vinyl bromide **213** and allylic alcohol **236**, intermolecular Heck reaction gave alkenyl ketone **237** in 35% yield. The corresponding ketone **237** was subjected to dihydroxylation and acidic cyclisation conditions, producing D ring structure as a single compound, whose structure was proven by nOe study.

Interestingly, the dihydroxylation of **237** gave a pair of diastereoisomers with 1:1 selectivity, but the proposed undesired diastereoisomer of **238** was not observed after acid mediated cyclisation. These results proved the hypothesis discussed in Scheme 4.09, which was that the undesired diastereoisomer would be unlikely to form a D ring type-skeleton due to steric hindrance. Taking this into consideration, 32% yield for two steps of dihydroxylation and cyclisation was quite satisfying. Further

optimisation of these reactions is currently under investigation in the group.



Scheme 4.12 Matthew Reeves' work on formation of D ring using migratory Heck reaction

4.5 Summary

In conclusion, the Second Generation Strategy improved the key coupling with respect to the yield and reaction stoichiometry. Using vinyl bromide **213** and alkyne **217**, enyne **218** could be made in 54% yield with only 1.2 equivalents of alkyne **217**. In particular, 51% yield could still be achieved when only slight excess of alkyne (1.02 eq.) **217** was used. However, the diastereoselectivity of the AD reaction was only moderate and we were unable to assign the newly-generated stereogenic centre directly. Further functionalisation by oxidation was attempted but was also unsuccessful. It was also suggested that the undesired diastereoisomer of tertiary alcohol **222/223** would not cyclise to the final D ring skeleton due to its steric hindrance. At this point we decided not to pursue further studies on this route and we

chose to develop a new approach to the D ring which will be discussed in the next chapter.

Chapter 5

Third Generation Strategy for the Synthesis of the D Ring

5.1 Introduction

5.1.1 Summary of First and Second Generation Strategies

In order to synthesise the D ring skeleton, there were two major factors that could be concluded from Chapter 3 and Chapter 4. One is the yield and number of equivalents of each coupling partner used in the key coupling; the other is the ease of further functionalisation towards the desired D ring skeleton.

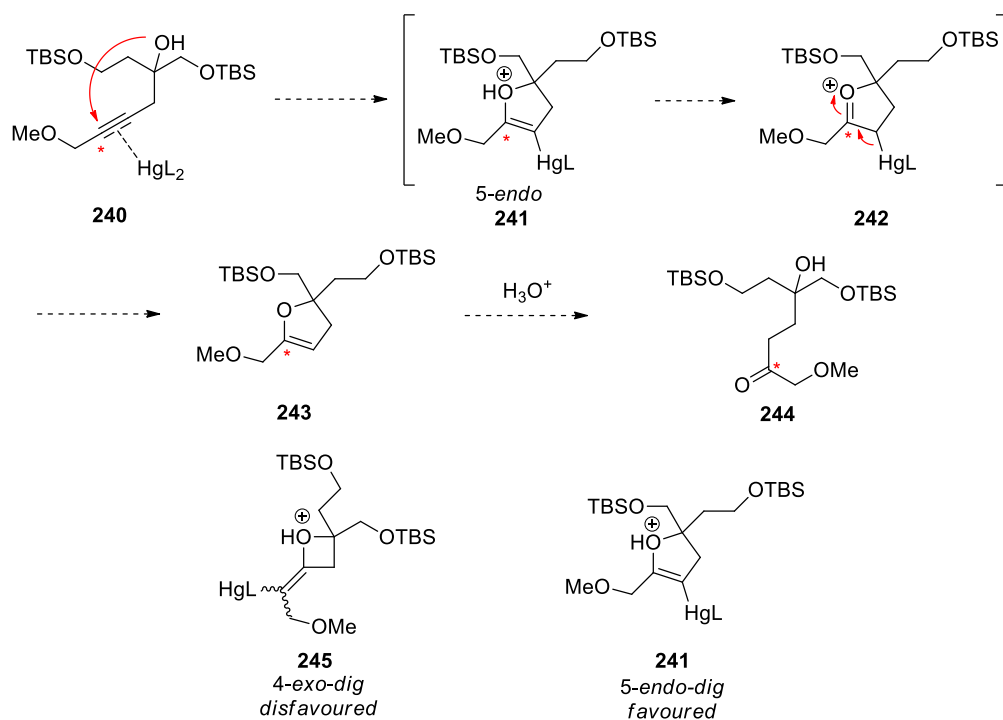
The syntheses in Chapter 3 prepared the skeleton of the D ring on simplified substrates, but the results of the key alkyne-epoxide coupling were not satisfying (epoxide **161**→alcohol **152**, 41% yield, 2 eq. of alkyne **145** used). The syntheses in Chapter 4 achieved the key Sonogashira coupling in reasonable yields (vinyl bromide **213**→propargylic alcohol **218**, 1.2 eq. of alkyne **217** used, 54% yield; or 1.02 eq. of alkyne **217** used, 51% yield), but the further functionalisation afterwards was not an easy task.

Therefore, a new strategy was needed to fulfill both of the requirements to meet our target.

5.1.2 Design of a Third Generation Strategy

Concerning the potential difficulty in functionalisation demonstrated in the Second Generation Strategy, the coupling substrates from the First Generation Strategy were reconsidered as a potential starting point. In the new system, the key coupling step required further optimisation, and a new functionalisation strategy was necessary due

to the difficulties we encountered during the application to an advanced system. In this case, a new hydration approach was proposed instead of the previous hydrosilylation-oxidation process (Scheme 5.01).

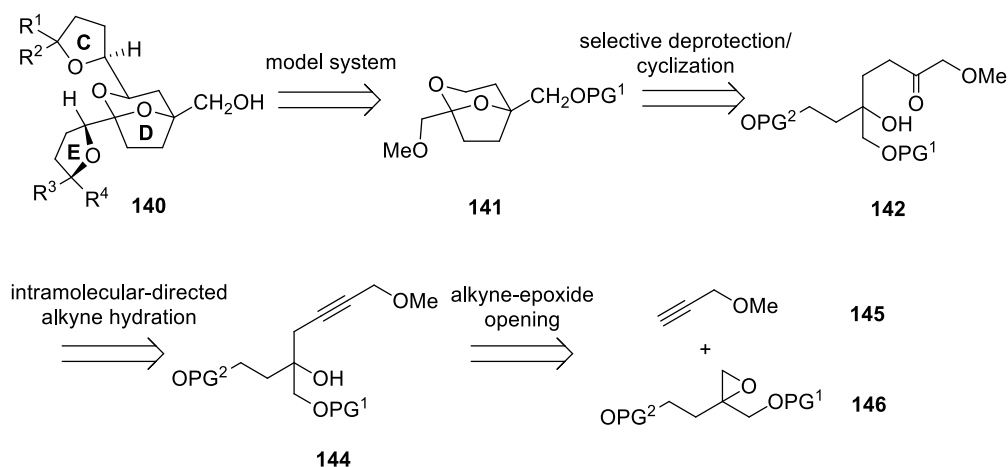


Scheme 5.01 Proposed intramolecular-directed alkyne hydration

The regioselectivity for this hydration can be controlled intramolecularly by the tertiary hydroxyl group. Starting with alkyne **240**, under the activation of Hg(II) , there are two possible intermediates **245** (4-*exo-dig*) and **241** (5-*endo-dig*). According to Baldwin's rules, 5-*endo-dig* is favoured while 4-*exo-dig* is disfavoured. Therefore organomercurial **241** will be the most probable intermediate. Tautomerisation of **241** gives subsequent oxonium **242**, which then undergoes elimination to produce vinyl ether **243**. Final acidic hydrolysis of **243** proceeds to ketone **244**. There was also some recent literature in support of this idea (Scheme 5.02).^[98]



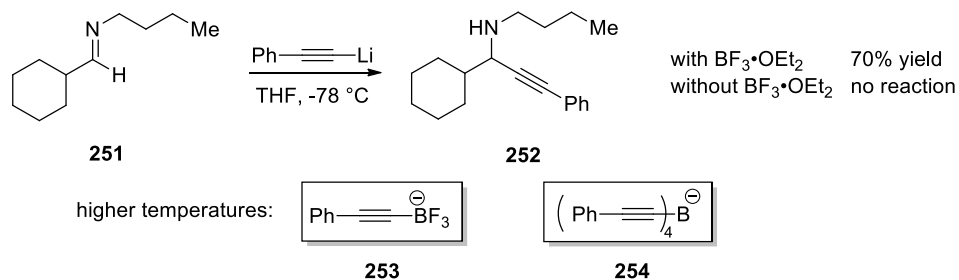
Having these ideas in mind, CDE portion **140** could be simplified to bicycle **141**, which could be prepared from ketone **142** using a selective deprotection/cyclisation strategy. In order to synthesise ketone **142**, an intramolecularly-directed hydration of the alkyne could be performed based on alkyne **144**, which could be synthesised by the nucleophilic attack of terminal alkyne **145** onto epoxide **146**.

Scheme 5.03 Retrosynthesis of D ring skeleton **140**

5.3 Synthetic Route

5.3.1 Lewis Acid Promoted Coupling

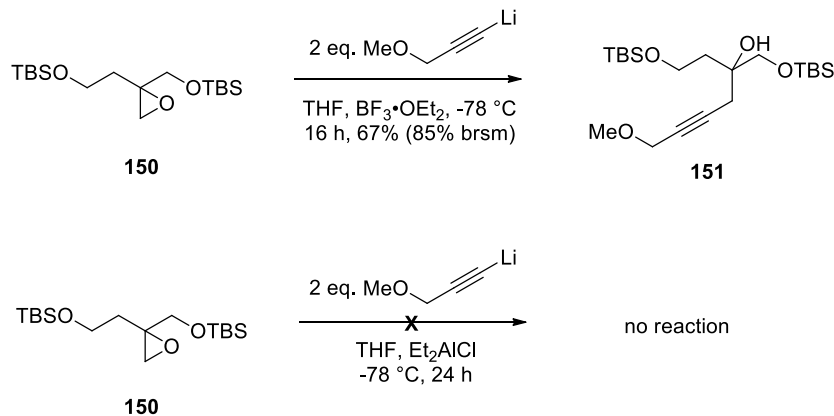
The alkyne-epoxide coupling was investigated initially. In the First Generation



Scheme 5.05 Literature examples of reactions involve organolithiums and $\text{BF}_3 \cdot \text{OEt}_2$

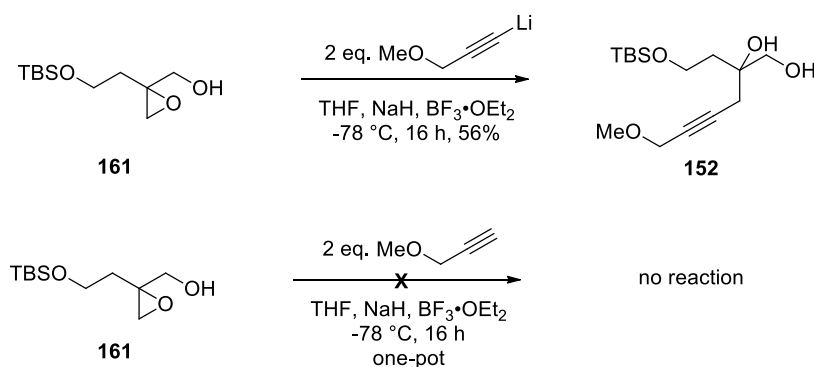
Keeping the temperature issue in mind, the reaction (Scheme 5.06) was carried out carefully by slow addition (approx. 0.2 mL/min) of $\text{BF}_3 \cdot \text{OEt}_2$ along the side of the flask at -78°C . The resultant reaction mixture was left at -78°C for 16 h, giving desired product **151** in 67% yield (85% brsm, 2 eq. of alkyne and *n*-BuLi was used).

When Et_2AlCl was used, no reaction was observed (Scheme 5.06).



Scheme 5.06 Results of epoxide opening reaction using different Lewis acids

With the success of the epoxide opening reaction by using $\text{BF}_3 \cdot \text{OEt}_2$, a similar reaction was tested on glycidol **161**. Applying the conditions described in Scheme 5.07 with 1 eq. of NaH, diol **152** was obtained in 56% yield. However, the one-pot procedure did not work when trying to use extra NaH instead of *n*-BuLi.



Scheme 5.07 Results of epoxide opening reaction using NaH

5.3.2 Hydration and Further Functionalisation

Having the coupling product **151** in hand, the hydration reaction was examined next. As described in Table 5.1, all of the starting material was consumed within 5 minutes using HgCl₂ (Entry 1), and 4 spots was observed on TLC plate. There was no change on TLC if the reaction was left to stir overnight. Analysis of the crude reaction mixture using LRMS suggested a major peak at $m/z = 211.1$, which matched the mass of cyclised product **257** or desilylated product **256** (plus Na⁺). ¹H NMR spectroscopic analysis of the crude mixture showed that the C≡CCH₂CRR'OH multiplet ($\delta = 2.40\text{--}2.56$ ppm) next to the alkyne was missing. The data obtained implied the possibility of the formation of cyclised product **257**, while the identities of byproducts were still a mystery due to the difficulty of purification.

With the positive results from HgCl₂, another mercury salt Hg(OTf)₂ was tested. Interestingly, only one TLC spot was obtained in 30 minutes. Spectroscopic analysis following flash column chromatography purification revealed that the isolated product was compound **257**, whose spectroscopic data matched the same compound prepared

in the First Generation Strategy (see SI). The results suggested that the cyclisation was complete in one step using these hydration conditions.

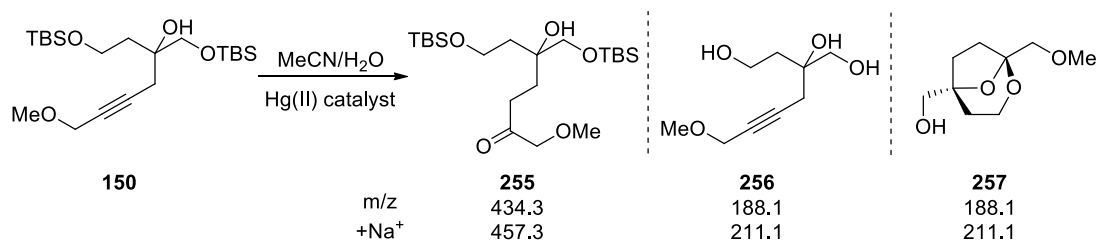
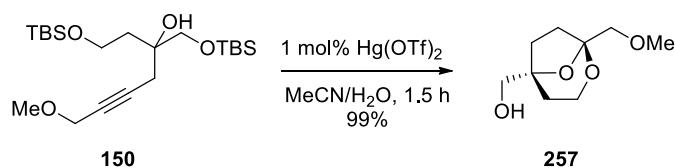


Table 5.1 Condition Screening of Alkyne Hydraton

Entry	Catalyst	Catalyst loading (eq.)	Time (min)	Results (TLC)
1	HgCl_2	0.01	90	4 spots
2	$\text{Hg}(\text{OTf})_2$	0.01	120	1 spot, 99%
3	$\text{Hg}(\text{OAc})_2$	0.01	90	1 spot, 99%

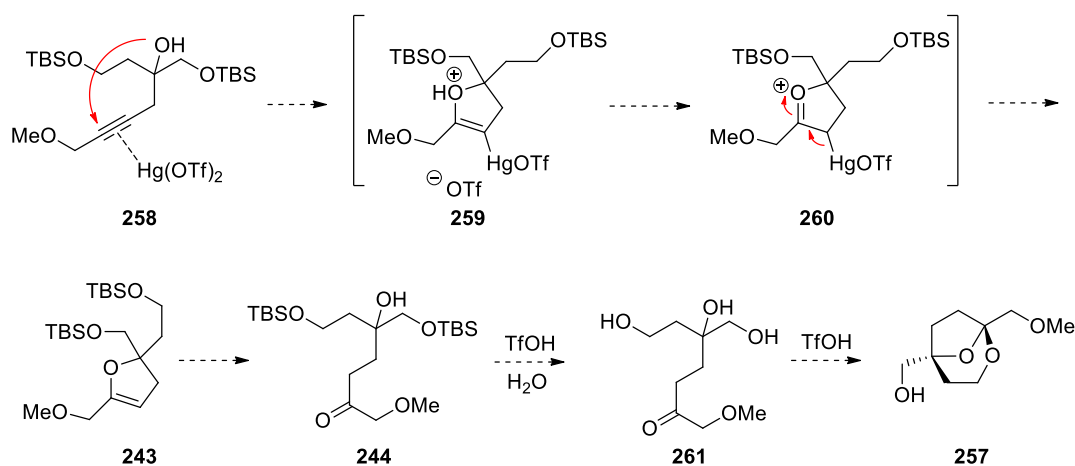


Scheme 5.08 One pot synthesis of alcohol **257**

The proposed mechanism was shown in Scheme 5.09. Catalytic amount of $\text{Hg}(\text{OTf})_2$ first promoted the hydration of alkyne **258** to give ketone **244**. Meanwhile, $\text{Hg}(\text{OTf})_2$ was partially hydrolysed to generate a trace amount of TfOH , which then deprotected the two primary TBS groups to form triol **261**. Cyclisation then took place in the presence of TfOH to produce final product **257**.

The proposed mechanism suggested that the counter-ion of the mercury salt was the key to the success of all of these transformations. The counter-ion may make the

corresponding mercury salt soluble in water, and, more importantly, easy to hydrolyse to produce the acid that could promote the deprotection and cyclisation. Based on this hypothesis, the hydration of alkyne **150** by using 1 mol% of $\text{Hg}(\text{OAc})_2$ as catalyst also provided cyclisation product **257** quantitatively.

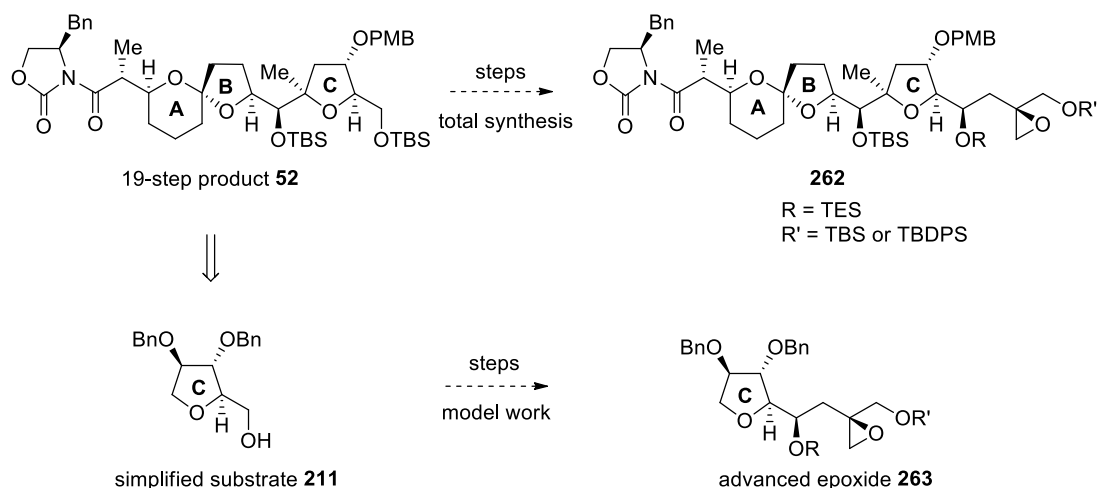


Scheme 5.09 Proposed mechanism for the formation of alcohol **257**

5.4 Application to Advanced Systems

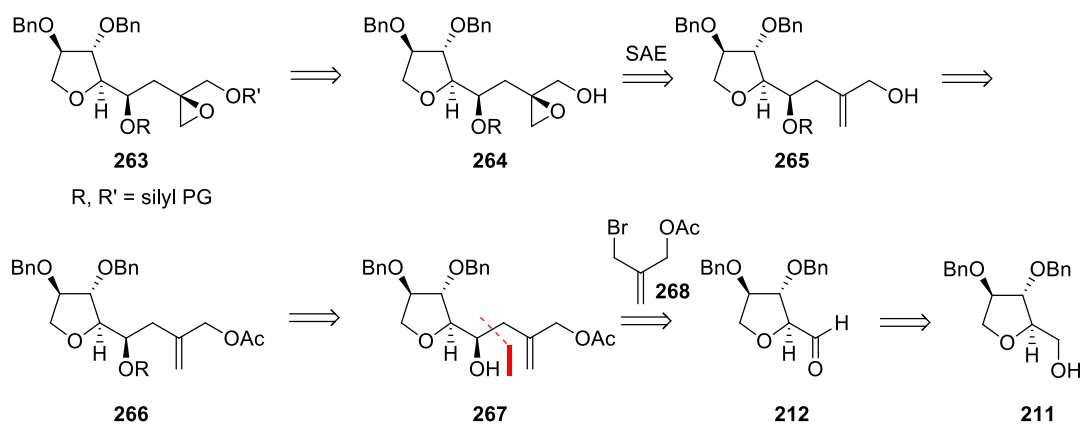
5.4.1 Coupling Fragments Analysis

Having obtained positive results from the simplified model, we then decided to work on the synthesis of advanced epoxide **263** to attempt the key coupling with alkyne **145** (Scheme 5.10). In the new system, we decided to use the Sharpless Asymmetric Epoxidation (SAE) strategy to build the stereogenic centre on the epoxide because the stereoselectivity can be predicted using Sharpless' model.^[101]



Scheme 5.10 Structure of model compound and ABC fragment of PTX-4

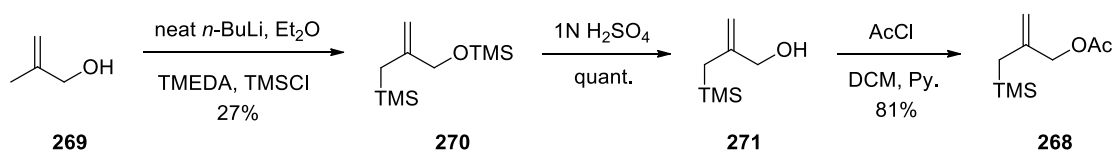
A retrosynthetic strategy to obtain epoxide **263** is illustrated in Scheme 5.11. The desired silyl-epoxide could be obtained by a sequence of SAE and silyl-protection from allylic alcohol **265**. SAE precursor **265** could then be prepared from homoallylic alcohol **267** using a TES protection and saponification strategy. Homoallylic alcohol **267** could be synthesised using Felkin–Anh controlled allylation from alkene **268** and aldehyde **212**, which could be easily made from the corresponding primary alcohol **211**.



Scheme 5.11 Retrosynthesis of epoxide **263**

5.4.2 Synthesis of Epoxide 263

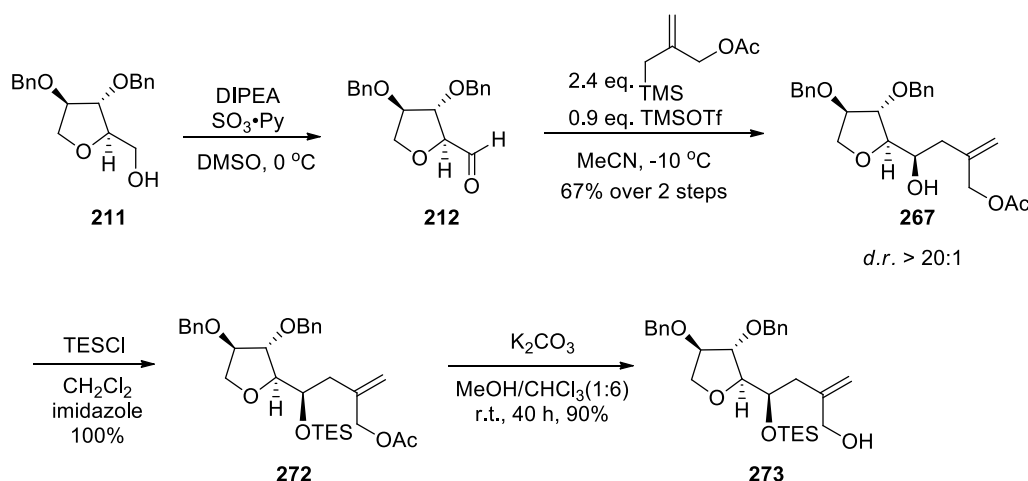
Coupling fragment alkene **268** needed to be synthesised prior to the coupling presented in Scheme 5.11. Following a procedure first developed by Trost and co-workers,^[102] alcohol **271** could be prepared on a multi-gram scale. Acetyl protection of the subsequent alcohol **271** resulted in coupling fragment **268** in 81% yield. ¹H NMR of acetate **268** clearly showed a methyl singlet at δ 2.11 ppm, indicated the formation of acetate. Spectroscopic data of **268** are consistent with those previously reported.^[102]



Scheme 5.12 Synthesis of Coupling Fragment **268**

With a reliable source of alkene **268** in hand, the synthetic route towards epoxide **263** could then be investigated. Similar to the process of making vinyl bromide **213** in the Second Generation Strategy, homoallylic alcohol **267** was prepared in an oxidation-alkylation process in 67% overall yield and over 20:1 *d.r.*. The stereogenic centre of the newly formed secondary alcohol was predicted by the Felkin–Anh model (see Chapter 4) and also confirmed by Mosher’s ester analysis (see SI). TES protection of resulting alcohol **267** led to acetate **272**, which was then hydrolysed to give allylic alcohol **273** under mild basic conditions in 90% yield. Initial attempt at this deprotection using standard K₂CO₃/MeOH conditions only resulted in the deprotection of both acetate and secondary TES groups. Reaction monitoring by TLC

showed that under the standard conditions the acetate deprotection was actually faster and could only be selectively removed between 2–10 minutes (5 mg scale to 50 mg scale), but the reaction time varied on the scale and the concentration of K_2CO_3 . Therefore, diluted basic conditions were used to make the reaction easy to control.



Scheme 5.13 Synthesis of SAE Precursor **273**

Having obtained allylic alcohol **273**, we next examined the SAE reaction. Initial attempts to perform this reaction showed that the byproduct aldehyde **275** was easily formed (Entry 1). A possible explanation was that the catalyst used could easily promote the Lewis acid assisted rearrangement of the epoxide (Scheme 5.14). Based on this hypothesis, lower catalyst loading and shorter reaction time were attempted (Entry 2). A better result of 23:77 (aldehyde/epoxide) was obtained, but it still compromised the isolated yield.

Based on the proposed mechanism in Scheme 5.14, it was suggested that increasing the steric hindrance of the titanium catalyst might be beneficial towards inhibiting the

formation of the epoxide. Therefore, a bulky titanium catalyst $\text{Ti}(\text{O}-t\text{-Bu})_4$ was used in Entry 3 & 4, and the product ratios were improved substantially (4:96 in Entry 3 and 2:98 in Entry 4). When reducing the loading of $\text{Ti}(\text{O}-t\text{-Bu})_4$ to 0.9 eq., the selectivity remained the same (Entry 5).

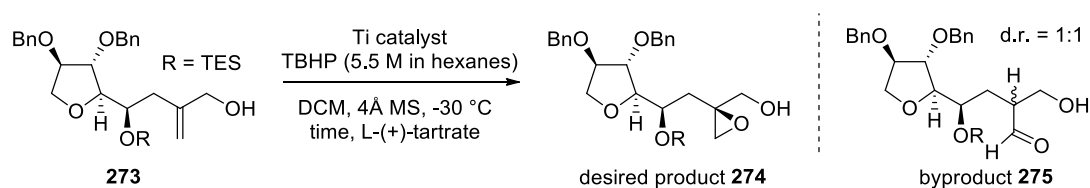
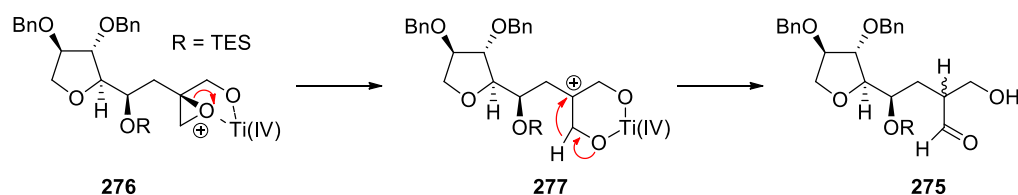


Table 5.2 Condition screening of SAE reaction

Entry	Catalyst	Catalyst loading (eq.)	TBHP Loading (eq.)	Time (h)	Results ^a (aldehyde:epoxide)
1	$\text{Ti}(\text{O}-i\text{-Pr})_4$	2.2	5	48	56:44 ^c
2	$\text{Ti}(\text{O}-i\text{-Pr})_4$	1.1	7 ^b	20	23:77 ^c
3	$\text{Ti}(\text{O}-t\text{-Bu})_4$	1.3	9 ^d	60	4:96 ^c
4	$\text{Ti}(\text{O}-t\text{-Bu})_4$	1.3	9 ^d	48	2:98 ^e
5	$\text{Ti}(\text{O}-t\text{-Bu})_4$	0.9	9 ^d	42	2:98 ^e

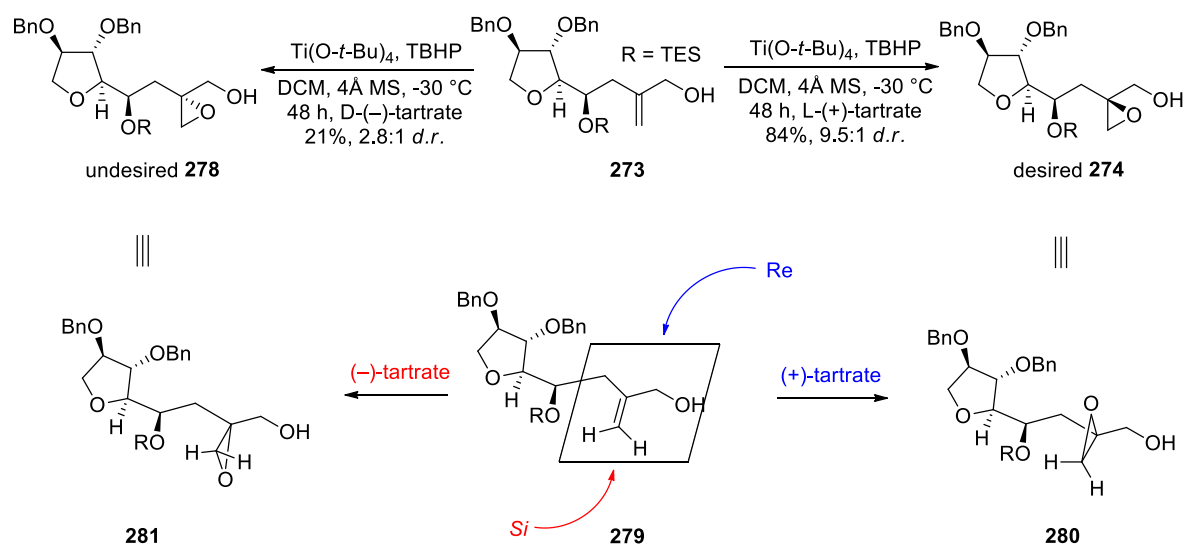
a) The ratio was calculated based on the integration of aldehyde and Bn-CH_2 peaks from the corresponding ^1H NMR spectra due to the interference of OH peaks; b) 2 extra eq. TBHP were added after 8 h; c) (+)-diisopropyl L-tartrate was used; d) 2 extra eq. TBHP were added after 12 h; another 2 extra eq. TBHP were added after 24 h; e) (+)-di-*tert*-butyl L-tartrate was used.



Scheme 5.14 Proposed mechanism for the formation of aldehyde **275**

Based on the optimal conditions obtained in Entry 4, we could then study on the selectivity of SAE using both L- and D-tartrates. When D-tartrate was used, the undesired epoxide was obtained at 21% yield and 2.8:1 *d.r.* (Scheme 5.15).

Delightfully, the desired epoxide was obtained in a much better yield and diastereoselectivity (84% yield, 9.5:1 *d.r.* using $\text{Ti}(\text{O}-t\text{-Bu})_4$ as catalyst). The stereogenic centre was assigned based on predictive model in Scheme 5.15.

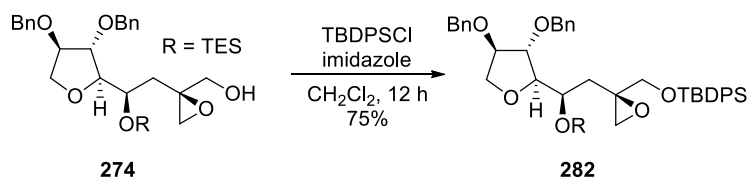


Scheme 5.15 Results of SAE and the prediction of stereogenic centre

The *d.r.* value was calculated based on the integration of epoxide doublets (see SI, 500 MHz, δ 2.75ppm, D-tartrate epoxide; δ 2.61 ppm, L-tartrate epoxide).

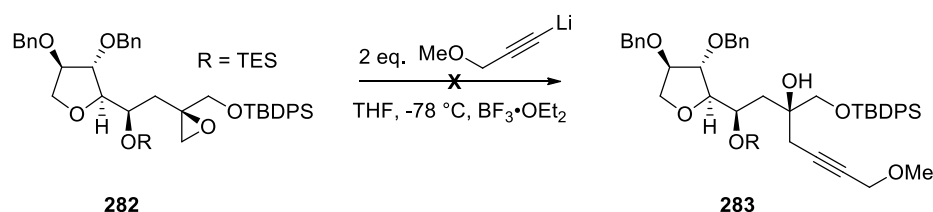
5.4.3 Coupling of Epoxide **274** and Alkyne **145**

After the desired epoxide **274** was obtained by SAE, a TBDPS group was used to protect the primary alcohol to give **282** as the coupling precursor.



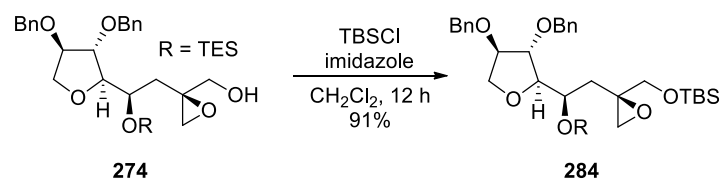
Scheme 5.16 Synthesis of coupling precursor **282**

Unfortunately, when the optimal coupling condition was applied to epoxide **282**, no change was observed by TLC monitoring after 16 h at $-78\text{ }^{\circ}\text{C}$. ^1H NMR of the reaction crude showed that the epoxide CH_2 still remained at δ 2.75 ppm.



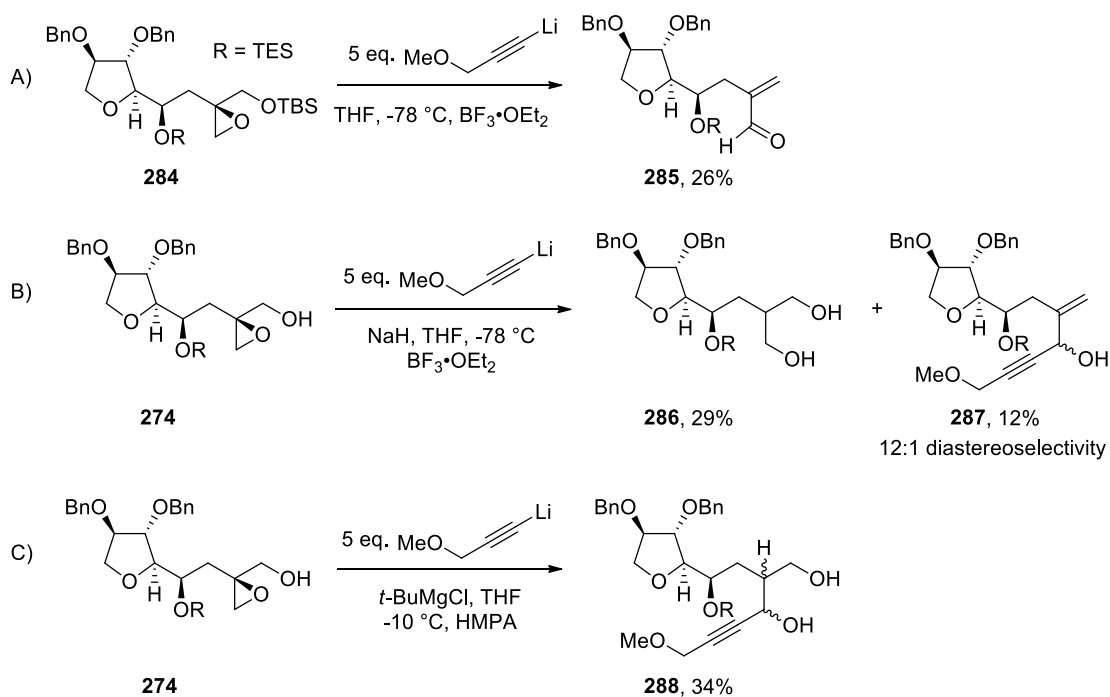
Scheme 5.17 Failed coupling attempt based on epoxide **282**

We thought that TBDPS protecting group might be too bulky for this reaction. Therefore it was decided to put TBS onto the primary alcohol.



Scheme 5.18 Synthesis of coupling precursor **284**

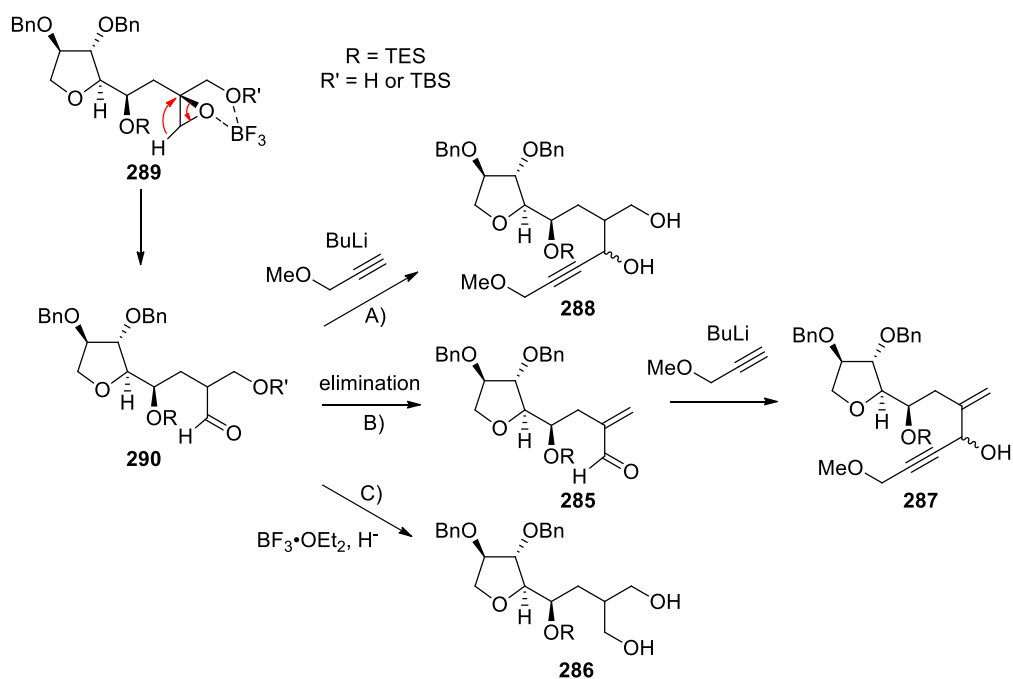
Based on epoxide **284** and hydroxyl epoxide **274**, a series of conditions were applied as described in Scheme 5.19. Entries A and B employed the conditions developed in the Third Generation Strategy. However, only byproducts **285**, **286** and **287** were obtained. When the conditions developed in the First Generation Strategy was applied, only propargylic alcohol **288** was obtained (Entry C).



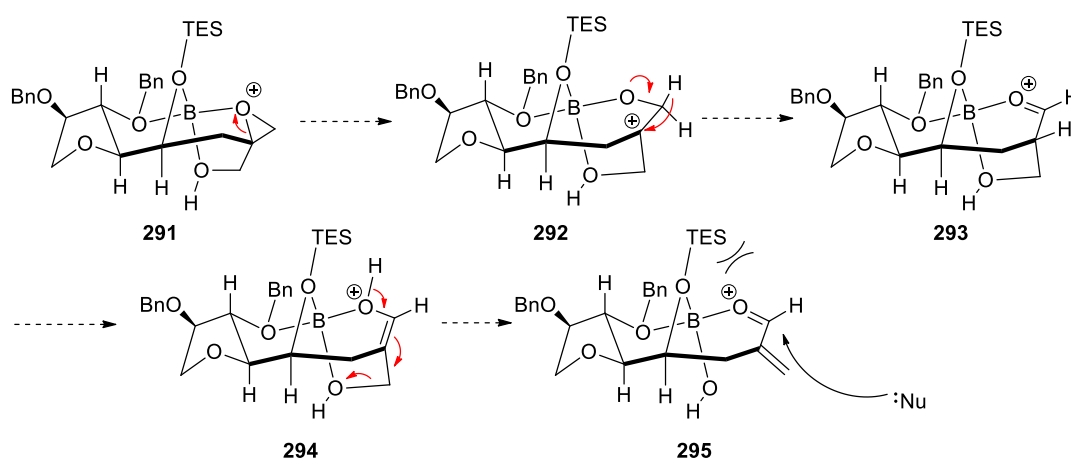
Scheme 5.19 Results of the key coupling

To account for the formation of byproducts aldehyde **285**, diol **286**, allylic alcohol **287** and propargylic alcohol **288**, it was proposed that the epoxide rearranges to an aldehyde *via* a chelation affect (Scheme 5.20, Scheme 5.21).^[79]

Based on aldehyde **290**, propargylic alcohol **288** was obtained by nucleophilic addition using alkynyllithium (Scheme 5.20, Entry A). Aldehyde **290** could also undergo an elimination process to give conjugated aldehyde **285**. Nucleophilic addition to the subsequent aldehyde **285** generated allylic alcohol **287** with 12:1 diastereoselectivity. Surprisingly, NaH was proposed to act as a H^- source to perform a reduction under the Lewis acidic conditions (Entry C).



Scheme 5.20 Proposed mechanisms for the generation of byproducts



Scheme 5.21 Proposed chelation effect by oxygen atoms

Some of the results (Scheme 5.19) also gave supporting evidence for the chelation effect proposed in Scheme 5.21. The coupling byproduct **287** gave 12:1 diastereoselectivity, which suggested that a substrate-controlled addition is highly possible. While in Scheme 5.21, the TES group in **295** blocked the top face, thus

making the nucleophile attack from the more favoured bottom face.

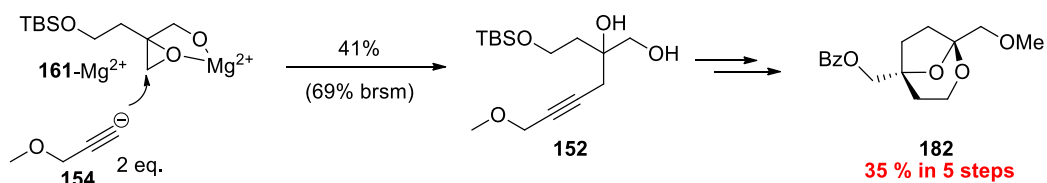
Based on all these analyses, it was decided that the current advanced model compound was not ideal for the synthesis. Therefore the Third Generation Strategy was stopped at this stage.

5.5 Conclusion

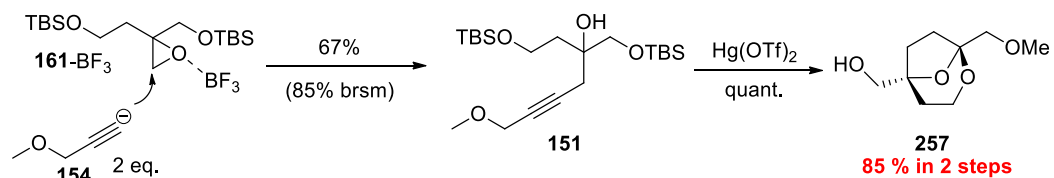
The Third Generation Strategy achieved the key coupling at 67% yield (85% brsm) by using two equivalents of nucleophile. The functionalisation towards the D ring structure was achieved in a single step quantitatively using catalytic amounts of $\text{Hg}(\text{OTf})_2$ or $\text{Hg}(\text{OAc})_2$ for a regioselective alkyne hydration. The results obtained are so far the best we have for constructing the D ring (Scheme 5.23).

The application of the Third Generation Strategy on advanced model substrates was unsuccessful. Analysis suggested that it maybe the nature of the model compound we chose. However, we have still developed a reliable synthetic route to accessing the coupling precursor, and we learned that the chelation effect might result in the rearrangement of the corresponding epoxides.

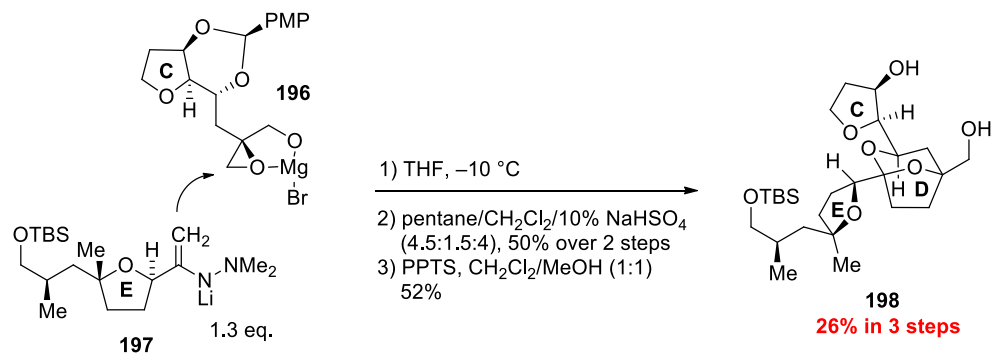
First Generation Strategy



Third Generation Strategy



Evans' Synthesis



Scheme 5.22 Comparison of different D ring formation strategies

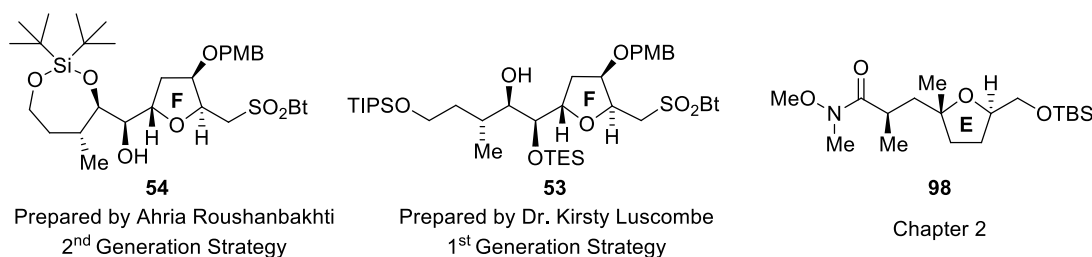
Chapter 6

Synthesis of EFG Fragment of Pectenotoxin-4

6.1 Introduction

6.1.1 Fragments that have been Prepared in the Donohoe Research Group

Having obtained the skeletons of the FG fragment (unpublished work by Ahria Roushanbakhti, Dr. Michael Tucker^[58] and Dr. Kirsty Luscombe^[56]) and E ring fragment **98** (from Chapter 2), we can now consider the methods to unite these two fragments together.



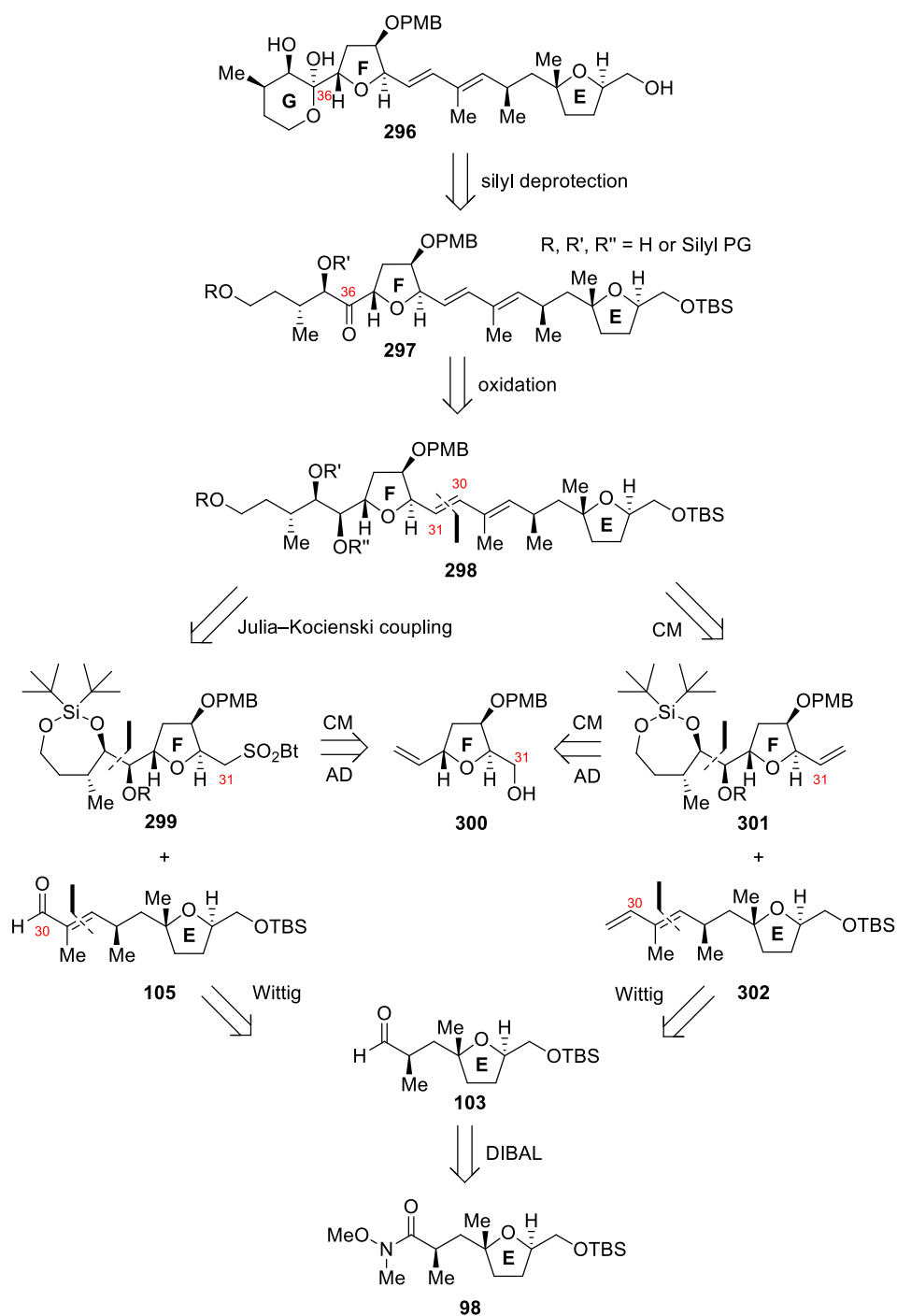
Scheme 6.01 Fragments of the EFG system that have been made in the group

6.1.2 Retrosynthesis

In order to synthesise EFG fragment **296**, a sequence of oxidation and silyl deprotection can be used from diene **298** (Scheme 6.02). Diene **298** can be prepared from two methods either using a Julia–Kocienski olefination^[47] or a cross metathesis (CM).

The FG portion sulfone **299**, which will be the nucleophilic partner in the Julia–Kocienski olefination, has been synthesised previously in the group (Scheme 6.01).^[57] The coupling partner of CM strategy, alkene **301**, could be readily accessed from its C31 alcohol precursor using an oxidation and Wittig reaction sequence.

Both of the two possible E ring portion aldehyde **105** and diene **302** can be derived from the same aldehyde precursor **103** by Wittig reactions. The subsequent aldehyde **103** is a DIBAL reduction product from Weinreb amide **98**, which has been prepared earlier (see Chapter 2).

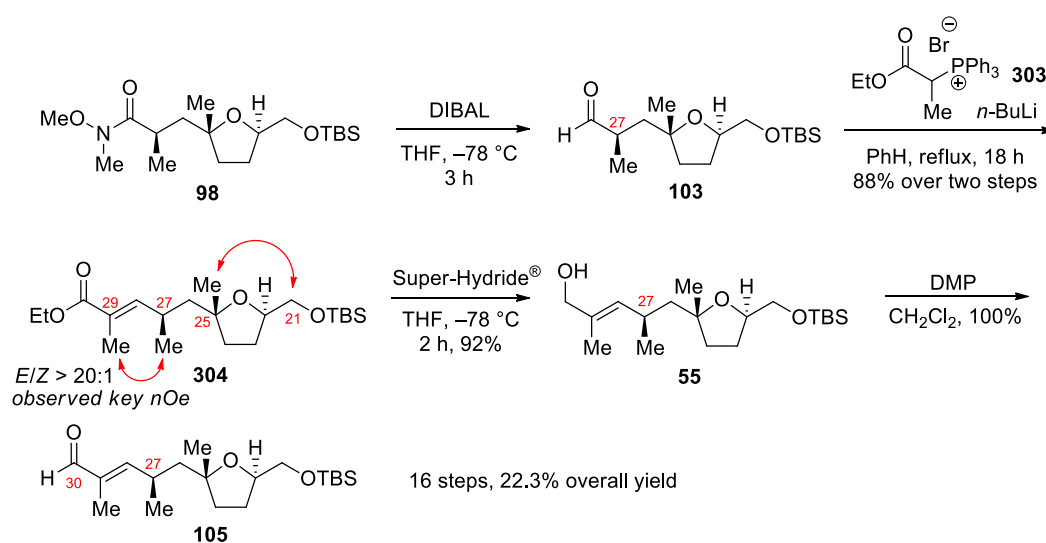


Scheme 6.02 Retrosynthetic analysis of the EFG fragment

6.2 Preparation of Julia–Kocienski Olefination Precursors

As sulfone **299** had been prepared earlier (work by Ahria Roushanbakhti), the Julia–Kocienski olefination strategy seemed to be the natural option to study. Therefore, the synthesis of the other coupling partner aldehyde **105** was first investigated.

Starting from Weinreb amide **98**, DIBAL reduction afforded aldehyde **103**, which was carried through to the next Wittig reaction without further purification to give ester **304** in 88% yield over two steps (Scheme 6.02). Reduction of ester **304** by using Super-Hydride[®] produced allylic alcohol **55** in 92% yield. DMP oxidation finally gave conjugated aldehyde **105**, which was used without further purification for the upcoming Julia–Kocienski olefination. nOE analysis of ester **304** showed strong correlations between C29 methyl and C27 methyl, and C25 methyl and H21, providing strong evidence for the formation of *E*-alkene and *trans* THF geometry.



Scheme 6.03 Optimised synthetic route towards aldehyde **105**

Allylic alcohol **55** was first synthesised by a previous group member Dr. Paul Winship, yet some of the steps needed further optimisation. The Wittig reaction was found to be the most nontrivial one. Dr. Paul Winship had reported the isomerisation of C27 during the Wittig at 2:1 to 4:1 ratio (desired/undesired).^[55] Later repetitive work carried by Dr. Michael Tucker suggested that the yield of Wittig reaction depended on the quality of pre-made Wittig reagent, which was accounted for the poor reproducibility.^[58] Thus, Wittig salt **303** was treated with NaH in THF prior to the addition of aldehyde **103**, giving Wittig product **304** in 71% yield over 20:1 *E/Z* ratio. No epimerisation of C27 was observed.

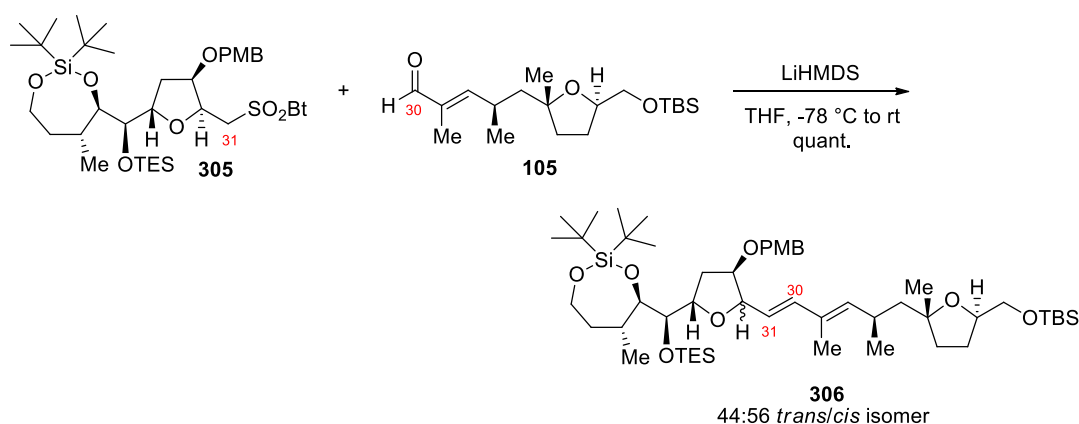
In this work, during the optimisation of the Wittig reaction, it was discovered that using commercially available pre-made Wittig carbene species would result in a significant decrease in yields (<10%). Upon the treatment of *n*-BuLi and Wittig salt **303**, benzene was found to be the best solvent. Toluene gave a messy TLC and THF only led to the decomposition of starting material using their conditions. Ester **304** was finally obtained in 88% yield in two steps, and no isomerisation of C27 was observed by ¹H NMR.

6.3 Key Julia–Kocienski Coupling

Having both aldehyde **105** and sulfone **305** in hand, the key coupling step could then be examined.

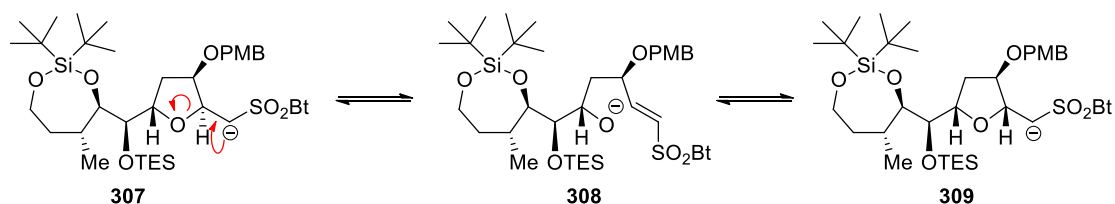
The first attempt was practised on a 0.8 mg scale (aldehyde; 2.5 eq. of sulfone). The

reaction worked in quantitative yield, and the ^1H NMR spectrum of the isolated product showed a number of unexpected alkene peaks. Although extensive COSY studies indicated that actually the isolated product was a mixture of *trans* and *cis* THF isomers (two sets of H31 alkene peaks that correlate to two different H32 peaks), both of the diastereoisomers gave coupling constant at 15.6–15.8 Hz (C30), indicating the *trans* geometry of the double bond (C30–C31) in both cases.



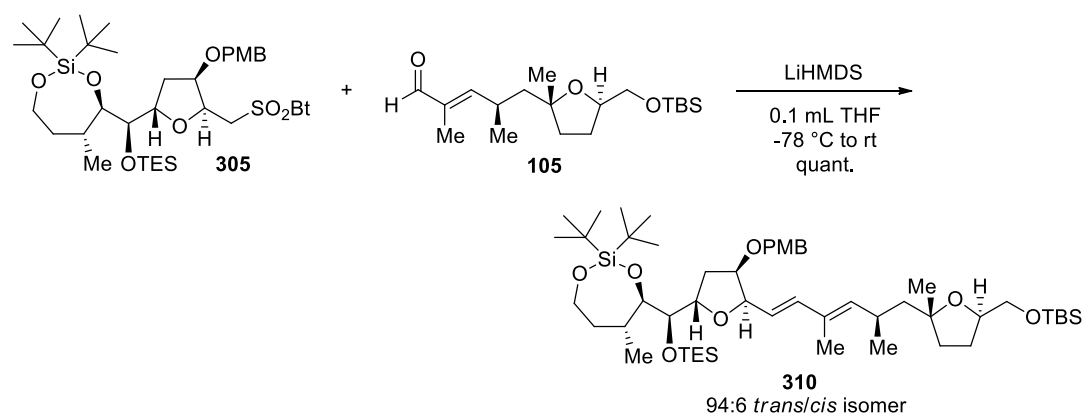
Scheme 6.04 Initial attempt of the Julia–Kocienski olefination

The proposed mechanism for this unexpected isomerisation is illustrated in Scheme 6.05. Once the sulfone is deprotonated, E1cB elimination (retro-Michael addition) was likely to have occurred. Due to the incomplete conversion of the E1cB elimination or the poor selectivity of the oxa-Michael addition, the coupling fragment sulfone **305** would be a mixture of *cis* and *trans* isomers before the coupling.



Scheme 6.05 Proposed mechanism for the formation of *cis* byproduct

Based on the proposed mechanism, we thought that the concentration of the reaction might be too low (0.8 mg aldehyde, 0.0024 mmol; 5.0 mg sulfone, 0.0062 mmol; 1.0 mL THF), which gave enough time for isomerisation of the anion to take place before its addition to the aldehyde (Scheme 6.05). Therefore we decided to increase the concentration of the reaction to accelerate the addition of sulfone **305** onto aldehyde **105**. Pleasingly, the selectivity increased to 94:6 when only 0.1 mL of THF was used, and only *E*-alkene was observed based on ^1H NMR.



Scheme 6.06 Optimised Julia–Kocienski olefination

In this case, the geometry of THF was supported by nOe experiments carried by Ahria Roushanbakhti on a similar compound **311**. Although the protecting group of O36 was different, we still thought it was a good indication of the THF geometry of coupling product **310**. The observed nOe correlations included TMS/H31, H31/Me29, Me29/H27 and H30/H28. Furthermore, the correlation between H35 and H32 was not observed. Based on these data, we assigned **310** to contain *trans*-THF rings and *E*-alkene.

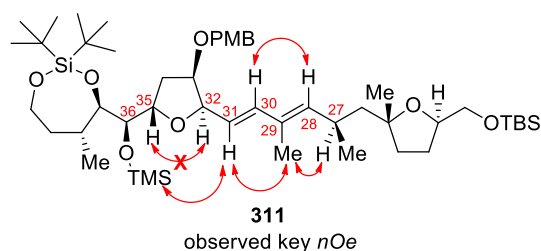


Figure 6.1 Observed key *nOe* correlations of **311** by Ahria Roushanbakhti

Having obtained coupling product **310** with good diastereoselectivity, the transformation of the secondary OTES group to a ketone would be the next target. In order to achieve this, various acidic and basic conditions were attempted to effect the deprotection of the OTES group, but unfortunately none of them could selectively deprotect the secondary OTES over the primary OTBS (Table 6.1).

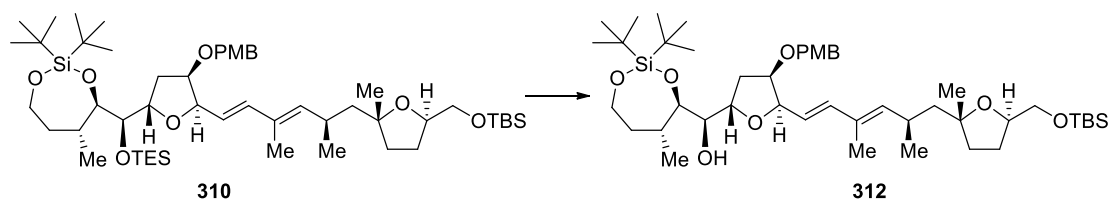


Table 6.1 Condition screening of the deprotection of **310**

Entry	Conditions	Time (h)	Result
1	PPTS, MeOH	2	double deprotection ^a
2	PPTS, THF/H ₂ O (1:3)	3	double deprotection ^a
3	PPTS, CH ₂ Cl ₂ /H ₂ O (1:1)	6	no reaction
4	K ₂ CO ₃ , MeOH	12	no reaction
5	LiOH, MeOH	24	double deprotection ^a

a) Double deprotection means that both of the secondary TES and primary TBS were removed

Due to the difficulty in achieving the selective deprotection, we then attempted the Julia–Kocienski olefination using free alcohol **54** with one extra equivalent of base

added. To our surprise, the isolated product was major *cis* isomer, whose ^1H NMR spectrum is presented (Figure 6.2) in comparison with *trans* product **310** and *trans/cis* mixture **306**. One of the possible explanations is that the *cis* isomer is more thermodynamically stable compared to its *trans* epimer.

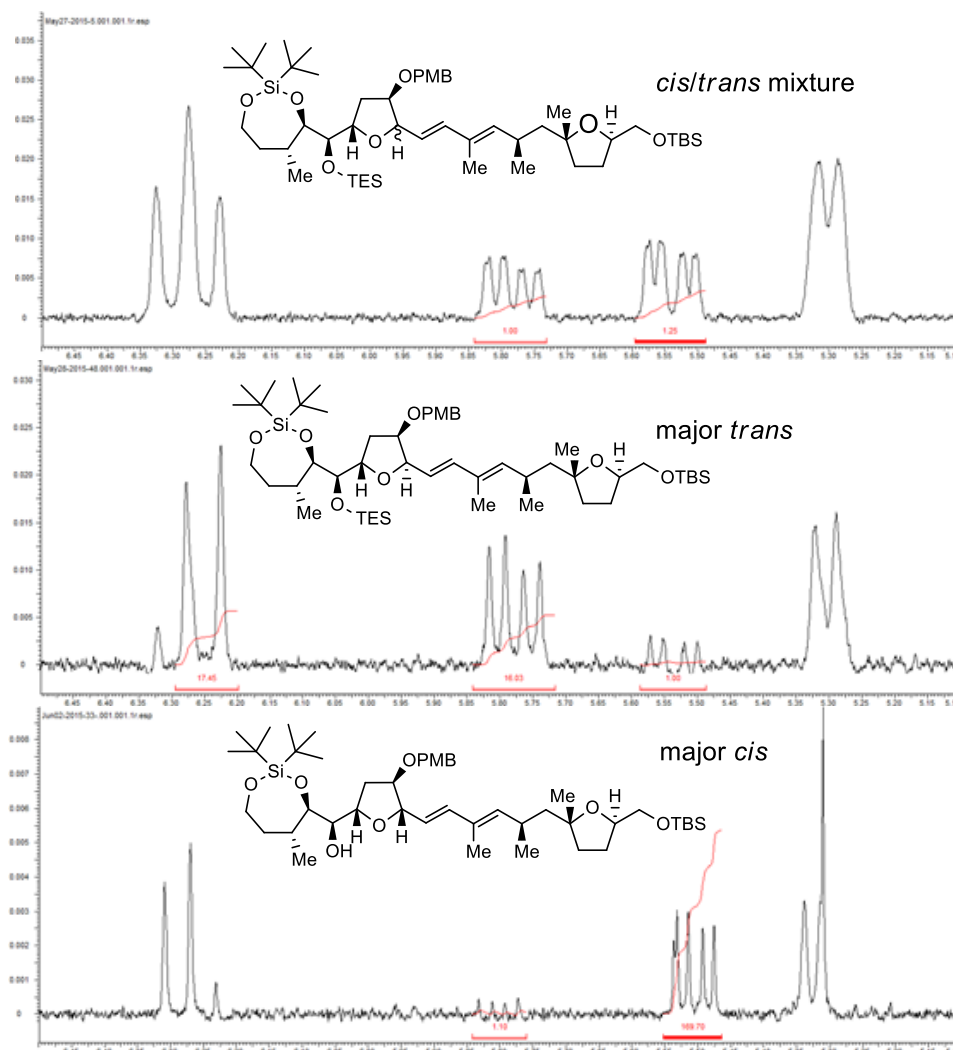
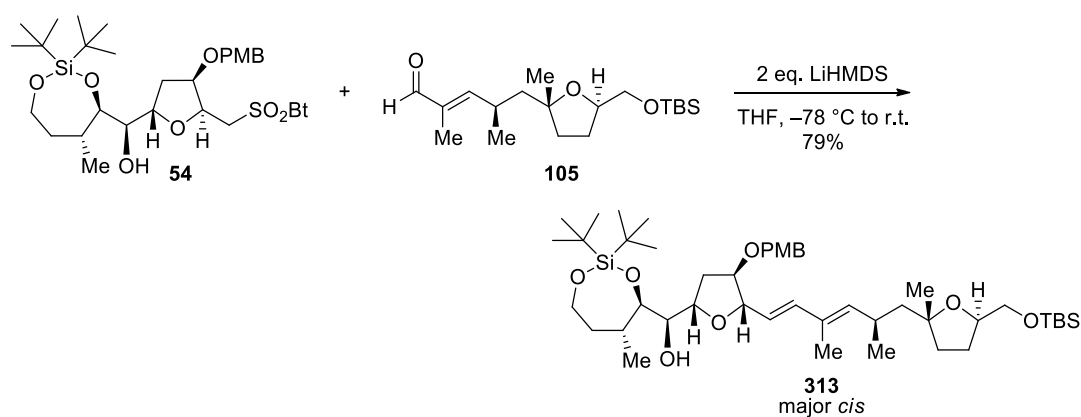


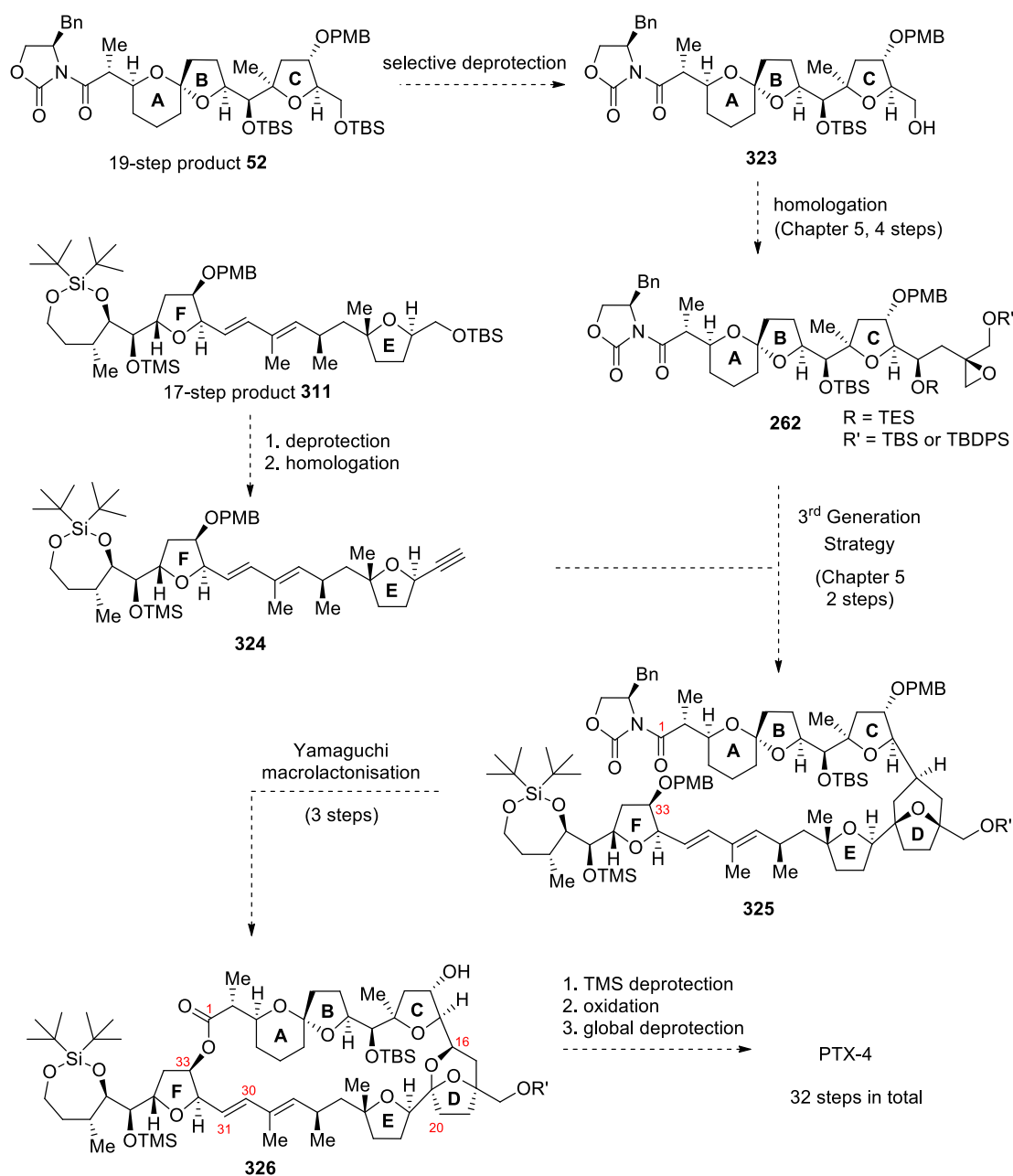
Figure 6.2 ^1H NMR spectrum of Julia–Kocienski olefination products
(mixture/*trans*/*cis*)



Scheme 6.07 Julia–Kocienski olefination with free alcohol **54**

Based on the results so far, it seemed that the only solution was to change the protecting groups of the secondary alcohol. Pleasingly, this new protecting group strategy worked.

Starting from alcohol **54**, TMS protection followed by Julia–Kocienski olefination gave diene **311** in excellent yield. Coupling product **311** was obtained with 88:12 *trans/cis* selectivity of THF geometry, and only *E*-alkene was observed based on ^1H NMR. (Starting with coupling product **311**, the later steps were a collaborative work with Ahria Roushanbakhti, and the majority of the experiments were performed by him). Selective deprotection of secondary TMS and oxidation of the subsequent alcohol afforded ketone **315**. Global silyl deprotection with TAS-F furnished the desired EFG fragment of PTX-4. The formation of **296** was supported by ^1H NMR (H35 shifts from δ 5.14 ppm to 4.46 ppm) and ^{13}C NMR (new peak at δ 97.0 ppm).



Scheme 6.09 End-game strategy for the synthesis of PTX-4

Starting with compound **52**, a 19-step product first synthesised by Dr. Radoslaw Lipinski in the group, primary TBS deprotection will give alcohol **323**, which can be subjected to the homologation sequence performed in Chapter 5 to produce epoxide **262**. By using alkyne derivative **324** from FG ring coupling product **311**, the ABCDE species **325** can be synthesised based on an alkyne-epoxide coupling and

alkyne-hydration sequence developed in Chapter 5. After this, protecting group manipulation and Yamaguchi macrolactonisation of **325** can be performed to give the 26-membered ring product **326**, which then undergoes selective deprotection, oxidation and global deprotection process to generate final natural product PTX-4 in 32 steps.

Chapter 7

Experimental

7.1 Experimental Techniques

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX200 (^1H 200 MHz, ^{13}C 50 MHz), DPX300 (^1H 300 MHz, ^{13}C 75 MHz), AVB400 (^1H 400 MHz, ^{13}C 101 MHz), AVF400 (^1H 400 MHz, ^{13}C 101 MHz), DPX400 (^1H 400 MHz, ^{13}C 101 MHz), DQX400 (^1H 400 MHz, ^{13}C 101 MHz), AVB500 (^1H 500 MHz, ^{13}C 126 MHz), AVC500 (^1H 500 MHz, ^{13}C 126 MHz), AVD500 (^1H 500 MHz, ^{13}C 126 MHz) spectrometer in CDCl_3 , Benzene- d_6 or d_6 -DMSO and referenced to residual solvent peaks or to tetramethylsilane as an internal standard. Chemical shifts δ are quoted in parts per million (ppm) to the nearest 0.01 for ^1H and 0.1 for ^{13}C . Coupling constants J are quoted in Hz to the nearest 0.1 and splittings are recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sxt), multiplet (m) and broad (br.). Assignments were based upon DEPT, COSY and HSQC experiments.

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as thin films. Absorption maxima are quoted in wavenumbers (cm^{-1}) and labelled as strong (s), medium (m), weak (w) and broad (br.).

Mass spectra were recorded on a Fisons Platform II spectrometer under electrospray ionisation (ESI). Relative intensities of assignable peaks are quoted as percentage values. High resolution mass spectra are given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM). Calibration was performed *via* the lock-mass of tetraoctylammonium bromide for positive ions and sodium dodecyl sulfate for negative ions.

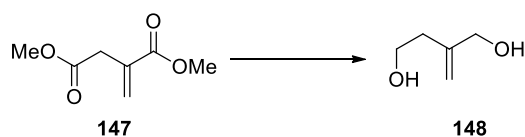
Benzene, Et₂O, Pentane, Toluene, THF, CH₂Cl₂, MeOH and MeCN were dried by purification through two activated alumina purification columns.¹¹ Acetone and hexamethylphosphoramide were dried by 4Å molecular sieves. Petrol refers to the petroleum ether fraction that boils in the range of 30–40 °C or 40–60 °C. Reagents were obtained from ACROS, Sigma–Aldrich, Fluka, TCI and Alfa Aesar, and were used as supplied or purified *via* procedures as described by Perrin and Armarego.^[103] All non-aqueous reactions were carried out in flame-dried glassware under an atmosphere of Argon.

Flash column chromatography was carried out on silica gel (60 Å, 0.033–0.070 mm, BDH) using Still's method^[104], with head pressure provided by bellows. The solvent system is quoted in parentheses. Reactions and columns were monitored by thin layer chromatography analysis on Merck DC-Keisegel 60 F₂₅₄ 0.2 mm precoated plates. Spots were visualised by UV light (λ_{max} = 254 nm) and/or staining with basic potassium permanganate solution, PMA or acidic vanillin solution as deemed appropriate for the compound.

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

7.2 Experimental Data

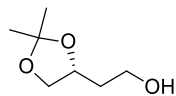
2-Methylenebutane-1,4-diol (**148**)



To a solution of diester **147** (1.00 mL, 7.11 mmol) in THF (50 mL) cooled to $-78\text{ }^{\circ}\text{C}$ was added DIBAL-H (38.0 mL, 1.0 M in hexanes, 38 mmol) dropwise over 15 min. The mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$ and then warmed to r.t. After 1 h the reaction mixture was cooled to $0\text{ }^{\circ}\text{C}$ and water (4 mL) was added (caution!) dropwise over 15 min, during which the reaction mixture slowly turned into a gelatinous suspension. Aqueous NaOH (8 mL, 1.0 M) was added over 10 min. After 3 h of stirring, solid Na_2SO_4 (10 g) was added and the mixture was stirred for 12 h. The solids were filtered away and the filter cake washed with THF (60 mL). The solvent was removed *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 2:1] yielded diol **148** (629 mg, 6.16 mmol, 87%) as a colourless oil.

$^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 5.08 (1H, s, $\text{C}=\text{CH}_A\text{H}_B$), 4.94 (1H, s, $\text{C}=\text{CH}_A\text{H}_B$), 4.04 (2H, s, $\text{C}=\text{CRCH}_2\text{OH}$), 3.77–3.56 (4H, m, $\text{CH}_2\text{CH}_2\text{OH} + 2 \times \text{OH}$), 2.33 (2H, t, $J = 5.9\text{ Hz}$, $\text{CH}_2\text{CH}_2\text{OH}$); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 146.1, 113.4, 65.9, 61.5, 36.9. Spectroscopic data are consistent with those previously reported.^[105]

(R)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (72)

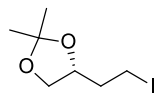


72

To a stirring solution of borane dimethyl sulphide (31.9 mL, 336 mmol) in THF (150 mL) at 0 °C was added trimethoxyborane (36.2 mL, 325 mmol) in one portion. The resulting solution was stirred at 0 °C for 5 min before (*R*)-malic acid (15.0 g, 112 mmol) in tetrahydrofuran (75 mL) was added. The resulting solution was stirred at r.t. for 16 h before methanol (30 mL) was added dropwise. The solvent was removed *in vacuo* and the resulting residue purified by filtration through a plug of silica [SiO₂, MeOH/EtOAc, 1:4]. The resulting triol was immediately dissolved in acetone (450 mL) before Amberlyst 15 (50 mg, cat.) was added. The resulting mixture was stirred for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/Et₂O, 4:1 to 1:1] afforded acetone 72 as a colourless oil (13.2 g, 90.4 mmol, 81%).

$[\alpha]_D^{20} +2.8$ ($c = 1.0$, CH₂Cl₂); ¹H NMR δ_H (400 MHz, CDCl₃): 4.28 (1H, quin, $J = 6.3$ Hz, CHOR), 4.09 (1H, dd, $J = 7.8, 6.3$ Hz, CH_AH_BOR), 3.80 (2H, t, $J = 5.6$ Hz, CH₂OH), 3.60 (1H, d, $J = 7.8$ Hz, CH_AH_BOR), 2.39 (1H, br. s, OH), 1.82 (2H, q, $J = 6.6$ Hz, CH₂CH₂OH), 1.43 (3H, s, 1 × C(CH₃)), 1.36 (3H, s, 1 × C(CH₃)); ¹³C NMR (101 MHz, CDCl₃) δ_C: 109.1, 75.1, 69.4, 60.6, 35.5, 26.8, 25.6. Spectroscopic data were consistent with those previously reported.^[55]

(*R*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane (71)

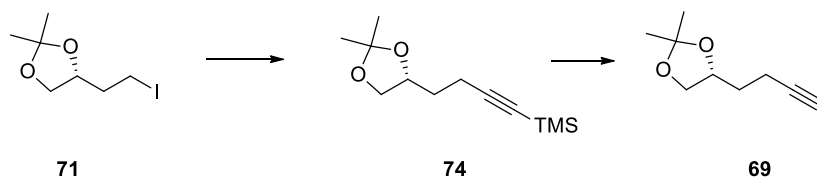


71

To a solution of triphenylphosphine (24.2 g, 92.6 mmol) and imidazole (9.00 g, 132 mmol) in diethyl ether (250 mL) and acetonitrile (80 mL) at 0 °C was added iodine (23.4 g, 92.8 mmol) portionwise over 30 minutes. After complete addition of iodine, acetone **72** (9.60 g, 66.2 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 1 h before being warmed to r.t. for 1 h. The reaction was quenched by the addition of methanol (40 mL) and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/Et₂O, 40:1] afforded iodide **71** as a colourless oil (15.3 g, 59.7 mmol, 90%).

[α]_D²⁰ +21.8 (*c* 1.0, CH₂Cl₂); ¹H NMR δ _H (400 MHz, CDCl₃): 4.23–4.14 (1H, m, CHOR), 4.09 (1H, dd, *J* = 8.0, 6.2 Hz, CH_AH_BOR), 3.58 (1H, dd, *J* = 8.0, 6.5 Hz, CH_AH_BOR), 3.32–3.19 (2H, m, CH₂I), 2.16–1.98 (2H, m, CH₂CH₂I), 1.41 (3H, s, 1 × CH₃), 1.36 (3H, s, 1 × CH₃); ¹³C NMR δ _C (126 MHz, CDCl₃): 109.2, 75.7, 68.6, 37.8, 27.0, 25.5, 1.2. Spectroscopic data were consistent with those previously reported.^[55]

(*R*)-4-(But-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (69)



Two-pots procedure:

To a stirred solution of TMS-acetylene (13.7 mL, 99.2 mmol) in tetrahydrofuran (160 mL) at $-78\text{ }^{\circ}\text{C}$ was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (36.2 mL, 298 mmol) followed by *n*-BuLi (1.6 M in hexanes, 66.1 mL, 105.7 mmol). The resulting solution was stirred for 30 minutes before iodide **71** (16.8 g, 66.1 mmol) in tetrahydrofuran (40 mL) was added. The resultant solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min before being warmed to r.t. and stirred for a further 1 h. The reaction was quenched with a saturated solution of ammonium chloride (80 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether ($3 \times 200\text{ mL}$). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO_2 , Petrol/ Et_2O , 40:1] afforded silyl-alkyne **74** as a colourless oil (12.6 g, 55.7 mmol, 85%).

$[\alpha]_{\text{D}}^{20} +7.2$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 4.18 (1H, quin, $J = 6.4\text{ Hz}$, CHOR), 4.11–4.06 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BOR}$), 3.62–3.56 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BOR}$), 2.42–2.26 (2H, m, $\text{CH}_2\text{C}\equiv\text{C}$), 1.88–1.79 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BCH}_2\text{C}\equiv\text{C}$), 1.77–1.68 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BCH}_2\text{C}\equiv\text{C}$), 1.40 (3H, s, $1 \times \text{CH}_3$), 1.36 (3H, s, $1 \times \text{CH}_3$), 0.16–0.13 (9H, m,

Si(CH₃)₃); ¹³C NMR δ_C (126 MHz, CDCl₃): 108.7, 106.2, 85.0, 75.0, 69.2, 32.7, 26.9, 25.6, 16.4, 0.1. Spectroscopic data were consistent with those previously reported.^[55]

To a stirred solution of silyl-alkyne **74** (11.6 g, 51.9 mmol) in methanol (60 mL) was added potassium carbonate (7.86 g, 56.4 mmol). The resulting mixture was stirred for 4 h at r.t., then filtered and concentrated onto silica onto silica *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/Et₂O, 40:1] afforded alkyne **69** as a colourless oil (7.20 g, 46.8 mmol, 90%).

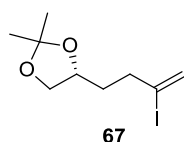
[α]_D²⁰ +4.4 (*c* = 1.0, CH₂Cl₂); ¹H NMR δ_H (400 MHz, CDCl₃): 4.25–4.17 (1H, m, CHOR), 4.08 (1H, dd, *J* = 8.0, 6.0 Hz, CH_AH_BOR), 3.58 (1H, t, *J* = 7.2 Hz, CH_AH_BOR), 2.35–2.28 (2H, m, CH₂C≡C), 1.96 (1H, t, *J* = 2.8 Hz, C≡CH), 1.88–1.68 (2H, m, CH₂CH₂C≡C), 1.41 (3H, s, 1 × CH₃), 1.36 (3H, s, 1 × CH₃); ¹³C NMR δ_C (126 MHz, CDCl₃): 108.9, 83.5, 74.7, 69.1, 68.7, 32.6, 26.9, 25.6, 15.0. Spectroscopic data were consistent with those previously reported.^[55]

One-pot procedure:

To a stirred solution of TMS-acetylene (31.4 mL, 228 mmol) in tetrahydrofuran (500 mL) at –78 °C was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (83.1 mL, 684 mmol) followed by *n*-BuLi (1.6 M in hexanes, 152 mL, 243 mmol). The resulting solution was stirred for 30 min before a solution of iodide **71** (38.56 g, 151 mmol) in tetrahydrofuran (120 mL) was added. The resultant solution was stirred at –78 °C for 15 minutes before being warmed to r.t. and stirred for a further 3 h. To the

reaction mixture was then added MeOH (200 mL) and potassium carbonate (38.0 g, 273 mmol). The resulting mixture was stirred overnight at r.t. before being filtered and concentrated onto silica *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/Et₂O, 40:1] afforded alkyne **69** as a colourless oil (21.45 g, 139 mmol, 92%).

(R)-4-(3-Iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (67)

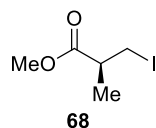


A flame dried schlenk tube was charged with [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (118 mg, 0.217 mmol) and purged with argon for 10 minutes before tetrahydrofuran (8 mL) and diisobutylaluminium hydride (1.23 M in THF, 7.63 mL, 9.40 mmol) were added in one portion sequentially. The resultant black mixture was cooled to 0 °C before alkyne **69** (1.10 g, 7.23 mmol) in anhydrous THF (3 mL) was added dropwise. The resulting mixture was warmed to r.t. and stirred for 2 h before being cooled to 0 °C. A solution of *N*-iodosuccinimide (3.23 g, 14.5 mmol) in anhydrous THF (20 mL) was added dropwise, then the resulting mixture was warmed to r.t. and stirred for a further 1 h before aq. sat. Rochelle's salt solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The

combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated onto silica *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/Et₂O, 40:1] afforded alkenyl iodide **67** as a colourless oil (1.75 g, 6.21 mmol, 87%).

$[\alpha]_D^{20}$ -1.2 ($c = 1.0$, CH₂Cl₂); ¹H NMR δ_H (400 MHz, CDCl₃): 6.07 (1H, d, $J = 1.2$ Hz, C=CH_AH_B), 5.71 (1H, d, $J = 1.2$ Hz, C=CH_AH_B), 4.13–4.02 (2H, m, CHOR + CH_AH_BOR), 3.58–3.52 (1H, m, CH_AH_BOR), 2.61–2.41 (2H, m, CH₂C(I)=CH₂), 1.81–1.74 (2H, m, CH₂CH₂C(I)=CH₂), 1.41 (3H, s, 1 × CH₃), 1.34 (3H, s, 1 × CH₃); ¹³C NMR δ_C (126 MHz, CDCl₃): 126.0, 111.0, 108.9, 74.5, 69.2, 41.7, 33.3, 27.0, 25.7; IR ν_{max} (thin film)/cm⁻¹ 2985, 2937, 1618, 1369, 1259, 1214, 1157, 1064; **m/z** (ESI⁺) C₉H₁₅IO₂ predicted 305.0008 (M+Na⁺), found 305.0011, ($\Delta = +1.0$ ppm). Spectroscopic data are consistent with those previously reported.^[55]

Methyl (S)-3-iodo-2-methylpropanoate (**68**)

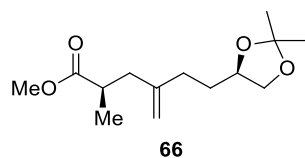


To a solution of triphenylphosphine (27.8 g, 106 mmol) and imidazole (7.49 g, 110 mmol) in diethyl ether (240 mL) and acetonitrile (80 mL) at 0 °C was added iodine (27.9 g, 110 mmol) portionwise over 30 min. After complete addition of iodine, (R)-(-)-3-hydroxy-2-methylpropionic acid methyl ester **70** (10.0 g, 84.7 mmol) was

added dropwise. The resulting solution was stirred at 0 °C for 1 h before being warmed to r.t. for 1 h. The reaction was quenched by the addition of methanol (40 mL) and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/Et₂O, 15:1] afforded iodide **68** as an oil (18.6 g, 81.6 mmol, 97%).

[α]_D²⁰ –24.3 (*c* = 1.0, CH₂Cl₂); ¹H NMR δ _H (400 MHz, CDCl₃): 3.73 (3H, d, *J* = 0.8 Hz, OCH₃), 3.38 (1H, ddd, *J* = 9.6, 6.4, 0.8 Hz, CH_AH_BI), 3.26 (1H, ddd, *J* = 9.6, 6.4, 0.8 Hz, CH_AH_BI), 2.81 (1H, q, *J* = 6.8 Hz, CHCH₃), 1.28 (3H, d, *J* = 7.2 Hz, CHCH₃); ¹³C NMR δ _C (125 MHz, CDCl₃): 173.8, 52.1, 42.2, 18.2, 6.9; IR ν _{max} (thin film)/cm^{–1} 2985, 2937, 2871, 1741, 1617, 1454, 1370, 1213, 1064; *m/z* (ESI⁺) C₅H₉IO₄ predicted 250.9539 (M+Na⁺), found 250.9542, (Δ = +1.2 ppm). Spectroscopic data are consistent with those previously reported.^[55]

Methyl (R)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methyl-4-methylenehexanoate (66)

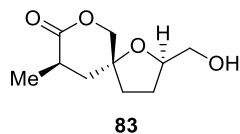


To a solution of iodide **68** (11.4 g, 50.0 mmol) in benzene (200 mL) was added zinc/copper couple powder (11.0 g) and *N,N*-dimethylacetamide (20.0 mL). The resulting suspension was degassed with argon before being sonicated at 45 °C for 2 h. In a separate two-neck flask containing a solution of vinyl iodide **67** (7.00 g, 25.0

mmol) in benzene (200 mL) was added tetrakis(triphenylphosphine)palladium(0) (867 mg, 0.750 mmol). The resulting yellow solution was degassed with argon before hexamethylphosphoramide (20.0 mL) was added. The solution of the organozinc was added to the solution of vinyl iodide **67** *via* a cannula. The combined mixture was heated at 80 °C for 2 h before being diluted with ethyl acetate (400 mL) and filtered through Celite[®]. The filtrate was then washed with aq. sat. NaHCO₃ (200 mL), brine (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/EtOAc, 25:1 to 15:1] afforded alkene **66** as a yellow oil (5.70 g, 22.2 mmol, 90%).

[α]_D²⁰ -15.7 (*c* = 1.0, CH₂Cl₂); ¹H NMR δ _H (400 MHz, CDCl₃): 4.78 (1H, s, C=CH_AH_B), 4.74 (1H, s, C=CH_AH_B), 4.08–4.00 (2H, m, CHOR + CH_AH_BOR), 3.64 (3H, s, OCH₃), 3.51 (1H, t, *J* = 7.1 Hz, CH_AH_BOR), 2.64 (1H, sxt, *J* = 7.1 Hz, CHCH₃), 2.42 (1H, dd, *J* = 14.4, 7.6 Hz, CH_AH_BCHCH₃), 2.17–1.94 (3H, m, CH_AH_BCHCH₃ + CH₂CH₂C=CH₂), 1.81–1.70 (1H, m, CH_AH_BCOR), 1.68–1.56 (1H, m, CH_AH_BCOR), 1.39 (3H, s, 1 × CH₃), 1.33 (3H, s, 1 × CH₃), 1.12 (3H, d, *J* = 7.1 Hz, CHCH₃); ¹³C NMR δ _C (101 MHz, CDCl₃): 176.7, 145.9, 111.3, 108.7, 75.6, 69.3, 51.5, 40.1, 37.7, 31.6, 26.9, 25.6, 16.9; IR ν _{max} (thin film)/cm⁻¹ 2985, 2938, 1738, 1557, 1370, 1213, 1162, 1068; *m/z* (ESI⁺) C₁₄H₂₄O₄ predicted 279.1567 (M+Na⁺), found 279.1562, (Δ = -1.8 ppm). Spectroscopic data are consistent with those previously reported.^[55]

(2*R*,5*R*,9*R*)-2-(Hydroxymethyl)-9-methyl-1,7-dioxaspiro[4.5]decan-8-one (83)

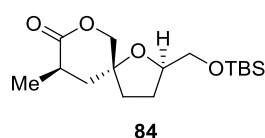


To a stirred solution of alkene **66** (4.36 g, 17.0 mmol) in acetonitrile (180 mL) was added pyridine *N*-oxide (3.23 g, 34.0 mmol). A solution of citric acid (2.45 g, 12.8 mmol) in water (60 mL) and a solution of potassium osmate dihydrate (2.5 mol%, 157 mg, 0.426 mmol) in water (60 mL) were added sequentially. The resulting green solution was then stirred for 5 min before Sc(OTf)₃ (8.37 g, 17.0 mmol) was added. The resultant mixture was heated to 60 °C for 16 h and then cooled down to r.t. The reaction was then quenched with Na₂SO₃ (1.0 g) and stirred for 30 min before ethyl acetate (300 mL) and water (150 mL) were added. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/EtOAc, 2:1] three times afforded lactone **83** (2.57 g, 12.8 mmol, 76%) as a pale yellow oil.

[α]_D²⁰ –6.6 (*c* = 1.0, CH₂Cl₂); ¹H NMR δ_H (400 MHz, CDCl₃): 4.23–4.13 (3H, m, OCH + CCH₂O), 3.71 (1H, dd, *J* = 11.7, 3.2 Hz, CH_AH_BOH), 3.50 (1H, dd, *J* = 11.7, 5.4 Hz, CH_AH_BOH), 2.93–2.79 (1H, m, CHCH₃), 2.15 (1H, dd, *J* = 13.9, 6.4 Hz, CH_AH_BCHCH₃), 2.07–1.75 (5H, m, 2 × THF-CH₂ + OH), 1.65 (1H, t, *J* = 13.3 Hz, CH_AH_BCHCH₃), 1.18 (3H, d, *J* = 6.7 Hz, CHCH₃); ¹³C NMR δ_C (101 MHz, CDCl₃):

174.7, 79.8, 79.4, 75.4, 64.8, 39.8, 35.4, 32.4, 26.6, 16.2; **IR** ν_{max} (thin film)/ cm^{-1} 3436 br./s, 2938, 2877, 1727, 1460, 1379, 1260, 1151, 1031; **m/z** (ESI⁺) C₁₀H₁₆O₄ predicted 223.0941 (M+Na⁺), found 223.0943, (Δ = +0.1 ppm). Spectroscopic data are consistent with those previously reported.^[55]

(2R,5R,9R)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-9-methyl-1,7-dioxaspiro[4.5]decan-8-one (84**)**

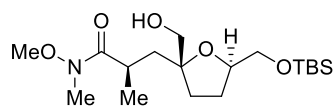


To a solution of lactone **83** (2.57 g, 12.9 mmol) in CH₂Cl₂ (130 mL) was added *N,N*-dimethylaminopyridine (157 mg, 1.29 mmol) and imidazole (1.75 g, 25.7 mmol). The resultant solution was stirred until all of the reagents had dissolved. To the solution was added *tert*-butyldimethylsilyl chloride (2.14 g, 14.2 mmol) in one portion, and the resulting mixture stirred for 2 h before ethyl acetate (300 mL) and water (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/EtOAc, 15:1 to 10:1] afforded TBS-lactone **84** as a colourless oil (3.69 g, 11.7 mmol, 69% over two steps from **66**).

[α]_D²⁰ +2.2 (*c* = 1.0, CH₂Cl₂); **¹H NMR** δ_{H} (400 MHz, CDCl₃): 4.19–4.09 (3H, m,

OCH + CCH₂O), 3.63 (1H, dd, J = 10.8, 4.2 Hz, CH_AH_BOTBS), 3.57 (1H, dd, J = 10.8, 3.7 Hz, CH_AH_BOTBS), 2.85 (1H, dquin, J = 13.1, 6.7 Hz, CHCH₃), 2.12 (1H, dd, J = 13.6, 6.4 Hz, CH_AH_BCHCH₃), 2.04–1.85 (3H, m, THF-CH₂ + THF-CH_AH_B), 1.79–1.69 (1H, m, THF-CH_AH_B), 1.63 (1H, t, J = 13.3 Hz, CH_AH_BCHCH₃), 1.23 (3H, d, J = 6.8 Hz, CHCH₃), 0.89 (9H, s, SiC(CH₃)₃), 0.06 (6H, s, Si(CH₃)₂); ¹³C NMR δ_C (101 MHz, CDCl₃): 175.0, 80.0, 79.3, 75.2, 65.2, 40.1, 35.6, 32.3, 26.8, 25.9, 18.4, 16.0, −5.3, −5.4; IR ν_{max} (thin film)/cm^{−1} 2930, 2857, 1737, 1462, 1378, 1255, 1134, 1079; m/z (ESI⁺) C₁₆H₃₀O₄Si predicted 337.1806 (M+Na⁺), found 337.1799, (Δ = −2.1 ppm). Spectroscopic data are consistent with those previously reported.^[55]

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide (96)



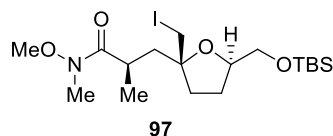
96

To a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (2.81 g, 28.7 mmol) in tetrahydrofuran (30 mL) at 0 °C was added trimethylaluminium (14.3 mL, 28.7 mmol, 2.0 M in heptane) dropwise. The resulting solution was stirred at 0 °C for 10 min before a solution of lactone **84** (1.822 mg, 5.79 mmol) in tetrahydrofuran (30 mL) was added dropwise. The resultant solution was stirred at 0 °C for 5 h before ethyl acetate (90 mL) and a sat. aq. solution of potassium sodium tartrate (90 mL)

were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of potassium sodium tartrate (60 mL), brine (60 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/EtOAc, 3:1] afforded amide **96** as a colourless oil (2.155 g, 5.73mmol, 99%).

[α]_D²⁰ –40.1 (*c* = 1.0, CH₂Cl₂); ¹H NMR δ _H (400 MHz, CDCl₃): 4.09–4.00 (1H, m, OCH), 3.71 (3H, s, OCH₃), 3.70 (1H, dd, *J* = 10.7, 3.5, CH_AH_BOTBS), 3.54 (1H, dd, *J* = 10.7, 3.3 Hz, CH_AH_BOTBS), 3.39–3.31 (1H, m, CH_AH_BOH), 3.30–3.22 (2H, m, CH_AH_BOH + CH₂OH), 3.20 (3H, s, NCH₃), 3.18–3.07 (1H, m, CHCH₃), 2.24 (1H, dd, *J* = 14.3, 10.4 Hz, CH(CH₃)CH_AH_B), 2.07 (1H, ddd, *J* = 12.2, 8.4, 4.0 Hz, THF-CH_AH_BCH), 1.94–1.84 (2H, m, THF-CH₂C), 1.66 (1H, dt, *J* = 12.2, 8.9 Hz, THF-CH_AH_BCH), 1.40 (1H, dd, *J* = 14.4, 2.7 Hz, CH(CH₃)CH_AH_B), 1.13 (3H, d, *J* = 7.1 Hz, CHCH₃), 0.93–0.83 (9H, m, SiC(CH₃)₃), 0.09–0.01 (3H, m, 2 × Si(CH₃)); ¹³C NMR δ _C (101 MHz, CDCl₃): 178.6, 85.4, 79.6, 67.2, 65.4, 61.4, 40.4, 34.5, 32.5, 31.0, 27.5, 25.9, 19.8, 18.4, –5.4, –5.5; IR ν _{max} (thin film)/cm^{–1} 3458 br./s, 2930, 2858, 1638, 1463, 1389, 1255, 1090; *m/z* (ESI⁺) C₁₈H₃₇O₅Si predicted 398.2333 (M+Na⁺), found 398.2335, (Δ = +0.5 ppm). Spectroscopic data are consistent with those previously reported.^[55]

(R)-3-((2R,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2-(iodomethyl)tetrahydrofuran-2-yl)-N-methoxy-N,2-dimethylpropanamide (97)

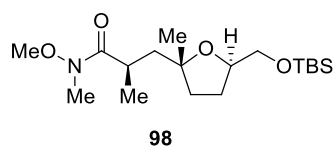


To a stirred solution of amide **96** (582 mg, 1.55 mmol) in toluene (16 mL) was added triphenylphosphine (813 mg, 3.10 mmol), imidazole (211 mg, 3.10 mmol) and iodine (667 mg, 2.64 mmol) sequentially. The resulting solution was heated to 80 °C for 3 h before being cooled to r.t. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with an aq. solution of sodium thiosulfate (0.1 M, 50 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/EtOAc, 15:1 to 10:1] afforded iodide **97** as a colourless oil (600 mg, 1.24 mmol, 79%).

[α]_D²⁰ −10.4 (*c* = 1.0, CH₂Cl₂); ¹H NMR δ _H (400 MHz, CDCl₃): 4.12–4.03 (1H, m, OCH), 3.72 (3H, s, OCH₃), 3.60 (2H, d, *J* = 4.6 Hz, CH₂OTBS), 3.32 (1H, d, *J* = 10.3 Hz, CH_AH_BI), 3.22 (1H, d, *J* = 10.3 Hz, CH_AH_BI), 3.18 (3H, s, NCH₃), 3.06 (1H, br. s., CHCH₃), 2.27 (1H, dd, *J* = 14.4, 8.6 Hz, CH(CH₃)CH_AH_B), 2.07–1.76 (5H, m, 2 × THF-CH₂ + CH(CH₃)CH_AH_B), 1.19 (3H, d, *J* = 6.8 Hz, CHCH₃), 0.90 (9H, s, Si(CH₃)₃), 0.06 (6H, s, Si(CH₃)₂); ¹³C NMR δ _C (101 MHz, CDCl₃): 178.2, 83.4, 80.6, 65.6, 61.6, 41.7, 35.5, 32.6, 30.8, 27.7, 25.9, 19.5, 18.3, 15.8, −5.3, −5.4; IR ν _{max} (thin film)/cm^{−1} 2956, 2930, 2857, 1665, 1463, 1386, 1255, 1085; *m/z* (ESI⁺) C₁₈H₃₆INO₄Si predicted 508.1350 (M+Na⁺), found 508.1352, (Δ = +0.4 ppm).

Spectroscopic data are consistent with those previously reported.^[55]

(R)-3-((2R,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-N-methoxy-N,2-dimethylpropanamide (98)

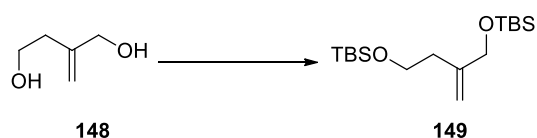


To a stirred solution of iodide **97** (934 mg, 1.92 mmol) in methanol (30 mL) was added palladium on carbon (216 mg, 10 wt%, caution!) and triethylamine (266 μ L, 0.190 mmol). The resulting mixture was purged argon three times and with H₂ gas five times, before being stirred under an atmosphere of H₂ for 12 h. The resulting mixture was filtered through Celite[®] and concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, Petrol/EtOAc, 8:1] afforded amide **98** as a colourless oil (679 mg, 1.89 mmol, 98%).

[α]_D²⁰ –12.2 (*c* = 1.0, CH₂Cl₂); **¹H NMR** δ_{H} (400 MHz, CDCl₃): 4.00–3.91 (1H, m, OCH), 3.70 (3H, s, OCH₃), 3.59 (1H, dd, *J* = 10.4, 4.6 Hz, CH_AH_BOTBS), 3.49 (1H, dd, *J* = 10.4, 5.5 Hz, CH_AH_BOTBS), 3.15 (3H, s, NCH₃), 3.15–3.05 (1H, m, CHCH₃), 2.07 (1H, dd, *J* = 14.2, 8.6 Hz, CH(CH₃)CH_AH_B), 1.98–1.87 (1H, m, THF-CH_AH_B), 1.80–1.57 (3H, m, THF-CH_AH_B + THF-CH₂), 1.48 (1H, dd, *J* = 14.2, 3.7 Hz, CH(CH₃)CH_AH_B), 1.17–1.09 (6H, m, CH(CH₃) + CCH₃), 0.86 (9H, s, SiC(CH₃)₃), 0.02 (6H, s, Si(CH₃)₂); **¹³C NMR** δ_{C} (101 MHz, CDCl₃): 178.9, 82.7, 79.1, 66.2, 61.4,

44.0, 37.6, 31.2, 28.1, 26.3, 25.9, 19.7, 18.3, -5.3, -5.4; **IR** $\nu_{\max}$ (thin film)/ cm^{-1} 2931, 2858, 1667, 1463, 1386, 1254, 1102; **m/z** (ESI⁺) C₁₈H₃₇NO₄Si predicted 382.2384 (M+Na⁺), found 382.2380, (Δ = -1.0 ppm). Spectroscopic data are consistent with those previously reported.^[55]

2,2,3,3,10,10,11,11-Octamethyl-6-methylene-4,9-dioxa-3,10-disiladodecane (149)

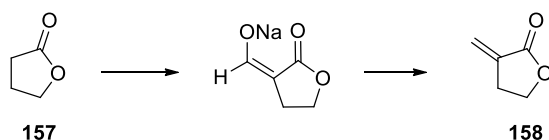


To a solution of **148** (40.0 mg, 0.392 mmol) in CH₂Cl₂ (10 mL) was added imidazole (133 mg, 1.95 mmol) and TBSCl (290 mg, 1.92 mmol) at r.t. sequentially. The solution was stirred for 6 h before quenched with water (20 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 20:1] yielded **149** (106 mg, 0.321 mmol, 82%) as a colourless oil.

¹H NMR δ_{H} (400 MHz, CDCl₃): 5.09 (1H, d, J = 1.5 Hz, C=CH_AH_B), 4.85 (1H, s, C=CH_AH_B), 4.09 (2H, s, C=CRCH₂OTBS), 3.72 (2H, s, CH₂CH₂OTBS), 2.25 (2H, t, J = 6.9 Hz, CH₂CH₂OTBS), 0.92 (9H, s, *t*-Bu_a), 0.90 (9H, s, *t*-Bu_b), 0.08 (6H, s, Si(CH₃)_{2A}), 0.06 (6H, s, Si(CH₃)_{2B}); **¹³C NMR** δ_{C} (101 MHz, CDCl₃): 146.0, 110.0, 66.1, 62.6, 36.4, 25.9, -5.3, -5.4. Spectroscopic data were consistent with those

previously reported.^[106]

3-Methylenedihydrofuran-2(3H)-one (**158**)

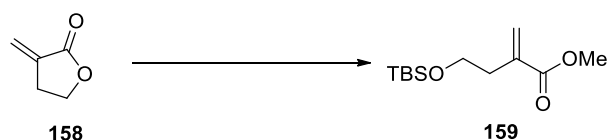


A stirred suspension of NaH (8.0 g of 60 wt% oil dispersion, 200 mmol) in anhydrous Et₂O (160 mL) under Argon was treated slowly with absolute EtOH (1.20 mL, 22.0 mmol), followed immediately by a mixture of ethyl formate (16.2 mL, 200 mmol) and α -butyrolactone **157** (15.4 mL, 200 mmol) over 1.25 h. The rate of addition was controlled to give a steady reflux and evolution of H₂. After completing the addition, the mixture was stirred for a further 30 min and the solid was filtered, washed with diethyl ether (2 $\times$ 100 mL), and dried *in vacuo* to give α -formyl- γ -butyrolactone sodium salt (25.0 g, 184 mmol, 92%).

A stirred suspension of paraformaldehyde (25.0 g, 830 mmol) in anhydrous THF (300 mL) at r.t. in a 1L flask under Argon was treated with this product (25.0 g, 184 mmol) and the mixture immediately heated to reflux for 1 h. The mixture was cooled to 10 °C and treated with sat. aq. K₂CO₃ (50 mL) and Et₂O (150 mL), and the organic layer was separated, dried, and evaporated to dryness to afford a pale yellow oil. Flash column chromatography [SiO₂, Petrol/EtOAc, 2:1] yielded **158** (12.8 g, 131 mmol, 71% for this step, 65% overall) as a colourless oil.

¹H NMR δ_{H} (400 MHz, CDCl₃): 6.22 (1H, d, J = 1.3 Hz, C=CH_AH_B), 5.65–5.62 (1H, m, C=CH_AH_B), 4.36 (2H, td, J = 7.3, 3.7 Hz, CH₂CH₂OR), 3.00–2.94 (2H, m, CH₂CH₂OR); **¹³C NMR** δ_{C} (101 MHz, CDCl₃): 170.7, 133.5, 122.2, 65.3, 27.8. Spectroscopic data were consistent with those previously reported.^[75]

Methyl 4-((*tert*-butyldimethylsilyl)oxy)-2-methylenebutanoate (159)



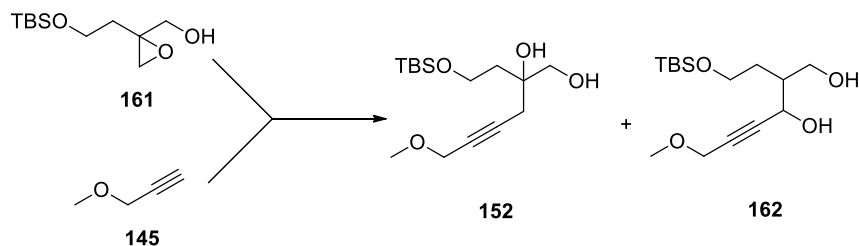
To a solution of **158** (289 mg, 2.95 mmol) in MeOH (20 mL) was added *p*TSA monohydrate (20 mg, 0.10 mmol) in one portion at r.t. The reaction was then heated to reflux for 3 h before being quenched with sat. aq. NaHCO₃ (10 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was carried to next step without further purification.

To the solution of crude product in CH₂Cl₂ (15 mL) was added imidazole (1.0 g, 15 mmol) and TBSCl (2.2 g, 14 mmol) at r.t., respectively. The reaction was stirred for 5 h before quenched with H₂O (20 mL) and diluted with Et₂O (20 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated

To a solution of crude **160** (2.68 g) in CH₂Cl₂ (50 mL) was added *m*CPBA (4.00 g, 23.2 mmol) slowly at r.t. The reaction was stirred for 2 h before being quenched with sat. aq. Na₂S₂O₃/NaHCO₃ (50 mL) and diluted with Et₂O (30 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 4:1] yielded **161** (1.93 g, 8.30 mmol, 81% overall) as a colourless oil.

¹H NMR δ_H (400 MHz, CDCl₃): 3.88–3.62 (4H, m, CH₂OH + CH₂CH₂OTBS), 2.86 (1H, d, *J* = 4.8 Hz, CH_AH_BOCR₂), 2.77–2.68 (2H, m, CH_AH_BOCR₂ + CH₂OH), 1.96 (1H, ddd, *J* = 14.7, 6.8, 4.0 Hz, CH_AH_BCH₂OTBS), 1.79 (1H, ddd, *J* = 14.7, 7.5, 4.2 Hz, CH_AH_BCH₂OTBS), 0.91 (9H, s, *t*-Bu), 0.09 (6H, s, 2 × SiCH₃); **¹³C NMR** δ_C (101 MHz, CDCl₃): 64.6, 59.7, 58.8, 51.5, 36.1, 25.8, 18.2, –5.5; **IR** ν_{max} (thin film)/cm^{–1} 3435br/s, 2930s, 2858s, 1472w, 1255s, 1099s, 835s, 777s; **m/z** (ESI⁺) C₁₁H₂₄O₃Si predicted 255.1387 (M+Na⁺), found 255.1382, (Δ = –1.9 ppm).

2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6-methoxyhex-4-yne-1,2-diol (**152**)



To a solution of epoxide **161** (1.648 g, 7.10 mmol) in anhydrous THF (3 mL) was

added *t*-BuMgCl (7.10 mL, 1.0 M in THF) dropwise at -78°C . The reaction was kept at -78°C for 15 min, and then moved to r.t. and stirred for a further 30 min. In a separate reaction vessel, to a solution of alkyne **145** (1.17 mL, 0.99 g, 14.1 mmol) in anhydrous THF (5 mL) was added *n*-BuLi (8.88 mL, 1.6 M in hexane) at -78°C and stirred for 15 min, followed by the addition of DMPU (3.4 mL, 28.1 mmol). The reaction was then warmed to 0°C stirring for a further 45 min.

The solution of deprotonated alkyne was added to the epoxide-*t*-BuMgCl complex solution at 0°C . After 90 min the reaction was quenched with water (20 mL) and then diluted with Et₂O (20 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 4:1 to 2:1] yielded diol **152** (889 mg, 2.94 mmol, 41%) as a colourless oil. Starting material **161** (658 mg, 2.83 mmol) was also recovered.

¹H NMR δ_{H} (400 MHz, CDCl₃): 4.08 (2H, s, CH₃OCH₂), 4.02–3.83 (4H, m, CH₂OH + CH₂CH₂OTBS), 3.60 (1H, br. s, CH₂OH), 3.36 (3H, s, CH₃OCH₂), 2.74 (1H, br. s, CR₃OH), 2.62–2.45 (2H, m, CH₂C $\equiv$ CR), 1.99–1.80 (2H, m, CH₂CH₂OTBS), 0.91 (9H, s, *t*-Bu), 0.11 (6H, s, 2 $\times$ SiCH₃); **¹³C NMR** δ_{C} (101 MHz, CDCl₃): 82.7, 78.4, 74.1, 67.8, 60.1, 60.0, 57.5, 37.0, 28.0, 25.8, 18.0, -5.6 ; **IR** ν_{max} (thin film)/cm⁻¹ 3434br./s, 2930s, 2857s, 1471w, 1256s, 1188w, 1095s, 896w, 837s, 778s; **m/z** (ESI⁺) C₁₅H₃₀O₄Si predicted 325.1806 (M+Na⁺), found 325.1806, ($\Delta = -0.1$ ppm).

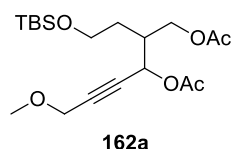
2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6-methoxyhex-4-yne-1,3-diol (**162**)

(one-pot procedure):

To a solution of alkyne **145** (170 mg, 2.43 mmol) in anhydrous THF (3 mL) was added BnMgCl (3.20 mL, 1.0 M in Et₂O) and triethylamine (0.10 mL, 0.72 mmol) at −78 °C. The reaction was kept at −78 °C for 15 min, and then stirred at r.t. for 1 h. Afterwards to the solution was added epoxide **161** (233 mg, 1.00 mmol) at −78 °C. After stirring for 2 h, the solution was allowed to warm to r.t. and was continued stirring for a further 3 h and then quenched with water (10 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 4:1 to 2:1] yielded diol **162** (176 mg, 0.582 mmol 58%) as a colourless oil.

The structure of **162** was determined by its acetylation product **162a**.

2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6-methoxyhex-4-yne-1,3-diyl diacetate
(162a)



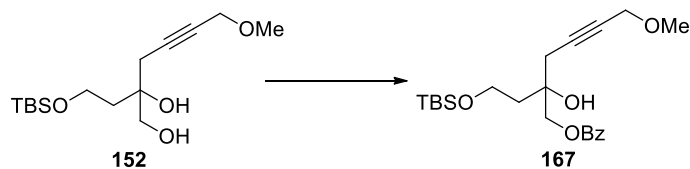
To a solution of **162** (62.0 mg, 0.205 mmol) in CH₂Cl₂ (1 mL) was added pyridine (2 mL) and Ac₂O (0.70 mL, 7.43 mmol) at r.t. The reaction was stirred for 5 h before

being quenched with H₂O (10 mL) and diluted with Et₂O (10 mL). The phases were separated and the organic layer was washed with HCl (2 × 10 mL, 1 M aq. solution) and sat. aq. NaHCO₃ (10 mL). The washed organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 10:1] yielded acetylated product **162a** (46.8 mg, 0.121 mmol, 59%) as a colourless oil.

¹H NMR δ_H (400 MHz, CDCl₃): 5.63–5.43 (1H, m, CHR₂OAc), 4.29–4.02 (2H, m, CH₂OAc), 4.12 (2H, s, CH₃OCH₂), 3.70 (2H, t, *J* = 6.2 Hz, CH₂OTBS), 3.36 (3H, s, CH₃OCH₂), 2.34–2.19 (1H, m, CHR₂CH₂OAc), 2.08 (3H, s, CH₃COR), 2.05 (3H, s, CH₃COR), 1.92–1.75 (1H, m, CH_aH_bCH₂OTBS), 1.69–1.52 (1H, m, CH_aH_bCH₂OTBS), 0.88 (9H, s, *t*-Bu), 0.05 (6H, s, 2 × SiCH₃); ¹³C NMR δ_C (101 MHz, CDCl₃): 170.9, 169.7, 82.5, 81.9, 64.3, 63.5, 60.7, 59.7, 57.6, 38.8, 30.6, 30.2, 25.9, 20.9, 28.2, –5.4; IR ν_{max} (thin film)/cm^{–1} 2930s, 1743s, 1472w, 1369w, 1224s, 1099s, 1022s, 906w, 836s, 777s; *m/z* (ESI⁺) C₁₉H₃₄O₆Si predicted 409.2017 (M+Na⁺), found 409.2005, (Δ = –2.9 ppm).

2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-hydroxy-6-methoxyhex-4-yn-1-yl

benzoate (**167**)

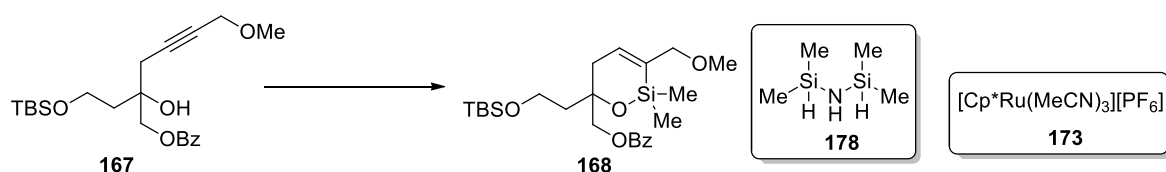


To a solution of **152** (105 mg, 0.35 mmol) in THF (3 mL) was added triethylamine (0.50 mL, 3.6 mmol) and BzCl (73 mg, 0.52 mmol) at r.t. After 2 h, the reaction was quenched with water (10 mL) and diluted with Et₂O (10 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 20:1 to 6:1] yielded tertiary alcohol **167** (113 mg, 0.278 mmol, 80%) as a colourless oil.

¹H NMR δ_H (400 MHz, CDCl₃): 8.06 (2H, d, *J* = 7.3 Hz, *o*-ArH), 7.61–7.54 (1H, m, *p*-ArH) 7.48–7.42 (2H, m, *m*-ArH), 4.41 (2H, s, CH₂OBz), 4.38 (1H, s, OH), 4.06 (2H, s, CH₃OCH₂), 3.99 (2H, t, *J* = 5.6 Hz, CH₂OTBS), 3.34 (3H, s, CH₃OCH₂), 2.73 (1H, dt, *J* = 16.8, 2.2 Hz, CH_AH_BC≡CH₂OCH₃), 2.63 (1H, dt, *J* = 16.8, 2.2 Hz, CH_AH_BC≡CH₂OCH₃), 2.08–1.92 (2H, m, CH₂CH₂OTBS), 0.91 (9H, s, *t*-Bu), 0.11 (6H, s, 2 × SiCH₃); **¹³C NMR** δ_C (101 MHz, CDCl₃): 166.3, 133.1, 130.0, 129.7, 128.4, 82.4, 78.5, 73.5, 68.6, 65.8, 60.1, 57.5, 36.3, 28.6, 25.8, 18.0, –5.6; **IR** ν_{max} (thin film)/cm^{–1} 3453 br/s, 2930s, 1722s, 1451w, 1269s, 1093s, 902w, 836s, 778s, 711s; **m/z** (ESI⁺) C₂₂H₃₄O₅Si predicted 429.2068 (M+Na⁺), found 429.2071,

($\Delta = +0.8$ ppm).

(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(methoxymethyl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)methyl benzoate (168**)**



A solution of **167** (755 mg, 1.86 mmol) in 1,1,3,3-tetramethyldisilazane **178** (2.0 mL) at r.t. was slowly heated to 50 °C for 2 h in a sealed tube. When cooling down, the reaction was left on high vacuum for 1 h to remove the excess **178**. The residue was redissolved in CH₂Cl₂ (8 mL) under Argon at 0 °C and then Ru catalyst **173** (80 mg, 10 mol%) was added. The reaction was stirred for a further 2 h at r.t. before concentrated onto silica *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 20:1] yielded alkene **168** (642 mg, 1.38 mmol, 74%) as a colourless oil.

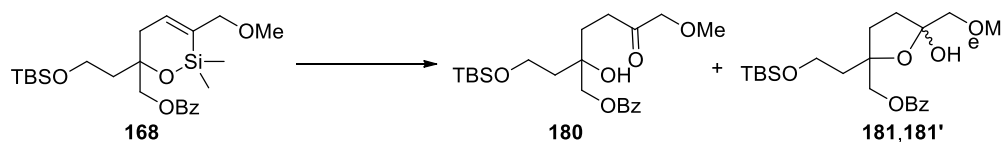
¹H NMR δ_{H} (400 MHz, CDCl₃): 8.04 (2H, d, $J = 7.3$ Hz, *o*-ArH), 7.61–7.51 (1H, m, *p*-ArH), 7.50–7.39 (2H, m, *m*-ArH), 6.47 (1H, br. s, CR₂=CHR), 4.30 (1H, d, $J = 11.0$ Hz, CH_AH_BOBz), 4.22 (1H, d, $J = 11.0$ Hz, CH_AH_BOBz), 4.02–3.99 (2H, m, CH₃OCH₂), 3.80 (2H, t, $J = 6.7$ Hz, CH₂OTBS), 3.29 (3H, s, CH₃OCH₂), 2.47 (2H, d, $J = 4.3$ Hz, CH₂CH=CR₂), 2.01–1.89 (2H, m, CH₂CH₂OTBS), 0.87 (9H, s, *t*-Bu), 0.23 (3H, s, CH=CRSi(CH₃)_A(CH₃)_B), 0.21 (3H, s, CH=CRSi(CH₃)_A(CH₃)_B), 0.11 (6H, s, 2 × TBS–CH₃); **¹³C NMR** δ_{C} (101 MHz, CDCl₃): 166.2, 138.4, 138.2, 132.9,

130.2, 129.7, 128.3, 76.6, 74.7, 69.1, 58.8, 57.8, 41.0, 35.0, 25.9, 18.2, 0.3, -5.4 ; **IR**
 ν_{max} (thin film)/ cm^{-1} 2955s, 1723s, 1452w, 1315s, 1250s, 1096s, 1029w, 906w, 832s,
776s, 710s; **m/z** (ESI^+) $\text{C}_{24}\text{H}_{40}\text{O}_5\text{Si}$ predicted 487.2306 ($\text{M}+\text{Na}^+$), found 487.2302, (Δ
 $= -0.9$ ppm).

**2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-hydroxy-6-methoxy-5-oxohexyl
benzoate (180)**

and

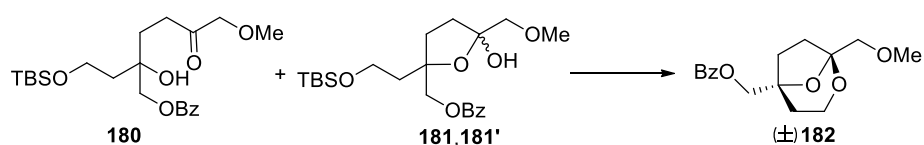
**(2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-hydroxy-5-(methoxymethyl)tetrahydr
ofuran-2-yl)methyl benzoate (181, 181')**



To a solution of **168** (190 mg, 0.41 mmol) in MeOH/THF (10 mL, MeOH/THF = 2:1) was added KHCO_3 (250 mg, 2.5 mmol), KF (150 mg, 2.6 mmol), H_2O_2 (4.0 mL, 30% solution in H_2O) and Ac_2O (0.05 mL, 0.53 mmol) at r.t. sequentially. The reaction was stirred at r.t. for 9 h before being quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ (10 mL) slowly and diluted with Et_2O (20 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column

chromatography [SiO₂, Petrol/EtOAc, 6:1 to 2:1] yielded a mixture of **180**, **181** and its diastereoisomer **181'** (140 mg, 1:1:1, 81 %). Starting material **168** was also recovered (15.9 mg, 0.0342 mmol). The mixture were carried through to the next step directly.

1-(Methoxymethyl)-2,8-dioxabicyclo[3.2.1]octan-5-yl)methyl benzoate (**182**)



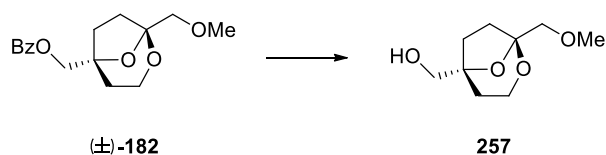
To a solution of a mixture **180**, **181** and **181'** (103.5 mg, 0.244 mmol) in anhydrous MeOH (3 mL) was added Ac₂O (0.05 mL, 0.53 mmol) at r.t. and then stirred for 1 h. The reaction mixture was then directly concentrated to dryness *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 6:1] yielded acetal **182** (69.0 mg, 0.236 mmol, 79% over two steps, 97% for this step) as a colourless oil.

¹H NMR δ_H (400 MHz, CDCl₃): 8.06 (2H, d, *J* = 7.3 Hz, *o*-Ar*H*), 7.61–7.53 (1H, m, *p*-Ar*H*) 7.48–7.41 (2H, m, *m*-Ar*H*), 4.40 (2H, ABq, *J* = 11.9 Hz, CH₂OBz), 4.09–4.03 (2H, m, CH₂CH₂OR), 3.54 (2H, s, CH₃OCH₂), 3.44 (3H, s, CH₃OCH₂), 2.30–2.19 (1H, m, CH_AH_BCH₂OR), 2.19–2.11 (2H, m, THF-*H*), 2.00–1.92 (2H, m, THF-*H*), 1.39 (1H, d, *J* = 12.6 Hz, CH_AH_BCH₂OR); **¹³C NMR** δ_C (101 MHz, CDCl₃): 166.3, 133.1, 129.8, 129.7, 128.4, 106.6, 82.1, 75.2, 68.4, 59.8, 59.7, 31.9, 31.2, 30.1; **IR** ν_{max} (thin film)/cm⁻¹ 2954s, 1720s, 1451w, 1315s, 1273s, 1113s, 1070w, 1027w, 977w, 943w, 896w, 713s; **m/z** (ESI⁺) C₁₆H₂₀O₅ predicted 315.1203 (M+Na⁺), found

315.1205, ($\Delta = +0.7$ ppm).

((1*R*,5*R*)-1-(Methoxymethyl)-2,8-dioxabicyclo[3.2.1]octan-5-yl)methanol (257**)**

Procedure A:

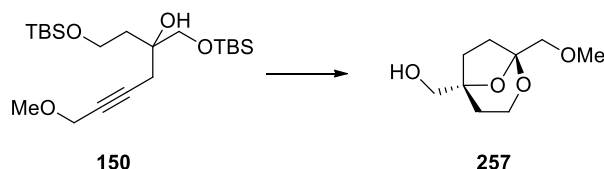


To a solution of **182** (13 mg, 0.045 mmol) in MeOH (0.5 mL) was added aq. NaOH (0.3 mL, 1 M) at r.t. The reaction was allowed to stir at r.t. for 4 h before being quenched with sat. aq. NaHCO₃ (2 mL) and diluted with Et₂O (3 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 4:1 to 1:1] yielded deprotection product **257** (7.6 mg, 0.040 mmol, 91%) as a colourless oil.

¹H NMR δ_{H} (200 MHz, CDCl₃): 4.06 (2H, dd, $J = 9.2, 2.1$ Hz, CH₂CH₂OR), 3.72 (1H, d, $J = 11.7$ Hz, CH_AH_BOH), 3.58 (1H, $J = 11.7$ Hz, CH_AH_BOH), 3.44 (3H, s, CH₃OCH₂), 2.20–1.98 (4H, m, CH_AH_BCH₂OR + 3 × THF-*H*), 1.86–1.69 (2H, m, THF-*H* + OH), 1.29–1.19 (1H, m, CH_AH_BCH₂OR); **¹³C NMR** δ_{C} (50 MHz, CDCl₃): 106.3, 82.1, 75.2, 66.8, 59.8, 59.7, 31.8, 31.6, 28.3; **IR** ν_{max} (thin film)/cm⁻¹ 3410 br./s, 2954s, 1315s, 1273s, 1113s, 1070w, 1027w, 977w, 943w, 896w, 713s. **m/z** (ESI⁺)

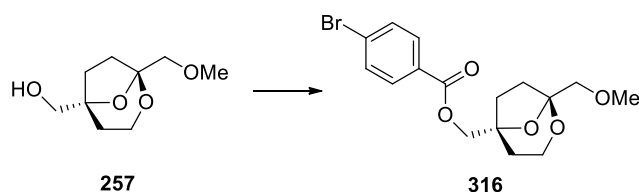
C₉H₁₆O₄ predicted 211.0946 (M+Na⁺), found 211.0951, (Δ = +2.4 ppm).

Procedure B:



To a solution of **150** (41 mg, 0.099 mmol) in anhydrous MeCN (1.5 mL) was added H₂O (0.05 mL, 3 mmol) at r.t. The reaction was allowed to stir at r.t. for 30 min before concentrated onto silica *in vacuo*. Flash column chromatography [SiO₂, 100% EtOAc] yielded cyclisation product **257** (18.4 mg, 0.098 mmol, 99%) as a colourless oil. All of the spectroscopic data for the product are consistent with procedure A.

(1*R*,5*R*)-5-((4-Bromophenoxy)methyl)-1-(methoxymethyl)-2,8-dioxabicyclo[3.2.1]octane (316)

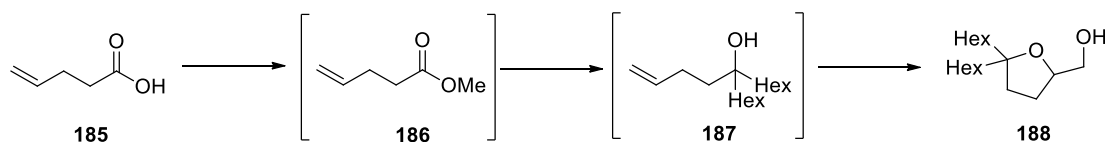


To a solution of alcohol **257** (7.5 mg, 0.040 mmol) in anhydrous THF (0.5 mL) was added triethylamine (0.10 mL, 0.72 mmol) and 4-bromobenzoyl chloride (17 mg, 0.077 mmol) sequentially at r.t. The reaction was allowed to stir for 2 h before being quenched with water (2 mL) and diluted with Et₂O (3 mL). The phases were separated

and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 10:1 to 2:1] yielded ester **316** (7.0 mg, 0.019 mmol, 47%) as a colourless solid.

¹H NMR δ_H (400 MHz, *d*₆-DMSO): 7.93–7.74 (4H, m, Ar*H*), 4.46–4.16 (2H, m, CH₂OAr), 4.01–3.84 (2H, m, CH₂CH₂OR), 3.35 (2H, s, CH₃OCH₂), 3.33 (3H, s, CH₃OCH₂), 2.11–1.78 (5H, m, CH_AH_BCH₂OR + 4 × THF-*H*), 1.39 (1H, dd, *J* = 12.6, 3.3 Hz, CH_AH_BCH₂OR); **¹³C NMR** δ_C (101 MHz, *d*₆-DMSO): 165.6, 132.9, 132.1, 129.5, 128.5, 107.4, 82.3, 74.9, 69.1, 59.8, 59.6, 32.0, 31.2, 30.2; **IR** ν_{max} (thin film)/cm⁻¹ 2956s, 1721s, 1590m, 1484w, 1398w, 1272s, 1174m, 1102s, 1068m, 1012s, 872w, 756s; **m/z** (ESI⁺) C₁₆H₁₉BrO₅ predicted 393.0308 (M+Na⁺), found 393.0301, (Δ = -1.8 ppm). **M.P.** 229–232 °C

(5,5-Dihexyltetrahydrofuran-2-yl)methanol (**188**)



To a solution of **185** (2.00 g, 20.0 mmol) in MeOH (10 mL) was added *p*TSA monohydrate (100 mg, 0.53 mmol) at r.t. The solution was then heated to reflux for 2 h. The reaction was cooled to r.t. and quenched with sat. aq. NaHCO₃ (30 mL) and then diluted with Et₂O (50 mL). The phases were separated and the organic layer was

washed with water (3×30 mL) and brine (2×10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give crude **186**. The crude product was carried through to the next step without further purification.

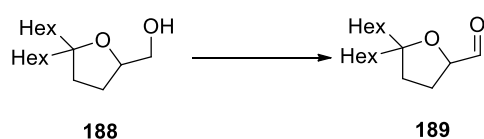
To the solution of crude **186** in anhydrous Et₂O (50 mL) was added *n*-HexMgBr (30 mL, 2.0 M in Et₂O, 60 mmol) at -78 °C. After 15 min, the reaction was allowed to warm to r.t. and stirred for a further 1 h. The reaction was then quenched with water (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give crude **187**. The crude product was carried through to the next step without further purification.

To the solution of crude **187** in CH₂Cl₂ (50 mL) was added *m*CPBA (7.40 g, 70 wt %, 30 mmol) carefully at r.t. The reaction was stirred for 48 h before being quenched with aq. sat. Na₂S₂O₃/NaHCO₃ (50 mL) and diluted with diethyl ether (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 10:1 to 5:1] yielded alcohol **188** (3.278 g, 12.1 mmol, 61% over 3 steps) as a colourless oil.

¹H NMR δ_{H} (400 MHz, CDCl₃): 4.05–3.95 (1H, CHCH₂OH), 3.67–3.39 (2H, m, CHCH₂OH), 2.44 (1H, br. s, OH), 1.92–1.65 (4H, m, THF-*H*), 1.52–1.34 (4H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 1.24 (16H, br., $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 0.85 (6H, t, $J = 6.4$ Hz, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$); **¹³C NMR** δ_{C} (101 MHz, CDCl₃): 86.0, 78.7, 65.2, 39.2, 38.5, 35.1,

31.9, 31.8, 29.9, 27.6, 24.4, 24.1, 22.6, 14.0; **IR** $\nu_{\max}$ (thin film)/ cm^{-1} 3427 br./s, 2928s, 2858s, 1460s, 1378w, 1040s, 880w, 725w; **m/z** (ESI^+) $\text{C}_{17}\text{H}_{34}\text{O}_2$ predicted 293.2451 ($\text{M}+\text{Na}^+$), found 293.2443, ($\Delta = -2.6$ ppm).

5,5-Dihexyltetrahydrofuran-2-carbaldehyde (**189**)

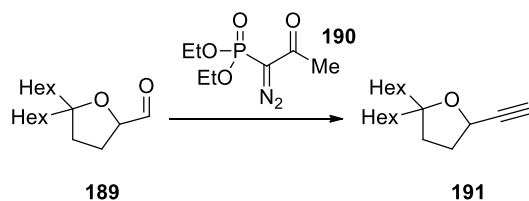


To a solution of **188** (724 mg, 2.68 mmol) in $\text{CH}_2\text{Cl}_2/\text{THF}/\text{H}_2\text{O}$ (10 mL/10 mL/0.01 mL) was added DMP (1.70 g, 4.01 mmol) at r.t. The reaction was stirred overnight, and then quenched with aq. sat. $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ (20 mL), diluted with Et_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO_2 , Petrol/ EtOAc , 10:1] yielded aldehyde **189** (473 mg, 1.76 mmol, 66%) as a colourless oil.

^1H NMR δ_{H} (400 MHz, CDCl_3): 9.66 (1H, d, $J = 1.5$ Hz, RCHO), 4.28–4.22 (1H, CHCHO), 2.22–1.95 (2H, m, CH_2CHCHO), 1.80–1.65 (2H, m, $\text{CH}_2\text{CH}_2\text{CHCHO}$), 1.60–1.41 (4H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 1.32–1.21 (16H, br., $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 0.92–0.85 (6H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$); **^{13}C NMR** δ_{C} (101 MHz, CDCl_3): 203.6, 88.1, 82.7, 38.7, 38.3, 34.7, 31.8, 29.8, 27.8, 24.4, 24.2, 22.6, 14.1; **IR** $\nu_{\max}$ (thin film)/ cm^{-1} 2929s, 2858s, 1735s, 1461s, 1378w, 1075s, 725w; **m/z** (ESI^+) $\text{C}_{17}\text{H}_{32}\text{O}_2$

predicted 269.2475 ($M+H^+$), found 269.2477, ($\Delta = +0.7$ ppm).

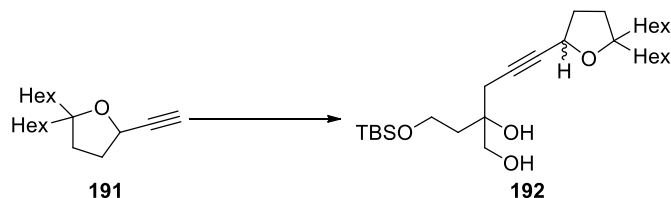
5-Ethynyl-2,2-dihexyltetrahydrofuran (**191**)



To a solution of **189** (293 mg, 1.09 mmol) in MeOH (5 mL) was added K_2CO_3 (200 mg) and diethyl-1-diazo-2-oxopropylphosphonate **190** (1.9 mL, 1.2 M in MeCN, 2.3 mmol) at r.t. The reaction was stirred overnight before concentrated onto silica *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 25:1] yielded alkyne **191** (264 mg, 1.00 mmol, 92 %) as a colourless oil.

1H NMR δ_H (400 MHz, $CDCl_3$): 4.58 (1H, td, $J = 6.6, 2.0$ Hz, $CHC\equiv CH$), 2.41 (1H, d, $J = 2.0$ Hz, $CHC\equiv CH$), 2.25–2.15 (1H, m, $CH_aH_bCHC\equiv CH$), 2.07–1.96 (1H, m, $CH_aH_bCHC\equiv CH$), 1.92–1.83 (1H, m, $CH_aH_bCH_2CHC\equiv CH$), 1.77–1.66 (1H, m, $CH_aH_bCH_2CHC\equiv CH$), 1.55–1.38 (4H, m, $2 \times CH_3(CH_2)_4CH_2R$), 1.28 (16H, d, $J = 9.6$ Hz, $2 \times CH_3(CH_2)_4CH_2R$), 0.92–0.84 (6H, m, $2 \times CH_3(CH_2)_4CH_2R$); **^{13}C NMR** δ_C (101 MHz, $CDCl_3$): 86.9, 84.7, 72.0, 67.3, 38.7, 35.0, 33.7, 31.8, 29.9, 24.4, 22.6, 14.1; **IR** ν_{max} (thin film)/ cm^{-1} 3313w, 2929s, 2858s, 1460s, 1336w, 1044s, 651s, 626s; **m/z** (ESI^+) $C_{18}H_{32}O_2$ predicted 287.2345 ($M+Na^+$), found 287.2335, ($\Delta = -3.7$ ppm).

2-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-5-(5,5-dihexyltetrahydrofuran-2-yl)pent-4-yne-1,2-diol (192**)**



To a solution of epoxide **161** (228 mg, 0.86 mmol) in anhydrous THF (3 mL) was added *t*-BuMgCl (1.06 mL, 1.0 M in THF) dropwise at $-78\text{ }^{\circ}\text{C}$. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min, and then warmed to r.t. and stirred for a further 30 min.

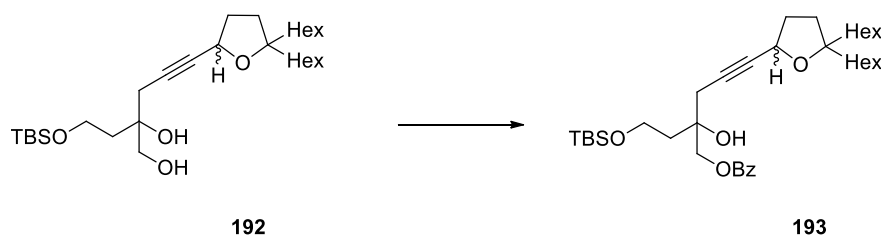
In a separate reaction vessel, to a solution of alkyne **191** (520 mg, 1.97 mmol) in anhydrous THF (5 mL) was added *n*-BuLi (1.23 mL, 1.6 M in hexanes) at $-78\text{ }^{\circ}\text{C}$. The reaction was kept at $-78\text{ }^{\circ}\text{C}$ for 15 min, and then added DMPU (0.48 mL, 3.97 mmol). The reaction was then warmed to $0\text{ }^{\circ}\text{C}$ and stirred for a further 45 min.

The solution of deprotonated alkyne was added to the epoxide-*t*-BuMgCl complex solution at $0\text{ }^{\circ}\text{C}$. The reaction was quenched in 2 h with water (20 mL) and then diluted with Et₂O (20 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 6:1 to 4:1] yielded diol **192** (221 mg, 0.44 mmol, 52%, 1:1 *d.r.*) as a colourless oil.

Data are reported for the mixture of diastereoisomers.

$^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 4.62–4.52 (1H, m, $\text{CH}_2\text{CHC}\equiv\text{C}$), 4.01–3.51 (5H, m, $\text{CH}_2\text{OH} + \text{CH}_2\text{CH}_2\text{OTBS} + \text{CH}_2\text{OH}$), 2.80–2.68 (1H, m, CR_3OH), 2.55 (2H, ABq, $J = 17.0$ Hz, $\text{CH}_2\text{C}\equiv\text{CR}$), 2.22–1.67 (6H, m, $\text{CH}_2\text{CH}_2\text{OTBS} + 4 \times \text{THF-H}$), 1.65–1.35 (4H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 1.31–1.19 (16H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 0.94–0.85 (15H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R} + t\text{-Bu}$), 0.13–0.08 (6H, m, $2 \times \text{SiCH}_3$); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 86.4, 83.6, 80.1, 74.1, 68.0, 67.7, 60.1, 39.4, 38.8, 36.9, 35.0, 34.0, 31.9, 31.8, 29.9, 28.1, 25.9, 25.8, 24.5, 24.1, 22.7, 18.0, 14.1, –5.4; IR ν_{max} (thin film)/ cm^{-1} 3427br./s, 2929s, 2857s, 1464m, 1255m, 1092s, 836s, 777s; m/z (ESI^+) $\text{C}_{29}\text{H}_{56}\text{O}_4\text{Si}$ predicted 519.3840 ($\text{M}+\text{Na}^+$), found 519.3832, ($\Delta = -1.6$ ppm).

2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-(5,5-dihexyltetrahydrofuran-2-yl)-2-hydroxypent-4-yn-1-yl benzoate (193)



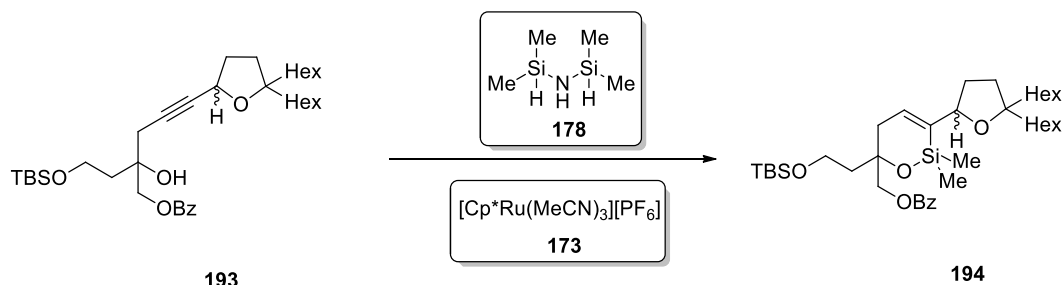
To a solution of **192** (221 mg, 0.445 mmol) in THF (3 mL) was added triethylamine (1.0 mL, 7.2 mmol) and BzCl (0.30 mL, 2.26 mmol) at r.t. The reaction was quenched with water (10 mL) and diluted with Et_2O (10 mL) in 12 h. The phases were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash

column chromatography [SiO_2 , Petrol/EtOAc, 20:1] yielded tertiary alcohol **193** (262 mg, 0.436 mmol, 98%) as a colourless oil.

Data are reported for the mixture of diastereoisomers.

^1H NMR δ_{H} (400 MHz, CDCl_3): 8.06 (2H, d, $J = 7.6$ Hz, *o*-ArH), 7.61–7.53 (1H, m, *p*-ArH), 7.48–7.41 (2H, m, *m*-ArH), 4.66–4.51 (1H, m, $\text{CH}_2\text{CHC}\equiv\text{C}$), 4.46–4.23 (2H, m, CH_2OBz), 4.03–3.62 (3H, m, $\text{CH}_2\text{CH}_2\text{OTBS} + \text{CR}_3\text{OH}$), 2.76–2.55 (2H, m, $\text{CH}_2\text{C}\equiv\text{CR}$), 2.19–1.54 (6H, m, $\text{CH}_2\text{CH}_2\text{OTBS} + \text{THF-H}$), 1.52–1.35 (4H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 1.31–1.21 (16H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R}$), 0.94–0.84 (15H, m, $2 \times \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{R} + t\text{-Bu}$), 0.14–0.08 (6H, m, $2 \times \text{SiCH}_3$); **^{13}C NMR** δ_{C} (101 MHz, CDCl_3): 166.3, 166.2, 133.2, 133.0, 130.6, 130.1, 129.8, 129.7, 128.9, 128.4, 86.4, 83.6, 79.9, 74.0, 73.6, 68.8, 67.7, 66.8, 66.6, 60.2, 59.9, 59.1, 56.3, 51.0, 47.6, 39.4, 39.4, 38.8, 36.3, 35.3, 35.0, 34.5, 34.0, 31.9, 31.8, 29.9, 28.5, 25.8, 24.5, 24.1, 22.6; **IR** ν_{max} (thin film)/ cm^{-1} 2929s, 2857s, 1724s, 1452w, 1269s, 1094s, 1027s, 900w, 835s, 777s, 710s; **m/z** (ESI^+) $\text{C}_{36}\text{H}_{60}\text{O}_5\text{Si}$ predicted 623.4102 ($\text{M}+\text{Na}^+$), found 623.4104, ($\Delta = +0.4$ ppm).

(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(5,5-dihexyltetrahydrofuran-2-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)methyl benzoate (194**)**



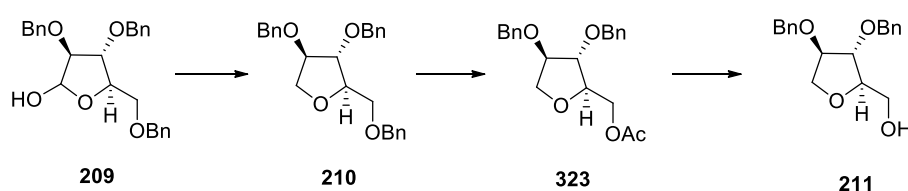
A solution of **193** (39.7 mg, 0.066 mmol) in 1,1,3,3-tetramethyldisilazane **178** (0.6 mL) at r.t. was slowly heated to 50 °C for 2.5 h in a sealed tube. The reaction was then left on high vacuum for 1 h to remove the excess **178**. The residue was redissolved in anhydrous CH₂Cl₂ (0.8 mL) under Argon and Ru catalyst **173** (4 mg, 10 mol %) was added at 0 °C. The reaction was stirred for a further 2 h at r.t. before concentrated onto silica *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 25:1] yielded alkene **194** (14.0 mg, 0.021 mmol, 32%) as a colourless oil.

Data are reported for the mixture of diastereoisomers.

¹H NMR δ_H (200 MHz, CDCl₃): 8.05 (2H, d, *J* = 7.5 Hz, *o*-ArH), 7.63–7.51 (1H, m, *p*-ArH), 7.51–7.37 (2H, m, *m*-ArH), 6.46 (1H, t, *J* = 4.3 Hz, CR₂=CHR), 4.48–4.33 (1H, m, CH₂CHC=C), 4.32–4.16 (2H, m, CH₂OBz), 3.80 (2H, td, *J* = 6.7, 2.6 Hz, CH₂CH₂OTBS), 2.45 (2H, d, *J* = 4.1 Hz, CH₂C=C), 2.13–1.57 (6H, m, CH₂CH₂OTBS + THF-*H*), 1.55–1.40 (4H, m, 2 × CH₃(CH₂)₄CH₂R), 1.37–1.20 (16H, m, 2 × CH₃(CH₂)₄CH₂R), 0.88 (15H, s, 2 × CH₃(CH₂)₄CH₂R + *t*-Bu), 0.30–0.17 (6H,

m, $2 \times \text{C}=\text{CRSi}(\text{CH}_3)_2$), 0.04 (6H, s, $2 \times \text{TBS}-\text{CH}_3$); ^{13}C NMR δ_{C} (50 MHz, CDCl_3): 165.0, 140.8, 134.1, 133.9, 131.5, 128.9, 128.3, 127.0, 83.6, 80.6, 80.4, 73.1, 73.0, 68.1, 67.6, 57.6, 39.9, 39.6, 38.1, 37.0, 34.5, 33.6, 32.2, 30.5, 28.6, 24.6, 23.0, 22.9, 21.3, 16.9, 13.9, 12.8, 0.1, 0.0, -6.7; IR ν_{max} (thin film)/ cm^{-1} 2929s, 2857s, 1725s, 1463w, 1271s, 1250s, 1095s, 1026m, 834s, 779m, 710s; m/z (ESI $^{+}$) $\text{C}_{38}\text{H}_{66}\text{O}_5\text{Si}_2$ predicted 681.4341 ($\text{M}+\text{Na}^{+}$), found 681.4349, ($\Delta = +1.1$ ppm).

((2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)methanol (211**)**



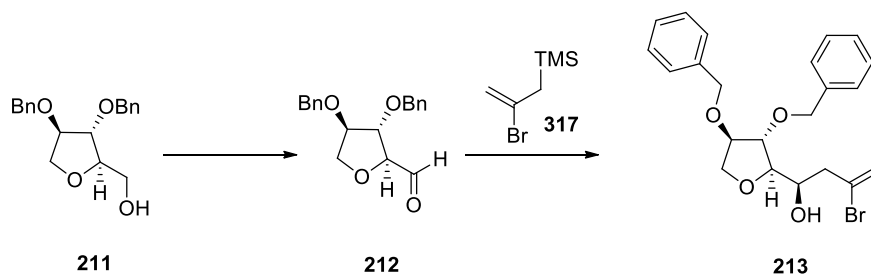
To a stirred solution of commercially available **209** (2.855 g, 6.80 mmol) in anhydrous MeCN (35 mL), under N_2 , were added triethylsilane (4.5 mL, 28.8 mmol) and then freshly distilled $\text{BF}_3 \cdot \text{OEt}_2$ (1.80 mL, 14.4 mmol). The reaction was left stirring at r.t. for 45 min. After that, it was quenched with H_2O (30 mL) and diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2×30 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude aldehyde product **210** (2.70 g) was obtained as colourless oil and carried to next step without further purification.

To a stirred solution of **210** (2.70 g) in Ac₂O (27 mL) was added CF₃COOH (7 mL) at 0 °C. The reaction was stirred for 3 h before pouring into ice water (400 mL) and Et₂O (300 mL). The organic layer was separated and added K₂CO₃ carefully. The resulting organics were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude **323** was then directly subjected to saponification in MeOH (50 mL) with MeONa (10 mL, 25 wt% in MeOH). The reaction was quenched in 30 min with 100 mL H₂O and diluted with Et₂O (150 mL). The aqueous layer was extracted with Et₂O (2 × 200 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 6:1 to 2:1] afforded alcohol **211** (1.957 g, 6.23 mmol, 92% over three steps) as a colourless oil.

¹H NMR δ_H (400 MHz, CDCl₃): 7.38–7.30 (10H, m, ArH), 4.55 (2H, d, *J* = 1.3 Hz, CH₂CHOCH₂), 4.51 (2H, s, CH₂CHCHOCH₂), 4.04 (1H, m, CH_AH_BCH), 3.91 (1H, dd, *J* = 10.4, 4.4 Hz, CH_AH_BCH), 4.06–3.98 (3H, m, 2 × BnOCH + HOCH₂CH), 3.79 (1H, dd, *J* = 11.7, 3.3 Hz, CH_AH_BOH), 3.68 (1H, dd, *J* = 11.7, 4.5 Hz, CH_AH_BOH);

¹³C NMR δ_C (101 MHz, CDCl₃): 137.9, 129.0, 128.7, 128.0, 127.5, 84.9, 84.1, 83.1, 72.4, 72.0, 71.5, 63.2. Spectroscopic data are consistent with those previously reported.^[86]

(R)-1-((2R,3S,4R)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-3-bromobut-3-en-1-ol
(213)



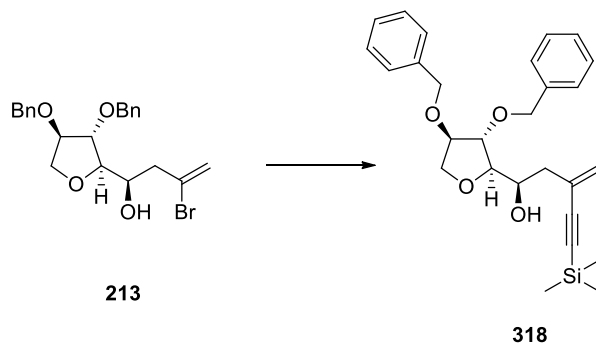
To a stirred solution of alcohol **211** (1.99 g, 6.33 mmol) in anhydrous CH_2Cl_2 (25 mL) was added DMSO (1.35 mL, 19.0 mmol), *N,N*-diisopropylethylamine (2.70 mL, 15.4 mmol), $\text{SO}_3 \cdot \text{Py}$ (2.58 g, 16.3 mmol) at 0 °C sequentially. The reaction was stirred at 0 °C for 3 h, then quenched with aq. sat. $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ solution (100 mL), diluted with diethyl ether (80 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 100 mL) and the combined organic layers were washed with aq. sat. CuSO_4 (2 × 100 mL) and brine (100 mL). The resulting organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude aldehyde **212** was obtained as pale yellow oil and carried to next step without further purification.

To a stirred solution of crude aldehyde **212** (assumed 6.01 mmol) in anhydrous CH_3CN (40 mL) was added (2-bromoallyl)trimethylsilane **317** (3.00 g, 15.5 mmol) at 0 °C. To the mixture was then added TMSOTf (3.31 g, 14.9 mmol) dropwise at –10 °C. The reaction was kept at –10 °C for 12 h before being quenched with aq. sat.

NaHCO₃ solution (80 mL), diluted with diethyl ether (80 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 80 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 12:1 to 10:1] yielded vinyl bromide **213** (2.01 g, 4.64 mmol, 73% over two steps) as a colourless oil (*d.r.*>20:1).

[α]_D²⁰ +17.1 (c = 0.5, CHCl₃); ¹H NMR δ _H (400 MHz, CDCl₃): 7.37–7.16 (10H, m, ArH), 5.60 (1H, s, C=CH_AH_B), 5.46 (1H, s, C=CH_AH_B), 4.49 (2H, dd, *J* = 22.0, 12.0 Hz, CHCHOCH₂Ph), 4.47 (2H, s, CH₂COCH₂Ph), 4.16–4.05 (2H, m, CHOH + CH₂CHOBn), 4.03–3.95 (2H, m, CH_AH_BCHOBn + CH₂CHCHOBn), 3.84–3.72 (2H, m, CH_AH_BCHOBn + CHCHOH), 2.59 (1H, dd, *J* = 14.8, 3.5 Hz, CH_AH_BC=C), 2.47–2.34 (2H, m, CH_AH_BC=C + CHOH); ¹³C NMR δ _C (101 MHz, CDCl₃): 137.8, 137.5, 130.1, 129.0, 128.7, 128.0, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 119.6, 86.6, 82.5, 82.4, 71.9, 71.5, 71.1, 68.8, 45.3; IR ν _{max} (thin film)/cm⁻¹ 3460br/s, 2867w, 1631s, 1496w, 1454s, 1207w, 1073s, 1027s, 893w, 737s, 698s; *m/z* (ESI⁺) C₂₂H₂₅⁷⁹BrO₄ predicted 455.0828 (M+Na⁺), found 455.0823, (Δ = – 1.2 ppm).

(R)-1-((2R,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-3-methylene-5-(trimethylsilyl)pent-4-yn-1-ol (318)

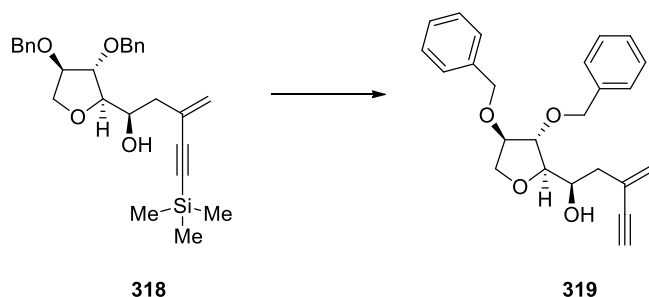


To a reaction flask was added $\text{Pd(PPh}_3)_4$ (26.7 mg, 0.023 mmol) and CuI (8.9 mg, 0.046 mmol). The flask was degassed with argon before anhydrous THF (5 mL), vinyl bromide **213** (137 mg, 0.32 mmol), TMS-acetylene (230 mg, 2.35 mmol) and Et_3N (330 mg, 3.27 mmol) were added sequentially. The reaction mixture was heated at 60 °C for 2 h before it was quenched with aq. sat. NH_4Cl solution (15 mL), diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×20 mL) and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO_2 , Petrol/ EtOAc , 15:1 to 10:1] afforded enyne **318** as a pale yellow oil (124 mg, 0.275 mmol, 87%).

$[\alpha]_{\text{D}}^{20} +20.8$ ($c = 1.0$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 7.35–7.17 (10H, m, ArH), 5.43 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.26 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.49 (2H, s, $\text{CH}_2\text{COCH}_2\text{Ph}$), 4.45 (2H, d, $J = 3.4$ Hz, $\text{CHCHOCH}_2\text{Ph}$), 4.12 (1H, d, $J = 3.2$ Hz, CH_2CHOBN), 4.09–4.03 (1H, m, CHOH), 4.01–3.94 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN} + \text{CH}_2\text{CHCHOBN}$),

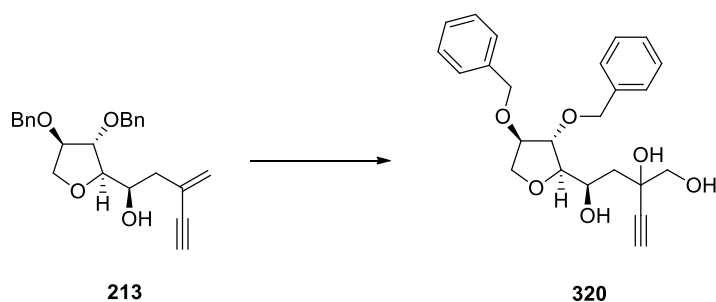
3.84–3.77 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN} + \text{CHCHOH}$), 2.54 (1H, d, $J = 2.4$ Hz, CHOH), 2.37 (1H, dd, $J = 14.0, 4.3$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{C}$), 2.17 (1H, dd, $J = 14.0, 8.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{C}$), 0.12 (9H, s, TMS- H); ^{13}C NMR δ_C (101 MHz, CDCl_3): 137.8, 137.6, 131.1, 129.3, 129.1, 129.0, 128.6, 128.4, 128.1, 128.0, 127.8, 127.7, 126.2, 125.0, 105.1, 95.1, 86.9, 82.6, 82.6, 71.8, 71.5, 71.1, 69.5, 41.1, 0.0; IR ν_max (thin film)/ cm^{-1} 3470br/s, 2899w, 1496w, 1454s, 1250s, 1074s, 876s, 842s, 737s, 698s; m/z (ESI^+) $\text{C}_{27}\text{H}_{34}\text{O}_4\text{Si}$ predicted 473.2119 ($\text{M}+\text{Na}^+$), found 473.2112, ($\Delta = -1.4$ ppm).

(*R*)-1-((2*R*,3*S*,4*R*)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-3-methylenepent-4-yn-1-ol (319**)**



ArH), 5.48 (1H, s, C=CH_AH_B), 5.32 (1H, s, C=CH_AH_B), 4.55–4.39 (4H, m, CH₂COCH₂Ph + CHCHOCH₂Ph), 4.15–4.04 (2H, m, CH₂CHOBn + CHOH), 4.03–3.94 (2H, m, CH_AH_BCHOBn + CH₂CHCHOBn), 3.84–3.74 (2H, m, CH_AH_BCHOBn + CHCHOH), 2.86 (1H, s, C≡CH), 2.45 (1H, br.s., CHOH), 2.38 (1H, dd, *J* = 14.1, 4.3 Hz, CH_AH_BC=C), 2.17 (1H, dd, *J* = 14.1, 8.7 Hz, CH_AH_BC=C); ¹³C NMR δ_C (101 MHz, CDCl₃): 137.5, 137.4, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 126.9, 125.6, 86.8, 83.4, 82.4, 82.4, 78.0, 71.7, 71.4, 70.9, 69.2, 40.8; IR ν_{max} (thin film)/cm⁻¹ 3287br./s, 2919w, 1496w, 1454s, 1072s, 1028s, 911w, 737s, 698s; m/z (ESI⁺) C₂₄H₂₆O₄ predicted 401.1723 (M+Na⁺), found 401.1719, (Δ = −1.1 ppm).

(4R)-4-((2R,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-ethynylbutane-1,2,4-triol (320)



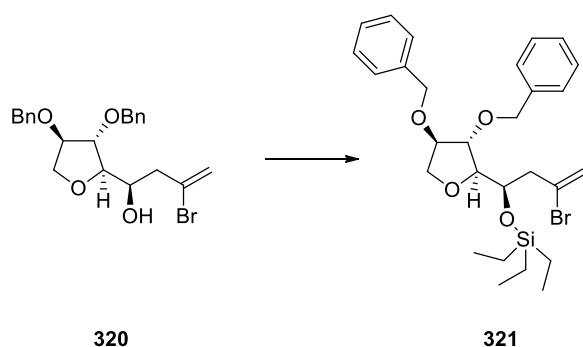
To a stirred solution of enyne **319** (83.0 mg, 0.220 mmol) in *t*-butanol/water (3.0 mL, 1:1 mixture) was added (DHQ)₂PHAL (34.4 mg, 0.044 mmol), potassium carbonate (90.8 mg, 0.658 mmol), methanesulfonamide (62.4 mg, 0.662 mmol) and potassium

ferricyanide (216.6 mg, 0.658 mmol). The resultant mixture was stirred vigorously at r.t. until all reagents had dissolved. The mixture was cooled to 0 °C, then potassium osmate dihydrate (8.0 mg, 0.0218 mmol) was added. The mixture was left to stir at 0 °C for 12 h. The resultant mixture was then quenched with aq. sat. Na₂SO₃ solution (20 mL) and stirred for 30 min before ethyl acetate (20 mL) was added. The two layers were separated and the organic layer washed with water (20 mL). The combined aqueous layers were then extracted with ethyl acetate (3 × 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography: First column [SiO₂, CHCl₃/MeOH, 100:3] and then second column [SiO₂, CHCl₃/MeOH, 100:1] afforded diol **320** as a colourless oil (20.7 mg, 0.050 mmol, *d.r.* = 3:1, 23%).

[α]_D²⁰ +18.3 (*c* = 0.6, CHCl₃); ¹H NMR δ _H (400 MHz, CDCl₃): 7.42–7.28 (10H, m, ArH), 4.57 (2H, d, *J* = 3.0 Hz, CH₂COCH₂Ph), 4.54–4.51 (2H, m, CHCHOCH₂Ph), 4.20 (1H, dt, *J* = 9.2, 3.4 Hz, CHOH), 4.16–4.10 (1H, m, CH₂CHOBn), 4.09–4.03 (2H, m, CH_AH_BCHOBn + CH₂CHCHOBn), 3.88 (1H, dd, *J* = 9.9, 3.5 Hz, CH_AH_BCHOBn), 3.85 (1H, t, *J* = 3.6 Hz, CHCHOH), 3.74–3.67 (2H, m, CH₂OH), 3.43 (1H, br. s., CH₂OH), 3.00 (1H, br. s., CR₃OH), 2.65–2.54 (1H, m, CHOH), 2.52 (1H, s, C≡CH), 2.02 (1H, d, *J* = 3.0 Hz, CH_AH_BC=C), 1.84 (1H, dd, *J* = 14.4, 9.2 Hz, CH_AH_BC=C); ¹³C NMR δ _C (101 MHz, CDCl₃): 137.4, 137.2, 128.6, 128.6, 128.1, 128.1, 128.0, 127.9, 87.4, 83.5, 82.5, 82.5, 73.8, 71.9, 71.5, 71.0, 69.8, 69.3, 68.2, 41.5; IR ν _{max} (thin film)/cm⁻¹ 3413br/s, 2923s, 2859s, 1735w, 1457s, 1372w, 1332w, 1107s, 1059s, 740s, 698s; *m/z* (ESI⁺) C₂₄H₂₈O₆ predicted 435.1778 (M+Na⁺), found

435.1769, ($\Delta = -2.0$ ppm).

(((*R*)-1-((2*S*,3*S*,4*R*)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-3-bromobut-3-en-1-yl)oxy)triethylsilane (321**)**

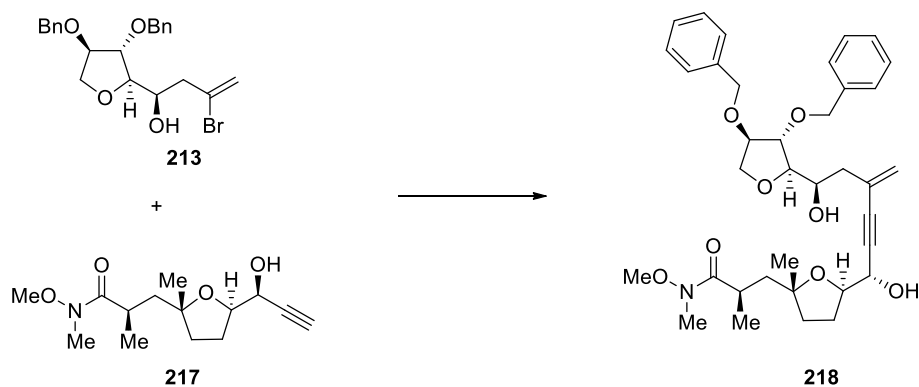


To a stirred solution of alcohol **320** (200 mg, 0.462 mmol) in anhydrous CH_2Cl_2 (10 mL) was added imidazole (94 mg, 1.38 mmol) and TESCl (139 mg, 0.92 mmol) at r.t. The reaction was stirred at r.t. for 5 h before it was concentrated onto silica *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 20:1 to 12:1] yielded product **321** (237 mg, 0.433 mmol, 94%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} +18.3$ ($c = 0.6$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 7.30–7.19 (10H, m, ArH), 5.55–5.49 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.35 (1H, d, $J = 1.5$ Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.50 (2H, d, $J = 2.2$ Hz, $\text{CHCHOCH}_2\text{Ph}$), 4.44 (2H, d, $J = 6.8$ Hz, $\text{CH}_2\text{COCH}_2\text{Ph}$), 4.14 (1H, dt, $J = 7.3, 4.4$ Hz, CHOH), 4.07 (1H, dd, $J = 4.8, 1.5$ Hz, $\text{CH}_2\text{CHCHOBN}$), 4.02 (1H, dt, $J = 4.8, 2.2$ Hz, CH_2CHOBN), 3.91 (1H, dd, $J = 10.0, 2.2$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN}$), 3.83 (1H, dd, $J = 10.0, 4.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN}$), 3.71 (1H, t, $J = 4.4$ Hz, CHCHOH), 2.60 (1H, ddd, $J = 14.4, 4.5, 0.7$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{C}$), 2.47 (1H, dd, $J = 14.4, 7.3$ Hz,

CH_AH_BC=C), 0.90–0.84 (9H, m, TES-CH₃), 0.59–0.51 (6H, m, TES-CH₂); ¹³C NMR δ_C (101 MHz, CDCl₃): 137.9, 137.9, 130.9, 128.5, 128.4, 127.8, 127.8, 127.7, 119.7, 86.0, 83.7, 83.6, 71.9, 71.4, 71.3, 69.8, 45.9, 7.0, 5.2; IR ν_{max} (thin film)/cm⁻¹ 3413br/s, 2923s, 2859s, 1735w, 1457s, 1372w, 1332w, 1107s, 1059s, 740s, 698s; m/z (ESI⁺) C₂₈H₃₉⁷⁹BrO₄Si predicted 569.1699 (M+Na⁺), found 569.1690, (Δ = -2.0 ppm).

(*R*)-3-((2*R*,5*R*)-5-((1*S*,6*R*)-6-((2*R*,3*S*,4*R*)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-1,6-dihydroxy-4-methylenehex-2-yn-1-yl)-2-methyltetrahydrofuran-2-yl)-N-methoxy-N,2-dimethylpropanamide (218**)**

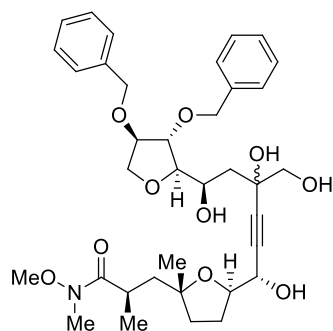


To a flame dried Schlenk tube was added [PdCl₂(MeCN)₂] (4.4 mg, 0.017 mmol), XPhos (15.7 mg, 0.033 mmol) and Cs₂CO₃ (126 mg, 0.387 mmol) under Argon. To this mixture was then injected anhydrous CH₃CN (2.0 mL) and vinyl bromide **213** (60.0 mg, 0.139 mmol). The pale yellow suspension was stirred for 30 min before alkyne **217** (45.0 mg, 0.167 mmol) was added. The resultant solution was stirred at

80 °C for 2 h before being quenched with aq. sat. NH_4Cl solution (20 mL) and diluted with ethyl acetate (20 mL). The two layers were separated and the aqueous layer was then extracted with ethyl acetate (3×20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO_2 , Petrol/EtOAc, 6:1 to 1:1 to 1:2] recovered vinyl bromide (28.4 mg) and afforded product **218** as a colourless oil (46.6 mg, 0.075 mmol, 54%).

$[\alpha]_{\text{D}}^{20} +24.6$ ($c = 2.2$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 7.35–7.19 (10H, m, ArH), 5.39 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.26 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.55–4.40 (5H, m, $\text{CH}_2\text{COCH}_2\text{Ph} + \text{CHCHOCH}_2\text{Ph} + \text{CHC}\equiv\text{C}$), 4.12 (1H, d, $J = 3.2$ Hz, BnOCHCHCHOH), 4.04 (2H, dt, $J = 7.2, 3.7$ Hz, $\text{CH}_2\text{CHCHOH} + \text{CH}_2\text{CHOH}$), 4.02–3.92 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBn} + \text{CH}_2\text{CHOBn}$), 3.86–3.74 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBn} + \text{CH}_2\text{CHCHOBn}$), 3.66 (3H, s, OCH_3), 3.19–3.01 (4H, m, $\text{NCH}_3 + \text{CHC}=\text{O}$), 2.59–2.44 (2H, m, $\text{CHCHOH} + \text{CH}_2\text{CHOH}$), 2.36 (1H, dd, $J = 13.8, 4.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{C}$), 2.21–2.05 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{C} + \text{O}=\text{CCHCH}_\text{A}\text{H}_\text{B}$), 1.98–1.86 (1H, m, $\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$), 1.75–1.56 (3H, m, $\text{CH}_2\text{CH}_2\text{CH} + \text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$), 1.45 (1H, dd, $J = 14.2, 3.4$ Hz, $\text{O}=\text{CCHCH}_\text{A}\text{H}_\text{B}$), 1.15 (3H, s, CR_3CH_3), 1.10 (3H, d, $J = 6.8$ Hz, CHCH_3); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 137.6, 137.5, 128.6, 128.5, 128.0, 127.9, 127.8, 127.1, 124.6, 87.8, 86.9, 85.5, 83.9, 82.4, 81.0, 71.8, 71.5, 71.0, 69.3, 64.4, 61.5, 43.9, 41.1, 37.6, 31.0, 28.9, 26.3, 19.8; IR ν_{max} (thin film)/ cm^{-1} 3287br/s, 2919w, 1496w, 1454s, 1072s, 1028s, 911w, 737s, 698s; m/z (ESI^+) $\text{C}_{36}\text{H}_{47}\text{NO}_8$ predicted 644.3199 ($\text{M}+\text{Na}^+$), found 644.3192, ($\Delta = -1.1$ ppm).

(R)-3-((2R,5R)-5-((1S,6R)-6-((2R,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-1,4,6-trihydroxy-4-(hydroxymethyl)hex-2-yn-1-yl)-2-methyltetrahydrofuran-2-yl)-N-methoxy-N,2-dimethylpropanamide (222/223)



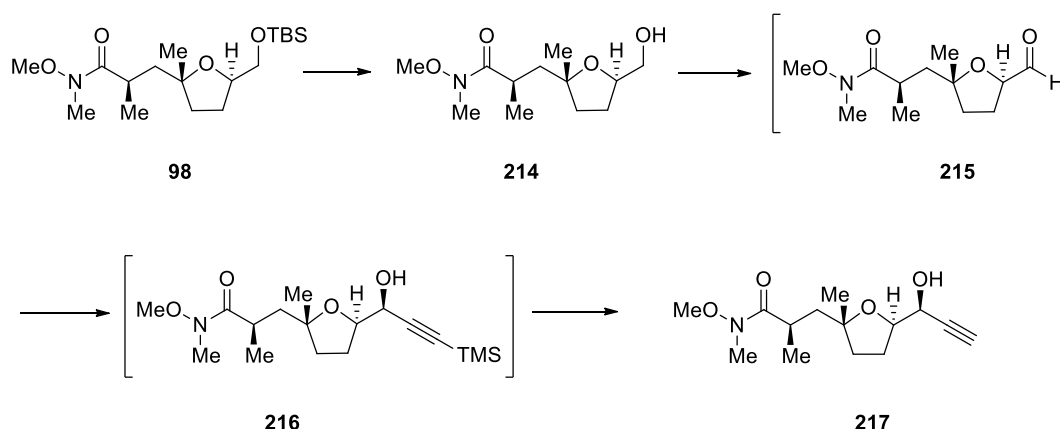
222/223

Potassium ferricyanide (84.1 mg, 0.255 mmol), potassium carbonate (35.3 mg, 0.257 mmol), potassium osmate dihydrate (3.1 mg, 0.0084 mmol), (DHQD)₂PHAL (13.4 mg, 0.0172 mmol) and methanesulfonamide (24.3 mg, 0.256 mmol) were added to H₂O (0.5 mL) and *t*-BuOH (0.5 mL). The mixture was stirred until all the solids had dissolved and then allowed to cool to 0 °C. To the stirring mixture was added enyne **218** (53 mg, 0.085 mmol) and the reaction was stirred at 0 °C for 16 h. The reaction mixture was subjected to filtration through a plug of silica [SiO₂, CHCl₃/MeOH, 100:6]. The filtrate were then concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, CHCl₃/MeOH, 100:2 to 100:4] afforded **223** (44.7 mg, 0.068 mmol, 80%) as a white solid. Spectroscopic data showed **223** was a mixture of diastereoisomers (*d.r.* 2.3:1), the ratio of diastereoisomers are calculated in Appendix 2.

Potassium ferricyanide (15.9 mg, 0.048 mmol), potassium carbonate (6.7 mg, 0.048

mmol), potassium osmate dihydrate (0.3 mg, 0.00084 mmol), (DHQ)₂PHAL (1.0 mg, 0.0013 mmol) and methanesulfonamide (4.6 mg, 0.048 mmol) were added to H₂O (0.3 mL) and *t*-BuOH (0.3 mL). The mixture was stirred until all the solids had dissolved and then allowed to cool to 0 °C. To the stirring mixture was added enyne **218** (7.0 mg, 0.011 mmol) and the reaction was stirred at 0 °C for 20 h. The reaction mixture was filtered through a plug of silica [SiO₂, CHCl₃/MeOH, 100:6]. The filtrate were then concentrated *in vacuo*. Purification by flash column chromatography [SiO₂, CHCl₃/MeOH, 100:2 to 100:4] afforded **222** (4.0 mg, 0.0061 mmol, 55%) as a colourless oil. Spectroscopic data showed **222** was a mixture of diastereoisomers (*d.r.* 1.4:1), the ratio of diastereoisomers are calculated in Appendix 2.

(*R*)-3-((2*R*,5*R*)-5-((*S*)-1-Hydroxyprop-2-yn-1-yl)-2-methyltetrahydrofuran-2-yl)-N-methoxy-N,2-dimethylpropanamide (217**)**



To a stirred solution of **98** (740 mg, 2.06 mmol) in anhydrous THF (10 mL) was added TBAF (6.7 mL, 1.0 M in THF, 6.7 mmol) at r.t. The reaction was kept at r.t. for

3 h before it was quenched with aq. sat. ammonium chloride (50 mL). The two layers were separated and the aqueous layer was then extracted with diethyl ether (4×50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO_2 , Petrol/ Et_2O , 1:1 to 1:2] afforded alcohol **214** as a colourless oil (504 mg, 2.06 mmol, 99%).

$[\alpha]_{\text{D}}^{20} -7.6$ ($c = 0.2$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 4.06 (1H, dd, $J = 5.2$, 3.2 Hz, CHCH_2OH), 3.73 (3H, s, CH_3O), 3.66 (1H, dd, $J = 11.4$, 3.2 Hz, $\text{CH}_\text{A}\text{H}_\text{BOH}$), 3.45 (1H, dd, $J = 11.4$, 5.2 Hz, $\text{CH}_\text{A}\text{H}_\text{BOH}$), 3.19 (3H, s, CH_3N), 3.15 (1H, br. s., CHCH_3), 2.67 (1H, br. s., OH), 2.16 (1H, dd, $J = 14.2$, 9.0 Hz, $\text{CH}_3\text{CHCH}_\text{A}\text{H}_\text{B}$), 2.03–1.87 (2H, m, $\text{CH}_2\text{CH}_\text{A}\text{H}_\text{BCH}$), 1.86–1.75 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.70–1.63 (1H, m, OH), 1.53 (1H, dd, $J = 14.2$, 3.5 Hz, $\text{CH}_3\text{CHCH}_\text{A}\text{H}_\text{B}$), 1.20–1.15 (6H, m, $\text{CH}_3\text{C} + \text{CHCH}_3$); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 176.3, 83.0, 79.0, 65.2, 61.5, 44.0, 37.8, 31.0, 27.2, 26.7, 19.8; **IR** ν_{max} (thin film)/ cm^{-1} 3463br./s, 2967s, 2935s, 1643s, 1462s, 1249s, 1055s, 995s; **m/z** (ESI^+) $\text{C}_{12}\text{H}_{23}\text{O}_4\text{N}$ predicted 268.1525 ($\text{M}+\text{Na}^+$), found 268.1520, ($\Delta = -1.9$ ppm).

To a stirred solution of alcohol **214** (270 mg, 1.10 mmol) in anhydrous CH_2Cl_2 (15 mL) was added DMSO (0.98 mL, 13.8 mmol), *N,N*-Diisopropylethylamine (2.17 mL, 12.4 mmol), $\text{SO}_3\cdot\text{Py}$ (1.90 g, 22.1 mmol) at 0 °C sequentially. The reaction was kept at 0 °C for 3 h before it was quenched with aq. sat. $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ solution (100

mL), diluted with diethyl ether (80 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2×100 mL) and the combined organic layers were washed with aq. sat. CuSO_4 (2×100 mL) and brine (100 mL). The resulting organics were then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude aldehyde **215** was obtained as pale yellow oil and carried through to the next step without further purification.

To a reaction flask was added $\text{Zn}(\text{OTf})_2$ (2.53 g, 6.97 mmol) and the powder was stirred at 130°C in oil bath for 2 h under vacuum. The resultant white powder was cooled to r.t., then (+)-methylephedrine (1.35 g, 7.54 mmol), toluene (15 mL) and Et_3N (1.10 mL, 7.90 mmol) were added. The mixture was stirred for 30 min before TMS-acetylene (1.0 mL, 7.09 mmol) was added and stirred for a further 30 min. The crude aldehyde **215** (1.10 mmol) was then added dropwise, and the reaction was kept at r.t. for 12 h. The reaction mixture was concentrated onto silica *in vacuo*. Flash column chromatography [SiO_2 , Petrol/ EtOAc , 1:1] yielded TMS-alkyne **216** (248 mg, 0.726 mmol, 66% over two steps) and alkyne **217** (50.0 mg, 0.186 mmol, 17% over two steps) as colourless oil.

TMS-alkyne **216**

$[\alpha]_{\text{D}}^{20} -13.2$ ($c = 0.6$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 4.33 (1H, d, $J = 3.3$ Hz, CHOH), 4.04 (1H, td, $J = 7.3, 3.3$ Hz, CHCHOH), 3.67 (3H, s, CH_3O), 3.13 (3H, s, CH_3N), 3.08 (1H, br. s., CHCH_3), 2.67 (1H, br. s., OH), 2.14–2.04 (1H, m, $\text{CH}_3\text{CHCH}_{\text{AHB}}$), 1.99–1.90 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.77–1.61 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$),

1.46 (1H, dd, $J = 14.2, 3.7$ Hz, $\text{CH}_3\text{CHCH}_A\text{H}_B$), 1.16 (3H, s, CH_3C), 1.10 (3H, d, $J = 7.1$ Hz, CHCH_3), 0.10 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR δ_{C} (101 MHz, CDCl_3): 178.5, 103.6, 90.1, 83.7, 80.8, 64.4, 61.4, 43.7, 37.3, 30.9, 26.2, 26.1, 19.6, -0.3 ; IR ν_{max} (thin film)/ cm^{-1} 3288br/s, 2965s, 2928s, 1644s, 1462s, 1249s, 1106w, 1054s, 997s, 841s, 760w, 639w; m/z (ESI^+) $\text{C}_{17}\text{H}_{31}\text{O}_4\text{NSi}$ predicted 364.1920 ($\text{M}+\text{Na}^+$), found 364.1933, ($\Delta = +3.6$ ppm).

To a stirred solution of TMS-alkyne **216** (164 mg, 0.481 mmol) in methanol (4 mL) was added potassium carbonate (1.0 g, 7.2 mmol). The resulting mixture was stirred for 5 h at r.t. before being filtered and concentrated *in vacuo* onto silica. Purification by flash column chromatography [SiO_2 , Petrol/ Et_2O , 1:1] afforded alkyne **217** as a colourless oil (123 mg, 0.457 mmol, 95%).

alkyne **217**

$[\alpha]_{\text{D}}^{20} -9.9$ ($c = 0.4$, CHCl_3); ^1H NMR δ_{H} (400 MHz, CDCl_3): 4.46–4.37 (1H, m, CHOH), 4.18–4.06 (1H, m, CHCHOH), 3.73 (3H, s, CH_3O), 3.26–3.08 (4H, m, $\text{CH}_3\text{N} + \text{CHCH}_3$), 2.52–2.35 (2H, m, $\text{C}\equiv\text{CH} + \text{OH}$), 2.23–2.10 (1H, m, $\text{CH}_3\text{CHCH}_A\text{H}_B$), 2.08–1.96 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.86–1.66 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.52 (1H, dd, $J = 14.2, 3.4$ Hz, $\text{CH}_3\text{CHCH}_A\text{H}_B$), 1.21 (3H, s, CH_3C), 1.16 (3H, dd, $J = 7.0, 1.6$ Hz, CHCH_3); ^{13}C NMR δ_{C} (101 MHz, CDCl_3): 178.0, 84.0, 81.8, 80.8, 73.8, 63.8, 61.5, 43.9, 37.5, 32.6, 31.0, 26.3, 26.1, 19.8; IR ν_{max} (thin film)/ cm^{-1} 3286br/s, 2969s, 2928s, 1643s, 1462s, 1388w, 1181w, 1106w, 1053s, 995s, 936w, 702w, 608w; m/z (ESI^+) $\text{C}_{14}\text{H}_{24}\text{O}_4\text{N}$ predicted 270.1700 ($\text{M}+\text{H}^+$), found 270.1696, ($\Delta = -1.4$ ppm).

6-(4-Methoxybut-2-yn-1-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxo-3,10-disiladodecan-6-ol (151)

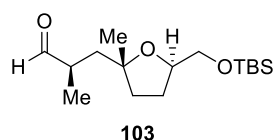


To a solution of alkyne **145** (60.8 mg, 0.867 mmol) in anhydrous THF (2.0 mL) was added *n*-BuLi (0.347 mL, 2.5 M in hexane, 0.868 mmol) at $-78\text{ }^{\circ}\text{C}$. The mixture was then stirred at $0\text{ }^{\circ}\text{C}$ for 15 min and cooled to $-78\text{ }^{\circ}\text{C}$. To the resultant pale yellow solution was added epoxide **150** (106 mg, 0.306 mmol) and redistilled $\text{BF}_3\cdot\text{OEt}_2$ (123 mg, 0.866 mmol) at $-78\text{ }^{\circ}\text{C}$ dropwise. The reaction was kept at $-78\text{ }^{\circ}\text{C}$ for 6 h before being quenched with aq. sat. NaHCO_3 solution (20 mL), diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether ($3 \times 20\text{ mL}$) and the combined organic layers were washed with brine (40 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO_2 , Petrol/EtOAc, 30:1] recovered epoxide **150** (22.4 mg) and afforded alcohol **151** as a colourless oil (85.4 mg, 0.205 mmol, 67%).

^1H NMR δ_{H} (400 MHz, CDCl_3): 4.08 (2H, t, $J = 2.2\text{ Hz}$, $\text{HOCR}_2\text{CH}_2\text{OTBS}$), 3.92–3.82 (2H, m, $\text{CH}_2\text{CH}_2\text{OTBS}$), 3.65 (1H, s, OH), 3.58 (2H, s, $\text{OCH}_2\text{C}\equiv\text{C}$), 3.35 (3H, s, CH_3O), 2.56–2.40 (2H, m, $\text{CCH}_2\text{C}\equiv\text{C}$), 1.92–1.75 (2H, m, $\text{CH}_2\text{CH}_2\text{OTBS}$), 0.94–0.83 (18H, m, $2 \times \text{SiC}(\text{CH}_3)_3$), 0.10–0.01 (12H, m, $2 \times \text{Si}(\text{CH}_3)_2$); **^{13}C NMR** δ_{C} (101 MHz, CDCl_3): 83.5, 77.9, 74.0, 67.3, 60.2, 59.9, 36.8, 28.1, 26.0, 18.2, -5.5 ; **IR**

ν_{max} (thin film)/ cm^{-1} 3492br./w, 2954s, 2929s, 2857s, 1471w, 1361w, 1254s, 1089s, 904w, 835s, 775s, 732w, 668w; m/z (ESI^+) $\text{C}_{21}\text{H}_{44}\text{O}_4\text{Si}_2\text{Na}$ predicted 439.2670 ($\text{M}+\text{Na}^+$), found 439.2659, ($\Delta = -2.5$ ppm).

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2-methylpropanal (103)



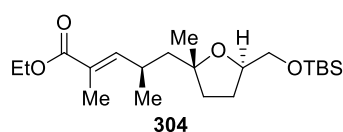
To a stirred solution of amide **98** (300 mg, 0.834 mmol) in tetrahydrofuran (15 mL) at -78 °C was added diisobutylaluminium hydride (1.65 mL, 2.03 mmol, 1.23 M in THF). The resulting solution was stirred at -78 °C for 3 h before being quenched with ethyl acetate (15 mL). The resulting mixture was warmed to r.t. before a sat. aq. solution of potassium sodium tartrate (40 mL) was added. The layers were separated and the aqueous layer extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting pale yellow oil (302 mg) was pure enough and carried to next step without further purification.

$[\alpha]_{\text{D}}^{20} +11.2$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 9.41 (1H, d, $J = 4.2$ Hz, CHO), 3.91–3.70 (1H, m, CHCH_2OSi), 3.55 (2H, t, $J = 4.3$ Hz, CH_2OSi), 2.57–2.29 (1H, m, $\text{CH}(\text{CH}_3)$), 2.09 (2H, dd, $J = 14.6, 9.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}(\text{CH}_3)$),

1.96–1.75 (4H, m, $\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)$), 1.56 (1H, dd, $J = 14.6, 3.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}(\text{CH}_3)$), 1.21 (3H, s, CCH_3), 1.10 (3H, d, $J = 7.1$ Hz, $\text{CH}(\text{CH}_3)$), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR δ_C (101 MHz, CDCl_3): 204.0 ($\text{C}=\text{O}$), 82.6 ($\text{C}(\text{CH}_3)$), 79.6 (CHCH_2OSi), 65.6 (CH_2OSi), 43.2 ($\text{CH}_2\text{CH}(\text{CH}_3)$), 42.7 ($\text{CH}(\text{CH}_3)$), 36.1 ($\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)$), 28.4 ($\text{C}(\text{CH}_3)$), 28.0 ($\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)$), 26.0 ($\text{SiC}(\text{CH}_3)_3$), 18.4 ($\text{SiC}(\text{CH}_3)_3$), 15.4 (CHCH_3), -5.3 (SiCH_3), -5.4 (SiCH_3); IR ν_max (thin film)/ cm^{-1} 2958, 2935, 2853, 1725, 1462, 1375; m/z (ESI^+) $\text{C}_{16}\text{H}_{32}\text{O}_3\text{Si}$ predicted 323.2013 ($\text{M}+\text{Na}^+$), found 323.2006, ($\Delta = -2.2$ ppm). Spectroscopic data are consistent with those previously reported.^[55]

Ethyl

(*E*)-(*R*)-5-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate (304)

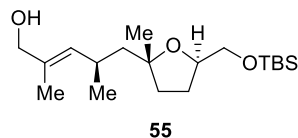


To a stirred suspension of (1-(ethoxycarbonyl)ethyl)triphenylphosphonium bromide (1.32 g, 2.98 mmol) in benzene (20 mL) at r.t. was added *n*-BuLi (1.19 mL, 2.98 mmol, 2.5 M in hexanes) dropwise. The solution changed from brown to yellow in 30min, a solution of crude aldehyde **103** (302 mg, assumed 0.834 mmol) in tetrahydrofuran (3.0 mL) was added dropwise, and then heated to reflux. After 18 h

the reaction was quenched with a sat. aq. solution of ammonium chloride (30 mL), diluted with ethyl acetate (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 25:1] yielded ester **304** as a colourless oil (281 mg, 0.731 mmol, 88 % over two steps).

[α]_D²⁰ – 9.8 (*c* = 0.2, CH₂Cl₂); ¹H NMR δ _H (400 MHz, CDCl₃): 6.62 (1 H, dd, *J* = 9.8, 1.2 Hz, C=CH), 4.20 (2 H, q, *J* = 7.2 Hz, CH₃CH₂O), 3.98–3.88 (1 H, m, OCH), 3.62 (1 H, dd, *J* = 10.4, 4.4 Hz, CH_AH_BOSi), 3.62 (1 H, dd, *J* = 10.4, 5.5 Hz, CH_AH_BOSi), 2.74–2.60 (1 H, m, CHCH₃), 1.90–1.75 (5 H, m, C=C(CH₃)CO₂ + THF-CH₂), 1.73–1.55 (4 H, m, THF-CH₂ + CH(CH₃)CH₂), 1.28 (3 H, d, *J* = 7.2 Hz, CH₃CH₂O), 1.16 (3 H, s, CCH₃), 1.06 (3 H, d, *J* = 7.2 Hz, CH(CH₃)), 0.89 (9 H, s, SiC(CH₃)₃), 0.05 (6 H, s, Si(CH₃)₂); ¹³C NMR δ _C (101 MHz, CDCl₃): 168.5 (C=O), 149.1 (C=CH), 124.2 (C=CH), 82.9 (C(CH₃)), 79.6 (CHCH₂OSi), 66.1 (CH₂OSi), 60.6 (CO₂CH₂CH₃), 48.1 (CHCH₃), 37.5 (CH₂CH₂C(CH₃)), 30.1 (CH₂CH(CH₃)), 28.4 (C(CH₃)=CH), 26.9 (CH₂CH₂C(CH₃)), 26.0 (SiC(CH₃)₃), 21.5 (C(CH₃)), 18.5 (SiC(CH₃)₃), 14.3 (CHCH₃), 12.3 (CO₂CH₂CH₃), –5.3 (SiCH₃), –5.4 (SiCH₃); IR ν _{max} (thin film)/cm^{–1} 2959, 2930, 2856, 1710, 1466, 1366, 1252; *m/z* (ESI⁺) C₂₁H₄₀O₄Si predicted 407.2588 (M+Na⁺), found 407.2579 (Δ = –2.2 ppm). Spectroscopic data are consistent with those previously reported. ^[55]

(E)-(R)-5-((2R,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-en-1-ol (55)

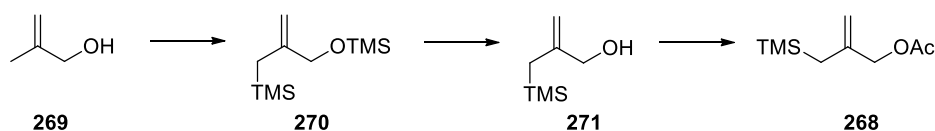


To a stirred solution of ester **304** (75 mg, 0.195 mmol) in dichloroethane (5.0 mL) at -78°C was added Super-Hydride[®] (0.78 mL, 0.78 mmol, 1 M in tetrahydrofuran) dropwise. The resulting solution was stirred at -78°C for 2 h before water (10 mL) and ethyl acetate (15 mL) were added. The resulting mixture was warmed to r.t. and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×15 mL) and the combined organic layers washed with brine (15 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography [SiO_2 , Petrol/EtOAc, 10:1 to 5:1] afforded alcohol **55** as a colourless oil (61 mg, 0.178 mmol, 92%).

$[\alpha]_{\text{D}}^{20} -1.2$ ($c = 0.5$, CH_2Cl_2); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 5.27 (1H, dd, $J = 9.6$, 1.2, $\text{C}=\text{CH}$), 4.00–3.96 (2H, m, CH_2OH), 3.95–3.89 (1H, m, OCH), 3.61 (1H, dd, $J = 10.4$, 5.2 Hz, $\text{CH}_\text{A}\text{H}_\text{BOTBS}$), 3.54 (1H, dd, $J = 10.4$, 5.6 Hz, $\text{CH}_\text{A}\text{H}_\text{BOTBS}$), 2.63–2.52 (1H, m, CHCH_3), 1.97–1.87 (1H, m, $\text{THF-CH}_\text{A}\text{H}_\text{B}$), 1.82–1.72 (2H, m, $\text{THF-CH}_\text{A}\text{H}_\text{B} + \text{THF-CH}_\text{A}\text{H}_\text{B}$), 1.69 (3H, s, $\text{C}=\text{C}(\text{CH}_3)\text{CH}_2\text{OH}$), 1.66–1.48 (4H, m, $\text{THF-CH}_\text{A}\text{H}_\text{B} + \text{CH}(\text{CH}_3)\text{CH}_2 + \text{CH}_2\text{OH}$), 1.18 (3H, s, $\text{CH}_2(\text{CH}_2\text{R})\text{CCH}_3$), 0.97 (3H, d, $J = 6.8$ Hz, $\text{CH}(\text{CH}_3)$), 0.90 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.06 (6H, s, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 134.1, 131.5, 83.4, 79.0, 69.1, 66.5, 48.4, 37.2, 28.9, 28.4, 27.2,

25.9, 22.6, 18.4, 13.7, -5.3; **IR** $\nu_{\max}$ (thin film)/cm⁻¹ 3392 br./s, 2956, 2928, 2858, 1462, 1254, 1100, 1008; **m/z** (ESI⁺) C₁₉H₃₈O₃Si predicted 365.2482 (M+Na⁺), found 365.2491 (Δ = +2.5 ppm). Spectroscopic data are consistent with those previously reported.^[55]

2-((Trimethylsilyl)methyl)allyl acetate (268)



A 500 mL three-necked flask equipped with mechanical stirring, N₂ inlet, and septum was charged with *n*-BuLi (2.5 M in hexanes, 100 mL, 250 mmol). The bulk of hexane was removed *in vacuo* by using a high vacuum pump. Anhydrous Et₂O (132 mL) and TMEDA (40 mL, 264 mmol) were added at 0 °C. 2-Methyl-2-propen-1-ol (8.53 g, 119 mmol) was added *via* syringe pump over 1 h. THF (60 mL) was then introduced, and the reaction turned from cloudy to clear orange colour. The reaction was allowed to warm up to r.t. over 4–6 h and then was stirred for 32 h. To this dark red gummy mixture was added TMSCl (63.7 mL, 502 mmol) rapidly at -10 °C. The reaction mixture was stirred for 10 min and diluted with 1 L of Et₂O. The dark cloudy mixture was washed with aq. sat. NaHCO₃ (250 mL), H₂O (250 mL), aq. sat. CuSO₄ (2 × 250 mL), H₂O (100 mL) and brine (200 mL). The resulting organic layers were then dried over K₂CO₃, filtered and concentrated *in vacuo*. Filtration using flash column

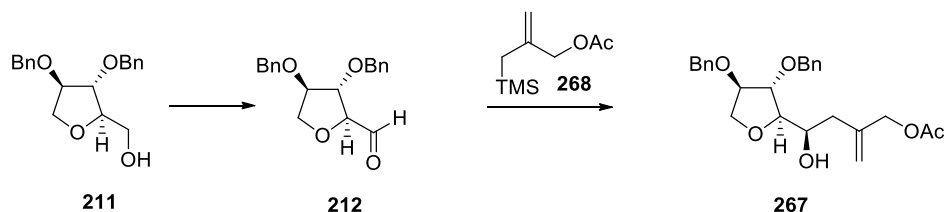
chromatography [SiO₂, Petrol/Et₂O/Et₃N, 100:1:1] yielded crude alkene **270** (7.0 g, 32 mmol, 27%) as a colourless oil.

To a solution of **270** (assuming 7.0 g, 32 mmol) in 80 mL THF was added 20 mL 1 N H₂SO₄. The mixture was stirred rigorously for 0.5 h at r.t. Anhydrous K₂CO₃ was added carefully until bubbling subsided. The reaction was diluted with 300 mL of ether, washed with q. sat. NaHCO₃ (100 mL) and brine (100 mL). The resulting organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo* with care (20 °C, 150 mbar). The crude colourless oil (4.7 g) was carried through to the next step without further purification.

To a solution of **271** (2.20 g, 15.2 mmol) in CH₂Cl₂ (20 mL) was added pyridine (4.28 mL, 52.9 mmol) and AcCl (1.85 mL, 26.0 mmol) at r.t. After 3 h, the reaction was quenched with water (10 mL) and diluted with Et₂O (10 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* with care. Flash column chromatography [SiO₂, Petrol/Et₂O/Et₃N, 40:1:0.5] yielded acetate **268** (2.32 g, 0.278 mmol, 81%) as a colourless oil.

¹H NMR δ_H (200 MHz, CDCl₃): 4.89 (1H, d, *J* = 1.5 Hz, CH_AH_B=CR₂), 4.77–4.70 (1H, m, CH_AH_B=CR₂), 4.44 (2H, s, CH₂OAc), 2.11 (3H, s, CH₃CO), 1.59–1.52 (2H, m, CH₂-TMS), 0.05 (9H, s, TMS). Spectroscopic data are consistent with those previously reported.^[102]

(R)-4-((2R,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-4-hydroxy-2-methylnobutyl acetate (267**)**



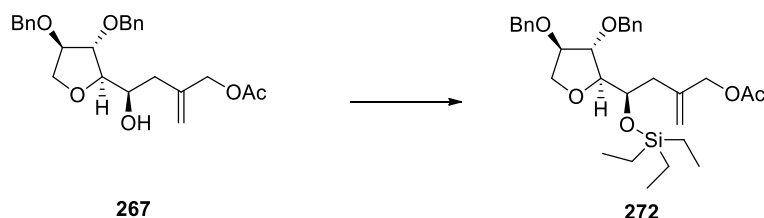
To a stirred solution of alcohol **211** (1.00 g, 3.18 mmol) in anhydrous CH₂Cl₂ (15 mL) was added DMSO (0.85 mL, 12.0 mmol), *N,N*-diisopropylethylamine (1.75 mL, 10.0 mmol), SO₃·Py (1.65 g, 10.4 mmol) at 0 °C respectively. The reaction was stirred at 0 °C for 3 h before it was quenched with aq. sat. NaHCO₃/Na₂S₂O₃ solution (40 mL), diluted with diethyl ether (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were washed with aq. sat. CuSO₄ (2 × 50 mL) and brine (50 mL). The resulting organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude aldehyde **212** was obtained as a pale yellow oil and carried through to the next step without further purification.

To a stirred solution of crude aldehyde **212** (assumed 3.18 mmol) in anhydrous CH₃CN (15 mL) was added 2-((trimethylsilyl)methyl)allyl acetate **268** (1.60 g, 8.59 mmol) at 0 °C. To the mixture was then added TMSOTf (639 mg, 2.88 mmol) dropwise at −10 °C. The reaction was kept at −10 °C for 12 h before it was quenched with aq. sat. NaHCO₃ solution (40 mL), diluted with diethyl ether (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 30 mL)

and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 10:1 to 7:1 to 5:1] yielded alcohol **267** (905 mg, 2.12 mmol, 67% over two steps, *d.r.* > 20:1) as a colourless oil.

$[\alpha]_D^{20} +11.3$ ($c = 0.5$, CHCl₃); **¹H NMR** δ_H (400 MHz, CDCl₃): 7.33–7.17 (10H, m, ArH), 5.09 (1H, d, $J = 1.2$ Hz, C=CH_AH_B), 5.00 (1H, s, C=CH_AH_B), 4.49 (4H, s, CH₂CHCHOCH₂Ph + C=CCH₂OAc), 4.45 (2H, d, $J = 2.4$ Hz, CH₂CHOCH₂Ph), 4.11 (1H, d, $J = 3.2$ Hz, CH₂CHCHOBn), 4.01–3.95 (2H, m, CH₂CHOBn + CH_AH_BCHOBn), 3.90 (1H, dtd, $J = 9.1, 4.4, 2.3$ Hz, R₂CHOH), 3.82–3.77 (1H, m, CH_AH_BCHOBn), 3.73 (1H, dd, $J = 4.4, 3.2$ Hz, BnOCHCHCHOH), 2.53 (1H, d, $J = 2.3$ Hz, R₂CHOH), 2.31 (1H, dd, $J = 14.7, 3.9$ Hz, CH_AH_BC=CH₂), 2.06 (1H, dd, $J = 14.7, 9.1$ Hz, CH_AH_BC=CH₂), 2.00 (3H, s, CH₃C=O); **¹³C NMR** δ_C (101 MHz, CDCl₃): 170.7, 140.5, 137.5, 129.0, 128.6, 128.0, 115.2, 87.2, 82.7, 82.6, 72.1, 71.6, 71.2, 69.1, 66.9, 37.5, 21.0; **IR** $\nu_{\max}$ (thin film)/cm⁻¹ 3469 br./s, 2922w, 2868w, 1738s, 1454w, 1372w, 1233s, 1074s, 739s, 699s; **m/z** (ESI⁺) C₂₅H₃₀O₆ predicted 449.1935 (M+Na⁺), found 449.1937 ($\Delta = +0.6$ ppm).

(R)-4-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-methylene-4-((triethylsilyl)oxy)butyl acetate (272)

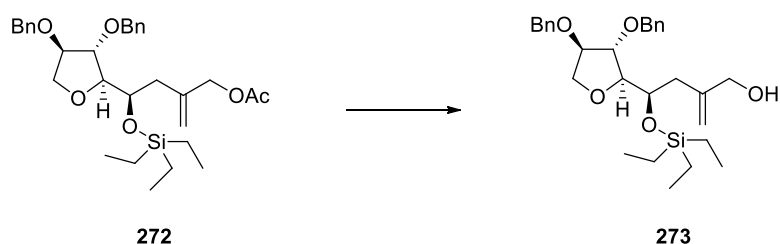


To a stirred solution of alcohol **267** (1.920 g, 4.50 mmol) in anhydrous CH_2Cl_2 (20 mL) was added imidazole (804 mg, 11.8 mmol) and TESCl (1.42 g, 9.42 mmol) at r.t. The reaction was kept at r.t. for 5 h before it was concentrated onto silica *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 15:1] yielded alkene **272** (2.431 g, 4.50 mmol, 100%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} -7.7$ ($c = 0.4$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 7.34–7.17 (10H, m, ArH), 5.05 (1H, d, $J = 1.5$ Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.97 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.56–4.36 (6H, m, $\text{CH}_2\text{CHCHOCH}_2\text{Ph} + \text{C}=\text{CCH}_2\text{OAc} + \text{CH}_2\text{CHOCH}_2\text{Ph}$), 4.11–4.08 (1H, m, CH_2CHOBN), 4.03–3.99 (1H, m, $\text{CH}_2\text{CHCHOBN}$), 3.95 (1H, q, $J = 5.6$ Hz, R_2CHOTES), 3.90 (1H, dd, $J = 9.9, 2.0$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN}$), 3.82 (1H, dd, $J = 9.9, 4.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN}$), 3.70 (1H, dd, $J = 5.0, 4.3$ Hz, BnOCHCHCHOTES), 2.26 (2H, d, $J = 5.6$ Hz, $\text{CH}_2\text{C}=\text{CH}_2$), 1.99 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 0.94–0.82 (9H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.59–0.47 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 170.6, 140.2, 138.0, 128.7, 128.4, 127.7, 115.6, 85.7, 83.9, 83.7, 71.7, 71.4, 71.3, 70.7, 67.4, 37.8, 20.9, 7.0, 5.1; **IR** ν_{max} (thin film)/ cm^{-1} 2953w, 2877w, 2361w, 1742s, 1456w, 1371w, 1231s, 1082s, 1024w, 737s, 699w; **m/z** (ESI^+) $\text{C}_{31}\text{H}_{44}\text{O}_6\text{Si}$ predicted

563.2799 ($M+Na^+$), found 563.2793 ($\Delta = -1.1$ ppm).

(R)-4-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-methylene-4-((triethylsilyl)oxy)butan-1-ol (273)

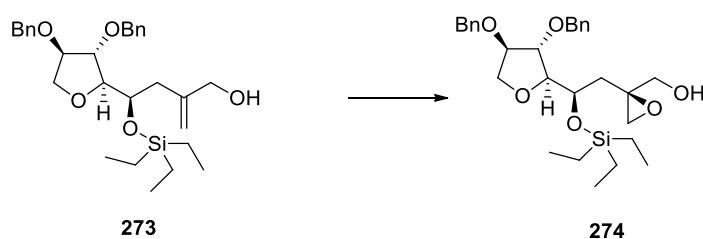


To a stirred solution of acetate **272** (33.0 mg, 0.061 mmol) in $CHCl_3/MeOH$ (1.0 mL, 6:1) was added K_2CO_3 (24 mg, 0.17 mmol) at r.t. and stirred for 44 h before it was concentrated onto silica *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 6:1 to 3:1] yielded alcohol **273** (27.3 mg, 0.055 mmol, 90%) as a colourless oil.

$[\alpha]_D^{20} -9.1$ ($c = 0.5$, $CHCl_3$); 1H NMR δ_H (400 MHz, $CDCl_3$): 7.34–7.19 (10H, m, ArH), 5.05 (1H, d, $J = 1.5$ Hz, $C=CH_AH_B$), 4.92 (1H, s, $C=CH_AH_B$), 4.56–4.38 (4H, m, $CH_2CHCHOCH_2Ph + CH_2CHOCH_2Ph$), 4.07 (1H, d, $J = 3.2$ Hz, CH_2CHOBN), 4.02–3.98 (1H, m, $CH_2CHCHOBN$), 3.96 (2H, d, $J = 5.1$ Hz, $C=CCH_2OH$), 3.94–3.89 (2H, m, $R_2CHOTES + CH_AH_BCHOBN$), 3.86–3.81 (1H, m, CH_AH_BCHOBN), 3.77 (1H, dd, $J = 6.4, 3.4$ Hz, $BNCHCHCHOTES$), 2.55 (1H, t, $J = 6.0$ Hz, $C=CCH_2OH$), 2.38 (1H, dd, $J = 14.3, 5.1$ Hz, $CHCH_AH_BC=C$), 2.25 (1H, dd, $J = 14.3, 5.4$ Hz, $CHCH_AH_BC=C$), 0.90–0.82 (9H, m, $Si(CH_2CH_3)_3$), 0.57–0.49 (6H, m, $Si(CH_2CH_3)_3$); ^{13}C NMR δ_C (101 MHz, $CDCl_3$): 145.0, 137.9, 128.9, 128.7, 128.4, 127.8, 127.7,

114.4, 85.7, 84.0, 83.4, 71.6, 71.4, 71.3, 66.9, 38.0, 6.9, 5.1; **IR** $\nu_{\max}$ (thin film)/ cm^{-1}
3454 br./s, 2953s, 2876w, 1456w, 1240w, 1080s, 1014w, 736s, 698w; **m/z** (ESI^+)
 $\text{C}_{29}\text{H}_{42}\text{O}_5\text{Si}$ predicted 521.2694 ($\text{M}+\text{Na}^+$), found 521.2692 ($\Delta = -0.3$ ppm).

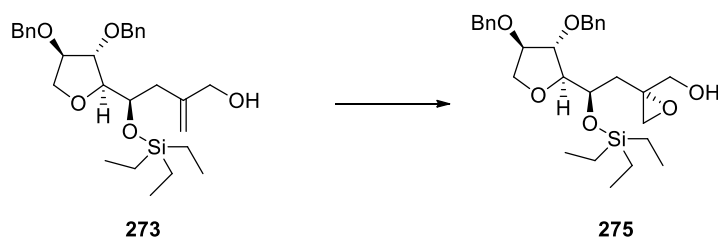
((S)-2-((R)-2-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-((triethylsilyl)oxy)ethyl)oxiran-2-yl)methanol (274)



To a stirred solution of L-(+)-diisopropyl tartrate (126 mg, 0.54 mmol) and 4Å molecular sieves (100 mg) in anhydrous CH_2Cl_2 (8 mL) was added $\text{Ti}(\text{Ot-Bu})_4$ (123 mg, 0.43 mmol) at r.t. and stirred for 30 min. The solution was cooled to -30 °C, then alcohol **273** (315 mg, 0.632 mmol) and anhydrous TBHP solution (0.55 mL, 5.5 M in hexanes, 3.0 mmol, avoid metal needles!) were added. The reaction was stirred at -30 °C for 42 h before it was quenched with aq. sat. Rochelle's salt solution (20 mL), diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×20 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 5:1 to 3:1] yielded epoxide **274** (275 mg, 0.534 mmol, 84% yield, 81% *d.e.* by ^1H NMR) as a colourless oil.

$[\alpha]_D^{20} +11.3$ ($c = 0.4$, CHCl_3); $^1\text{H NMR}$ δ_{H} (500 MHz, Benzene- d_6): 7.31–7.14 (10H, m, ArH), 4.52–4.44 (4H, m, $\text{CH}_2\text{CHCHOCH}_2\text{Ph} + \text{CH}_2\text{CHOCH}_2\text{Ph}$), 4.24–4.13 (3H, m, $\text{CH}_2\text{CHOBN} + \text{CH}_2\text{OH}$), 4.05 (1H, dd, $J = 6.2, 3.6$ Hz, $\text{CH}_2\text{CHCHOBN}$), 3.91–3.85 (2H, m, $\text{CH}_A\text{H}_B\text{CHOBN} + \text{BNOCCHCHOTES}$), 3.75 (1H, dd, $J = 9.8, 4.1$ Hz, $\text{CH}_A\text{H}_B\text{CHOBN}$), 3.68 (1H, t, $J = 4.9$ Hz, R_2CHOTES), 2.81 (1H, d, $J = 4.8$ Hz, epoxide- CH_AH_B), 2.70 (1H, d, $J = 4.8$ Hz, epoxide- CH_AH_B), 2.28–2.18 (2H, m, $\text{CH}_2\text{OH} + \text{TESOCHCH}_A\text{H}_B$), 1.92 (1H, dd, $J = 14.7, 5.8$ Hz, $\text{TESOCHCH}_A\text{H}_B$), 1.01–0.95 (9H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.68–0.61 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); $^{13}\text{C NMR}$ δ_{C} (126 MHz, Benzene- d_6): 138.9, 138.8, 86.9, 84.8, 84.2, 72.1, 71.8, 71.7, 70.3, 65.5, 58.0, 51.4, 37.9, 7.6, 5.8; $\text{IR } \nu_{\text{max}}$ (thin film)/ cm^{-1} 3412 br./s, 2981s, 2888w, 1457w, 1381s, 1252w, 1149w, 1089s, 954w, 815w, 699w; m/z (ESI^+) $\text{C}_{29}\text{H}_{42}\text{O}_6\text{Si}$ predicted 537.2648 ($\text{M} + \text{Na}^+$), found 537.2652 ($\Delta = +0.8$ ppm).

((R)-2-((R)-2-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-((triethylsilyl)oxy)ethyl)oxiran-2-yl)methanol (275)

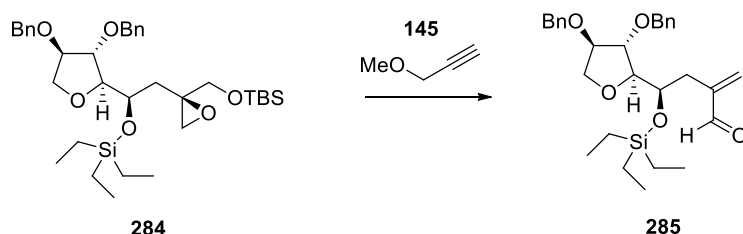


To a stirred solution of D-(–)-diisopropyl tartrate (5.0 mg, 0.021 mmol) and 4Å molecular sieves (5 mg) in anhydrous CH_2Cl_2 (1.0 mL) was added $\text{Ti}(\text{Ot-Bu})_4$ (4.8 mg,

0.017 mmol) at r.t. and stirred for 30 min. The solution was cooled to $-30\text{ }^{\circ}\text{C}$, then alcohol **273** (48.0 mg, 0.096 mmol) and anhydrous TBHP solution (66 μL , 5.5 M in hexane, 0.36 mmol, avoid metal needles!) were added. The reaction was stirred at $-30\text{ }^{\circ}\text{C}$ for 42 h before it was quenched with aq. sat. Rochelle's salt solution (20 mL), diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether ($3 \times 20\text{ mL}$) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 5:1 to 3:1] yielded epoxide **275** (10.3 mg, 0.020 mmol, 21% yield, 47% *d.e.* by ^1H NMR) as a colourless oil.

$[\alpha]_{\text{D}}^{20} -2.5$ ($c = 0.2$, CHCl_3); ^1H NMR δ_{H} (500 MHz, Benzene- d_6): 7.31–7.05 (10H, m, ArH), 4.51–4.42 (4H, m, $\text{CH}_2\text{CHCHOCH}_2\text{Ph} + \text{CH}_2\text{CHOCH}_2\text{Ph}$), 4.28 (1H, d, $J = 3.8\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$), 4.24–4.11 (3H, m, $\text{CH}_2\text{CHOBN} + \text{CH}_\text{A}\text{H}_\text{B}\text{OH} + \text{CH}_2\text{CHCHOBN}$), 3.96 (1H, dd, $J = 5.2, 4.1\text{ Hz}$, $\text{CH}_2\text{CHCHOBN}$), 3.91–3.83 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN} + \text{BNCHOCHCHOTES}$), 3.78–3.61 (1H, m, 4.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBN}$), 3.55 (1H, dd, $J = 12.2, 7.6\text{ Hz}$, R_2CHOTES), 2.62 (1H, d, $J = 5.0\text{ Hz}$, epoxide- $\text{CH}_\text{A}\text{H}_\text{B}$), 2.57 (1H, d, $J = 5.0\text{ Hz}$, epoxide- $\text{CH}_\text{A}\text{H}_\text{B}$), 2.32–2.14 (2H, m, $\text{CH}_2\text{OH} + \text{TESOCHCH}_\text{A}\text{H}_\text{B}$), 2.04–1.96 (1H, m, $\text{TESOCHCH}_\text{A}\text{H}_\text{B}$), 1.05–0.95 (9H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.72–0.65 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR δ_{C} (125 MHz, Benzene- d_6): 138.9, 138.8, 87.6, 84.6, 84.1, 72.2, 71.8, 71.7, 70.4, 65.2, 58.4, 51.5, 38.7, 7.6, 5.8; IR ν_{max} (thin film)/ cm^{-1} 3413 br./s, 2981s, 2889w, 1457w, 1381s, 1252w, 1149w, 1089s, 815w, 699w; m/z (ESI^+) $\text{C}_{29}\text{H}_{42}\text{O}_6\text{Si}$ predicted 537.2648 ($\text{M} + \text{Na}^+$), found 537.2650 ($\Delta = +0.4\text{ ppm}$).

(R)-4-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-methylene-4-((triethylsilyl)oxy)butanal (285)

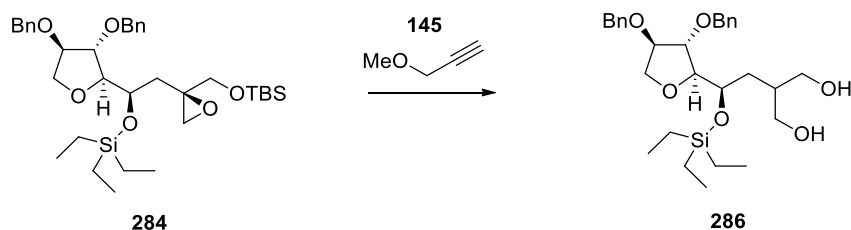


To a stirred solution of alkyne **145** (10.2 mg, 0.15 mmol) in anhydrous THF (1.0 mL) and anhydrous 4Å molecular sieves (10 mg) was added *n*-BuLi (58 µL, 2.5 M in hexanes, 0.15 mmol) at -78°C . The reaction was stirred at -78°C for 15 min, and then warmed to 0°C and stirred for a further 15 min. To the solution of deprotonated alkyne was added epoxide **284** (18.2 mg, 0.029 mmol) and $\text{BF}_3\cdot\text{OEt}_2$ (20.5 mg, 0.15 mmol) slowly at -78°C . After 44 h, the reaction was quenched with aq. sat. NaHCO_3 solution (10 mL), diluted with diethyl ether (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×10 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 20:1 to 15:1] yielded product **285** (3.7 mg, 0.0074 mmol, 26%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} +4.1$ ($c = 0.3$, CHCl_3); $^1\text{H NMR}$ δ_{H} (500 MHz, CDCl_3): 9.53 (1H, s, RCHO), 7.42–7.22 (10H, m, ArH), 6.35 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 6.06 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.64–4.56 (2H, m, $\text{CH}_2\text{CHCHOCH}_2\text{Ph}$), 4.56–4.50 (2H, m, $\text{CH}_2\text{CHOCH}_2\text{Ph}$), 4.23–4.17 (1H, m, $\text{CH}_2\text{CHCHOBn}$), 4.11–4.05 (2H, m, $\text{CH}_2\text{CHOBn} + \text{CHOTES}$), 3.98 (1H, dd, $J = 10.1, 2.1$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBn}$), 3.90 (1H, dd, $J = 10.1, 4.8$ Hz,

CH_AH_BCHOBN), 2.59 (1H, dd, *J* = 14.0, 5.1 Hz, CH_AH_BC=CH₂), 2.44 (1H, dd, *J* = 14.0, 6.9 Hz, CH_AH_BC=CH₂), 0.98–0.84 (9H, m, Si(CH₂CH₃)₃), 0.65–0.54 (6H, m, Si(CH₂CH₃)₃); ¹³C NMR δ_C (125 MHz, CDCl₃): 194.5, 146.5, 137.9, 136.9, 128.4, 127.8, 127.7, 86.1, 84.0, 83.5, 71.9, 71.4, 71.2, 69.9, 32.5, 6.9, 5.1; IR ν_{max} (thin film)/cm⁻¹ 3431s, 2927s, 1719s, 1454w, 1271w, 1097s, 1028w, 740w, 699w; *m/z* (ESI⁺) C₂₉H₄₀O₅Si predicted 519.2543 (M+Na⁺), found 519.2540 (Δ = −0.6 ppm).

2-((*R*)-2-((2*S*,3*S*,4*R*)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-((triethylsilyl)oxy)ethyl)propane-1,3-diol (286**)**

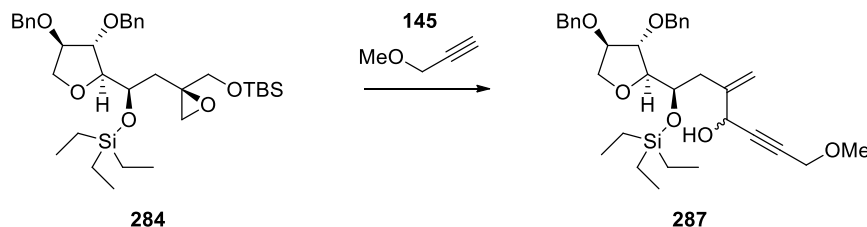


To a stirred solution of alkyne **145** (10.2 mg, 0.15 mmol) in anhydrous THF (1.0 mL) was added *n*-BuLi (58 μL, 2.5 M in hexanes, 0.15 mmol) at −78 °C. The reaction was kept at −78 °C for 15 min, and then moved to 0 °C to stir for a further 15 min. In a separate reaction vessel, to a stirred solution of epoxide **284** (24.0 mg, 0.047 mmol) in THF (0.5 mL) was added NaH (3.7 mg, 60 wt% in mineral oil, 0.26 mmol) at 0 °C. The reaction was stirred for a further 15 min at 0 °C, then the solution of deprotonated alkyne was added at −78 °C. To the mixture was then added BF₃·OEt₂ (20.5 mg, 0.15 mmol) slowly at −78 °C. After 16 h, the reaction was quenched with aq. sat. NaHCO₃

solution (10 mL), diluted with diethyl ether (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×10 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 2:1 to 1:2] yielded diol **286** (7.0 mg, 0.014 mmol, 29%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} -4.4$ ($c = 0.1$, CHCl_3); $^1\text{H NMR}$ δ_{H} (500 MHz, CDCl_3): 7.41–7.26 (10H, m, ArH), 4.62–4.45 (4H, m, $\text{CH}_2\text{CHOCH}_2\text{Ph} + \text{CH}_2\text{CHCHOCH}_2\text{Ph}$), 4.08 (2H, dd, $J = 3.9, 1.3$ Hz, $\text{CH}_2\text{CHOBn} + \text{CH}_2\text{CHCHOBn}$), 4.04–3.94 (2H, m, CHOTES + CHCHOTES), 3.94–3.89 (1H, m, $\text{CH}_A\text{H}_B\text{CHOBn}$), 3.87 (1H, dd, $J = 6.5, 3.4$ Hz, $\text{CH}_A\text{H}_B\text{CHOBn}$), 3.74–3.60 (4H, m, $2 \times \text{CHCH}_2\text{OH}$), 2.75 (1H, br. s, OH), 2.21 (1H, br. s, OH), 2.04–1.96 (1H, m, CHCH_2OH), 1.69 (1H, dt, $J = 14.8, 5.3$ Hz, $\text{TESOCHCH}_A\text{H}_B$), 1.55 (1H, ddd, $J = 14.8, 8.0, 4.7$ Hz, $\text{TESOCHCH}_A\text{H}_B$), 0.99–0.90 (9H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.66–0.57 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); $^{13}\text{C NMR}$ δ_{C} (125 MHz, CDCl_3): 137.9, 137.8, 128.4, 127.8, 127.6, 86.5, 84.3, 83.0, 71.6, 71.4, 71.2, 70.4, 66.4, 65.8, 38.9, 32.5, 6.9, 5.1; **IR** ν_{max} (thin film)/ cm^{-1} 3384br./s, 2981s, 2919w, 1719s, 1456w, 1381s, 1265s, 1075s, 955w, 800w, 737w, 627w; **m/z** (ESI^+) $\text{C}_{29}\text{H}_{44}\text{O}_6\text{Si}$ predicted 539.2805 ($\text{M}+\text{Na}^+$), found 519.2812 ($\Delta = +1.4$ ppm).

**(7*R*)-7-((2*S*,3*S*,4*R*)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-1-methoxy-5-methyl
ene-7-((triethylsilyl)oxy)hept-2-yn-4-ol (287)**

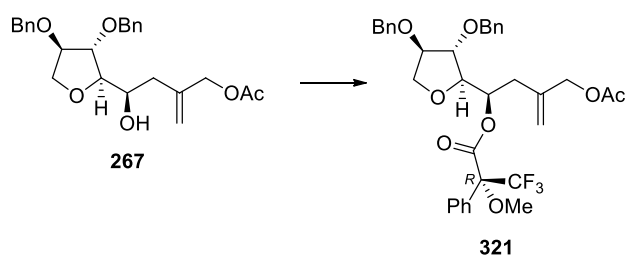


To a stirred solution of alkyne **145** (10.2 mg, 0.15 mmol) in anhydrous THF (1.0 mL) was added *n*-BuLi (58 μ L, 2.5 M in hexanes, 0.15 mmol) at $-78\text{ }^{\circ}\text{C}$. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min, and then warmed to $0\text{ }^{\circ}\text{C}$ and stirred for a further 15 min. In a separate reaction vessel, to a stirred solution of epoxide **284** (24.0 mg, 0.047 mmol) in THF (0.5 mL) was added NaH (3.7 mg, 60% in mineral oil, 0.26 mmol) at $0\text{ }^{\circ}\text{C}$. The reaction was stirred for a further 15 min at $0\text{ }^{\circ}\text{C}$ before the solution of deprotonated alkyne was added at $-78\text{ }^{\circ}\text{C}$. To the mixture was then added $\text{BF}_3\cdot\text{OEt}_2$ (20.5 mg, 0.15 mmol) slowly at $-78\text{ }^{\circ}\text{C}$. After 16 h, the reaction was quenched with aq. sat. NaHCO_3 solution (10 mL), diluted with diethyl ether (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether ($3 \times 10\text{ mL}$) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 2:1] yielded allylic alcohol **287** (3.1 mg, 0.0055 mmol, 12%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} +9.9$ ($c = 0.2$, CHCl_3); $^1\text{H NMR}$ δ_{H} (500 MHz, CDCl_3 , diastereoisomer is marked as * if it is identifiable): 7.40–7.27 (10H, m, ArH), 5.44 (5.36*, 1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.16 (5.13*, 1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.90–4.83 (1H, m, $\text{C}=\text{CCHOH}$),

4.62–4.47 (4H, m, CH₂CHOCH₂Ph + CH₂CHCHOCH₂Ph), 4.17–4.10 (2H, m, MeOCH₂), 4.10–4.04 (2H, m, CH₂CHOBN + CH₂CHCHOBN), 4.04–3.96 (2H, m, CHOTES + CHCHOTES), 3.94–3.85 (2H, m, CH₂CHOBN), 3.38 (3.37*, 3H, s, OCH₃), 2.71–2.56 (2H, m, CH_AH_BC=CH₂), 2.39 (1H, dd, *J* = 14.6, 5.3 Hz, CH_AH_BC=CH₂), 0.99–0.86 (9H, m, Si(CH₂CH₃)₃), 0.69–0.57 (6H, m, Si(CH₂CH₃)₃); ¹³C NMR δ_C (125 MHz, CDCl₃): 143.4, 137.8, 137.7, 128.4, 127.6, 118.3, 116.8, 86.7*, 86.1, 85.5, 85.0*, 84.1, 83.9*, 83.2, 81.4, 71.5, 71.2, 66.5, 60.0, 57.5, 36.6, 6.9, 5.0; IR ν_{max} (thin film)/cm⁻¹ 3404w, 2925s, 2859w, 2358w, 2338w, 1717s, 1455w, 1265s, 1100s, 739w, 700w; *m/z* (ESI⁺) C₃₃H₄₆O₆Si predicted 589.2961 (M+Na⁺), found 589.2953 (Δ = −1.4 ppm).

(*R*)-3-(Acetoxymethyl)-1-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)tetrahydrofuran-2-yl)but-3-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (321)

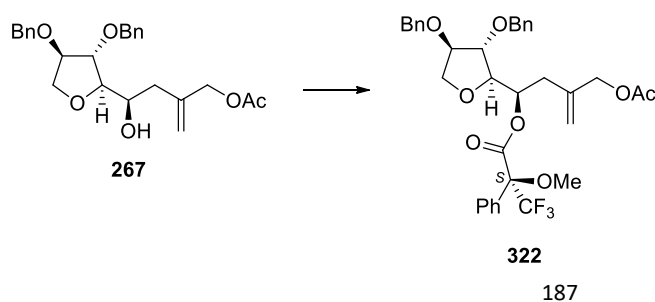


To a stirred solution of alcohol **267** (20.0 mg, 0.047 mmol) in anhydrous CH₂Cl₂ (1.0 mL) was added dicyclohexylcarbodiimide (19.3 mg, 0.094 mmol), DMAP (2 mg, 30% mol) and (*R*)-Mosher's acid (22.0 mg, 0.094 mmol) at r.t. and stirred 12 h. The mixture was directly concentrated onto silica *in vacuo*. Flash column chromatography

[SiO₂, Petrol/EtOAc, 8:1 to 7:1] yielded ester **321** (12.9 mg, 0.020 mmol, 43%) as a colourless oil.

[α]_D²⁰ +29.1 (*c* = 0.3, CHCl₃); ¹H NMR δ _H (400 MHz, CDCl₃): 7.62–7.52 (2H, m, ArH), 7.42–7.22 (13H, m, ArH), 5.57 (1H, ddd, *J* = 9.2, 5.0, 3.7 Hz, R₂CHOC=O), 5.00 (1H, s, C=CH_AH_B), 4.86 (1H, s, C=CH_AH_B), 4.53–4.41 (6H, m, CH₂CHOCH₂Ph + CH₂CHCHOCH₂Ph + C=CCH₂OAc), 4.10–4.05 (2H, m, CH₂CHCHOBn + CH₂CHOBn), 4.04–3.99 (1H, m, CH_AH_BCHOBn), 3.95–3.89 (2H, m, CH_AH_BCHOBn + BnOCHCHCHOCHOC=O), 3.51 (3H, d, *J* = 1.0 Hz, OCH₃), 2.52 (1H, dd, *J* = 15.0, 3.7 Hz, ROCHCH_AH_BC=CH₂), 2.33 (1H, dd, *J* = 15.0, 9.2 Hz, ROCHCH_AH_BC=CH₂), 2.04 (3H, s, CH₃C=O); ¹³C NMR δ _C (101 MHz, CDCl₃): 166.1, 138.4, 137.6, 137.4, 129.5, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 117.0, 83.9, 83.8, 82.8, 77.4, 73.4, 72.0, 71.9, 71.3, 66.6, 55.5, 34.4, 29.7, 20.9; IR ν _{max} (thin film)/cm⁻¹ 2924w, 2854w, 1745s, 1453w, 1370w, 1237s, 1169s, 1107s, 1021s, 736w, 699s, 608w; *m/z* (ESI⁺) C₃₅H₃₇O₈F₃ predicted 665.2333 (M+Na⁺), found 665.2326 (Δ = -1.0 ppm).

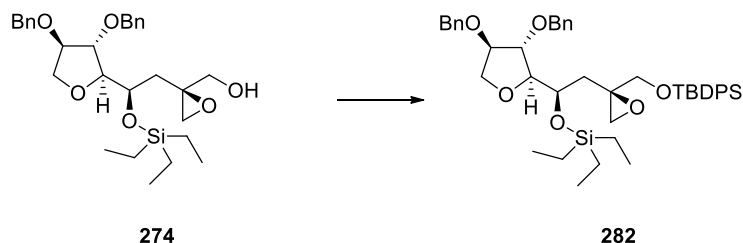
(R)-3-(Acetoxymethyl)-1-((2R,3S,4R)-3,4-bis(benzyloxy)tetrahydrofuran-2-yl)but-3-en-1-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (322)



To a stirred solution of alcohol **267** (20.0 mg, 0.047 mmol) in anhydrous CH₂Cl₂ (1.0 mL) was added dicyclohexylcarbodiimide (19.3 mg, 0.094 mmol), DMAP (2 mg, 30% mol) and (*R*)-Mosher's acid (22.0 mg, 0.094 mmol) at r.t. and stirred 12 h. The mixture was directly concentrated onto silica *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 8:1 to 7:1] yielded ester **322** (17.0 mg, 0.026 mmol, 56%) as a colourless oil.

[α]_D²⁰ -9.9 (*c* = 0.4, CHCl₃); ¹H NMR δ _H (400 MHz, CDCl₃): 7.62–7.51 (2H, m, ArH), 7.41–7.21 (13H, m, ArH), 5.61–5.51 (1H, m, R₂CHOC=O), 5.13 (1H, s, C=CH_AH_B), 5.00 (1H, s, C=CH_AH_B), 4.62 – 4.51 (2H, m, C=CCH₂OAc), 4.51–4.42 (2H, m, CH₂CHOCH₂Ph), 4.37–4.26 (2H, m, CH₂CHCHOCH₂Ph), 4.04–4.01 (1H, m, CH₂CHOBN), 3.94–3.86 (4H, m, CH₂CHCHOBN + CH₂CHOBN + BNCHCHCHOCH=O), 3.50 (3H, s, OCH₃), 2.64 (1H, dd, *J* = 15.3, 3.1 Hz, ROCHCH_AH_BC=CH₂), 2.40 (1H, dd, *J* = 15.3, 9.2 Hz, ROCHCH_AH_BC=CH₂), 2.04 (3H, s, CH₃C=O); ¹³C NMR δ _C (101 MHz, CDCl₃): 170.6, 166.0, 139.0, 137.6, 131.9, 129.6, 128.5, 128.4, 127.9, 127.8, 127.7, 116.7, 83.8, 83.6, 82.6, 77.4, 73.5, 71.8, 71.7, 71.3, 66.6, 55.5, 34.9, 20.8; IR ν _{max} (thin film)/cm⁻¹ 2918w, 1745s, 1453w, 1239s, 1170s, 1108s, 1020s, 736w, 699s, 611w; *m/z* (ESI⁺) C₃₅H₃₇O₈F₃ predicted 665.2333 (M+Na⁺), found 665.2319 (Δ = -2.1 ppm).

((R)-1-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-((R)-2-(((tert-butyl diphenylsilyl)oxy)methyl)oxiran-2-yl)ethoxy)triethylsilane (282)

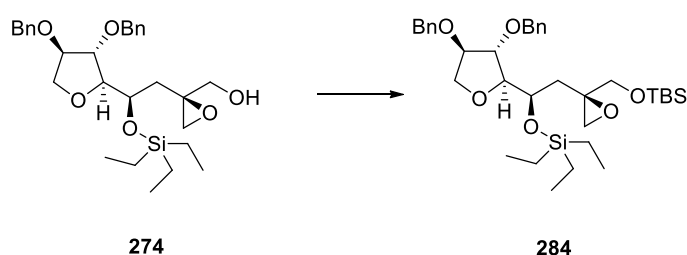


To a stirred solution of alcohol **274** (69.5 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (2 mL) was added imidazole (19 mg, 0.28 mmol) and TBDPSCl (62 mg, 0.23 mmol) at r.t. The reaction was kept at r.t. for 12 h before it was concentrated onto silica *in vacuo*. Flash column chromatography [SiO_2 , Petrol/EtOAc, 18:1] yielded epoxide **282** (76.1 mg, 0.101 mmol, 75%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} +9.3$ ($c = 1.0$, CHCl_3); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 7.80–7.62 (10H, m, ArH), 7.49–7.23 (10H, m, ArH), 4.61–4.40 (4H, m, $\text{CH}_2\text{CHCHOCH}_2\text{Ph} + \text{CH}_2\text{CHOCH}_2\text{Ph}$), 4.07 (2H, dd, $J = 4.4, 1.7$ Hz, CH_2OTBDPS), 4.04–3.98 (2H, m, $\text{CH}_2\text{CHOBn} + \text{CH}_2\text{CHCHOBn}$), 3.91–3.83 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBn} + \text{BnOCHCHCHOTES}$), 3.78–3.69 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOBn} + \text{R}_2\text{CHOTES}$), 2.82 (1H, d, $J = 5.1$ Hz, epoxide- $\text{CH}_\text{A}\text{H}_\text{B}$), 2.74 (1H, d, $J = 5.1$ Hz, epoxide- $\text{CH}_\text{A}\text{H}_\text{B}$), 2.21–2.13 (1H, m, $\text{TESOCHCH}_\text{A}\text{H}_\text{B}$), 1.70 (1H, dd, $J = 14.7, 7.6$ Hz, $\text{TESOCHCH}_\text{A}\text{H}_\text{B}$), 1.08 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.00–0.82 (9H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.64–0.48 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); $^{13}\text{C NMR}$ δ_{C} (101 MHz, CDCl_3): 137.9, 135.7, 135.6, 135.2, 134.8, 133.3, 129.7, 128.4, 127.8, 127.7, 127.6, 86.8, 84.1, 83.5, 77.4, 71.8, 71.4, 71.3, 69.0, 65.2, 58.1, 50.3, 36.1, 26.8, 19.3, 7.0, 5.1; **IR** ν_{max} (thin film)/ cm^{-1} 2981s, 2888w, 1469w, 1376s,

1266s, 1104s, 951w, 822w, 704w; **m/z** (ESI⁺) C₄₅H₆₀O₆Si₂ predicted 775.3826 (M+Na⁺), found 775.3820 ($\Delta = -0.8$ ppm).

((R)-1-((2S,3S,4R)-3,4-bis(Benzyloxy)tetrahydrofuran-2-yl)-2-((R)-2-((tert-butylidimethylsilyl)methyl)oxiran-2-yl)ethoxy)triethylsilane (284)

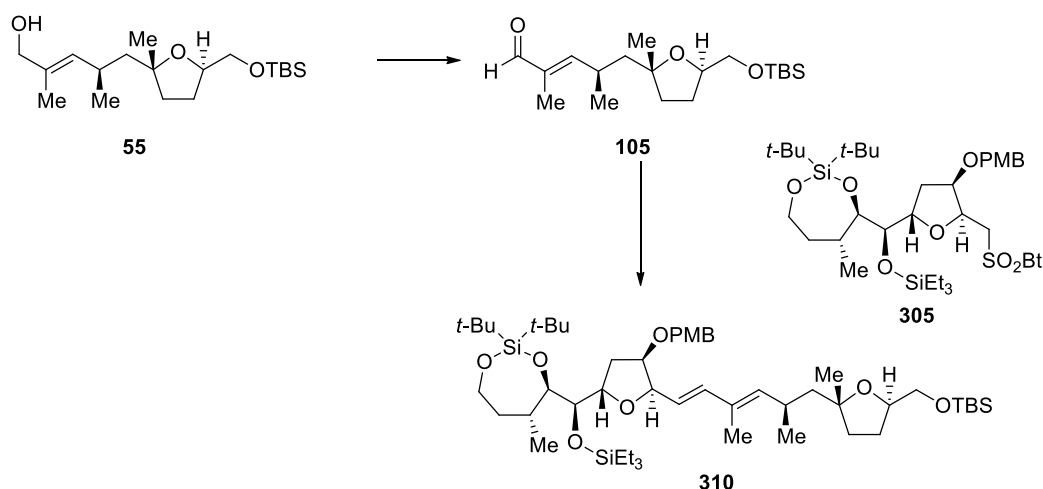


To a stirred solution of alcohol **274** (133 mg, 0.26 mmol) in anhydrous CH₂Cl₂ (5 mL) was added imidazole (72 mg, 1.06 mmol) and TBSCl (108 mg, 0.72 mmol) at r.t. The reaction was stirred at r.t. for 12 h, then quenched with aq. sat. NaHCO₃ solution (20 mL), diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography [SiO₂, Petrol/EtOAc, 20:1] yielded epoxide **284** (148 mg, 0.241 mmol, 91%) as a colourless oil.

[α]_D²⁰ -11.4 (*c* = 0.3, CHCl₃); **¹H NMR** δ_H (400 MHz, CDCl₃): 7.43–7.28 (10H, m, ArH), 4.62–4.44 (4H, m, CH₂CHCHOCH₂Ph + CH₂CHOCH₂Ph), 4.10–4.06 (2H, m, CH₂OTBS), 4.06–4.02 (1H, m, CH₂CHOBn), 3.98 (1H, d, *J* = 9.3 Hz,

CH₂CHCHOBn), 3.89 (1H, dd, *J* = 10.0, 4.5 Hz, BnOCHCHCHOTES), 3.84 (1H, d, *J* = 11.7 Hz, CH_AH_BCHOBn), 3.77 (1H, t, *J* = 4.5 Hz, R₂CHOTES), 3.66 (1H, d, *J* = 11.7 Hz, CH_AH_BCHOBn), 2.79–2.71 (2H, m, epoxide-CH₂), 2.21–2.11 (1H, m, TESPOCHCHAH_B), 1.65 (1H, dd, *J* = 14.7, 7.1 Hz, TESPOCHCHAH_B), 1.00–0.92 (9H, m, Si(CH₃)₃), 0.92–0.88 (9H, m, Si(CH₂CH₃)₃), 0.68–0.58 (6H, m, Si(CH₂CH₃)₃), 0.07 (3H, s, SiCH₃), 0.06 (3H, s, SiCH₃); ¹³C NMR δ_C (101 MHz, CDCl₃): 137.9, 128.4, 127.7, 127.6, 86.7, 84.1, 83.5, 77.4, 71.8, 71.4, 71.3, 69.1, 65.0, 58.0, 50.4, 35.9, 25.9, 18.4, 7.0, 5.2, –5.4; IR ν_{max} (thin film)/cm^{–1} 2953s, 2875w, 1723s, 1455w, 1262s, 1098s, 839s, 713w; *m/z* (ESI⁺) C₃₅H₅₆O₅Si₂ predicted 635.3564 (M+Na⁺), found 635.3572 (Δ = +1.3 ppm).

(4*R*,5*R*)-2,2-di-*tert*-Butyl-4-((*R*)-((2*S*,4*R*,5*R*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((triethylsilyl)oxy)methyl)-5-methyl-1,3,2-dioxasilepane (310)



To a solution of alcohol 55 (0.80 mg, 0.0024 mmol) in CH₂Cl₂ (1 mL) was added

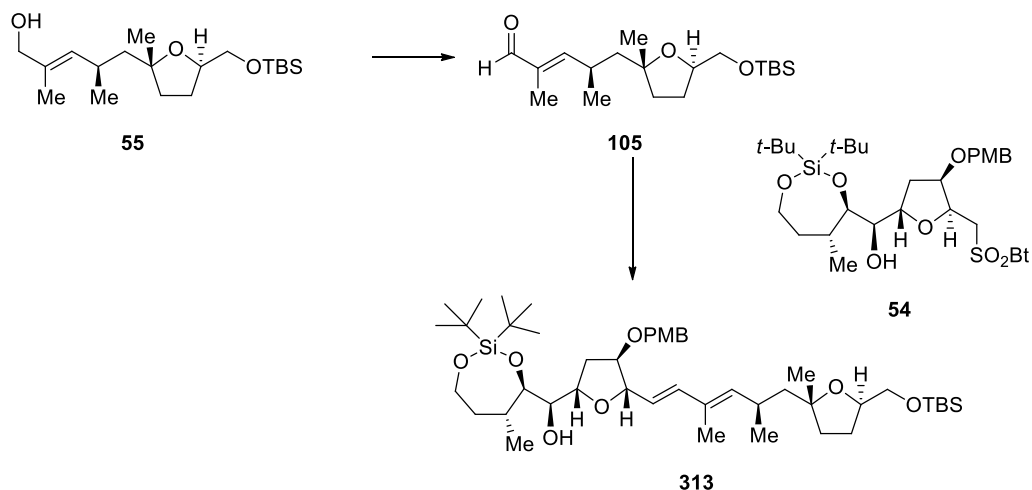
DMP (10 mg, 0.024 mmol) at r.t. The reaction was stirred for 2 h at r.t., and then quenched with aq. sat. $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ (5 mL), diluted with Et_2O (5 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Crude aldehyde **105** was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **105** (0.80 mg, 0.0024 mmol) and sulfone **305** (4.0 mg, 0.0050 mmol) in anhydrous THF (0.1 mL) was added LiHMDS (8.0 μL , 1.0 M in toluene, 0.0080 mmol) at -78°C . The reaction was kept at -78°C for 45 min before being warmed to 0°C and stirred for a further 15 min. The reaction was quenched with aq. sat. NaHCO_3 solution (10 mL), diluted with diethyl ether (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×10 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Preparative thin layer chromatography [SiO_2 , Cyclohexane/ EtOAc , 25:1] yielded alkene **310** (2.2 mg, 0.0024 mmol, 100% over two steps) as a colourless oil.

$[\alpha]_{\text{D}}^{20} -3.8$ ($c = 0.1$, CH_2Cl_2); $^1\text{H NMR}$ δ_{H} (300 MHz, CDCl_3): 7.25–7.17 (2H, m, ArH), 6.91–6.80 (2H, m, ArH), 6.25 (1H, d, $J = 15.7$ Hz, $\text{CH}=\text{CHC}(\text{CH}_3)=\text{CH}$), 5.78 (1H, dd, $J = 15.7, 7.5$ Hz, $\text{CH}=\text{CHC}(\text{CH}_3)=\text{CH}$), 5.30 (1H, d, $J = 9.4$ Hz, $\text{CH}=\text{CHC}(\text{CH}_3)=\text{CH}$), 4.58–4.38 (3H, m, $\text{PMB-CH}_2 + \text{TESOCHCHCH}_2\text{CHOPMB}$), 4.38–4.23 (1H, m, $\text{PMBOCHCHCH}=\text{CHR}$), 4.07–3.89 (4H, m, $\text{TBSOCH}_2\text{CH} +$

PMBOCH + (*t*-Bu)₂SiOCH₂), 3.81 (3H, s, OCH₃), 3.70–3.42 (4H, m, TBSOCH₂ + TESOCH + TESOCHCHOSi), 2.77–2.59 (C=CHCHCH₃), 2.27 (1H, dd, *J* = 13.0, 6.7 Hz, PMBOCHCH_AH_B), 2.17–1.95 (3H, m, 3 × THF-*H*), 1.90 (1H, dt, *J* = 11.5, 5.9 Hz, CH₃CHCHRO), 1.86–1.77 (3H, m, 1 × THF-H + (*t*-Bu)₂SiOCH₂CH₂), 1.77–1.59 (3H, m, PMBOCHCH_AH_B + CH₃CHCH₂-THF), 1.56 (3H, s, CH₃C=CH), 1.18 (3H, s, CH₂(CH₂R)CCH₃), 1.01 (18H, d, *J* = 5.7 Hz, 2 × (CH₃)₃CSiO₂), 0.97–0.86 (15H, m, TESOCHCH(O)CHCH₃ + C=CHCHCH₃ + Si(CH₂CH₃)₃), 0.90 (9H, s, SiC(CH₃)₃), 0.77–0.52 (6H, m, Si(CH₂CH₃)₃), 0.06 (6H, s, Si(CH₃)₂); ¹³C NMR δ_C (126 MHz, CDCl₃): 140.4, 135.4, 130.7, 130.6, 130.4, 129.0, 125.7, 113.7, 84.6, 83.4, 82.6, 81.8, 81.0, 80.5, 79.1, 78.8, 77.7, 70.9, 66.2, 55.3, 48.6, 42.1, 38.4, 37.6, 34.6, 29.7, 28.4, 26.6, 26.0, 22.7, 21.5, 18.4, 14.1, 12.5, 7.2, 5.5, –1.0, –5.3; IR ν_{max} (thin film)/cm^{–1} 2927s, 2956s, 1717w, 1466w, 1257w, 1169w, 1114s, 1015w, 827w, 776w, 734w, 644w, 628w; *m/z* (ESI⁺) C₅₂H₉₄O₈Si₃ predicted 953.6154 (M+Na⁺), found 953.6135 (Δ = –2.0 ppm).

(*R*)-((2*S*,4*R*,5*S*)-5-((*R*,1*E*,3*E*)-6-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-3,5-dimethylhexa-1,3-dien-1-yl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)((4*R*,5*R*)-2,2-di-*tert*-butyl-5-methyl-1,3,2-dioxasilepan-4-yl)methanol (**313**)



To a solution of alcohol **55** (0.80 mg, 0.0024 mmol) in CH₂Cl₂ (1 mL) was added DMP (10 mg, 0.024 mmol) at r.t. The reaction was stirred for 2 h at r.t., and then quenched with aq. sat. Na₂S₂O₃/NaHCO₃ (5 mL), diluted with Et₂O (5 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Crude aldehyde **105** was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **105** (0.79 mg, 0.0023 mmol) and sulfone **54** (4.0 mg, 0.0058 mmol) in anhydrous THF (0.1 mL) was added LiHMDS (11.6 μL, 1.0 M in toluene, 0.0116 mmol) at −78 °C. The reaction was kept at −78 °C for 45 min before being warmed to 0 °C and stirred for a further 15 min. The reaction was

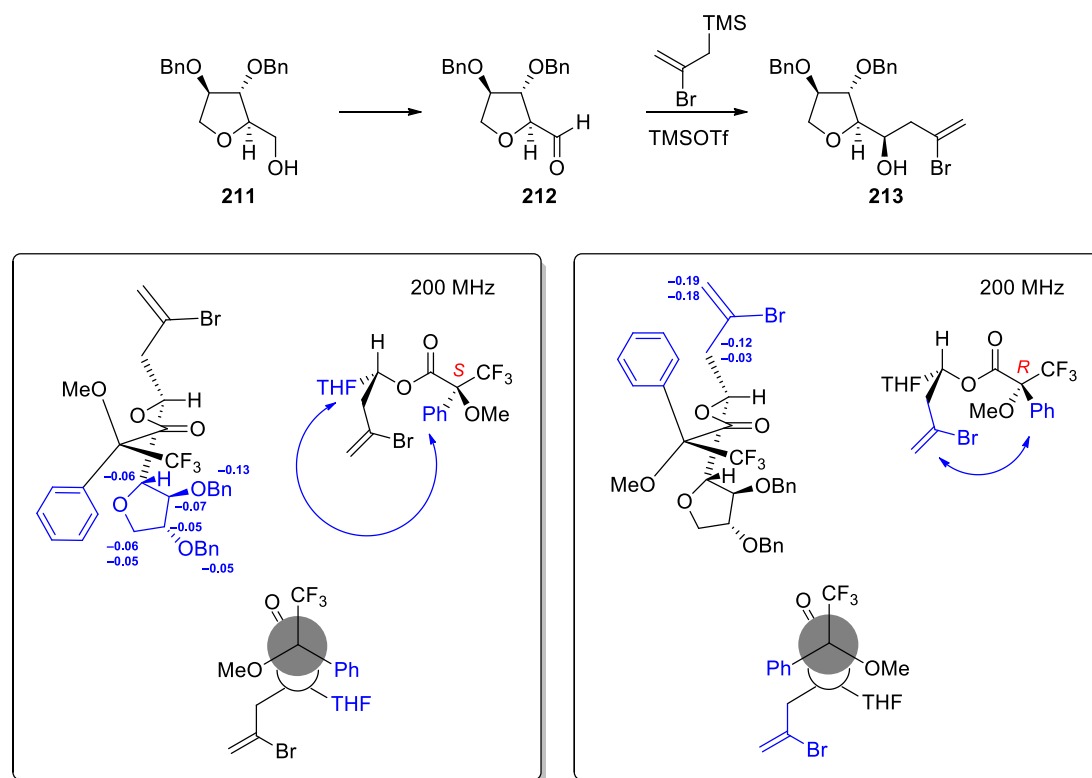
quenched with aq. sat. NaHCO_3 solution (10 mL), diluted with diethyl ether (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×10 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Preparative thin layer chromatography [SiO_2 , Cyclohexane/EtOAc, 25:1] yielded alkene **313** (1.5 mg, 0.0018 mmol, 79%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} -17.3$ ($c = 0.1$, CH_2Cl_2); $^1\text{H NMR}$ δ_{H} (400 MHz, CDCl_3): 7.22–7.14 (2H, m, ArH), 6.86–6.76 (2H, m, ArH), 6.24 (1H, d, $J = 15.7$ Hz, $\text{CH}=\text{CHC}(\text{CH}_3)=\text{CH}$), 5.52–5.38 (1H, m, $\text{CH}=\text{CHC}(\text{CH}_3)=\text{CH}$), 5.33–5.22 (1H, m, $\text{CH}=\text{CHC}(\text{CH}_3)=\text{CH}$), 4.49–4.31 (3H, m, PMB- CH_2 + PMBOCHCHCH=CHR), 4.24 (1H, dt, $J = 9.6, 6.6$ Hz, HOCHCHCH₂CHOPMB), 4.02–3.80 (4H, m, $(t\text{-Bu})_2\text{SiOCH}_2$ + PMBOCH + TBSOCH₂CH), 3.76 (3H, s, OCH₃), 3.64–3.53 (4H, m, TBSOCH₂ + HOCHCHOSi + HOCH), 2.62 (1H, br. s., $\text{C}=\text{CHCHCH}_3$), 2.41 (1H, ddd, $J = 13.1, 6.6, 1.3$ Hz, PMBOCHCH_AH_B), 2.07–1.80 (5H, m, $4 \times \text{THF-H} + \text{CH}_3\text{CHCHRO}$), 1.76–1.57 (5H, m, $(t\text{-Bu})_2\text{SiOCH}_2\text{CH}_2 + \text{PMBOCHCH}_A\text{H}_B + \text{CH}_3\text{CHCH}_2\text{-THF}$), 1.51 (3H, s, $\text{CH}_3\text{C}=\text{CH}$), 1.21 (3H, s, $\text{CH}_2(\text{CH}_2\text{R})\text{CCH}_3$), 1.01 (18H, d, $J = 5.7$ Hz, $2 \times (\text{CH}_3)_3\text{CSiO}_2$), 0.98 (6H, d, $J = 1.2$ Hz, HOCHCH(O)CHCH₃ + $\text{C}=\text{CHCHCH}_3$), 0.84 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.00 (6H, s, $\text{Si}(\text{CH}_3)_2$); **IR** ν_{max} (thin film)/ cm^{-1} 2930s, 2957s, 1718w, 1514w, 1464w, 1253s, 1106s, 828s, 742w, 648w, 616w; **m/z** (ESI^+) $\text{C}_{46}\text{H}_{80}\text{O}_8\text{Si}_2$ predicted 817.5470 ($\text{M}+\text{H}^+$), found 817.5483 ($\Delta = +1.6$ ppm).

Appendix 1: Mosher's Esters Data

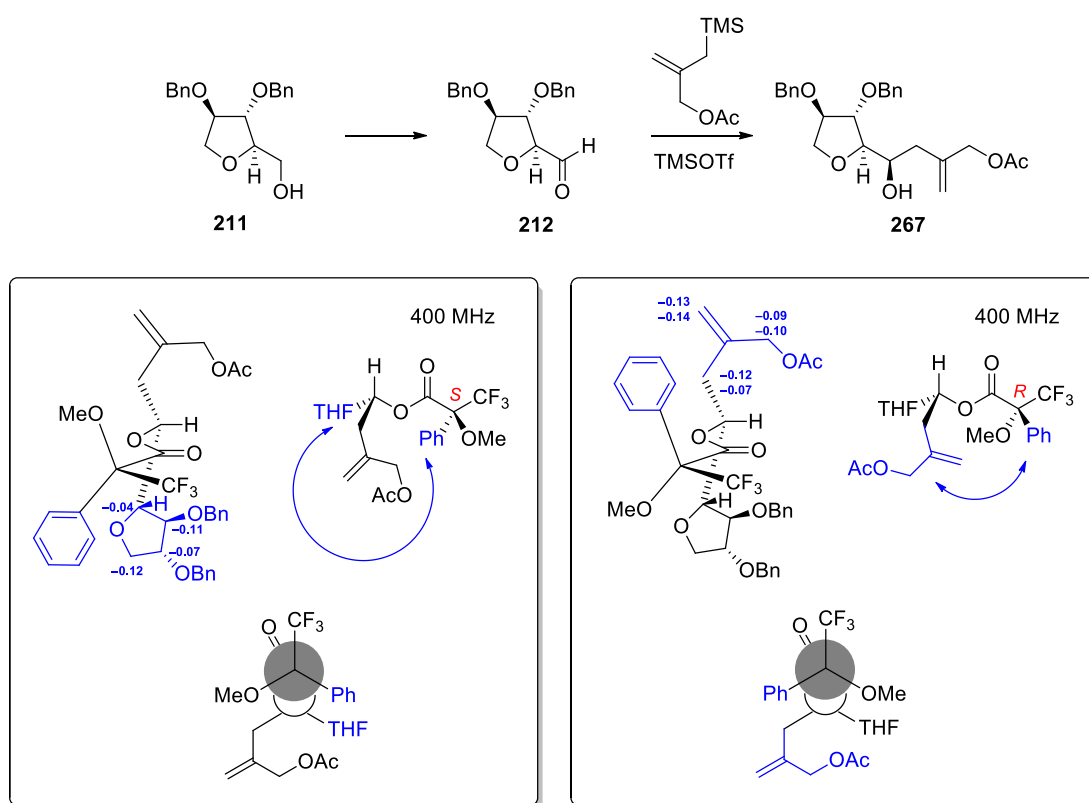
The configuration of the newly-generated stereogenic centre was determined by Mosher's ester analysis. The phenyl group in the ester has a magnetic shielding effect on protons above or below the plane of aryl ring, resulting in more upfield chemical shift for affected protons. The chemical shifts of the protons are assigned by COSY and HSQC to the nearest 0.01 ppm for multiplets around 4.10–3.80 ppm.

For vinyl bromide **213**, a substantial change in chemical shift can be observed when subjected to reaction with (*R*)-Mosher's acid or (*S*)-Mosher's acid chloride. The chemical shifts of the alkene protons move upfield by 0.18–0.19 ppm, and two allylic protons move upfield by 0.03 and 0.12 ppm respectively. When treated with (*S*)-Mosher's acid or (*R*)-Mosher's acid chloride, the subsequent ester presents an upfield movement of chemical shift of THF moiety around 0.05–0.07 ppm. Therefore, the above analysis suggests that the newly generated stereogenic centre should be assigned as alcohol **213** presented in Scheme 7.01. The conformation in Scheme 7.01 was suggested by Mosher and co-workers, that in the substructure C(H)-O-C(=O)-C-CF₃ of each Mosher's ester, these atoms are coplanar.



Scheme 7.01 Mosher's ester analysis of **213**

For allyl acetate **267**, a substantial change in chemical shift can be observed when subjected to reaction with (*R*)-Mosher's acid or (*S*)-Mosher's acid chloride. The chemical shifts of the alkene protons move upfield by 0.13–0.14 ppm, and two allylic protons move upfield by 0.09 and 0.10 ppm respectively. When treated with (*S*)-Mosher's acid or (*R*)-Mosher's acid chloride, the subsequent ester presents an upfield movement of chemical shift of THF moiety around 0.04–0.12 ppm. Therefore, the above analysis suggests that the newly generated stereogenic centre should be assigned as alcohol **267** presented in Scheme 7.02.



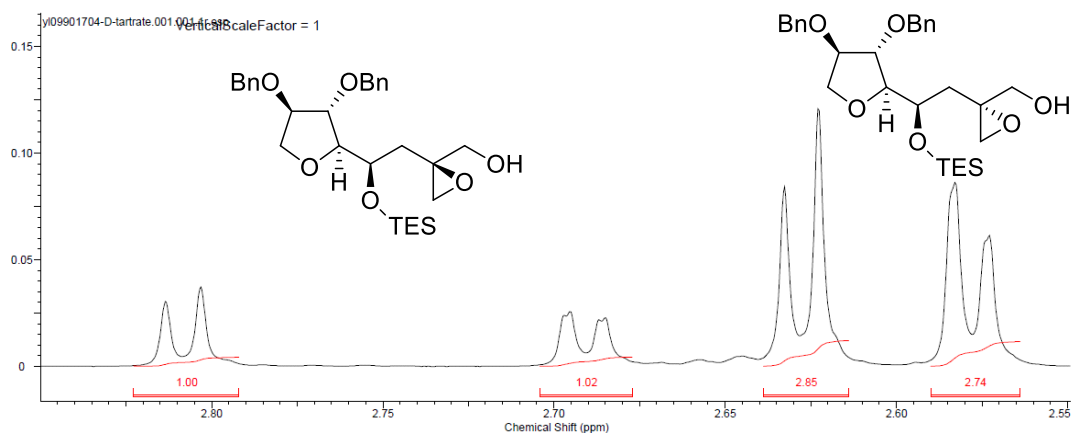
Scheme 7.02 Mosher's ester analysis of **267**

Appendix 2: Determination of Diastereoselectivity

Determination of diastereoselectivity of Sharpless asymmetric epoxidation on **273**:

D-(-)-tartrate (gives *R* isomer as major product)

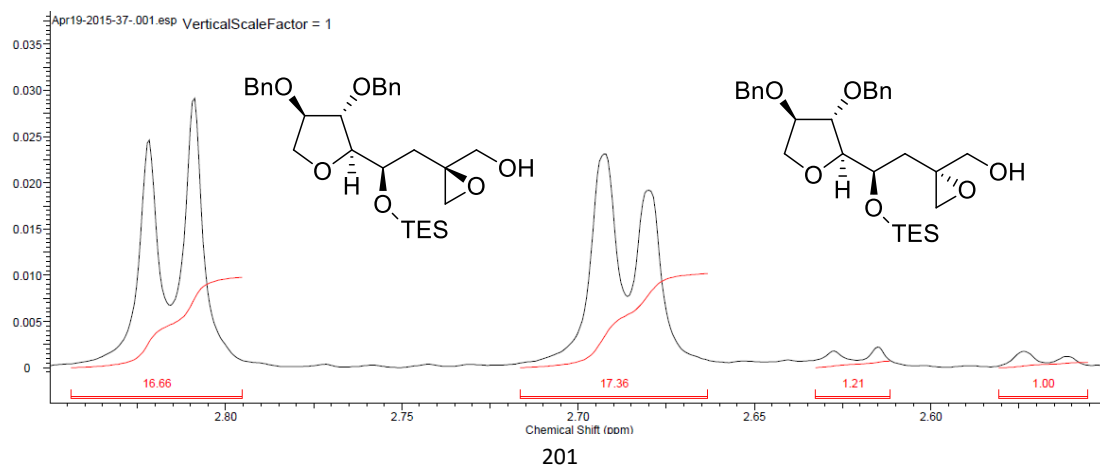
Average selectivity: $(1.00+1.02)/(2.85+2.74)=1:2.8$ (*S/R*)



L-(+)-tartrate (gives *S* isomer as major product)

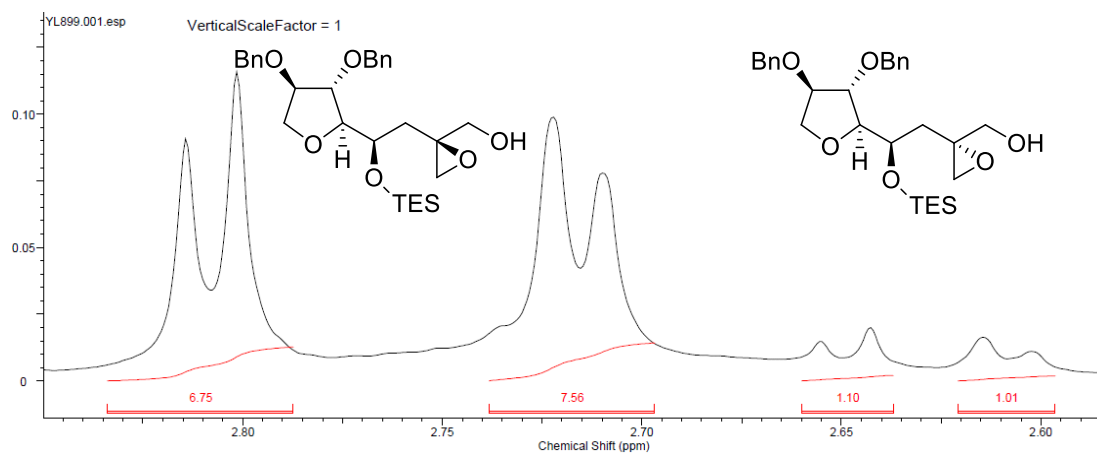
The reaction mixture was separated into two portions. The selectivity was calculated based on the mass and selectivity of each portion.

Portion 1: 133 mg



Average selectivity: $(16.66+17.36)/(1.21+1.00)=15.4:1$ (S/R)

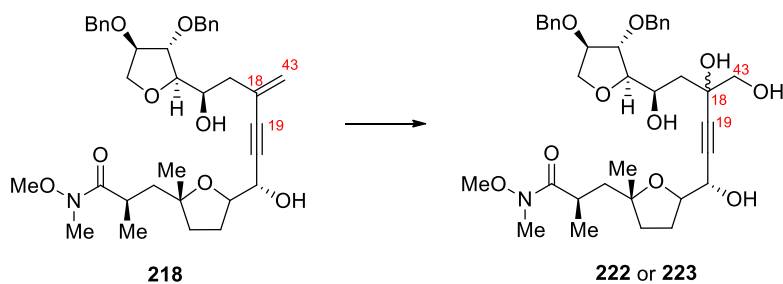
Portion 2: 142 mg



Average selectivity: $(6.75+7.56)/(1.10+1.01)=6.78:1$ (S/R)

Therefore, the combined selectivity for SAE using L-(+)-tartrate is (S/R):

$$\frac{133 \times \frac{15.4}{1 + 15.4} + 142 \times \frac{6.78}{6.78 + 1}}{133 \times \frac{1}{1 + 15.4} + 142 \times \frac{1}{6.78 + 1}} = \frac{124.9 + 123.7}{8.1 + 18.2} = \frac{248.6}{26.3} = 9.5:1$$



Scheme 7.03 Determination of diastereoselectivity of AD product

The selectivity of AD reaction was calculated based on ^{13}C NMR. Two sets of peaks have been chosen for analysis in red and blue colour. ^{13}C NMR is usually not recommended for integration due to different relaxation time of different carbons and decoupling issue, which enhances the signal of carbons with more hydrogens on them. In this case, carbons with chemical shift 88.40/88.29 ppm are selected because they are assigned as a pair of diastereoisomer of C19 alkyne carbon, which does not have protons nearby. Assuming that both of **222** and **223** have similar relaxation time, we can then estimate the diastereoselectivity based on the integration of these two peaks on ^{13}C NMR. Therefore, the diastereoselectivity is suggested as 2.3:1 (DHQD) and 1.4:1 (DHQ).

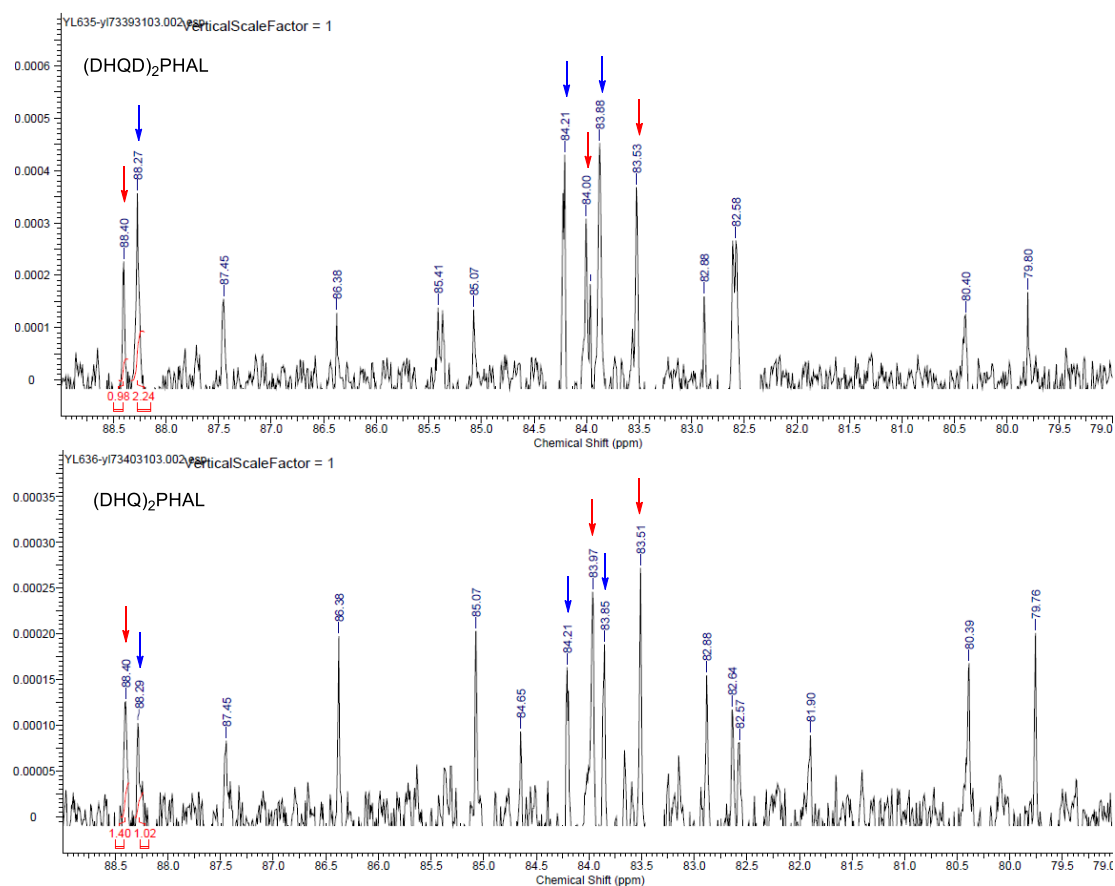
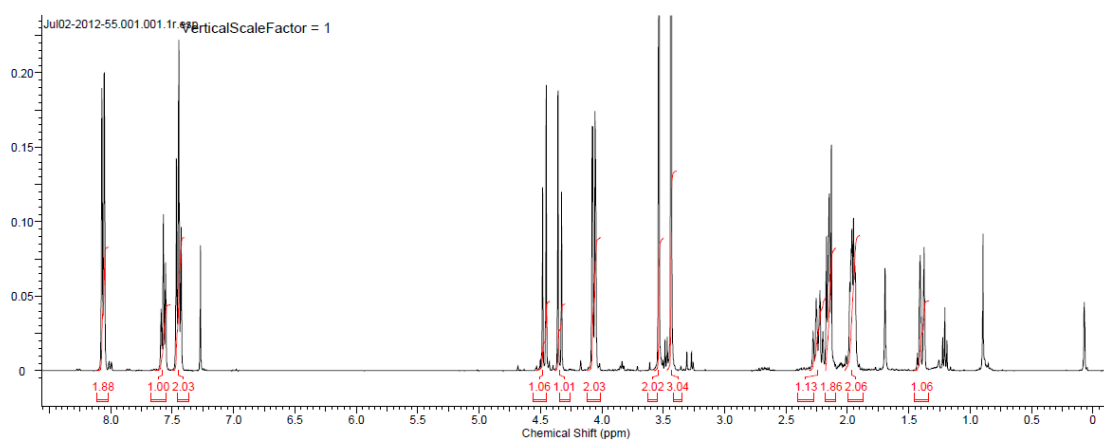


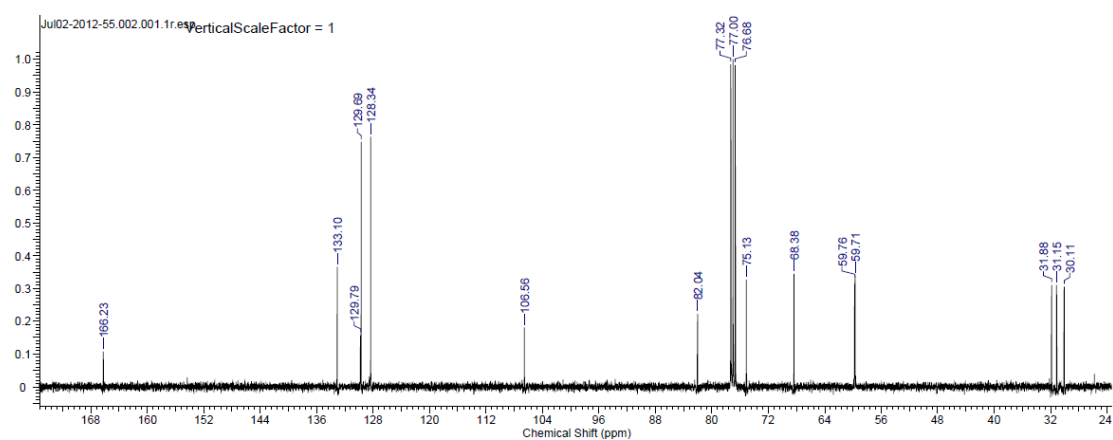
Figure 7.1 Determination of the diastereoselectivity of **222** and **223** using ^{13}C NMR

Appendix 3: Selected Key NMR Spectra

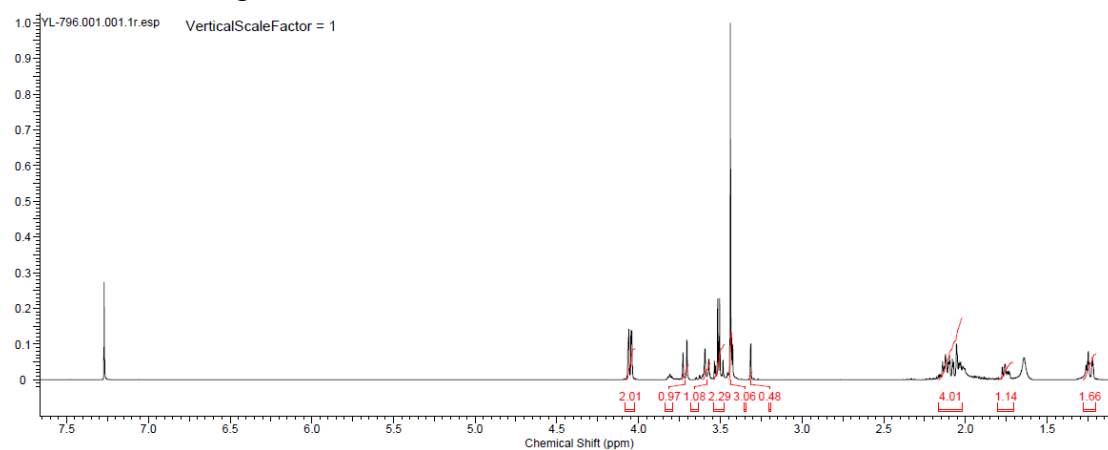
^1H NMR of D ring core **182**



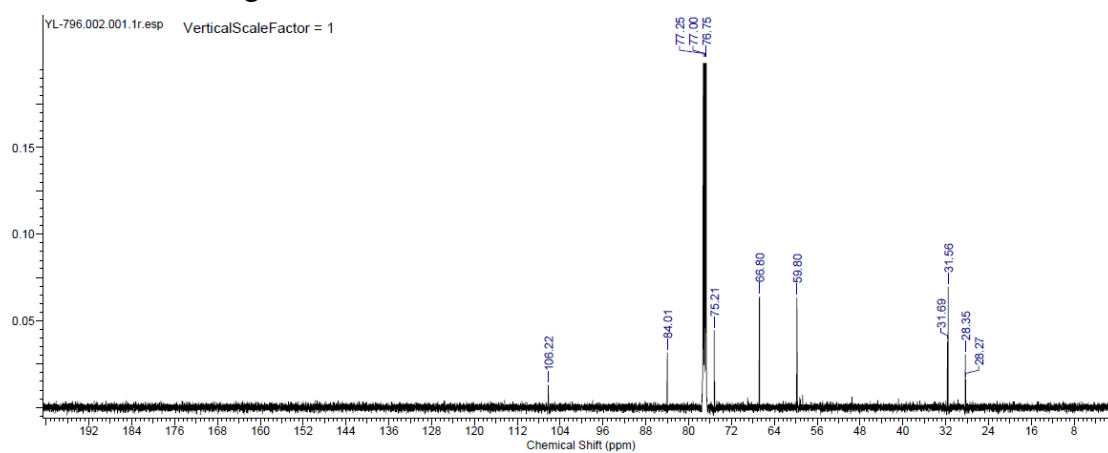
^{13}C NMR of D ring core **182**



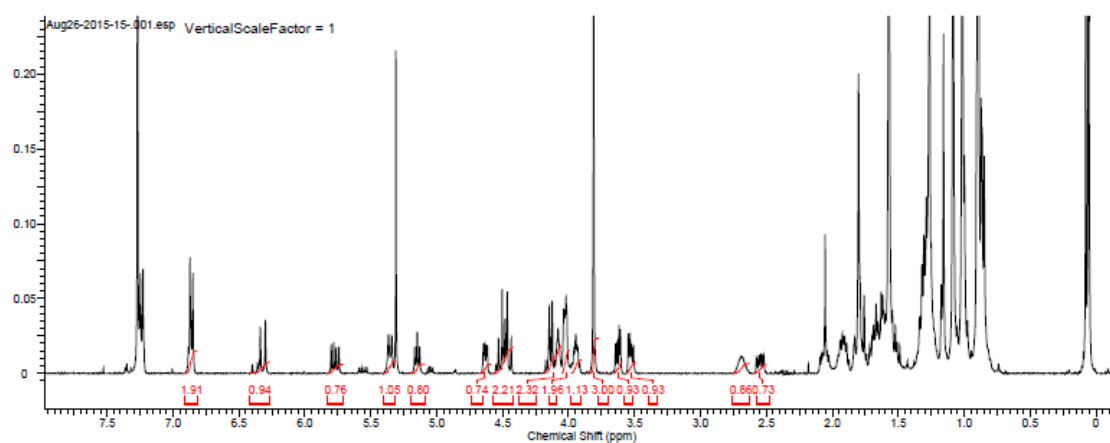
^1H NMR of D ring core **257**



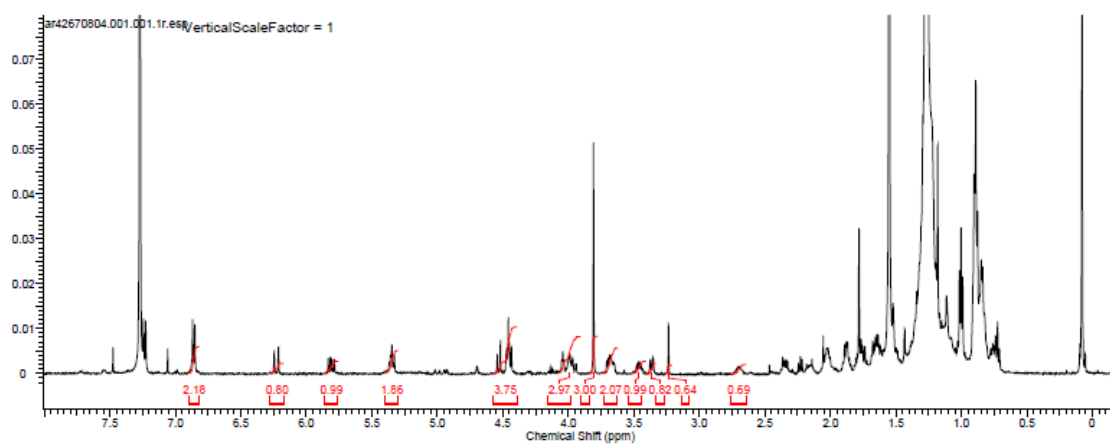
^{13}C NMR of D ring core **257**



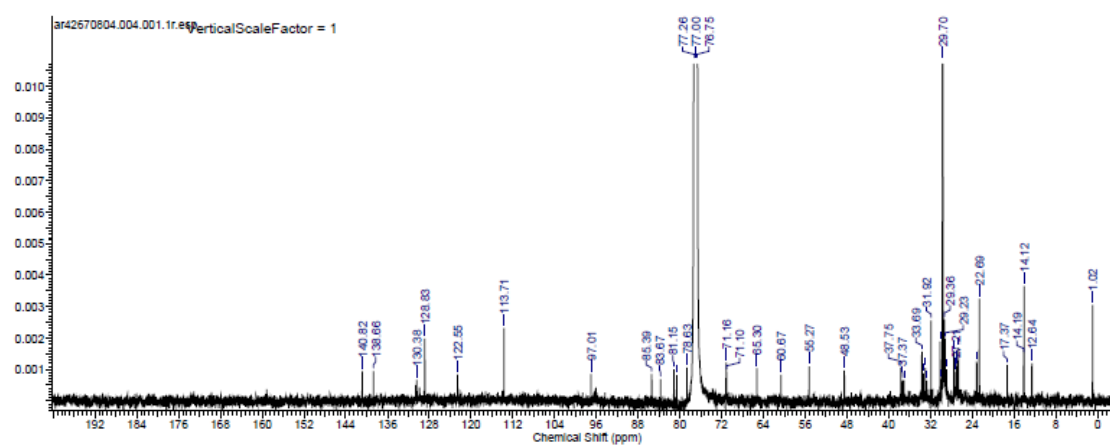
^1H NMR of ketone **315** (provided by Ahria Roushanbakhti)



^1H NMR of EFG fragment **296** (provided by Ahria Roushanbakhti)



^{13}C NMR of EFG fragment **296** (provided by Ahria Roushanbakhti)



Appendix 4: References

-
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